Vaxzevria: Periodic safety update report assessment

29th December 2021 to 28th June 2022

This document consists of:

1. The PRAC assessment report of the Vaxzevria periodic safety update report (PSUR) covering the period 29 December 2021 to 28 June 2022, and;

2. The Vaxzevria PSUR itself.

The PSUR is a pharmacovigilance document intended to provide an evaluation of the risk-benefit balance of the medicinal product during the reference period mentioned above.

The objective of the PSUR is to present a comprehensive and critical analysis of the risk-benefit balance of the product, taking into account new or emerging safety information in the context of cumulative information on risk and benefits. The marketing authorisation holder is legally required to submit PSURs at defined time points after the authorisation of a medicinal product.

EMA's safety committee, the PRAC, assesses information in the PSUR to determine if there are new risks identified for a medicine and/or if its risk-benefit balance has changed. The outcome of this assessment is summarised in the PRAC assessment report of the PSUR.

The PSUR and the PRAC assessment report of the PSUR include information about **suspected** side effects, i.e. medical events that have been observed following the use of the vaccine, but which are not necessarily related to or caused by the vaccine itself. Information on suspected side effects should not be interpreted as meaning that the vaccine or the active substance causes the observed event or is unsafe to use.

Only a detailed evaluation and scientific assessment of all available data, as described in the PRAC assessment report of the PSUR, can determine the impact of new data on the benefits and risks of a medicine.

Further information on the safety of COVID-19 vaccines and on PSUR submission and assessment is available on the EMA website.

This document may contain redactions for commercially confidential information (CCI) and protected personal data (PPD) in accordance with applicable legislation and guidance.

EMA/PRAC/1098/2023
Pharmacovigilance Risk Assessment Committee (PRAC)

PRAC PSUR assessment report

Procedure no.: EMEA/H/C/PSUSA/00010912/202206

Active substance(s): COVID-19 Vaccine (ChAdOx1-S [recombinant]) (Vaxzevria)

Period covered by the PSUR: 29/12/2021 To: 28/06/2022

Centrally authorised Medicinal product(s): For presentations: See Annex A	**Marketing Authorisation Holder**
Vaxzevria	AstraZeneca AB

Status of this report and steps taken for the assessment

Current step	Description	Planned date	Actual Date
☐	Start of procedure:	15 Sept 2022	15 Sept 2022
☐	PRAC Rapporteur's preliminary assessment report (AR)	14 Nov 2022	14 Nov 2022
☐	MS/PRAC members and MAH comments	14 Dec 2022	14 Dec 2022
☐	PRAC Rapporteur's updated assessment report following comments	29 Dec 2022	23 Dec 2022; 05 Jan 2023
☐	Oral explanation	N/A	N/A
☒	PRAC recommendation	12 Jan 2023	12 Jan 2023

Procedure resources	
PRAC Rapporteur	Name: Jean-Michel Dogné Tel: Email:
Contact person - PRAC Rapporteur	Name: Tel: Email:
Assessor – PRAC Rapporteur	Name: Email: Name: Email: Name: Email: Name: Email: Name: Email: Name: Email:
EMA Procedure Lead	Name: Tel: Email:
EMA Procedure Assistant	Name: Tel: Email:

Table of contents

1. Background information on the procedure

This is the assessment of PSUR(s) submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) for COVID-19 Vaccine (ChAdOx1-S [recombinant]) (Vaxzevria).

2. Assessment conclusions and actions

This is the **third Periodic Benefit-Risk Evaluation Report (PBRER)** for VAXZEVRIA (AZD1222/ VAXZEVRIA). It summarises safety and efficacy/effectiveness data for the period **from 29 December 2021 to 28 June 2022**, and places it in the context of the cumulative data and the overall benefit risk profile.

VAXZEVRIA is a monovalent vaccine composed of a single recombinant, replication-deficient chimpanzee adenovirus (ChAdOx1) vector encoding the S glycoprotein of SARS CoV-2. Following administration, the S glycoprotein of SARS-CoV-2 is expressed locally stimulating neutralizing antibody and cellular immune responses.

VAXZEVRIA is indicated for active immunization of individuals ≥18 years old for the prevention of COVID-19. The VAXZEVRIA primary vaccination course consists of two separate doses of 0.5 ml each. The second dose should be administered between 4 and 12 weeks after the first dose. A booster dose (third dose) of 0.5 ml may be given to individuals who completed the primary vaccination course with VAXZEVRIA or an mRNA COVID-19 vaccine at least 3-months after completing the primary vaccination course.

VAXZEVRIA is supplied as a vial containing either 8 doses or 10 doses per vial, 0.5 mL per dose for intramuscular (IM) injection.

VAXZEVRIA was first authorised for emergency use in the United Kingdom on 29 December 2021. The vaccine received **conditional marketing authorization in the EU on 29 January 2021**. As of 28 June 2022, VAXZEVRIA has been approved for conditional marketing authorisation or emergency use authorisation in 93 countries. VAXZEVRIA is distributed via COVID-19 Vaccines Global Access (COVAX) to more than 80 countries

During the period under review:

- There were no actions taken for safety reasons
- The EU-SmPC was updated to include in Section 4.8: '**Tinnitus**' (uncommon), '**Paraesthesia / Hypoaesthesia**' (uncommon), and '**Transverse Myelitis**' (Not known)

Exposure

The estimated **cumulative exposure of clinical trial subjects** is approximately **35,921 healthy volunteers** who have received VAXZEVRIA and 1523 who have received AZD2816.

The estimated **cumulative exposure from post approval experience** is over 2,79 billion doses distributed globally and over **2,09 billion doses administered worldwide**. **In the EU,** there were approximately **69 million doses administered** (i.e. **~39 million Dose 1**, **~30 million Dose 2**, and ~22,000 Booster dose).

Signals

During the period under review, there were **3 validated signals by the MAH**:

- *GBS:* closed; considered as an important potential risk by the MAH (categorised as an important identified risk by the PRAC). The MAH closed a signal of GBS based on a cumulative review of post-marketing, clinical and literature data. The cumulative review did not provide additional information compared to the data discussed in the previous PBRER, except a few new articles published. The PRAC considers that the available data did not change the current knowledge regarding GBS after Vaxzevria and that GBS is appropriately described in the EU-PI (sections 4.4 and 4.8) and in the EU-RMP (important identified risk), and no further action is required.
- There were two signals (Hypoaesthesia and Paraesthesia, and Tinnitus) that were closed during or shortly after the reporting interval. Both signals of "Paraesthesia and hypoaesthesia" and "Tinnitus" were assessed in the context of the previous PSUR procedure (late breaking information) which led to the inclusion of the 3 events in the section 4.8 of the EU-SmPC (i.e., Paraesthesia [uncommon], Hypoaesthesia [uncommon], and Tinnitus [uncommon].

After the DLP, the MAH **validated 2 signals**:

- *Immune thrombocytopenia (ITP):* The signal for ITP was re-opened based on well-documented case reports of ITP with VAXZEVRIA from the published literature. ITP is listed in Section4.8 of the Eu-SmPC and is an Important identified risk in the EU-RMP
- *Cutaneous vasculitis:* The signal was identified based on well-documented case series from published literature cases. Subsequently a signal was received from PRAC. This led to the inclusion of cutaneous vasculitis in the ADRs of Vaxzevria in Section 4.8. This is further discussed in below Section 3 – Recommendations.

New safety information

During the reporting period, **no new safety concerns** were identified.

The safety concerns remained unchanged, except 'Anaphylaxis' which was removed from the important identified risks as it is now considered fully characterised and no additional RMM are ongoing or planned.

During the reporting period, **new information** became available regarding ***Cutaneous vasculitis***. Cumulatively, 258 cases were identified, including 12 cases of rechallenge all confirmed as BCC Level 1-3. Based on the evaluation of currently available information, the MAH considers that there is a reasonable possibility of a causal association between Vaxzevria and cutaneous vasculitis. An update of the EU-PI is thus requested (see below Section – Recommendations).

Several safety topics (**Health Authority Requests** and **Other identified risks not categorised as important**) were under close monitoring during the reporting period. Following the assessment of these issues, the PRAC concluded:

- To **close the monitoring** of Tinnitus, Reactogenicity, Paraesthesia/Hypoaesthesia, Sarcoidosis, Subacute thyroiditis, Rhabdomyolysis, Viral reactivation (Non-Zoster), Booster dosing, Myocarditis, and Exacerbation of diabetes, adrenal insufficiency and hypertension.

  These events do not need to be further discussed through PBRERs unless significant new safety information is identified
- To **continue the monitoring** of VTE, ADEM, Hearing loss, Menstrual disorders (literature and serious cases), Glomerulonephritis and nephrotic syndrome including IgA nephropathy (literature only) and Fatal cases. In addition, new daily persistent headache should be reviewed.

  These topics should continue to be discussed in the next PBRER.

Moreover, **EMA validated 2 signals** after the DLP:

- A signal of Pemphigus/pemphigoid was validated in October 2022. The signal was confirmed on 1st Dec 2022. The MAH should provide additional data by 09.02.2023 (see ongoing procedure SDA 113; EPITT 19858).
- A signal of Myositis was validated in December 2022 (EPITT 19882). The signal is confirmed as a cumulative review is requested for the next PSUR (see Section 4).

Besides, the **WHO-UMC** shared in September 2022 (i.e. after the DLP) a **signal** on **Severe cutaneous adverse reactions (**SCAR). This should be discussed in the next PBRER.

New benefit information

Regarding the benefit, there are some new data on related to (i) the use of Vaxzevria as heterologous booster and (ii) a rapid waning of antibody titres and vaccine effectiveness, but persistence of effectiveness against severe forms. There are no new data on efficacy that alters the conclusions of previous assessments, which are describe in the approved product information.

These data provide supportive evidence of Vaxzevria immunogenicity and safety profile when used as a heterologous booster. Yet, these findings should be further explored in the Omicron era.

Benefit/risk balance

The risk-benefit balance of Vaxzevria **remains unchanged**. However, the risks of SARS-CoV-2 infection and the context of treatment and prevention of the disease have evolved. TTS, CVST and GBS, the key risks identified for Vaxzevria, have been reported more frequently in young adults who benefit less from vaccination. This observation led to question the B/R balance in the younger population and for several EU Member States to restrict the use of the vaccine, especially after more alternative vaccines were made available.

3. Recommendations

Based on the PRAC review of data on safety and efficacy, the PRAC considers that the risk-benefit balance of medicinal products containing COVID-19 Vaccine (ChAdOx1-S [recombinant]) (Vaxzevria) remains unchanged but recommends that the terms of the marketing authorisation(s) should be varied as follows:

Scientific conclusions and grounds for variation to the terms of the marketing authorisations

In view of available data on **cutaneous vasculitis** from literature and spontaneous reporting including in the majority of cases a close temporal relationship and in some cases, a positive rechallenge, the PRAC agrees that a causal relationship between COVID-19 Vaccine (ChAdOx1-S [recombinant]) (Vaxzevria) and cutaneous vasculitis is at least a reasonable possibility.

The PRAC concluded that the product information of product containing COVID-19 Vaccine (ChAdOx1-S [recombinant]) (Vaxzevria) should be amended accordingly.

Precise scope:

Update of section 4.8 of the SmPC to add cutaneous vasculitis with a frequency 'not known'based on data assessed within this procedure. The Package leaflet is updated accordingly.

The following changes to the product information of medicinal products containing COVID-19 Vaccine (ChAdOx1-S [recombinant]) (Vaxzevria) are recommended (new text **underlined and in bold**, deleted text ~~strike-through~~):

Summary of Product Characteristics

- Section 4.8

The following adverse reaction(s) should be added under the SOC Skin and subcutaneous tissue disorders with a frequency **Not known**: **Cutaneous vasculitis**

Package Leaflet

- Section 4

Frequency **Not known**: **inflammation of blood vessels in the skin, often with a rash or small red or purple, flat, round spots under the skin's surface or bruising (cutaneous vasculitis)**

4. Issues to be addressed in the next PSUR

The MAH(s) should also address the following issues in the next PSUR:

Acute disseminated encephalomyelitis (ADEM)

The MAH is requested to provide a discussion of ADEM, including but not be limited to:

(i) an updated cumulative review of cases of ADEM,
(ii) an updated literature review, with a focus on new relevant epidemiological studies,
(iii) a discussion on the need to update the PI and/or RMP.

Moreover, the MAH is requested to carefully review the evaluation of cases of ADEM as discrepancies regarding the BCC evaluation (e.g. case [redacted] classified as BCC Level 2 whereas a 4-month FU suggests a monophasic disease course) and WHO-UMC causality assessment (e.g. case [redacted] assessed as unlikely due to incorrect TTO) have been noticed.

Menstrual disorders

The MAH is requested to provide and discuss an updated literature review of Menstrual disorders. Besides, the MAH is requested to further discuss the serious cases requiring hospitalization and the cases resulting in death.

Glomerulonephritis and nephrotic syndrome including IgA nephropathy

The MAH is requested to further search for literature on GN/SN following COVID-19 vaccination, with a special focus to Adeno-vectored vaccines, relapse and flare up, and measured kidney alterations after vaccination.

Venous Thromboembolism

The MAH is requested to further investigate VTE by providing an updated literature review, with a focus on new relevant epidemiological studies.

Thrombosis

The MAH is requested to provide a tabular summary of the fatal cases reporting a thrombotic event after dose 3 (or dose 4) of the vaccine.

Use in immunocompromised patients

The MAH is requested to verify the PTs reported in fatal cases, especially regarding TTS and Thrombocytopenia.

Severe cutaneous adverse reactions (SCAR)

Following a potential signal of SCAR identified by WHO-UMC, the MAH is requested to provide a cumulative review of cases reported with Vaxzevria together with a review of literature. A discussion on the need to update the PI should be included.

Hearing loss

The MAH is requested to provide and discuss an updated review of hearing loss cases with a recovered with sequelae or not recovered outcome.

New daily persistent headache

The MAH is requested to provide a cumulative review of cases of new daily persistent headache in association with Vaxzevria, including spontaneous reports and data from the literature and clinical trials. The analysis should include an overall discussion of the cases, as well as an individual causality assessment of each cases.

Myositis

A signal of Myositis was validated in December 2022 (EPITT 19882). The signal is confirmed, and a cumulative review is requested for the next PSUR. Please, refer to the PRAC recommendation for the signal of myositis with Vaxzevria (EPITT no: 19882) for the list of questions to be addressed.

5. PSUR frequency

☒Changes of PSUR frequency are proposed

The current frequency of submission should be changed **from 6 months to 1 year** at the first possibility. The list of Union reference dates (EURD) should be updated accordingly.

The next PSUR should be submitted according to the current EurD list (i.e. **next DLP: 28 December 2022** and next submission date: 08 March 2023). The PSUR cycle will be updated for the **following PSUR** which should submitted with a **DLP of 28 December 2023**.

The request to change the PSUR frequency is supported by:

- *The gain of experience with Vaxzevria*: with more than 2 billion doses administered worldwide, the safety profile of Vaxzevria is becoming well known. Moreover, the monitoring of most of the safety topics followed as 'Health authority request' has been stopped in the current and previous PBRERs.
- *No change in the indications of the vaccine*: Currently, no paediatric indication has been submitted for Vaxzevria. Regarding the booster indication, available data do not suggest a different safety profile for the booster dose.
- *No change in the composition of the vaccine*: The MAH did not submit any request for significant changes in the component of the vaccine.
- *Decrease in the use of Vaxzevria*: A sharp decreased in the use of Vaxzevria is observed in the EU as EU countries do not favour Vaxzevria for booster vaccination campaign.

Annex: preliminary PRAC Rapporteur assessment comments on PSUR

1. PSUR Data

1.1. Introduction

This Periodic Benefit Risk Evaluation Report (PBRER) for COVID-19 Vaccine (ChAdOx1-S [recombinant]) (Vaxzevria) covers the period **from 29 December 2021 to 28 June 2022**.

The International Birth Date (**IBD**) is **29 December 2020**.

VAXZEVRIA is a monovalent vaccine composed of a single recombinant, replication-deficient chimpanzee adenovirus (ChAdOx1) vector encoding the S glycoprotein of Hunan-Hu-1 strain of the Severe Acute Respiratory Coronavirus 2 (SARS CoV-2). Following administration, the S glycoprotein of SARS CoV-2 is expressed locally stimulating neutralizing antibody and cellular immune responses.

VAXZEVRIA is indicated for active immunisation of individuals ≥18 years for the prevention of COVID-19.

VAXZEVRIA is supplied as a vial containing either 8 doses or 10 doses per vial, 0.5 mL per dose for intramuscular (IM) injection. VAXZEVRIA vaccination course consists of two separate doses of 0.5 ml each. The second dose should be administered between 4 and 12 weeks after the first dose. It is recommended that individuals who receive a first dose of VAXZEVRIA complete the vaccination course with VAXZEVRIA. A booster dose (third dose) of 0.5 ml may be given to individuals who completed the primary vaccination course with VAXZEVRIA or another authorised COVID 19 vaccine. The third dose should be administered at least 3 months after completing the primary vaccination course. The status of approval and the recommendation in national prescribing information (PI) documents relating to the booster dose vary.

The MAH proposes to update the product information as part of the submission of this PBRER to include cutaneous vasculitis in section 4.8 of the SmPC and section 4 of the PL.

Rapporteur assessment comment:
The booster indication was approved on 15 May 2022 within the variation procedure II/052.
The inclusion of cutaneous vasculitis in the list of ADR is further discussed in Section 2.3.34 of this AR.

1.2. Worldwide marketing authorisation status

VAXZEVRIA was first approved for active immunisation in individuals 18 years of age and older for the prevention of COVID-19 in United Kingdom (UK) on 29 December 2020. It received conditional marketing authorisation in the EU on 29 January 2021.

VAXZEVRIA has been approved either for conditional marketing authorisation or emergency use authorisation in 93 countries managed by AstraZeneca and its partners – Serum Institute of India (SII), R-pharm, Fiocruz, and Verity Pharmaceuticals. VAXZEVRIA is also distributed via COVID-19 Vaccines Global Access programme (COVAX), in collaboration with United Nations Children's Fund (UNICEF) and Pan American Health Organization (PAHO), under a World Health Organization (WHO) Emergency Use Listing to more than 80 countries.

The MAH provided a summary of the worldwide marketing authorisation status applicable to COVID 19 VACCINE ASTRAZENECA', which is not copied here but can be retrieved from Table 1 of section 2 in PSUR#3.

1.3. Overview of exposure and safety data

1.3.1. Actions taken in the reporting interval for safety reasons

No significant actions related to safety were taken or proposed during the reporting period.

1.3.2. Changes to reference safety information

The reference safety information is the Core Data Sheet (CDS).

The VAXZEVRIA CDS in effect at the beginning of the reporting period was dated 02 November 2021 (version 10.0). During this reporting period, the VAXZEVRIA CDS was updated to include the safety related changes summarised in Table 1.

For the purpose of this PBRER, the **CDS dated 11 May 2022 (version 18.0)**, is the reference for both the benefit and risk sections.

Table 1 - Summary of safety-related changes to the VAXZEVRIA CDS during the reporting period.

CDS version date	CDS Section Number – CDS Section Title - Detail of the safety-related change
06 January 2022	**CDS Section 4.6 - Pregnancy and lactation** Updated pregnancy wording to reflect current safety data on administration of VAXZEVRIA in pregnant women, based on available data from AstraZeneca Global Safety database, the pregnancy registry and literature. Updated recommendation to consider use of VAXZEVRIA during pregnancy when benefits outweigh potential risks.
16 January 2022	**CDS Section 4.6 - Pregnancy and lactation** **Breastfeeding** Updated wording to reflect current non-clinical, clinical and post-marketing data on use of VAXZEVRIA during breastfeeding.
04 February 2022	**CDS Section 4.2 - Posology and method of administration** **Posology** Recommendation for use of a **booster dose** (third dose) in individuals who completed the primary vaccination course with VAXZEVRIA or another authorised COVID-19 vaccine. Timing for administration of the booster dose is at least 3 months after completing the primary vaccination course. **CDS Section 4.4 – Special warnings and special precautions for use** **Interchangeability** The text has been revised to clarify that limited data are available regarding the interchangeability of VAXZEVRIA with other COVID-19 vaccines. Text has been added to inform that the available data on the use of VAXZEVRIA as a booster dose following primary vaccination with another COVID-19 vaccine are presented in sections 4.8 and 5.1. **CDS Section 4.8 – Undesirable effects** **Summary of safety profile** Safety information from the AstraZeneca sponsored **study D7220C00001**, and the externally sponsored study RHH-001, has been included.
02 March 2022	**CDS Section 4.8 – Undesirable effects** Addition of **paraesthesia and hypoaesthesia** to the summary of post-authorisation data, with frequency uncommon.
11 May 2022	**CDS Section 4.4 – Special warnings and special precautions for use** The warning on Neurological events has been updated to specifically reference very rare events of **Guillain-Barré Syndrome** as having been reported following vaccination with VAXZEVRIA.

Post data-lock point (DLP), the VAXZEVRIA CDS was updated on 01 July 2022 (**Version 19.0**) to include **Tinnitus** as an Adverse Drug Reaction (ADR) in Section 4.8 with the frequency uncommon, further information regarding this change is presented in Section 14, 16.2.5.2 and 16.3.4.3.

Rapporteur assessment comment:

The reference safety information for this PSUR is the CDS version 18.0, dated of 11 May 2022. It is noted that changes to the CDS and EU-PI may differ. The main **differences between the CDS v18.0 and the current EU-PI** are highlighted in the Table below.

	CDS (11.05.2022)	**EU-PI (12.10.2022)**
Section 4.3 Contraindications	Patients who have experienced major venous and/or arterial thrombosis in combination with thrombocytopenia following vaccination with any COVID-19 vaccine	Individuals who have experienced thrombosis with thrombocytopenia syndrome (TTS) following vaccination with Vaxzevria (see section 4.2)
	/	Individuals who have previously experienced episodes of capillary leak syndrome (see also section 4.4)
Section 4.4 Special warnings and special precautions for use	Hypersensitivity including anaphylaxis […] Appropriate medical treatment and supervision should always be readily available […] An additional dose of the vaccine should not be given to those who have experienced a severe hypersensitivity reaction to a previous dose of COVID-19 Vaccine AstraZeneca.	Hypersensitivity and anaphylaxis […] Appropriate medical treatment and supervision should always be readily available […]. Close observation for at least 15 minutes is recommended following vaccination. An additional dose of the vaccine should not be given to those who have experienced anaphylaxis to a previous dose of Vaxzevria.
	Thromboembolism and thrombocytopenia […] Whilst specific risk factors for thromboembolism in combination with thrombocytopenia have not been identified, cases have occurred in patients with a previous history of thrombosis, as well as in patients with autoimmune disorders, including immune thrombocytopenia. The benefits and risks of vaccination should be considered in these patients.	Coagulation disorders - Thrombosis with thrombocytopenia syndrome […]
	Thromboembolism and thrombocytopenia Events of cerebrovascular venous and sinus thrombosis without thrombocytopenia have been reported very rarely following vaccination with Vaxzevria, although a causal relationship has not been established. These events can be fatal and may require different treatment approaches than TTS. Healthcare professionals should consult applicable guidance.	Coagulation disorders - Cerebrovascular venous and sinus thrombosis Events of cerebrovascular venous and sinus thrombosis without thrombocytopenia have been observed very rarely following vaccination with Vaxzevria. Some cases had a fatal outcome. The majority of these cases occurred within the first four weeks following vaccination. This information should be considered for individuals at increased risk for cerebrovascular venous and sinus thrombosis. These events may require different treatment approaches than TTS and healthcare professionals should consult applicable guidance.

	/	Coagulation disorders - Thrombocytopenia Cases of thrombocytopenia, including immune thrombocytopenia (ITP), have been reported after receiving Vaxzevria, typically within the first four weeks after vaccination. Very rarely, these presented with very low platelet levels (<20,000 per µL) and/or were associated with bleeding. Some of these cases occurred in individuals with a history of immune thrombocytopenia. Cases with fatal outcome have been reported. If an individual has a history of a thrombocytopenic disorder, such as immune thrombocytopenia, the risk of developing low platelet levels should be considered before administering the vaccine and platelet monitoring is recommended after vaccination.
	Thromboembolism and thrombocytopenia […] Healthcare professionals should be alert to the signs and symptoms of thromboembolism and thrombocytopenia, as well as coagulopathies. Vaccinated individuals should be instructed to seek immediate medical attention if they develop symptoms such as a severe or persistent headaches, blurred vision, confusion, seizures, shortness of breath, chest pain, leg swelling, leg pain, persistent abdominal pain or unusual skin bruising and or petechia a few days after vaccination. Individuals diagnosed with thrombocytopenia within 21 days of vaccination with COVID-19 Vaccine AstraZeneca, should be actively investigated for signs of thrombosis. Similarly, individuals who present with thrombosis within 21 days of vaccination should be evaluated for thrombocytopenia.	Coagulation disorders (*general warning for all TTS, CVST, and TP*) Healthcare professionals should be alert to the signs and symptoms of thromboembolism and/or thrombocytopenia. Those vaccinated should be instructed to seek immediate medical attention if they develop symptoms such as shortness of breath, chest pain, leg swelling, leg pain, persistent abdominal pain following vaccination. Additionally, anyone with neurological symptoms including severe or persistent headaches, blurred vision, confusion or seizures after vaccination, or who experiences spontaneous bleeding, skin bruising (petechia) beyond the site of vaccination after a few days, should seek prompt medical attention. Individuals diagnosed with thrombocytopenia within three weeks after vaccination with Vaxzevria, should be actively investigated for signs of thrombosis. Similarly, individuals who present with thrombosis within three weeks of vaccination should be evaluated for thrombocytopenia.
	/	Capillary leak syndrome Very rare cases of capillary leak syndrome (CLS) have been reported in the first days after vaccination with Vaxzevria. […]

	Neurological events Very rare events of demyelinating disorders, including Guillain-Barré syndrome (GBS), have been reported following vaccination with COVID-19 Vaccine AstraZeneca. A causal relationship has not been established. As with other vaccines, the benefits and potential risks of vaccinating individuals with COVID-19 Vaccine AstraZeneca should be considered.	Neurological events Guillain-Barré syndrome (GBS) and transverse myelitis (TM) have been reported very rarely following vaccination with Vaxzevria. Healthcare professionals should be alert of GBS and TM signs and symptoms to ensure correct diagnosis, in order to initiate adequate supportive care and treatment, and to rule out other causes.
	/	Risk of very rare events after a booster dose The risk of very rare events (such as coagulation disorders including thrombosis with thrombocytopenia syndrome, CLS, GBS and TM) after a booster dose of Vaxzevria has not yet been characterised.
	Interchangeability There are limited safety, immunogenicity and efficacy data available regarding the interchangeability of Vaxzevria with other COVID-19 vaccines. For the available data on the use of Vaxzevria as a booster dose following primary vaccination with another COVID-19 vaccine, see sections 4.8 and 5.1.	/
	/	Limitations of vaccine effectiveness Protection starts from approximately 3 weeks after the first dose of Vaxzevria. Individuals may not be fully protected until 15 days after the second dose is administered. As with all vaccines, vaccination with Vaxzevria may not protect all vaccine recipients (see section 5.1).
Section 4.8 Undesirable effects	Thrombocytopenia (very rare). The majority of reported events occurred in individuals aged 18-59 years old.	Thrombocytopenia (common) [In clinical trials, transient mild thrombocytopenia was commonly reported (see section 4.4)] Immune thrombocytopenia (not known) [Cases have been reported post-marketing (see also section 4.4)] Guillain-Barré syndrome (very rare), Transverse myelitis (very rare), Facial paralysis (rare) Capillary leak syndrome (not known) Cerebrovascular venous and sinus thrombosis (not known) Hypersensitivity (not known), decreased appetite (uncommon), Lethargy (uncommon), Muscle spasms (uncommon), Asthenia (common), Injection site bruising (very common) **Tinnitus (uncommon)**

The MAH indicated that the CDS was updated in July 2022 (after the DLP) to include **Tinnitus** in section 4.8. Tinnitus was included in the EU-PI as an outcome of the previous PSUR assessment report.

Moreover, a new signal of **cutaneous vasculitis** has been assessed within this PSUSA procedure. This event is now considered as an ADR of Vaxzevria (see Section 2.3.34 for further details).

1.3.3. Estimated exposure and use patterns

COVID-19 VACCINE ASTRAZENECA was first approved for active immunisation of individuals ≥18 years for the prevention of COVID-19 in United Kingdom (UK) on 29 December 2020. It received conditional marketing authorisation in the EU on 29 January 2021.

1.3.3.1. Cumulative subject exposure in clinical trials

Estimates of overall cumulative subject exposure are provided in Table 2, based on actual enrolment/randomisation schemes for ongoing trials.

Table 2 - Estimated cumulative subject exposure from clinical trials

Treatment	Number of subjects
VAXZEVRIA	35921
AZD2816[a]	1523
MenACWY	10949
Rabies vaccine	200
Placebo	11960

Cumulative numbers from initiation of the first clinical trials up to 28 June 2022. Participants rolled over from COV001 and COV002 into COV009, no additional dosing in COV009. COV009 excluded to avoid double-reporting.
MenACWY Meningococcal Vaccine.
aAZD2816 is a vaccine developed from AZD1222 targeting variants of SARS-CoV-2. AZD2816 is used in Study D7220C00001 which is further described in Section 7.2.1.

Cumulative summary tabulations of exposure by age/sex are presented in Table 3 below.

Table 3 - Estimated cumulative subject exposure to VAXZEVRIA and AZD2816 from completed and ongoing clinical trials by age and sex

	Number of subjects		
Age range (years)	**Male**	**Female**	**Total**
1-11	56	55	111
12-17	76	74	150
18-64	24894	25059	49953
>=65	5869	4371	10240
Missing	70	29	99
Total	**30965**	**29588**	**60553[a]**

Rapporteur assessment comment:

As of 28 June 2022, a total of 60,553 subjects were enrolled in completed and ongoing clinical trialsThese include 35,921 subjects who were exposed to VAXZEVRIA and 1,523 subjects who were exposed to AZD2816 (targeting variants of SARS-CoV-2).

Of these 60,553 subjects, 30,965 were males and 29,588 were females. Most of the participants (49,953; 82.49%) were aged between 18 to 64 years old, followed by age group >=65 years old (10,240; 16.9%), age group 12 to 17 years old (150; 0.24%) and age group 1 to 11 years old (111; 0.18%).

1.3.3.2. Cumulative and interval patient exposure from marketing experience

1.3.3.2.1 Cumulative doses distributed

Table 4 - VAXZEVRIA exposure, based on doses distributed, by Region

Region[b]	Exposure by doses distributed		Percentage (%)	
	Interval (01.01.2022-30.06.2022)	Cumulative (Up to 30.06.2022)	Interval	Cumulative
Europe	29510320	248197720	7.88	8.74
International	86484220	643723840	23.08	22.68
North America	10135700	19089200	2.70	0.67
Japan	9324970	62663140	2.49	2.21
Serum Institute of India[a]	169901970	1636706540	45.34	57.66
Fiocruz[a]	39371540	187985690	10.51	6.62
R-Pharm[a]	0	10358700	0.00	0.36
BKT[a]	30000000	30000000	8.01	1.06
Total	374728720	2838724830		

A more detailed breakdown of doses distributed across the countries within the EU can be found in Appendix 6 of PSUR#3.

PRAC Rapporteur's comment:

As of 30 June 2022 (DLP), a total of ~2.8 billion doses of VAXZEVRIA have been distributed, including ~374 million doses during the reporting interval, which is ~5 times (80%) less doses than during the previous reporting period (~1.8 billion doses in previous PSUR).

1.3.3.2. Cumulative doses administered

Cumulative administered doses are presented in Tables 5-7.

Table 5 - VAXZEVRIA interval and cumulative exposure based on doses administered, by Region/Country

Region	Interval		Cumulative			Percentage (%)	
	Dose 1	Dose 2	Dose 1	Dose 2	Dose3/4/ Booster	Interval	Cumulative
European Union	-198213	-8990	38913369	29816443	21772	-0.04	3.28
United Kingdom	-70731	-17121	24732840	24149323	58324	-0.02	2.33
Afghanistan	975338		975338		0	0.20	0.05
Australia	25076	74595	6898909	6814620	92395	0.02	0.65
Philippines	4629436		9811327	9010123	3028907	0.93	0.90
India	315166797		1579378046		0	63.02	75.29
Canada	7107		2234973	576005	1584	0.00	0.13
Argentina	224621	382033	10174372	9933058	6582393	0.12	0.96

Region	Interval		Cumulative			Percentage (%)	
	Dose 1	Dose 2	Dose 1	Dose 2	Dose3/4/ Booster	Interval	Cumulative
Bangladesh	6243827	11760870	20549140	19132540	10720392	3.60	1.89
Colombia	5308052	3372486	5308052	3372486	1583401	1.74	0.41
Ecuador	1739254	1419111	1739254	1419111	3866573	0.63	0.15
Iran	5596067	5039783	5596067	5,039783	3541319	2.13	0.51
Japan	58707	58819	58707	58819	0	0.02	0.01
Brazil	4619234		62233985	57429004	17358176	0.92	5.70
Chile	4230		410041	139629	2655470	0.00	0.03
Guatemala	302863	481376	2033337	1607041	818849	0.16	0.17
Ghana	10096925		10096925		0	2.02	0.48
Lebanon	31915		720793		0	0.01	0.03
Iraq	717233		717233		0	0.14	0.03
Mexico	49783383		49783383		0	9.96	2.37
Malaysia	3266	3604	2046604	2025975	1619351	0.00	0.19
Nepal	5374928	4598237	5374928	4598237	4026870	1.99	0.48
Peru	2241032	2099522	2241032	2099522	3609650	0.87	0.21
Saint Lucia	37850	34810	37850	34810	0	0.01	0.01
Taiwan	8072059	7162679	8072059	7162679	59488	3.05	0.73
Thailand	14078238	28660820	14078238	28660820	5869808	8.55	2.04
New Zealand	4475		3314	3619	1885	0.00	0.00
South Korea	-124712		11076305	9242971	2058	-0.02	0.97
Uruguay	2214		46684	44454	179	0.00	0.00
Grand Total	**500073105**		**2097714177**		**65518844**	**100**	**100**

Table 6 - Vaccine Doses Administered by Age Group

Age Group	Interval				Cumulative			
	Dose 1	Dose 2	Total	%age	Dose 1	Dose 2	Total	%age
18-24	852720	833133	1685853	-8.09	2035765	1850025	3885790	3.51
25-49	-1160235	-1105032	-2265267	10.87	13384413	12230226	25614639	23.14
50-59	68901	75778	144679	-0.69	11324258	10624908	21949166	19.83
60-69	1118171	1066270	2184441	10.48	17734853	17056392	34791245	31.43
70-79	227896	245582	473478	-2.27	10156603	9963679	20120282	18.17
≥80	182594	183273	365867	-1.76	2146616	2067526	4214142	3.80
Unknown	15221621	-8203022	23424643	112.43	74904	35478	110382	0.09
Total	**13931574**	**-6904018**	**20835592**	**100**	**56857412**	**53828234**	**110685646**	**100**

Table 7 - Vaccine Doses Administered by Gender Group

Gender group	Total doses administered		Percentage (%)
	Interval	Cumulative	Cumulative
Male	203875	30893573	49.35
Female	-126120	31569658	50.44
Unspecified	-66946	131451	0.21
Total	**10809**	**62594682**	**100**

Exposure by doses administered is used as part of Observed versus Expected (O/E) Analyses, refer to Appendix 8 of PSUR#3 for further details.

PRAC Rapporteur's comment:

As of 30 June 2022, a total of ~38 million first doses, ~29 million second doses and ~22,000 booster doses have been administered cumulatively in the EU; and a total of ~2.2 billion doses have been administered worldwide.

During the reporting interval, in the EU, -198213 first doses and -8990 second doses were administered. The MAH explained that the weekly administered data is subject to change every week. The administered data for the PBRER reporting interval is derived by subtracting the previous report's cumulative from current cumulative values (Current Cumulative - Previous Cumulative = Current Interval) across all the countries. Therefore, the negative values here is due to a greater cumulative value from previous report in comparison to current report.

Data per gender is still not available for EU countries. The MAH claimed that since ECDC does not include gender breakdown at country level, this cannot be provided. However, it commits to continue its efforts to collect exposure data by country, age, and gender for all EU countries as it has been already requested.

1.3.4. Data in summary tabulations

Cumulative summary tabulations of serious adverse events from clinical trials

A cumulative summary tabulation of serious adverse events (SAEs) from AstraZeneca-sponsored interventional clinical trials that have been reported during the Vaxzevria clinical development programme, from the Development International Birth Date (DIBD) to the data lock point (28 June 2022), organised by SOC, is presented in Appendix 2 of PBRER.

Cumulative and interval summary tabulations from post-marketing data sources

Cumulative and interval summary tabulations of adverse reactions (ie, AEs considered as "a reasonable possibility of a causal relationship between the medicinal product and the event" for Table 2 Appendix 2) that have been reported from marketed experience with Vaxzevria, from the IBD to the data lock point, organised by SOC, are presented in Appendix 2 of PBRER.

Rapporteur assessment comment:

A cumulative total of 1,946 cases representing 4,437 serious adverse events have been reported from AstraZeneca-sponsored **interventional clinical trials**. However, the vast majority of these case reports were still blinded as they contained only expected Suspected Serious Adverse Reactions.

A cumulative total of 2,834,138 adverse events, originating from 754,981 cases, have been spontaneously reported from **post-marketing exposure**, of which 488,841 adverse events, from 130,369 cases, were reported during the interval period. The majority of the AEs reported during the interval and cumulative period were from the SOCs 'General disorders and administration site conditions', 'Nervous system disorders', 'Musculoskeletal and connective tissue disorders' and 'Gastrointestinal disorders'.

Cumulatively, most commonly spontaneously reported adverse events were Headache, Pyrexia, Chills, Fatigue and Myalgia. Most commonly spontaneously reported serious AEs were Headache, Pyrexia, Fatigue, Chills and Nausea.

During the period under review, most commonly spontaneously reported serious AEs were COVID-19,

Vaccination failure, Headache, Fatigue and Pyrexia.

Based on the number of spontaneously reported adverse events and the estimated number of doses administered (500,073,105 doses), approximately 0.98 adverse events/1,000 doses occurred during the period under review, which is in line with the previous interval period (0.6/1,000 doses). For the overall period from launch up to the DLP of this PSUR, the occurrence of adverse events was estimated at 1.35/1,000 doses.

No new important safety information is identified from the data in summary tabulations. The distribution of events over the different SOCs and the most commonly reported PTs are in line with the known safety profile of Vaxzevria.

1.3.5. Findings from clinical trials and other sources

1.3.5.1. Completed and ongoing clinical trials

During the reporting period, one study investigating the safety and the immunogenicity of VAXZEVRIA was completed (study D8111C00002, Phase I/II study in Japan). A summary of findings is described in Section 7.1 of the PBRER.

There were 11 (COV001, COV002, COV003, COV004, COV005, COV006, COV008, COV009, D8110C00001, **D8110C00010** and D7220C00001) ongoing clinical trials during the reporting period.

There was no clinically important information that arose from ongoing clinical trials during the reporting period.

Rapporteur assessment comment:

The MAH detailed in this section there was 1 completed CT during the reporting period: study D8111C00002, Phase I/II in Japan. A high-level description of the findings of the completed trial and 7 of the 11 ongoing clinical trials is available in Section 7.1 of the PBRER. Data analyses were not completed for the remaining 4 ongoing clinical trials.

There were 11 ongoing clinical trials during the reporting period:

COV001 – PhI/II – UK –1077 healthy adults 18 to 55 years - single IM dose or a 2- dose IM regimen of the low dose (LD) (~2.5 x10^{10} vp) and/or the standard dose (SD) (~5x10^{10} vp) of COVID-19 VACCINE ASTRAZENECA or the comparator, meningococcal vaccine (MenACWY).

COV002 – PII/III – UK- 10,812 participants ≥ 18 years of age (in addition 60 HIV-infected) - single IM dose or a 2-dose IM regimen of the LD and/or the SD or the comparator, MenACWY.

COV003 – Ph III – Brazil – 10,416 participants ≥ 18 years of age - 2-dose IM regimen of the SD or, MenACWY or the MenACWY as the prime dose and saline placebo as boost dose.

COV004 – Ph Ib/II- Kenya - ~400 healthy adults ≥ 18 years – Ib (~40 participants): 1 IM SD dose or rabies vaccine as control – II (~360 participants): 2-dose SD or rabies vaccine.

COV005 – Ph I/II – South Africa - 2130 participants with and without HIV aged 18-65 years - 2-dose IM regimen of the SD or saline placebo. Ph I (HIV-uninfected; n=70 and HIV-infected n=100). Ph II with 1900 HIV uninfected.

COV006 – Ph II – UK - ~300 healthy children and adolescents 6-17 year - SD dose (4 or 12 weeks apart) or active control (licensed Meningococcal B vaccine) IM.

COV008 – Ph I – UK – 54 healthy adults 18-40 years – 1 or 2 doses of intranasal ChAdOx1 nCOV-19 ($5x10^9$ vp, $2x10^{10}$ vp or $5x10^{10}$ vp).

COV009 – Post-approval follow-up for COV001 and 002 trials – long term safety and immunogenicity. Up to 1,077 participants will be eligible for enrolment for the COV001 cohort and up to 10,812 participants for the COV002 cohort. No treatment given. Duration 12 months.

D8110C00001 – Ph III - US, Chile, Peru- 32,451 participants ≥ 18 years of age - 2 IM doses of either SD or saline placebo 4 weeks apart. At least 25% of participants ≥ 65 years.

D7220C00001 – Ph II/III – multi-country - ~2590 participants ≥18 years to study AZD2816 (for prevention of COVID-19 caused by variant strains). Goal: 1300 previously vaccinated participants receiving single-dose vaccination and 1290 unvaccinated participants receiving 2-dose primary vaccination. Participants will receive COVID-19 VACCINE ASTRAZENECA (5×10^{10} vp) or AZD2816 (5×10^{10} vp). Dosing intervals will be 4 weeks (for COVID-19 VACCINE ASTRAZENECA and AZD2816) or 12 weeks (AZD2816 only).

D8111C00010 (added compared to previous PBRER) – Ph IV – multi-country - ~360 participants ≥ 18 years of age. Previously unvaccinated immunocompromised adults will receive 3 IM doses of AZD1222. As of 28 June 2022 there have been 34 participants enrolled in the study.

Findings:

For COV001, COV002, COV003 and COV005: There was not a significant change in the safety profile during the reporting period.

For D8110C00001: The results of data analyses performed on DCO3 (database lock 02 Sept 2021) data set became available during the reporting period for this PBRER. VE estimates were generally consistent with the statistically significant result from the primary efficacy analysis using the data from the 05 March 2021 data cut-off. During the reporting period immunogenicity data became available showing the waning of humoral immunogenicity through 6 months. These data support administration of a booster dose of AZD1222 as early as 3 months following primary series vaccination. Safety results at the 6-month data cut-off were generally consistent with safety findings at the primary analysis, with no new or emerging safety issues identified.

For D7220C00001: No emergent safety issues were identified. There were no clinically meaningful differences between the safety profiles of booster doses of AZD1222 and AZD2816. Analyses of data through to data cut-off, up to a maximum of 107 days after booster dose, did not identify any emergent safety issues.

For D8111C00002: Ph I/II – Japan - 256 participants ≥ 18 years of age - 2 IM doses of either VAXZEVRIA with 5x1010 vp (nominal) or placebo administered 4 weeks apart. The MAH concluded that AZD1222 administered in 2 IM injections was generally well-tolerated and had an acceptable safety profile in Japanese adult participants across all age groups (18 to 55 years, 56 to 69 years, and ≥ 70 years), and the number of SAEs in addition to the unsolicited AEs, was low. The MAH noted that AZD1222 elicits strong early immune responses against SARS-CoV-2 in the Japanese adult population across all the age groups; however, waning of immune responses, with neutralizing antibodies (NAbs) below the lower limit of quantification, was observed in a large proportion of participants by Day 365.

Overall, based on review of the data for the completed (1) and ongoing clinical trials (11), no new safety signal was identified during the reporting period.

1.3.5.2. Other clinical trials

The MAH has identified relevant publications whose main results are summarised by the PRAC assessor:

1. **Third dosing booster** (Munro et al 2021, Clemens et al 2022, Jara et al 2022, Muñoz-Valle et al 2022).

   A heterologous booster dose after a 2-dose primary series of CoronaVac (inactivated whole-virion adjuvanted vaccine), using Vaxzevria, Comirnaty or Jcovden, elicited a significantly superior response in anti-Spike IgG concentration and pseudo-neutralising titres compared to homologous boosting with CoronaVac (Clemens, 2022).

   In Chile, heterologous boosting with VAXZEVRIA, following a two-dose CoronaVac primary vaccination series, yielded vaccine effectiveness of 97.7% against COVID-19-related hospitalisation, 98.9% against ICU admission, and 98.1% against death (Jara, 2022).

   In Chile again, a heterologous booster dose after primary immunisation with Convidecia (Ad5-nCov), using Vaxzevria, Jcovden, Comirnaty, and Spikevax, elicited a superior neutralising antibodies response in the boosted group versus the unboosted group, whith no difference between vaccines (Muñoz-Valle).

   The MAH commented that no additional safety concerns have been raised by the use of Vaxzevria in combination with other COVID-19 vaccine classes.

2. The **persistence of immunogenicity** following immunization with VAXZEVRIA (Xinxue Liu et al. 2022)

   A third dose booster of VAXZEVRIA given after primary immunization with two doses of BNT/BNT was able to yield similar immune response than a homologous third dose booster of BNT.

   Anti-Spike antibodies persisted for at least 84 days after primary immunisation with AZD1222 followed by a booster with Jcovden. The decay ratio of anti-Spike IgG GMT between Days 28 and 84 suggested greater persistence of anti-Spike antibodies with JCOVDEN than with BNT. The decay rate of cellular responses were similar between all the vaccine schedules and doses.

   The anti-spike IgG in adenoviral vector vaccine arms (VAXZEVRIA and Ad26) after the BNT/BNT prime were the most persistent schedules up to D84.

3. Real world evidence data on **duration of protection** (Andrews et al 2022a)

   Whilst VE peaked in the early weeks after administration of the second dose, a decline was observed at 20 weeks after vaccination to 44.3% with the VAXZEVRIA vaccine and to 66.3% with the COMIRNATY vaccine. Waning of vaccine effectiveness was greater in persons 65 years of age or older than in those 40 to 64 years of age. However, VE against hospitalization remained high at 80.0% (95% CI: 76.8 to 82.7) with the VAXZEVRIA vaccine and 91.7% (95% CI: 90.2 to 93.0) with the COMIRNATY vaccine, and death was 84.8% (95% CI: 76.2 to 90.3) and 91.9% (95% CI: 88.5 to 94.3), respectively. The authors do point out that the analysis with VAXZEVRIA boosters is to be subject to bias because this vaccine was not recommended as a booster in the UK.

4. Real world evidence data on **protection against variants** of concern (Andrews et al 2022b; Kirsebom et al 2022)

   No effect against the Omicron variant was observed from 20 weeks after a primary vaccination with VAXZEVRIA, but the VE of a booster dose with VAXZEVRIA was 55.6% at 2 to 4 weeks and 46.7% at 5 to 9 weeks following booster administration. This decrease in VE was also noted with a third homologous dose of BNT and mRNA-1273.

In another study conducted in England, a test-negative case control design was used to estimate the VE of a VAXZEVRIA or COMIRNATY booster following a primary series of VAXZEVRIA against symptomatic disease and hospitalisation in Omicron era. In those aged **40-64 years**, VE against symptomatic disease increased to 61.2% (40.9 to 74.6%) one week after receiving a booster with VAXZEVRIA as compared to 58.2% (57 to 59.4%) amongst those who received a COMIRNATY booster. Waning of protection was described for both, VAXZEVRIA and COMIRNATY third dose boosters. Protection against symptomatic disease in those aged **65 years and older** peaked at 66.1% (16.6 to 86.3%) and 68.5% (65.7 to 71.2%) among those who received VAXZEVRIA and COMIRNATY boosters, respectively, and waned to 44.5% (22.4 to 60.2%) and 54.1% (50.5 to 57.5%), respectively, after 5 to 9 weeks.

VE against hospitalisation following infection with the SARS-CoV-2 Omicron variant peaked at 82.3% (64.2 to 91.3%) after an VAXZEVRIA booster and 90.9% after a third dose booster with (88.7 to 92.7%) booster.

MAH's conclusion: No information relevant to the benefit risk assessment of VAXZEVRIA was identified from any other clinical trial or study sources, during the reporting period.

Rapporteur assessment comment:

The MAH identified other studies from the literature.

These studies did not bring new important information on the safety of Vaxzevria.

New information was about:

- The use of Vaxzevria as an heterologous booster (3rd dose): immunologic and vaccine effectiveness data support the use of Vaxzevria as heterologous booster after primary vaccination with various other COVID-19 vaccines. Yet, these findings should be further explored in the Omicron era.
- Waning of the immune response after primary vaccination and booster is observed for Vaxzevria and other vaccines. Effectiveness against hospitalisation and death is longer sustained than effectiveness against infection.

1.3.5.3. Vaccination errors

Please note that Vaccination errors data is not reproduced here (see Section 9.2 and Appendix 11 of PBRER)

Rapporteur assessment comment:

Interval review: A total of 7728 case reports, including 8104 vaccination error AEs have been identified during the reporting period. This is comparable to 7805 case reports and 8434 vaccination error AEs as reported during the previous reporting interval. The most frequently reported AEs belong to the SOC General disorders and administration site conditions (2197 interval AEs). **Interval case reports represent 42.54% of cumulative cases (18164)**.

Of the 7728 case reports, 560 were reported as serious (169 case reports were medically confirmed and 391 were consumer reports). In 5788 (75%) cases no associated AEs were reported in connection with the vaccination error. Other AEs were co-reported in the remaining 1940 (25%) case reports, of which 523 (27%) cases were serious including 27 case reports with a fatal outcome.

Cumulative review: A total of 18164 case reports, including 19593 vaccination error AEs, have been identified during the cumulative period. Of those 18164 case reports, 1644 were considered serious (429 case reports were medically confirmed and 1215 were consumer reports). In 13075 (72%) cases no other

AEs were reported in connection with the vaccination error. Other AEs were co-reported in the remaining 5089 (28%) case reports, of which 1559 (31%) cases were serious, including 58 case reports with a fatal outcome.

Notably, there were 27 case reports with fatal outcome during reporting interval which is 13% less than 27 fatal case reports as reported in previous PSUR#2.

As requested the MAH presented all fatal cases associated with vaccination error in details.

A cumulative review of vaccination error case reports with fatal outcome is provided in Appendix 11 of PSUR#3. Interchange of vaccine products (n=21) and Incorrect route of product administration (n=14) were the most frequently reported vaccination error events. Most of the reports with incorrect route of administration (intravenous, subcutaneous) were consumer reports and there was limited information on the actual medication error.

Most frequently reported AEs (≥3) were : Headache (7); Pyrexia (6); Cardiac arrest (6); Dyspnoea (6); Death (5); Cerebrovascular accident (5); Myalgia (4); Vomiting (4); Nausea (4); Dizziness (4); Loss of consciousness (4); Arthralgia (4); Myocardial infarction (4); Hypoaesthesia (4); Paraesthesia (4); Asthenia (4); Pain (3); Thrombosis (3); Immobile (3); Confusional state (3); Malaise (3); COVID-19 (3); Exposure during pregnancy (3); and Hemiplegia (3).

Reported causes of death in these cases were Dyspnoea (3), Death (2), Thrombosis (2), Multiple organ dysfunction syndrome (1), Abortion spontaneous (1), Pulmonary embolism (1), Confusional state (1), Loss of consciousness (1), Coronary artery occlusion (1), Nausea (1), Coronary artery thrombosis (1), Rash (1), COVID-19 (1), Cerebral thrombosis (1), Cardiac arrest (1), Dementia Alzheimer's type (1), Myocardial infarction (1), Diarrhoea (1), Skin discolouration (1), Pyrexia (1), Asthenia (1), Circulatory collapse (1), Vein rupture (1), Urosepsis (1), Haemorrhage intracranial (1), Vomiting (1), Headache (1) and Hypersensitivity (1).

The MAH concluded that the review of these fatal cases did not identify safety issues in relation to type of vaccination errors.

In conclusion, some medication errors are expected to occur despite written instructions and educational activities for HCPs administering the vaccine. The number of cases, the type and seriousness of the reported medication errors are comparable to the previous PSUR#2. These cases do not indicate any trends of systemic substantial errors or a need for additional risk mitigation activity.

The MAH's conclusion is accepted that at the moment no new relevant patterns of (potential) vaccination errors were identified.

1.3.5.4. Literature

Relevant literature articles containing new and significant safety findings relevant to COVID 19 VACCINE ASTRAZENECA published during the review period were retrieved. Articles of interest related to event reviews completed as part of Health Authority requests, Important identified and Potential risks or Missing information have been included within the review of those safety concerns throughout section 2.3. Literature articles from clinical/observational/real world studies on vaccine effectiveness and booster dose are summarized in Section 1.3.5.2.

Other articles containing new and significant safety findings are summarized below.

Vaccine-related cutaneous manifestations : Avallone et al 2022 conducted a systematic review of 229 articles according to the PRISMA guidelines with the objective to provide an extensive overview of all the vaccine-related cutaneous manifestations reported in the literature thus far. A search on MEDLINE,

PubMed, Scopus, and Cochrane Library was conducted using the combination of the following keywords and medical subject heading (MeSH) terms: COVID vaccine, dermatology, rash, skin, cutaneous, BNT162, COMIRNATY, AstraZeneca, and mRNA-1273. The time range of our search was from 01 March 2020 to 04 November 2021.

Results: A total of 229 articles with data from 4649 patients with SARS-CoV-2 vaccine-related dermatological manifestations were included in the analysis. A total of 5941 SARS-CoV-2 vaccine-related dermatological manifestations were gathered. Local injection-site reactions were the most frequently observed, followed by rash/unspecified cutaneous eruption, urticarial rashes, angioedema, herpes zoster, morbilliform/maculopapular/erythematous macular eruption, pityriasis rosea and pityriasis rosea-like eruptions, and other less common dermatological manifestations. Flares of pre-existing dermatological conditions were also reported. Rash/Unspecified cutaneous eruption was the most common dermatological manifestation reported for AstraZeneca vaccine.

Overall conclusion as per author: Cutaneous adverse reactions following SARS-CoV-2 vaccine administration seem to be heterogeneous, rather infrequent, and not life-threatening. Vaccinated patients should be monitored for skin manifestations, and dermatological evaluation should be offered, when needed.

AstraZeneca comment: Cutaneous adverse events such as rash and urticaria and injections site reactions are listed in the VAXZEVRIA CDS. Cutaneous reactions are the most common form of ADRs, occurring in 2%–3% of inpatient and in approximately 2% of outpatient patients in general population. Also, a large majority of cutaneous reactions post vaccination were mild and self-limiting, and public health benefit of vaccination is considered to outweigh the rare occurrence of these events.

Rapporteur assessment comment:
The data from Avallone et al. 2022 do not raise any new safety concern.

1.3.6. Lack of efficacy in controlled clinical trials

Study D8111C00002 is already discussed in **Error! Reference source not found.**The study assessed the safety and immunogenicity of VAXZEVRIA in 256 participants in Japan across all age groups. Expected waning in humoral responses against SARS-CoV-2 was observed over the course of the one-year follow up; however, total spike and RBD mean antibody titres remained elevated above Day 15 levels.

Recent publications support the thesis that VAXZEVRIA confers good VE against symptomatic COVID-19 resulting from infection with the Omicron variant and it is particularly effective in preventing severe disease, hospitalizations and death.

No other data regarding lack of efficacy that would constitute a significant risk to the treated population were received during the reporting period.

Immunogenicty data on Omicron variant of concern

Researchers at the University of Oxford have assessed neutralization of the emerging Omicron sub-lineages BA.4 and BA.5 (in addition to BA.2) by serum from individuals vaccinated with 3 doses of VAXZEVRIA or COMIRNATY (Tuekprakhon et al 2022). Assays were performed using serum obtained 28 days following the 3rd dose. While BA.4/5 showed reduced neutralization compared with BA.1 and BA.2, the reductions were modest. For VAXZEVRIA, neutralization titers for BA.4/5 were reduced 2.1-fold compared with BA.1 ($p < 0.0001$) and 1.8-fold compared with BA.2 ($p < 0.0001$). For COMIRNATY, neutralization titers were reduced 3.1-fold ($p < 0.0001$) and 3.1-fold ($p < 0.0001$) compared with BA.1

and BA.2, respectively. The authors concluded that although these reductions in titers may reduce the effectiveness of the vaccines at preventing infection, it would be expected that protection would remain against severe disease.

CD8+ T cell responses are thought to be particularly important for the prevention of severe disease. T cell Receptors (TCR) sequencing analysis has identified that the immunodominant region of Spike recognised by CD8+ T cells (Swanson et al 2021) is not impacted by the Spike mutations present in the Omicron variant (including BA.4/BA.5 sublineages). T cell data are now available from the ongoing AstraZeneca-sponsored study D7220C00001, in which participants received a 3rd booster dose of VAXZEVRIA after a primary series of VAXZEVRIA or an mRNA vaccine. Analysis of spike peptide T-cell responses at Day 14 after a 3rd booster dose of VAXZEVRIA showed similar levels of CD4+ and CD8+ T cells against the ancestral SARS-CoV-2 strain or the Omicron variant. These data support the conclusion that protection would remain against severe disease caused by Omicron variant sub-lineages.

MAH's Conclusion: Real-world evidence has since supported the effectiveness of VAXZEVRIA in preventing infection, particularly severe infection leading to hospitalisation, by the Omicron variant.

Rapporteur assessment comment:

This chapter does not bring new important safety information.

Results from study D8111C00002 confirms waning of humoral response over a one-year follow-up period.

Tuekprakhon et al found modest reduced neutralisation for BA.4/5 than for BA.1 and BA.2 after three dose vaccination with Vaxzevria or Comirnaty. However, the authors concluded that protection should remain against severe disease.

The protection against severe forms of the diseases is also supported by findings from study D7220C00001 which showed similar levels of CD4+ and CD8+ against the ancestral SARS-COV-2 strain and the Omicron variant.

1.3.7. Late-breaking information

After the data lock point of the PBRER (28 June 2022), VAXZEVRIA CDS was updated on 01 July 2022 (CDS Version 19.0) and 2 signals were validated.

CDS Update

VAXZEVRIA CDS was updated to include **Tinnitus** as an ADR Section 4.8 with frequency of uncommon.

Signal Evaluation

Immune thrombocytopenia (ITP): The signal for ITP was re-opened based on well-documented case reports from the published literature. AstraZeneca internally validated the signal on 06 July 2022 and the topic is currently undergoing evaluation as per AstraZeneca's signal detection and evaluation processes. Conclusions and any recommended actions for this signal will be communicated in the next PBRER, or earlier as necessary.

Cutaneous Vasculitis (CV): The signal for CV was identified based on well-documented case series from published literature cases. Subsequently a request on the same topic was received from PRAC PSUR assessment report. AstraZeneca internally validated the signal on 15 July 2022.

On 18 August 2022, upon further evaluation of this topic AstraZeneca considered that there is a reasonable possibility of causal relationship between VAXZEVRIA and Cutaneous vasculitis. CDS Section 4.8 is in the progress to be updated to include cutaneous vasculitis as an ADR (frequency: not known).

Literature: An AstraZeneca co-authored article (**Error! Reference source not found.**) regarding the risk of thrombosis with thrombocytopenia was published on-line on 19 August 2022. This article presents a review of ICSR case characteristics reported to AstraZeneca through to 28 December 2021. This article includes data and analyses already included in previous PBRERs/monthly summary reports, as well as in the cumulative review presented in section **Error! Reference source not found.**of this PBRER, and therefore presents no new, additional evidence. The article does not change the characterisation of this risk.

Rapporteur assessment comment:

CDS update for tinnitus: Tinnitus was included in the section 4.8 of the EU-SmPC as an outcome of the previous PSUR assessment report. Please refer to section 1.3.2. for further details.

Signal of ITP: ITP is a listed as an ADR in the EU-PI and included in the important identified risks in the EU-RMP. Up to date, ITP was not recognised as an ADR nor an important identified risk by the MAH. Please refer to section 2.3.2. for further details.

Signal of cutaneous vasculitis: the MAH proposes to include cutaneous vasculitis in the section 4.8 of the SmPC based on the evaluation of available data. Please refer to section 2.3.34. for further details.

Literature for TTS: the MAH co-published a review of TTS cases which have been reported to him. The data are in line with the current state of knowledge regarding the risk of TTS.

Signal of corneal graft rejection: on 01 September 2022, PRAC finalised its review of corneal graft rejection with Vaxzevria. It concluded that the available evidence does not support a causal relationship between Vaxzevria and CGR.

Signal of pemphigus and pemphigoid: on 04 October 2022, EMA validated a signal of pemphigus and pemphigoid (EPITT n°19858). The confirmation of the signal is currently ongoing.

Potential signal of SCAR: after the DLP of the PSUR, WHO-UMC identified 1 signal of SCAR with COVID-19 vaccines. **The MAH is requested to provide a cumulative review of cases reported with Vaxzevria, as well as a review of the literature. A discussion on the need to update the PI should be included.**

[***Request for the next PBRER***].

2. Signal and risk evaluation

2.1. Summary of safety concerns

Table 8 presents a summary of the safety concerns included in the Core RMP for VAXZEVRIA (Version 5.0, dated 09 November 2021) and the EU RMP for VAXZEVRIA (Version 4 succession 2, dated 02 December 2021) that were in effect at the beginning of the reporting period.

Table 8 - Summary of safety concerns at the beginning of the reporting period [from Appendix R3 of the PBRER]

Risk Category	Core Risk Management Plan (V5)	EU Risk Management Plan (V4 S2)
Important identified risk	Thrombosis in combination with Thrombocytopenia	Thrombosis with thrombocytopenia Syndrome
		Thrombocytopenia, including immune thrombocytopenia
		Guillain-Barré syndrome
		Anaphylaxis
Important potential risk	Cerebrovascular venous sinus thrombosis without thrombocytopenia	
		Thrombosis
	Immune-mediated neurological conditions	Nervous system disorders, including immune-mediated neurological conditions
	Vaccine-associated enhanced disease (VAED)	Vaccine-associated enhanced disease (VAED), including vaccine associated enhanced respiratory disease (VAERD)
Missing information	Use of AZD1222 in pregnant and breastfeeding women	Use during pregnancy and while breastfeeding
	Use of AZD1222 in subjects with severe immunodeficiency	Use in immunocompromised patients
	Use of AZD1222 in subjects with severe and or uncontrolled underlying disease	Use in frail patients with co-morbidities (eg. chronic obstructive pulmonary disease, diabetes, chronic neurological disease, cardiovascular disorders)
	Use of AZD1222 with other vaccines	Use in patients with autoimmune or inflammatory disorders
		Interactions with other vaccines
		Long-term safety

2.2. Signal evaluation

Two validated signals were closed during the reporting period: Hypoaesthesia and Paraesthesia and Guillain-Barré syndrome.

One signal, Tinnitus, was validated during the reporting period and closed after the DLP for the report.

- Tabular overview of signals: new, ongoing or closed during the reporting interval 29.12.2021 to 28.06.2022.

Signal term	Date detected	Status (new, ongoing or closed)	Data closed (for closed signals)	Source or trigger of signal	Reason summary	Method of signal evaluation	Outcome, if closed
Guillain-Barré syndrome (GBS)	24.01.2022	Closed	13.05.2022	Regulatory Authority	Regulatory Authority Enquiry or Request	Quantitative Signal Detection System (Observed versus Expected analysis), Literature review, Qualitative data analysis (Individual Case Safety Report or Case Series), Clinical trials, Epidemiology analysis	Change to Reference Safety Information and Product Labelling Summary: CDS section 4.4. and CPIL updated to include wording on GBS.
Hypoaesthesia and Paraesthesia	01.12.2021	Closed	02.03.2022	Regulatory Authority	Regulatory Authority Enquiry or Request	Quantitative Signal Detection System, Literature article, Clinical trials	Change to Reference Safety Information and Product Labelling
Tinnitus	11.05.2021	Ongoing		Regulatory Authority	Regulatory Authority Enquiry or Request	Quantitative Signal Detection system External Quantitative Signal Detection system Literature Qualitative data analysis Eudravigilance Clinical trial	Change to Reference Safety Information and Product Labelling Summary: Update to Include "Tinnitus" in section 4.8 in CDS and section 4 in PL

Rapporteur assessment comment:

The signals of '**GBS**', '**Hypoaesthesia and Paraesthesia**', and '**Tinnitus**' were closed by the MAH and are discussed below.

During the reporting period, 1 other signal was assessed by EMA:

- EMA validated a signal of Glomerulonephritis and nephrotic syndrome (EPITT 19805). The PRAC Rapporteur did not confirm the signal (6 May 2022) but requested further discussion for the current PBRER under review (See Section 2.3.27 on Health Authority requests)

After the DLP of this PBRER,

- The MAH re-open the signal of ITP (see Section 1.3.7 for further details). Of note, Immune thrombocytopenia is described in the EU-PI (sections 4.4 and 4.8). Thrombocytopenia, including immune thrombocytopenia is an important identified risk in the EU-RMP.
- The MAH validated a signal of Cutaneous vasculitis (see Section 1.3.7 for further details) and received a similar request from PRAC during previous PBRER assessment. Based on its assessment, the MAH is proposing to include cutaneous vasculitis in section 4.8. This signal is further discussed in Section 2.3.34.
- PRAC assessed and closed a signal of Corneal Graft Rejection. No update of the PI or RMP was requested. The topic should be monitored under routine pharmacovigilance (EPITT 19791, PRAC recommendation on 01 Sep 2022)
- EMA validated a signal of Histiocytic necrotizing lymphadenitis (EPITT 19837, not confirmed on 17 Jul 2022). The PRAC Rapporteur did not confirm the signal based on the low number of cases [<3] and absence of disproportionality [ROR<1].

2.2.1. Closed and rejected/refuted signals

There were no closed and rejected/refuted signals during the reporting period.

2.2.2. Closed signals categorised as important potential risks

There was one closed signal, Guillain-Barré syndrome (GBS), that was categorized as Important potential risk during the reporting period.

Guillain-Barré syndrome

Method(s) of evaluation: Comprehensive cumulative review of clinical and post-marketing reports and the literature (including case reviews and epidemiological studies) of GBS [MedDRA SMQ narrow Guillain-Barré syndrome]. Medical review according to Brighton collaboration and causality assessment according to WHO-UMC causality criteria. Quantitative Signal Detection System (Observed versus expected analysis), stratified by age, gender, dose and using different risk windows with incidence rates from ACCESS protocol.

Outcome of the evaluation: AstraZeneca **clarified the existing language on demyelinating disorders in Section 4.4 of CDS with inclusion of GBS specifically**. In line with this, the relevant text on GBS was added to the CPIL. AstraZeneca believes that this may help the vaccinees seek early medical care irrespective of the underlying aetiology of GBS.

MAH's Conclusions: Although AstraZeneca's position is that **a reasonable possibility of a causal association does not exist between VAXZEVRIA and GBS** at this time, AstraZeneca acknowledges

the 1432 case reports in our Safety database, the published evidence, and the increased O/E ratio in some categories amidst the complexities including the role of COVID 19 possibly causing GBS in the background. However, the available data on GBS is mainly from spontaneously reported cases, which are voluntary and often have limited information or have predisposing / confounding factors for GBS. Four (4) out of 1432 cases were considered "Probable" according WHO-UMC criteria, despite having some missing information as explained above. The incidence rates that are used for the O/E analyses are conservative, as other reliable sources have higher rates. In addition, the rates are since pre-pandemic times and not accounting for the COVID-19 pandemic in the background.

Although there are epidemiological articles describing a temporal association to the first dose of VAXZEVRIA, the risk was approximately 4 times greater after a COVID-19 infection. Therefore, there are still gaps in understanding on the incidence rate of GBS in the context of the effect of COVID-19 pandemic in the background.

Taking this into consideration, AstraZeneca will continue to closely monitor GBS as part of our surveillance activities and take further actions as deemed necessary.

Rapporteur assessment comment:

Data on GBS were thoroughly assessed in several MSSRs and in previous PSURs. GBS is currently listed in section 4.8 of the EU-SmPC and a warning is included in section 4.4. GBS is an important identified risk of Vaxzevria, included in the EU-RMP (see Sections 2.3.3 and 2.4 for further details).

During the period of this PBRER, the MAH closed a signal of GBS based on a cumulative review of post-marketing, clinical and literature data. The cumulative review presented in Appendix 20 of the PBRER [DLP of 28.12.2021] did not provide additional information compared to the data discussed in the previous PBRER [same DLP], except a few new articles:

- **Kaulen et al. 2022** identified 8 cases of neurological autoimmune conditions in temporal association with the first dose of Vaxzevria through a single-centre prospective case study. These cases included 2 cases of GBS which were treated with IVIG, resulting in a favourable outcome.
- **Li et al. 2022** performed a population based historical rate comparison study and a self-controlled case series analysis in UK and Spain. The study sample comprised ~8,3 million people who received at least 1 dose of COVID-29 vaccines (including ~4,4 millions of Vaxzevria vaccinees) and ~0,74 million of unvaccinated individuals. No signal was observed between COVID-19 vaccines and the events of Bell's palsy, encephalomyelitis and GBS. However, infection with SARS-CoV-2 was associated with an increased risk of these events.
  For example in the data from UK (cohort analysis), the standardised incidence ratio for GBS was estimated to 0.74 (0.41 to 1.33) after a 1st dose of Vaxzevria and to 3.53 (1.83 to 6.77) after a SARS-CoV-2 positive test. The SCCS was not performed for GBS because of limited statistical power. Of note, these results are not in line with data from previously published epidemiological studies. In particular, the more robust SCCS study from Patone et al. (2021) included more than 20 million people vaccinated with Vaxzevria and showed an increased risk of GBS, with an IRR [1-28d] of 2.04 [95%CI 1.60-2.60].

In conclusion, available data did not change the current knowledge regarding GBS after Vaxzevria.

The PRAC Rapporteur does not agree with the MAH's conclusion that a reasonable possibility of a causal association does not exist between VAXZEVRIA and GBS at this time.

However, as GBS is appropriately described in the EU-PI (sections 4.4 and 4.8) and in the EU-RMP (important identified risk), no further action is required.

2.2.3. Closed signals categorised as important identified risks

There were no closed signals categorised as important identified risks during the reporting period.

2.2.4. Closed signals that are potential risks not categorised as important

There were no closed signals that are potential risks not categorised as important during the reporting period.

2.2.5. Closed signals that are identified risks not categorised as important

There were two signals (Hypoaesthesia and Paraesthesia, and Tinnitus) that were closed during or shortly after the reporting interval.

Hypoaesthesia and Paraesthesia

Method(s) of evaluation: Comprehensive cumulative review of clinical and post-marketing reports and the literature (including case reviews and epidemiological studies) of hypoaesthesia and paraesthesia [MedDRA PTs: Hypoaesthesia; Paraesthesia]. Quantitative data review using the reporting odds ratio (ROR) from EVDAS data.

Outcome of the evaluation: VAXZEVRIA CDS Section 4.8 (undesirable effects) updated with 'Hypoaesthesia' and 'Paraesthesia'

MAH's Conclusions: Based on the evaluation of currently available information from all available sources, with particular focus on post-market data, AstraZeneca considers that **there is a reasonable possibility of a causal association between VAXZEVRIA and hypoaesthesia and paraesthesia**. Many of these events were co-reported with reactogenicity events. The information regarding hypoaesthesia and paraesthesia will be added to the CDS and the company will continue to conduct routine pharmacovigilance activities on this safety topic.

Tinnitus

Method(s) of evaluation: Comprehensive cumulative review of clinical and post-marketing reports and the literature (including case reviews and epidemiological studies) of tinnitus [MedDRA PT: Tinnitus]. Medical review and causality assessment according to WHO-UMC causality criteria for medically confirmed cases. Quantitative Signal Detection System using EVDAS data and observed versus expected analysis), stratified by age and risk window 0-42 days, with incidence rates from Stohler et al 2019.

Outcome of the evaluation: Update to include "Tinnitus" in section 4.8 in VAXZEVRIA CDS with frequency "uncommon" based on clinical trial data and section 4 of PIL

MAH's Conclusions: Based on the evaluation of currently available information from various sources, AstraZeneca considers that **there is a reasonable possibility of a causal association between VAXZEVRIA and tinnitus**. VAXZEVRIA CDS Section 4.8 (undesirable effects) was updated (post DLP) to include 'Tinnitus'. When used in accordance with the revised prescribing information, the benefits of VAXZEVRIA continue to outweigh the risks.

Rapporteur assessment comment:

Both signals of "Paraesthesia and hypoaesthesia" and "Tinnitus" were assessed in the context of the previous PSUR procedure which led to the inclusion of the 3 events in the section 4.8 of the EU-SmPC (i.e. Paraesthesia [uncommon], Hypoaesthesia [uncommon], and Tinnitus [uncommon].

2.3. Evaluation of risks and safety topics under monitoring

2.3.1. Important Identified Risk – Thrombosis in combination with thrombocytopenia/Thrombosis with thrombocytopenia syndrome

Please note that TTS data is not reproduced here (Section 16.3.2.1 and 15.2.15 (Request from Health Canada) of the PBRER).

MAH's Summary

The highest number of cases were reported from UK (55%) while receiving 49.02 million doses of the total worldwide doses.

The analysis of thrombosis in combination with thrombocytopenia following the second dose of VAXZEVRIA showed that the rate of events was extremely low and lower than after administration of the first dose. The majority of the vaccinees who experienced TTS events post Dose 2 were male (59% vs 42%) and were older (Median age was 65.5 years vs. 45 years) compared to first dose recipients. The median time to onset of second dose cases was 14 days compared to 12 days for the cases with first dose.

Overall, the most common events were Cerebral venous sinus thrombosis, Deep vein thrombosis, Pulmonary embolism, and Thrombosis.

The time to onset was available for all doses in 78% (1875/2391) of cases; TTO was reported in 77% (1637/ 2123) for Dose 1 and 89% (232/ 260) for Dose 2. Overall, there were more fatal reports for TTO within 14 and 21 days. Seventy-three (73%) percent of the fatal reports occurred with 14 days compare to 64% for all cases and 87% of the fatal report occurred with 21 days compare to 80% for all cases.

The highest fatality rate for all dosage in female vaccinees was 28/117 (24%) in 18 to 29 years of age and male vaccinees was 21/93 (23%) in 30 to 39 years of age. The fatality rate in female vaccinees in Dose 1 found 28/111 (25%) in 18-29 years, whereas in male vaccinees it was 16/72 (22%) in 18 to 29 years of age and 21/92 (22%) in 30 to 39 years. The fatality rate in Dose 2 found in females was 2/27 (33%) in 60 to 69 years of age and in males 7/45 (15%) in 70 to 79 years age group.

No new or emerging concern regarding TTS post-booster has been identified with booster doses of VAXZEVRIA.

The highest number of fatal reports (28%) occurred due to HLT of Cerebrovascular venous and sinus thrombosis. Cerebral haemorrhage was the most common bleeding event associated with fatal event. The total number and percent of fatal reports since April 2021 are decreasing compared to January 2021 to March 2021. There is an increased fatality rate in December 2021; however, only 25 cases were reported in this month received which could explain the sharp increase in the percentages. There is an increased fatality rate in April 2022 (9 reported fatal events out of 31 reports) compared to the earlier months December 2021 and March 2021. Number and percent of fatal reports since April 2021 has decreased compared to January to March 2021 and percent of fatal reports decreased from May 2022 to June 2022.

The arterial events were reported highest in the age groups of 50 to 59 and 60 to 69 years. The distribution of events in male and female was roughly equal. The mixed or the combined arterial and venous events were equally distributed in age groups of 30 to 39, 40 to 49, 50 to 59 and 60 to 69 years, and the distribution of cases in female and male was roughly equal. The venous events were reported highest in the age groups of 40 to 49, 50 to 59, and 60 to 69 years; the occurrence in females was higher than in males.

The most common confounding factors in descending order of frequency in all 2391 cases were

autoimmune conditions, malignancy, history of heparin, obesity, and concomitant use of contraceptives. The most common confounding factors in the confirmed reports were history of heparin use and malignancy. The dates of heparin administered were not reported in all cases.

MAH's conclusion

Based on currently available data, no new safety information concerning TTS was identified. The current risk minimisation measures described in the product information are considered adequate.

From the data identified during the reporting period and also taking into account the cumulative experience, no updates to the VAXZEVRIA CDS or RMP are warranted at this time.

Thrombosis in combination with thrombocytopenia/TTS is contained in Section 4.4 (Special warnings and special precautions for use) and 4.8 in the VAXZEVRIA CDS. In addition, VAXZEVRIA is contraindicated (CDS Section 4.3) for use in any persons who have experienced thrombosis in combination with thrombocytopenia with any COVID-19 vaccine. Finally, thrombosis in combination with thrombocytopenia/ TTS is listed as an Important Identified Risk in the Core and EU RMPs for VAXZEVRIA. As such, the topic will continue to be kept under close safety surveillance by AstraZeneca and further actions will be taken as deemed appropriate.

Rapporteur assessment comment:

Cumulatively, up to 28 June 2022, 2391 cases of thrombosis in combination with thrombocytopenia (TCP) have been reported, of which 260 cases were reported after the 2nd dose and 6 cases after the 3rd dose. During the current reporting interval, 447 cases (255 initial, 192 follow-up) were received.

Cumulatively, the majority of the cases were reported in the UK (55%). Median age (56 years), median time to onset (12 days) and gender distribution (53% females) were similar to the previous PBRER (PBRER02). Overall, 80% of the cases occurred within 21 days after vaccination.

Location of thrombotic events: Most frequently reported PTs were similar to PBRER02: Pulmonary embolism (n=843), DVT (n=506), Thrombosis (n=488), CVST (n=463), Thrombosis with thrombocytopenia syndrome (n=345) and Portal vein thrombosis (n=185).

Reporting rates for TTS, in the UK and EEA (Table 196 and 197 of the PBRER): Overall EEA TTS reporting rate with risk window of 42 days was estimated at 14.01/million doses (7.19/million when considering confirmed, probable and possible cases). Reporting rate in EEA was highest post dose 1, in individuals <60 years (~35 cases/million doses; all cases). EEA TTS reporting rate (42d risk window) following dose 1 (25.41/million) was clearly higher than following dose 2 (1.44/million). These estimates were in line with UK reporting rates following dose 1 (21.72/million) and post-dose 2 (3.98/million).

The MAH provided **observed versus expected** (O/E) analyses for TTS and for CVST with TCP, with results in line with PBRER02.

The MAH applied the MHRA **Case Classification** for TTS to all cases: 1561 (65%) cases were categorized as confirmed/probable/possible (14% =confirmed, 16% = probable and 35% = possible), the remaining 34% of the cases did not meet the criteria and 1 case was considered unlikely. There was no difference in the case categorization criteria between dose 1, dose 2, and fatal case reports. Of the Dose 2 cases (n=260), only 5% met the confirmed criteria, 18% the probable criteria, 47% the possible criteria and 28% were categorized as criteria not met.

The MAH also applied the CDC working case definition for TTS to all 2391 cases: 699 (29%) of the cases met the CDC criteria of TTS (26% = Tier 1 TTS case, 3% = Tier 2 TTS case). In response to the Request from Health Canada (section 15.2.15), the MAH noted that as the MHRA case definition results in a larger number of cases being at least possible cases compared to the CDC definition, this is considered to be the

most conservative and suitable definition to use in this context.

Fatal cases: 414 of the 2391 TTS cases had a fatal outcome (case fatality rate (CFR) of 17% = CFR of PBRER02). The CFR was highest within individuals <40 years of age (23%). Overall CFR for TTS has decreased since the start of the signal (14% in April 2021 compared to 23-36% in January-March 2021). There was an increased fatality rate from December 2021 (28%) to April 2022 (29%) compared to the earlier months, however the absolute number of fatal reports was low in this period (7-11 fatal reports, 25-43 total cases) and CFR decreased again in May 2022 (17%) and June 2022 (18%).

TTS after Dose 2: Up to 28 June 2022, 260 cases of TTS following the second dose were retrieved (compared to 211 cases in PBRER02). Majority were male (59%; previous PBRER02 63%) with median age 65.5 years and median TTO 14 days. Pulmonary embolism (122 cases) followed by DVT (70 cases) was most frequently reported. Twenty-six cases had a fatal outcome, corresponding to a CFR of 10%, which is lower than the CFR for dose 1 cases (17%).

TTS after Dose 3: Cumulatively, 8 cases of TTS following the third dose were retrieved, of which 6 cases occurred after a Vaxzevria booster and 2 cases after a mRNA booster. Median age was 28 years and median TTO 12 days. The ratio female to male was equal. One case had a fatal outcome, but contained very limited information as it was based on a social media post and it was unclear if Vaxzevria was used as a booster dose. One case was classified as probable and 2 cases as possible according to the MHRA Case Classification. The remaining 3 cases did not mee the criteria, including the fatal case. No new concern regarding TTS has been identified with booster doses of Vaxzevria.

Mechanism of TTS: The MAH reviewed new literature regarding the potential mechanism of action of TTS with Vaxzevria and retrieved 4 relevant articles. Cohen et al. (2022) demonstrated that Vaxzevria did not result in an increased rate of detection of anti-PF4 IgG post-vaccination compared to placebo during the first 15 days after vaccination. These data were assessed as part of the type II variation EMEA/H/C/005675/II/0038. Pitkanen et al. (2021) suggested that VITT is triggered by antibodies against adenovirus vector and PF4-polyanion complexes which strongly co-activate complement and platelets. Bhur et al. (2022) investigated blood and thrombus specimens of a female patient who suffered severe stroke due to VITT after vaccination with ChAdOx1 in comparison to 13 control stroke patients with similar clinical characteristics. The thrombus of the VITT-patient exclusively revealed complement factors and high amounts of DNase and LL-37 and serum tests indicated either less efficient NET-inhibition or enhanced NET-induction in the blood of the VITT-patient. Schönborn et al. (2022) noted that Covid-19 did not restimulate anti–PF4 antibodies in a cohort of 11 patients with a history of VITT.

The MAH's hypothesis for the mechanism of TTS is that ChAdOx1-PF4 complexes are recognized by pre-existing B-cell clones encoding pathogenic anti-PF4 IgG. The boosted production of TTS inducing anti-PF4 antibodies (IgG) subsequently triggers thrombosis via activation of platelets and neutrophils. However, as also discussed during a EMA workshop[1], several gaps in the understanding of TTS remain to be elucidated.

Health Canada is conducting a comprehensive review on TTS to determine whether there is a need for additional risk minimization measures in Canada for Vaxzevria and requested the MAH to provide specific information on this topic (see section 15.2.15 of the PBRER). The majority of the requested information is included anyway in the PBRERs and does not bring additional data compared to the data in section 16.3.2.1.

Upon request of Health Canada, the MAH discussed observational studies on TTS in Appendix 17 of the PBRER. Data from observational studies showed an increased risk of TTS following vaccination with the

[1] European Medicines Agency. EMA workshop on thrombosis with thrombocytopenia syndrome. Virtual workshop, 27 June 2022. https://www.ema.europa.eu/en/events/ema-workshop-thrombosis-thrombocytopenia-syndrome

first dose of Vaxzevria. The highest relative risk was observed in younger age groups. However, the risk associated with Vaxzevria was much lower than following COVID-19 infection. These studies have some limitations as only one study used clinician-verified validation of TTS cases and results across studies lacked consistency, although different studies covered largely the same population (UK) during overlapping time periods (Dec 2020 – Apr 2021).

CVST with Thrombocytopenia: data presented were similar to those presented in PBRER02.

In conclusion, no new safety information concerning TTS could be identified. The current risk minimisation measures described in the product information are considered adequate.

2.3.2. Important Identified Risk (EU-specific) – Thrombocytopenia, including immune thrombocytopenia

Please note that Thrombocytopenia, including immune thrombocytopenia data is not reproduced here (Appendix R3 - Section 2.2.1 of the PBRER).

MAH's summary

Cumulatively, **2752 case** reports of Thrombocytopenia without co-reported thromboembolic events were received. Out of the 2752 cases, 66.4% (1830) cases are with Thrombocytopenia alone without any associated haemorrhage and/or thrombosis reports, 32.5 % (891) cases are Thrombocytopenia with spontaneous bleeding and 1.1% (31) cases are with Thrombocytopenia with menstrual bleeding. Most frequent bleeding events reported were **contusion** and **Petechiae**. Most of the cases were reported from United Kingdom and Australia.

There were **92** (3.3%) reports with **fatal outcome**, with majority of 55 (59.7%) of 92 cases reported in females. Overall, the death rate was higher in age group over 50 years (71 out of 92 cases) and 44 cases out of 92 (48%) were in patient with thrombocytopenia associated with bleeding.

Out of the total 2752 case reports received for Thrombocytopenia without co-reported thromboembolic events, the WHO-UMC causality was assessed as follows: **1694 (61.5%)** cases were assessed as **Possible** and in 1317 (77.7%) out of 1694 cases, the assessment was based solely on the reasonable TTO parameter and no information was available on assessments of other etiologies, or the vaccinees' medical history, comorbidities, concomitant medications, etc. For the remaining 377 (22.2%) of 1694 cases this assessment was based on a reasonable TTO although the event could also be explained by the vaccinees' diseases. 873 (31.7%) of case reports were assessed as Unassessable/Unclassifiable, 179 (6.5%) cases were assessed as Unlikely, **6** (0.2%) cases assessed as **Probable-Likely**. None of the cases met WHO-UMC criteria for Certain (including immune thrombocytopenia).

The results of the **O/E analyses** for all thrombocytopenia cases in risk windows 21 and 42 days (along with unknown TTO for both risk windows) suggest that observed cases were significantly less than expected cases.

A review of the published **literature** did not identify any new safety information on this topic in association with VAXZEVRIA.

MAH's conclusion

From the data identified during the reporting period, and taking into account the cumulative experience, **no new information** on thrombocytopenia was received during the reporting period that changes the present understanding and description of the important identified risk in EU RMP and as an ADR in EU SmPC.

However, after the data-lock point of this PBRER, AstraZeneca validated a **signal for Immune Thrombocytopenia** based on new well-documented case reports of Immune Thrombocytopenia with VAXZEVRIA from the published **literature**. Evaluation of this validated signal is ongoing as per AstraZeneca's signal detection and evaluation processes.

Thrombocytopenia, including immune thrombocytopenia will continue to be kept under close surveillance by AstraZeneca.

Rapporteur assessment comment:

"Thrombocytopenia, including immune thrombocytopenia" (ITP) is listed in the RMP as an important potential risk and in the SmPC section 4.8, "Thrombocytopenia" is listed with frequency 'common' and "Immune thrombocytopenia" is listed with frequency 'not known'. In addition, the risk of thrombocytopenia including ITP is described in section 4.4 of the SmPC. This paragraph refers to the risk of bleeding and the reports of fatal cases.

While mild and transient thrombocytopenia was a common finding from clinical trial, the cases reported from post-marketing experience contain a high proportion of serious cases (92%). Less severe cases remain probably undiscovered.

Twenty two (22) of the **92 fatal cases** were reported during this PSUR period. The reported cause of death was variable and, in many cases, involved more than one event. These causes of death are similar to other causes of death reported previously.

During the reporting period, a literature search found 20 articles including **32 literature cases**. Three cases from the literature were classified as probable-likely according to WHO-UMC classification.

Overall, information collected on thrombocytopenia including immune thrombocytopenia does not modify the conclusion of previous assessment. No change to the SmPC sections 4.4 and 4.8 is warranted. New information on thrombocytopenia does not change the B/R balance of Vaxzevria.

2.3.3. Important Identified Risk (EU-specific) – Guillain-Barré Syndrome

Please note that GBS data is not reproduced here (Appendix R3 - Section 2.2.2 and Appendix 20 of the PBRER).

MAH's Summary

During the period covered by this report (29 December 2021 to 28 June 2022), **361 cases** were reported, out of which 211 (58.4%) were reported by healthcare professionals (medically confirmed).

Out of the 361 cases, **98 cases met the BCC 1 to BCC 3 level criteria**. When the 98 are assessed according to WHO-UMC causality criteria 8 did not have sufficient information to do a causality assessment and were assessed as "Unassessable/unclassifiable", 16 were assessed as "Unlikely", and **74** were assessed as **"Possible"** causality to VAXZEVRIA.

Out of the 74 cases assessed for WHO-UMC causality deemed as "Possible", **66 had limited information** on other aetiologies, medical history, concomitant medications, etc., and **8 cases had risk factors or confounders**. Cases were considered to have "risk factors/confounders" where the event could also be explained by the vaccinee's diseases, relevant risk factors that were present, or concomitant medications that could potentially contribute to the development of the event.

The **observed versus expected analysis** of cumulative cases reported with TTO within all risk windows (14 days, 30 days and 42 days) from vaccination suggested that **observed cases are significantly less than expected**. However, when cases with an unknown time to onset are included as a conservative

approach, observed cases are significantly more than expected for 14 days risk window and significantly less than expected for 30 and 42 days risk window. Furthermore, an observed versus expected analysis of cases meeting the BCC Level 1, 2, or 3 with TTO within 14 days from vaccination suggested that observed cases are significantly more than expected, while for TTO within 30 days and 42 days from vaccination suggested that observed cases are significantly less than expected.

When cases from EEA and UK, or UK alone are analysed according to age group and sex, as well as 14, 30, and 42 day windows, numbers of cases become very small, resulting in some categories where observed is greater than expected and in some categories less than expected. Also, there is high variability in these data, making an assessment on causal association not possible.

During the reporting period of the PBRER (29 December 2021 to 28 June 2022), a **signal of GBS was validated**, based on new information from retrospective analysis as well as well-documented case reports of GBS with COVID-19 VACCINE ASTRAZENECA from the published literature.

Although there are epidemiological articles describing a temporal association to the first dose of VAXZEVRIA, the risk was approximately 4 times greater after a COVID-19 infection. Therefore, there are still gaps in understanding the effect of the COVID-19 pandemic in the background. The comparison the authors of literature articles carried out between VAXZEVRIA and Comirnaty had limitations due to the differences in the populations receiving the vaccine, ie, VAXZEVRIA was mostly used in an elderly population that is more prone to develop GBS.

Taking this into consideration, AstraZeneca **included GBS in the existing language on demyelinating disorders in Section 4.4 of the CDS**. In line with this, the relevant text on GBS was added to the CPIL **to inform the vaccinees to seek early medical care irrespective of the underlying aetiology of GBS**.

Based on the review of available evidence from literature and from reports in the safety database on the topic of the facial diplegia/bifacial weakness with paraesthesia variant of GBS**, AstraZeneca considers that there is not sufficient evidence to confirm any particular clinical features associated with vaccination or establish a causal association with VAXZEVRIA**.

AstraZeneca will continue to closely monitor GBS as part of our surveillance activities (nervous system disorders, including immune mediated neurological conditions) and take further actions as deemed necessary.

MAH's conclusion

From the data identified during the reporting period, and also taking into account the cumulative experience, no new information on GBS to warrant any changes in the EU SmPC and EU RMP.

Rapporteur assessment comment:

The MAH provided a review of cases reported during the interval period (29 Dec 2021-28 Jun 2022). Of the 361 cases, 98 cases met the BCC levels 1-3. Causality assessment according to WHO-UMC causality criteria classified 76 cases as with a possible and none with a probable causal association with Vaxzevria. Most of the cases (88%) were classified as possible with limited information.

Cumulatively, 1703 cases were reported, most of which were serious (99.5%). 37 cases (2.2%) had a fatal outcome.

Pattern and variant of GBS: In the reporting period, 22 cases of GBS had facial diplegia/bifacial weakness as symptoms. However, only 1 case described the GBS variant of interest (i.e. bifacial weakness and paraesthesia [BWP]) in a 39 years old male. The AEs occurred 16 days after the 1st dose of Vaxzevria and required hospitalisation the patient was treated with immunoglobulin and the AEs improved.

Overall, no clinical pattern has been identified after vaccination with Vaxzevria. Facial diplegia in interval cases of GBS has been reported at a lower frequency (i.e. ~6%) than described in the literature (i.e. up to 50%).

In the literature, Andreozzi et al. (2022) published 2 cases of BWP variant of GBS, both occurring after the 1st dose of Vaxzevria. The authors also performed a systematic literature review and identified 11 additional cases of BWP variant after COVID-19 vaccination.

Besides, Kim et al. (2022) retrospectively reviewed medical records and identified 13 patients with GBS post COVID-19 vaccination, including 8 cases after Vaxzevria. The variants identified in the review were paraparetic GBS (n=3), Miller fisher syndrome (n=1) and acute cervicobrachial weakness (n=1). No case of BWP variant was observed.

O/E analysis: Observed versus expected analysis only showed a significant increase when cases with unknown TTO were included in the analysis with a 14 day risk period.

These findings are similar to those observed in the previous PSUR.

Of note, Atzenhoffer et al 2022 published in the literature an O/E analysis using spontaneous data from VigiBase and exposure information from Our World in Data (DLP 15.10.2021). The authors identified an imbalance for adenovirus-vectored COVID-19 vaccines with an O/E ratio >2.0 but not for mRNA-based vaccines (i.e. RR adeno: 5.57 (5.13–6.03) per 100,000 py; RR mRNA: 1.39 (1.31–1.47); background incidence : 1.2–3.1 per 100,000 py). The authors highlighted some limitations in their analysis including limited clinical data from VigiBase and lack of exposure data stratified by age and sex. Moreover, the background incidence rates used in the analysis were lower than those from the MAH and derived from ACCESS protocol.

Mechanism of action: The literature reviewed identified several papers (Aliasin et al. 2022; Chen et al. 2022; Shafiq et al. 2022) discussing hypotheses for GBS occurring after COVID-19 vaccination. Briefly, the following mechanisms of action have been suggested:

- binding of the S protein to the sialic acid located on the gangliosides and glycoproteins of the neurons' cell membrane. Antibodies attacking to S protein might also respond against the antigens on the myelin sheaths;

- similarity of vaccine epitopes with myelin or axon epitopes, which after recognition can trigger cellular and humoral immune responses, leading to antibodies synthesis aberrantly against myeline, following a degradation of axon or myelin membranes due to direct exposure of vaccine virus or vaccine-related products;

- molecular mimicry and production of autoantibodies;

- immune overactivation or dysregulation in patients who already have an underlying predisposition to autoimmune disease.

However, the exact mechanism still remains to be elucidated.

Closed signal: the MAH reviewed a signal of GBS during the reporting period and concluded that a warning should be added in the CDS (see Section 2.2.2 for further details). Of note, in the EU-PI of Vaxzevria, a warning was already included in section 4.4 before the review of the MAH's signal.

Overall conclusion: information becoming available during the period under review did not raise any new safety concern. Moreover, data from spontaneous reporting and the literature did not suggest that a specific clinical pattern, such as BWP variant, is associated with GBS cases reports after Vaxzevria vaccination.

As previously discussed, the PRAC Rapporteur considers that a causal association between Guillain-Barré and Vaxzevria should be considered at least a reasonable possibility (disagreement with the MAH's opinion). Currently, GBS is **appropriately described in the EU-PI** (sections 4.4 and 4.8) **and in the EU-RMP** (important identified risk). Moreover, GBS will continue to be closely monitored as part of the surveillance activities including routine PhV and PASS. No further action is required.

2.3.4. Important Identified Risk (EU-specific) – Anaphylaxis

Please note that Anaphylaxis data is not reproduced here (Regional Appendix R3 - Section 2.2 of the PBRER)

During the period covered by this report, 3168 cases were received for the AESI of Anaphylaxis, reporting 3758 AEs that were part of the Anaphylaxis AESI concept. Cumulatively, there have been 20557 case reports of Anaphylaxis.

MAH's conclusion

From review of the interval and cumulative data, there is no new safety information on Anaphylaxis that changes the present understanding and description of the risk.

During the reporting interval, Anaphylaxis was reclassified as non-important identified risk and removed from the list of safety concerns at the request of EMA (see section 3). AstraZeneca will not discuss this topic in the future PBRERs, unless significant new safety information arises.

Rapporteur assessment comment:

During the current reporting period 3168 cases were reported, and these cases reported 3758 AEs. Cumulatively, a total of 20557 AEs belonging to the Anaphylaxis AESI concept were reported. It is noted that there were 23 (0.93%) fatal cases during the reporting period.

The data provided in the PSUR do not raise any new safety issue. The current warning in section 4.4 is sufficient to minimise the risk of anaphylaxis and the risk of anaphylaxis and hypersensitivity is appropriately described in section 4.8.

Anaphylaxis is no longer an important identified risk as it is now considered fully characterised and no additional RMM are ongoing or planned.

2.3.5. Important potential risk(EU-specific) – Thrombosis

Please note that Thrombosis data is not reproduced here (Regional Appendix R3 - Section 2.1.1 of the PBRER).

MAH's summary

A total of 2567 cases were received in the reporting period and 18690 cumulatively.

Frequently reported thrombosis events (>150 events) included Pulmonary embolism (518, 20.2%), Cerebrovascular accident (438, 17.1%), Deep vein thrombosis (387, 15.1%), Thrombosis with thrombocytopenia syndrome (235, 9.2%), and Myocardial infarction (185, 7.2%).

The highest number of cases were received from Brazil 497 cases (19.4%) followed by UK 493 cases (19.2%) and Germany with 385 cases (15.0%). A total of 1300 case reports were reported in females, and 1198 were reported in males, and in 69 cases the gender was not reported. Out of 2567, 5 cases occurred in the paediatric population (One in 3 weeks and 6 days, one in one year and 9 months, one in

12 years and two in 17 years) and in 206 cases age was not reported. The overall median age was 59 years with a range of 0 (3 weeks and 6 days) to 97 years for all cases where age was reported.

Of the 2567 case reports received during the reporting interval, 371 (14.5%) cases had a fatal outcome compared to a cumulative fatality rate of 8.1% (1512 fatal out of 18690 thrombosis case reports). There were 224 medically confirmed cases and 147 non-medically confirmed cases with a fatal outcome. There was no marked difference in the interval versus the cumulative fatality rate. 371 fatal reports were received in the interval; 110 (29.6%) were initial reports and 261 (70.4%) were follow-ups. 55 (14.9%) of the 110 initial reports were medically confirmed. The large number (261) of follow up reports in the interval accounts for higher fatality rate for the interval. Of the initial reports, 30 (27.3%) were from Brazil.

The overall cumulative thrombosis fatality rate was highest (14.5%) in vaccines aged 80 years and most of these reports were in vaccinees with underlying comorbidities. The cumulative case fatality rate in vaccinees aged 18-29 years, 30-39 years, and 40-49 years was 11.6%, 9.3%, and 7.0 respectively. However, in the 18-29, 30-39-, and 40-49-years age group, 21.3% (27 out of 127 fatal reports), 15.1% (35 out of 232 fatal reports) and 12.0% (39 out of 325 fatal reports) of the fatal case were due to thrombosis in combination with thrombocytopenia which may explain increased fatality rate in vaccinees aged < 50 years.

MAH's conclusion

From the data identified during the reporting period, and considering the cumulative experience, no new information on Thrombosis was received during the reporting period that changes the present understanding and description of the important potential risk. No changes to the EU SmPC are warranted at this time. AstraZeneca will continue to monitor safety information for Thrombosis as part of the routine safety surveillance activities for VAXZEVRIA and take further actions as deemed appropriate.

Rapporteur assessment comment:

During the period under review, 2567 cases (2543 serious, 1337 medically confirmed) were retrieved for the AESI of Thrombosis. However, almost half of the identified cases (1214) were follow-up cases. Cumulatively up to 28 June 2022, 18,690 cases reporting Thrombotic events, with and without thrombocytopenia, were retrieved.

The reported cases show similar information/trends regarding gender and age distribution (median age 59 years, 52% females), TTO (median TTO 12 days), type of thromboembolic event and outcome as in the previous PSUR (PSUR02). The case fatality rate for the reporting interval is 14.9% compared to a cumulative case fatality rate of 8.1%. The higher fatality rate for the interval is due to the large number of fatal follow-up reports (261 out of 371 fatal reports (70.4%)) received during the interval.

Out of the 2567 case reports, 402 occurred after dose 2 and 20 occurred after dose 3. Of note, 5 (25%) of the 20 case reports post dose 3 had a fatal outcome and three of these fatal cases involved individuals under the age of 70 (22, 45 and 62 years old). Co-reported AEs in the 5 fatal cases included (1 each): acute myocardial infarction, coronary artery thrombosis, dyspnoea, ischaemic stroke, myocardial infarction, pulmonary embolism, respiratory distress and thrombosis with thrombocytopenia syndrome. Since information on medical history, concomitant drugs and co-reported AEs was not provided on case level, but only for the 5 fatal cases combined, it was not possible to assess the causality for these five cases. **In the next PBRER, the MAH should provide a tabular summary of the fatal cases reporting a thrombotic event after dose 3 (or dose 4) of the vaccine. [*Request for the next PBRER*]**

As requested, the MAH discussed the cases where thromboembolic events occurred both after dose 1 and dose 2 (potential 'rechallenge' cases). All 10 cases contained limited information or reported important

confounding factors. There were no cases of recurrence of thromboembolic events after dose 3.

The MAH performed overall O/E analyses using global data and O/E analyses by age and gender using UK data. All analyses were carried out with risk windows of 14, 28 and 42 days. None of the O/E analyses showed a disproportionality and observed cases were significantly less than expected for all stratifications.

The PRAC rapporteur agrees with the MAH's conclusion and to continue to closely monitor this important potential risk.

2.3.6. Important potential risk – CVST without thrombocytopenia

Please note that data on CVST without thrombocytopenia is not reproduced here (Section 16.3.1.1 of the PBRER).

MAH's summary

AstraZeneca continued to review the safety information for CVST without thrombocytopenia from sources including clinical trials, post-marketing reports, and the published literature for the reporting period.

There were no reports of CVST without thrombocytopenia related AEs in the Oxford pooled studies. There was 1 report of Cerebral venous/Cerebral venous sinus thrombosis identified in the VAXZEVRIA group in US Study (D8110C00001), however, there was no new safety information received in the reporting period.

A review of the post-marketing data did not identify any index case or a new safety signal. There were no case reports with positive re-challenge (after the first and second dose of the vaccine). There are 573 and 89 cases for the cumulative and reporting period respectively. Cumulatively, there was a preponderance for female gender (61%) versus males (35%), and 68% cases were in age group 18-64 years. Twelve (12) fatal cases (92%) out of all 13 fatal cases (in all age groups) were reported in females in the reporting period. Cumulatively, 28 (60.8%) out of all 46 fatal cases were reported in females. There was no significant difference noted between the cumulative and reporting period in terms of the volume and distribution of cases.

A review of the published literature did not identify any new safety information on this topic in association with VAXZEVRIA.

The Observed versus Expected analysis was carried out using incidence rates from ACCESS: SIDIAP PCHOSP and Truven MarketScan (2019). SIDIAP PCHOSP is representative of the general population in terms of age, sex, and geographic distribution and that the rate was used by the EMA, and this would permit a comparison of the O/E analysis conducted by EMA, whereas Truven MarketScan was used for consistency with background rates for TTS generated using MarketScan. The results showed observed cases are more than expected in the general population globally. The age stratifications suggest that the O/E ratio is higher in younger age groups than in the older age groups and that the O/E ratio is higher in females than in males. However, it is important to note that O/E analyses are complementary to routine signal detection methods, and are not designed to determine a causal relationship; confounding factors were not considered in O/E (such as possible COVID-19 infections or other possible causes for CVST without thrombocytopenia).

CVST without thrombocytopenia is an important potential risk in the VAXZEVRIA Core Risk Management Plan and the topic will continue to be kept under close surveillance by AstraZeneca.

MAH's conclusion

From the data identified during the reporting period and also taking into account the cumulative experience, AstraZeneca considers that there is currently insufficient evidence of a reasonable possibility of causal relationship between VAXZEVRIA and CVST without thrombocytopenia. CVST without thrombocytopenia is included in section 4.4 (section 4.4 Warnings and Precautions) of the CDS to inform prescribers that these events may require different treatment approaches than TTS. Healthcare professionals should consult applicable guidance. No changes to the CDS or product leaflets are warranted at this time.

AstraZeneca will continue to monitor safety information for CVST without thrombocytopenia as an important potential risk and take further actions as deemed appropriate.

Rapporteur assessment comment:

Cumulatively, up to 28 June 2022, 573 cases of CVST without thrombocytopenia have been reported (566 serious, 340 medically confirmed), compared to 508 cases in PSUR02. Taking into account the estimated number of doses administered cumulatively (2,097,714,177), approximately 0.27 cases/1 million doses occurred during the overall period, which is slightly lower than in the previous PSUR02 (0.32/1 million doses).

The updated cumulative review of cases of CVST without thrombocytopenia resulted in similar information/trends regarding age and gender distribution (median age 51 years, 61% females), reported CVST PTs, outcome, and case fatality rate (8%) as the cumulative review provided in PSUR02. Information on TTO was not provided for the cumulative period.

During the current **reporting period**, 89 cases (53 initial, 36 follow-up) of CVST without thrombocytopenia were retrieved. All cases were serious and 49 of them were medically confirmed. The majority of the cases were reported in females (70%). Median age was 45.5 years (age range: 20-90 years). Median TTO was 12.5 days (range 0-301 days) compared to 39 days (range 0-301 days) for the cumulative period in PSUR02.

Thirteen of the 89 cases had a fatal outcome, resulting in a case fatality rate (CFR) of 14.6% compared to a cumulative CFR of 8%. The higher CFR for the reporting interval is due to the large proportion of fatal follow-up reports (6 out of 13 reports (46%)) received during the interval. Confounding factors (i.e. comorbidities, risk factors, concomitant medications) were reported in 23.5% of the patients. The CVST event occurred post 2nd dose in 12 case reports (13%). There were no cases with a positive rechallenge (CVST event(s) both after dose 1 and dose 2).

The MAH performed causality assessment using WHO-UMC criteria. Out of the 89 cases reported during the current interval period, 1 case was classified as 'Conditional/Unclassified', 13 cases (15%) as 'Unlikely', 28 cases (31%) as 'Unassessable' (of which 23 with limited information and 5 with confounders), and 47 cases as 'Possible' (53%) (of which 37 with limited information and 10 with confounders).

A literature review on CVST did not identify new relevant safety information.

The results of the MAH's updated O/E analyses for CVST without thrombocytopenia were in line with PSUR02. Observed cases were significantly higher than expected in the general population globally for all risk windows except for the risk window of 42 days when cases with unknown TTO were excluded. The age and gender stratifications suggest that the O/E ratio is higher in the younger age groups than in the older age groups and higher in females than in males.

As initially discussed in MSSR07, the PRAC Rapporteur disagrees with the MAH's conclusion on causality. A causal association between CVST without thrombocytopenia and Vaxzevria should be considered at

least a reasonable possibility. Cerebrovascular venous and sinus thrombosis is listed with frequency unknown in section 4.8 of the SmPC and a warning on the risk of CVST without thrombocytopenia was included in section 4.4.

In conclusion, no new safety information concerning CVST without thrombocytopenia could be identified. The current risk minimisation measures described in the product information are considered adequate. The MAH should continue to closely monitor cases of CVST without thrombocytopenia, present updates in the next PBRERs, and discuss relevant literature.

2.3.7. Important potential risk –Immune-mediated neurological conditions / Nervous system disorders, including immune-mediated neurological conditions during the reporting period

Cumulatively, a total of **36033 cases** from literature, clinical studies, non-interventional studies and spontaneous sources were reported within the concept of immune-mediated neurological disorders. This includes a total of **5641 cases** reported **during the period under review**.

The **most commonly reported PTs** (interval) were Paraesthesia (2976), Hypoaesthesia (1982), Neuralgia (358), **Guillain-Barre syndrome (318)**, Sensory disturbance (232), Neuropathy peripheral (93), **Myelitis transverse (80)**, Sensory loss (79), Polyneuropathy (63), Optic neuritis (49), **Encephalitis (42)**, **Acute disseminated encephalomyelitis (37)**, Myelitis (35), Multiple sclerosis (33), Chronic inflammatory demyelinating polyradiculoneuropathy (28), Multiple sclerosis relapse (24), Neuritis (19), **Miller Fisher syndrome (18)**, Demyelination (18), Neuromyelitis optica spectrum disorder (15), Myelopathy (14), Peripheral sensory neuropathy (12), Myelin oligodendrocyte glycoprotein antibody-associated disease (12).

2.3.7.1. Encephalitis, including fatal

Please note that the Encephalitis data is not reproduced here (Section 16.3.1.2.1 of the PBRER).

During the period covered by this report, **93 cases** (64 initial case reports and 29 follow-up cases) were reported using the narrow MedDRA SMQ: Noninfective Encephalitis (excluding Acute disseminated encephalomyelitis) and HLT: Encephalopathy.

Out of the 93 cases: 90 (96.8%) cases are serious and 58 (62.4%) were medically confirmed.

Gender/age: there were 50 (53.8%) reports for female vaccinees, 39 (41.9%) were for male vaccinees [gender not reported in 4.3% cases]. 65 (69.9%) of vaccinees were from the age group of 18 <65 (adult) and median age is 52 years.

Doses: there were 60 cases after dose 1, 18 cases after dose 2 and 1 case reported with booster dose; no case of rechallenge was reported.

TTO: the median TTO was 13 days; (44) (47.3%) cases were within the risk window of 2-42 days.

Fatalities: there were **6 (2.4%) cases with fatal outcome**.

The cause of death for 1 case was reported as not related to encephalitis and it was reported as left parietal extensive intracerebral congestive haemorrhage. In the remaining cases the cause of death was **encephalitis (BCC1/possible with confounder)**, hypoxic encephalopathy (BCC4), encephalopathy (BCC4), myelin oligodendrocyte glycoprotein antibody positive encephalomyelitis (BCC4), and hypoxic ischemic encephalopathy (BCC4).

The case of fatal encephalitis ([redacted]) assessed as a BCC1 possibly related with confounder was

from MHRA. It was reported that a 49/M patient with a medical history of bipolar disorder experienced encephalitis on day 1. On further narrative review, it was stated that patient experienced dizziness on an unknown date after the first dose of AZ vaccine and was hospitalized due to this. The patient was diagnosed with encephalitis 3 weeks after admission. Therefore, TTO was conservatively presumed to be within the risk window and the causality assessed as 'possible with confounder' (i.e. confounder was concomitant medication valproate sodium).

The review of 6 case reports with fatal outcome did not identify any substantial evidence of a causal association between encephalitis and VAXZEVRIA.

BCC criteria and causality assessment[WHO-UCM criteria]: out of the 93 cases, **1 case** fulfilled **level 1** criteria (fatal case), **6 cases** fulfilled **level 2** criteria, **8 cases** fulfilled **level 3** criteria, **57 cases** fulfilled **level 4** criteria, and **21 cases** fulfilled **level 5** criteria.

Out of the 15 cases with BCC level 1-3, 3 cases were evaluated as possible with confounders, 9 cases as possible with limited information, 2 cases as unlikely and 1 case was unassessable/unclassifiable.

Cumulatively (up until 28 December 2021), a total of **343 cases** were identified.

Observed Versus Expected Analysis: the O/E analysis of **cumulative cases** for encephalitis showed that **observed cases occurred significantly less frequently than expected** for all cases (343) and cases with BCC 1-3 (49), all age stratifications in EEA/UK, Brazil, and Australia, and risk windows. The contribution of under-reporting cannot be estimated, but observed cases are significantly below expected and do not indicate a signal.

Overall, the clinical pattern of case presentation and numbers of reports are broadly consistent with what might be expected from the natural epidemiology of encephalitis, and there are no specific biological mechanism for development of encephalitis post vaccination with VAXZEVRIA.

MAH's conclusion: from the data identified during the reporting period and taking into account the cumulative experience, there is currently insufficient evidence of a causal association between encephalitis and VAXZEVRIA.

No further updates to the VAXZEVRIA CDS (i.e. Section 4.4 currently warnings on Neurological events and encephalitis) or RMP are warranted at this time. As such, the topic will continue to be to be closely monitored as part of AstraZeneca's ongoing surveillance efforts for the important potential risk of nervous system disorders, including immune mediated neurological conditions

Rapporteur assessment comment:

The MAH provided a review of interval cases of encephalitis, including a causality assessment according to the WHO-UMC. Out of 93 cases, only a minority fulfilled BC Level 1-3 criteria. (i.e. 1 fatal case BC level 1, 6 cases BC Level 2 and 8 cases BC Level 3). 9 cases were assessed as possibly related with limited information and 3 cases as possibly related with confounders.

Regarding fatal cases, there was 1 case classified as BC Level 1 reporting encephalitis as the cause of death. The case was described in a 49 male subject with a medical history of bipolar disorder and was confounded with the concomitant administration of valproate sodium. Other cases were classified as BC Level 4 (n=4) or reported cause of death was not encephalitis (n=1).

The O/E analysis cleared showed an O/E ratio significantly lower than 1.

The literature review performed by the MAH did not identify any relevant articles other than several case reports (8 papers describing 12 cases of encephalitis).

In conclusion, available data **did not raise any new safety signal**. Routine monitoring of encephalitis

as part of the monitoring of the important potential risk of Nervous system disorders, including immune-mediated neurological conditions is appropriate.

2.3.7.2. Transverse myelitis

Please note that Transverse myelitis data is not reproduced here (Section 16.3.1.2.2. of the PBRER).

During the period covered by this report, **112 cases** [*Search strategy*: MedDRA PTs Myelitis transverse, Myelitis, and Acute necrotizing myelitis, and LLT MOG-transverse myelitis].

Out of the 112 cases: 96 (85.7%) cases are serious and 47 (42.0%) were medically confirmed.

Gender/age: there were 55 (49.1%) reports for female vaccinees, 54 (48.2%) were for male vaccinees [gender not reported in 2.7% cases]. The median age was 50 years.

Doses: there were 35 cases after dose 1, 22 cases after dose 2 and 3 cases reported with third/booster dose; no case of rechallenge was reported.

TTO: the median TTO was 15 days; 60 cases occurred within 42 days [TTO unknown in 38 cases].

Fatalities: there were **1 case with fatal outcome** : The patient received a Flu vaccine and AZ vaccine about 3 weeks apart and subsequently developed neurological features of myelopathy - with encephalopathy; termed atypical GBS and myelitis, although the features could be solely related to TM. The pattern of neurological symptoms is consistent with transverse myelitis (longitudinally extensive TM as well as plexitis are noted in the narrative suggesting Imaging obtained of spinal cord), with an encephalopathy of hypoxic ischemic origin as noted upon hospital admission. Patient refused initial recommended admission which was based on lower extremity weakness and sensory change and urinary retention with upper extremity being normal. Upon admission approx. 2 days later there was a noted aspiration pneumonia and cognitive changes including delirium. There was insufficient information on exclusion of other causes of acute delirium. Insufficient response to IvIg, methylprednisolone and plasma exchange suggests possible non-immune etiology. Additionally, there was insufficient information on medical history, CNS investigations results (CSF), radiological investigations (although longitudinally extensive transverse myelitis was mentioned as well as plexitis), clinical and radiological course of transverse myelitis, autopsy and etiological work-up (in the context of fever, hypoxia). The **BCC case classification for transverse myelitis was considered as BCC3** due to clinical observations and fever. There is insufficient information on imaging, carcinoma work up (plexitis),CSF investigation and autopsy. TTO of neurologic symptoms at a reasonable time-frame to both vaccinations (1 month to Influenza vaccine, 2 weeks to COVID-19 vaccine). BCC case classification for GBS was considered as BCC4, considering the lack of information in regard other clinical symptoms, electrophysiology test and CSF. The **WHO-UMC causality assessed as Possible based on temporal association for TM**.

BCC criteria and causality assessment[WHO-UCM criteria]: out of the 112 cases, **no case** fulfilled **level 1** criteria, **13 cases** fulfilled **level 2** criteria, **9 cases** fulfilled **level 3** criteria, **68 cases** fulfilled **level 4** criteria, and **22 cases** fulfilled **level 5** criteria.

Out of the **22 cases with BCC level 2-3**, 4 cases were evaluated as possible with confounders [including early development of multiple sclerosis, concomitant paraneoplastic syndrome, possible pre-existing spinal pathology], 15 cases as possible with limited information, 2 cases as unlikely and 1 case was unassessable/unclassifiable.

The **CSF results** as available (15 out of 22 cases) presented a varied picture with respect to extent of pleocytosis (normal count in 1 case, less than 100 cells/uL in 7 cases, more than 100 in 7 cases).

Information on oligoclonal bands in TM cases was reported in 5 out of 22 cases (3 negative and 2

positive).

Information on **serum or CSF levels on anti-neuronal antibodies** was reported in 13 out of 22 cases : 5 cases had positive anti-neuronal antibodies (MOG-Ab positive in 4 cases and NMO-Ab positive in 1 case), and 8 had negative results.

To summarize, either there was limited information or CSF picture including neuronal antibodies had a varied presentation to identify any singular etiopathogenetic possible role of VAXZEVRIA

Cumulatively (up until 28 June 2022), a total of **354 cases** were identified.

Observed Versus Expected Analysis: When the observed versus expected analysis is carried out **overall for global reports** for all ages and genders, the number of observed cases is **significantly less** than expected for all stratifications provided.

When **stratified by age only in the UK** (using ADVANCE EUROPE rates, including cases with known TTO), observed cases are **more or significantly more** than expected for all age groups, except for the age group 45-64 years (observed cases are less than expected). When the cases with an unknown TTO are included for all age groups, observed cases are more than expected with a significant disproportionality.

When **stratified by gender and age in the UK** (using UKTHIN rates, including cases with known TTO), the observed cases for **females** are **more than expected** in all the age groups except for 45-64 years (observed cases were significantly less than expected), without the result being significant. Observed cases were significantly more than expected for females overall when cases with unknown TTO were included. For **males**, the observed cases **more than expected** in the youngest age group (15-24 years), the oldest age group (65+ years), and overall. When cases with unknown TTO were included, all age groups had observed higher than expected.

In addition, an observed versus expected analysis of cumulative cases meeting **Brighton collaboration criteria levels 1-3** showed that the observed number of TM cases fulfilling case definition are either **less than or significantly less** than the number of expected cases in all risk windows.

Observed vs expected analyses overall and stratified by BCC, age, gender and dose number were provided but are not reproduced here (please refer to PBRER Section 16.3.1.2.2 - Tables 188-193 and Appendix 9 Tables 44-52).

Literature: 1 article (Netravathi et al 2022) was identified and its assessment did not find any safety finding with impact on benefit-risk profile of VAXZEVRIA (see Section 2.3.7.3. for further discussion).

Mechanism: The pathogenesis for TM is thought to be immune-mediated from infection, para-infectious processes, autoimmune disease, or paraneoplastic processes. The exact mechanism of TM following immunization is unknown.

MAH's conclusion: from the data identified during the reporting period and taking into account the cumulative experience, there is currently insufficient evidence of a causal association between Transverse myelitis and VAXZEVRIA. It is AstraZeneca's opinion that no changes to the VAXZEVRIA CDS (i.e. Section 4.4 currently warnings on Neurological events) and RMP are warranted based on the review of currently available information. Surveillance of Transverse Myelitis will continue to be closely monitored as part of AstraZeneca's ongoing surveillance efforts for the important potential risk of Nervous system disorders, including immune-mediated neurological conditions.

Rapporteur assessment comment:

The MAH provided a review of interval cases of transverse myelitis, including a BCC classification and causality assessment according to the WHO-UMC. Out of 112 interval cases, **22 cases fulfilled BC Level**

2-3 criteria (no BCC level 1 case), among which **19 were assessed as possibly related** (with limited information [15] or with confounders [4]). When available, CSF results were presented. It was shown that **information was either limited or the CSF picture including anti-neuronal antibodies had a varied presentation** to identify any singular etiopathogenetic possible role of Vaxzevria. However, data remained very limited precluding any definitive conclusion at this stage.

The updated O/E analyses provide similar results compared to those presented in the previous PBRER.

The literature review performed by the MAH identified 1 article that did not raise any new safety concern.

In conclusion, updated review of PM data, O/E analysis and literature did not provide any new significant data. As previously discussed, the PRAC Rapporteur considers that a **causal relationship between Vaxzevria and Transverse Myelitis is at least a reasonable possibility** (disagreement with the MAH's opinion). The risk of transverse myelitis is considered to be **appropriately described in the current EU-PI** (Warning in **section 4.4**; TM listed in **section 4.8**). Moreover, TM will continue to be closely monitored as part of the surveillance of the important potential risk of Nervous system disorders, including immune-mediated neurological conditions. This includes routine PhV and PASS.

2.3.7.3. Acute disseminated encephalomyelitis (ADEM)

Please note that ADEM data is not reproduced here (Section 15.2.12 of the PBRER).

MAH's summary

On review of AstraZeneca's Global Safety Database **cumulatively to 28 June 2022**, a total of **80 cases of ADEM** with the use of VAXZEVRIA have been received (57 from spontaneous sources). This includes **37 interval cases**. All of the reported cases were serious, including 56 (70%) medically confirmed cases.

Dose: The majority of the cases were reported after the 1st dose. None of the cases that occurred after the 1st dose were identified to have positive rechallenge or worsened after the 2nd/3rd dose.

Age/Gender: The **age** range was 22 to 90 years with a **median of 53 years**; within the age range (19 to 61 years) mentioned by Schwarz et al 2001. 43 (**54%**) cases were reported in **female** vaccinees.

Seriousness/Outcome: In 46 (57.5%) cases, ADEM was reported to cause hospitalization, and in 45 (56.3%) cases ADEM was considered a medically important event. In 27 (33.8%) cases the events had a favourable outcome (recovering/resolving/resolved).

Five (**5**; 6.3%) cases had a **fatal outcome**. In the 5 fatal cases, the WHO-UMC causality was considered as **"Possible" with limited information in 1 case**, **"Possible" with confounders in 1 case**, "Unlikely" in 2 cases, and "Unassessable" in 1 case. Two (2) cases met BCC level 2 and 1 case met BCC level 1. No significant safety concerns were seen on review of ADEM cases with fatal outcome. In 25 (31.3%) cases the outcome was not recovered. The **case fatality rate of 6.3%** is in line with previously document case fatality rates in ADEM (5% to 50%; Borlot et al 2011).

TTO: The **median TTO was 8 days** [*TTO reported in 50 (62.5%) cases*]

BCC criteria and causality assessment[WHO-UCM criteria]: **3** (3.8%) cases fulfilled **BCC level 1**, **26** (32.5%) fulfilled **BCC level 2**, **5** (6.3%) fulfilled **BCC level 3** of the diagnostic criteria for certainty.

Of the 3 cases fulfilling BCC level 1, 2 cases were assessed as "Possible" with limited information and 1 case was assessed as "Unlikely" per the WHO UMC causality assessment criteria.

On review of the 56 (70%) medically confirmed cases, 25 (44.6%) cases met BCC level 1 to 3 and the WHO-UMC causality was assessed as **"Possible" with confounders in 12** (48%) cases, **"Possible" with limited information in 6** (24%) cases and "Unlikely" in 4 (16%) cases. The remaining 3 cases

(12%) had insufficient case details for a comprehensive causal assessment.

Pre-clinical/Clinical studies: no events of Acute disseminated encephalomyelitis.

O/E analysis (Tables 140-144 of PBRER): the O/A analysis of all ADEM cases suggested that **overall**, the observed numbers were significantly **less than the expected** numbers **in the 42-day risk windows**. The observed numbers were **greater than expected** in a few **sub group stratifications** and may be explained by reporting bias for increased reporting of cases with a shorter risk window for the passive event reporting of rare diseases. Review of cases in these subgroups where observed numbers were above expected showed that most cases had insufficient information to make any causality assessment.

EVDAS ROR: On review of the PT 'Acute disseminated encephalomyelitis' in EudraVigilance database, it exceeded the disproportionality assessment threshold. ADEM is a rare and serious event and when this event is compared against the drugs in EVDAS, especially in the context of global rollout of COVID-19 vaccines, it is expected to show a disproportionality. Therefore, this finding is not considered significant.

Trend analysis over time: The analysis identified a peak in reporting in Mar/Apr and Nov/Dec 2021, which may be due to the prevalence of COVID-19 infection in the community as it coincided with COVID-19 pandemic peaks rather than with vaccine exposure. AstraZeneca does not consider the trend analysis to be suggestive of increased risk due to VAXZEVRIA.

Mechanism: The review of mechanism of action articles and case reports found no conclusive evidence linking proof of mechanism in either a mechanism-based study or further exploration of mechanism in the same case were identified. No new safety signals were identified from review of literature.

MAH's conclusion

AstraZeneca's review of the cases in the safety database, O/E analysis, clinical and pre-clinical databases, literature and external databases does not bring any new information that will alter the current benefit-risk profile for the event ADEM in association with VAXZEVRIA. As is already stated in Section 4.4 of the CDS that neurological events, which includes demyelinating disorders such as Guillain-Barré Syndrome (GBS), are very rare events reported following vaccination with VAXZEVRIA. A causal relationship has not been established. As with other vaccines, the benefits and potential risks of vaccinating individuals with VAXZEVRIA should be considered. Therefore, AstraZeneca considers that no updates to CDS or RMP are required.

ADEM will continue to be closely monitored as part of AstraZeneca's ongoing surveillance efforts for the important potential risk of nervous system disorders, including immune-mediated neurological conditions.

Rapporteur assessment comment:

The MAH provided an updated cumulative review of cases of ADEM, including a BCC classification and causality assessment according to the WHO-UMC. Cumulatively, **80 serious cases of ADEM**, including 56 medically confirmed cases, have been identified. About 46% if the cases have been reported from the interval period.

Review of the cases: Compared to the information available in the previous PSUR, 14 papers including 23 cases of ADEM were published in the **literature** (i.e. 12 in 2022 and 2 in 2021). These include several well documented cases, among which **3 cases classified with a *BCC Level 1*** by the MAH:

[redacted] ***Mumoli et al 2021]*** : this case describes occurrence of **ADEM anti-MOG antibody-positive** in a **45 years subject** (gender unknown) without any familiar and personal history of neurological diseases. The subject developed reactogenicity events within 12 hours after administration of Dose 1 Vaxzevria. First signs of ADEM occurred **7 days after vaccination** (i.e. backpain, numbeness and hypoaesthesia of knees, thighs and perineum, followed by urinary retention the day after). The subject was hospitalised because of deterioration of clinical status and extensive neurological examinations

and laboratory work-up were performed. Due to MRI features (including follow-up at 3 months), CSF findings (including stable anti-MOG titer at 3 months), and negativity of CNS infections, a diagnosis of anti-MOG antibody-positive ADEM was made. The authors concluded that the close temporal relationship with vaccination and onset of clinical and neuroradiological features is highly suggestive of anti-MOG ADEM related to ChAdOx1nCov19 vaccine. However, it is difficult to assess whether the vaccination was causal or coincidental although many potential other causes have been excluded.

The *MAH* classified the case as *BCC Level 1 with an unlikely causality* due to rapid TTO (within 12 hours of vaccination). The TTO for ADEM was erroneously based on the onset of the reactogenic events.

[redacted] **[Australia ; Permezel et al 2022]** : this article describes a **fatal case of ADEM** in a poly-medicated **63/M** with a history of vertigo (likely due to vestibular dysfunctional), insulin-dependent type II diabetes mellitus with ischemic heart disease, atrial fibrillation, iron deficiency anaemia, dyslipidaemia and anxiety. First signs and symptoms of ADEM developed **12 days after the 1st dose** of Vaxzevria before neurological deterioration in the first adays after admission. The patient died 20 days after hospitalisation. Based on the rapid clinical and radiological progression, a diagnosis of ADEM was favoured over CNS lymphoma. ADEM was diagnosed by ante mortem neuropathology and confirmed by post-mortem autopsy. Various infectious causes and malignancy were excluded. There was no evidence of meningitis, vasculitis or encephalitis. The cause of death was registered as ADEM in the setting of recent Astra Zeneca COVID-19 vaccination.

The *MAH* classified the case as *BCC Level 1 with a causality assessment of possible with limited information* (see Table 133 of PBRER).

[redacted] ***Sivji et al 2022]*** : this case describes occurrence of **ADEM** in a **45/F** who was previously asymptomatic. The symptoms started **3 weeks after 2nd dose** of Vaxzevria. There were multifocal large lesions (tumefactive demyelination). Radiological results were in favour of demyelination. CSF cytology was negative for atypical cells. Infections were ruled out by extensive infective panel for bacteria, fungi, and viruses in CSF. Vasculitis work up was negative. Causes of recurrent demyelination such as NMOSD (including AQP-4 and MOG antibodies) and multiple sclerosis were ruled out. Autoimmune encephalitis and paraneoplastic antibody panel were also negative. The subject had good improvement with steroids, although it required slow taper. The authors concluded of a rare case of ADEM noticed after Vaxzevria vaccination.

The *MAH* classified the case as *BCC Level 1 with a causality assessment of possible with limited information* (see Table 133 of PBRER).

Overall, the PRAC Rapporteur agrees with the **BCC classification level 1** for the **3 cases**, (i.e. absence of recurrence/relapse of illness was observed up to 3 months, and in the fatal case, ADEM diagnosis was confirmed by ante-mortem biopsy and autopsy). Regarding the causality assessment:

- the **fatal case** [redacted] suggests a **possible causal association** (i.e. plausible TTO, exclusion of some alternate causes, patient with several co-morbidities and poly-medicated) and,

- the **2 other cases** [redacted] suggest a **probable causal association** (i.e. plausible TTO, extensive work-up to exclude other possible causes, patients without any familiar and personal history of neurological diseases or previously asymptomatic)

In addition to this, **26 case of *BCC Level 2*** were identified by the MAH, including **22 cases** assessed as with a **possible causal relationship** as they occurred within the risk period of 2-42 days. Most of the possible cases were considered with limited information (n=16) and confounders/alternate possible explanations could be identified in 6 cases. However, most of the cases were from the literature (n=16) and include several well documented reports (see Table 134 of PBRER).

For example, **6 cases from the EU** were **published** and are assessed by the PRAC Rapporteur with an **at least a possible causal association** with Vaxzevria:

Ancau et al (2022) [redacted] published **3 cases** of an haemorrhagic variant of ADEM, named acute **hemorrhagic encephalomyelitis (AHEM)** after Vaxzevria. All 3 cases were serious and 1 had a fatal outcome [redacted] **fatal case in 55/F** [no autopsy], [redacted] in **61/M**, and [redacted] in **25/F**). In all 3 cases, first symptoms occurred **within 9**

days, (extensive) work-up excluded several viral and bacterial infections, COVID-19 test was negative and screening for auto-immune glial- and neuronal-targeting antibodies as well as paraneoplastic autoantibodies proved negative. The fatal case lacked current history of medical diagnoses just prior to events, the 61/M had a history of hypothyroidism and polymyalgia rheumatica and medical/family/past history was not available for the 25/F subject.

Escola et al (2022) [redacted] described 1 case report of **MOG Ab-associated encephalomyelitis 9 days after the 1st dose** of Vaxzevria in a **43/F** subject with unremarkable medical history, except for migraine. This case reported an atypical presentation of MOG Ab-associated encephalomyelitis that mimic bacterial infection. An autoimmune disorder was suspected and bacterial meningomyelitis was considered the main differential diagnosis. However, extensive infectious evaluation was performed for over 1500 pathogens and was found to be negative. Of note, the subject exhibited a low anti-Sars-CoV-2 serum titre. The 2nd dose for vaccination was an mRNA vaccine and no relapse of symptoms was observed. The PRAC rapporteur considered this case of ADEM as **probably causally related** with Vaxzevria vaccination.

Rinaldi et al (2022) [redacted] presented a case of **ADEM** in a **45/M** without any previous neurological history [redacted]). The TTO was **12 days** after vaccination. Serology panel was negative for recent infection but positive IgG were detected for multiple viruses known to produce latent infection (i.e. adenovirus, herpes simplex 1, HHV6, cytomegalovirus, EBV VCA, EBNA, parvovirus B19, toxoplasma, and VZV). Of note, AQP-4 antibodies were negative, but a positivity to anti-MOG was confirmed. Finally, the authors described that a 4-month follow-up showed complete recovery and no relapses, suggesting a monophasic disease course. It is therefore unclear to the PRAC Rapporteur why this case has not been considered as BCC Level 1. Moreover, as recent infections have been excluded, the case may be considered with a probable causality assessment.

Finally, Simone et al (2021) [redacted] described a case of **ADEM associated with MOG Ab** in a **51/F** subject with no significant medical history and with a negative SARS-CoV-2 PCR test [redacted]. Adverse events occurred **2 weeks** after COVID-19 vaccination with a viral vector. CSF analysis showed lymphocyte pleocytosis, negative oligoclonal bands, normal synthesis rate and positivity for anti-MOG-IgG antibody. Borrelia IgM antibodies was positive in serum but Borrelia-PCR was negative in serum and CSF. Autoimmunity associated with Borrelia infection is a confounder leading to or associated with MOG.

Clinical pattern: Overall, the analysis of PM cases did not identify any particular clinical pattern for cases that occurred after Vaxzevria vaccination. Some cases were associated with positive MOG-antibody, whereas other cases were not.

O/E analysis: the updated analyses provide similar results to those presented in the previous PBRER. Briefly, the O/E analysis using BCC Level 1-3 cases did not yield a ratio significantly greater than 1 for any of the risk windows (14 days, 30 days, 42 days), nor for the different stratifications (i.e. age/gender/region).

ROR analysis in EVDAS: a disproportionality reporting if ADEM was observed with Vaxzevria (i.e. ROR of 1.06). Of note, in an updated analysis with a DLP of 14/10/2022, the PRAC Rapporteur identified a similar disproportionality for Vaxzevria (i.e. ROR[-] of 1,10; ROR of 1,39; n=77 PT ADEM), but also overall for all COVID-19 vaccines (i.e. ROR[-] of 1,27; ROR of 1,45; n=299 PT ADEM).

Epidemiological study: at this stage, no well-designed observational studies assessing the risk of ADEM after Vaxzevria is available. Netravathi et al 2022 performed an observational comparative analysis study in a tertiary care centre in India. The study consists in a case series analysis (period from May to Dec 2021) of patients with different CNS demyelinating disorders presenting within 6 weeks of vaccination against COVID-19 versus controls (i.e. patients previously diagnosed with 1 CNS demyelination disorder or subjects not vaccinated within 6 weeks of the demyelination). The authors suggest that demyelination disorders in vaccinees have a different presentation than in controls (e.g. in term of MOG-antibody positivity). However, the study remains descriptive and has too many limitations to allow drawing any strong conclusion.

Mechanism of action: several hypotheses were made but the exact mechanism of action remains to be elucidated.

Conclusion: The updated review of PM data, O/E analysis and literature **confirmed a potential signal of ADEM after Vaxzevria**. This is mainly triggered by several well-documented cases of BCC Level 1-3 suggesting an at least possible causal association with Vaxzevria; and more particularly 3 new cases of BCC Level 1 including one possible case with a fatal outcome and 2 probable cases.

However, O/E analysis remains unconclusive considering its limitations (i.e. cases of BCC L1-3 vs all cases, risk window including 0-2 days post vaccination, low number of cases when stratified by age and gender etc.).

As previously stated, ADEM is an exclusion diagnosis which makes the interpretation of spontaneous reports challenging, as well as the conduct of O/E analysis. It should be highlighted that the updated cumulative review of ADEM cases identified 19 cases out of 80 which fulfilled BC level 5 criteria. This means that ADEM diagnosis was excluded for almost 25% of cases reports.

At this stage, more robust epidemiological data are missing to further evaluate the association.

In conclusion, as a warning related to Neurological events is already included in section 4.4, an update of the EU-PI is considered not needed at this stage. **However, ADEM should continue to be carefully monitored. A discussion of ADEM should be provided in the next PBRER, including but not be limited to:**

(i) an updated cumulative review of cases of ADEM,

(ii) an updated literature review, with a focus on new relevant epidemiological studies,

(iii) a discussion on the need to update the PI and/or RMP.

Moreover, the MAH is requested to carefully review the evaluation of cases of ADEM as discrepancies regarding the BCC evaluation (e.g. case [redacted] classified as BCC Level 2 whereas a 4-month FU suggests a monophasic disease course) and WHO-UMC causality assessment (e.g. case [redacted] assessed as unlikely due to incorrect TTO) have been noticed.

[***Request for next PBRER***]

2.3.8. Important potential risk – Vaccine-Associated Enhanced Disease (VAED) / Vaccine-Associated Enhanced Respiratory Disease (VAERD)

Please note that VAED/VAERD data is not reproduced here (Section 16.3.1.3. of the PBRER).

Summary of data

Interval Period: During the interval period covered by this report, **555 events from 519 cases** (278 initial and 241 follow-up) were retrieved under this AESI concept, which includes Pneumonia (196), COVID-19 pneumonia (135), Coagulopathy (66), Respiratory failure (48), Breakthrough COVID-19 (26), Acute respiratory failure (23), Multiple organ dysfunction syndrome (20), Pneumonitis (19), Organ failure (7), Cytokine storm (4), Autoimmune myositis (3), Pulmonary haemorrhage (3), Acute lung injury (1), Cytokine release syndrome (1), Immune-mediated myositis (1), Mechanical ventilation (1), Vaccine associated enhanced respiratory disease (1).

Among these 519 cases, the majority were from spontaneous sources (492, 94.8%), followed by non-interventional studies (14, 2.7%), literature (11, 2.1%), and AZ-sponsored clinical trials (2, 0.4%). Of these 519 cases, 321 cases (299 serious and 22 non-serious) were medically confirmed with the use of VAXZEVRIA. There were 210 (40.5%) case reports from elderly vaccinees, 274 (52.8%) from adult

vaccinees, and age was unknown in 35 (6.7%) vaccinees. The outcome of potential VAED/VAERD events was fatal in 136 of the total 519 (26.2%) cases reported during the interval period.

Cumulative data: There have been **2139 case reports** of potential VAED/VAERD which included 2238 events. These events include Pneumonia (911), COVID-19 pneumonia (380), Coagulopathy (376), Respiratory failure (188), Pneumonitis (104), Multiple organ dysfunction syndrome (93), Acute respiratory failure (75), Pulmonary haemorrhage (29), Breakthrough COVID-19 (26), Organ failure (15), Cytokine storm (12), Autoimmune myositis (5), Mechanical ventilation (5), Vaccine associated enhanced disease (5), Immune-mediated myositis (4), Acute lung injury (3), Cytokine release syndrome (3), Coronavirus pneumonia (1), Cytokine increased (1), SARS-CoV-2 sepsis (1), Vaccine associated enhanced respiratory disease (1).

Among these 2139 cases, the majority were from spontaneous sources (2077, 97.1%), followed by non-interventional studies (30, 1.4%), literature (28, 1.3%), and AZ-sponsored clinical trials (4, 0.2%). Of these 2139 cases, 1044 cases were reported from females and 1052 from males; and in the remaining 43 cases, gender was unknown. Among total cases, 997 (941 serious and 56 non-serious) were medically confirmed cases with the use of VAXZEVRIA. There were 839 (39.2%) case reports from elderly (≥65 years of age) vaccinees, 1133 (53%) from adult (18 - 64 years of age) vaccinees, 1 from a paediatric vaccinee, and age was unknown in 166 (7.8%) vaccinees. In 415 of the 2139 cases, the outcome of events was reported as fatal.

Literature: A total of 75 (64 from Embase and 11 from InsightMeme) search results were obtained. Of these, none identified any new safety information or discussions of the mechanism of action relevant to the review of this topic.

Summary: On review of 519 cases of VAED/VAERD received during the reporting period, a majority (459 out of 519, 88.4%) of them were reported as serious, of which 299 cases were medically confirmed, and 136 out of 519 (26.2%) cases reported fatal outcomes. These cases had insufficient information on dose latency, medical history, concomitant medications, baseline medical condition prior to vaccination, clinical course, diagnostic and etiologic workup, and storage and transport conditions of the vaccine, which precluded a proper causal assessment. No hypothesized mechanism/pathways have been identified to date. No new safety information on this topic was identified through the review of the literature.

MAH's Conclusion

Based on evaluation of the available data during this reporting period and considering the cumulative experience, there is **insufficient evidence of a reasonable possibility** of a causal association between VAED/VAERD and VAXZEVRIA.

In conclusion, it is AstraZeneca's opinion that no changes to the VAXZEVRIA CDS or RMP are warranted based on the review of currently available information.

Since the concept of VAED/VAERD is an Important Potential Risk and an AESI with VAXZEVRIA, AstraZeneca recognizes the need for surveillance and will continue to closely monitor the reported events of VAED/VAERD.

Rapporteur assessment comment:

During the interval period covered by this report, **555 events from 519 cases** (278 initial and 241 follow-up) were retrieved.

Cumulatively 2139 case reports of potential VAED/VAERD were identified (2238 events). The 5 most frequent events were Pneumonia (911), COVID-19 pneumonia (380), Coagulopathy (376), Respiratory failure (188) and Pneumonitis (104).

The MAH concludes that there is insufficient evidence of a reasonable possibility of a causal association between VAED/VAERD and VAXZEVRIA. **This is endorsed**.

The MAH will continue to closely monitor the reported events of VAED/VAERD. **This is noted.**

No new safety information emerged during the reporting interval.

2.3.9. Other identified risks not categorised as important – Reactogenicity

For the reporting period, a total of 79137 cases involving 218686 events of reactogenicity were identified from the Safety database. Of these 79137 cases, there were 2481 serious and medically confirmed initial cases of reactogenic events with VAXZEVRIA. Of the 2481 cases, 1549 (62.5%) occurred in females, 846 (34%) in males, and 86 (3.5%) were of unknown gender. Of these 2481 cases, the distribution of the reactogenic events were as follows: Pyrexia (1234), Headache (1026), Myalgia (591), Fatigue (496), Nausea (352), Chills (344), Malaise (313), Arthralgia (270), Vomiting (318), Injection site pain (53), Lymphadenopathy (51), Injection site erythema (09), Injection site swelling (13), Injection site warmth (06), Injection site pruritus (0) and Injection site bruising (1).

Cumulatively, a total of 501840 cases of reactogenicity were identified from the global safety database. Of these 501840 cases, there were 13940 serious, medically confirmed cases of reactogenic events with VAXZEVRIA. Of the 13940 cases, 9663 (69%) occurred in females, 3998 (29%) in males, and 279 (2%) cases were of unknown gender. Of these 13940 cases, the distribution of the reactogenic events were as follows: Pyrexia (6655), Headache (6498), Myalgia (2909), Fatigue (2704), Nausea (2456), Chills (2368), Malaise (1797), Arthralgia (1784), Vomiting (1777), Injection site pain (405), Lymphadenopathy (301), Injection site erythema (71), Injection site swelling (53), Injection site warmth (25), Injection site pruritus (11) and Injection site bruising (04).

Reactogenicity is considered appropriately described in the COVID-19 VACCINE ASTRAZENECA CDS. A review of the safety information identified during the reporting period, and also taking into account the cumulative experience did not change the current understanding of this topic.

Rapporteur assessment comment:

Since launch, a total of **~1,2 million AEs of reactogenicity** (did not find this info in current PBRER) were reported in 501840 cases. These include 218686 events reported during the period covered by this PSUR#3. Serious medically confirmed cases involved mainly women (i.e. 69% cases in females vs 29% in males) and presented a **reactogenicity profile similar to that described in the PI**.

In conclusion, data provided by the MAH, as well as found in the literature did not raise any new safety issue. The reactogenicity profile of Vaxzevria is considered as appropriately described in the PI.

Reactogenicity do not need to be further discussed through PBRERs unless significant new safety information is identified.

2.3.10. Other identified risks not categorised as important – Tinnitus

Please note that data on Tinnitus is not reproduced here (See Sections 15.2.1 and 16.3.4.2 of the PBRER).

Summary of data

A cumulative search of the AstraZeneca Global Patient Safety Database through 30 April 2022 was conducted for AE reports of Tinnitus in association with the use of VAXZEVRIA.

In clinical studies: An imbalance between VAXZEVRIA and placebo is noted in the US study (D8110C00001), for tinnitus and VAXZEVRIA (28 [0.1%] versus 3 [<0.1%]); randomization ratio was 2:1). Out of the 28 events reporting Tinnitus in the AZD1222 arm, 10 reported having the event resolved within 7 days after event onset, 6 resolved after a longer time (8-78 days), 1 was resolving and 11 events had not yet resolved at the time of reporting.

In AZ Global Safety Database: 7442 cases reporting an AE of Tinnitus were retrieved. A majority of the events were reported within 3 days (65%) and within 7 days (78%) after vaccination (any dose). Of these, 12 reported a recurrence or worsening (interpreted as rechallenge), and of those, 9 cases reported a risk factor or a confounding factor. However, due to the recurrence and temporal relationship to both doses, causality with VAXZEVRIA cannot be excluded.

In regards the AE duration, 12.6% of 7442 cases reported outcomes of recovered or recovered with sequelae. Of those 84% of the cases recovered within 7 days and occurred within the reactogenicity period. Of note, 66.3% of the total number of cases report the event as "Not recovered", although, follow-up information is rarely provided. An O/E analysis showed that the observed events were significantly less than the expected events for all age, sex stratifications, and risk windows.

The medical/scientific literature review revealed one new case report with a temporal association with VAXZEVRIA, yet an alternative explanation for the event (glaucoma) was observed. With regard to mechanism of action for COVID-19 vaccines and tinnitus, the authors considered it undetermined and unconfirmed. Though, potential pathophysiological mechanisms discussed included molecular mimicry, autoimmune reaction, and anxiety- related reaction.

The quantitative signal searches from external databases (EVDAS and WHO VigiBase) for VAXZEVRIA - Tinnitus shows disproportionate reporting.

Literature (mechanism of action): Based on the available literature (14 relevant articles retrieved), the precise mechanism of action is still not clear, however, some possible mechanisms of action were proposed by the authors, such as:

- A hypersensitivity reaction causing an abnormal autoimmune response; mediated by circulating immune complexes or cytotoxic vestibule-cochlear autoantibodies which can lead to a localised inflammation that damages the inner ear microvessels, or a vasculitic event with subsequent localised damage to the cochlea. (Ciorba et al 2018, Shamriz et al 2018, Oldstone 2014, Ahmed et al 2021, Parrino et al 2021, Garg and Paliwal 2021, Pisani et al 2022 and Di Mauro et al 2022).
- An immunisation anxiety-related reaction is also postulated, as anxiety has also been related to the severity and persistency of Tinnitus. (Elarbed et al 2021, Parrino et al 2021, Pisani et al 2022, Gold et al 2020).
- Molecular mimicry, considering a cross reactivity between anti-spike SARS-CoV-2 antibodies and otologic antigens, plus hepta-peptide resemblance between the coronavirus spike glycoprotein and human proteins. The anti-spike antibodies may potentially react with antigens anywhere along the auditory pathway and initiate an inflammatory reaction involving the tympanic membrane, ossicular chain, cochlea, cochlear vessels, organ of Corti, etc. (Kanduc and Shoenfeld 2020, Tseng et al 2021, Vojdani et al 2020, Ahmed et al 2021, Pisani et al 2022, Garg and Paliwal 2021, Wichova H et al 2021).
- Autoimmune inner ear disease also must be considered in the differential diagnosis, which may have increased the likelihood of a dysregulated autoimmune response, although it typically differs in clinical presentation. (Medina et al 2022, Parrino et al 2021, Ciorba et al 2018).

Despite these possible mechanisms of action, the authors have also suggested the review of pre-existing history of autoimmune disorder and anxiety which have been related to the severity and persistency of Tinnitus (Elarbed et al 2021, Pisani et al 2022, Ahmed et al 2021, Parrino et al 2021). This also includes

underlying infections, such as COVID-19 (Di Mauro et al 2022), or a history of glaucoma, thrombosis, or vascular conditions (Ahmed et al 2021).

MAH's comment: AstraZeneca acknowledges the authors' views and suggestions concerning the mechanism of action. However, any further exploration of the hypothesized mechanisms in mechanism-based studies or demonstration of a conclusive mechanism could not be identified and thereby any specific mechanism of action for Tinnitus following COVID-19 vaccination remains speculative.

MAH's conclusion

Based on the evaluation of currently available information from various sources, AstraZeneca considers that there is a reasonable possibility of a causal association between VAXZEVRIA and tinnitus. VAXZEVRIA CDS Section 4.8 (undesirable effects) is updated to include 'Tinnitus' during this reporting period (01 July 2022). A review of the safety information identified during the reporting period, and also taking into account the cumulative experience did not change the current understanding of this topic.

It is AstraZeneca's opinion that this topic is adequately described in the updated VAXZEVRIA CDS and will no longer discuss it in future PBRERs, unless significant new safety information arises.

Rapporteur assessment comment:

As requested by the PRAC rapporteur, the MAH presented a discussion on relevant literature on plausible mechanism of action. Several hypotheses to explain the association have been suggested but the exact mechanism of action remains to be elucidated.

An AZ Global Safety Database search retrieved 7442 cases (**DLP 30 April 2022**) reporting an AE of Tinnitus. A **majority of the events were reported within 3 days** (65%) and within 7 days (78%) after vaccination (any dose). Of these, **12 cases** reported a recurrence or worsening (interpreted as **rechallenge)**, and of those, 9 cases reported a risk factor or a confounding factor. However, due to the recurrence and temporal relationship to both doses, it is likely related with Vaxzevria.

In regards the AE duration, 12.6% of 7442 cases reported outcomes of recovered or recovered with sequelae. Of those 84% of the cases **recovered within 7 days** and occurred within the reactogenicity period. Of note, 66.3% of the total number of cases report the event as "Not recovered", although, follow-up information is rarely provided. An O/E analysis showed that the observed events were significantly less than the expected events for all age, sex stratifications, and risk windows.

Tinnitus is appropriately described in the Section 4.8 of EU-SmPC. **The MAH will no longer discuss it in future PBRERs, unless significant new safety information arises. This is endorsed**

2.3.11. Other identified risks not categorised as important – Hypoaesthesia and Paraesthesia

Please note that data on Hypoaesthesia and Paraesthesia is not reproduced here (see Section 16.3.4.3 of the PBRER).

MAH's Conclusion

Based on the evaluation of currently available information from all available sources, with particular focus on post-market data, AstraZeneca considers that there is a reasonable possibility of a causal association between VAXZEVRIA and hypoaesthesia and paraesthesia. Many of these events were co-reported with reactogenicity events. The information regarding hypoaesthesia and paraesthesia were added to the CDS and the company will continue to conduct routine pharmacovigilance activities on this safety topic. Hypoaesthesia and Paraesthesia are considered appropriately described in the VAXZEVRIA CDS (Section

4.8). A review of the safety information identified during the reporting period, and also taking into account the cumulative experience did not change the current understanding of this topic.

Rapporteur assessment comment:

A cumulative search of the AstraZeneca Safety Database (data cut-off: 12 December 2021) retrieved **10,736 cases** reporting an AE with a PT of **hypoaesthesia** (19% medically confirmed reports, 50% serious events). Approximately 48% of the events had an outcome of recovered, recovered with sequelae, or were recovering. Duration of the events was not presented. Of the 10,736 cases that reported hypoaesthesia, 1019 (9.5%) reported hypoaesthesia as a solo event.

The search retrieved **17,721 cases** reporting an AE with a PT of **paraesthesia** (16% medically confirmed reports, 43% serious events). For events with known TTO, the majority (65%) occurred on the same day or within 1-3 days following vaccination. Approximately 45% of the events had an outcome of recovered, recovered with sequelae, or were recovering. Duration of the events was not presented. Of the 17,721 cases that reported paraesthesia, 2030 (11.5%) reported paraesthesia as a solo event.

This signal was already described and assessed in the previous PBRER AR as late breaking information and section 4.8 was modified accordingly following this assessment. This was endorsed in the previous PRAC meeting.

Paraesthesia/Hypoaesthesia do not need to be further discussed through PBRERs unless significant new safety information is identified.

2.3.12. Other potential risks not categorised as important – AESI

The AESIs for the COVID-19 VACCINE ASTRAZENECA and associated PTs are listed in Appendix 7 of the PSUR. AESIs have been included for review in Section 16.3 and Appendix 8 of the PSUR (O/E Analyses).

AESI for which the O/E analysis resulted in a ratio >1 are presented in Table 9.

Table 9 - Observed versus expected analyses for AESI and Safety Concerns in the COVID-19 VACCINE ASTRAZENECA RMP –cumulative to December 2021 with rate ratio above one (built by the Assessor from Appendix 8)

Medical Concept	Observed cases	Expected cases	Risk Window (days)	Background rate/100,000 person-years	Rate ratio (CI 95%)
Anaphylaxis type reactions	11278	554.79	2	22.6	20.33 (19.95 - 20.71)
Anaphylaxis type reactions b (including unknown TTO)	16620	554.79	2	22.6	29.96 (29.5 - 30.42)
Angioedema – Hypersensitivity c	3472	2454,84	2	100	1.41 (1.37 - 1.46)
Angioedema – Hypersensitivityc (including unknown TTO)	4795	2454,84	2	100	1.95 (1.9 - 2.01)
Angioedema – Hypersensitivity c	3472	2454,84	2	100	1.41 (1.37 - 1.46)
Acute disseminated encephalomyelitis	37	25,78	14	0,15	1.44 (1.01 - 1.98)
Acute disseminated encephalomyelitis (including unknown TTO) encephalomyelitis (including unknown TTO)	68	25,78	14	0,15	2.64 (2.05 - 3.34)
Acute disseminated encephalomyelitis including unknown TTO)	73	55,23	30	0,15	1.32 (1.04 - 1.66)
GBS Overall [e](including unknown TTO)	892	776,71	14	4,52	1.15 (1.07 - 1.23)

Rapporteur assessment comment:

The following AESI had a Observed significantly > Expected : Anaphylaxis type reactions, Angioedema – Hypersensitivity, GBS and Acute disseminated encephalomyelitis. These events, with the except of ADEM, are included in Section 4.8 of the EU-SmPC. ADEM is discussed in 2.3.7.3 of this AR.

No new safety concerns were identified.

2.3.13. Missing information – Use of COVID-19 VACCINE ASTRAZENECA in pregnant and breastfeeding women / Use during pregnancy and while breastfeeding

Please note that data on Use in pregnant and breastfeeding women / Use during pregnancy and while breastfeeding is not reproduced here (Section 16.3.5.1 of the PBRER).

MAH's conclusion on Use of AZD1222 in pregnant women

In summary, the cumulative and periodic review up until 28 June 2022 of all reports of exposure to VAXZEVRIA during pregnancy did not identify any new safety concerns for the mother or the babies. The reported adverse events are similar between the pregnant and non-pregnant populations.

The results of the O/E analyses for spontaneous abortion (UK reports) suggest that observed cases are less than would be expected in the unvaccinated pregnant women.

Based on these interval and cumulative reviews of the currently available data, it is AstraZeneca's opinion that no updates to product labelling or RMP are warranted. Use of VAXZEVRIA during pregnancy remains as Missing information for the product and is closely monitored.

MAH's conclusion on Use of AZD1222 in Breastfeeding women

From the data identified during the reporting period, and also taking into account the cumulative experience, there is no new safety information or a safety concern identified with the exposure to VAXZEVRIA during pregnancy or breast feeding. Use of VAXZEVRIA in pregnant and breastfeeding women / Use during pregnancy and while breastfeeding will continue to be considered missing information for VAXZEVRIA.

Use of VAXZEVRIA in pregnant and breastfeeding women / Use during pregnancy and while breastfeeding will be primarily investigated in the ongoing non-interventional pregnancy registry study (D8110C00003) of women exposed to VAXZEVRIA immediately before or during pregnancy as part of the C-VIPER Registry Consortium. Refer to Appendix 4 for additional details.

Rapporteur assessment comment:

During the reporting period, of the total of **1403 pregnancy** case reports, there were 131 cases of spontaneous abortion (SAB), 3 cases of abortion missed, 42 case reports with abnormal neonatal outcome, 4 case reports of stillbirth, 29 case reports of premature babies, 10 case reports of foetal death, 5 case reports of sudden infant death syndrome, 13 case reports with breech presentation, and 3 case reports of ectopic pregnancy. Pregnancy outcome was not available for the majority of cases.

A total of **131 pregnancy cases resulted in spontaneous abortion**, of which 83% (109 out of 131) were reports from consumers and 17% (22 out of 131) of the reports were medically confirmed, with 71% of the reports being from the UK. O/E analysis showed that spontaneous abortions were significantly lower than expected.

Of the **1403 pregnancy cases, 1096 cases** had reported AEs in both mothers and infants. Most of the AEs reported in these cases were known reactogenicity events (Headache, Pyrexia, Fatigue, Chills, Myalgia, Nausea, Pain in extremity and Arthralgia). There were 82 cases with 218 AEs that occurred in the pediatric population, with the top 3 AEs being: Foetal exposure during pregnancy (50), Exposure via breast milk (22) and COVID-19 (10).

During the interval period, there were **32 reports** pertaining to infant exposure to VAXZEVRIA during **breastfeeding**. Overall, 3 cases were serious (of which 1 was medically confirmed). Within these 32 reports, (3 serious, 29 non-serious) there were 68 events in infants following breastfeeding. Of these 68 events, 9 were serious adverse events. Most frequent reported PT was Pyrexia.

From the data identified during the reporting period, and also taking into account the cumulative experience, no causal relationship could be established between adverse maternal and foetal outcomes and VAXZEVRIA. No safety concerns arise from exposure to breast feeding. This is endorsed.

2.3.14. Missing information – Use of COVID-19 VACCINE ASTRAZENECA in subjects with severe immunodeficiency / Use in immunocompromised patients

Please note that data on Use in subjects with severe immunodeficiency / immunocompromised patients is not reproduced here (Section 16.3.5.2 and 16.4.3.2 of the PBRER).

MAH's summary

In total, **14,928 cases** subjects with severe immunodeficiency and immunocompromised patients were in included in the AstraZeneca's post-marketing database, and 936 for the reporting period. Cases were assessed by age, sex, type of event, and outcome.

Cumulatively **120** cases had a **fatal outcome**, (22 were reported in interval period) and 1109 were hospitalised. There were 249 COVID-19 reports cumulatively, however many did not have sufficient information for complete assessment.

The review and analysis of the available literature did not highlight any particular safety concerns with VAXZEVRIA when used in immunocompromised patients. There were no articles identified with a specific reference to any new safety concerns associated with VAXZEVRIA.

In summary, the review of available data from spontaneous reports regarding subjects with severe immunodeficiency and in immunocompromised patient's did not identify an index case or other evidence of a new or emerging signal.

MAH's conclusion

This cumulative and periodic review of the Use of VAXZEVRIA in subjects with severe immunodeficiency/Use in immunocompromised patients did not indicate any new safety concerns. Overall, the review of the currently available data did not reveal any new safety information in immune-compromised individuals that has not been identified in the overall population.

Use of VAXZEVRIA in subjects with severe immunodeficiency/Use in immunocompromised patients will be investigated primarily in the ongoing non-interventional post-marketing observational study using existing secondary health data sources (D8110R00002 [US] and D8111R00006 [EU/UK]) study of subgroups exposed to AZD1222. Refer to Appendix 4 for additional details.

AstraZeneca will continue to monitor safety information in vaccinees with severe immunodeficiency and in

immunocompromised patients as part of the routine safety surveillance activities for VAXZEVRIA and take further actions as deemed appropriate.

Rapporteur assessment comment:

The review of the cases did not bring new safety information. An imbalance of cases spontaneously reported in women was previously observed and is confirmed with 73% of reports in females.

The 22 **deaths** (2.4%) reported during this period ranged from 18 to 86 years with a median of 66 years, which is similar to the age pattern observed cumulatively. The reported PTs with a fatal outcome in order of frequency (>8) were **Thrombosis with thrombocytopenia syndrome** (16), Cyanosis (16), Dyspnoea (14), Acute respiratory distress syndrome (12), Gangrene (12), Vasculitis (12), Psoriasis (10), Psoriatic arthropathy (12).

This list differs from the same list of PTs reported cumulatively, in which the most frequently reported PTs were Death (26), Headache (23), Dyspnoea (20), **Immune thrombocytopenia** (16), **Thrombocytopenia** (16), Cardiac arrest (15), Malaise (14), Cerebrovascular accident (12), Circulatory collapse (12), COVID-19 (11), Myocardial infarction (11), **Cerebral venous sinus thrombosis** (10), Photophobia (10), Pneumonia (10), Cerebral haemorrhage (9), Hemiplegia (9), Seizure (9), Vomiting (9).

In the next PSUR, the MAH should verify the PTs reported in fatal cases, especially regarding TTS and Thrombocytopenia. [*Request for the next PSUR*]

A search in the literature identified 5 relevant articles:

- Benning et al showed impaired neutralization against emerging variants in kidney transplant recipients after a two-dose vaccination using Vaxzevria, mRNA vaccine, or both. The authors concluded that additional vaccination was necessary in these patients;
- Callagen et al. studied vaccine effectiveness in solid organ transplant (SOT) recipients and found a 31% reduction in risk of death with 2 doses of Vaxzevria compared with unvaccinated individuals;
- Neagoie et al. found that 66% of patients in a cohort of allogenic transplanted patients showed a humoral response. The incidence of positive serology was lower in patients who underwent the vaccination within the first 18 months after allo-SCT;
- Osei-Boadu et al. studied side effects of the vaccines (Comirnaty and Vaxzevria) and flare up of arthritis or underlying autoimmune condition in 532 patients. Fifteen patients reported arthritis flare;
- Whitaker et al. found a reduced antibody response and vaccine effectiveness after a second dose of COVID-19 vaccine with no statistical difference between Comirnaty and Vaxzevria (around 60% VE for both vaccines).

In conclusion, the review of pharmacovigilance data and literature did not identify new safety concerns in subjects with severe immunodeficiency. The efficacy of the vaccine in this population is uncertain and alternate protective measures should be maintained.

2.3.15. Missing information (EU-specific) – Use in patients with autoimmune or inflammatory disorders

Please note that data on Use in patients with autoimmune or inflammatory disorders is not reproduced here (Appendix R3 - Section 2.3.1 of the PBRER).

Summary of data

A search in the MAH's Global Safety database identified a cumulative total of **21,591 reports** in

individuals with underlying autoimmune or inflammatory disorders (1,996 during the reporting period). There were 77% of the cases reported in females. There were **190** (0.9%) cases with **fatal outcome**.

Of the 21,591 reports, **218 (1%)** cases involved 222 events of **exacerbation/flares** of the underlying condition. Adverse events included: Ankylosing spondylitis (4), Autoimmune disorder (3), Autoimmune haemolytic anaemia (1), Colitis ulcerative (8), Crohn's disease (21), Cryoglobulinaemia (1), Henoch-Schonlein purpura (1), Inflammatory bowel disease (1), Juvenile idiopathic arthritis (1), Multiple sclerosis (6), **Multiple sclerosis relapse** (30), Myasthenia gravis (2), Polymyalgia rheumatica (2), **Psoriasis** (50), Psoriatic arthropathy (1), Raynaud's phenomenon (2), **Rheumatoid arthritis** (74), Sarcoidosis (1), Still's disease (3), Systemic lupus erythematosus (9), and Vasculitis (1).

In 33 cases (2 in the reporting period), the vaccinees considered their current flare out of pattern mainly because they had not had a flare in a long time prior to the vaccine or considered their autoimmune disease to be well-controlled. There was insufficient information to exclude alternative aetiologies.

The MAH did not provide information from the literature

MAH's conclusion

From the data identified during the interval and cumulative periods, an increased risk of exacerbation/flares of the underlying disease following vaccination was not seen. A difference in the safety profile of this population from that of the general population was not seen.

Use of VAXZEVRIA in patients with autoimmune and/or inflammatory disorders will continue to be considered as Missing Information in the EU Risk Management Plan and monitored as part of surveillance activities for VAXZEVRIA.

Rapporteur assessment comment:

A search in the MAH safety database identified **21,591 cumulative cases**, including 1,996 cases during the reporting period. The review of these new cases did not bring new safety information.

The proportion of cases in individuals with autoimmune or inflammatory underlying condition and reporting a flare of their condition remains small (1%). In some cases, the role of the vaccine cannot be excluded.

No information from the literature was provided. In the previous PSUR, the MAH identified 15 articles about safety in patients with autoimmune or inflammatory underlying condition, but none was specific to Vaxzevria.

No new important safety information came from the review of these cases.

2.3.16. Missing information – Use of COVID-19 VACCINE ASTRAZENECA in subjects with severe and / or uncontrolled underlying disease / Use in frail patients with co-morbidities (eg, chronic obstructive pulmonary disease [COPD], diabetes, chronic neurological disease, cardiovascular disorder)

The MAH provided a cumulative review in individuals identified as having severe and/or uncontrolled underlying disease or were identified as frail" – see section 16.3.5.3 of the PBRER.

MAH's Conclusion

This review of the cumulative and periodic data in individuals with frailty, severe and/or uncontrolled underlying disease and comorbidities did not revile any new safety concern. There was no increase in events seriousness (for all discussed topics) or severity. In the subjects with supplemental oxygen use

there was 2 fold increase in the number of the fatal cases reported in (5.3%) (9.7%) the current interval period (77 vs. 35 respectively) as compared to the previous PBRER. This was due to increased severity of underlying acute or chronic hypoxemia causing detrimental decrease in oxygen saturation in patients with uncontrolled pulmonary infection, COPD, bronchitis, congestive heart failure, and Covid-19.

Out of the 77 fatal cases reported during the reporting interval, 35 were follow-up reports. Of note, out of the 42 new reports received by AstraZeneca during the reporting interval, 31 cases had the onset date at an earlier point during 2021 before the start of the reporting interval, however, were not reported to AstraZeneca until later. Therefore, this increase could possibly be explained by reporting backlog for some markets.

In summary, no abnormal trends or significant new safety concerns were identified in the interval period with respect to the cumulative data. Majority of the adverse events reported in patients with frailty and/or uncontrolled underlying disease were either related or heavily confounded by patients' medical history and underlying disorders or were consistent with the known safety profile of the vaccine.

This cumulative and periodic review of currently available data from the use of VAXZEVRIA in subjects with frailty, severe and/or uncontrolled underlying diseases and comorbidities did not identify any new safety concerns.

This topic will continue to be considered missing information and will be kept under close surveillance by AstraZeneca.

Use of VAXZEVRIA in subjects with severe or uncontrolled underlying disease/Use in frail patients will be investigated primarily in the ongoing non-interventional post-marketing observational study using existing secondary health data sources (D811110R00002 [US] and D8111R00006 [EU/UK]) study of subgroups exposed to VAXZEVRIA. Refer to Appendix 4 for additional details.

Rapporteur assessment comment:

This review presented the cumulative and periodic data in individuals identified as having severe and/or uncontrolled underlying disease or were identified as frail for the following categories.

Frailty: Cumulatively, 768 cases were identified, out of which majority (77.7%) were reported in females. Of these 768 cases, 422 (54.9%) were serious; reported seriousness criteria were medically important (294), disability (109), hospitalization (65), life threatening (26), and death (88).

Hip Fracture: Cumulatively, 26 cases were reported, Of the 26 cases, 76.9% (20 cases) were reported in females and 23.1% (6 cases) were in males. Age ranged from 18 years to <65 years in 34.6% of the reports, 65+years in 65.4%.

Cachexia: Cumulatively, 198 cases were reported, 148 (74.7%) were serious, reported seriousness criteria were medially important (84), disability (33), hospitalization (52), life threatening (14), and death (10). , The remaining 50 (25.3%) reports were non serious.

Bladder Incontinence: Cumulatively, 4584 cases were reported: 67.6% (3097) in females, 30.2% (1385) in males and gender was not reported in the remaining 2.2% (100) of cases. Age ranged from 0 to <18 years in 0.1% (3) of the reports; 18 to <65 years in 65.7% (3011) cases, 65+ years in 25.6% (1172) and age was not reported in the remaining 7.9% (361) of cases. The age group of adolescent, adult and elderly and foetus (age was not specified) was reported for 0.8% (37) cases. The majority of reports (82.2%) were from consumers with the remaining 17.8% being medically confirmed.

Dementia: Cumulatively, 2802 cases were reported, 2088 (74.5%) were serious, reported seriousness criteria were medically important (1440), disability (549), hospitalization (634), life threatening (214), and death (183). , The remaining 714 (25.5%) reports were non serious.

Long term Frailty: Cumulatively, 789 cases were reported, 704 (89.2%) were serious, reported seriousness criteria were medically important (513), disability (160), hospitalization (221), life threatening (82), and death (59). , The remaining 85 (10.8%) reports were non serious.

Metastatic Cancer: Cumulatively, 789 cases were reported, 704 (89.2%) were serious, reported seriousness criteria were medically important (513), disability (160), hospitalization (221), life threatening (82), and death (59).

Supplemental Oxygen Use: Cumulatively, 2987 cases were reported, 2198 (73.6%) were serious, reported seriousness criteria were medically important (1378), disability (265), hospitalization (1000), life threatening (320), and death (251). The remaining 789 (26.4%) cases were non serious.

Palliative Care: Cumulatively, 105 cases were reported, 102 (97.1%) were serious, reported seriousness criteria were medically important (58), disability (17), hospitalization (47), life threatening (9), death (30).

Pressure Ulcers: Cumulatively, 3966 cases were reported, 2287 (57.7%) were serious, reported seriousness criteria were medically important (1869), disability (315), hospitalization (364), life threatening (91), and death (57). The remaining 1679 (42.3%) cases were non serious.

No abnormal trends or significant new safety concerns were identified in the interval period with respect to the cumulative data. Majority of the adverse events reported in patients with frailty and/or uncontrolled underlying disease were either related or heavily confounded by patients' medical history and underlying disorders.

No new important safety information came from the review of these cases.

2.3.17. Missing information – 16.3.5.4 Use of COVID-19 VACCINE ASTRAZENECA with other vaccines / Interactions with other vaccines

Please note that data on co-administration is not reproduced here (Section 16.3.5.4 of the PBRER).

A cumulative review of cases reporting AEs after vaccination with VAXZEVRIA with other vaccines, including seasonal Influenza vaccine, Herpes vaccines, Pneumococcal vaccine and Varicella vaccine was undertaken.

Co-administration with Influenza Vaccine

Reporting interval: 1297 cases, including 4288 AEs were identified (86.6% spontaneous cases, 13.7% non-interventional/post-marketing cases, 0.1% Clinical trial, and 0.2% literature).

Cumulative search: 13185 cases, including 56430 AEs were identified (90.3% spontaneous cases, 9.6% non-interventional/post-marketing cases, 0.02% Clinical trial, and 0.07% literature).

Co-administration with Herpes vaccine

Reporting interval: 2 spontaneous cases (1 fatal and 1 non-serious) were identified.

The fatal case [redacted] describes a 75-year-old female with a medical history including pleural effusion, asthma, obesity, gallstones, and seronegative arthritis. She received the Pneumococcal vaccine on 02-Oct-2002, herpes simplex vaccine on 29-OCT-2020, dose 1 of unknown COVID-19 vaccine on an unknown date, dose 2 of VAXZEVRIA on 21-APR-2021, and dose 3 of Covid-19 mRNA Vaccine Biontech on 06-NOV-2021. On 07-Nov-2021, she experienced events of COVID-19 and Feeling hot. On 19-Nov-2021, she experienced Abdominal pain. On an unknown dates, she experienced Thrombosis, Pulmonary embolism, and Chills. On 20-Nov-2021, she died from the events of Thrombosis, Pulmonary embolism,

COVID-19, Chills, Feeling hot, and Abdominal pain. An autopsy was performed. The cause of death was pulmonary embolism (confirmed at autopsy), deep vein thrombosis (confirmed at autopsy) and covid-19 (confirmed at autopsy). No additional information was reported.

MAH's Comment: Current pandemic situation of COVID-19 and vaccinee's obesity status could be considered as a contributory risk factor for COVID-19 while the age of the patient could be considered as contributory to the fatality of Thrombosis, Pulmonary embolism and COVID-19. The surgical history and the medical history of obesity could be considered as confounding factors for Pulmonary Embolism and Thrombosis. Due to limited information on the baseline health characteristics of the patient before vaccination, circumstances leading to the events, family history of the patient, possible risk factors, and clinical course of COVID-19, the evaluation did not find evidence to suggest a causal relationship between the events and VAXZEVRIA.

Cumulative search: a total 3 cases, including the two cases from the reporting interval were identified.

Co-administration with Pneumococcal vaccine

Reporting interval: 110 cases, including 305 AEs were identified (99.1% spontaneous cases and 0.9% non-interventional/post-marketing cases).

Of 4 fatal cases, two have been identified as duplicates of each other and the consolidated case is detailed below in the Varicella vaccine (Reporting interval) section. Of the remaining 2 fatal cases, one [redacted] involved a 73-year-old male with a history of autoimmune disorder, hepatitis C, and overweight. He received VAXZEVRIA on an unknown date. It was not reported when he received the Pneumococcal vaccine. During Aug-2021, he experienced Subdural haematoma. On 31-Aug-2021, he experienced Thrombocytopenia. On an unknown dates, he experienced Syncope, Fall, Contusion, Haemorrhage, Loss of consciousness, and Platelet count decreased. He died from the event of Thrombocytopenia on 31-Aug-2021. An autopsy was not performed. The cause of death was Thrombocytopenia.

MAH's Comment: The events could be in association with each other and with reported event of Platelet count decreased. Vaccinee's advanced age, medical history of possible Diabetes mellitus and Autoimmune disorder could be considered as confounding factors to the events. Due to limited information […], the evaluation did not find evidence to suggest a causal relationship between the events and VAXZEVRIA.

Cumulative search: 387 cases, including 1592 AEs, were identified (93.0% spontaneous cases, 6.7% non-interventional/post-marketing cases, and 0.3% literature cases).

Co-administration with Varicella vaccine

Reporting interval: 17 cases, including 45 AEs, were identified (100% spontaneous cases).

Cumulative search: 60 cases, including 206 AEs, were identified (93.3% spontaneous cases, and 6.7% non-interventional/post-marketing cases).

MAH's conclusion

This cumulative and periodic review of the Use of VAXZEVRIA with other vaccines did not indicate any new safety concerns.

Use of VAXZEVRIA with other vaccines will continue to be considered missing information for VAXZEVRIA. Use of VAXZEVRIA with other vaccines will be investigated primarily in the ongoing non-interventional post-marketing observational study using existing secondary health data sources (D811110R00002 [US] and D8111R00006 [EU/UK]) study of subgroups exposed to VAXZEVRIA.

Rapporteur assessment comment:

A cumulative review of cases of concomitant administration of Vaxzevria with seasonal Influenza vaccine, Herpes vaccines, Pneumococcal vaccine and Varicella vaccine was performed.

Among the co-administration subset, majority of the reported events were mainly reactions as seen with Vaxzevria alone and are mainly consistent with the known Vaxzevria safety profile. No increase in severity/frequency has been described but this will be further assessed in the PhV plan.

In conclusion, the review of spontaneous data on co-administration did not reveal any new significant information. Use of Vaxzevria with other vaccine will continue to be monitored as a missing information through ongoing PASS study.

2.3.18. Missing information (EU-specific) – Long-term safety

See Section 4.3.2 and Section 2.3.2 in Regional Appendix R3.

There are no known risks with a potentially delayed onset, with the exception of the theoretical concern of VAED/VAERD. There is currently no evidence suggesting an adverse long-term safety concern.

At 6-months follow-up from Study D8110C00001 the AEs observed were consistent with the safety findings at the primary analysis. In the AZD1222 group, a small proportion of SAEs and AESIs were reported, with no clinically meaningful findings. Overall, VAXZEVRIA remains well-tolerated up to 6 months post dose. Long-term safety will be evaluated through follow-up in ongoing clinical studies in the VAXZEVRIA clinical development programme.

Rapporteur assessment comment:

This is endorsed.

2.3.19. Other safety issue – Fatal events

The MAH provided an overview of fatal events, both cumulatively and during reporting interval. Data on fatalities is not reproduced here (Section 6.3.2 of the PBRER).

MAH's conclusion

From the review of data available during the reporting period for all fatal case reports (including sudden death) and also taking into account the cumulative experience along with the O/E analysis of fatal cases there is no new safety information identified on this topic in association with VAXZEVRIA.

Rapporteur assessment comment:

Cumulatively through 29 December 2020 to 28 June 2022, there have been **6399 fatal cases**. Out of 6399 cases, age of vaccinees was reported in 5352 cases (84%) and was unknown in 1047 cases (16%). In 2799 (52%) of the 5352 case reports, the vaccinees were aged 65 years and above. The median age of the fatal cases was 65 years. The gender distribution as reported in 6117 cases (96%) was 2780 females (45%) and 3337 males (55%).

Cumulatively out of the 6399 case reports with fatal outcome, 3935 (52%) were medically confirmed and 2464 (48%) were consumer reports. Cumulatively, **five fatal cases** [redacted] **were reported with the booster dose**, however there was insufficient information on dates of vaccination, medical history and cause of death (the only reported PT was 'death'). Of the 6399 cases, 364 (6%) were reported as sudden Death. Case reports of sudden Death (see Section 6.3.2.2 of the PBRER), are included in the overall number of cases with fatal outcome.

Cumulative O/E analyses were conducted for fatal cases, and were stratified by age group and gender where administration data was available. **O/E was significantly below 1 for all subgroups.**

Among the cases reporting fatal outcome, no specific pattern regarding underlying conditions or cause of death could be identified. **No new safety concerns were identified.**

2.3.20. Other safety issue – Lack of efficacy

The MAH provided an overview of reported cases of lack of efficacy. Data on lack of efficacy is not reproduced here (See Section 6.3.1 of the PBRER).

MAH's conclusion

Review of all the lack of efficacy reports did not demonstrate any specific trend or safety information associated with use of VAXZEVRIA. The imbalance of reporting rates during the reporting period and cumulatively is noted. Of note, 95.0% of the reports (16120/16964) during the reporting interval and 87.5% (19856/22705) of the reports cumulatively were from Austria. This is due to a local reporting system where cases from the epidemiological reporting system for COVID-19 are linked with the vaccination passport and submitted to Eudravigilance/AstraZeneca in bulk.

Rapporteur assessment comment:

Given the known limits of the vaccine effectiveness of COVID-19 VACCINE ASTRAZENECA the reported cases are to be expected and do not raise new safety concerns.

2.3.21. Health Authority requests – Hearing loss

Please note that data on Hearing loss is not reproduced here (See Section 15.2.2. of the PBRER).

MAH's summary

Sudden hearing loss is known to occur naturally at an incidence that increases with age, and with a range of acquired and inherited risk factors involved (Lin RJ et al 2012).

Of the 1719 hearing loss cases reported cumulatively through 28 June 2022, the TTO was within 28 days for 1078 (62.7%) of the case reports that reported TTO. 281 out of 1719 cases were medically confirmed. Underlying cause/confounding factors were noted in 34.9% of medically confirmed cases.

Cases were assessed by age, sex, type of event, and outcome. The characteristics of the events and of the individuals with events were as expected for the general population, including the observation of increased incidence in the elderly. No unusual trends or clusters were identified. None of the cases met WHO-UMC criteria for Certain or Probable/Likely.

Of the 1719 cases, there were 2 fatal cases, of which 1 case was medically confirmed. These cases either had limited information on the or there were presence of confounders for the occurrence of the event and fatal outcome.

Review of medically confirmed reports did not raise any new relevant safety information for VAXZEVRIA. Most of the case reports (196 [69.8%]) were considered "Possible" related to VAXZEVRIA based on the suggestive TTO. 132 (47%) case reports also had presence of other risk factors/ confounders and 64 (22.8%) cases had limited information for a complete assessment. The O/E analysis results showed observed cases of hearing loss to be significantly less than expected for all stratifications.

From the review of literature, there is no confirmed mechanism, pathway or mediator identified for the

occurrence of hearing loss in association with VAXZEVRIA.

In summary, the review of available data from spontaneous reports regarding hearing loss did not identify an index case or other evidence of a new or emerging signal.

MAH's conclusion

Based on the review of the currently available cumulative data, AstraZeneca considers that there is insufficient evidence to suggest a causal association between hearing loss and VAXZEVRIA. It is AstraZeneca's opinion that no changes to the CDS or RMP are warranted at this time. Hearing loss will continue to be monitored as part of AstraZeneca's routine surveillance activities for VAXZEVRIA. AstraZeneca will no longer discuss the topic future PBRERs, unless significant new safety information arises.

Rapporteur assessment comment:

As requested by PRAC rapporteur, the MAH presented an updated cumulative review of all medically confirmed cases of Hearing loss, including an age-stratified analysis. Additionally the MAH provided a complete review of the literature, including a discussion on possible mechanism.

Cumulative review (DLP 22 June 2022)

The MAH's databases search (HLT hearing losses) retrieved a total of **1719 case reports** (**1831 events**) of which 281(16.83%) were being medically confirmed and 1324 (77.02%) cases were reported serious. Of these 1719 cases / 1831 events:

• **Dose**: **1547 (92.7%)cases** were reported **after the first dose**; 114 (6.8%), 4, and 3 , after second dose, both doses and third dose [unknown dose in 50 cases].

Rechallenge cases: in **4 case reports** (spontaneous, medically confirmed), the vaccinees experienced Hearing loss after the first dose, and a recurrence or worsening with the second dose of vaccination. These include 1 case classified as BCC Level 3 with a WHO-UMC possible causality with confounders. The 3 other cases were classified as BCC Level 4 with unassessable or unlikely causality.

• **Age/Gender**: The age ranged from 18 to 93 years (**median: 54 years**). 1057 (61.5%) cases were reported in females.

• **TTO: median TTO was 3 days**. Among the known TTO cases; 424(34.36%), 859(69.61%), and 1078 (87.35%) cases were reported in ≤1 day, ≤10 days, and ≤28 days, respectively.

• **Reported PTs**: Among medically confirmed 298 events, **hypoacusis** (n=103, 34.5%), **deafness** (n=69, 23.15%), **sudden hearing loss** (n=43, 14.42%), **deafness unilateral** (n=33, 11.07%) and deafness neurosensory (n=28, 9.83%) were the most reported events.

Tinnitus (n=595, 9.2%) and headache (n=425, 6.5%) were the most common events that were co-reported in these cases with Hearing loss.

• **Outcome**: The outcome was reported in 28.9% (529) events as Recovered and/or Recovering, 3.8% (70) recovered with sequelae, not recovered 53.2% (975), and 2 AEs (0.1%) had a fatal outcome [unknown outcome in 13.9 % (255) events].

• **AE duration**: When known, AEs duration ranged from 0 to 348 days with a **median duration of 2 days**; 91 (72.8%) resolved within 7 days and 34 (27.2%) resolved after days.

• **Brighton Collaboration Classification Assessment**: Out of the 281 medically confirmed cumulative case reports, **8** (2.8%) cases fulfilled **BCC Level 1** criteria, **4** (1.4%) fulfilled **BCC Level 2** criteria, **6** (2.1%) fulfilled **BCC Level 3** criteria**,** 260 (92.5%) fulfilled BCC Level 4 criteria and 3 (1.1%) fulfilled BCC

Level 5 criteria.

• **WHO-UMC causality assessment** (for medically confirmed cases; n=281): causality was considered as **Possible for 196 cases.** Among these, **64 cases had risk factors/confounders** and remaining **132 cases had limited information**. WHO-UMC causality was considered as Unlikely and unassessable/unclassifiable for 31 and 54 cases, respectively.

Observed versus expected (O/E) analysis

O/E analysis parameters: (i) background IR of Sensorineural Hearing Loss of 309.86 per 100,000 persons per year (Truven Marketscan, 2019); (ii) DLP of 28 June 2022; (iii) risk window of 0-28 days; (iv) stratification by age and gender in the EEA, UK, Brazil, and Australia.

Results: **observed cases were significantly less than expected** for all cases globally and by age and gender stratifications.

Medical literature including plausible mechanism of action

The MAH identified and presented following study articles:

• A **systematic literature review** (Pisani et al 2022) on audio-vestibular events, such as sudden sensorineural hearing loss (SSNHL), tinnitus, dizziness, and vertigo after COVID-19 vaccination hypothesizes a possible autoimmune aetiology, according to the mechanism of cross-reaction. This hypothesis has been further corroborated by the collection of clinical data on patients. However, limitation of the study is the absence of RT-PCR testing to rule out COVID-19 infection.

• Several literature case reports were identified.

• Different hypotheses for a mechanism of action were described in the literature:

- Viral infection and vascular compromise,
- Auto-immunogenicity (eg, autoimmune process involving molecular mimicry, bystander activation of autoreactive T-cells that may involve the vestibulocochlear nerve)
- Biological mechanisms (eg, recent findings of the ability of SARS-CoV-2 to directly infect human vestibular hair and Schwann cells)
- Effect of synthesis of IgG

However, there is no confirmed mechanism of action for SNHL with VAXZEVRIA.

Conclusion

Overall, the review of cases (cumulative, interval and medically confirmed) shows a temporal relationship where majority (92.7%) of the cases reported after first dose and majority of the events occurred within 10 days post vaccination. Median TTO was 3 days and majority of the cases resolved within 7 days. However among 281 medically confirmed cases, 8 (2.8%) cases fulfilled BCC Level 1 criteria, 4 (1.4%) fulfilled BCC Level 2 criteria, 6 (2.1%) fulfilled BCC Level 3 criteria. The WHO-UMC case causality analysis assessed the majority (69%) of the cases as possibly related to Vaxzeria. All of these cases either had confounder or limited information. In the O/E analysis, the observed cases were significantly less than expected for all cases globally and by age and gender stratifications. The review of scientific literature did not identify any confirmed mechanism of action of hearing loss in association with Vaxzevria. Therefore it is agreed with MAH that no update to the PI or RMP are needed at this stage and Hearing loss should continue to be monitored as part of routine surveillance process.

2.3.22. Health Authority requests – Booster dosing

Please note that data on Boosting dose is not reproduced here (Section 15.2.3 of the PBRER).

MAH's summary and conclusion

Overall, the most frequently reported AEs with VAXZEVRIA booster use are consistent with the known safety profile of the vaccine, with the majority of AEs being non-serious (68.1%). The majority of unlisted AE profiling was also non-serious (56.3%), and the most frequently reported unlisted PT was "off-label use" (95) which mostly involved vaccinees receiving 3rd dose of VAXZEVRIA in countries where use of the vaccine as a booster has or had not yet been approved, and the PT "Adverse event" (70), which refer to unspecified AEs. On review of unlisted clinical AEs, no abnormal trend was identified cumulative till 28 June 2022, and in general the cases were poorly documented which is further confirmed by the fact that only 34.6% of all unlisted cases were medically confirmed overall, and additionally only 15% of serious unlisted cases were medically confirmed. Although the majority of unlisted AESIs were serious, there were relatively few unlisted AESIs reported (7.9%), and medically confirmed (21.3%). No trends for AESIs were identified when compared with the AESIs reported with primary vaccination.

A review of booster reports involving homologous and heterologous dosing with VAXZEVRIA within the vaccination regimen did not identify any new safety concerns. The nature and severity of adverse events reported with homologous or heterologous dosing did not differ from the currently known safety profile of VAXZEVRIA.

It is AstraZeneca's opinion that no changes to the CDS or the Risk Management Plan (RMP) are warranted at this time. AstraZeneca will continue to monitor adverse event reports involving booster dosing with VAXZEVRIA as part of ongoing routine surveillance activities.

Rapporteur assessment comment:

Cumulatively, through 28 June 2022, a total of **1104** reports have been received of confirmed 'booster' dosing involving VAXZEVRIA. Of the 1104 reports received, 352 (31.9%) were reported as serious and 472 (42.8%) were medically confirmed.

A total of **3741 AEs** were reported within the 1104 reports of booster dosing with VAXZEVRIA through 28 June 2022. Of these 3741 AEs, **1228 (32.8%) were reported as serious due** to the AE being considered as medially important (974, [79.3%]), the AE was reported to have resulted in disability (241 [19.6]), required hospitalization (262 [19.8]), was life threatening (85 [6.9]), and/or resulted in death (40 [3.3]).

AE were similar for homologous and heterologous dosing.

20 reports involving 30 adverse events reporting a fatal outcome with a third booster dose of VAXZEVRIA. There is currently insufficient evidence to suggest a reasonable possibility of a causal relationship between VAXZEVRIA and the fatal AEs.

A review of booster reports involving **homologous and heterologous dosing** with VAXZEVRIA within the vaccination regimen **did not identify any new safety concerns.** The nature and severity of adverse events reported with homologous or heterologous dosing did not differ from the currently known safety profile of VAXZEVRIA.

It is AstraZeneca's opinion that no changes to the CDS or the Risk Management Plan (RMP) are warranted at this time. AstraZeneca will continue to monitor adverse event reports involving booster dosing with VAXZEVRIA as part of ongoing routine surveillance activities. **This is endorsed. Cases of boosting dosing do not need to be further discussed through PBRERs unless significant new safety information is identified.**

2.3.23. Health Authority requests – Menstrual disorders

Please note that Menstrual disorders data is not reproduced here (see Section 15.2.4 of the PBRER)

MAH's summary

Cumulative review of case reports: Menstrual disorders are very common and have high incidence rates regardless of vaccination; and stress (physical or psychological) is a common aetiology. There are **20994 reports of menstrual disorder** reported globally for VAXZEVRIA. The number of reports is relatively low compared to both the number of people vaccinated and the prevalence of menstrual disorders generally (Kwak et al 2019). The **TTO median was 8 days** and most of the reports (76%) were reported within 28 days post vaccination. Most of events were reported in the age groups 35-44 (31.5%), 25-34 (23.1%) and 45-54 (22.1%).

The **most reported** menstrual disorders were **heavy menstrual blood loss (6547)**, followed by **amenorrhoea/oligomenorrhoea (5518)** and **other menstrual disorders (5356)**. Menstrual disorders can be very diverse and different per individual. Although the reported menstrual events were categorised in 9 categories, many of the reports contained multiple menstrual events and fell into multiple categories.

The most frequent co-reported AEs were known systemic and local reactions. These are very common reactions and were to be expected. Other reactions that were frequently co-reported were reactions related to the menstrual cycle, such as breast changes and mood swings.

A total **48% of menstrual disorder events** had **not resolved at the time of reporting**. It is possible that, women reported their complaints before they fully recovered which is understandable since menstrual disorders such as amenorrhoea and irregular menstrual cycle generally can take a longer time to recover.

Due to insufficient information available in these reports, these findings do not provide more insight on the possible relationship between VAXZEVRIA and menstrual disorders. In summary, the review of available data from spontaneous reports regarding menstrual disorders **did not identify an index case or other evidence of a new or emerging signal**.

Literature summary: As pointed out in Von Woon et al 2022, Laganà et al 2022, Muhaidat et al 2022 articles, **there seems to be an association between COVID-19 vaccination (regardless of type) and menstrual disorders**. The conclusion by Wang et al 2022 that is no link between menstrual disorders and COVID-19 infection but rather vaccination is plausible giving that both mRNA and adenovirus-vectored vaccines were both associated with menstrual change. Many of the literature available recommended future work to examine the potential biological mechanisms that may explain an association between COVID-19 vaccination and menstrual disorders. The design of most studies reviewed did not consider control groups, hence it is impossible to make causal inferences from them. The actual incidence rate of menstrual disorders with COVID-19 vaccination is still unclear due to problems of overestimating, underestimating and biases. However, there seem to be more calls for studies designed particularly to aid the determination of causal inference and also confirm biologic mechanisms that will adequately explain the effects of COVID vaccination on menstrual disorders.

MAH's Conclusion

Based on the review of the updated cumulative data, AstraZeneca considers that **there is insufficient evidence to suggest a causal association** between menstrual disorders and VAXZEVRIA. It is AstraZeneca's opinion that no changes to the CDS or RMP are warranted at this time. AstraZeneca will closely monitor safety information for Menstrual disorders as part of the ongoing safety surveillance activities for VAXZEVRIA.

Rapporteur assessment comment:

As requested the MAH presented an in-depth evaluation of all available data and recently published literature, including a discussion on possible mechanism. Additionally the MAH also presented a refined review of cases of rechallenge.

Cumulative review of the cases (DLP 28 June 2022)

Cumulatively**, a total of 20994 cases** have been identified and **a total of 27145 adverse events** of interest were reported:

• ***Dose***: **11748 (68.3%), 5415 (31.5%)** and 46 (0.27%) cases were **reported after the first dose, second dose** and third dose, respectively. Only 1 case was reported after both doses. This medically confirmed **rechallenge case** was reported which had a **limited information** for further assessment

• ***Age***: the **median age was 41 years**; 2148 cases (~10%) were reported in women over 50 years of age;

• ***Seriousness***: **7960 (37.9%) cases were considered serious** and **1323 (6.3%) cases were medically confirmed.** Reported seriousness criteria were mainly medically important event (85.2% of reported events), followed by disability (9.2%) and hospitalization (4.4%). The reported AE resulted in death in 2 cases;

• ***Time to Onset***: 76% of the events with known TTO were reported within 28 days post vaccination; **median TTO was 8 days**. Overall, the TTO was distributed as followed: **0-2 days (21.2%), 3-7 days (12.6%), 8-14 days (10.1%), 15-28 days (12.6%), >** 29 days (17.4%) and unknown (26%).

• ***Co-reported PTs***: The most frequently co-reported AEs were systemic AEs (i.e. reactogenicity), as well as some menstruation symptoms (e.g. breast complaints, mood swings and hot flushes; the latter can be related to menopause as well).

• ***Medical history***: The most common reported medical history were Suppressed lactation, Suspected COVID-19, Pregnancy, Disease risk factor (unspecified), Asthma, and Immunodeficiency (995 medical history reported). A total of 197 vaccinees were pregnant at the time of reporting of menstrual disorder event; and 80 vaccinees had co-reported event of abortion.

• ***Outcome***: 10012 out of 27145 events (**37%**) had **resolved/resolved with sequelae/resolving** (and 46% in medically confirmed reports); 12974 events (**48%**) not recovered at time of reporting; 2 cases reported a fatal outcome.

For cases which recovered, the **median duration of events** was **7 days**.

• ***Reported PTs***: **Heavy menstrual bleeding (6547 events, 24%)** was the most reported PT followed by **Amenorrhoea/ oligomenorrhoea (5518 events, 20%)**. 16421 (78.2%) cases reported only one menstrual disorder event, 3587 (17.1%) cases reported 2 menstrual disorder events and 986 (4.7%) cases reported 3 to 5 menstrual disorder events.

- Majority of the **heavy menstrual bleeding** events were reported in the age group of 35-44 (34%) followed by 45-54y (27%) and 25-34y (19%). For most women the duration of the bleeding was either unknown or the woman was not recovered yet (46%). However, in the medically confirmed reports 48% heavy menstrual blood loss events had resolved. **Out of 1046 events with a known duration, 760 (73%) had a bleeding duration of less than 14 days.** According to the MAH, no trend was observed in terms of concomitants medication or medical history.

- Majority of the **Amenorrhoea/oligomenorrhoea** events were reported in the age group of 35-44 years (30%) followed by 25-34y (27%) and 45-54y (19%) years. The majority of the events (52%)

had not recovered at the time of reporting, 31% resolved/were resolving, and 2% resolved with sequalae, at the time of reporting**. In 313 (46%) events of amenorrhoea/oligomenorrhoea out of 545 events, the reported duration was longer than 14 days.** Of note, 230 women had history of pregnancy, 37 were pregnant at the time of vaccination or after vaccination, 64 women had history of breast feeding, 37 and 33 women had history of endometriosis and polycystic ovaries respectively.

- All **other events** including with PTs: Menstrual disorder (3238), Vaginal haemorrhage (1880), Uterine haemorrhage (103), Menometrorrhagia (76), and Anovulatory cycle (33). Most of the events (42%) had not recovered at the time of reporting, however 41% were resolved/resolving/resolved with sequalae. **Out of 793 events with a known duration, 582 (73.4%) had resolved within 14 days of onset.**

• ***Reporting trend analysis over time***: The peak of reports received at the time when Menstrual Disorders were discussed in media suggest a media concern. However, the distribution of date of onset follows the vaccination campaign.

Literature

The MAH identified and discussed seven (7) publications on:

• A **prospective observational study** (Von Woon et al 2022) included **79 menstruating women** who logged at least three consecutive cycles, during which time they each received at least one dose of COVID-19 vaccine which included Pfizer (65 [82.3%]), Moderna (11 [14%]) and **AstraZeneca (3 [3.8%])**. The **results showed that a dose of the COVID-19 vaccine was associated with a delay to start of menstruation in the subsequent period in spontaneously cycling participants (2.3 days after dose 1; 1.3 days after dose 2).** No significant change was noted in self-reported menstrual flow in the period or withdrawal bleed following vaccination, either in spontaneously cycling participants, or in those taking hormonal contraception. No association between menstrual changes and other commonly reported side effects of vaccination, such as sore arm, fever, and fatigue.

• A **survey** (Laganà et al 2022) evaluated menstrual irregularities after the first and second doses of the COVID-19 vaccine in Italy through a survey distributed by social media [**Vaxzevria n=9**; JnJ n=3; Comirnaty n=133; Spikevax n:19]. The results showed that approximately **50% to 60% of reproductive-age women who received the first dose of the COVID-19 vaccine reported menstrual cycle irregularities, regardless of the type of administered vaccine. The occurrence of menstrual irregularities seems to be slightly higher (60% to 70%) after the second dose.** Menstrual irregularities after both the first and second doses of the vaccine were found to self-resolve in approximately half the cases within 2 months.

• A **retrospective online survey** (Baena-García et al 2022) described the prevalence of perceived premenstrual and menstrual changes after COVID-19 vaccine administration in Spain from June to September 2021. A total of 14153 women (mean age 31.5 ± 9.3 years old) who had received the full course of vaccination at least three months earlier were included in this cross-sectional study [**Vaxzevria n=2224** ; JnJ n=725; Comirnaty n=8727; Spikevax n=2476]. **The most predominant menstrual changes were more menstrual bleeding (43%), more menstrual pain (41%), delayed menstruation (38%), fewer days of menstrual bleeding (34.5%), and shorter cycle length (32%).** The study concluded that women vaccinated against COVID-19 usually perceive mild menstrual and premenstrual changes and future studies are warranted to clarify the physiological mechanisms behind these widely reported changes.

• In a **cross-sectional investigation online self-administered survey** (Muhaidat et al 2022) the prevalence and impact of menstrual abnormalities after the COVID-19 vaccination (Comirnaty n=1099; Sinopharm n=801 and **Vaxzevria n=304**) was investigated among females (2269, mean age of 34.3 ±

8.5) residing within the Middle East and North Africa during July and August 2021. **The results showed 66.3% females were having menstrual symptoms post-vaccination, thereof 46.7% after the first dose. Among the participants, 75.1% had regular menstrual cycles before taking the vaccine for the last year, and 24.9% had irregular menstrual cycles.** Vaccine type did not significantly influence the incidence of abnormalities ($p < 0.05$).

• A **prospective, active observational**, PASS (Rogers et al 2022) study reported on the incidence of adverse events (AEs), reactogenicity symptoms, menstrual changes and overall self-rated improvement in health and well-being after COVID-19 vaccination in 16265 participants registered through a website [**Vaxzevria 2 doses n=5947, 1 dose n=331**; Comirnaty 2 doses n= 4240, 1 dose n=270]. Overall **rates of women aged 18–59 reporting menstrual symptoms** in the 12 weeks after vaccination were **low (0.3%)**. Unadjusted percentages of reporting menstrual symptoms, including menstrual cycle alteration or intermenstrual bleeding (12 events), heavy bleeding (11) or painful periods/cramping (5) within 12 weeks of vaccination were higher after COMIRNATY vaccinations (0.6% after first dose, 0.4% after second dose) than after ChAdOx1 (0.2% after first dose, 0.2% after second dose). However, there was no difference between vaccines after adjusting for age in a proportional hazards model and overall cumulative rates were low. Participants reported these events as 25% mild, 54% moderate and 21% severe; none resulted in hospitalisation. The study provides reassuring data on low rates of AEs after COVID-19 vaccination.

• A **literature review** (Nazir et al 2022) using digital databases to systematically identify the studies reporting any menstrual abnormalities after the COVID-19 vaccine. A total of 78,138 vaccinated females were included in this review from 14 studies. **Of these, 39,759 (52.05%) had some form of a menstrual problem after vaccination. Menorrhagia, metrorrhagia, and polymenorrhea were the most observed problems** and the overall study-level rate of menstrual abnormality ranged from 0.83% to 90.9%. The review concluded that further prospective cohort studies are needed to identify the temporal link between menstrual cycle changes.

• A **prospective study** (Wang et al 2022) reported the associations of SARS-CoV-2 infection and COVID-19 vaccination with menstrual cycle characteristics. The study involved prospectively following 3858 pre-menopausal women in the Nurses' Health Study 3 (NHS3) living in the United States or Canada [Vaxzevria n=7; JnJ n=84; Comirnaty n=2145; Spikevax n=1282]. **Authors concluded that COVID-19 vaccination may be associated with short-term changes in usual menstrual cycle length, particularly among women whose cycles were short, long or irregular before vaccination.** These results underscore the importance of monitoring menstrual health in vaccine clinical trials. Future work should examine the potential biological mechanisms.

Additionally, the assessor found the following relevant publication on this topic:

• A global, **retrospective cohort study** (Edelman et al, 2022)[2] **of prospectively collected data** compared **vaccinated individuals** [vaccinated cohort : BNT162b2 n=9929; mRNA-1273 n=2608; **ChAdOx1 nCoV-19 n=1353**; Ad26.COV2.S n=283] with the unvaccinated group and showed **an adjusted increase in menstrual cycle length of less than one day with both first and second vaccine doses.** Individuals who received two doses of a covid-19 vaccine in a single cycle had an adjusted increase in cycle length of 3.70 days compared with the unvaccinated. **Cycle length changes did not remain in the cycle after vaccination**, except in the group that received two vaccine doses in one cycle, where cycle length changes were attenuated but still increased compared with the unvaccinated group. Cycle length changes due to covid-19 vaccination appear similar across the different vaccine types. **No differences found in menses length in any group of vaccinated individuals,**

[2] Edelman A, Boniface ER, Male V, Cameron ST, Benhar E, Han L, Matteson KA, Van Lamsweerde A, Pearson JT and Darney BG. Association between menstrual cycle length and covid-19 vaccination: global, retrospective cohort study of prospectively collected data. BMJ Medicine 2022;1:e000297. doi: 10.1136/bmjmed-2022-000297

compared with the unvaccinated cohort.

• Using a **self-controlled case-series study**, Trogstad et al. (2022)[3], observed an increased risk of heavy bleeding after COVID-19 vaccination (i.e. RR of 1.90 (95% CI: 1.69-2.13) for Dose 1; RR of 1.84 (1.66-2.03) for Dose 2). The analysis was performed in a cohort of 5688 women aged 18-30 years (Comirnaty n=3295; Spikevax n=2020; No vaccine n=478). Increased risk after vaccination was also observed for other menstrual disturbances. The authors concluded that they found a **significant increase in menstrual disturbances after vaccination**, particularly for heavier bleeding than usual, longer duration and for short interval between menstruations. Mechanisms underlying these findings may involve bleeding disturbances in general, as well as endocrine alterations.

Conclusion

Overall, the review of cases shows a temporal relationship where majority of the events occurred within 28 days post vaccination. Median TTO was 8 days. Majority of the heavy menstrual bleeding (80%) and Amenorrhoea/oligomenorrhoea (76%) events were reported in the age group of 25-54 yrs similar to overall menstrual disorders combined. Among cases which recovered, the median duration of symptoms was 7 days and majority of the AEs resolved within 8 days. Cases mainly occurred after the first dose and there was only 1 case of rechallenge, with limited information. Considering the TTO, a causal association cannot be ruled out. However, there was not a clear pattern of reported disorders. Heavy menstrual bleeding, amenorrhoea/oligomenorrhoea and other menstrual disorders were reported more or less in a similar proportion (i.e. 6547 AEs, 5518 AEs and 5378 AEs respectively).

In the literature, several surveys and studies suggested that COVID-19 vaccination was associated with menstrual disorders. Here again, the studies relate to a wide range of menstrual disorders. Moreover, the studies present some limitations and biases, and mainly include mRNA vaccines. For example, the study of Trogstad (2022) which showed a significant increase in heavy menstrual bleeding did not include Vaxzevria vaccinated women.

In conclusion, available data cannot confirm nor rule out a possible association between menstrual disorders and Vaxzevria. More particularly, the level of evidence from the literature is not sufficient at this stage to support an update of the PI. Safety information for Menstrual disorders will be closely monitored by the MAH as part of the ongoing safety surveillance activities for Vaxzevria, which is supported. **Cases of menstrual disorders do not need to be further discussed through PBRERs unless significant new safety information is identified. More relevant information is expected to be provided from the update review of the literature. [*Request for the next PBRER*]**

2.3.24. Health Authority requests – Myocarditis

Please note that myocarditis data is not reproduced here (Section 15.2.5 of the PBRER).

MAH's summary

Of 761 Myocarditis cases, no gender preponderance was noted between males (50.9%) and females (49.1%). The majority of events (48.3%) were for vaccinees between the ages 40 to 64 years. The majority (65.0%) of cases were reported after Dose 1 as compared to Dose 2 (22.7%) and Dose 3 (0.8%). Out of 763 events from 761 reports, 99.9% events were serious with 2.8% resulting in death. There have been 266 (214 initial reports and 52 follow-up) additional case reports of Myocarditis compared to previous PBRER (with DCO December 2021 that discussed 593 cases). Of 761 case reports, 1.6% fulfilled BCC 1 criteria, 6.8% fulfilled BCC 2 criteria, no case fulfilled BCC 3 criteria, 51.2% fulfilled

[3] Trogstad L, Laake I, Robertson AH, Mjaaland S, Caspersen IH, Juvet LK, Magnus P, Feiring B. Increased Occurrence of Menstrual Disturbances in 18- to 30-Year-Old Women after COVID-19 Vaccination (January 1, 2022). http://dx.doi.org/10.2139/ssrn.3998180

BCC 4, and 40.3% fulfilled BCC 5 criteria. WHO-UMC causality assessment for Myocarditis was performed for 64 cases (BCC levels 1, 2 and 3 cases), and none of the cases met WHO-UMC criteria for "Probable" (Likely) or "Certain". A total of 45.3% were considered as possibly related, 21.9% were considered as unlikely related, 25.0% were considered as Unassessable/Unclassifiable and 7.9% were considered as Conditional/Unclassified. In addition, 34.4% were identified with relevant risk/confounding factors and 65.6% cases had limited information for a comprehensive causal assessment. There were no case that reported a recurrence/worsening of myocarditis with a subsequent dose of VAXZEVRIA. There were no index cases identified from review of case reports. Observed vs expected analysis suggests that observed number of cases regardless of age, gender, dose and various risk windows did not exceed the expected number of cases. A review of literature suggests various hypothesized mechanisms for development of Myocarditis mainly in association with mRNA vaccines.

MAH's conclusion

From the data identified during the reporting period and also taking into account the cumulative experience, it is AstraZeneca's opinion that currently there is insufficient evidence of a causal association between myocarditis and VAXZEVRIA. AstraZeneca did not find evidence of a new or emerging signal for Myocarditis to suggest a need to update the VAXZEVRIA CDS or RMP. Myocarditis is an AESI for VAXZEVRIA and will continue to be kept under close surveillance by AstraZeneca.

Rapporteur assessment comment:

Cumulatively, **761 cases of myocarditis** have been reported, of which 266 cases (214 initial, 52 follow-up) were received during the current reporting interval. Out of the 761 cases, 65% occurred after dose 1, 22.7% after dose 2 and 0.8% after dose 3 (11.4% unknown). There were no cases with a positive rechallenge (i.e. recurrence/worsening of myocarditis after dose 2 or 3). All cases were serious and 29% of the cases were medically confirmed.

Approximately half of the cases (52%) were reported from the UK. The ratio female (49%) to male (51%) was almost equal. The median age was 48 years (range: 10-95 years). Most cases with known age were reported in vaccinees aged 18 to 40 years (33%) and 41 to 64 years (48%). In 50% of the cases, **time to onset** (TTO) was unknown; from cases with available data, 67% had a TTO within the risk window of 2 to 42 days (median TTO: 12 days; TTO range: 0 to 344 days). The PT 'myopericarditis' was reported in 59 cases.

The MAH classified the cases using the **Brighton Collaboration Classification (BCC) case definition for myocarditis**. Out of the 761 case reports, 12 (1.6%) fulfilled level 1 criteria, 52 (6.8%) fulfilled level 2 criteria, none fulfilled level 3 criteria, 390 (51.2%) fulfilled level 4 criteria and 307 (40.3%) fulfilled level 5 criteria. As requested, the MAH performed **causality assessment according to WHO-UMC criteria** for the 64 myocarditis cases fulfilling BCC Level 1, 2 or 3. Twenty-nine (29) cases were classified as 'Possible' (of which 8 with risk factors/confounders and 21 with limited information), 14 cases as 'Unlikely', 5 cases as 'Conditional/Unclassified', and 16 cases as 'Unassessable' (of which 7 with risk factors/confounders and 9 with limited information). Out of the 29 cases with a possible causal association, 3 cases fulfilled BCC level 1 criteria and 26 cases fulfilled BCC level 2 criteria for diagnostic certainty of myocarditis.

Twenty-one (21) of the 761 cases (2.8%) had a **fatal outcome**. Four fatal cases occurred within the risk window of 2-42 days, of which 2 fulfilled BCC Level 4 criteria and 2 BCC Level 5 criteria. Outcomes in the remaining case reports were: Not Recovered (39%), Recovering (19%), Recovered (13%), Recovered With Sequelae (5%), and Unknown/missing (22%).

The MAH conducted an **O/E analysis** for all reported cases of myocarditis with stratifications by risk window (7, 14, 21, 42 days), age group, gender and dose. Observed cases occurred less frequently than

expected for all stratifications, except for UK males aged 18-29 years with risk window 7 and 14 days, where observed cases were more than expected without being statistically significant. The MAH's O/E analysis does not confirm the results of the SCCS study of Patone et al. (2021), who observed an increase in the risk of myocarditis within a week of receiving the first dose of Vaxzevria (discussed in the AR of PBRER02).

A **literature review** on myocarditis in association with Vaxzevria and other COVID-19 vaccines did not identify new relevant safety information. During the period under review, no new publications on relevant epidemiological studies or a conclusive mechanism of action were identified.

In conclusion, **no new safety information concerning myocarditis could be identified.** The PRAC rapporteur agrees with the MAH's conclusion that at this stage no causal relationship between myocarditis and Vaxzevria could be established. The MAH will continue to closely monitor this AESI, which is endorsed. **Cases of myocarditis do not need to be further discussed through PBRERs unless significant new safety information is identified**.

2.3.25. Health Authority requests – Sarcoidosis

Please note that data on Sarcoidosis is not reproduced here (Section 15.2.6 of the PBRER).

MAH's summary

Cumulatively through DLP 28 June 2022, a total of 68 case reports of sarcoidosis with the use of VAXZEVRIA have been received using a broad search strategy, of which 85.3% of the reported events were serious and 14.6% were non-serious. The age range was 21years to 67 years and median age was reported as and 49.4 years.30.8% of cases were medically confirmed and 69.1% were not medically confirmed.

The most common PTs reported were Cutaneous Sarcoidosis 2 (2.7%), Loefgren syndrome 3 (4.0%), Neurosarcoidosis 5 (6.7%), Pulmonary sarcoidosis 5 (6.7%), Cardiac sarcoidosis 2 (2.7%), Sarcoidosis 57 (76.0%) and Ocular sarcoidosis 1 (1.3%).

Amongst 75 events reported for sarcoidosis received cumulatively through 28 June 2022, 35 (46.7%) had a reported outcome not recovered, 16 (21.3%) for recovering/resolved, 8 (10.7%) recovered with sequeale and 16 (21.3%) had outcome unknown.

OE analysis showed that observed cases were significantly less than expected cases.

WHO UMC case causality analysis conducted for all case reports, the majority of the case reports (24 [35.3%]) were considered possible with limited information, possible with confounder (20 [29.4%]) and unassesable/unclassifiable with limited information (19 [27.9%]) related to VAXZEVRIA.

Overall, the clinical pattern of case presentation and numbers of reports are broadly consistent with what might be expected from the natural epidemiology of sarcoidosis, and no specific biological mechanism through which VAXZEVRIA vaccine could cause or contribute to the development of sarcoidosis has been identified.

MAH's conclusion

Based on the review of the updated cumulative data, AstraZeneca considers that there is insufficient evidence to suggest a causal association between sarcoidosis and VAXZEVRIA. It is AstraZeneca's opinion that no changes to the CDS or RMP are warranted at this time. The topic will continue to be closely monitored as part of AstraZeneca's ongoing surveillance activities. AstraZeneca will no longer discuss the topic future PBRERs, unless significant new safety information arises.

Rapporteur assessment comment:

Cumulatively**, 68 case** reports of Sarcoidosis with **75 events** were identified. Age ranged from 21 to 67 years (median: 49 years), 29 (42.6%) concerned male patients and 38 (55.9%) concerned female patients, 21 (31.8%) case reports were medically confirmed and 47 (68.2%) were non-medically confirmed.

64 (85.3%) of the events were serious (17 medically confirmed and 47 non-medically confirmed) and reported seriousness criteria were medically important event (45 [60.0%]), disability (15 [20.04%]), hospitalization (22 [29.3%]), life threatening (3 [4.0%]).

9 **(27.9%) were identified with relevant risk / confounding factors**, History of Sarcoidosis (11), Immunodeficiency (4), Hypertension (2) and Neoplasm/Cancer (2).

O/E analysis showed an observed **significantly < expected (O/E ratio (95% CI) 0 (0 - 0.01)**)

Literature did not contain relevant new safety information regarding Sarcoidosis and its association with Vaxzevria. There is no hypothesised mechanism for the development of sarcoidosis in association with Vaxzevria.

WHO UMC case causality analysis was conducted for all case reports, the majority of the case reports (24 [35.3%]) were **considered possible with limited information, possible with confounder (20 [29.4%]) and unassesable/unclassifiable with limited information (19 [27.9%]**).

In the previous PSUSA the MAH was asked to redo the causality assessment and provide a proper causality assessment, subsequently 44 cases were classified as possible. **Issue resolved.**

The MAH considers that there is insufficient evidence to suggest a causal association between sarcoidosis and VAXZEVRIA and that no changes to the CDS or RMP are warranted at this time. The topic will continue to be closely monitored as part of AstraZeneca's ongoing surveillance activities. AstraZeneca will no longer discuss the topic future PBRERs, unless significant new safety information arises.

This is endorsed. Cases of Sarcoidosis do not need to be further discussed through PBRERs unless significant new safety information is identified.

2.3.26. Health Authority requests – Subacute thyroiditis

Please note that data on Subacute thyroiditis is not reproduced here (Section 15.2.7 of the PBRER).

MAH's Summary

Cases were assessed by age, sex, type of event, and outcome. Of the 178 case reports of subacute thyroiditis with the use of VAXZEVRIA have been received, of which 64.6% of the reported events were serious and 35.4% were non-serious. The age range was 19 to 83 years and mean and median age was reported as 51 years and 50 years, respectively. The case reports were reported more in females 138 (77.5%) compared to males 35 (19.7%). 29.2% of cases were medically confirmed and 70.8% were not medically confirmed. Subacute thyroiditis is generally reported in the 3rd to 5th decade, and is 1.9 to 6 times more frequent in females (Fatourechi et al 2003). For the event of subacute thyroiditis, the most common PTs reported were Autoimmune thyroiditis (49), Thyroiditis (60), Thyroiditis acute (22), and Thyroiditis subacute (56).

Amongst 178 case reports for subacute thyroiditis received cumulatively through DLP 28 June 2022, 64 events had a reported outcome of recovered or recovering, the outcome of recovered with sequelae was reported in 7 case reports, and the case outcome of Not recovered was reported in 88 of the case reports. No fatal event pertaining to searched term of 'Subacute thyroiditis' was reported. The TTO was varied and

ranged from 0 to 1 day to more than 42 days and there was no trend or pattern seen. Of the 178 Subacute thyroiditis cases reported globally and included in AstraZeneca's post-marketing database, there were 118 case reports in which the TTO was within the risk window of 42 days. Underlying cause/confounding factors were noted in 9.6% of these cases.

The characteristics of the events and of the individuals with events were as expected for the general population, including the observation of increased incidence in the elderly. No usual trends or clusters were identified. None of the cases met WHO-UMC criteria for Certain or Probable/Likely. Of the 178 cases, there were no fatal cases.

The O/E analysis results for subacute thyroiditis showed observed cases to be significantly less than expected.

The majority of non-medically confirmed case reports had limited information. Of the total number of case reports, 52 (29.2%) were medically confirmed. WHO-UMC case causality assessment for majority 32 (61.5%) medically confirmed case reports was "Possible" with limited information; these cases lacked information about medical history, concomitant medications, or laboratory values and no trend was seen. However, 4 (7.7%) case reports demonstrated possible risk factors/confounders and were assessed as possible with confounders. In 6 (11.5%) cases the time to onset was outside the risk window of 42 days and therefore assessed as unlikely related to VAXZEVRIA. In 10 (19.2%) cases the time to onset was unknown and were assessed as "Unassessable".

Overall, none of the case reports raised any new relevant safety concerns for subacute thyroiditis cumulatively until DLP 28 June 2022 during the reporting period. Also, in summary, the review of available data from spontaneous reports regarding of Subacute thyroiditis did not identify an index case or other evidence of a new or emerging signal.

MAH's Conclusion

Based on the review of the available cumulative data, AstraZeneca considers that currently there is insufficient evidence of a causal association between subacute thyroiditis and VAXZEVRIA. It is AstraZeneca's opinion that no changes to the VAXZEVRIA CDS or RMP are warranted at this time. Subacute thyroiditis is an AESI for VAXZEVRIA and will continue to be closely monitored as part of AstraZeneca's ongoing surveillance activities. AstraZeneca will no longer discuss the topic future PBRERs, unless significant new safety information arises.

Rapporteur assessment comment:

Cumulatively, **178 case reports** of subacute thyroiditis with the use of VAXZEVRIA have been received, of which 64.6% of the reported events were serious and 35.4% were non-serious. The age range was 19 to 83 years and mean and median age was reported as 51 years and 50 years, respectively. The case reports **were reported more in females 138 (77.5%) compared to males 35 (19.7%).** 29.2% of cases were medically confirmed and 70.8% were not medically confirmed. For the event of subacute thyroiditis, the most common PTs reported were Autoimmune thyroiditis (49), Thyroiditis (60), Thyroiditis acute (22), and Thyroiditis subacute (56).

64 events had a reported outcome of recovered or recovering, the outcome of recovered with sequelae was reported in 7 case reports, and the case outcome of not recovered was reported in 88 of the case reports. No fatal event was reported. The TTO was varied and ranged from 0 to 1 day to more than 42 days and there was no trend or pattern seen. There were 118 case reports in which the TTO was within the risk window of 42 days. Underlying cause/confounding factors were noted in 9.6% of these cases.

The **O/E analysis** results for subacute thyroiditis showed observed cases **to be significantly less** than expected.

Review of literature did not identify any new safety information on this topic.

According to the MAH, none of the case reports raised any new relevant safety concerns for subacute thyroiditis and the review of available data from spontaneous reports regarding of Subacute thyroiditis did not identify an index case or other evidence of a new or emerging signal.

The MAH considers that currently there is insufficient evidence of a causal association between subacute thyroiditis and VAXZEVRIA and that no changes to the VAXZEVRIA CDS or RMP are warranted at this time. Subacute thyroiditis is an AESI for VAXZEVRIA and will continue to be closely monitored as part of AstraZeneca's ongoing surveillance activities **This is endorsed.**

Cases of Subacute thyroiditis do not need to be further discussed through PBRERs unless significant new safety information is identified.

2.3.27. Health Authority requests – Glomerulonephritis AND Nephrotic syndrome (including IgA Nephropathy)

Rapporteur assessment comment:

In May 2022, EMA identified a signal on 'glomerulonephritis and nephrotic syndrome' after COVID-19 vaccination after performing signal detection in EudraVigilance (EV) and after reviewing scientific literature. This signal was sent in parallel for Comirnaty, JCOVDEN and SPIVKEVAX.

At that time, a search in EV for HLT 'Glomerulonephritis and nephrotic syndrome' yielded 85 cases associated with Vaxzevria, including 4 case from the literature (15 March 2022). No disproportionate reporting was found. Eleven (11) cases were identified from 9 articles in the literature and 4 cases of ANCA-associated vasculitis. Most patients improved with treatment and three patients required dialysis.

WHO-UMC identified a safety signal of IgA nephropathy following administration of COVID-19 vaccines after screening VigiBase. A majority of the cases (88%) followed administration of mRNA based vaccines and 13% of the cases were associated with Vaxzevria.

At that time, PRAC concluded that a separate signal procedure was not warranted but asked the MAH questions to further discuss the topic. MAH's responses are discussed here-after.

Request to the MAH

The MAH is requested to submit:

- *a cumulative review of cases based on search conducted at the level of HLT "glomerulonephritis and nephrotic syndrome";*
- *causality assessments of the cases;*
- *a review of articles published during the PSUR reporting period;*
- *a discussion on the need for updating product information and/or risk management plan, and submit proposal as required.*

Additional note to the MAH: Published cases should be submitted to Eudravigilance and attempts should be made to follow up on poorly documented spontaneous cases.

Background information

The major **pathological types** of glomerulonephritis (GN) are IgA nephropathy (IgAN), membranous nephropathy (MN), membrano-proliferative glomerulonephritis (MPGN), mesangial proliferative glomerulonephritis, minimal change disease (MCD), focal segmental glomerulosclerosis (FSGS), post-

infectious glomerulonephritis, idiopathic crescentic proliferative glomerulonephritis, ANCA-associated necrotising crescentic glomerulonephritis, anti-glomerular basement membrane disease (**Error! Reference source not found.**, **Error! Reference source not found.**).

The underlying pathogenetic **mechanism** is immune-mediated (humoral as well as cell-mediated pathways may be active) followed by consequent inflammatory response. Kidney biopsy is mandatory for diagnosis (**Error! Reference source not found.**).

The **age standardized rates** in 2019 for incidence of acute glomerulonephritis per 100,000 population were 9.45 (95% uncertainty interval, 7.72 to 11.55) and the mortality rate was 0.13 (95% uncertainty interval, 0.10 to 0.16) (Guo et al 2021). IgA Nephropathy (or Berger's disease) is the most common of all glomerulonephritis with an incidence estimated to be 2.5 per 100,000 patient years (Sethi et al 2016; McGrogan 2011).

Nephrotic syndrome (NS) represents the clinical manifestations of several kidney diseases, characterized clinically by the presence of peripheral edema, heavy proteinuria, hypoalbuminemia, and hypercholesterolemia. Most adult patients with NS have primary glomerular diseases, including FSGS, MN, and MCD) (Kodner 2016; Hull and Goldsmith, 2008; Oth and Ritz 1998). Although the population incidence of NS is estimated to be approximately 3 per 100,000 person-years (Gao et al 2021).

Review of the cases

The cumulative search retrieved a total of **115 case** reports containing 130 events of Glomerulonephritis AND Nephrotic syndrome (including IgA Nephropathy). Fourteen (14) cases were identified in the literature and have been submitted to EudraVigilance. Hundred (100) of the 115 cases were serious.

The most frequent PTs (n>5) were Nephrotic syndrome (43), GN minimal lesion (16), IgAN (13), granulomatosis with polyangiitis (11), GN (9), and focal segmental glomerulosclerosis.

From the 115 cases, 95 (83%) were reported after first dose, 16 (14%) after second dose, and 4 (3%) after both first and second dose. Three cases experienced the events after the first dose and had a recurrence or worsening of the event with the second dose (**positive rechallenge**). Two of these cases were assessed as per WHO-UMC causality as possible and one as unlikely. An additional case reported information of ongoing resolution of the event of granulomatosis with polyangiitis despite administration of 2nd vaccine dose. No specific trend in case of recurrence was identified.

Out of **66 medically confirmed cases** pertaining to Glomerulonephritis AND Nephrotic syndrome (including IgA Nephropathy), **7** case reports reported a **relapse or flare-up** of pre-existing condition.

The following observations were made from a review of the 115 case reports:

- Vaccinee age was reported in 110 (95.6%) case reports and ranged 19 to 95 years (median: 58 years).
- There was no specific gender predilection; 58 (50.4%) males and 57 (49.6%) females.
- A total 66 (57.4%) case reports were medically confirmed and 49 (42.6%) were consumer reports.
- Of the total 115 case reports, the time to onset (**TTO**) from VAXZEVRIA administration to Glomerulonephritis AND Nephrotic syndrome (including IgA Nephropathy) was reported in 76 case reports and ranged 0 days to 333 days (median: 14 days). Seventy-nine percent (79%) of the cases were reported within 42 days after vaccination.
- One hundred and twelve (116 ; 86.2%) of the events were serious, including **one death** and 14 (9.3%) hospitalisations. The remaining 18 were non-serious. The fatal outcome was a event of

glomerulonephritis proliferative in 78 year-old patient with other pulmonary conditions including pneumonia, emphysema and interstitial lung disease.

- 39 cases (34%) had information on medical history and concomitant medications. The confounders were pre-existing renal conditions (13), infections (11%), pre-existing dyslipidemia, diabetes mellitus (9%), neoplasms (6%) and auto-immune disorders (7%).
- **WHO-UMC causality assessment** was performed for the 115 case reports and is as follows:
    - "Possible" with limited information for 48 (42%) case reports,
    - "Possible" with confounders for 18 (16%) case reports,
    - "Unlikely" for 22 (19%) case reports,
    - "Unassessable/Unclassified" with limited information for 15 (13%) case reports,
    - "Unassessable/Unclassified" with confounders for 12 (10%) case reports.

Fourty-six (46) PTs of **Nephrotic syndrome** in 43 cases were identified.

- 36 cases were serious with no fatal event;
- The mean TT0 was 39 days and the median TTO was 18 days;
- Out of 23 medically confirmed cases, 18 (78%) were assessed on WHO-UMC causality scale as 'Possible' based on temporal association.
- Four case report reported a relapse or flare-up of pre-existing nephrotic syndrome. Three cases presented after first dose and the fourth case after the second dose.
- Out of 23 medically confirmed cases, 8 (35%) were identified with relevant risk/confounding factors.

Overall, none of the case reports raised any new relevant safety concerns for the event of VAXZEVRIA and nephrotic syndrome.

Thirteen (13) events of **IgA nephropathy** (IgAN) were identified:

- 9 (69%) cases were serious with no fatal outcome;
- Co-reported events were haematuria or concurrent IgA vasculitis (Henoch-Schonlein purpura in 3 cases);
- 3 cases were confirmed with renal biopsy. None of the cases had information on immunotyping IgA deposits (such as IgA1) or other immunological determinant;
- In 7 cases with medical history, 4 cases had reported a past history of IgAN. In two of these cases, TTO was same day and 1 day respectively;
- TTO was reported in 10 cases. In 6/13 cases, TTO to the presenting symptom of IgAN ranged between 0-3 days. This short TTO may be possibly explained by innate non-specific immunity or pre-existing disease pathogenesis rather than adaptative immunity to the vaccine;
- In 7 out of 13 cases, the assessment as per WHO-UMC scale was considered as Possible;

In summary, on cumulative review of 13 cases pertaining to IgA nephropathy, based on insufficient case details (on medical history, concomitant medications, etiological work-up) for a comprehensive causal assessment or based on confounders, there is unsubstantiated evidence to support a causal relationship of IgA nephropathy to VAXZEVRIA.

Observed versus expected

Parameters:

- DLP: 28 June 2022
- Risk window: 0-42 days
- Cases with unknown TTOs were included
- Background rate incidences: based on Go et al 2021 for Glomerulonephritis / Nephrotic syndrome and McQuarrie et al 2014. for IgA nephropathy.
- Exposure: base on doses administered in 13 markets

Results:

Observed events for Glomerulonephritis and Nephrotic syndrome (including IgA Nephropathy) were significantly less than the expected events provided using the risk window of 42 days.

Literature

The search identified a total of 90 relevant abstracts. From these, 56 concerned mRNA vaccines, 13 multiple COVID-19 vaccines [including Vaxzevria (n=5)], 10 concerned vector based vaccines and 5 concerned inactivated vaccines.

Three relevant articles with an observational controlled study design and consensus review were identified and are summarised by the PRAC assessor here-after:

- **Diebold et al., 2022. Incidence of new onset glomerulonephritis after SARS-CoV-2 mRNA vaccination is not increased[4].**

  This nationwide (Swiss) retrospective cohort and case-control study is specific to mRNA vaccine. The authors used a database of 229 kidney biopsies in patients aged >18 years with IgAN, PINGN, MCD, and MN. The authors did not demonstrate an association between mRNA vaccines and new-onset GN. The authors concluded that most temporal association between vaccination and GN are likely coincidental.

- **Stevens et al, 2022. Perspective on COVID-19 vaccination in patients with immune-mediated kidney diseases: consensus statement form the ERA-IWG and EUVAS[5]**

  This is a review article and summary of consensus from Immunonephrology Working Group (IWG) of the European Renal Association (ERA) and the European Vasculitis Society (EUVAS). This consensus statement provides an updated overview of vaccine efficacy in patients with immune-mediated kidney diseases (IMKD) in respect to their treatment. This review considers all vaccine platforms.

  In the section on the safety of COVID-19 vaccines in immune-mediated kidney diseases, the authors discussed the risk of *de novo* and relapsing/flaring GN.

  Most IMKD relapsed/flared were diagnosed after the second dose of the COVID-19 vaccine, with the exception of MCD, which was usually found after the first dose. The authors also report three cases of positive rechallenge.

  The authors conclude that patients with immune-mediated kidney diseases should be prioritized to receive booster doses as early as possible, as reduced vaccine response is anticipated in many cases. Most disease onset or relapse/flare of immune-mediated kidney disease can be successfully treated in a standard manner. Reported side effects (including recurrence of disease or de novo glomerulonephritis) are rare and large population-based investigations are necessary to provide evidence of a true association. The benefits of COVID-19 vaccines clearly outweigh the potential risks.

[4] https://www.kidney-international.org/article/S0085-2538(22)00697-4/fulltext
[5] https://academic.oup.com/ndt/article/37/8/1400/6542380?login=false

- **Zan et al, 2022**. **Safety evaluation of COVID-19 vaccine in patients with IgA nephropathy or IgA nephritis. Kidney international report[6].**

  The authors retrospectively investigated 367 patients with IgAN. Forty-six percent (46%) of the patients received at least 1-dose vaccination and most patients were injected with an inactivated vaccine (Coronavac or BBIBP-CorV). There were 2 flare-up events. There was no significant difference between the baseline and postvaccination proteinuria and hematuria. Estimated glomerular filtration had a mild but statistically significant difference (68.39 [23.18] vs. 67.33 [23.53] ml/min per 1.73 m2; P - 0.03) from pre-vaccination to post-vaccination. Glomerular filtration rate decline was temporary. The authors concluded that , although the vaccine was well tolerated, close monitoring of kidney function after vaccination should be offered to intervene as early as possible.

Potential mechanism of action

Glomerulonephritis and nephrotic syndrome:

- Abnormal T cell mediated glomerular damage (Leclerc et al 2021, Biradar et al 2022, Neves et al 2022, Schaubschlager et al 2022, Timmermans et al 2022)
- B cell pathway mediated podocytopathy (Timmermans et al 2022)
- Molecular mimicry between SARS CoV-2 spike protein and self -antigens on the podocytes (Leclerc et al 2021) – the self-antigens were unspecified
- Aberrant activation of the immune system in predisposed individuals (Leclerc et al 2021)

Specific mechanisms for IgA Nephropathy:

- anti-glycan antibodies that cross-react with pre-existing under-galactosylated IgA1 (Abramson et al 2021; Kudose et al, 2021; Park et al 2021; Roberts 2021) and increase of pathogenic IgA production post vaccination similar to the influenza vaccine (Abramson et al 2021; Carr et al 2021; Farooq et al 2021; Li NL et al 2021; Nihei 2022; Negrea and Rovin 2021; Wu et al 2021)
- robust T-helper and B cell response in the germinal centre by mRNA vaccination (Abramson et al 2021; Chan et al 2022)
- subclinical IgAN becoming apparent (Abramson et al 2021; Acharya et al 2021; Chan et al 2022) ; Fujita et al, 2022; Hanna et al, 2021; Klomjit et al 2021; Lo and Chan 2021)
- potent stimulation of immune response from mRNA-based vaccine compared to other vaccines (Abramson et al 2021; Acharya et al 2021),
- stimulation of Gut-associated lymphoid tissue and other mucosal tissues (Chan et al 2022; Hamza and Beers, 2021) or aberrant mucosal immunity response (Roberts 2021)
- molecular mimicry (Fujita et al, 2022; Kanamori 2022)
- delayed type hypersensitivity (Rahim et al 2021; Plasse et al 2021)
- systemic cytokine-mediated flare (Kudose et al, 2021; Park et al 2021)
- mRNA based production of aberrant glycosylated IgA via Toll-like receptors (TLRs) signalling (Matsuzaki et al, 2021).

MAH's Comments The review of mechanisms proposed by the authors included both vaccine type specific and vaccine non-specific mechanisms. For IgAN, the mechanism of presence of subclinical IgA pathology was explored further, however, an inconsistent association of IgAN flare/reactivation with patient receiving multiple vaccine types was observed. The remaining mechanisms are hypothesis and further evidence on the pathway or mediators leading to the glomerular injury are lacking. Thus, there is insufficient comprehensive evidence for a conclusive mechanism for glomerulopathies following VAXZEVRIA vaccination and that evidence from other vaccine types cannot be comprehensively extrapolated to all other vaccines.

[6] https://www.kireports.org/article/S2468-0249(22)01245-1/fulltext

MAH's Conclusion

Based on the review of the currently available data, AstraZeneca considers that there is insufficient evidence to suggest a causal association between VAXZEVRIA and Glomerulonephritis AND Nephrotic syndrome (including IgA Nephropathy). It is AstraZeneca's opinion that no updates to CDS or RMP are warranted at this time.

AstraZeneca will continue to monitor safety information for Glomerulonephritis AND Nephrotic syndrome (including IgA Nephropathy) as part of routine safety surveillance activities and take further actions as deemed necessary.

Rapporteur assessment comment:

Cumulative review of the cases:

The MAH reviewed **115 case reports** of various types of **glomerulonephritis (GN) and nephrotic syndrome (NS)**. Some characteristics of the events may be highlighted:

- There were three cases of positive rechallenge;
- About 10% of reports were possible cases of flare/relapse: 7/66 cases of GN, 4/46 cases of NS, and 4 cases with past history of IgAN out of 13 IgAN;
- 80% of the cases occurred within 42 days after vaccination

Causality assessment of the cases

From the 115 case reports, **56% were assessed 'Possible'** according to WHO-UMC causality criteria.

Literature

The **three publications** that were discussed were not specific to Vaxzevria. Overall, these publications do not support an association between COVID-19 vaccine and new-onset of glomerulonephritis (Diebold). Some cases of relapse/flare up of immune-mediated kidney disease (IMKD) were reported (Stevens, Zan). Difference in the glomerular filtration before and after vaccinations were also noted but these are transient (Zan).

All publications stressed the importance to vaccinated immune-mediated kidney diseases (IMKD) patients against COVID-19 and concluded that the benefit of the vaccine overweight the risks in this population.

Hypotheses on several mechanisms leading to alteration kidney, mainly to podocytes, were discussed in the literature. The mechanism is still open for discussion.

Need for updating product information and/or risk management plan

The MAH concludes that there is no need to update product information or the Risk Management Plan.

The PRAC Rapporteur agrees that there is no strong evidence of an association between Vaxzevria and new onset of glomerulonephritis and nephrotic syndrome. However, cases of relapse/flare up are observed. According to authors, these relapses are managed through standard procedures. Some changes in glomerular filtration were also measured. However, these observations are not specific to Vaxzevria and related to other COVID-19 vaccines.

In consequence, no update to the SmPC or RMP is warranted for Vaxzevria at this stage.

In the next PBRER, the MAH is requested to further search for literature on GN/SN following COVID-19 vaccination, with a special focus to Adeno-vectored vaccines, relapse and flare up, and measured kidney alterations after vaccination. [*Request for the next PBRER*]

2.3.28. Health Authority requests – Rhabdomyolysis

Please note that data on Rhabdomyolysis is not reproduced here (Section 15.2.9 of the PBRER).

MAH's summary

Rhabdomyolysis was actively monitored in UMC's signal detection activities for COVID-19 vaccines due to it being marked as an AESI. WHO identified signal of rhabdomyolysis for COVID-19 vaccines.

The incidence of Rhabdomyolysis in general population is unknown. On literature review Mckenna MC et al 2019 is concerned with the incidence rate in hospitalised patients. Rhabdomyolysis is known to occur naturally at an overall annual incidence of 59 cases per 100,000 persons (McKenna MC et al 2019) per annum. The natural aetiology is multifactorial but includes traumatic injury, exertion, medicines, infections and metabolic causes. The classic presentation is of muscle pain, weakness, pigmenturia, and a marked elevation of serum CPK five to ten times above the upper limit of normal (ULN) serum levels (Chavez L O et al 2016).

Ninety-two (92) Rhabdomyolysis cases were reported globally and included in AstraZeneca's post-marketing database. Cases were assessed by age, sex, type of event, and outcome. The characteristics of the events and of the individuals with events were as expected for the general population, including the observation of increased incidence in the elderly. No usual trends or clusters were identified. The time to onset (TTO) was available in 63 (68.5%) case reports and ranged from 0 days to 266 days (median: 3 days). Of 63 cases, 51 (81.0%) cases were within TTO range of 1-42 days.

Of 92 cases, 54 (58.7%) cases were reported with PT of Rhabdomyolysis and in 2 (2.2%) cases the CPK value were more than 1000 U/L with PT Muscle necrosis and Myopathy along with additional symptoms of muscle pain and muscle weakness. In 33 cases, Rhabdomyolysis was not reported as a PT (with CPK value not stated) and in 3 cases CPK was less than 1000 U/L without Rhabdomyolysis reported. Hence these 36 cases were unlikely to meet the definition of Rhabdomyolysis. Of 92 cases, 56 cases were considered for WHO-UMC causality. None of the cases met WHO-UMC criteria for Certain or Probable/Likely. 62.5% were considered as Possible, 14.3% were considered as Unlikely, 1.8% were Conditional/Unclassified and 21.4% were considered as Unassessable/Unclassifiable related to VAXZEVRIA. Amongst 56 cases, 46.4% were identified with relevant risk/confounding factors and 53.6% cases had limited information for a comprehensive causal assessment.

Of 92 cases, there were 4 fatal cases which were assessed as Possible as per WHO-UMC causality (3 cases had relevant confounders and 1 case had limited information).

The O/E analysis results for rhabdomyolysis showed observed cases to be significantly less than expected for all age and Global and EU/UK reports.

In summary, the review of available data from spontaneous reports regarding rhabdomyolysis did not identify an index case or other evidence of a new or emerging signal.

MAH's conclusion

Based on the currently available cumulative data, AstraZeneca considers that there is insufficient evidence to suggest a causal relationship between VAXZEVRIA and Rhabdomyolysis. It is AstraZeneca's opinion that no update to the CDS or RMP is warranted at this time.

Rhabdomyolysis is an AESI for VAXZEVRIA and will continue to be kept under close surveillance by AstraZeneca. AstraZeneca will no longer discuss the topic in future PBRERs, unless significant new safety information arises.

Rapporteur assessment comment:

Ninety-two (92) Rhabdomyolysis cases were reported globally and included in AstraZeneca's post-marketing database. Cases were assessed by age, sex, type of event, and outcome. The characteristics of the events and of the individuals with events were as expected for the general population, including the observation of increased incidence in the elderly. No usual trends or clusters were identified. The time to onset (TTO) was available in 63 (68.5%) case reports and ranged from 0 days to 266 days (median: 3 days). Of 63 cases, **51 (81.0%) cases were within TTO range of 1-42 days.**

Of 92 cases, 56 cases were considered for WHO-UMC causality. None of the cases met WHO-UMC criteria for Certain or Probable/Likely. **62.5% were considered as Possible**, 14.3% were considered as Unlikely, 1.8% were Conditional/Unclassified and 21.4% were considered as Unassessable/Unclassifiable related to Vaxzevria. Amongst 56 cases, 46.4% were identified with relevant risk/confounding factors and 53.6% cases had limited information for a comprehensive causal assessment.

Of 92 cases, there were **4 fatal cases which were assessed as Possible as per WHO-UMC causality** (3 cases had relevant confounders and 1 case had limited information).

The O/E analysis results for rhabdomyolysis showed observed cases to be **significantly less than expected for all age and Global and EU/UK reports.**

The MAH considers that there is insufficient evidence to suggest a causal relationship between VAXZEVRIA and Rhabdomyolysis and that that no update to the CDS or RMP is warranted at this time. The MAH will continue to be kept under close surveillance by AstraZeneca. **This is endorsed.**

Cases of Rhabdomyolysis do not need to be further discussed through PBRERs unless significant new safety information is identified.

2.3.29. Health Authority requests – Exacerbation of type 1/type 2 mellitus diabetes

Please note that data on Exacerbation of type 1/type 2 mellitus diabetes is not reproduced here (Section 15.2.10.1 of the PBRER).

MAH's summary

Overall medical summary of all case reports: Cumulatively through DLP (28 June 2022), a total of 383 reports of eDM with the use of VAXZEVRIA have been received, of which 53.0% of the reported cases were serious and 46.9% were non-serious. 12 fatal events were reported, all of them were confounded by pre-existing inadequate control of DM, or by other strong confounding factors or were not the direct cause of death. The age range was 20 to 89 years and median age was reported as 57 years. More cases were reported for adult patients compared to the elderly, 63.8% and 29.4%, respectively, and more cases were reported for female that for male vaccinees, 60.8% and 38.9%, respectively. 30.5% of cases were medically confirmed and 69.5% were consumer reports.

Most of the cases were reported after the first dose of VAXZEVRIA, 280 (73.3%). There were no case reports identified with rechallenge for eDM after the first dose and second dose of vaccination.

Of the serious cases, the most were medically important, 77.5%, followed by hospitalization, 26.0%, life threatening, 13.2%, disability, 10.8% and fatal, 5.9%.

For eDM, the most common PTs reported were Blood glucose increased (166), Hyperglycaemia (116), Diabetes mellitus inadequate control (48), Blood glucose fluctuation (38) and Diabetic ketoacidosis (20).

The most commonly co-reported events were Pyrexia (25.8%) and Headache (28.4%).

The TTO was reported in 348 (90.8%) cases. The median TTO was 0 days (median) respectively. TTO ranged from 0 to 213 days, and was unknown in 35 (9.1%) case reports.

Amongst 383 cases, 118 had a reported outcome recovered or recovered with sequelae. The majority of the events were reported as recovered at time of reporting, and the different case report source was as followed: Clinical trial (2); Spontaneous (377); and Literature (4). Amongst 1188 cases with reported outcome Recovered or Recovered with sequelae, the event duration was reported in 43 [36.1%] cases. The mean duration was 7.0 days. For 36 cases (83.7% of the events with reported duration), the events of interest resolved within 7 days and for the remaining 7 (16.3%) cases the events resolved between 8 and 77 days after onset.

The majority of case reports cumulatively through DLP (28 June 2022), 62.4% contained insufficient information to confirm causality assessment. A total of 30.5% of eDM cases included relevant risk/confounding factors.

On further WHO UMC case causality analysis conducted for case reports of eDM, none were considered as certain or probable and 10.2% were considered unlikely related to VAXZEVRIA. About, 69.5% case reports were assessed as possibly related to VAXZEVRIA, however these cases had either limited information or presence alternate etiologies.

Overall, none of the case reports raised any new relevant safety concerns for eDM cumulatively till DLP, and we are not aware of any specific biological mechanism through which VAXZEVRIA vaccine could cause eDM.

MAH's conclusion

AstraZeneca was requested to provide a cumulative review on exacerbations of type 1/type 2 mellitus diabetes in vaccinees who received VAXZEVRIA based on the corresponding signal identified by WHO UMC. WHO UMC identified 90 case reports of exacerbation of diabetes, that includes 22 cases for VAXZEVRIA. However, lack of information available in the reports precluded any conclusions on the impact of the hyperglycaemia exacerbation. The report also included cases and case series published in the literature, a hypothetical mechanism of such toxicity, and recommendations from medical societies, which contained no official recommendations regarding the use of vaccines in patients with diabetes. WHO-UMC concluded that these findings do not amount to a contraindication of COVID-19 vaccination in patients with these conditions. On review of the WHO UMC signal report, AstraZeneca have found that the report does not contain definitive evidence on causal association between VAXZEVRIA and exacerbation of diabetes.

Based on the currently available cumulative data, AstraZeneca considers that there is insufficient evidence to suggest a causal relationship between eDM and VAXZEVRIA. It is the opinion of AstraZeneca that no changes to the CDS or RMP are warranted at this time.

AstraZeneca will continue to monitor safety information for eDM as part of the routine safety surveillance activities for VAXZEVRIA. AstraZeneca will not discuss the topic future PBRERs, unless significant new safety information arises.

Rapporteur assessment comment:

As requested by PRAC rapporteur, the MAH presented a cumulative review of the cases and a discussion on the WHO-UMC identified signal (12.04.2022) of exacerbation of Diabetes Mellitus (DLP 28 June 2022).

The MAH's database search retrieved **383 cases (409 events) with history of DM** were further analysed for exacerbation of type 1/type 2 mellitus diabetes (eDM).

Most of cases **(53%) were considered serious**, including 12 cases with a fatal outcome.

Most of cases **(73%)** occurred after the 1st dose. No case of rechallenge was identified.

Vaccinee age ranged from 20 to 89 (median: 57 years), and **244 (63.8%) reports referred to adult vs 113 (29.4%) to elderly** vaccinees, in 26 case reports age group was not available.

A slight gender imbalance was observed with 233 (60.8%) cases reported in female.

Blood glucose **increased (n=166, 43.34%)and Hyperglycaemia (n=115, 30%)** were the most frequently reported events of interest events, respectively.

TTO ranged from 0 to 213 days (**median: 0 days)**; and most of the cases occurred within 0-5 days (n=315, 85% cases) of vaccination.

When a recovered outcome was reported, the mean event duration was 7 days (duration reported in 43 [36.1%] cases).

Cases with fatal outcome: Fatal outcome was reported in 12 cases, of which 5 (41.7%) were medically confirmed. Diabetic ketoacidosis (n=5, 41, 46.6%), Blood glucose increased (n=3, 42, 24%), and hyperglycaemia (n=3, 42, 24%) were the most frequently reports PTs associated with fatal outcome cases, respectively. Overall, the TTO was reported for 10 of the 12 fatal events and ranged from 0 to 213 days after receiving vaccine. The risk window for TTO was considered to be between 0 and 7 days, inclusive. Of the 12 fatal case reports the WHO-UMC causality was considered possibly related in 5 (41.7%) cases, unlikely related in 5 (41.7%) cases due to TTO being outside the risk window, and in 2 (16.7%) cases it was considered to be unassessable due to unknown TTO. The MAH explained that the Diabetic ketoacidosis was reported in all cases assessed as possibly related, all the cases contained strong confounding factors: inadequate control or compliance in 2 cases, concurrent pneumonia, recently developed circulatory collapse and myocardial infarction. All remaining fatal cases also reported confounding factors or alternative explanation. **This is accepted.**

According to the WHO-UMC causality scale, most cases, 266 (69.5%) were assessed as possibly related to VAXZEVRIA, including 169 cases with limited information and 97 cases with possible confounders. Other cases were classified as unassessable/unclassifiable (78; 20.4%) or unlikely related (39; 10.2%).

Literature: 15 articles were identified in a literature search but none of them were considered relevant for further evaluation and presentation.

Conclusion

Overall, the review of cases shows a temporal relationship where majority of the events occurred within 0 to 5 days post vaccination. However, most of the cases (69.5%) lack sufficient information for an in-depth medical evaluation. Besides, the 5 fatal cases considered possibly related (WHO-UMC) were strongly confounded. It is agreed that available information do not raise any new safety concern and **Exacerbation of type 1/type 2 mellitus diabetes will not be further discussed in next PBRERs, unless significant new safety information arises**.

2.3.30. Health Authority requests – Exacerbation of Adrenal insufficiency

Please note that data on Exacerbation of Adrenal insufficiency is not reproduced here (Section 15.2.10.2 of the PBRER).

MAH's summary

Overall medical summary of all case reports: Cumulatively through 28 June 2022, a total of 86 case reports of Adrenal insufficiency were reported. Of the 86 case reports, 25 (29.1%) case reports had 26 pre-existing medical history PTs of adrenal disease indicating Exacerbation of Adrenal Insufficiency. All 25

cases were from spontaneous sources and were serious. 7 were medically confirmed. 23 of the 25 case reports were from United Kingdom. The age range in these cases was between 18 to 78 years with a mean of 56 years. 70.8% of these cases were reported in females. TTO ranged between 0 to 30 days and the mean was 4.7 days. Overall, 57.7 % of the 25 cases had a PT of Adrenal insufficiency acute reported. 46.1% had a favourable outcome (resolved/resolving). Of the 25 cases 17 were assessed as possibly related to VAXZEVRIA using the WHO-UMC causality assessment. However, all cases were found to have risk factors/confounders which could also explain the exacerbation

Cumulatively through 28 June 2022, a total of 86 case reports of Adrenal insufficiency were reported. Of the 86 case reports, 25 (29.1%) case reports had 26 pre-existing medical history PTs of adrenal disease indicating Exacerbation of Adrenal Insufficiency. All 25 cases were from spontaneous sources and were serious. 7 were medically confirmed. 23 of the 25 case reports were from United Kingdom. The age range in these cases was between 18 to 78 years with a mean of 56 years. 70.8% of these cases were reported in females. TTO ranged between 0 to 30 days and the mean was 4.7 days. Overall, 57.7 % of the 25 cases had a PT of Adrenal insufficiency acute reported. 46.1% had a favourable outcome (resolved/resolving). Of the 25 cases 17 were assessed as possibly related to VAXZEVRIA using the WHO-UMC causality assessment. However, all cases were found to have risk factors/confounders which could also explain the exacerbation

Overall, none of the case reports raised any new safety concerns for Exacerbation of Adrenal Insufficiency cumulatively through 28 June 2022, and the company is not aware of any confirmed biological mechanism through which VAXZEVRIA vaccine could cause an exacerbation of adrenal insufficiency.

Literature summary: Two literature case reports of Adrenal insufficiency were identified, of which, both are linked with case reports in the AstraZeneca Global Safety Database.

Literature review cumulatively though 28 June 2022 did not establish a definitive causal association between VAXZEVRIA and Exacerbation of Adrenal Insufficiency.

MAH's conclusion

Based on the currently available data, AstraZeneca considers that there is insufficient evidence of a causal association between Exacerbation of Adrenal insufficiency and VAXZEVRIA. It is AstraZeneca's opinion that no changes to the CDS or RMP are warranted at this time..

AstraZeneca will continue to monitor safety information regarding Exacerbation of Adrenal Insufficiency as part of the routine safety surveillance activities for VAXZEVRIA. AstraZeneca will not discuss the topic future PBRERs, unless significant new safety information arises.

Rapporteur assessment comment:

As requested by PRAC rapporteur, the MAH presented a cumulative The MAH presented a cumulative review of the cases and a discussion on the WHO-UMC identified signal (12.04.2022) of adrenal insufficiency.

The MAH's search retrieved a total of 86 case reports, cumulatively, of which **25 case reports** had pre-existing medical history of adrenal disease suggesting Exacerbation of Adrenal Insufficiency. All cases were serious, but none was fatal. 7 cases were medically confirmed. **6 (24%)** cases were reported after the **first dose** and **1** after **second dose**.

Adrenocortical insufficiency (n=15, 57.7%) and acute adrenal insufficiency (n=10, 38.5%) were the most reported events followed by Addison's disease (n=1, 3.8%).

Vaccinee age (reported in 24 case) ranged 18 to 78 years (median: 58.5 years) and 17 (70.8%) cases concerned females vs 7 cases reported in males.

TTO was known in 13 case reports and ranged from 0 to 30 days (**median: 0 day**). Most of the cases occurred **within 1 day (n=7, 53.84%) and 1-14 days (n=5, 38.4%)**.

The baseline status of the adrenal insufficiency at the time of vaccination was provided in only one case which had history of several years with adrenal fatigue; and 22 patients with history of adrenal insufficiency had steroid therapy in their history or were concomitantly treated with steroids at the time of the vaccination.

Outcome was reported as follows: **46.1% (12/26) of the events were favourable** (resolved or resolving), 7.8% (2/26) of the events was not recovered/not resolved. The outcome of the remaining 46.1% (12/26) of events were reported as unknown or not reported.

According to **WHO-UMC causality** analysis, **17 cases** were assessed as **possible with risk factors/confounders.** 8 cases were Unassessable/Unclassifiable with risk factors/confounders and 8 were Unassessable/Unclassifiable with limited information.

Considering the exposure to Vaxzevria, the reporting rate for Exacerbation of Adrenal Insufficiency is quite low.

Literature: 5 articles were identified in the literature search including 2 relevant articles (Maguire et al 2021 and Varona et al 2021) for further discussion. These were literature case reports with Vaxzevria

Mechanism of action: The MAH discussed the publication of Zhao and Wu 2022 who summarized the influence of COVID-19 vaccines on the endocrine system and explored the pathogenic mechanisms. The authors hypothesised that autoimmune/inflammatory syndrome induced by vaccine adjuvants (ASIA) could be one of the possible mechanisms. ASIA has been suggested in the past to explain some AEs (e.g. type 1 diabetes, primary ovarian failure, etc) observed after several vaccines (e.g. HVP, HBV, Flu). However, ASIA remains an hypothetical mechanism that need to be confirmed.

Conclusion

Overall, data that are currently available do not suggest any new safety concern. **Exacerbation of Adrenal insufficiency will not be further discussed in next PBRERs, unless significant new safety information arises. This is endorsed**.

2.3.31. Health Authority requests – Exacerbation of Hypertension

Please note that data on Exacerbation of Hypertension is not reproduced here (Section 15.2.10.3 of the PBRER).

MAH's summary

Overall medical summary of all case reports: Cumulatively through DLP (28 June 2022), a total of 129 reports of exacerbation of hypertension with the use of VAXZEVRIA have been received, of which 54% were serious and 46% were non-serious. The age range was 33 to 94 years and mean and median age was reported as 63 years and 63.5 years, respectively. Forty two (42%) of cases were medically confirmed and 58% were consumer reports.

Cumulatively through DLP (28 June 2022) of the 129 cases, the TTO was reported in 105 (81%) cases. The mean and median TTO was 12 days and 127 days respectively.

Amongst 129 events received cumulatively through DLP (28 June 2022), 65 (50%) events had a reported outcome recovered or recovered with sequelae.

One event in 129 case reports (0.7%) was reported with fatal outcome cumulatively through DLP [28 June 2022], which was non-medically confirmed. There was insufficient information on the baseline control status and clinical course of hypertension, and the fatal outcome is likely due to the multiple co-morbidities.

Cumulatively through DLP (28 June 2022), of the 129 case reports reporting the exacerbation of hypertension with VAXZEVRIA use, there was 1 (0.7%) case report with potential recurrence/rechallenge.

These 129 case reports received cumulatively through DLP (28 June 2022) were analysed by AstraZeneca and found to have limited information (including information on baseline control of hypertension, prior/ongoing therapy and treatment information) and/or are confounded by alternative aetiologies including the possibility of a concurrent COVID-19 infection.

Upon further WHO-UMC case causality analysis conducted for the 129 case reports, the majority of case reports (108 [84%]) were considered possibly related to VAXZEVRIA. However, 95 of these 108 (88%) case reports also demonstrated possible risk factors/confounders and 13 of these 108 (12%) cases had limited information to confirm causality assessment.

Literature summary: 12 articles were identified from a cumulative literature search, of which none were considered relevant for further evaluation and presentation as they discussed either non-hypertension related adverse events or mRNA based vaccine events.

Literature review cumulatively though 28 June, 2022 did not identify any article elucidating a possible pathogenic mechanism leading to exacerbation of hypertension with VAXZEVRIA.

MAH's conclusion

Based on the currently available data, AstraZeneca considers that there is currently insufficient evidence of a causal association between Exacerbation of hypertension and VAXZEVRIA. It is AstraZeneca's opinion that no changes to the CDS or RMP are warranted at this time.. AstraZeneca will continue to monitor safety information for Exacerbation of hypertension as part of the ongoing safety surveillance activities for VAXZEVRIA. AstraZeneca will not discuss the topic future PBRERs, unless significant new safety information arises.

Rapporteur assessment comment:

As requested by PRAC rapporteur, the MAH presented a cumulative The MAH presented a cumulative review of the cases and a discussion on the WHO-UMC identified signal (12.04.2022) of Exacerbations of Hypertension

The MAH's search retrieved a total of **129 case reports** of exacerbation of hypertension reporting 129 events, including 70 serious case reports and 54 (42%) medically confirmed reports . **115(89%)** cases were reported **after the first dose**, 8(6%) after the second dose and 1 (0.7%) after the third dose. There was 1 case of rechallenge (AE reported after both dose 1 and dose 2) which was fatal.

Vaccinee age was reported in 119 case reports and ranged 33 to 94 years (**median age: 63.5 years**). Of the 129 case reports, 102 (79%) cases concerned patients >50 years old and most of cases **73% (93)** concerned **female** patients.

TTO was known in 105 (81%) case reports and ranged from 0 days to 254 days (**median TTO: 12 day**). Most of the cases occurred **within 1 day (n=47, 44.7%) and 2-5 days (n=5, 28.5%)**.

The AE outcome was reported in 49% (63/129) as favourable (resolved or resolving), 1% (2/129) of the events were recovered/resolved with sequelae, and 25% (32/129) of the events were not recovered/ not resolved. One case had a fatal outcome.

In this fatal case, the patient experienced exacerbation of hypertension after the first dose, and a recurrence of exacerbation of hypertension with the second dose of vaccination indicating potential recurrence / rechallenge. This case report was consumer report received from regulatory authority. Fatal outcome was present in this case [redacted], which is described in fatal cases above. WHO-UMC Causality Assessment for this case is Unassessable/Unclassifiable with risk factors/confounders.

According to WHO-UMC causality scale, 95 cases were assessed as possible with risk factors/confounders and 13 cases as Possible with Limited information. Other cases were Unassessable/Unclassifiable with risk factors/confounders (n=15) and Unassessable/Unclassifiable with limited information (n=6).

Overall, 110 (85%) cases were identified with relevant risk/confounding factors.

Literature: no relevant articles

Conclusion

Overall, data that are currently available do not suggest any new safety concern. **Exacerbation of Hypertension will not be further discussed in next PBRERs, unless significant new safety information arises. This is endorsed**.

2.3.32. Health Authority requests – PAM LEG 103: Review of pulmonary embolism (PE), coronary artery disease (CAD) including myocardial infarction (MI) and venous and arterial thromboses – Further data provision

Following submission of the EMA LEG procedure (Post-Authorisation Measure LEG 103) PRAC requested that the following data should be included in this PBRER:

1. A review of the literature for new publications on epidemiologic studies of interest related to these safety endpoints, including a presentation of a cumulative overview table of all epidemiological studies (similar to table 17 of the assessment report)
2. O/E analysis of the safety endpoints using data where age and age/gender stratified analysis are possible with reliable estimates of vaccine exposure (ie, UK and EEA data). Background rates used should be clearly and explicitly documented, including information that may be useful for interpretation: countries, databases, time period, population. The MAH should discuss the comparability between the populations and systems that give rise to the observed and expected cases and discuss potential biases giving limitations in the comparability. If the source comes from a systematic review/meta-analysis, then reporting ranges and 95% CIs of the estimates can also be useful to assess the heterogeneity and precision of the estimates.

Literature Review

After careful review five articles discussing the association between VAXZEVRIA and thromboembolism were summarised and added to the previous summary of seven for the EMA LEG procedure. The five new articles are presented first in Table 10 and Table 11 presents a summary of large population-based studies on relative risk or risk difference of studied events.

Table 10 - Design overview of large population-based studies and AstraZeneca's comments

Reference, Country	Data source	Time period	Design	Comparator	AstraZeneca comments
Berild et al, 2022, Denmark, Norway and Finland	The Norwegian Immunization Register SYSVAK, the Finnish National Vaccination Register, and the Danish Vaccination Register (exposure) and the national patient registers (outcome)	January 1, 2020, to May 16, 2021.	Self-controlled case series	The risk period was 28 days postvaccination. The control period was January 1, 2020 to 14 days prior to vaccination, or COVID infection.	• Nationwide registers including the whole populations used. However, less severe cases from primary care not included. • Patient acted as their own control; therefore, time invariant confounding was controlled for. • Selection effect by including only those with outcome • Control period included 2020 to allow adjustment for seasonal variability, this may have introduced a bias, since access to health care may have been affected by the pandemic. • A pre-risk period of 14-days was used to ensure events did not influence subsequent exposures.
Rahman et al, 2022, Malaysia.	Malaysia Vaccine Administration System (MyVAS) database and the Malaysian Data Warehouse (MyHDW), a national health data repository that collects data from public and private hospitals in Malaysia	1 February 2021 to 30 September 2021	Self-controlled case series	The risk period was 21 days postvaccination. The control period was between 1 February 2021 and 30 September 2021, except a 14-day pre vaccination risk window and the vaccination day (day 0).	• Nationwide registers including the whole populations used. About 8% were vaccinated with VAXZEVRIA. • Less severe cases from primary care not included. • Patient acted as their own control; therefore, time invariant confounding was controlled for. • A pre-risk period of 14-days was used to ensure events did not influence subsequent exposures. • Selection effect by including only those with outcome. • Due to the vaccination roll out the sample have a large proportion of frontline health workers, elderly, and risk groups. • Opt-in stream for the ChAdOx1-S vaccine was introduced in May 2021-due to high demand it was reintroduced to regular roll out.
Chen et al, 2022, multi-country	Pubmed, Embase, Cochrane COVID-19 Study Register, Cochrane Library, Chinese National Knowledge Infrastructure, Wanfang Data Knowledge Service Platform (Wanfang) and SinoMed.	Published 1 January 2020 to 20 October 2021.	Systematic review and meta-analysis	Unvaccinated population or population that received placebo	• Much heterogeneity among the studies, the I^2 (a test of heterogeneity) of most AEs was above 90%. • Grouped viral vector vaccines: JCOVDEN, ChAdOx1 and Sputnik V. • Study population in some studies are comprised of patient groups such as transplant recipients or cancer patients, while some includes health care workers, health care workers with previous severe allergic diseases, and the general population.

Reference, Country	Data source	Time period	Design	Comparator	AstraZeneca comments
					• The adverse event rates of venous and arterial thrombosis would differ between these populations and to meta-analyse them makes interpretation difficult.
Corrao et al, 2022, Lombardy, Italy	The Regional Health Service (RHS) management, the registry of patients with a confirmed diagnosis of SARS-CoV-2 infection and the COVID-19 vaccination registry	27 December 2020 to 3 May 2021	Cohort study	Unvaccinated or pre-vaccination person time, matched on sex and age 1:10	• The outcomes were measured in a hospital setting, so they did not include milder cases treated in primary care. • A large number of health conditions were considered as confounders and adjusted for. • Residual confounding still probable. • Population-based but only include one region.
Hviid et al, 2022, Denmark	The Danish vaccination register and the Danish National Patient Register	27 December 2020 to 13 April 2021	Cohort study	Unvaccinated risk time from all individuals starting on 27 December 2020. Those who were still unvaccinated after 28 days then contributed with another 28-day observation period, and so forth until any vaccination, event, or censoring, whichever came first.	• Only included frontline personnel: health care and social services workers. • Adjusted for several confounding including comorbid conditions associated with risk for severe COVID-19 using inverse probability weights. • Outcomes measured in a hospital setting- milder cases not included. • The median age at study start was 44 years, and 82% of participants were female-results are not generalisable to other groups.
Whitely et al 2022, England	Primary care (GPES), covid and vaccination (NIMS, GDPPR), secondary care (HES, SUS) pharmacy (NHS BSA), and death registrations.	8 December 2020 to 18 March 2021	Cohort study	Unvaccinated or pre-vaccination person time	• Adjusted for several confounding factors. • End date before diagnostic effort was expected to be concentrated in people receiving VAXZEVRIA. • Unmeasured confounding and misclassification of confounding factors is probable.
Hippisley-Cox et al 2021 England	COVID and vaccination (NIMS, GDPPR), secondary care (HES, SUS), and death registrations.	1 December 2020 to 24 April 2021.	Self-controlled case series (SCCS)	Exposed time periods (after vaccination or SARS-CoV-2 infection) compared with unexposed baseline periods in people with the outcome of interest (excluding the pre-risk interval)	• SCCS method widely used in vaccine research. Robustness of the findings for most outcomes. • Detailed data for risk periods after vaccine exposure. • Less severe cases from primary care not included. • Selection bias by including only those with outcome.
Botton et al 2022, France	SNDS (France), hospital discharge diagnoses linked to vaccination files, 18 to 74 years old	06 February 2021 to 20 July 2021 for VAXZEVRIA.	Self-controlled case series (SCCS)	Three weeks following the first dose, and if applicable the second and third doses. All other observation periods were considered reference periods.	• Large study population representing the population of France with high vaccine exposure. • SCCS design widely used in vaccine research • Crude case definitions used for thrombosis.

Reference, Country	Data source	Time period	Design	Comparator	AstraZeneca comments
					• A case-only analysis risks selection bias by including only those individuals pre-disposed to experiencing thrombotic events.
Andrews et al 2022, England	Vaccination (NIMS), secondary care (SUS), and death registrations.	30th November 2020 to 18th April 2021	Cohort study	Unvaccinated period with an offset for population at risk (person days).	• Less severe cases not included. • Vaccinated cohort was compared to an unvaccinated cohort, but only for few confounders were adjusted for, not including health relevant comorbidities. This may have led to an overestimation of RIs.
Burn et al 2021a, UK	CPRD (primary care medical records)	8 December 2020 to 6 March 2021. Follow up time was 28 days from their first vaccination.	Cohort study with historical controls	A general population background cohort, followed from a primary care visit or contact between 1 January 2017 and 31 December 2019 to 31 December 2019.	• Differences in study periods when using historical controls can lead to confounding. • Primary care data, possible underestimation of outcomes diagnosed in hospital. • Adjusted for age and sex only, thus risk of residual confounding.
	SIDIAP, Catalonia, Spain	27 December 2020 to 19 May 2021	Cohort study with historical controls	Historical controls present in the database 1 January 2017 followed until 31 December 2019	• Differences in study periods when using historical controls can lead to confounding. • Historical general population cohort were younger and healthier, compared to vaccinated cohorts, reflecting vaccination guidelines adjusted for age and sex only, thus risk of residual confounding.
Burn et al 2021b, Spain	CMBD register (discharge diagnoses), Catalonia, Spain	01 January 2021 to 18 April 2021.	Cohort study with historical controls	General population in Catalonia on 1 January 2019 with follow up to 31 December 2019	• Differences in study periods when using historical controls can lead to confounding. • Adjusted for age and sex only, thus risk of residual confounding.

Table 10 - Summary of large population-based studies on relative risk or risk difference of studied events

Reference, Country	Design (time window)	Relative risk (95% Confidence interval)					
		MI	CVST	PE	VTE	ATE	IS
Berild et al, 2022, Denmark, Norway and Finland	Self-controlled case series (28-days)	0.92 (0.82-1.03) (CAD including angina and atherosclerotic heart disease)			1.83 (1.56 to 2.15)	2.99 (1.74-5.13)	1.21 (1.05-1.40) (Cerebral thromboembolic events)
Rahman et al, 2022, Malaysia	Self-controlled case series (21-days)	1.02 (0.69, 1.51)			2.22 (1.17 to 4.21)		1.14 (0.80, 1.63)
Chen et al, 2022, multi-country	Systematic review and meta-analysis (Differed between studies)				1.128 (1.023 to 1.1244) NOTE: viral vector vaccines	1.167 (1.103 to 1.234) NOTE: viral vector vaccines	
Corrao et al, 2022, Lombardy, Italy.	Cohort study (1-28 days)				Women <50: 2.43 (1.05 to 5.63) 50–59: 1.53 (0.54 to 4.38) 60–69: 0.78 (0.28 to 2.18) 70–79: 0.39 (0.21 to 0.72) 80+(no cases) Men <50: 0.29 (0.04–2.12) 50–59: 1.12 (0.34–3.69) 60–69: 0.81 (0.39–1.68) 70–79: 0.40 (0.24–0.69) 80+: 1.18 (0.14–9.88)		

Reference, Country	Design (time window)	Relative risk (95% Confidence interval)					
		MI	CVST	PE	VTE	ATE	IS
Hviid et al, 2022, Denmark	Cohort study (0-28 days) **NOTE: risk difference per 100 000 vaccinations**		1.68 (-0.64 to 4.00)	0.93 (-2.35 to 4.21)	Splanchnic vein thrombosis: 0.84 (-0.80 to 2.48) DVT (risk difference): 8.35 (0.21 to 16.49)	<3 events: Not estimable	
Whiteley et al 2022, England	Cohort study (fully adjusted rates 1-28 days)	<70 years : 0.88 (0.83–0.94), 70+years: 0.76 (0.71–0.81)		<70 years: 0.95 (0.85–1.05), 70+years: 0.54 (0.48–0.61)	<70 years: 0.97 (0.90–1.05) 70+years: 0.58 (0.53–0.63)	<70 years: 0.90 (0.86–0.95), 70+years: 0.76 (0.73–0.79)	<70 years: 0.90 (0.84–0.96), 70+years: 0.77 (0.73–0.82)
Hippisley-Cox et al 2021, England	SCCS (8-14 days)		4.01, (2.08 to 7.71)		1.10 (1.02 to 1.18)	1.02 (0.98 to 1.06)	1.07 (1.00 to 1.14)
Botton et al 2022, France	SCCS (8-14 days only the treatment studied)	1.28 (1.12–1.47)		1.30 (1.04–1.62)			1.10 (0.93–1.31)
Andrews et al 2022, England	Cohort study (4-13 days fully adjusted rates)				15-39 years: 2.2 (1.7-3.0), 40-64 years: 1.3 (1.1-1.4) 65+ years: 0.9 (0.8-1.0)		
Burn et al 2021a, UK	Cohort study, adjusted age/ sex	0.84 (0.76 to 0.94)	2.32 (0.97 to 5.58)	1.23 (1.09 to 1.39)	1.07 (0.98 to 1.18)	0.81 (0.73 to 0.89)	0.75 (0.60 to 0.95)
Burn et al 2021b, Spain	Cohort study, adjusted age/ sex	0.98 (0.70–1.37)		1.01 (0.60–1.71)	1.15 (0.83–1.58)	0.98 (0.79 to 1.21)	0.96 (0.72–1.27)
Laporte et al 2021, Spain	Cohort study, adjusted age/ sex		0.42 (0.09 to 2.01)		3.68 (2.27–6.01)		

ATE Arterial thromboembolism, CVST Cerebrovascular venous and sinus thrombosis, MI Myocardial Infarction, VTE Venous thromboembolism, PE pulmonary embolism

Arterial thrombosis (ATE), ischaemic stroke (IS) and myocardial infarction (MI):

Six studies assessed the association between VAXZEVRIA and MI. Three (Berild et al, 2022,; Burn et al 2021a; Rahman et al, 2022) found no association and two (Burn et al 2021b; Whiteley et al 2022) found there was a decreased risk and only one study found an increased risk of MI post vaccination (Botton et al 2022).

Seven studies assessed the association between VAXZEVRIA and IS (Table 9 and Table 10). Four found no statistically significant associations (Rahman et al, 2022, Hippisley-Cox et al 2021, Botton et al 2022, Burn et al 2021b) and two studies found a decreased risk (Whiteley et al 2022, Burn et al 2021a) and one found an increased risk of IS post vaccination (Berild et al, 2022).

Six studies assessed the association between VAXZEVRIA and ATE (Table 9 and Table 10). Two studies found no association (Hippisley-Cox et al 2021; Burn et al 2021b). Two studies found a decreased risk (Whiteley et al 2022, Burn et al 2021a) and two studies found an increased risk of ATE post vaccination (Berild et al, 2022, Chen et al, 2022), one of the studies was a meta-analysis assessing all viral vector vaccines (Chen et al, 2022).

Based on these varied results AstraZeneca cannot draw any conclusions on an association between VAXZEVRIA vaccination and arterial thrombosis, IS or MI.

Venous thromboembolism (VTE), pulmonary embolism (PE) and Cerebrovascular venous and sinus thrombosis (CVST):

Four studies assessed the association between VAXZEVRIA and CVST (Table 9 and Table 10), one of which reported a statistically significant association (Hippisley-Cox et al 2021). Five studies assessed the association between VAXZEVRIA and PE, two of which found no association, one reported a decreased risk in those 70 or over, and two found an increased risk after VAXZEVRIA vaccination. Eleven studies assessed the association between VAXZEVRIA and VTE, two reported no statistically significant association and one reported a decreased risk in those 70 or older, one reported a decreased risk for those 70-79 and an increased risk for woman younger than 50 and eight reported an increased risk after VAXZEVRIA vaccination.

The majority of the studies assessing the association between VAXZEVRIA and VTE did report an association between exposure to AZD1222 and an increased risk of VTE. The associations were found in both SCCS studies that compare post vaccination time to control time in those with the outcome, and cohort studies using non-vaccinated or historical controls. In the studies that presented results stratified by sex and age the increased risk was higher, or only present in younger age groups and in women (Andrews et al 2022; Corrao et al, 2022). Relative risks by sex and age group can be found in Appendix 2, for the studies where they were available. The highest relative risk was found in Laporte et al 2021, who found those vaccinated with VAXZEVRIA had 3.68 times higher risk of VTE compared to historical controls. This study only adjusted for sex and age, and did not exclude participants with history of study outcomes, making confounding likely. Other studies reported between a 10% (corresponding to 66 excess case per 1 million vaccinations, Hippisley-Cox et al 2021) and a 2.43 times increased risk (corresponding to 23,207 citizens vaccinated per one harmful event among women <50, Corrao et al, 2022) and a risk difference of 8.35 cases (95% CI 0.21 to 16.49) of DVT per 100 000 vaccinations in frontline health care personnel consisting mainly of younger women (Hviid et al, 2022). Though residual confounding may still be present in the studies reviewed, a suggestion of a modest potential association between VAXZEVRIA and VTE, especially in younger women, requires further review of new evidence.

Observed Versus Expected Analysis

Please note that O/E data and the discussion by the MAH is not reproduced here (See Section 15.2.11. and Appendix 9 of the PBRER).

MAH's Conclusion

Both embolic and thrombotic events and CAD including MI occur in all ages and are more common as age advances. AstraZeneca did not find evidence of a new or emerging signal from review of the O/E analysis.

Rapporteur assessment comment:

Following submission of the EMA LEG procedure (Post-Authorisation Measure LEG 103) related to pulmonary embolism (PE), coronary artery disease (CAD) including myocardial infarction (MI) and venous and arterial thromboses, the following data was included in this PBRER:

1. A review of the literature for new publications on epidemiologic studies of interest related to these safety endpoints.

Five new articles discussing the association between Vaxzevria and thromboembolism were summarised and risk estimates were added to the previous summary in the EMA LEG procedure (**Error! Reference source not found.** and **Error! Reference source not found.** above).

Using a self-controlled case series (Denmark, Norway and Finland), **Berild et al**. found a small increased risk for venous (RR 1.83 (1.56 to 2.15)) and arterial thrombosis RR (2.99 (1.74-5.13)) following Vaxzvria. Of note, small increased RR were also observed for both mRNA vaccines. Two notably high rates were observed following Vaxzevria: 12.04 (95% CI, 5.37-26.99) for cerebral venous thrombosis and 4.29 (95% CI, 2.96-6.20) for thrombocytopenia (both are listed in the EU-SmPC). The authors discussed that a main assumption of the SCCS method is that experiencing a study event does not influence the subsequent probability of getting vaccinated. This bias is difficult to adjust for, and therefore, they included a post hoc negative control outcome. For this post hoc analysis on Finnish and Danish data, the authors performed a similar analysis using femoral fracture as a negative control outcome. Femoral fracture is especially common in elderly individuals and may result in long-term incapacity which may affect the probability of being vaccinated. They found an association of femoral fracture with COVID-19 vaccinations, up to a RR of 2, cautioning that the SCCS method may yield weak but positive associations because of this bias. Thus, any positive low-grade association for a serious outcome that may result in long-term incapacity should be interpreted with caution.

The SCCS by **Rahman et al.** (Malaysia) noted a small increased risk of VTE following Vaxzevria (IRR 2.22; 95% CI 1.17-4.21) and Comirnaty (IRR 1.24; 95% CI 1.02-1.49). The authors noted that the weak association required further consideration of the clinical importance of the results.

A systematic review and meta-analysis by **Chen et al.** noted a small increased risk of VTE (RR 1.128; 95% CI 1.023-1.244) and ATE (RR 1.167; 95% CI 1.103-1.234) for the viral vector vaccines (these included Ad26.COV2.S, ChAdOx1 and Sputnik V).

A cohort study from Italy by **Corrao et al.** noted an increased risk of VTE, only in women < 50 years (IRR of 2.4, 95% CI 1.1–5.6), but not in other age groups or in men. **Hviid et al.** (Denmark) performed a cohort study in frontline personnel and noted a significant risk difference at 28 days for DVT (RD 8.35 [95% CI 0.21 to 16.49] per 100 000 vaccinations), but not for CVST or thrombocytopenia following Vaxzevria.

2. O/E analysis: these analyses did not find evidence of a new or emerging signal.

Overall, regarding arterial thrombosis, ischaemic stroke, myocardial infarction and pulmonary embolism, the data do not raise new safety concerns and these events do not need to be further discussed as part of the health authority requests, unless significant new safety information is identified. Thrombosis will continue to be monitored as an EU-specific important potential risk (see Section 2.3.5).

Regarding venous thromboembolism, some literature data suggest a possible relationship with Vaxzevria,

but the findings are not consistent across studies and residual confounding cannot be ruled out. **To address the inconsistent risk estimations of venous thromboembolism observed in the literature studies, the MAH should further investigate this topic by providing an updated literature review, with a focus on new relevant epidemiological studies. [*Request for the next PBRER*]**

Moreover, the MAH is asked to discuss the interest of conducting a meta-analysis of all available data from the MAH studies as well as any published studies in the next PBRER. [*Request for RSI*]

2.3.33. Health Authority requests – Viral reactivation (Non-zoster)

Please note that data on Viral reactivation (Non-zoster) is not reproduced here (Section 15.2.13 of the PBRER).

MAH's summary

Overall medical summary of all case reports: Cumulatively through DLP 28 June 2022 a total of 56 reports of Viral reactivation (Non-Zoster) with the use of VAXZEVRIA have been received, of which 92.9% of the reported events were serious. The age range was 22 to 88 years and mean and median age was reported as 51 years and 49.5 years, respectively. The cases were predominantly in females (55.4%).

Of the 56 reports, 25.0% of cases of Viral reactivation (Non-Zoster) occurred after the first dose and 8.9% after the second dose. The dose number was unknown in 64.3% of cases.

One case (1.8%) was reported with a fatal outcome, however, the cause of death confirmed by autopsy was an ischaemic stroke, co-reported hepatitis B assessed by reporter as serious due to hospitalization, ischemic stroke was also assessed as a life-threatening event, a viral reactivation could not be comprehensively confirmed as there was insufficient information on previous HBV DNA status. Two more events were reported as life threatening. The first event of hepatitis E was reported as a life threatening, however, a viral reactivation could not be comprehensively confirmed as there was insufficient information on previous hepatitis E history. The second event of herpes simplex encephalitis was reported by consumer as a life threatening, however, there is a limited information on patient concomitant medications and comorbidities that precluded a proper assessment.

Of the 56 cases, 38 (67.9%) were assessed as "Possible with Limited information" and 13 (23.2%) as "Possible with risk factors/confounders". One case (1.8%) was considered "Probable-Likely". Although the patient had viral serology findings suggesting past infection of EBV and CMV, both viruses are known to have latent and lytic phases. Reactivation of only one virus was seen (CMV) and can be explained by viral derived factors (such as its known natural history). The remaining four cases (7.1%) were assessed as "Unlikely".

Of the four serious cases highlighted by PRAC reported to the French pharmacovigilance system, two were assessed as "Possible; with limited information", one as "Possible; with alternate cause or confounders", and one as "Unassessable/Unclassifiable with limited information".

Overall, none of the case reports raised any new relevant safety concerns for Viral Reactivation (Non-zoster) cumulatively till 28 June 2022.

Literature summary: 765 articles were identified from a cumulative review of the literature. Of these, 758 articles were considered irrelevant for further evaluation and presentation based on the topic of interest "virus reactivation in association with VAXZEVRIA and other COVID19 vaccines".

Seven literature case reports of viral reactivation were identified; the cases were reviewed as part of Global Safety Database review. On review of any remaining case report articles, no new safety concerns were identified.

MAH's conclusion

Based on the review of the currently available cumulative data, AstraZeneca considers that there is insufficient evidence to suggest a causal association with VAXZEVRIA.It is AstraZeneca's opinion that no changes to the CDS or RMP on this topic are warranted at this time. Viral reactivation will continue to be monitored as part of AstraZeneca's routine surveillance activities. AstraZeneca will no longer discuss the topic future PBRERs, unless significant new safety information arises.

Rapporteur assessment comment:

Cumulatively through DLP 28 June 2022 a total of **56 reports of Viral reactivation (Non-Zoster)** with Vaxzevria have been received, 92.9% of the reported events were serious. The age range was 22 to 88 years and mean and median age was reported as 51 years and 49.5 years, respectively. The cases were predominantly in females (55.4%).

25.0% of cases of Viral reactivation (Non-Zoster) occurred after the first dose and 8.9% after the second dose. The dose number was unknown in 64.3% of cases.

One case (1.8%) was reported with a fatal outcome, however, the cause of death confirmed by autopsy was an ischaemic stroke, co-reported with hepatitis B assessed by reporter as serious due to hospitalization, ischemic stroke was also assessed as a life-threatening event, and a viral reactivation could not be comprehensively confirmed as there was insufficient information on previous HBV DNA status.

Two more events were reported as life threatening. The first event of hepatitis E was reported as a life threatening, however, a viral reactivation could not be comprehensively confirmed as there was insufficient information on previous hepatitis E history. The second event of herpes simplex encephalitis was reported by consumer as a life threatening, however, there is a limited information on patient concomitant medications and comorbidities that precluded a proper assessment.

Of the 56 cases, **38 (67.9%) were assessed as "Possible with Limited information**" and **13 (23.2%) as "Possible with risk factors/confounders". One case (1.8%) was considered "Probable-Likely".** The remaining four cases (7.1%) were assessed as "Unlikely".

Seven literature case reports of viral reactivation were identified; the cases were reviewed as part of the Global Safety Database review. On review of any remaining case report articles, no new safety concerns were identified.

The MAH considers that there is insufficient evidence to suggest a causal association with Vaxzevria and that that no changes to the CDS or RMP on this topic are warranted at this time. The MAH will continue to monitor viral reactivation as part of AstraZeneca's routine surveillance activities. **This is endorsed.** Although there are a number of possible cases and one case that is probable, given the large exposure and the fact that viral activation took place for a diverse range of viruses, makes that the uncertainty is large.

Cases of Viral reactivation (Non-Zoster) do not need to be further discussed through PBRERs unless significant new safety information is identified.

2.3.34. Health Authority requests – Cutaneous vasculitis

The signal of cutaneous vasculitis was identified in April 2022 during AstraZeneca's routine surveillance activities from series of published literature case reports. Subsequently on 23 June 2022, in the updated PSUR AR, PRAC requested AstraZeneca to assess cutaneous vasculitis (external) in the upcoming PBRER (DLP: 28 June 2022). AstraZeneca internally validated the signal on 15 July 2022.

Please note that Cutaneous vasculitis data is not reproduced here (see Appendix 16 of the PBRER and Addendum to Clinical Overview on Cutaneous Vasculitis).

MAH's Summary

CV is a not an uncommon disorder, and is characterized by an inflammation of the blood vessel walls and skin lesions. The condition is self-limited and spontaneously resolves within 2 to 4 weeks.

Pre-clinical/Clinical studies: no data / no events of cutaneous vasculitis.

Cumulative review of cases (DLP 28 June 2022): 258 case reports with **258 events** were identified. Majority of the adverse events (AEs) were serious (91.9%).

Gender/Age: There was a higher female (59.3%) to male (40.7%) ratio with a **median age of 61 years**.

TTO: 83% of AEs were reported within a TTO of 14 days; of which 61.5% occurred ≤ 7 days and 33.7% in ≤ 3 days after vaccination (any dose).

Dose: In 90.5% of cases, the event occurred after the first dose; in 7.8% cases after the second dose, and **3.5% cases reported CV after both doses** (**12 cases of rechallenge**).

Outcome: Recovered/recovering in 69.5% of cases; Not recovered in 23.6% of cases (at the time of reporting). However, due to the self-limiting nature of the event and the fact that most of the cases are consumer reports received via regulatory authorities, follow-up information is rarely available.

BCC criteria and causality assessment[WHO-UCM criteria]: **2 cases** were assessed as **BCC Level 1**, **16 cases** as **BCC Level 2**,and **240 cases** as **BCC Level 3**, according to BCC classification Zanoni et al 2016. Out of these 258 cases, **1 case** was assessed as **Certain**, **3 cases Probable**, and **156** of cases were assessed as **Possible with limited information** according to WHO-UMC classification.

Among the 258 cases, there were 20 histopathology confirmed cases, of which there was 1 "Certain" case and 2 "Probable" cases according to WHO-UMC causality criteria.

Among the 258 cases, there were **12 cases** reported **recurrence or worsening** (interpreted as **rechallenge**) **of CV after receiving a second dose** of VAXZEVRIA. According to BCC classification, **10** cases were assessed as **Level 3**, **1** as **Level 2** and the **remaining** as **Level 1**. Using WHO-UMC classification, **1 case** was assessed as **Certain** and majority (**9**) of the remaining cases were assessed as **Possible with limited information** such medical history, concomitant medications, risk factors, etiologic and diagnostic workup. However, due to the recurrence and temporal relationship to both doses, causality with VAXZEVRIA cannot be excluded.

Observed versus expected analysis: The results showed observed cases to be l**ess than or significantly less than** expected for global cases, and for all age and gender stratifications, using the risk windows of 14 and 42 days, and also including cases with unknown time to onset.

There are several uncertainties and assumptions to the OE analysis, including potential under-reporting, appropriateness of background incidence rates used, and possible misclassification of cases of CV.

Literature review – Mechanism of Action: A cumulative literature search retrieved **2 relevant articles** that hypothesized **potential mechanisms** with COVID-19 vaccines leading to CV. The hypothesised

mechanisms include an inflammatory response to vaccine component/antigen encoding SARS CoV 2 spike glycoprotein, depositing in micro-vessels, targeting vascular endothelium and resulting in a neutrophil-rich inflammatory reaction possibly due to the molecular mimicry between SARS CoV-2 and vaccine components such the spike protein. Another hypothesis involved activation of autoreactive B/T cells, antibody formation, and immune complex deposition within small vessels, leading to activation of the complement system and recruitment of leukocytes. However, these broad mechanisms remain speculative given the absence of a specific immune mechanism, mediators or pathway.

MAH's conclusion: Based on the evaluation of currently available information from various sources, AstraZeneca has determined that **there is a reasonable possibility of a causal association between Vaxzevria and CV**.

Vaxzevria CDS **Section 4.8** (undesirable effects) is **updated** to include '**Cutaneous vasculitis'** with **frequency of not known** (considering the post-marketing setting). When used in accordance with the revised prescribing information, the benefits of Vaxzevria continue to outweigh the risks.

Rapporteur assessment comment:

The MAH provided an evaluation of Cutaneous vasculitis [CV] following MAH's and EMA identification of a signal (Appendix 16 of PBRER and Clinical Overview on CV).

A cumulative search (DLP of 28 June 2022) retrieved 258 cases reporting an AE of cutaneous vasculitis: 118 cases reported the PT 'Cutaneous vasculitis' and 140 cases reported other vasculitis PTs (for which CV was identified by narrative review). Among the 258 cases, there were 20 histopathology confirmed cases, including 1 case with a certain causal association with Vaxzevria and 2 cases with a probable causality assessment. Besides, 12 rechallenge cases were identified (i.e. recurrence or worsening of CV after the 2nd Dose), all confirmed as BCC Level 1-3. The MAH classified only 1 case with a certain causality assessment and considered the majority of cases with a possible association with limited information. This is questionable considering the rechallenge of CV after the 2nd dose.

The MAH also reviewed literature case reports highlighted by the EMA. However, it is unclear whether those cases have been taken into account in the cumulative review or not. Overall, the MAH classified those cases as followed:

- 1 case with BCC Level 1 and with a certain causality assessment;
- 9 cases with BCC Level 2, including 1 case with a probable causal association and 8 cases possibly related to vaccination (5 with limited information and 3 with possible confounders); and
- 7 cases with BCC Level 3, including 1 case with a probable causality assessment and 6 cases with a possible causal association with limited information.

The O/E analysis did not show an increased number of CV events after Vaxzevria. However, the analysis has several limitations discussed by the MAH and is hardly conclusive.

Finally, different hypotheses to explain a possible mechanism of action have been proposed.

Based on the evaluation of currently available information, the MAH considers that there is a reasonable possibility of a causal association between Vaxzevria and cutaneous vasculitis. This is endorsed, as well as the inclusion of ***Cutaneous vasculitis*** in **Section 4.8 of SmPC** with a ***frequency of not known***.

The proposal of the MAH of **PIL Section 4** is acknowledged. The PRAC Rapporteur proposed to slightly update the wording to align the signs/symptoms with the other vector-based COVID-19 vaccine:
Not known: inflammation of blood vessels in the skin, often with a rash ~~and~~ or small red or purple, flat, round spots under the skin's surface or bruising (cutaneous vasculitis)

[**Request for PI update**]

2.4. Characterisation of risks

At the end of the reporting period, the VAXZEVRIA safety specification presented in the global core-RMP (Version 7.0, dated 22 Feb 2022) and in the EU-RMP (Version 5 succession 1, submitted 31 Mar 2022) included the following important identified and important potential risks, and missing information (see Table 11).

Table 11 - Characterisations of the safety concerns (core-RMP v7.0 [22 Feb 2022]; EU-RMP v5 S1 [02 Nov 2021])

Safety concerns	Characterisation (DLP 28 June 2022)
Important Identified Risks	
Thrombosis in combination with thrombocytopenia[core] / Thrombosis with thrombocytopenia syndrome[EU]	*Frequency* • Post-market: **2392 cumulative cases** • Clinical-trials: **no cases** *Potential mechanism*: The exact mechanism is unknown. Several hypothetical biological mechanisms have been proposed (Greinacher et al 2021). Among them a study by Baker et al 2021, proposes an interaction between the ChAdOx1 vaccine vector used in VAXZEVRIA and PF4; however, it is unknown if the adenoviral ChAdOx1 interaction with PF4 is actually platelet activating or thrombogenic (causal of blood clots). Greinacher et al 2021 suggested that ChAdOx1 itself or proteins contained within the vaccine can bind to PF4 to form immune complexes which may drive a B-cell response causing high-titre anti-PF4 antibodies resulting in TTS. However, none of these hypotheses have been confirmed. *Risk factors*: There are no known risk factors.
Thrombocytopenia, including immune thrombocytopenia[EU]	*Frequency* • Post-market: **4975 cumulative cases** • Clinical-trials: in study D8110C00001, thrombocytopenia was reported in **2 participants (<0.1%) in the VAXZEVRIA group**, and immune thrombocytopenia was reported in **1 participant (<0.1%) in the placebo group**. In the long-term safety analysis at 6-months, **1 additional event** of thrombocytopenia was reported in a participant in the VAXZEVRIA group. None None of these events were serious. *Potential mechanism*: The exact mechanism of thrombocytopenia, including immune thrombocytopenia following immunisation with VAXZEVRIA is unknown. *Risk factors*: There are no known risk factors for the development of thrombocytopenia following vaccination. In general, individuals with a history of thrombocytopenic disorder, such as immune thrombocytopenia, the risk of developing low platelet levels should be considered before administering the vaccine and platelet monitoring is recommended after vaccination as described in Section 4.4 of the SmPC.
Guillain-Barré Syndrome[EU]	*Frequency* • Post-market: **1703 cumulative cases**

Safety concerns	Characterisation (DLP 28 June 2022)
	• Clinical-trials: **1 case of a demyelinating event** (SAE initially reported as GBS, subsequently diagnosed as Chronic inflammatory demyelinating polyradiculoneuropathy) *Potential mechanism*: Exact mechanism of GBS following immunization with VAXZEVRIA is unknown. Although the underlying aetiology and pathophysiology of GBS are not completely understood, it is believed that immune stimulation plays a central role in its pathogenesis (Sejvar et al 2011). *Risk factors*: There are no known risk factors for the development of GBS following vaccination. In general, infection with the bacteria Campylobacter jejuni is one of the most common risk factors for GBS. People also can develop GBS after having the flu or other infections such as cytomegalovirus and Epstein-Barr virus. On very rare occasions, people develop GBS in the days or weeks after getting a vaccination (CDC 2019).
Important Potential Risks	
Thrombosis[EU]	*Frequency* • Post-market: **18690 cases** • Clinical-trials: in the USA study, thromboembolic events were reported in **0.1%** (23/21587 participants) in the vaccine group and <0.1% (9/10792 participants) in the placebo group. In the **long-term safety** analysis at 6-months, thromboembolic events were reported in **0.3%** in thr vaccine group (n=68) vs 0.1% in the placebo group (n=14). In the pooled Oxford studies, thromboembolic events were reported in **0.1%** (7/12282 participants) in the vaccine group and 0.2% (18/11962 participants) in the control group. There were no reports of cerebral venous sinus/cerebral venous thrombosis or splanchnic vein thrombosis. One event of mesenteric vein thrombosis was reported in the control group in the Oxford studies. No concurrent AEs of thrombocytopenia or platelet count decrease were reported in participants with a thromboembolic event. *Potential mechanism*: The mechanism is unknown. *Risk factors*: There are no known risk factors identified.
CVST without thrombocytopenia[core]	*Frequency* • Post-market: **573 cumulative cases** • Clinical-trials: **no cases** *Potential mechanism*: The exact mechanism of CVST without thrombocytopenia following administration with VAXZEVRIA is unknown. *Risk factors*: There are no known risk factors for the development of CVST without thrombocytopenia following vaccination
Immune-mediated neurological conditions[core]/Nervous system	*Frequency* • Post-market: **36033 cumulative cases**, including 5641 interval cases. During the reporting period, the most commonly reported PTs were:

Safety concerns	Characterisation (DLP 28 June 2022)
disorders, including immune-mediated neurological conditions[EU]	Paraesthesia (2976), Hypoaesthesia (1982), Neuralgia (358), Guillain-Barre syndrome (318), Sensory disturbance (232), Neuropathy peripheral (93), Myelitis transverse (80), Sensory loss (79), Polyneuropathy (63), Optic neuritis (49), Encephalitis (42), Acute disseminated encephalomyelitis (37), Myelitis (35), Multiple sclerosis (33), Chronic inflammatory demyelinating polyradiculoneuropathy (28), Multiple sclerosis relapse (24), Neuritis (19), Miller Fisher syndrome (18), Demyelination (18), Neuromyelitis optica spectrum disorder (15), Myelopathy (14), Peripheral sensory neuropathy (12), Myelin oligodendrocyte glycoprotein antibody-associated disease (12) • Clinical-trials: In the USA study, neurologic or neuroinflammatory AESIs were reported **in 0.6%** (121/21,587 participants) in the VAXZEVRIA group and 0.4% (48/10,792 participants) in the placebo group. There were 5 non-serious AEs of facial paralysis, 1 SAE of a demyelinating event in the VAXZEVRIA group (event initially reported as GBS, which was subsequently diagnosed as an SAE of Chronic inflammatory demyelinating polyradiculoneuropathy). In the pooled Oxford studies, neurologic or neuroinflammatory AESIs were reported **in 0.7%** (81/12,282 participants) in the VAXZEVRIA group and 0.8% (90/11,963 participants) in the control group. The most frequently reported events were non-serious AEs of facial paralysis (4 vs 3). There were 3 SAEs of demyelinating events (2 cases in the VAXZEVRIA group [1 case of transverse myelitis, and 1 case of multiple sclerosis in a participant with pre-existing, but previously unrecognised, multiple sclerosis], and 1 case of myelitis in the control group.) *Potential mechanism*: Several hypothetical biological mechanisms have been proposed to explain the pathophysiology of neurologic adverse reactions following immunisation; most involve the concept of immunity and the possibility that the vaccine's immunostimulatory effect results in an aberrant immunologic response (Stratton KR et al 1994). *Risk factors*: There are no known risk factors for the development of nervous system disorders, including immune-mediated neurological conditions, following vaccination.
Vaccine-associated enhanced disease (VAED)[cote] /Vaccine-associated enhanced respiratory disease (VAERD)[EU]	*Frequency* • Post-market: **2139** cases of **potential** VAED/VAERD; **no** cases of **confirmed** VAED/VAERD • Clinical-trials: In the USA study, **COVID-19 related AESIs** were reported in **1.7%** (374/21587 participants) of the **VAXZEVRIA group** and in **3.4%** (362/10792 participants) of the **placebo group**. In the pooled Oxford studies as of 07 December 2020, COVID-related AESIs were reported in **0.1%** (15/12282 participants) of the COVID-19 VACCINE ASTRAZENECA group and **0.3%** (36/11963 participants) of the control group.

Safety concerns	Characterisation (DLP 28 June 2022)
	Potential mechanism: The pathogenesis of VAED in the context of SARS CoV 2 is unclear and there are no consistent mechanisms or immune markers of disease enhancement from non-clinical studies (Haynes et al 2020). *Risk factors*: There are no known risk factors identified for VAED/VAERD.
Missing information	
Use of COVID-19 VACCINE ASTRAZENECA in pregnant and breastfeeding women[core]/Use during pregnancy and while breastfeeding[EU]	Data from more than **400 case reports of pregnant women** or women who became pregnant after receiving VAXZEVRIA do not suggest unusual patterns of pregnancy complications or foetal/neonatal outcomes. No increased risk of maternal thrombosis in combination with thrombocytopenia has been observed. Preliminary non-clinical safety studies have not indicated any concern to date, and available non-clinical, clinical and post-marketing data do not suggest a risk to breastfed newborns/infants. As VAXZEVRIA is intended for use in mass vaccination campaigns in a large proportion of the global population, the collection of pregnancy and infant outcomes data with the aim of further characterising the safety profile in this population, is still considered necessary.
Use of COVID-19 VACCINE ASTRAZENECA in subjects with immunodeficiency[core]/Use in immunocompromised patients[EU]	Vaccines may be less effective in severely immunocompromised subjects. Although there is no evidence that the safety profile of this population receiving VAXZEVRIA will be different to that of the general population, given the paucity of data, the possibility cannot be excluded. Use of VAXZEVRIA in subjects with severe immunodeficiency will continue to be investigated in the planned PASS and in ongoing clinical study COV005.
Use in patients with autoimmune or inflammatory disorders[EU]	There is no evidence from COVID-19 VACCINE ASTRAZENECA clinical studies to date that the safety profile of this population differs from that of the general population. However, given the paucity of data, the possibility cannot be excluded. Use in patients with autoimmune or inflammatory disorders will be investigated in the ongoing PASS studies.
Use of COVID-19 VACCINE ASTRAZENECA in subjects with severe and/or uncontrolled underlying disease[core]/Use in frail patients with co-morbidities (eg, COPD, diabetes, chronic neurological disease, cardiovascular disorders)[EU]	There is no evidence that the safety profile of this population receiving COVID-19 VACCINE ASTRAZENECA will be different to that of the general population, given the paucity of data, the possibility cannot be excluded. Use of VAXZEVRIA in patients with severe and/or uncontrolled disease will continue to be investigated in the planned PASS.
Use of COVID-19 VACCINE ASTRAZENECA with other vaccines[core]/Interactions with other vaccines[EU]	There is currently limited information regarding the safety, immunogenicity, and efficacy of VAXZEVRIA when co-administered with other vaccines (eg, concurrently with seasonal illness vaccines). While there is currently no evidence to suggest the safety profile or efficacy of VAXZEVRIA when co-administered with other vaccines would be impacted, given the paucity of data, the possibility of an interaction causing an altered safety profile or reduced efficacy of either VAXZEVRIA or the co-administered vaccine cannot be excluded.

Safety concerns	Characterisation (DLP 28 June 2022)
	The co-administration of VAXZEVRIA with other vaccines (either together, or 30 days before or after administration) will continue to be investigated in the planned PASS.
Long-term safety[EU]	There are no known risks with a potentially delayed onset, with the exception of the theoretical concern of VAED/VAERD. There is currently no evidence suggesting an adverse long-term safety concern. At 6-months follow-up from Study D8110C00001 the AEs observed were consistent with the safety findings at the primary analysis. In the AZD1222 group, a small proportion of SAEs and AESIs were reported, with no clinically meaningful findings. Overall, VAXZEVRIA remains well-tolerated up to 6 months post dose. Long-term safety will be evaluated through follow-up in ongoing clinical studies in the VAXZEVRIA clinical development programme.

[CORE] : core-RMP specific safety concern
[EU] : EU-RMP specific safety concern

Rapporteur assessment comment:

During the period under review, the following issue was removed from the safety concerns for Vaxzevria:

- Anaphylaxis is no longer considered as an Important Identified Risk in the EU-RMP. Anaphylaxis has been re-classified as 'non-important identified risk' because it is now considered fully characterised and no additional RMM are ongoing or planned.

3. Benefit evaluation

3.1. Benefits previously identified

- **Long-term efficacy**: D8110C00001 DCO3 (30 July 2021) supports maintenance of efficacy for at least 6-months (VE= 66.98% and a lower bound of the 95% CI of 58.87%.). A closely similar level of efficacy is obtained across age groups.
- **Efficacy against variants:** overall VE in sequenced variants is similar to the VE of the primary analysis in study D8110C00001. Preliminary live virus neutralization data from exploratory analysis suggest that 2-dose primary series immunization will likely provide protection against infection with the Variants of Concern, including Omicron, and clinically meaningful protection against hospitalization and severe disease would be maintained.
- **Efficacy against variants**: an AZD1222 booster in participants previously vaccinated with a primary series of Vaxzevria or mRNA vaccine, elicits strong humoral immune responses against a range of Variants of Concern (Flaxman et al 2021, Munro et al 2021 and is likely to provide clinically meaningful protection against hospitalization and severe disease.

3.2. New information on the benefits

During the reporting period of this PBRER, key data and relevant information became available on:

1) Long-term protection and waning (AstraZeneca sponsored studies D8110C00001 and D8111C00002)
    - D8110C00001: 90% of participants were unblinded. For the primary efficacy endpoints in the double-blind period (78 days for AZD1222 and 71 days for placebo), vaccine efficacy was 67.0% (P>0.001). AZD1222 elicited humoral response over time with waning is observed at day 180.

- D8111C00002: in 256 participants in Japan across all age groups, and after one year of follow up, it was observed that humoral responses against SARS-CoV-2 waned over time from previously reported peak responses post-second dose. At Day 365, anti-SARS-CoV-2 spike-binding and receptor-binding domain mean antibody titres remained above Day 15 levels across all ages. Neutralizing antibody titres declined and were below detection levels in many participants by Day 365.

2) Homologous and Heterologous Third dose booster

- D7220C00001: The humoral immune response to a booster dose of AZD1222 in participants previously vaccinated with either AZD1222 or an mRNA vaccine was non-inferior to the response elicited by primary vaccination with AZD1222 (AZD1222 cohort GMT ratio: 1.03 [95% CI: 0.92 to 1.15]; mRNA cohort GMT ratio: 3.08 [95% CI: 2.78 to 3.41]);
- Xinxue Liu et al. 2022 evaluated the persistence of immunogenicity after seven COVID-19 vaccines given as third dose boosters following two doses of VAXZEVRIA or COMIRNATY in the UK over the course of 3 months.

  The anti-spike IgG in adenoviral vector vaccine arms (ChAd and Ad26) after the BNT/BNT prime showed the most persistent schedules up to D84. The immunogenicity at D84 post boost for ChAd and Ad26 was similar to, or higher than, the three dose BNT schedule (BNT/BNT/BNT), especially in older people.
- RHH-001 (Clemens et al 2022), evaluated AZD1222 as a heterologous booster after a 2-dose primary series of the inactivated whole-virion adjuvanted vaccine CoronaVac. After 28 days, all heterologous boosting elicited a significantly superior response ($p<0.0001$) in anti-Spike IgG concentration and pseudo-neutralising titres compared to homologous boosting with CoronaVac.
- Jara et al 2022 also evaluated the vaccine effectiveness of AZD1222 as a heterologous booster after a 2-dose primary series of CoronaVac. Heterologous boosting with AZD1222, following a two-dose CoronaVac primary vaccination series, yielded vaccine effectiveness of 97·7% (95% CI: 97·3-98·0) against COVID-19-related hospitalisation, 98·9% (95% CI: 98·5%-99·2%) against ICU admission, and 98·1% (95% CI: 97·3–98·6) against death.
- Muñoz-Valle et al 2022 evaluated AZD1222 as a heterologous booster after primary immunisation with the adenoviral vector vaccine Convidecia (CanSino Biologics Inc, China). At baseline, the median percentage of neutralizing antibodies was similar in booster and control groups (78.16% vs. 78.65%, $p > 0.05$), but at 6 months post-booster was significantly higher in the boosted group versus controls (96.41% vs. 89.33%, $p = 0.0004$), with no differences between vaccines. There were also no differences in adverse events between booster vaccines.

3) Vaccine effectiveness against dominant SARS-COV-2 variant of concern omicron

- A recent test-negative case-control study examined the VE against symptomatic disease caused by the Delta and Omicron variants (Andrews et al 2022). No effect against the Omicron variant was observed from 20 weeks after a primary vaccination with AZD1222, but the VE of a booster dose was 55.6% at 2 to 4 weeks and 46.7% at 5 to 9 weeks following booster administration. This decrease in VE was also noted with a third homologous dose of COMIRNATY and mRNA-1273.
- A test-negative case control design was used to estimate the VE of an AZD1222 or COMIRNATY booster following a primary series of AZD1222 against symptomatic disease and hospitalisation after infection with the SARS-CoV-2 Omicron variant in England (Kirsebom et al 2022). Protection against symptomatic disease in those aged 65 years and older peaked at 66.1% and 68.5%

among those who received AZD1222 and COMIRNATY boosters, respectively, and waned to 44.5% and 54.1% after 5 to 9 weeks. VE against hospitalisation after infection with the SARS-CoV-2 Omicron variant peaked at 82.3% after an AZD1222 booster and 90.9% after a COMIRNATY booster. The authors noted differences between the population receiving AZD1222 and the population receiving COMIRNATY, with those receiving 3 doses of AZD1222 more likely to be in risk groups; this was also true for Andrews et al 2022.

- Effectiveness of a 2-dose primary series of AZD1222 remains high (61-71% VE) against hospitalisation due to Omicron variant in individuals 65+ years of age in England who completed their primary series >175 days previously (Kirsebom et al 2022, Stowe et al 2022).
- At 7+ days after a 3rd dose AZD1222 booster on top of an AZD1222 primary series, effectiveness against hospitalisation due to the Omicron variant is 82% (95% CI 64-91%). (Kirsebom et al 2022).
- Against symptomatic Omicron infection in Thailand, AZD1222 given as a 1st booster was shown to have 26% VE (95% CI 8-40), whilst AZD1222 as a 2nd booster offered significantly higher protection, with 71% VE (85% CI 59-79; Chariyalertsak et al 2022)
- Effectiveness of hybrid immunity (infection plus vaccination) against infection for AZD1222 vaccine as 1st booster peaked at 72.1% (95% CI: 71.4-72.8%) during a period when Omicron was dominant in Brazil. Protection against severe illness (hospitalization or death) provided by a 1st booster dose of AZD1222 peaked at 98.1% (95% CI: 97.7-98.5%) during an Omicron predominant period (Cerqueira-Silva et al 2022).
- In a prison population in Zambia that included over 10.5% of individuals who were living with HIV, effectiveness of an AZD1222 primary series against infection with Omicron was 89.4% (95% CI: 59.5-97.8%), whilst effectiveness against symptomatic infection with Omicron was 85.1% (95% CI: 19.5-98.0%; Simwanza et al 2022).

4) R-pharm multicentric study assessing the safety and immunogenicity of interchangeability of two different adenovirus vector vaccines (rAd26 and VAXZEVRIA).

"A Phase I/II Single-Blinded Randomised Safety and Immunogenicity Study in Adults of VAXZEVRIA and rAd26-S Administered as Heterologous Prime Boost Regimen for the Prevention of COVID 19".

Overall, AZD1222 and rAd26 S components have demonstrated an acceptable safety profile with no new safety concerns from combination use of vaccines (administered in either order) in healthy adults without known past laboratory confirmed SARS CoV 2 infection, positive SARS CoV 2 RT PCR test at screening, or seropositivity to SARS CoV 2 at screening.

Reactogenicity, as evaluated by the incidence of solicited AEs for 7 days post each dose, appeared to be greater in the sequence AZD1222/rAd26 S compared with the sequence rAd26 S/AZD1222, particularly with respect to the incidence of Grade 3 (severe) solicited local and systemic AEs observed during the first few days after injection. Overall, the reactogenicity findings were consistent with the known and well-established safety profile of AZD1222.

Rapporteur assessment comment:

New information on the benefit of Vaxzevria support:

- The use of Vaxzevria as heterologous booster;
- A rapid waning of antibody titres and vaccine effectiveness, but persistence of effectiveness against severe forms;

There are no new data on efficacy that alters previous assessments, which are describe in the approved

product information.

These data provide supportive evidence of AZD1222's immunogenicity and safety profile when used as a heterologous booster. Yet, these findings should be further explored in the Omicron era.

4. Benefit-risk balance

4.1. New information on the benefit of Vaxzevria

New efficacy/effectiveness data indicate an potential role of Vaxzevria in heterologous vaccination scheme. Yet, these findings should be further confirmed in the Omicron era and with new variants of interest.

Data also support effectiveness against severe forms of COVID-19 leading to hospitalisation or death.

New information on the benefit of Vaxzevria does not modify the conclusions of previous assessments.

4.2. New information on the risks of Vaxzevria

Safety items for which a **causal relationship** is considered as **a reasonable possibility** and which are proposed for addition in section 4.8 of the SmPC:

- Cutaneous vasculitis

Safety items for which new safety information **does not support a causal association** with Vaxzevria:

- Hearing loss
- Sarcoidosis
- Subacute thyroiditis
- Rhabdomyolysis
- Viral reactivation (Non-Zoster)
- Myocarditis
- Exacerbation of type 1/type 2 diabetes mellitus, adrenal insufficiency and hypertension
- Corneal graft rejection (see Section 1.3.7)

Safety items for which a **causal relationship** with Vaxzevria is **uncertain** and further discussion is required:

- Thrombosis, and more particularly VTE
- ADEM
- Menstrual disorders
- Glomerulonephritis and nephrotic syndrome, including IgA nephropathy

Of note, regulatory actions were taken regarding risks already identified in the previous PSUR:

- SmPC has been updated for tinnitus and paraesthesia/hypoaesthesia, (see section 1.3.1 and 1.3.2)
- RMP has been updated for anaphylaxis (which has been removed from the important identified risks)

Signals and safety topics identified after the data lock point:

- Pemphigus and pemphigoid, identified by EMA in October 2022: confirmation of the signal is ongoing
- SCAR: signal identified by WHO-UMC

Finally, it should be noted that no new risk or new level of risk was identified after a booster dose with Vaxzevria or after an heterologous boost following a primary vaccination with Vaxzevria.

The PRAC Rapporteur concludes that safety findings during the reporting period did not change significantly the level of concern regarding the safety of Vaxzevria.

4.3. Conclusion on the benefit/risk balance

The PRAC Rapporteur considers that safety information collected during the period under review [from 29.12.2021 to 28.06.2022] does not modify the B/R balance of the vaccine. However, the risks of SARS-CoV-2 infection and the context of treatment and prevention of the disease have evolved.

TTS, CVST and GBS, the key risks identified for Vaxzevria, are greater risks in young adults who benefit less from vaccination. This observation led to question the B/R balance in the younger population and for several EU Member States to restrict the use of the vaccine, especially after more alternative vaccines were made available. In the EU context, the use of vaccines in specific groups remains to the remit of the NITAGs and NIPs.

Overall, the benefit/risk balance for Vaxzevria remains **unchanged**.

5. Rapporteur Request for supplementary information

Venous Thromboembolism

To address the inconsistent risk estimations of venous thromboembolism observed in the literature studies, the MAH is asked to discuss the interest of conducting a meta-analysis of all available data from the MAH studies as well as any published studies in the next PBRER.

6. MAH responses to Request for supplementary information

RSI 01 – PI Update

Request to update of section 4.8 of the SmPC to add cutaneous vasculitis with a frequency 'not known' based on data assessed within this procedure and to update the Package leaflet accordingly.

The following changes to the product information of medicinal products containing COVID-19 Vaccine (ChAdOx1-S [recombinant]) (Vaxzevria) are recommended (new text underlined and in bold, deleted text strike through):

Summary of Product Characteristics

- Section 4.8

The following adverse reaction(s) should be added under the SOC Skin and subcutaneous tissue disorders with a frequency **Not known: Cutaneous vasculitis.**

The PRAC Rapporteur proposed to slightly update the wording to align the signs/symptoms with the other vector-based COVID-19 vaccine:
Not known: inflammation of blood vessels in the skin, often with a rash and ***or*** small red or purple, ***flat, round*** spots ***under the skin's surface or bruising (cutaneous vasculitis)***

MAH's response

AstraZeneca considers the proposed wording in the package leaflet to sufficiently describe the signs and symptoms of cutaneous vasculitis, but accepts the changes proposed by the PRAC Rapporteur and has included the requested wording as an imposition.

Rapporteur assessment comment:

The PI has been updated as recommended.

Issue resolved

RSI 02 - Venous Thromboembolism

To address the inconsistent risk estimations of venous thromboembolism observed in the literature studies, the MAH is asked to discuss the interest of conducting a meta-analysis of all available data from the MAH studies as well as any published studies in the next PBRER.

MAH's response

Studies are generally eligible to be combined in a meta-analysis if they are similar enough to be grouped together, with respect to their study designs, research questions, study and comparator populations, settings and context, interventions or exposures, data collection methods, time points of collection, measurements, and the consideration of within-study biases and reporting biases (McKenzie et al 2022).

Out of the twelve studies included in the last PBRER (covering the period 29 December 2021 to 28 June 2022), four are cohort studies using unvaccinated persons as a comparator, three are cohort studies using historical comparators, four are self-controlled case series which includes cases only comparing the time period after vaccination to an unexposed baseline period, and one was a systematic review and meta-analysis. Given these different designs, a meta-analysis would be problematic.

One of the included studies in the last PBRER (covering the period 29 December 2021 to 28 June 2022) was a systematic review with meta-analysis that found much heterogeneity among the studies, due to different study populations being included such as transplant recipients or cancer patients, health care workers, health care workers with previous severe allergic diseases, and the general population (Chen et al 2022). As included in the last PBRER (covering the period 29 December 2021 to 28 June 2022) the AstraZeneca assessment of this study is that the adverse event rates of venous and arterial thrombosis would differ between these populations and to meta-analyse them makes interpretation difficult. It is expected that the same issues would be encountered if meta-analysing data from published studies. Moreover, the outcome measures differ between the studies, with some including deep vein thrombosis (DVT) and pulmonary embolism (PE) (Burn et al 2021, Burn et al 2022; Hippisley-Cox et al 2021; Whitely et al 2022).

In one of AstraZeneca's ongoing PASS studies, the multi-country VAC4EU PASS, a meta-analysis of all adverse events of special interest is planned, including venous thromboembolism. The meta-analysis will combine results from the five databases included in the PASS: CPRD Aurum (UK) VID, Catalonia ARS (Spain), SIDIAP (Spain), Toscana Valencia (Italy), and PHARMO (the Netherlands) and the total sample will exceed 5 million participants. The final report is expected in April 2024.

In summary, given the heterogeneity of the published studies, AstraZeneca is of the opinion that conducting a meta-analysis of all available data would not add valuable information over the routine ongoing literature review, that will be submitted as part of the next PBRER (data lock point:28 December 2022), and the planned meta-analysis in the VAC4EU PASS.

Rapporteur assessment comment:

The MAH highlighted the heterogeneity in study design and methods of the 12 studies discussed in the last PBRER. It is agreed that this will make it difficult to compare the results of these studies and to combine them in a meaningful way in a meta-analysis. Moreover, the outcome measures differ between the studies, with some including deep vein thrombosis (DVT) and pulmonary embolism (PE). VTE is also influenced by multiple factors and it may be difficult to control for all of these factors in a meta-analysis.

As part of the MAH's PASS, a meta-analysis of all AESI is planned, including venous thromboembolism. The meta-analysis will combine results from the five European databases included in the PASS with a total sample of over 5 million participants. The final report is expected in April 2024. To note is that this meta-analysis may face similar challenges (discussed in procedure EMEA/H/C/005675/MEA007.7).

The MAH should discuss the topic of VTE by providing an updated literature review, with a focus on new relevant epidemiological studies (cfr. Section 4, issues to be addressed in the next PSUR).

Issue partially resolved data to be further discussed in the next PSUR.

7. Comments from Member States

Comments from EMA

On 8 December 2022, EMA sent out a validated signal for myositis [EPITT 19882], based on the following:

Background: Idiopathic inflammatory myopathies (IIM), also referred to as (autoimmune) myositis or autoimmune myopathies, are a group of autoimmune disorders with a heterogenous and specific spectrum of muscular and extra-muscular involvement. IIM classifications vary but the main subtypes include dermatomyositis (DM), polymyositis (PM), immune-mediated necrotising myopathy (IMNM) and inclusion body myositis (IBM). Forms of IIM that share features with other connective tissue diseases are referred to as overlap myositis (OM). These include antisynthetase syndrome (ASS). IIMs are rare conditions (DM/PM annual incidence 0.4-4 cases per 100,000 patients) more common in women and people of Black ethnicity. The usual onset age of PM is between 45-60 years while DM shows a bimodal age distribution (5-15 and 45-60 years).

Patients with IIM typically present with progressive symmetric proximal weakness that may manifest as difficulty rising from chairs, climbing stairs or combing one's hair. Patients with DM also show typical skin lesions (heliotrope rash, shawl sign, Gottron papules, mechanic's hands) while those with ASS experience a variable combination of myositis, arthritis, Raynaud phenomenon, mechanic's hands and interstitial lung disease (ILD). Diagnosis of IIMs is based on muscle biopsy (gold standard), clinical signs, serology (autoantibodies), laboratory parameters (e.g., creatine kinase), electromyography (EMG) and/or magnetic resonance imaging (MRI). Therapeutic management is based on immunomodulating and immunosuppressive agents […]. The 5-year survival rate is around 75%, with causes of death linked to generalised weakness, dysphagia/undernutrition, respiratory failure or infections.

IIMs are associated with both genetic factors (certain HLA subtypes) and environmental triggers such as drugs, infections, UV light, vitamin D deficiency, smoking and cancer. SARS-CoV-2 infection has been linked to a viral myositis attributable to direct myocyte invasion or induction of autoimmunity. COVID-19-induced myositis may vary in presentation, from typical dermatomyositis to rhabdomyolysis, and a paraspinal affliction with back pain. The pathophysiology of IIM is complex with various pathways: DM is a complement-mediated microangiopathy leading to destruction of capillaries, distal hypoperfusion and inflammatory cell stress on the perifascicular regions, while PM is characterised by cytotoxic CD8-positive T cells which clonally expand in situ and invade muscle fibres expressing the major histocompatibility

complex (MHC)-I. An autoimmune response to nuclear and cytoplasmic autoantigens is detected in 60 - 80% of patients with PM/DM. The autoantibodies involved in IIM are divided into myositis-specific autoantibodies (MSA), which are found primarily in patients with IIM, and myositis-associated autoantibodies (MAA), which are shared with other connective tissue diseases. […]. These antibodies are important markers of diagnosis and prognosis, and guide therapeutic management of IIM. […]

Seriousness: Idiopathic inflammatory myopathies (IIM) carry a significant morbidity. Seventy-five percent (75%) of cases in EudraVigilance (EV) are reported as serious, including 5 fatal cases.

Evidence: 21 literature cases from 11 articles, 209 cases in EV (including 12 of the 21 literature cases). Significant imbalance in observed-to-expected (O/E) analyses.

Table 1 - Literature cases of myositis in association with Vaxzevria

Aydinaj 2021	[redacted]	68M		2	3 weeks	rash, myalgia, muscle weakness			CK increased, biopsy	DM	Steroids	Improved	AstraZeneca-[redacted]
Base 2022	[redacted]	53M		1	2 days	myalgia, muscle weakness			CK 187U/L, myoglobinuria, MRI	Myositis	NSAIDs	Partially recovered	[redacted]
Capassoni 2021	[redacted]	37F		1	4 days	rash, arthritis, oedema, muscle weakness, neuropathic pain		PM-Scl	Skin biopsy, ANA+, EMG	PM	Steroids, IVIg	Recovered	AstraZeneca-[redacted]
De Marco 2022	[redacted]	68F		2	34 weeks	asthenia, dysphonia, impaired swallowing, Gottron's papules, heliotrope rash, shawl's sign, aspiration pneumonia	SAE-1		CK 536 U/L, CRP 55 mg/L, MRI, ANA+	Autoimmune myositis	Steroids, IVIg, MTX, HCQ	Partially recovered	
De Marco 2022	[redacted]	68F		2	25 weeks	asthenia, impaired swallowing, Gottron's papules, heliotrope rash, shawl's sign	Mi-2		CK>7000 U/L, CRP 24 mg/L, MRI, ANA+	Autoimmune myositis	Steroids, IVIg, MTX, HCQ	Recovered	
De Marco 2022	[redacted]	58F		1	4 weeks	amyopathic, sicca symptoms, shortness of breath, heliotrope rash, mechanics hands, ILD, pericardial effusion		PM-Scl, Ro	CRP 20 mg/L, ANA+	Autoimmune myositis	Steroids, cyclophosphamide, MMF	Partially recovered	
De Marco 2022	[redacted]	61M		1	2 weeks	asthenia, general malaise, weight loss			CK 17,000 U/L, EMG	Autoimmune myositis	Steroids, MTX	Partially recovered	
De Marco 2022	[redacted]	76F	Statin	2	5 weeks	asthenia, myalgia	PI-12	PM-Scl	CK 7598 U/L, EMG, MRI, biopsy	Autoimmune myositis	Steroids, azathioprine, IVIg	Recovered	
De Marco 2022	[redacted]	37F	SLE	1	4 weeks	asthenia, myalgia		Ro, RNP	CK 1299 U/L, EMG, MRI, biopsy, ANA+	Autoimmune myositis	Steroids, MTX	Ongoing	
De Marco 2022	[redacted]	78F		1	2 weeks	asthenia, myalgia, pulmonary embolism	Jo-1		CK 2725 U/L, CRP 53 mg/L, MRI, ANA+	Autoimmune myositis	Steroids, azathioprine, MTX	Recovered	
De Marco 2022	UK	67M	Statin	2	6 weeks	asthenia, dysphagia, respiratory arrest, renal failure, suspected myocarditis, infections, death		Ro, La	CK 149,430 U/L, CRP 220 mg/L, biopsy, ANA+	Autoimmune myositis	Steroids, IVIg, rituximab	Fatal	
De Marco 2022	[redacted]	83F	GCA	2	6 weeks	asthenia, general malaise, weight loss	SRP		CK 3070 U/L, CRP 19.5 mg/L, EMG, MRI	Autoimmune myositis	Steroids, MTX	Partially recovered	
Fatooq 2022	[redacted]	63M		1, 2	unk	shortness of breath, dyspnoea, myalgia, myopericarditis, pneumonitis			CK 4053 U/L, troponin 472 ng/ml, CRP 60, ANA+	Inflammatory myositis	Steroids	Recovered	AstraZeneca-[redacted]
Gonzalez 2022	[redacted]	58F		2	1 week	rash, Gottron's sign, dyspnoea, polyarthralgia, ILD	MDA5			DM	Tacrolimus, IVIg, PLEX, HCQ, nintedanib	Improved	AstraZeneca-[redacted]
Gupta 2021	[redacted]	46F		2	1 week	fever, arthralgia, weakness, fatigue, ILD	Jo-1	Ro	CRP 76 mg/L, EMG	Anti-Jo-1 syndrome	MTX, steroids, MMF	Recovered	[redacted]
Hocevar 2022	[redacted]	30-39M		1	1 day				unk	Myositis	Steroids	unk	AstraZeneca-[redacted]
Huang 2022	TW	44M		2	unk	myalgia, muscle weakness, anuria, vasculitis, rhabdomyolysis		PM-Scl	CT, CK elevated, biopsy	DM	Steroids, cyclophosphamide	Fatal	AstraZeneca-[redacted]
Mayamatton 2021	[redacted]	74M		1	2 days	fever, tachycardia, arthralgia, myalgia vasculitis			CRP 269 mg/L, D-dimer 2010 ng/ml, CT, MRI, biopsy	Myositis	Steroids	Recovered	AstraZeneca-[redacted]
Mayamatton 2021	[redacted]	75F		1	2 days	fever, arthralgia, myalgia, tachycardia			CRP 271 mg/L, CT, MR1	Myositis	Steroids, MMF	Recovered	AstraZeneca-[redacted]
Mayamatton 2021	[redacted]	80F		2	2 days	fever, fatigue, tachycardia			CRP 102 mg/L, MR1	Myositis	Steroids	Recovered	AstraZeneca-[redacted]
Rampal Guevara 2022	[redacted]	27M		1, 2	1 week, few days	arthralgia, myalgia, heliotrope rash, Gottron's papules, Holster sign		RNP	ESR, ANA+	Amyopathic DM	Steroids, MTX	Improved	AstraZeneca-[redacted]

CK: creatine kinase; CT: computed tomography scan; CRP: C-reactive protein; DM: dermatomyositis; EMG: electromyography; ESR: erythrocyte sedimentation rate; HCQ: hydroxychloroquine; GCA: giant cell arteritis; ILD: interstitial lung disease; IVIg: intravenous immunoglobulin; MMF: mycophenolate mofetil; MRI: magnetic resonance imaging; MTX: methotrexate; PLEX: plasma exchange; PM: polymyositis.

ROR: No signal of disproportionate reporting in EV for PT 'myositis' [ROR(-) 0.44, 152 cases] nor any other related term.

Exposure: Cumulative exposure as of June 2022: 2.09 billion doses administered worldwide, 69 million in the EU/EEA [sources: PSUR, ECDC]

Regulatory Context: Some myositis-related terms included in search strategies for other safety topics in PSURs (i.e., VAED/VAERD and rhabdomyolysis), but no dedicated discussion on myositis. Signal sent in parallel for Comirnaty and Spikevax.

Rapporteur assessment comment:

EMA identified a signal on myositis after vaccination with Vaxzevria based on EudraVigilance (EV) and literature data [EPITT 19882].

At the time of the signal validation, a total of 209 cases were retrieved from EV and described mainly Myositis (150), Dermatomyositis [DM] (28), and Polymyositis [PM] (21). The majority of the cases were reported from non-HCPs. Cases reports were mainly described in female (ratio female-to-male of 1.8 : 1) which might reflect the natural epidemiology of the disease. A prior history of myositis was reported in 11 cases. About 75% of cases were serious, including 5 cases with a fatal outcome. The range of TTO was quite large, from 0 to 274 days, with a median of 6 days.

No signal of disproportionate reporting was found for any of the reported PT. ROR(-) for most frequently reported PTs was as followed: myositis [n=152; ROR(-) 0.44] , dermatomyositis [n=28; ROR(-) 0.25], and polymyositis [n=23; ROR(-) 0.26].

Twenty-one (21) cases were identified from 11 articles in the literature. The diagnosis was 9 cases of autoimmune myositis, 5 cases of myositis, 3 cases of DM, and 1 case of each inflammatory myositis, amyopathic DM, PM, and anti-Jo-1 syndrome. Myositis-specific autoantibodies [MSA] were identified in 7 cases and myositis-associated autoantibodies [MAA] in 8 cases. Most patients improved and recovered with treatment and 1 case had a fatal outcome.

An O/E analysis was performed using UK and ES background rates, with stratification by gender, age and risk periods. A significant imbalance was observed when UK rates were used but not with ES rates (e.g. O/E ratio (7 days risk period) = 2.82 [95%CI 2.21 – 3.55] with UK rate and 0.89 [95%CI 0.7 – 1.12] for ES rates). When stratified by gender and age, an imbalance was observed for younger females (i.e. 20-29yo and 30-39yo) with both UK and ES rates.

Available safety information supports the need for further review of occurrence of myositis following vaccination with Vaxzevria.

It is therefore recommended that the MAH submits in the next PSUR (DLP 28 December 2022):

- a cumulative review of cases of myositis in association with Vaxzevria including spontaneous reports and data from the literature and clinical trials. The search strategy should be conducted at the level of HLT 'Muscle infections and inflammations';
- a causality assessment of the cases;
- an observed vs expected (O/E) analysis for all cases identified in EU and UK of myositis and related conditions with a risk window of 0 to 28 days and also including events with unknown TTO. For the calculations of the O/E analysis, the relevant and justifiable background incidence rate(s) should be used as well as exposure in EU/UK;
- a discussion on the plausibility and biological mechanism(s) for a possible causal association between myositis and related conditions and vaccination with Vaxzevria;
- a discussion on the need for updating product information and/or risk management plan, and submit proposal as required.

The MAH should ensure that all identified literature cases have been submitted to EudraVigilance and efforts should be made to follow up on other spontaneous cases which are currently subject to limited

information

[Request for the next PBRER]

Comments from MS1

We overall agree with Rapporteur's assessment, but would like to highlight some issues:

- **ADEM**: is cumulatively reviewed in this PSUR. This review showed 3 cases classified by the MAH as BCC level 1 (one of them confirmed by ante-mortem biopsy and autopsy) and the others with absence of recurrence/relapse of illness up to 3 months. In addition, the Rapporteur identified at least 6 cases from the literature with a possible causal association with Vaxzevria, and one of them would be a BCC level 1 case. Although the O/E analysis using BCC level 1-3 cases did not yield a ratio significantly greater than 1 for any of the risk windows or the different stratifications (age/gender/region), the Rapporteur notes a disproportional reporting of ADEM with Vaxzevria in EVDAS. The Rapporteur finally considers that a potential signal of ADEM after Vaxzevria exists and a new cumulative review of this issue is requested for the next PSUR. We acknowledged that the diagnosis of ADEM is challenging, especially regarding spontaneous cases usually lacking relevant data. For example, in the Spanish reporting database 4 cases were reported up to 28 November of 2021 and 3 of them were classified as BCC 2 cases by our expert panel. These cases could not be classified as BCC 1 level since data from biopsy or follow-up at three months were lacking, but a causal relationship with the vaccine could not be ruled out. ADEM is an important potential risk in the RMP, but not mentioned in the product information. Although we concur with the Rapporteur to request a new cumulative review of this topic, in our view, ADEM should be mentioned in section 4.4 with the other neurological events, so that physicians are warned to rule out other causes as stated section 4.4 for other neurological events.

  We agree that more robust epidemiological data are missing to further evaluate this association, but we are not sure that the studies included in the RMP and performed by the MAH could provide more information. However, some other studies promoted by EMA (eg. ROC 20) may provide further data.

- **Menstrual disorders**: we endorse the Rapporteur evaluation about this issue and no changes in the product information are needed at this stage. The Rapporteur proposes that cases of menstrual disorders do not need to be further discussed through PBRERs unless significant new safety information is identified. However, we consider that serious cases requiring hospitalization and the two cases resulted in death should be further described. Nonetheless, we also concur with the Rapporteur that more relevant information is expected to be provided from the updated review of the literature.

- **Hearing loss**: although there are cases that resolved within 7 days, this only applies to 90 cases/340 cases that recovered and reported time for recovering. There are still 975 cases where the patient did not recover and 70 patients that recovered with sequelae. Although we agree that no changes in the product information are warranted, the MAH should keep monitoring this issue in the next PSUR, focusing on the cases that recovered with sequelae and those that did not recover.

Rapporteur assessment comment:

ADEM

The comment from the MS1 is acknowledged.

However, as per the SmPC guidance:

- any adverse reactions described in section 4.4 or known to result from conditions mentioned in section 4.4 should also be included in section 4.8

- adverse events without at least a suspected causal relationship should **not** be listed in the SmPC.

Based on the guidance, and considering that possible causal relationship between ADEM and the vaccine has not been established yet, the PRAC Rapporteur considers that ADEM should not be listed in the SmPC section 4.4 at this stage. This topic will be further discussed in the next PSUR.

As further clarified by EMA (email of 21 Dec 2022), EMA-funded studies (i.e. ACCESS and ECVM) have provided the following information:

1) In ACCESS (see Table 3 of the article published in the journal Vaccine), it has been found that there is a very low background incidence rate of ADEM in the general population, ranging from 0.05 (0.00-0.14) per 100,000 person-years of observations in databases covering only general practitioners, 0.08 (0.00-0.38) in inpatient and EMR hospital databases and 0.33 (0.06-0.59) in GP & in-outpatient databases.

2) There were no cases of ADEM reported in the prospective ECVM study based on patients' reporting through an App, but the design of this study mainly allowed to collect data on signs and symptoms, not on medical diagnoses.

3) A study on the incidence of AESIs in four electronic health care records was performed in WP2 of the ECVM study. Table 4 (page 28) shows that for ADEM the pooled age-standardised background incidence rate in 2020 was 1.05 (0.92-1.18). For Vaxzevria, there was no statistically significant differences between the age-standardised incidence rates before and after vaccination with dose 1 or dose 2.

The association between Vaxzevria and ADEM would be difficult to investigate in epidemiological studies considering the low incidence rates of the disease and its insidious onset will render SCCS quite challenging.

However, as previously requested, the MAH should provide an updated literature review, with a focus on new relevant epidemiological studies.

Menstrual disorders

The comment from the MS1 is acknowledged.

The LoQ for the next PSUR has been updated accordingly.

Hearing loss

The comment from the PRAC MS1 is acknowledged.

The LoQ for the next PSUR has been updated accordingly.

Comments from MS2, MS3

A full endorsement comment was received.

Comments from MS4

We would like to highlight to the Rapporteur a case [redacted] of new daily persistent headache (NDPH) reported from a member of the public to the NCA. The case concerns a 61-year-old female who on same day as the first dose of Vaxzevria experienced blindness transient (lost vision twice/ seeing shapes), contusion (bruising), headaches (severe headaches), head discomfort (feeling pressure in

head), and discomfort (feeling pressure in neck). No detail on other relevant medical history was reported and the patient reported no concomitant medication. This case was initially received in June 2021 and eight follow-ups to the case have been reported by the patient since. The follow-ups describe that the severe headache pain has continued since receiving the first dose of Vaxzevria and the patient can no longer work or tolerate exercise. Results for blood tests, CT and MRI scans have been normal and in January 2022 the patient was diagnosed by her neurologist with refractory new daily persistent headache, following failure of several treatment options. At the time of the most recent follow-up the patient had not recovered.

In addition to this case report we conducted an initial search of EVDAS and have identified 43 cases reporting the PT 'new daily persistent headache' and the ROR (-) = 5.29.

Whilst acknowledging the limitations in the evidence base and the challenges in establishing a causal association considering the severity and impact on quality of life reported in [redacted] and the signal of disproportionality in EVDAS we would ask the Rapporteur to consider including a request for a cumulative review of all data sources for this topic for the next PSUR.

Rapporteur assessment comment:

The comment is acknowledged and agreed. Considering the severity of the event and the disproportionality in EV, a cumulative review of post-marketing, clinical and literature data has been requested to the MAH.

The LoQ for the next PSUR has been updated accordingly.

Appendix: Assessment of the responses to the questions

REQUESTS FOR THE NEXT PSUR

Request 1: Vaccination Errors

The MAH is requested to discuss all fatal cases associated with vaccination error in detail in the next periodic safety update reports (PSURs).

AstraZeneca response: The details are provided in the Vaccination Errors Section 9.2.1 and Appendix 11: Cases with reported vaccination error and case level outcome of fatal are included.

PRAC Rapporteur comment: data were provided and discussed as requested (see Section 1.3.5.3 of the AR). **Issue resolved**

Request 2: Glomerulonephritis and Nephrotic Syndrome

A cumulative review of cases based on search conducted at the level of high-level term (HLT) "glomerulonephritis and nephrotic syndrome".

- ***Causality assessments of the cases.***
- ***A review of articles published during the PSUR reporting period.***
- ***A discussion on the need for updating product information (PI) and/or risk management plan, and submit proposal as required.***

Additional note to the MAH: Published cases should be submitted to Eudravigilance and attempts should be made to follow up on poorly documented spontaneous cases.

AstraZeneca response: Please refer to Section 15.2.8.

PRAC Rapporteur comment: data were provided and discussed as requested (see Section 2.3.27 of the AR). **Issue partially resolved as literature data to be further discussed in the next PSUR.**

Request 3: Cutaneous Vasculitis

The MAH is requested to submit:

- ***A cumulative review of the cases of cutaneous vasculitis published in the literature after vaccination with VAXZEVRIA. The literature search should update the list of articles already retrieved by EMA. The search strategy should be explained.***
- ***A cumulative review of the reported cases of cutaneous vasculitis.***
- ***A discussion on the possible mechanisms of action that could lead to cutaneous vasculitis after vaccination with VAXZEVRIA.***
- ***A discussion on the need to update VAXZEVRIA PI for cutaneous vasculitis.***

AstraZeneca response: Based on a review of all currently available information, in particular case reports received from literature, AstraZeneca considers there is a reasonable possibility of a causal relationship between VAXZEVRIA and cutaneous vasculitis. AstraZeneca, therefore, recommends the European Union (EU) Summary of Product Characteristics (SmPC) section 4.8 be amended to include cutaneous vasculitis as an adverse drug reaction with frequency of "not known". Please refer to PBRER Section 14, Section 15.2.14, Appendix 16 (Cutaneous Vasculitis Evaluation), and EU Regional Appendix R1 (Proposed Product

Information) for further details.

PRAC Rapporteur comment: data were provided and discussed as requested (see Section 2.3.34 of the AR for comment on the proposed wording in the PI). **Issue resolved**

Request 4: Rhabdomyolysis

The MAH is requested to comment on the World Health Organization Uppsala Monitoring Centre (WHO-UMC) identified signal of rhabdomyolysis and to provide a cumulative review of cases reported with VAXZEVRIA. A discussion on the need to update the PI should be included.

AstraZeneca response: Please refer to Section 15.2.9.

PRAC Rapporteur comment: data were provided and discussed as requested (see Section 2.3.28). **Issue resolved**

Request 5: Exacerbations of Type 1/Type 2 Mellitus Diabetes, Adrenal Insufficiency, and Hypertension

The MAH is requested to comment on the WHO-UMC identified signal of exacerbation of these health issues and provide a cumulative review of cases reported with VAXZEVRIA. A discussion on the need to update the PI should be included.

AstraZeneca response: Please refer to Section 15.2.10 including subsection 15.2.10.1, subsection 15.2.10.2, and subsection 15.2.10.3.

PRAC Rapporteur comment: data were provided and discussed as requested (see Section 2.3.29). **Issue resolved**

Request 6: Hearing Loss

The MAH is requested to present an updated cumulative review of all medically confirmed cases of hearing loss, including an age-stratified analysis. A complete review of the literature, including a discussion on possible mechanism should also be provided.

AstraZeneca response: Please refer to Section 15.2.2.

PRAC Rapporteur comment: data were provided and discussed as requested (see Section 2.3.21). **Issue resolved**

Request 7: Menstrual Disorder

The MAH is requested to present an in-depth evaluation of all available data and recently published literature; a discussion on possible mechanism should also be provided. The MAH is requested to present a refined review of cases of rechallenge.

AstraZeneca response: Please refer to Section 15.2.4.

PRAC Rapporteur comment: data were provided and discussed as requested (see Section 2.3.23). **Issue partially resolved as literature data to be further discussed in the next PSUR.**

Request 8: Myocarditis

The MAH is requested to provide the following discussion for myocarditis

- ***A review of newly identified and cumulative cases.***

- ***A causality assessment of myocarditis cases (not provided in the current review).***
- ***A review of the literature for new publications on epidemiologic studies of interest and mechanistic discussions.***
- ***A discussion on new evidence on an association between myocarditis and VAXZEVRIA.***

AstraZeneca response: Please refer to Section 15.2.5.

PRAC Rapporteur comment: data were provided and discussed as requested (see Section 2.3.24). **Issue resolved**

Request 9: Sarcoidosis

The MAH is requested to update the cumulative review of sarcoidosis cases (HLT "acute and chronic sarcoidosis") from all available sources, including details of the underlying condition(s), time to onset, duration, outcome, and an assessment of the causal relationship with the vaccine (according to the WHO-UMC causality criteria). Depending on the results of this review, the MAH should also discuss the need for any potential amendment to the PI, as appropriate.

AstraZeneca response: Please refer to Section 15.2.6.

PRAC Rapporteur comment: data were provided and discussed as requested (see Section 2.3.25). **Issue resolved**

Request 10: Subacute Thyroiditis

The MAH is requested to provide:

- ***A review and discussion of the available literature on the relationship between subacute thyroiditis and vaccination with VAXZEVRIA.***
- ***A review of the medically confirmed cases with a formal causality assessment using WHO-UMC criteria and a case description that allows to reproduce the assessment.***

AstraZeneca response: Please refer to Section 15.2.7.

PRAC Rapporteur comment: data were provided and discussed as requested (see Section 2.3.26). **Issue resolved**

Request 11: Tinnitus

The MAH is requested to discuss relevant literature on plausible mechanism of action.

AstraZeneca response: Please refer to Section 15.2.1.

After the data lock point of the PBRER (28 June 2022), the VAXZEVRIA EU SmPC (EMEA/H/C/PSUSA/00010912/202112 (granted 08 August 2022 on European Commission Decision) was updated to include tinnitus (frequency: uncommon) in Section 4.8 Undesirable effects.

Please refer to Section 4 and Section 16.3.5.2 for further information.

PRAC Rapporteur comment: data were provided and discussed as requested (see Section 2.3.10). Tinnitus is appropriately described in the Section 4.8 of EU-SmPC. **Issue resolved**

Request 12: Booster Dosing

The MAH is requested to discuss any new information regarding booster dosing in the next PSUR.

AstraZeneca response: Please refer to Section 15.2.3.

PRAC Rapporteur comment: data were provided and discussed as requested (see Section 2.3.22). **Issue resolved**

Request 13: Viral Reactivation (Non-Zoster)

The MAH is asked to provide:

- ***An overview cumulative review of viral reactivation (in the high-level group term "viral infection disorders") from all available sources in the next PSUR, including details of the underlying condition(s), concomitant treatments, time to onset, duration, outcome, and an assessment of the causal relationship with the vaccine.***
- ***A discussion on the need for any potential amendment to the PI, as appropriate or other risk minimisation measures.***

AstraZeneca response: Please refer to Section 15.2.13.

PRAC Rapporteur comment: data were provided and discussed as requested (see Section 2.3.33). **Issue resolved**

Request 14: Benefit

The review of new efficacy/effectiveness data appears to be incomplete. In the next PSUR, the benefit evaluation should include clinical trial and post-marketing data on (long-term) effectiveness/efficacy including data on waning vaccine effectiveness against new SARS-COV-2 variants, data on booster dose, use of VAXZEVRIA in mixed schedules, and other effectiveness/efficacy topic at the time of the next reporting period.

AstraZeneca response: Please refer to Section 9.1 and Section 17. In addition, booster dosing data from post-marketing reports is discussed Section 15.2.3.

PRAC Rapporteur comment: data were provided and discussed as requested (see Section 1.3.5.2, Section 2.3.22 and 3.2). **Issue resolved**

Quality Comments

Quality Issue 1: percentages exposure

The MAH is reminded of the request from the previous Assessment Report to provide percentages for the exposure information in line with the bi-monthly SSR#7 (Aug-Sept 2021) to facilitate the review and quick evaluation by the assessors.

AstraZeneca response: Please refer to Section 5.2.1 where the percentages for the VAXZEVRIA exposure based on doses distributed are provided in Table 6, Table 7, Table 8, and Table 9.

PRAC Rapporteur comment: data were provided as requested (see Section 1.3.3.2 of the AR). **Issue resolved**

Quality Issue 2: causality scale

The MAH is reminded that the WHO-UMC causality scale should be used for every causality evaluation (see eg, topic: Sarcoidosis – Section 2.3.36) and to make efforts to correct discrepancies (see eg, discrepancy Hearing Loss Events – Section 2.3.28).

AstraZeneca response: For the vast majority of topics, including sarcoidosis and hearing loss, the WHO-UMC causality assessment algorithm has been applied as requested. Given that the definition of a plausible risk window is central to the algorithm, topics for which a plausible risk window cannot be defined (such as menstrual disorders) are not suitable for this approach. In addition, for the topic of "Thrombosis with Thrombocytopenic Syndrome", a specific case definition that incorporates probability of causality, as proposed by the Medicines and Healthcare products Regulatory Agency (MHRA), has been applied to judge individual case assessments based on the criteria as presented in Section 15.2.15, response to Question 1 d).

AstraZeneca apologizes for the discrepancies identified by PRAC in 2nd PBRER on hearing loss and has made efforts to prevent such discrepancies.

PRAC Rapporteur comment: the MAH clarified that for the vast majority of topics, including Sarcoidosis, the WHO-UMC causality scale has been applied. It is agreed that for the topic of "Thrombosis with Thrombocytopenic Syndrome", specific case definitions apply. Regarding discrepancies such as noted for Hearing loss, the MAH made efforts to prevent these. **Issue resolved.**

Periodic Safety Update Report	
Medicinal Product	COVID-19 Vaccine (ChAdOx1-S [recombinant])
Date	25 August 2022

Periodic Safety Update Report

for

VAXZEVRIA™ (AZD1222)

ATC Code: J07BX03

Note: The format and content of the PSUR are based on those for the Periodic Benefit-Risk Evaluation Report (PBRER) as described in the ICH E2C(R2) guideline – the term PBRER is used within the report itself.

VAXZEVRIA™ is a trade mark of the AstraZeneca group of companies.

Medicinal Products Covered:

Invented name of the medicinal product(s)	Marketing authorisation number(s)	Date(s) of authorisation[a]	Marketing authorisation holder
Vaxzevria	EU/1/21/1529/001-002	29 January 2021	AstraZeneca AB

[a] International Birth Date is underlined. This footnote is particularly applicable if there are numerous authorisation dates; if the list of authorisations is presented separately this footnote may be deleted.

Authorisation procedure in the European Union (EU):	Centralised
International Birth Date (IBD):	29 December 2020
EU Reference Date (EURD):	29 December 2020
Period covered:	29 December 2021 to 28 June 2022
Date of report:	25 August 2022
Marketing authorisation holder's name and address:	AstraZeneca AB 151 85 Södertälje Sweden E-mail address: [redacted]
Name and contact details of QPPV:	Magnus Ysander Pepparedsleden 1, 431 83 Mölndal, Sweden Telephone number: [redacted] E-mail address: [redacted]
Name and contact details of Deputy QPPV:	[redacted] Telephone number: [redacted] E mail address: [redacted]

The content of this Periodic Safety Update Report has been reviewed and endorsed by:	Magnus Ysander Qualified Person for Pharmacovigilance in the EU	Electronic signature is available at the end of the document

This PSUR is submitted according to the guidance:

User Guidance for Marketing Authorisation Holders (MAHs) for PSUR Repository

Periodic Benefit-Risk Evaluation Report

Medicinal Product	COVID-19 Vaccine (ChAdOx1-S [recombinant])
Date	25 August 2022

VAXZEVRIA™(AZD1222)

Periodic Benefit-Risk Evaluation Report

Period covered: 29 December 2021 to 28 June 2022

International birth date: 29 December 2020 (United Kingdom)

Note: This report contains unblinded clinical trial adverse event data.

VAXZEVRIA™(AZD1222)

Periodic Benefit-Risk Evaluation Report

Period covered: 29 December 2021 to 28 June 2022

International birth date: 29 December 2020 (United Kingdom)

The content of this Periodic Benefit-Risk Evaluation Report has been reviewed and endorsed by:

Magnus Ysander
Qualified Person for Pharmacovigilance in the EU

Electronic signature is available at the end of the document

EXECUTIVE SUMMARY

- **Introduction:** This Periodic Benefit-Risk Evaluation Report (PBRER) for VAXZEVRIA™ (AZD1222) summarises safety and efficacy/effectiveness data received and evaluated by AstraZeneca from 29 December 2021 to 28 June 2022, and places it in the context of the cumulative data and the overall benefit-risk profile.
- **Medicinal product:** VAXZEVRIA is a monovalent vaccine composed of a single recombinant, replication-deficient chimpanzee adenovirus (ChAdOx1) vector encoding the S glycoprotein of the Severe Acute Respiratory Coronavirus 2 (SARS-CoV-2). Following administration, the S glycoprotein of SARS-CoV-2 is expressed locally stimulating neutralizing antibody and cellular immune responses. VAXZEVRIA is indicated for active immunization of individuals ≥ 18 years old for the prevention of coronavirus disease 2019 (COVID-19). VAXZEVRIA is supplied as a vial containing either 8 doses or 10 doses per vial, 0.5 mL per dose for intramuscular (IM) injection. The VAXZEVRIA primary vaccination course consists of two separate doses of 0.5 ml each. The second dose should be administered between 4 and 12 weeks after the first dose. It is recommended that individuals who receive a first dose of VAXZEVRIA complete the vaccination course with VAXZEVRIA. A booster dose (third dose) of 0.5 ml may be given to individuals who completed the primary vaccination course with VAXZEVRIA or another authorised COVID-19 vaccine at least 3-months after completing the primary vaccination course. The approval and dosing interval of booster dose for VAXZEVRIA may vary according to the countries of authorisation.
- **Marketing approvals:** As of 28 June 2022, VAXZEVRIA has been approved for conditional marketing authorisation or emergency use authorisation in 93 countries managed by AstraZeneca and its partners – Serum Institute of India (SII), R-pharm, Fiocruz, and Verity Pharmaceuticals. VAXZEVRIA is distributed via COVID-19 Vaccines Global Access programme (COVAX), in collaboration with United Nations Children's Fund (UNICEF) and Pan American Health Organization (PAHO), under a World Health Organization (WHO) Emergency Use Listing to more than 80 countries.
- **Actions taken or proposed for safety reasons:**

  No significant actions related to safety were taken or proposed during the reporting period.
- **Safety changes to Reference Safety Information:**

  During this reporting period, the VAXZEVRIA (Core Data Sheet) CDS was updated to include the following safety-related changes:

  On 06 January 2022 CDS Section 4.6 - Pregnancy and lactation was updated with pregnancy wording to reflect current safety data on administration of VAXZEVRIA in pregnant women. Also, recommendation to consider use of VAXZEVRIA during pregnancy when benefits outweigh potential risks was updated.

  On 16 January 2022 CDS Section 4.6 - Pregnancy and lactation was updated with wording to reflect current non-clinical, clinical and post-marketing data on use of VAXZEVRIA during breastfeeding.

  On 04 February 2022 CDS Section 4.2 - Posology and method of administration was updated to include the recommendation for use of a booster dose (third dose) in

individuals who completed the primary vaccination course with VAXZEVRIA or another authorised COVID-19 vaccine. Timing for administration of the booster dose is at least 3 months after completing the primary vaccination course. The text in CDS Section 4.4 – Special warnings and special precautions for use was revised to clarify that limited data are available regarding the interchangeability of VAXZEVRIA with other COVID-19 vaccines.

On 02 March 2022 CDS Section 4.8 Undesirable effects was updated to add paraesthesia and hypoaesthesia to the summary of post-authorisation data, with frequency uncommon.

On 11 May 2022 CDS Section 4.4 – Special warnings and special precautions for use was updated to include the warning on Neurological events to specifically reference very rare events of Guillain-Barré Syndrome (GBS) as having been reported following vaccination with VAXZEVRIA.

- **Estimated cumulative exposure of clinical trial subjects:** Approximately 60153 patients and/or healthy volunteers have been enrolled into the clinical development programme, of which approximately 35921 have received VAXZEVRIA and 1523 have received AZD2816.
- **Estimated cumulative and reporting period patient exposure from post-approval (marketing) experience:** AstraZeneca is working directly with health departments in individual countries to determine the number of doses administered. Presently, administration data is available from the European Union, United Kingdom, Afghanistan, Argentina, Australia, Bangladesh, Brazil, Canada, Chile, Colombia, Ecuador, Guatemala, India, Iran, Iraq, Japan, Lebanon, Malaysia, Mexico, Nepal, New Zealand, Peru, Philippines, Saint Lucia, South Korea, Taiwan, Thailand and Uruguay. The cumulative number of doses administered in these territories/regions was confirmed as being over 2.09 billion doses. The number of doses distributed globally are over 2.79 billion doses cumulatively.
- **Late-breaking information:** On 01 July 2022, CDS Section 4.8 was updated to include 'Tinnitus' with frequency 'Uncommon'.

  The following signals were validated after the data-lock of this PBRER:

  Immune thrombocytopenia (ITP): The signal for ITP was re-opened based on well-documented case reports of ITP with VAXZEVRIA from the published literature.

  Cutaneous Vasculitis: The signal for cutaneous vasculitis was identified based on well-documented case series from published literature cases. Subsequently a signal was received from PRAC (Pharmacovigilance Risk Assessment Committee) PSUR (Periodic Safety Update Report) assessment report. Upon further evaluation the signal is confirmed and the CDS Section 4.8 is in progress to be updated to include cutaneous vasculitis as an ADR (frequency: not known). The updated CDS will be internally approved before the due date of this PBRER.
- **Summary of overall benefit-risk evaluation:**

  The clinical benefit demonstrated in clinical trials, combined with the overall safety profile of VAXZEVRIA has established a positive benefit-risk profile for the approved indications.

  The data received during the reporting period do not indicate a change in this positive benefit-risk profile for the approved indications.

- **Conclusions and actions**:

  It is AstraZeneca's opinion that the information in the current document and the CDS accurately reflects the known benefit-risk profile for VAXZEVRIA.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

Regional Appendices are relevant for submission as follows

European Union (EU)

Regional Appendix R1	Proposed Product Information
Regional Appendix R2	Proposed Additional Pharmacovigilance and Risk Minimisation Activities (Not produced as no proposals to report)
Regional Appendix R3	Summary of Ongoing Safety Concerns in the European Union
Regional Appendix R4	Reporting of Results from Post-Authorisation Safety Studies (Not produced as no information to report)
Regional Appendix R5	Effectiveness of Risk Minimisation (Not produced as not applicable)

The following Regional Appendices are not required for submission in EU

Regional Appendix R6	Individual Case Safety Reports
Regional Appendix R7	US Prescribing Information
Regional Appendix R8	Combination Product Five-day and Malfunction Report Analysis

LIST OF ABBREVIATIONS

The following abbreviations are used in this Periodic Benefit-Risk Evaluation Report.

Abbreviation or special term	Explanation
ACCP	American College of Chest Physicians
ACE	Angiotensin Converting Enzyme
ACO	Addendum to the Clinical Overview
ADEM	Acute Disseminated Encephalomyelitis
ADR	Adverse Drug Reaction
AEs	Adverse Events
AEFI	Adverse Event Following Immunization
AESI	Adverse Event of Special Interest
AIH	Autoimmune Hepatitis
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AMA	Autoimmune Disease Antibodies
AMN	Acute Macular Neuroretinopathy
AMOR	Acute Macular Outer Retinopathy
ANA	Antinuclear antibody
ANCA	Antineutrophil Cytoplasmic Antibodies
AOSD	Adult-Onset Still's Disease
APLS	Antiphospholipid Syndrome
ARDS	Acute Respiratory Distress Syndrome
ARS	Agenzia Regionale di Sanità
AST	Aspartate Aminotransferase
AV	Atrioventricular
AZ	AstraZeneca
AZOOR	Acute Zonal Occult Outer Retinopathy
AZOR	Acute Zonal Outer Retinopathy
BC	Brighton Criteria
BCC	Brighton Collaboration Criteria
BG	Background
BLAST	Basic Local Alignment Search Tool
BRCA1	Breast Cancer Gene 1
CABG	Coronary Artery Bypass Graft
CCC	Company Clinical Comment

Abbreviation or special term	Explanation
CDC	Centres for Disease Control and Prevention
CDS	Core Data Sheet
ChAdOx1	Chimpanzee Adenovirus
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CLS	Capillary Leak Syndrome
CMV	Cytomegalovirus
CNS	Central Nervous System
COPD	Chronic Obstructive Pulmonary Disease
COVAX	COVID-19 Vaccines Global Access
COVID-19	Coronavirus Disease 2019
CPRD	Clinical Practice Research Datalink
CRP	C-Reactive Protein
CSF	Cerebrospinal Fluid
CSR	Clinical Study Report
CT	Computed Tomography
CTPA	CT Pulmonary Angiogram
CU	Cutaneous
CV	Cardiovascular
CVST	Cerebral Venous Sinus Thrombosis
CVT	Cerebral Venous Thrombosis
DCR	Data Correction Request
DHPC	Direct Healthcare Professional Communication
DIBD	Development International Birth Date
DIC	Disseminated Intravascular Coagulation
DILI	Drug Induced Liver Injury
DLP	Data Lock Point
DNA	Deoxyribonucleic Acid
DVT	Deep Vein Thrombosis
EAR	Auricular
EAS	Enhanced Active Surveillance
EBV	Epstein–Barr virus
ED	Emergency Department
EEA	European Economic Area
EEG	Electroencephalography

Abbreviation or special term	Explanation
EF	Ejection Fraction
EKG	Electrocardiogram
EMA/EMEA	European Medicines Agency
ES_SIDIAP_PC	Spain Information System for the Development of Research in Primary Care
ESR	Erythrocyte Sedimentation Rate
EU	European Union
EUA	Emergency Use Authorizations
EVDAS	EudraVigilance Data Analysis System
F	Female
FDA	Food and Drug Administration
FDG	Fluorodeoxyglucose
FLAIR	Fluid-Attenuated Inversion Recovery
FSI	First Subject In
FVS	Fully Vaccinated Analysis Set
GBS	Guillain-Barre syndrome
GCS	Glasgow Coma Scale
GE	Gastroenteral
GGT	Gamma-Glutamyl Transferase
GI	Gastrointestinal
GP	General Practitioner
HAV	Hepatitis A Virus
HBV	Hepatitis B virus
HCP	Healthcare Professional
HCV	Hepatitis C Virus
HD	Hospitalization
HEV	Hepatitis E Virus
HIV	Human Immunodeficiency Virus
HIT	Heparin-Induced Thrombocytopenia
HLA	Human Leukocyte Antigen
HLH	Hemophagocytic Lymphohistiocytosis
HLT	High Level Term
IBD	International Birth Date
IC	Intracardiac
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use

Abbreviation or special term	Explanation
ICS	Intracavernous
ICSR	Individual Case Safety Reports
ICU	Intensive Care Unit
IF	Infiltration
IFA	Immunofluorescence Assay
IfH	Interface Hepatitis
IgG	Immunoglobin
IH	Respiratory (inhalation)
IJ	Intra-articular
IL	Interleukin
IM	Intramuscular
IMD	Immune-Mediated Diseases
IMEN	Intrameningeal
IMID	Immunomodulators
IN	Nasal
INR	International Normalized Ratio
IOC	Intraocular
IR	Incidence Rate
IS	Intradiscal (intraspinal)
ISTH	The International Society on Thrombosis and Haemostasis
ISYN	Intrasynovial
IV	Intravenous
IVIG	Intravenous Immunoglobulin
JIA	Juvenile Idiopathic Arthritis
LD	Low Dose
LDH	Lactate Dehydrogenase
LDSD	1 Low Dose and 1 Standard Dose
LETM	Longitudinal Extensive Transverse Myelitis
LFTs	Liver Function Tests
LGI	Leucine-rich Glioma Inactivated
LKM	Liver-Kidney Microsomal Antibody
LP	Lumbar Puncture
LpI	Lymphoplasmacytic Infiltrate
LSO	Last Subject Out
LT	Life Threatening

Abbreviation or special term	Explanation
LV	Left Ventricular
M	Male
MAH	Marketing Authorisation Holder
MB	Myocardial Band
MC	Medically Confirmed
ME	Myalgic Encephalomyelitis
MedDRA	Medical Dictionary for Regulatory Activities
MELAS	Mitochondrial Encephalopathy Lactic Acidosis and Stroke-like episodes
MenACWY	Meningococcal Vaccine
MHRA	Medicines and Healthcare Products Regulatory Agency
MIS-C/A	Multisystem Inflammatory Syndrome In Children/Adults
MOG-IGG	Anti-Myelin Oligodendrocyte Glycoprotein
MRI	Magnetic Resonance Imaging
mRNA	Messenger Ribonucleic Acid
MS	Multiple Sclerosis
MSSR	Monthly Summary Safety Report
NA	Neuralgic Amyotrophy
NAbs	Neutralizing Antibodies
NC	Non-confirmed
NEC	Necrotizing Enterocolitis
NHS	National Health Service
NICU	Neonatal Intensive Care Unit
NIPH	Norwegian Institute of Public Health
NMOSD	Neuromyelitis Optica Spectrum Disorder
NOS	Not Otherwise Specified
NS	Non-Serious
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
O/E	Observed/Expected
OCT	Optical Coherence Tomography
OHDSI	Observational Health Data Science and Informatics
PAHO	Pan American Health Organization
PAM	Post-Authorisation Measure
PAMM	Paracentral Acute Middle Maculopathy
PAR	Parenteral
PASS	Post-Authorisation Safety Study

Abbreviation or special term	Explanation
PBRER	Periodic Benefit-Risk Evaluation Report
PBC	Primary Biliary Cholangitis
PE	Pulmonary Embolism
PET	Positron Emission Tomography
PF4	Platelet Factor 4
PI	Prescribing Information
PO	Oral
PRAC	Pharmacovigilance Risk Assessment Committee
PSC	Primary Sclerosing Cholangitis
PSUR	Periodic Safety Update Report
PT	Preferred Term
PTT	Partial Thromboplastin Time
PU	Intravenous bolus
PVFS	Post Viral Fatigue Syndrome
PY	Person Years
RBD	Receptor-Binding Domain
RMP	Risk Management Plan
RNA	Ribonucleic Acid
RoH	Rosetting of Hepatocytes
RoR	Reporting odds Ratio
RT-PCR	Real-Time Polymerase Chain Reaction
RW	Risk Window
S	Serious
s	Seconds
SA	South Africa
SAB	Spontaneous Abortion
SAE	Serious Adverse Event
SARS	Severe Acute Respiratory Syndrome
SARS-CoV-2	Severe Acute Respiratory Coronavirus 2
SCON	Subconjunctival
SCRI	Self-Controlled Risk Interval
SD	Standard Dose
SDSD	2 Standard Doses
SII	Serum Institute of India
SIRS	Systemic Inflammatory Response Syndrome

Abbreviation or special term	Explanation
SLA	Soluble Liver Antigen
SLE	Systemic Lupus Erythematosus
SMA	Smooth Muscle Antibody
SmPC	Summary of Product Characteristics
SMQ	Standardised MedDRA Query
SOC	System Organ Class
SOT	Solid Organ Transplantation
SQ	Subcutaneous
SSC	Scientific and Standardisation Committee
SSI	Staten Serum institute
TCP	Thrombocytopenia
TCR	T cell Receptors
TGA	Therapeutic Goods Administration
THIN	The Health Improvement Network
TM	Transverse Myelitis
TPL	Transplacental
TPMT	Thiopurine Methyltransferase
TSH	Thyroid-Stimulating Hormone
TTO	Time To Onset
TTS	Thrombosis with Thrombocytopenia Syndrome
UK	United Kingdom
UKHSA	UK Health Securities Agency
ULN	Upper Limit Of Normal
UMC	Uppsala Monitoring Centre
UNICEF	United Nations Children's Fund
Unk	Unknown
USA/US	United States of America/United States
UTI	Urinary Tract Infection
VAED	Vaccine Associated Enhanced Disease
VAERD	Vaccine-Associated Enhanced Respiratory Disease
VAERS	Vaccine Adverse Event Reporting System
VE	Vaccine Efficacy
VID	Valencia Integrated Database
VIPER	Vaccines International Pregnancy Exposure Registry
VITT	Vaccine-Induced Thrombotic Thrombocytopenia

Abbreviation or special term	Explanation
VTE	Venous thromboembolism
WCN	World Congress of Neurology
WFN	World Federation of Neurology
WHO	World Health Organization
Y	Yes
Yrs	Years

1 INTRODUCTION

This Periodic Benefit-Risk Evaluation Report (PBRER) prepared by AstraZeneca for VAXZEVRIA™ (AZD1222) summarises the safety and efficacy/effectiveness information received and evaluated by AstraZeneca from worldwide sources between 29 December 2021 and 28 June 2022. It is compiled in accordance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E2C (R2) PBRER guideline and EU Good Pharmacovigilance Practices Module VII (Revision 1); the terms/terminology used in this report are consistent with this guidance, and applicable international regulatory requirements.

The VAXZEVRIA International Birth Date (IBD) is 29 December 2020.

VAXZEVRIA is a monovalent vaccine composed of a single recombinant, replication-deficient chimpanzee adenovirus (ChAdOx1) vector encoding the S glycoprotein of the Severe Acute Respiratory Coronavirus 2 (SARS-CoV-2). Following administration, the S glycoprotein of SARS-CoV-2 is expressed locally stimulating neutralizing antibody and cellular immune responses.

VAXZEVRIA is indicated for active immunisation of individuals ≥18 years for the prevention of Coronavirus Disease 2019 (COVID-19).

VAXZEVRIA is supplied as a vial containing either 8 doses or 10 doses per vial, 0.5 mL per dose for intramuscular (IM) injection. VAXZEVRIA vaccination course consists of two separate doses of 0.5 ml each. The second dose should be administered between 4 and 12 weeks after the first dose. It is recommended that individuals who receive a first dose of VAXZEVRIA complete the primary vaccination course with VAXZEVRIA. The CDS indicates that a booster dose (third dose) of 0.5 ml may be given to individuals who completed the primary vaccination course with VAXZEVRIA or another authorised COVID-19 vaccine. The third dose should be administered at least 3 months after completing the primary vaccination course. The status of approval and the recommendation in national prescribing information (PI) documents relating to the booster dose vary.

The inclusion of any information relating to a validated signal, important potential risk, or missing information within this PBRER should not be taken to imply that a causal association with the use of VAXZEVRIA has been established.

2 WORLDWIDE MARKETING APPROVAL STATUS

VAXZEVRIA was first approved for active immunisation in individuals 18 years of age and older for the prevention of COVID-19 in United Kingdom (UK) on 29 December 2020. It received conditional marketing authorisation in the EU on 29 January 2021.

VAXZEVRIA has been approved either for conditional marketing authorisation or emergency use authorisation in 93 countries managed by AstraZeneca and its partners – Serum Institute of India (SII), R-pharm, Fiocruz, and Verity Pharmaceuticals. VAXZEVRIA is also distributed via COVID-19 Vaccines Global Access programme (COVAX), in collaboration with United Nations Children's Fund (UNICEF) and Pan American Health Organization (PAHO), under a World Health Organization (WHO) Emergency Use Listing to more than 80 countries. A summary of the worldwide marketing approval status applicable to VAXZEVRIA with AstraZeneca as the MAH is provided in Table 1.

Table 1 Summary of worldwide marketing approval status applicable to VAXZEVRIA

Country	Date of Authorisation
Argentina	30 December 2020
Australia	15 February 2021
Brazil	12 March 2021
Brunei	27 May 2021
Canada	19 November 2021 (5 ml) 26 February 2021 (4 ml)
Chile	27 January 2021
Colombia	23 February 2021
Costa Rica	26 February 2021
Dominican Republic	30 December 2020
Ecuador	23 January 2021
El Salvador	30 December 2020
EU/EMA (incl. Iceland, Liechtenstein & Norway)	29 January 2021
Great Britain	24 June 2021
Guatemala	21 June 2021
Honduras	05 February 2021
Hungary	21 January 2021
Indonesia	23 April 2021
Japan	21 May 2021

Table 1 Summary of worldwide marketing approval status applicable to VAXZEVRIA

Country	Date of Authorisation
Korea, Republic Of (South)	10 February 2021 (Domestic Supply) 21 May 2021 (Overseas Supply)
Malaysia	02 March 2021
Maldives	20 June 2021
Mexico	04 January 2021
Montenegro	05 March 2021
New Zealand	29 July 2021
Panama	05 February 2021
Peru	07 September 2021
Philippines	28 January 2021
Serbia	05 March 2021
Taiwan	20 February 2021
Thailand	20 January 2021
Ukraine	20 April 2021
United Kingdom	29 December 2020
Uruguay	11 February 2021
Vietnam	21 October 2021
World Health Organization	15 February 2021 (South Korea supply) 16 April 2021 (European Union supply) 09 July 2021 (Japan supply) 09 July 2021 (Australian supply) 27 August 2021 (Canadian supply)

3 ACTIONS TAKEN IN THE REPORTING PERIOD FOR SAFETY REASONS

No significant actions related to safety were taken or proposed during the reporting period.

4 CHANGES TO REFERENCE SAFETY INFORMATION

AstraZeneca's reference safety information is the Core Data Sheet (CDS). The CDS covers material relating to safety, indications, dosing, pharmacology, and other information concerning the medicinal product (providing the medical and scientific information AstraZeneca believes is necessary for the safe and effective use of a product); it serves as the master document for regular implementation of material changes in national or local authorised product information.

The VAXZEVRIA CDS in effect at the beginning of the reporting period was dated 02 November 2021 (version 10.0).

During this reporting period, the VAXZEVRIA CDS was updated to include the safety-related changes summarised in Table 2.

Table 2 Summary of safety-related changes to the VAXZEVRIA CDS during the reporting period.

CDS version date	CDS Section Number – CDS Section Title Detail of the safety-related change	PBRER Section cross-reference, where applicable
06 January 2022	**CDS Section 4.6 - Pregnancy and lactation** Updated pregnancy wording to reflect current safety data on administration of VAXZEVRIA in pregnant women, based on available data from AstraZeneca Global Safety database, the pregnancy registry and literature. Updated recommendation to consider use of VAXZEVRIA during pregnancy when benefits outweigh potential risks.	Not applicable
16 January 2022	**CDS Section 4.6 - Pregnancy and lactation** **Breastfeeding** Updated wording to reflect current non‑clinical, clinical and post-marketing data on use of VAXZEVRIA during breastfeeding.	Not applicable
04 February 2022	**CDS Section 4.2 - Posology and method of administration** **Posology** Recommendation for use of a booster dose (third dose) in individuals who completed the primary vaccination course with VAXZEVRIA or another authorised COVID‑19 vaccine. Timing for administration of the booster dose is at least 3 months after completing the primary vaccination course. **CDS Section 4.4 – Special warnings and special precautions for use** **Interchangeability** The text has been revised to clarify that limited data are available regarding the interchangeability of VAXZEVRIA with other COVID-19 vaccines. Text has been added to inform that the available data on the use of VAXZEVRIA as a booster dose following primary vaccination with another COVID-19 vaccine are presented in sections 4.8 and 5.1. **CDS Section 4.8 – Undesirable effects** **Summary of safety profile**	Not applicable

Table 2 Summary of safety-related changes to the VAXZEVRIA CDS during the reporting period.

CDS version date	CDS Section Number – CDS Section Title Detail of the safety-related change	PBRER Section cross-reference, where applicable
	Safety information from the AstraZeneca sponsored study D7220C00001, and the externally sponsored study RHH-001, has been included.	
02 March 2022	**CDS Section 4.8 – Undesirable effects** Addition of paraesthesia and hypoaesthesia to the summary of post-authorisation data, with frequency uncommon.	Further information regarding this change is presented in Section 16.3.4.3
11 May 2022	**CDS Section 4.4 – Special warnings and special precautions for use** The warning on Neurological events has been updated to specifically reference very rare events of Guillain - Barré Syndrome as having been reported following vaccination with VAXZEVRIA.	Further information regarding this change is presented in Section 16.2.2.1

CDS Core Data Sheet

A copy of the VAXZEVRIA CDS in effect at the end of the reporting period is presented in Appendix 1. For the purpose of this PBRER, this CDS dated 11 May 2022 (version 18.0), is the reference for both the benefit and risk sections.

Post data-lock point (DLP), the VAXZEVRIA CDS was updated on 01 July 2022 (Version 19.0) to include Tinnitus as an Adverse Drug Reaction (ADR) in Section 4.8 with the frequency uncommon, further information regarding this change is presented in Section 14, 16.2.5.2 and 16.3.4.3.

5 ESTIMATED EXPOSURE AND USE PATTERNS

5.1 Cumulative subject exposure in clinical trials

Estimates of overall cumulative subject exposure are provided in Table 3, based on actual exposure data from completed clinical trials and the enrolment/randomisation schemes for ongoing trials.

Table 3 Estimated cumulative subject exposure from clinical trials

Treatment	Number of subjects
VAXZEVRIA	35921
AZD2816[a]	1523
MenACWY	10949
Rabies vaccine	200
Placebo	11960

Cumulative numbers from initiation of the first clinical trials up to 28 June 2022. Participants rolled over from COV001 and COV002 into COV009, no additional dosing in COV009. COV009 excluded to avoid double-reporting.

MenACWY Meningococcal Vaccine.

[a] AZD2816 is a vaccine developed from AZD1222 targeting variants of SARS-CoV-2. AZD2816 is used in Study D7220C00001 which is further described in Section 7.2.1.

Cumulative summary tabulations of exposure by age/sex and by racial group are presented in Table 4 and Table 5, respectively.

Table 4 Estimated cumulative subject exposure to VAXZEVRIA and AZD2816 from completed and ongoing clinical trials by age and sex

	Number of subjects		
Age range (years)	**Male**	**Female**	**Total**
1-11	56	55	111
12-17	76	74	150
18-64	24894	25059	49953
>=65	5869	4371	10240
Missing	70	29	99
Total	**30965**	**29588**	**60553[a]**

Data from completed and ongoing clinical trials as of 28 June 2022. All subjects from VAXZEVRIA/AZD2816 studies are included (VAXZEVRIA/AZD2816/placebo/comparator). Gender is based on biological sex at birth in COV008 study.

[a] Participants rolled over from COV001 and COV002 into COV009, no additional dosing in COV009. COV009 excluded to avoid double-reporting.

Table 5 Estimated cumulative subject exposure to VAXZEVRIA and AZD2816 from completed and ongoing clinical trials by racial group

Racial group	Number of subjects
American Indian Or Alaska Native	1289
Asian	2624

Table 5 Estimated cumulative subject exposure to VAXZEVRIA and AZD2816 from completed and ongoing clinical trials by racial group

Racial group	Number of subjects
Black Or African American	5884
Native Hawaiian Or Other Pacific Islander	81
White	46005
Other	1569
Multiple Categories Checked	1906
Missing	795
Total	60153[a]

Data from completed and ongoing clinical trials as of 28 June 2022. All subjects from VAXZEVRIA /AZD2816 studies are included (VAXZEVRIA/AZD2816/placebo/comparator).

Other race category includes multiple race categories.

400 subjects from COV004 excluded as race was not collected in this study.

[a] 400 subjects from Study COV004 not included since racial groups were not collected in this study. Participants rolled over from COV001 and COV002 into COV009, no additional dosing in COV009. COV009 excluded to avoid double-reporting.

5.2 Cumulative and interval patient exposure from marketing experience

5.2.1 Post-approval (non-clinical trials) exposure

The post-marketing patient exposure data in this report is presented by number of doses distributed and doses administered. All exposure is intended for the same indication and route of administration.

For doses distributed, this information has been provided below in section 5.2.1.1 and it includes dose distribution information across all markets, those where AstraZeneca is the Marketing Authorisation Holder (MAH) and those supported by the licence partners (SII, R-Pharm, Fiocruz, and Verity Pharmaceuticals).

For doses administered to vaccinees, this is a more accurate measure of vaccinee exposure and provides more detailed vaccinee-level data (eg, gender and age category). Therefore, AstraZeneca is continuing to work on the collection of this information at the country level, from relevant health departments, for all countries administering the VAXZEVRIA. However, at the time of this report, AstraZeneca has received exposure data based on doses administered to vaccinees in specific countries/regions only; additional information can be found in section 5.2.1.2 below.

5.2.1.1 Patient exposure – doses distributed

During this reporting period, the global post-marketing patient exposure (by doses distributed) to VAXZEVRIA was estimated to be over 327 million doses (11.7% of cumulative).

The cumulative global post-marketing patient exposure (by doses distributed) to VAXZEVRIA, since launch to 30 June 2022, have been estimated to be over 2.79 billion doses.

The regional dose distribution data is presented in Table 6.

Table 6 VAXZEVRIA exposure, based on doses distributed, by Region

Region[b]	Exposure by doses distributed		Percentage (%)	
	Interval (01 January 2022 to 30 June 2022)	Cumulative (Up to 30 June 2022)	Interval	Cumulative
Europe	29510320	248197720	7.88	8.74
International	86484220	643723840	23.08	22.68
North America	10135700	19089200	2.70	0.67
Japan	9324970	62663140	2.49	2.21
Serum Institute of India[a]	169901970	1636706540	45.34	57.66
Fiocruz[a]	39371540	187985690	10.51	6.62
R-Pharm[a]	0	10358700	0.00	0.36
BKT[a]	30000000	30000000	8.01	1.06
Total	374728720	2838724830		

[a] Data from Serum Institute of India, BKT, and R-Pharm is as of 30 June 2022 and from Fiocruz is as of 31 May 2022.

[b] Where AstraZeneca (AZ) is the Marketing Authorisation Holder, dose volumes cited represent doses dispatched from AZ manufacturing sites and contracted manufacturing sites. The destinations noted 'Region' represent what is known at the time of dispatch. Country to country donations may or may not be reflected dependent on the timing and type of donation.

A more detailed breakdown of doses distributed across the countries within the EU can be found in Appendix 6.

5.2.1.2 Post-marketing patient exposure data for reporting period and cumulatively

AstraZeneca has obtained exposure data based on doses administered to vaccinees in EU, Afghanistan, Argentina, Australia, Bangladesh, Brazil, Canada, Chile, Colombia, Ecuador, Ghana, Guatemala, India, Iran, Iraq, Japan, Lebanon, Malaysia, Mexico, Nepal, New Zealand, Peru, Philippines, Saint Lucia, South Korea, Taiwan, Thailand, UK and Uruguay. This information is summarised in Table 7 below and it represents the interval and cumulative

exposure (by doses administered). This data has either been provided to AstraZeneca directly from Government bodies or has been sourced from country specific websites.

Administration data from the licence partners (Serum Institute of India, Fiocruz and R-Pharm) have not been provided to AstraZeneca directly.

Please note that administration in other markets where the VAXZEVRIA is authorised has not yet been made available to AstraZeneca. As such, the doses administered presented in this report is less than the doses distributed. The cumulative global post-marketing patient exposure (by doses administered) to VAXZEVRIA, since launch to 30 June 2022, have been estimated to be over 2.09 billion doses.

Table 7 VAXZEVRIA interval and cumulative exposure based on doses administered, by Region/Country

Region	Interval		Cumulative			Percentage (%)	
	Dose 1	Dose 2	Dose 1	Dose 2	Dose3/Dose 4/Booster	Interval	Cumulative
European Union	-198213	-8990	38913369	29816443	21772	-0.04	3.28
United Kingdom	-70731	-17121	24732,840	24149323	58324	-0.02	2.33
Afghanistan	975338		975338		0	0.20	0.05
Australia	25076	74595	6,898,909	6814620	92395	0.02	0.65
Philippines	4629436		9811327	9010123	3028907	0.93	0.90
India	315166797		1579378046		0	63.02	75.29
Canada	7107		2234973	576005	1584	0.00	0.13
Argentina	224621	382,033	10174372	9933058	6582393	0.12	0.96
Bangladesh	6243827	11760870	20549140	19132540	10720392	3.60	1.89
Colombia	5308052	3372486	5,308,052	3372486	1583401	1.74	0.41
Ecuador	1739254	1419111	1739254	1419,111	3866573	0.63	0.15
Iran	5596067	5039783	5596067	5,039783	3541319	2.13	0.51
Japan	58707	58,819	58707	58819	0	0.02	0.01
Brazil	4619234		62233985	57429004	17358176	0.92	5.70
Chile	4230		410041	139629	2655470	0.00	0.03
Guatemala	302863	481376	2033337	1607041	818849	0.16	0.17
Ghana	10096925		10096925		0	2.02	0.48
Lebanon	31915		720,793		0	0.01	0.03

Table 7 VAXZEVRIA interval and cumulative exposure based on doses administered, by Region/Country

Region	Interval		Cumulative			Percentage (%)	
	Dose 1	Dose 2	Dose 1	Dose 2	Dose3/Dose 4/Booster	Interval	Cumulative
Iraq	717233		717233		0	0.14	0.03
Mexico	49783383		49783383		0	9.96	2.37
Malaysia	3266	3,604	2046604	2025975	1619351	0.00	0.19
Nepal	5374928	4598237	5374928	4598237	4026870	1.99	0.48
Peru	2241032	2099522	2241032	2099522	3609650	0.87	0.21
Saint Lucia	37850	34810	37850	34810	0	0.01	0.01
Taiwan	8072059	7162679	8072059	7162679	59488	3.05	0.73
Thailand	14078238	28660820	14078238	28660820	5869808	8.55	2.04
New Zealand	4475		3314	3619	1885	0.00	0.00
South Korea	-124712		11076305	9242971	2,058	-0.02	0.97
Uruguay	2214		46684	44454	179	0.00	0.00
Grand Total	**500073105**		**2097714177**		**65518844**	**100**	**100**

The data cut off for Iraq is 29 August 2021

The data cut off for Mexico is 29 April 2022

The data cut off for Afghanistan and Peru is 30 April 2022 and that of Canada is 19 June 2022

The data cut off for Iran is 25 June 2022.

The data cut off for Australia, European Union, Philippines and United Kingdom is 26 June 2022.

The data cut off for New Zealand is 28 June 2022

The data cut off for Colombia and Thailand is 29 June 2022.

The data cut off for Argentina, Bangladesh, Brazil, Chile, Ecuador, Ghana, Guatemala, India, Japan, Lebanon, Malaysia, Nepal, Saint Lucia, South Korea, Taiwan and Uruguay is 30 June 2022.

The weekly administered data is subject to change every week. The administered data for the PBRER reporting interval is derived by subtracting the previous report's cumulative from current cumulative values (Current Cumulative - Previous Cumulative = Current Interval) across all the Countries. Therefore, the negative values here is due to a greater cumulative value from previous report in comparison to current report.

A more detailed presentation of doses administered by country/states as well as vaccine administration by dose number, age and/or gender where provided for specified countries can be found in Appendix 6. However, a summary of the post-marketing patient exposure by age and gender (as currently available) is presented in Table 8 and Table 9, respectively.

Table 8 presents the vaccine doses administered by Age Group for the following specific countries:

- Australia, Austria, Belgium, Bulgaria, Croatia, Cyprus, Czechia, Denmark, Estonia, Finland, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden and UK.

Table 8 Vaccine Doses Administered by Age Group

Age Group	Interval				Cumulative			
	Dose 1	Dose 2	Total	Percentage (%)	Dose 1	Dose 2	Total	Percentage (%)
18-24	852720	833133	1685853	-8.09	2035765	1850025	3885790	3.51
25-49	-1160235	-1105032	-2265267	10.87	13384413	12230226	25614639	23.14
50-59	68901	75778	144679	-0.69	11324258	10624908	21949166	19.83
60-69	1118171	1066270	2184441	10.48	17734853	17056392	34791245	31.43
70-79	227896	245582	473478	-2.27	10156603	9963679	20120282	18.17
≥80	182594	183273	365867	-1.76	2146616	2067526	4214142	3.80
Unknown	15221621	-8203022	23424643	112.43	74904	35478	110382	0.09
Total	**13931574**	**-6904018**	**20835592**	**100**	**56857412**	**53828234**	**110685646**	**100**

The total doses administered by Age group do not reflect the total doses administered that appear in Table 7. This is due to the fact that doses administered by Age group are not available for all countries that have provided vaccine administration information.

Table 9 present the vaccine doses administered by Gender Group for the following specific countries:

- Australia and UK

Table 9 Vaccine Doses Administered by Gender Group

Gender group	Total doses administered		Percentage (%)
	Interval	Cumulative	Cumulative
Male	203875	30893573	49.35
Female	-126120	31569658	50.44
Unspecified	-66946	131451	0.21
Total	**10809**	**62594682**	**100**

The total doses administered by Gender group does not reflect the total doses administered that appears in Table 7. This is due to the fact that doses administered by Gender group is not available for all countries that have provided vaccine administration information.

Exposure by doses administered is used as part of Observed versus Expected (O/E) Analyses, refer to Appendix 8 for further details.

AstraZeneca will continue efforts to obtain exposure data by gender for each EU Member State, as currently the data provided via the European Centre for Disease Prevention and Control does not include gender breakdown at a country level. If this data become available, it will be included in future reports.

5.2.2 Post-approval use in special populations

It is not possible to provide an estimate of patient numbers exposed from post-approval use in special populations.

5.2.3 Other post-approval use

AstraZeneca is not aware of any patterns of use (for example overdose, drug abuse, misuse or off-label use) of VAXZEVRIA considered to be relevant for the interpretation of safety data.

6 DATA IN SUMMARY TABULATIONS

6.1 Reference information

The Medical Dictionary for Regulatory Activities (MedDRA), version 25.0, has been used for coding adverse events (AEs). The summary tabulations are arranged in the internationally agreed order by primary MedDRA System Organ Class (SOC), and refer to the Preferred Term (PT) level.

6.2 Cumulative summary tabulations of serious adverse events from clinical trials

A cumulative summary tabulation of serious adverse events (SAEs) from AstraZeneca-sponsored interventional clinical trials that have been reported during the VAXZEVRIA clinical development programme, from the Development International Birth Date (DIBD) to the data lock point (28 June 2022), organised by SOC, is presented in Appendix 2.

A summary of the total number of case reports with SAEs from AZD1222 (VAXZEVRIA) and AZD2816 clinical trials along with the total number of SAEs for each treatment is provided in Table 10.

Table 10 Summary tabulation of SAE case reports received from VAXZEVRIA (AZD1222) and AZD2816 clinical trials[a]

Treatment	Interval (29 December 2021 – 28 June 2022)		Cumulative (through 28 June 2022)	
	Number of Cases	Number of Serious Adverse Events	Number of Cases	Number of Serious Adverse Events
AZD1222	480	601	1934	2221
AZD2816[c]	25	26	38	40
MENACWY	122	143	764	830
Meningocccal Group B Vaccine	1	1	4	5
Placebo	325	423	1116	1329
Study procedure	3	3	9	12
Total[b]	**956**	**1197**	**1946**	**4437**

[a] Numbers presented in this table will not match those presented in Appendix 2, Table 1 due to differences in the date that the table and appendices were generated from the AstraZeneca Global Safety database.

[b] AZD2816 is a vaccine developed from AZD1222 targeting variants of SARS-CoV-2. AZD2816 is used in Study D7220C00001 which is further described in Section 7.2.1.

[c] Cases may have more than one treatment listed. Therefore, the sum of cases and SAEs will exceed the total.

A review of Table 1 of Appendix 2 has been completed for the PBRER period from 29 December 2021 to 28 June 2022 and there are no noteworthy changes in the absolute frequency numbers from the previous PBRER.

6.3 Cumulative and interval summary tabulations from post-marketing data sources

Cumulative and interval summary tabulations of adverse reactions (ie, AEs considered as "a reasonable possibility of a causal relationship between the medicinal product and the event" for Table 2 Appendix 2) that have been reported from marketed experience with VAXZEVRIA, from the IBD to the data lock point, organised by SOC, are presented in Appendix 2.

A summary of the total number of VAXZEVRIA case reports and corresponding adverse events received from Spontaneous sources by seriousness for both the interval and cumulative periods is provided in Table 11.

Table 11 Summary tabulation of VAXZEVRIA and AZD2816 case reports and adverse events received from spontaneous sources[a]

Case/Event Seriousness	Interval (29 December 2021 – 28 June 2022)		Cumulative (through 28 June 2022)	
	Number of Cases	Number of Adverse Events	Number of Cases	Number of Adverse Events
Serious	36456	95064	255333	945685
Non-Serious	93912	393777	499646	1888453
Not available/ Not entered	1	0	2	0
Total	**130369**	**488841**	**754981**	**2834138**

[a] Numbers presented in this table will not match those presented in Appendix 2 due to differences in the date that the table and appendices were generated from the AstraZeneca Global Safety database.

A review of Table 2 Appendix 2 has been completed for the PBRER period from 29 December 2021 and 28 June 2022 and there are no noteworthy changes in the absolute frequency numbers from the previous PBRER.

6.3.1 Lack of efficacy from Post-Marketing

Interval Period (29 December 2021 – 28 June 2022)

A search of the AstraZeneca Global Safety database for the reporting interval using the Lack of Efficacy standardised MedDRA query (SMQ), retrieved 16964 reports with the following 16973 AEs (PTs): Vaccination failure (16620), Drug ineffective (231), Therapy partial responder (72), Therapeutic product effect decreased (15), Therapeutic response decreased (6), Therapeutic product ineffective (6), Therapeutic response shortened (5), Therapeutic product effect incomplete (5), Drug tolerance (4), Drug effect less than expected (2), Disease progression (2), Treatment failure (1), Therapeutic product effect delayed (1), Drug level abnormal (1), Drug level decreased (1), and Drug resistance (1).

Of the 16964 reports, 16700 (98.4%) were medically confirmed (MC) and the remaining 264 (1.6%) were consumer reports. A total of 16632 (98.0%) reports were considered serious due to the AE being considered medically important (16367), required hospitalization (161), was life threatening (LT) (23), and/or resulted in death (81). Cases may have met more than one criteria for seriousness. The remaining 332 (2.0%) reports were non-serious (NS). Of the 16964 reports, 95.0% (16120) were reported from Austria.

There were 81 fatal cases in the reporting interval. Age was reported in 79 (97.5%) of these 81 cases with a median age of 75 years old; range 52 to 92 years. A total of 23 cases occurred in females, 55 in males, and 3 of unknown gender. Cause of death PTs included: Vaccination failure (71), COVID-19 (63), COVID-19 pneumonia (9), Drug ineffective (6), Pneumonia

(2), Incomplete course of vaccination (2), Asymptomatic COVID-19 (1), Vaccine associated enhanced respiratory disease (1), Acute respiratory distress syndrome (ARDS) (1), and Multiple organ dysfunction syndrome (1). Most fatal cases contained confounders, such as advanced age, hypertension, diabetes, asthma, alcoholism, obesity, COPD, cancer, stroke, heart failure/disease, dyslipidaemia, pulmonary embolism (PE), and myocardial infarction.

Of the 16883 non-fatal cases, the outcomes were as follows: Not recovered (146), Recovered (192), Recovered with sequelae (5), Recovering (140), and Unknown (16400).

Information on COVID-19 testing was available in 16464 reports; of these 16399 (99.61%) were reported as COVID-19 test positive, 63 (0.38%) were reported as COVID-19 test negative and 2 (0.01%) were reported as unknown. Further information on the 16399 reports (including 93 with first dose, 16279 with second dose, 5 with booster dose, and 22 with unknown dose) with a positive COVID-19 test is presented below:

- In 93 (0.6%) of the 16399 reports, COVID-19 test was positive after the receipt of the first dose of the vaccine; time to positive COVID-19 test was available for 66 (0.4%) cases and ranged from the same day as vaccination to 452 days with a median of 179 days. In 1 report, the date of the positive test result was before the first dose vaccination date. In 26 (0.2%) reports, time to positive Covid-19 test after first dose of vaccine was unknown.
- In 16279 (99.3%) reports, COVID-19 test was positive after the receipt of the second dose of the vaccine; time to positive COVID-19 test was available for 16259 (99.1%) cases and ranged from 7 days to 373 days with a median of 142 days. Time to positive COVID-19 test was 0 to 14 days in 2 cases and 15 to 373 days in 16257 cases. In 20 (0.1%) reports, time to positive COVID-19 test after second dose of vaccine was unknown.
- In 5 (0.03%) reports, COVID-19 test was positive after the receipt of the booster dose of the vaccine; time to positive COVID-19 test was available all 5 cases: 2, 19, 21, 102, and 105 days.
- In 22 (0.13%) reports, COVID-19 test was positive after the receipt of unknown dose of the vaccine; time to positive COVID-19 test was available for 12 (0.07%) cases and ranged from 77 days to 255 days with a median of 144 days. In 10 (0.06%) reports, time to positive Covid-19 test after unknown dose of vaccine was unknown.

Cumulative Review (29 December 2020 – 28 June 2022)

A cumulative search of the Global Safety database using the Lack of Efficacy SMQ, retrieved 22705 reports with the following 22737 PTs: Vaccination failure (21433), Drug ineffective (1076), Therapy partial responder (72), Therapeutic product ineffective (35), Therapeutic product effect decreased (23), Treatment failure (21), Disease progression (13), Therapeutic

product effect incomplete (11), Therapeutic response shortened (9), Therapeutic response decreased (9), Therapy non-responder (8), Drug effect less than expected (5), Drug tolerance (4), Drug level decreased (3), Therapeutic product effect delayed (3), Paradoxical drug reaction (2), Therapeutic reaction time decreased (2), Absence of immediate treatment response (1), Therapeutic response changed (1), Remission not achieved (1), Drug level abnormal (1), Therapeutic response delayed (1), Drug resistance (1), Device defective (1), and Diet failure (1).

Of the 22705 reports, 21639 (95.3%) were medically confirmed and the remaining 1066 (4.7%) were consumer reports. A total of 21379 (94.2%) reports were considered serious due to the AE being considered medially important (20636), the AE resulted in a congenital anomaly (1), the AE was reported to have resulted in disability (18), required hospitalization (491), was life threatening (81), and/or resulted in death (152). Cases may have met more than one criteria for seriousness. The remaining 1326 (5.8%) reports were non-serious. Of the 22705 reports, 87.5% (19856) were reported from Austria. Cumulatively, there have been 152 fatal cases.

Of the 22553 non-fatal cases, the outcomes were as follows:

Not recovered (559) Recovered (784), Recovered with sequelae (9), Recovering (461), and Unknown (20740).

Conclusion

Review of all the lack of efficacy reports did not demonstrate any specific trend or safety information associated with use of VAXZEVRIA. The imbalance of reporting rates during the reporting period and cumulatively is noted. Of note, 95.0% of the reports (16120/16964) during the reporting interval and 87.5% (19856/22705) of the reports cumulatively were from Austria. This is due to a local reporting system where cases from the epidemiological reporting system for COVID-19 are linked with the vaccination passport and submitted to Eudravigilance/AstraZeneca in bulk.

6.3.2 Fatal events, including case reports involving Sudden Death/Sudden cardiac death

6.3.2.1 Fatal Events

Interval Review (29 December 2021 – 28 June 2022)

Cumulatively from 29 December 2020 to 28 June 2022, there were 6399 fatal cases received. Of these, 1966 fatal cases (30.7%) were received during this reporting period (29 December 2021 to 28 Jun 2022) which includes 1165 (59%) initial reports and 801 (41%) follow-up reports. Out of these 1966 cases, 1642 cases (83.5%) had vaccinees' age reported and in 324 cases (16.5%) the age was unknown (see Table 12). In 720 of the 1643 case

reports, the vaccinees were aged 65 years and above. The median age was 62 years. The gender distribution as reported in 1868 (95%) cases was 846 (45%) female and 1022 (55%) male.

Of the 1966 case reports with fatal outcome during this reporting period, 1426 (72.5%) were medically confirmed and 540 (27.5%) were consumer reports. During the reporting period, 4 fatal cases ([redacted]) were reported with the booster dose, however there was insufficient information on relevant medical history and cause of death (the only reported AE was death). Of the 1966 cases, 156 (8%) were reported as sudden Death. Case reports of Sudden Death are included in the overall number of cases with fatal outcome, and are discussed in Section 6.3.2.2.

Distribution of fatal cases per age group during the reporting period is presented in Table 12.

Table 12 Fatal cases per age group (in years)

Age group	Fatal cases
< 18	1[a]
18-49	418
50-59	281
60-64	222
65-74	383
≥ 75	337
Unknown	324
Total	**1966**

[a] Insufficient case details received from regulatory source (Vaccination dates, off label use, medical history, autopsy) for patient with 12 years old.

Information regarding comorbid conditions was available in 603 (31%) out of 1966 cases. Important comorbid conditions included hypertension (n= 225), diabetes mellitus (n=108), coronary artery disease (n=47), chronic obstructive pulmonary disease (COPD) (n=37), type 2 diabetes mellitus (n=34), obesity (n=34), atrial fibrillation (n=26) and asthma (n=24).

Out of 1966 cases the cause of death cannot be determined in 686 (35%) cases due to insufficient information available in the reports. The reported cause of death in the remaining fatal case reports (1467) are presented in Table 13(Note: In some cases, single most relevant cause of death could not be determined due to insufficient information).

Table 13 Reported cause of death in Fatal Cases with VAXZEVRIA (n = 1467) during the Interval period: 29 December 2021 – 28 Jun 2022

Cause of Death	Fatal cases [a]
Cardiorespiratory causes	527
Infection [b]	301
Cerebrovascular accident without reported thrombocytopenia	76
Thrombosis with Thrombocytopenic syndrome [c]	89
(including cerebral venous sinus thrombosis (CVST))	(39)
(including Cerebral venous thrombosis (CVT))	(4)
(including Cerebral venous thrombosis (CVST and CVT))	(2)
(including Ischemic stroke)	(4)
(including pulmonary embolism)	(5)
(including intraabdominal thrombosis)	(3)
(including peripheral thrombosis)	(1)
(including haemorrhage)	(8)
Thrombosis (without thrombocytopenia)	65
Cerebral haemorrhage	58
Malignancy	26
CVT/CVST without thrombocytopenia	23
Seizure	22
Renal dysfunction	19
Multiple organ failure	17
Thrombocytopenia	17
Gastrointestinal causes	14
Hepatitis	9
Guillain Barre Syndrome	9
Thrombocytopenia with haemorrhage	8
Aneurysm	7
Anaphylaxis/ Hypersensitivity	6
Haemophagocytic lymphohistiocytosis	4
Vasculitis	3
CVT without thrombocytopenia	2
Pancreatitis	1
Others [d]	187
Total	**1467**

[a] In some cases, single most relevant cause of death could not be determined due to insufficient information.

[b] Causes of infection include COVID-19 and other causes, such as sepsis, pneumonia, pulmonary oedema

[c] The 8 subsets of Thrombosis with Thrombocytopenic syndrome (TTS) were placed in the brackets.

[d] Causes of death other than the categories listed in table above include but not limited to hypersensitivity pneumonitis, completed suicide, dermatomyositis, osteomyelitis and toxicity to various agents.

CVST- Cerebral Venous Sinus Thrombosis; CVT- Cerebral Venous Thrombosis

Of the 301 case reports where infections were reported as the cause of death, 220 cases (73%) reported COVID-19 as the cause of death. Out of 220 cases, 97 cases (44%) were reported after first vaccine dose and time to death or fatal outcome ranged from 4 days to 239 days (median 28 days) after vaccination. The remaining 123 (56%) fatal reports of COVID-19 infection were reported after the second dose of vaccination and the time to fatal outcome ranged from 9 days to 358 days (median 144 days). Other infections reported included: sepsis, urosepsis, acute pulmonary oedema, lower respiratory tract infection, tuberculosis, pneumonia, hypersensitivity pneumonitis, pneumonia bacterial, septic shock, severe acute respiratory syndrome (SARS), Creutzfeldt-Jakob disease, Pulmonary mucormycosis, Pneumocystis jirovecii pneumonia, and Encephalitis.

Cumulative Review (29 December 2020 – 28 June 2022)

Cumulatively through 29 December 2020 to 28 June 2022, there have been 6399 fatal cases. Out of 6399 cases, age of vaccinees was reported in 5352 cases (84%) and was unknown in 1047 cases (16%). In 2799 (52%) of the 5352 case reports, the vaccinees were aged 65 years and above. The median age of the fatal cases was 65 years. The gender distribution as reported in 6117 cases (96%) was 2780 females (45%) and 3337 males (55%).

Cumulatively out of the 6399 case reports with fatal outcome, 3935 (52%) were medically confirmed and 2464 (48%) were consumer reports. Cumulatively, five fatal cases ([redacted]) were reported with the booster dose, however there was insufficient information on dates of vaccination, medical history and cause of death (the only reported PT was 'death'). Of the 6399 cases, 364 (6%) were reported as sudden Death. Case reports of sudden Death, see Section 6.3.2.2, are included in the overall number of cases with fatal outcome.

Cumulative O/E analyses were conducted for fatal cases, and were stratified by age group and gender where administration data was available. References for background estimates obtained from the literature are provided in Appendix 9. The O/E analysis of fatal reports showed that observed cases occurred significantly less frequently than expected for all ages and by different age stratifications from European Economic Area (EEA)+UK+Brazil+ and Australia. Results of the O/E analyses are presented in Table 14, Table 15 and Table 16. Conservatively, the exposure for global reports (448306152) is based on doses administered in 13 regions/markets as explained in Appendix 8.

Table 14 Observed versus expected analyses for Fatal cases overall

Medical Concept	Observed cases	Expected cases	Risk Window	Background rate/100,000 person years	Rate ratio (CI 95%)	
Fatal Reports RW 42 [a]	3155	188550.2	42	365.75	0.02 (0.02 - 0.02)	Observed significantly < expected
Fatal Reports RW42+Unk TTO	5638	188550.2	42	365.75	0.03 (0.03 - 0.03)	Observed significantly < expected

[a] Includes global reports irrespective of age and gender.
[b] Global exposure was 448306152.
CI Confidence Interval, RW Risk Window, TTO Time to onset.

Table 15 Observed versus expected analyses for Fatal cases by age group from EU+UK+Brazil+Australia region

Medical Concept	Age Group	Risk Window	BG rates	Exposure	Observed cases [b]	Expected cases	Rate ratio (CI 95%)	
Fatal Reports [a] (from EU+UK +Brazil+ Australia)	18 – 49 RW 42	42	65.86	100987434	339	7648.16	0.04 (0.04 - 0.05)	Observed significantly < expected
	50 – 59 RW42	42	193.2	56425075	343	12535.66	0.03 (0.02 - 0.03)	Observed significantly < expected
	60 – 69 RW42	42	314.82	57182485	658	20701.1	0.03 (0.03 - 0.03)	Observed significantly < expected
	70+ RW 42	42	1010.74	31869628	1009	37041.15	0.03 (0.03 - 0.03)	Observed significantly < expected
	18 – 49 RW 42 + Unk TTO	42	65.86	100987434	599	7648.16	0.08 (0.07 - 0.08)	Observed significantly < expected

Table 15 Observed versus expected analyses for Fatal cases by age group from EU+UK+Brazil+Australia region

Medical Concept	Age Group	Risk Window	BG rates	Exposure	Observed cases [b]	Expected cases	Rate ratio (CI 95%)	
	50 – 59 RW42 + Unk TTO	42	193.2	56425075	482	12535.66	0.04 (0.04 - 0.04)	Observed significantly < expected
	60 – 69 RW42 + Unk TTO	42	314.82	57182485	902	20701.1	0.04 (0.04 - 0.05)	Observed significantly < expected
	70+ RW 42 + Unk TTO	42	1010.74	31869628	1490	37041.15	0.04 (0.04 - 0.04)	Observed significantly < expected

[a] Fatal report O/E by age group is based on cases reported from EU+UK+Brazil+Australia, as corresponding exposure was only available from this region.
[b] Includes cases reported within risk window of 42 days.
CI Confidence Interval; EU European Union.

Table 16 Observed versus expected analyses for Fatal cases by age group in UK

Medical Concept	Age Group	Risk window in days	BG rates	Exposure	Observed cases [b]	Expected cases	Rate ratio (CI 95%)	
Fatal Reports [a] (from UK)	18-29 (RW 42) UK	42	28.22	2129518	17	69.1	0.25 (0.14 - 0.39)	Observed significantly < expected
	30-39 (RW 42) UK	42	48.8	3566210	18	200.12	0.09 (0.05 - 0.14)	Observed significantly < expected
	40-49 (RW 42) UK	42	100.86	9705005	48	1125.6	0.04 (0.03 - 0.06)	Observed significantly < expected
	50-59 (RW 42) UK	42	193.2	13197033	91	2931.92	0.03 (0.02 - 0.04)	Observed significantly < expected
	60-69 (RW 42) UK	42	314.82	10157100	92	3677.05	0.03 (0.02 - 0.03)	Observed significantly < expected

Table 16 Observed versus expected analyses for Fatal cases by age group in UK

Medical Concept	Age Group	Risk window in days	BG rates	Exposure	Observed cases [b]	Expected cases	Rate ratio (CI 95%)	
	70-79 (RW 42) UK	42	553.23	7047791	140	4483.6	0.03 (0.03 - 0.04)	Observed significantly < expected
	80+ (RW 42) UK	42	1638.26	3024979	215	5698.67	0.04 (0.03 - 0.04)	Observed significantly < expected
	18-29 (RW 42+Unk) UK	42	28.22	2129518	33	69.1	0.48 (0.33 - 0.67)	Observed significantly < expected
	30-39 (RW 42+Unk) UK	42	48.8	3566210	52	200.12	0.26 (0.19 - 0.34)	Observed significantly < expected
	40-49 (RW 42+Unk) UK	42	100.86	9705005	96	1125.6	0.09 (0.07 - 0.1)	Observed significantly < expected
	50-59 (RW 42+Unk) UK	42	193.2	13197033	159	2931.92	0.05 (0.05 - 0.06)	Observed significantly < expected
	60-69 (RW 42+Unk) UK	42	314.82	10157100	186	3677.05	0.05 (0.04 - 0.06)	Observed significantly < expected
	70-79 (RW 42+Unk)	42	553.23	7047791	243	4483.6	0.05 (0.05 - 0.06)	Observed significantly < expected
	80+ (RW 42+Unk)	42	1638.26	3024979	313	5698.67	0.05 (0.05 - 0.06)	Observed significantly < expected

[a] Fatal report O/E by age group is based on cases reported from UK, as corresponding exposure was only available from this region.
[b] Includes cases reported within risk window of 42 days.

CI Confidence Interval; UK United Kingdom.

6.3.2.2 Case reports involving Sudden Death/Sudden cardiac death

Interval Review (29 December 2021 – 28 June 2022)

During the reporting period, 156 cases of sudden death/sudden cardiac death were reported (139 (89%) initial, 17 (11%) follow-up).

Of the 156 case reports with sudden death, 146 (94%) were medically confirmed and 10 (6%) were consumer reports. Sixty-two (62) (40%) vaccinees were female and 94 (60%) were male. Age of vaccinees ranged from 20 to 94 years with a median age of 67 years.

Out of 156 cases TTO was available for 22 cases. Out of 22 cases there were 18 cases (82%) where time to death ranged from 0 - 83 days (median 9.5 days) after receiving the first dose of the vaccine and there were 4 cases (18%) where time to death was 4 - 104 days (median 65.5 days) after receiving the second dose.

Of the 156 cases of sudden death, the causes of death were reported in 155 cases (99%) and included the following AEs (PTs): sudden cardiac death, cardiac arrest, myocardial infarction, left ventricular dysfunction, atrial fibrillation, aortic aneurysm rupture, acute coronary syndrome, cardiovascular disorder, visceral venous thrombosis, cor pulmonale acute, respiratory arrest, hypertension, haemorrhage intracranial, dyspnoea, ecchymosis, abdominal pain lower, COPD, thrombosis with thrombocytopenia syndrome (TTS), cardiac arrest, cardiac failure acute, haemorrhage, respiratory failure, peripheral artery thrombosis, fatigue, petechiae, petechiae, cerebral haemorrhage, pulmonary embolism, pulmonary oedema, necrosis ischaemic, brain oedema, pericarditis, pyrexia, and cardiovascular disorder.

The medical history (vaccinees may have had >1 comorbidity) included hypertension (n=71, 37%), diabetes mellitus (n=45, 23%), coronary artery disease (n=32, 16%), tobacco use (n=12, 6%) COPD (n=10, 5%), alcohol abuse (n=7, 4%), cerebrovascular accident (n=5, 3%), asthma (n=5, 3%), myocardial infarction and myocardial ischemia (n=5, 3%). The medical history was not reported in 44 (28%) cases.

Cumulative Review (29 December 2020 – 28 June 2022)

Cumulatively between 29 December 2020 to 28 June 2022, out of 364 cases, 214 (59%) cases containing the PT of sudden death and 150 (41%) case containing the PT of sudden cardiac death were reported.

Of the 364 case reports with sudden death outcome, 300 (82%) were medically confirmed and 64 (18%) were consumer reports. 143 (39%) vaccinees were female, 218 (61%) were male and 3 were unknown. Age of vaccinees ranged from 19 to 97 years with a median age of 67 years.

There were 87 cases (80%) where time to death ranged from 0 to 96 days after receiving the first dose of the vaccine, there were 22 cases (20%) where time to death was 0 to 73 days after receiving the second dose.

Of the 364 cases of sudden death, causes of death were identified in 240 cases (66%) and included the PTs of cardiac arrest, myocardial ischaemia, myocardial infarction, left ventricular dysfunction, atrial fibrillation, pneumonia, pulmonary embolism, pulmonary oedema, asthenia, hyperpyrexia, arthralgia, cardio-respiratory arrest, chest pain, aortic dissection, deep vein thrombosis (DVT), subarachnoid haemorrhage, aneurysm ruptured, contusion, cardiomegaly, multiple organ dysfunction syndrome, acute coronary syndrome, cardiovascular disorder, visceral venous thrombosis, cor pulmonale acute, respiratory arrest, hypertension, haemorrhage intracranial, dyspnoea, cardiac fibrillation, cerebral infarction, gastrointestinal (GI) haemorrhage, cerebrovascular accident, cardiac failure chronic, petechiae, coronary artery occlusion, coronary artery disease, sudden unexplained death in epilepsy, and circulatory collapse.

The medical history (vaccinees may have had >1 comorbidity) included COPD, hypertension, diabetes mellitus, schizophrenia, alcoholic cirrhosis, arterial occlusive disease, cardiac disorder, cardiac failure, myocardial infarction, dyslipidaemia, osteoarthritis, gastroesophageal reflux disease Parkinson's disease, multiple sclerosis (MS), obesity, renal failure, heart failure, frailty, dementia, hepatitis, epilepsy, hypothyroidism, polycythaemia vera, cancer, alcohol abuse, tobacco use, and transient ischemic attack, epilepsy, hypothyroid, renal cancer, fall, cerebral infarction, cardiac pacemaker insertion, depression, chronic respiratory failure, cardiac hypertrophy, Becker's muscular dystrophy and cerebrovascular accident, and cerebral palsy. The medical history was not reported in 122 (34%) cases.

Table 17 Observed versus expected analyses for Sudden death

Medical Concept	Observed cases	Expected cases	Risk Window	Background rate/100,000 person years	Exposure	Rate ratio (CI 95%)	
Sudden death (RW7)	112	5050.34	7	58.78	448306152	0.02 (0.02 – 0.03)	Observed significantly < expected
Sudden death (RW7 + Unk TTO)	291	5050.34	7	58.78	448306152	0.06 (0.05 - 0.06)	Observed significantly < expected

Reference for sudden death IR is ACCESS Rates. Willame et al 2021 [B] (Meta-analysis IR from 2010-2013 - 2017-2019 – Sudden Death (Narrow)).

From the review of data available during the reporting period for all fatal case reports (including sudden death) and also taking into account the cumulative experience along with the O/E analysis of fatal cases there is no new safety information identified on this topic in association with VAXZEVRIA.

7 SUMMARIES OF SIGNIFICANT FINDINGS FROM CLINICAL TRIALS DURING THE REPORTING PERIOD

7.1 Completed clinical trials

During the reporting period, one study investigating the safety and the immunogenicity of VAXZEVRIA was completed (study D8111C00002). A summary of findings is described below:

D8111C00002 (A Phase I/II Randomised, Double-blind, Placebo-controlled Multicentre Study in Participants Aged 18 Years or Older to Determine the Safety and Immunogenicity of VAXZEVRIA, a Non-replicating ChAdOx1 Vector Vaccine, for the Prevention of COVID-19): Phase I/II.

This study assessed the safety and immunogenicity of VAXZEVRIA in Japan. The population recruited included 256 healthy volunteers with a significant portion of elderly randomized 3:1 to receive VAXZEVRIA or saline placebo with 4 weeks dosing interval. Primary read-out 4 weeks after the second dose (Day 57) including reactogenicity, safety and immunogenicity were reported in previous PBRER.

During the reporting period for the current PBRER, we obtained results from primary data of the full year final read-out including safety and immunogenicity over time. This is the first long term evaluation of duration of humoral response to AZD1222 in a homogenous population where all participants received the same regimen (two vaccinations 4 weeks apart) with placebo AZD1222 administered in 2 IM injections was generally well-tolerated and had an acceptable safety profile in Japanese adult participants across all age groups (18 to 55 years, 56 to 69 years, and ≥ 70 years), and the number of SAEs reported between Day 58 and Day 365, in addition to the unsolicited AEs collected up to Day 57, was low.

In the AZD1222 group, antibody titers for the S and Receptor-Binding Domain (RBD) antigens and for the nAb (pseudoneutralization) to SARS-CoV-2 increased substantially after the first dose of study intervention, increasing further after the second dose. Data show a slightly decreasing trend in titers with increasing age, although a large variability was observed in the individual titers, with overlap in confidence intervals (CI) between cohorts. Mean antibody titers had dropped by Day 183, decreasing further by Day 365, due to the expected waning of humoral immunogenicity. By Day 365, mean titers of S- and RBD-binding antibodies remained above Baseline and Day 15 levels; however, a large proportion of participants had no measurable nAb (pseudoneutralization) at this time point.

Taking the above into account, these data suggest that AZD1222 elicits strong early immune responses against SARS-CoV-2 in the Japanese adult population across all the age groups; however, waning of immune responses, with neutralizing antibodies (NAbs) below the lower limit of quantification, was observed in a large proportion of participants by Day 365.

7.2 Ongoing clinical trials

There were 11 (COV001, COV002, COV003, COV004, COV005, COV006, COV008, COV009, D8110C00001, D8110C00010 and D7220C00001) ongoing clinical trials during the reporting period.

There was no clinically important information that arose from ongoing clinical trials during the reporting period.

7.2.1 Ongoing Clinical Trials – Study design and results obtained on safety and efficacy

This section provides summary from the 7 (COV001, COV002, COV003, COV005, COV006, D7220C00001 and D8110C00001) out of the 11 ongoing trials that are in scope for this report. Data analyses were not completed for the remaining 4 ongoing clinical trials, as study read-outs were not scheduled during the reporting period.

COV001 (A phase I/II study to determine efficacy, safety and immunogenicity of the candidate Coronavirus Disease (COVID-19) vaccine ChAdOx1 nCoV-19 in UK healthy adult volunteers): Phase I/II

COV001 is an Oxford-sponsored, single-blinded, multi-centre, randomised, controlled Phase I/II trial assessing the safety, efficacy and immunogenicity of ChAdOx1 nCoV-19 (VAXZEVRIA) in 1077 healthy adults 18 to 55 years of age in the UK. Trial participants are healthy and at increased risk for being exposed to the SARS-CoV-2 virus. Participants receive either a single IM dose or a 2- dose IM regimen of the low dose (LD) (~2.5 x1010 vp) and/or the standard dose (SD) (~5x1010 vp) of VAXZEVRIA or the comparator, meningococcal vaccine (MenACWY).The participants will be followed for 12 months from the last vaccination.

COV002 (A phase II/III study to determine the efficacy, safety and immunogenicity of the candidate Coronavirus Disease (COVID-19) vaccine ChAdOx1 nCoV-19): Phase II/III

COV002 is an Oxford-sponsored, single-blinded, multi-centre, randomised, controlled Phase II/III trial assessing the safety, efficacy and immunogenicity of ChAdOx1 nCoV-19 (VAXZEVRIA) in 10,812 participants in the UK. Trial participants are ≥ 18 years of age. years of age. In addition, a single arm group whereby up to 60 Human immunodeficiency virus (HIV) infected individuals who are stable on antiretroviral therapy

will be recruited and receive VAXZEVRIA vaccination. Participants are enrolled by age groups of 18 to 55 years, 56 to 69 years, and ≥ 70 years. Recruitment for this study focuses on health care professionals and other adults with high potential for exposure to COVID-19. Participants receive a single IM dose or a 2-dose IM regimen of the LD (~$2.5x10^{10}$ vp) and/or the SD (~$5x10^{10}$ vp) of VAXZEVRIA or the comparator, MenACWY, depending on the study group. The participants will be followed for 12 months from the last vaccination.

COV003 (A Randomised, Controlled, Phase III Study to Determine the Safety, Efficacy, and Immunogenicity of the Non-Replicating ChAdOx1 nCoV-19 Vaccine): Phase III

COV003 is an Oxford-sponsored, single-blinded, multi-centre, randomised, controlled Phase III trial assessing the safety, efficacy, and immunogenicity of ChAdOx1 nCoV-19 Vaccine (VAXZEVRIA) in 10416 participants in Brazil. Trial participants are ≥ 18 years of age, who are healthy or have medically stable chronic diseases and are at increased risk for being exposed to the SARS CoV- 2 virus. Participants are randomised to receive either a 2-dose regimen of the SD (~$5x10^{10}$ vp) of VAXZEVRIA or, MenACWY or the MenACWY as the prime dose and saline placebo as boost dose by means of an IM injection. The participants will be followed for 12 months from the last vaccination.

COV004 (A phase Ib/II single-blinded, randomised, controlled study to determine safety, immunogenicity and efficacy of the candidate Coronavirus Disease (COVID-19) vaccine ChAdOx1 nCoV-19 in adults in Kenya): Phase Ib/II

COV004 is an Oxford-sponsored, phase Ib/II trial single-blinded, randomised, controlled study of the SD (~$5x10^{10}$ vp) of ChAdOx1 nCoV-19 (VAXZEVRIA) in comparison to the rabies control vaccine in Kenya. The primary endpoints of the trial will be vaccine safety and immunogenicity of VAXZEVRIA vaccine as compared to the rabies control vaccine, with vaccine efficacy (VE) against COVID-19 evaluated as a secondary endpoint. Approximately 400 healthy adults ≥ 18 years of age (approximately 40 participants in Phase Ib and 360 participants in Phase II) with high potential exposure to SARS-CoV-2 will be randomised. In the phase Ib part of the study the participants receive 1 IM dose of the SD (~5x1010 vp) VAXZEVRIA or rabies vaccine as control. In the phase II part of the study a 2-dose regimen of the SD (~5x1010 vp) of VAXZEVRIA or rabies vaccine will be distributed at day 84 (3 months). The participants will be followed for 12 vp) of ChAdOx1 nCoV-19 (VAXZEVRIA) in comparison to the rabies control vaccine in Kenya. The primary endpoints of the trial will be vaccine safety and immunogenicity of VAXZEVRIA vaccine as compared to the rabies control vaccine, with vaccine efficacy (VE) against COVID-19 evaluated as a secondary endpoint. Approximately 400 healthy adults ≥ 18 years of age (approximately 40 participants in Phase Ib and 360 participants in Phase II) with high potential exposure to SARS-CoV-2 will be randomised. In the phase Ib part of the study the participants receive 1 IM dose of the SD (~$5x10^{10}$ vp) VAXZEVRIA or rabies vaccine as control. In the phase II part of the study a

2-dose regimen of the SD (~$5x10^{10}$ vp) of VAXZEVRIA or rabies vaccine will be distributed at day 84 (3 months). The participants will be followed for 12 months from the first vaccination.

COV005 (An adaptive phase I/II randomised placebo-controlled trial to determine safety, immunogenicity and efficacy of non-replicating ChAdOx1 SARSCoV-2 vaccine in South African adults living without HIV; and safety and immunogenicity in adults living with HIV): Phase I/II

COV005 is a double-blind, multi-centre, randomised, placebo-controlled Phase I/II trial assessing the safety, efficacy, and immunogenicity of ChAdOx1 SARSCoV-2 vaccine (VAXZEVRIA) in 2130 participants with and without HIV in South Africa (SA). Trial participants aged 18-65 years will receive a 2-dose IM regimen of the SD (5-7.5 x1010 vp) of VAXZEVRIA or saline placebo. The phase I study consists of two groups (HIV-uninfected adults; n=70, and HIV-infected adults; n=100), will be evaluated for safety and immunogenicity. The phase II part of the study will target 1900 participants (HIV uninfected) and will be evaluated for immunogenicity and efficacy. The total duration of the study will be 12 months from the day of enrolment for all participants.

Efficacy, safety, and immunogenicity results from pooled analyses including data from COV001, COV002, COV003 and COV005 studies:

The evaluation of the efficacy, immunogenicity and safety of VAXZEVRIA for prevention of COVID-19 is based on the pooled data from 4 ongoing clinical studies COV001 (UK), COV002 (UK), COV003 (Brazil), and COV005 (South Africa). The primary efficacy analysis demonstrated effective protection of VAXZEVRIA against COVID-19 with a VE of 66.73% (95% confidence interval [CI]: 57.41%, 74.01%) ($p< 0.001$) from 15 days after the second dose in seronegative participants receiving two standard doses (SDSD) or 1 low dose and 1 standard dose (LDSD). The pooled analyses demonstrated that VAXZEVRIA provides complete protection against COVID-19 hospital admission ≥ 22 days after the first SD dose in the seronegative analysis set. For the SDSD regimen, it was demonstrated that vaccine protection begins from 22 days after the first dose and extends at least until 12 weeks, allowing the second dose to be given in a flexible window between 4 to 12 weeks. VAXZEVRIA elicited a strong induction of humoral immunogenicity, as measured by different serological assays following the first dose and the second dose of VAXZEVRIA regardless the presence of co-morbid conditions at baseline, country, and age at screening. In summary, pooled analyses of the 4 ongoing University of Oxford-sponsored studies demonstrated a low incidence of SAEs in both the AZD1222 and control groups, with no difference in either frequency or type between the treatment groups The vaccine was well tolerated in pooled safety analyses. There was not a significant change in the safety profile during the reporting period.

COV006 (A single-blind, randomised, phase II study to determine safety and immunogenicity of the Coronavirus Disease (COVID-19) vaccine ChAdOx1 in UK healthy children and adolescents [aged 6-17]): Phase II

COV006 is an Oxford-sponsored, Phase II, single-blinded, active-controlled, randomised study in approximately 300 healthy children and adolescents aged 6-17 years in the UK, of 2 doses 4 or 12 weeks apart of ChAdOx1 nCoV-19 (VAXZEVRIA) or active control (licensed Meningococcal B vaccine) administered IM. The study will assess safety, tolerability and immunogenicity of a SD dose (~$5x10^{10}$ vp) of ChAdOx1 nCoV-19. The total duration of the study will be 12 months from the day of enrolment for all participants.

Summary of results on the safety and immunogenicity of VAXZEVRIA in children and adolescents.

The primary objective of this study was to determine the tolerability of the VAXZEVRIA in children aged 6–17 years, in a two-dose regimen with either a 28-day or 84-day dosing interval. A total of 262 participants aged 6–17 years were enrolled into the study and assigned to vaccination with either VAXZEVRIA or capsular group B meningococcal vaccine at a 28-day or 84-day interval.

The study demonstrated that participants who were seropositive at baseline had stronger immunogenic responses 28 days after first dose than at 28 days after the second dose of the VAXZEVRIA in the seronegative participants, suggesting that, in this population, a single dose of VAXZEVRIA may be able to offer protection against SARS-COV-2 in previously infected individuals. The authors also found that immune response in younger age groups (6-11 years old) was stronger when compared to older age groups (12–17 years) after both a first and second dose of vaccine with a 112-day interval.

Overall, VAXZEVRIA was well tolerated. As expected, fatigue and headache were the most commonly reported systemic solicited adverse events. The most common local solicited adverse events were pain and tenderness for all the ASTRAZENECA COVID-19 and capsular group B meningococcal groups following both doses. The proportion of participants reporting moderate to severe local reaction up to 7 days after vaccination was higher in those receiving the meningococcal vaccine than in those receiving the ASTRAZENACA COVID-19 vaccine. Even though more solicited systemic adverse events were reported in AZD1222 arm in comparison with the meningococcal vaccine arm, they were resolved within 48 hours following vaccination (Li et al 2022).

COV008 (A Phase I study to determine safety, tolerability and immunogenicity of intranasal administration of the COVID vaccine ChAdOx1 nCOV-19 in healthy UK adults): Phase I

COV008 is an Oxford-sponsored, Phase I, open label, dose escalation study in up to 54 healthy adults in the UK. In group 1a adults aged 18-40 years were eligible, the other groups included healthy adults aged 30-40 years. The study will investigate safety, tolerability and immunogenicity of one or two doses of intranasal ChAdOx1 nCOV-19 (5x109 vp, 2x1010 vp or 5x1010 vp), with randomisation between one and two dose groups. The total duration of the study will be 10 months from the day of enrolment for all participants.

COV009 (Post-approval follow-up for the COV001 and 002 trials, to determine the long-term safety and character of immunological response to the ChAdOx1 nCoV-19 coronavirus vaccine): Long-term follow-up

COV009 is an Oxford-sponsored, follow-up study of participants previously enrolled on the phase I/II (COV001) and phase II/III (COV002) trials to determine the long-term safety and character of immunological responses to the ChAdOx1 nCoV-19 vaccine. Up to 1,077 participants will be eligible for enrolment for the COV001 cohort and up to 10,812 participants for the COV002 cohort. No treatment will be given during this Study. Study duration is 12 months.

D8110C00001 (A Phase III Randomised, Double-blind, Placebo-controlled Multicentre Study in Adults to Determine the Safety, Efficacy, and Immunogenicity of VAXZEVRIA, a Non-replicating ChAdOx1 Vector Vaccine, for the Prevention of COVID-19): Phase III

D8110C00001 is an AstraZeneca-sponsored, Phase III randomised, double-blind, placebo-controlled, multi-centre study assessing the safety, efficacy, and immunogenicity of VAXZEVRIA compared to saline placebo for the prevention of COVID-19. Participants are adults ≥ 18 years of age who are healthy or have medically stable chronic diseases and are at increased risk for SARS-CoV-2 acquisition and COVID-19. A total of 32451 participants were randomised in a 2:1 ratio to receive 2 IM doses of either the SD (~$5x10^{10}$ vp) of VAXZEVRIA or saline placebo 4 weeks apart. Randomization was stratified by age (18-65 years, and ≥ 65 years), with at least 25% of participants enrolled in the older age stratum. Safety will be assessed for the duration of the study. All participants will remain on study for 2 years following administration of first dose of study intervention (Day 730).

Efficacy and safety results from study D8110C00001.

At the last PBRER, we reported results of data analyses obtained from data cut-off date of 30 July 2021. Briefly, using fully vaccinated analysis set (FVS), 325 events occurring ≥ 15 days post-second dose of study intervention were the adjudicated, yielding Vaccine Effectiveness (VE) estimate of 66.98% and a lower bound of the 95% CI of 58.87% (141 events in the VAXZEVRIA group and 184 events in the placebo group).

Vaccine Efficacy and duration of protection

A database lock occurred on 02 September 2021 (DCO3), following a 6-month data cut-off on 30 July 2021. The results of data analyses performed on DCO3 data set became available during the reporting period for this PBRER and are provided below.

The majority of participants (90.3% in the AZD1222 group and 89.8% in the placebo group) had been unblinded at the time of the data cut-off date of 30 July 2021 and the median follow-up time post second dose for the FVS over the double-blind period was 78.0 days for the AZD1222 group and 71.0 days for the placebo group. At this DCO3, evaluation of the primary and key secondary efficacy endpoints was repeated using the 6-month data cut-off date of 30 July 2021, as a final supportive analysis of overall vaccine efficacy for the double-blind period. A total of 325 adjudicated events met the primary endpoint definition [AZD122 arm 141/17617 (0.80); placebo arm 184/8528 (2.16)]. The resulting VE estimate with the 6-month data cut-off was 66.98% (95% CI: 58.87, 73.50) and was generally consistent with the primary efficacy analysis (05 March 2021 data cut-off date).

The VE estimate for the incidence of SARS-CoV-2 Real-Time Polymerase Chain Reaction (RT-PCR)-positive severe or critical symptomatic illness was 95.69% (95% CI: 66.33, 99.45) which was generally consistent with the primary efficacy analysis (05 March 2021 data cut-off date). Evaluation of the exploratory objectives of durability of the efficacy of 2 IM doses of AZD1222 against symptomatic COVID-19 illness and against SARS-CoV-2 infection was performed. For these evaluations, the censoring of follow-up time was at the date of first Emergency Use Authorization (EUA) vaccination; this captured participants with events irrespective of unblinding in the study. In these analyses, 18.4% of participants in the AZD122 group and 73.7% in the placebo group had received an EUA vaccine at the time of the data cut-off date of 30 July 2021 and the median follow-up time post second dose for the FVS censored at EUA vaccination was 201.0 days for the AZD1222 group and 82.0 days for the placebo group. A total of 547 adjudicated events met the primary endpoint definition. The VE estimate for the 6-month data cut-off analysis censored at EUA vaccination was 65.05% (95% CI: 58.46, 70.60). The VE estimate for the incidence of SARS-CoV-2 RT-PCR-positive severe or critical symptomatic illness was 92.12% (95% CI 78.17, 97.15).

It should be noted that for the 6-month data analysis, median duration of follow-up after the second dose was longer for participants in the AZD1222 group compared with participants in the placebo group prior to vaccination with an authorized/approved vaccine (201.0 days and 78.0 days, respectively). The duration of follow-up for participants in the placebo group was impacted by unblinding and the receipt of an Emergency Use Authorization vaccine.

Using the data cut-off date of 30 July 2021, analysis of the primary efficacy endpoint was conducted using the FVS, censored at EUA vaccination.

With this censoring approach, there were 328 events in the AZD1222 group and 219 events in the placebo group, with a VE estimate of 65.05% and a lower bound of the 95% CI of 58.46%, which is consistent with the overall VE estimate for 6-month data cut-off analysis against symptomatic illness for the double-blind period.

As with 6-month data cut-off analysis against symptomatic illness for the double-blind period, VE efficacy was observed across age groups. In participants ≥ 18 to < 65 years of age, there were 301 events in the AZD1222 group and 194 events in the placebo group, with a VE estimate of 62.43% and a lower bound of the 95% CI of 54.98%. In participants ≥ 65 years of age in the FVS, there were 27 events in the AZD1222 group and 25 events in the placebo group, with a VE estimate of 82.60% and a lower bound of the 95% CI of 70.00%.

Immunogenicity

During the reporting period immunogenicity data became available showing the waning of humoral immunogenicity through 6 months.

The humoral immunogenicity of AZD1222 was determined using validated bioanalytical methods to assess S-binding, RBD-binding, nucleocapsid-binding, and pseudo-neutralizing antibodies. All analyses excluded any assessments made after unblinding, after administration of an EUA vaccine, or after intake of other exclusionary restricted medication. Overall, AZD1222 generated a robust humoral response. For seronegative participants at baseline in the immunogenicity analysis set, an increase in S-binding antibodies was detectable 14 days after a first dose of AZD1222. S-binding antibodies further increased after a second dose, peaking 14 days after a second dose. Anti-S responses were maintained through at least Day 180, waning from the peak responses induced at D43 as expected but still above the titers observed after a first dose. Geometric Mean Titres (GMTs) in the placebo group were increased at Day 180, possibly due to under-reporting of EUA COVID-19 vaccines received outside of the study. RBD responses had similar kinetics of induction as S-binding antibodies. Neutralizing antibody responses had similar kinetics of induction as S-binding antibodies; however, GMTs peaked at 28 days after the second dose. Neutralizing antibody titers were maintained through at least Day 180 with titers still notably higher than those observed after a first dose.

Quantification of nAbs and Spike binding antibodies over time, demonstrated that highest level of nAbs was observed at Day 57 (28 days after Dose 2). At Day 90 (approximately 60 days after Dose 2), nAb levels had dropped by approximately 20%, with further waning to less than 50% of the maximum at Day 180. Anti-S and anti-RBD responses peak at Day 43 to Day 57 and wane by Day 180, as expected, though the levels remain above the baseline titres prior to vaccination. These data support administration of a booster dose of AZD1222 as early as 3 months following primary series vaccination.

Safety

Safety results at the 6-month data cut-off were generally consistent with safety findings at the primary analysis, with no new or emerging safety issues identified. Overall, AZD1222 remains well-tolerated up to 6 months post dose. The AE profile continued to be consistent with AEs commonly observed following vaccine administration. The majority of AEs following administration of AZD1222 were mild or moderate in severity. In the AZD1222 group, a small proportion of SAEs and Adverse Event of Special Interest (AESIs) were reported, with no clinically meaningful findings.

D7220C00001 (A Phase II/III Partially Double-Blinded, Randomised, Multinational, Active-Controlled Study in Both Previously Vaccinated and Unvaccinated Adults to Determine the Safety and Immunogenicity of AZD2816, a Vaccine for the Prevention of COVID-19 Caused by Variant Strains of SARS-CoV-2): Phase II/III

This is an AstraZeneca-sponsored, multi-country Phase II/III study to evaluate the safety and immunogenicity of AZD2816 as single-dose vaccination in previously vaccinated adult participants and as a 2-dose primary vaccination in previously unvaccinated adult participants. The participant population includes adults ≥18 years of age. years of age. A total of approximately 2590 SARS-CoV-2 nucleocapsid seronegative participants that have been screened and judged to be eligible for the study will be enrolled across these 2 populations with the goal of 1300 previously vaccinated participants receiving single-dose vaccination and 1290 unvaccinated participants receiving 2-dose primary vaccination. In addition, seropositive participants were enrolled (with a cap of 10% of the seronegative population or 225 participants) to support exploratory analysis is these participants.

In both the single-dose booster treatment regimen and the 2-dose primary vaccination treatment regimen, participants will receive study intervention consisting of IM administration of either AZD1222 (5×10^{10} vp) or AZD2816 (5×10^{10} vp). Participants receiving a 2-dose primary vaccination will be dosed at intervals of 4 weeks (for AZD1222 and AZD2816) or 12 weeks (AZD2816 only). All study participants will be followed for safety for 180 days after administration of their last vaccination dose.

Interim analysis of safety and immunogenicity results from the previously vaccinated participants that have received a booster dose of AZD1222 or AZD2816 have been reported.

The safety (through Day 29) and reactogenicity (through Day 8) of booster doses of AZD1222 or AZD2816 in participants previously vaccinated with either AZD1222 or a messenger ribonucleic acid (mRNA) vaccine, including for those in the Seronegative Safety Analysis Set, was consistent with the known safety profile of AZD1222 administered as a 2-dose primary series. No emergent safety issues were identified. There were no clinically meaningful differences between the safety profiles of booster doses of AZD1222 and

AZD2816. Analyses of data through to data cut-off, up to a maximum of 107 days after booster dose, did not identify any emergent safety issues.

Humoral immunogenicity data from the interim analysis indicate that a booster dose of either AZD1222 or AZD2816 in seronegative participants previously vaccinated with AZD1222 or an mRNA vaccine generates a strong humoral response to SARS-CoV-2 by 28 days after the booster is administered.

D8111C00010 (A Phase IV Open-Label, Non-Randomized, Multi-Cohort, Multi-centre Study in Previously Unvaccinated Immunocompromised Adults to Determine the Immunogenicity and Safety of AZD1222 Vaccine for the Prevention of COVID-19): Phase IV

This is an AstraZeneca-sponsored, Phase IV open-label, non-randomized, multi-cohort, multi-centre study to evaluate the immunogenicity and safety of AZD1222 for the prevention of COVID-19 in previously unvaccinated immunocompromised adults ≥18 years. Approximately 360 SARS-CoV-2 spike and nucleocapsid seronegative participants will be enrolled. Immunocompromised participants will receive primary vaccination with 3 IM doses of AZD1222 separated by 4 weeks and will continue to be followed to the end of the study. Immunocompetent participants will receive a third dose booster 6 months after dose 1 and will continue to be followed to the end of the study. The total duration of the study is 12 months. The first participant was enrolled in January 2022 and as of 28 June 2022 there have been 34 participants enrolled in the study.

7.2.2 Overall Safety, Efficacy and immunogenicity

The safety, efficacy and immunogenicity of a two-dose regimen of VAXZEVRIA has been currently investigated in 11 ongoing clinical trials. The initial VE against symptomatic disease of 66.7% (95% CI: 57.4%, 74.0%) ($p < 0.001$) demonstrated in a pooled analyses of four trials (COV001, COV002, COV003, COV005) was confirmed in a large study conducted mainly in the United States of America (USA) (VE=74%; 95CI: 65.34, 80.47). The vaccine has also shown to be highly immunogenic after a single dose, with increase in seroconversion after a second dose. Moreover, adults (including those over the age of 65 years) with pre-existing comorbidity showed similar VE and immune responses when compared to the general population. The safety of VAXZEVRIA has been evaluated in ongoing clinical trials. No safety concerns have arisen from these ongoing VAXZEVRIA /AZD2816 clinical trials.

7.3 Long-term follow-up

Participants completing VAXZEVRIA clinical trials are not subject to longer-term follow up beyond the 12-24 months as mentioned in the study protocols.

7.4 Other therapeutic use of medicinal product

There were no other AstraZeneca programmes that follow a specific protocol with solicited reporting for VAXZEVRIA.

7.5 New safety data related to fixed-combination therapies

This section is not applicable as VAXZEVRIA is not approved or under development as part of a fixed-combination product or a multi-drug regimen.

8 FINDINGS FROM NON-INTERVENTIONAL STUDIES

No relevant safety information or information with potential impact on the benefit or risk evaluations arose from AstraZeneca sponsored non-interventional studies of VAXZEVRIA during the reporting period.

A listing of AstraZeneca sponsored non-interventional Post-Authorisation Safety Studies (PASS) completed or ongoing during the reporting period is provided in Appendix 4.

9 INFORMATION FROM OTHER CLINICAL TRIALS AND SOURCES

9.1 Other clinical trials

During the reporting period, a review of the literature resulted in key relevant publications addressing the following:

1 Third dosing booster (Munro et al 2021, Clemens et al 2022, Jara et al 2022, Muñoz-Valle et al 2022)

2 The persistence of immunogenicity following immunization with VAXZEVRIA (Xinxue Liu et al. 2022)

Real world evidence data on duration of protection (Andrews et al 2022a)

Real world evidence data on protection against variants of concern (Andrews et al 2022b)

A *summary of these publications can be found in sub-sections below:*

9.1.1 Homologous and Heterologous third dosing booster:

During the reporting period, relevant studies that included data on VAXZEVRIA vaccine administered as a third dose booster are described below.

These data add to evidence previously described in the Munro et al 2021 study (COV-BOOST trial) reported in previous PBRER.

Clemens et al 2022 **study (RHH-001 trial)** evaluated VAXZEVRIA (previously AZD1222) as a heterologous booster after a 2-dose primary series of the inactivated whole-virion adjuvanted vaccine CoronaVac. This study also evaluated COMIRNATY (BNT162b2/Pfizer vaccine) and JCOVDEN (previously COVID-19 VACCINE Jansen/ AD26.COV2-S/Jansen vaccine) compared to a third dose homologous booster of CoronaVac. After 28 days, all heterologous boosting elicited a significantly superior response ($p<0.0001$) in anti-Spike IgG concentration and pseudo-neutralising titres compared to homologous boosting with CoronaVac. The VAXZEVRIA boost elicited a 90-fold rise in the anti-spike IgG from baseline versus a 12.4-fold rise in the homologous booster dosing. All heterologous booster regimens induced high concentrations of pseudo-virus nAbs. At Day 28, all groups except for the homologous boost in the older adults reached 100% seropositivity: geometric mean ratios (heterologous vs homologous) were 8.7 (95% CI: 5.9 to 12.9) for JCOVDEN, 21.5 (95% CI: 14.5 to 31.9) for COMIRNATY, and 10.6 (95% CI: 7.2 to 15.6) for AZD1222. Live virus nAbs were also boosted against the Delta (B.1.617.2) and Omicron variants (B.1.1.529). These data provide supportive evidence of AZD1222's immunogenicity when used as a heterologous booster.

Jara et al 2022 **study** also evaluated the vaccine effectiveness of VAXZEVRIA as a heterologous booster after a 2-dose primary series of CoronaVac (Sinovac COVID-19 vaccine). This study was a large prospective national cohort sample following campaign immunization with CoronaVac in Chile, and assessed the effectiveness of a third dose of either CoronaVac, COMIRNATY, or VAXZEVRIA. Heterologous boosting with VAXZEVRIA, following a two-dose CoronaVac primary vaccination series, yielded vaccine effectiveness of 97.7% (95% CI: 97.3 to 98.0) against COVID-19-related hospitalisation, 98.9% (95% CI: 98.5 to 99.2) against ICU admission, and 98.1% (95% CI: 97.3 to 98.6) against death. Safety information was not collected in this study. These data provide further supportive evidence of VAXZEVRIA's immunogenicity and efficacy profile when used as a heterologous booster.

Muñoz-Valle et al 2022 **study** evaluated VAXZEVRIA as a heterologous booster after primary immunisation with the adenoviral vector vaccine Convidecia (Ad5-nCoV,CanSino Biologics Inc, China). This study involved 62 participants from a prior study of Convidecia who had received a heterologous booster with VAXZEVRIA, JCOVDEN, COMIRNATY, or mRNA-127 at 4.5 to 5 months after single-dose primary vaccination with Convidecia. A control group of 62 unboosted individuals was matched with the boosted group for age, gender, treatment, COVID-19 history, and baseline antibody levels 21 days after primary vaccination. At baseline, the median percentage of neutralizing antibodies was similar in booster and control groups (78.16% vs. 78.65%, $p > 0.05$), but at 6 months post-booster was significantly higher in the boosted group versus controls (96.41% vs. 89.33%, $p = 0.0004$), with no differences between vaccines. There were also no differences in adverse events between booster vaccines. The authors concluded that a heterologous regimen of 1 dose of

Convidecia followed by a booster dose of a different vaccine is safe and results in a robust humoral immune response. These data support the use of VAXZEVRIA as a heterologous booster after a primary series of an adenovirus vector vaccine.

Summary and conclusions

Based on the studies discussed above, there is evidence that a heterologous 3rd booster dose of VAXZEVRIA elicits a strong and broad humoral immune response after a primary series of several vaccine classes. These include mRNA vaccines, as reported in D7220C00001 and COV-BOOST, inactivated whole virion vaccine, as reported in RHH-001 and the Jara study, and adenovirus vector vaccines, as reported in the Muñoz-Vallee study. There is limited information on the use of VAXZEVRIA with the protein subunit vaccine NVX-CoV2373, but use of NVX-CoV2373 after a primary series of VAXZEVRIA was immunogenic and did not raise any safety issues in COV-BOOST. Importantly, no additional safety concerns have been raised by the use of VAXZEVRIA in combination with other COVID-19 vaccine classes, whether as a heterologous booster or as a primary series followed by heterologous boost with another vaccine. AstraZeneca considers that data on the immunogenicity and safety profile of VAXZEVRIA support its use as a heterologous 3rd booster dose after a range of other COVID-19 vaccine classes.

9.1.2 Persistence of Immunogenicity

During the reporting period, relevant studies that included data on persistence of immunity of VAXZEVRIA are described below.

These data add to evidence previously described in Munro et al 2021 COVBOOST study described in previous PBRER.

Xinxue Liu et al. 2022 performed further analyses of data from COV-BOOST study to assess the persistence of humoral and cellular immune response against SARS-COV-2 infection three months after third dose boosters with different types of vaccines, including VAXZEVRIA. In this study, the authors demonstrated that, a third dose booster of VAXZEVRIA given after primary immunization with two doses of BNT/BNT was able to yield similar immune response when a homologous third dose booster of BNT was given after primary immunization with BNT/BNT. Moreover, anti-Spike antibodies persisted for at least 84 days after primary immunisation with AZD1222 followed by a booster with another adenoviral vector vaccine, namely Jcovden, a Janssen COVID-19 vaccine using another adenoviral vector platform (JCOVDEN). The decay ratio of anti-Spike IgG GMT between Days 28 and 84 was lower after a third dose booster with JCOVDEN than with BNT after primary vaccination with VAXZEVRIA, suggesting greater persistence of anti-Spike antibodies with JCOVDEN than with BNT. The Day 84 to Day 28 GMT ratio was 0.72 (95% CI: 0.68 to 0.77) for JCOVDEN and 0.43 (95% CI: 0.41 to 0.46) for COMIRNATY, with a

GMR for JCOVDEN versus COMIRNATY of 1.66 (95% CI: 1.45 to 1.90). These data indicate that while anti-Spike IgG at Day 84 was lower for JCOVDEN than for COMIRNATY after a AZD1222/AZD1222 primary series, the JCOVDEN booster had greater antibody persistence. GMRs for pseudo-neutralising and live viral nAbs of AZD1222 and JCOVDEN boosters at Day 28 and Day 84 were consistent with those seen for anti-Spike IgG. In addition, The decay rate of cellular responses were similar between all the vaccine schedules and doses. The authors concluded that, by Day 84 post- third dose booster, adenoviral vector vaccines may be as immunogenic as following a third dose of an mRNA vaccine. The anti-spike IgG in adenoviral vector vaccine arms (VAXZEVRIA and Ad26) after the BNT/BNT prime were the most persistent schedules up to D84.

9.1.3 Real world evidence data on duration of protection

Andrews et al 2022a**:** In the first of two publications falling within the reporting period (Andrews et al 2022a), vaccine effectiveness (VE) was estimated from a test-negative-control design of two doses of VAXZEVRIA, COMIRNATY, and mRNA-1273 vaccines against symptomatic disease as confirmed on polymerase-chain-reaction (PCR) testing, against hospitalization within 14 days after confirmation on PCR testing, and against death within 28 days after confirmation on PCR testing. The analysis was stratified to assess vaccine effectiveness against the alpha and delta variants during the periods when they were circulating. Moreover, VE of the VAXZEVRIA and COMIRNATY vaccines was assessed according to participant age and status with regard to coexisting conditions and over time since receipt of the second vaccine dose to investigate waning of effectiveness separately for the alpha and delta variants.

The authors report that whilst VE peaked in the early weeks after administration of the second dose, a decline was observed at 20 weeks after vaccination to 44.3% (95% confidence interval [CI]: 43.2 to 45.4) with the VAXZEVRIA vaccine and to 66.3% (95% CI: 65.7 to 66.9) with the COMIRNATY vaccine. Waning of vaccine effectiveness was greater in persons 65 years of age or older than in those 40 to 64 years of age. However, VE against hospitalization remained high at 80.0% (95% CI: 76.8 to 82.7) with the VAXZEVRIA vaccine and 91.7% (95% CI: 90.2 to 93.0) with the COMIRNATY vaccine, and death was 84.8% (95% CI: 76.2 to 90.3) and 91.9% (95% CI: 88.5 to 94.3), respectively. Greater waning in vaccine effectiveness against hospitalization was observed in persons 65 years of age or older in a clinically extremely vulnerable group and in persons 40 to 64 years of age with underlying medical conditions than in healthy adults. The authors do point out that the analysis with VAXZEVRIA boosters is particularly likely to be subject to bias because this vaccine was not recommended as a booster in the UK and persons who received VAXZEVRIA were likely to have done so because of contraindications to other vaccines.

9.1.4 Real world evidence data on protection against variants of concern

In the second publication from Andrews et al 2022b, a test-negative case-control study examined the VE against symptomatic disease caused by the Delta and Omicron variants. The study included a representative sample of the general population in England who had PCR tests performed when prevalence of Omicron had surpassed that of Delta variant in the UK. The data set included 886774 persons with symptomatic disease who were infected with the Omicron variant, 204154 persons infected with the Delta variant, and 1572621 test-negative controls.

Protection against severe COVID-19 or hospitalisations due to COVID-19 was not assessed in this study. No effect against the Omicron variant was observed from 20 weeks after a primary vaccination with VAXZEVRIA, but the VE of a booster dose with VAXZEVRIA was 55.6% at 2 to 4 weeks and 46.7% at 5 to 9 weeks following booster administration. This decrease in VE was also noted with a third homologous dose of BNT, with VE decreasing from 67.2% at 2 to 4 weeks to 45.7% after 10 or more weeks, and mRNA-1273, for which VE declined from 73.9% after 2 to 4 weeks to 64.4% after 5 to 9 weeks.

Kirsebom et al 2022 In another real-world evidence study conducted by the United Kingdom Health Security Agency (a test-negative case control design was used to estimate the VE of a VAXZEVRIA or COMIRNATY booster following a primary series of VAXZEVRIA against symptomatic disease and hospitalisation following infection with the SARS-CoV-2 Omicron variant in England. This study provides data on the vaccine effectiveness of VAXZEVRIA at least 25 weeks after primary immunizations during omicron era. The authors found that, in the age group 40-64 years and those aged 65 years and older, VE against symptomatic disease caused by the Omicron variant was 8.0% (6.0 to 9.9%) and 19.5% (11.7 to 26.6%), respectively. In those aged 40-64 years, VE against symptomatic disease increased to 61.2% (40.9 to 74.6%) one week after receiving a booster with VAXZEVRIA as compared to 58.2% (57 to 59.4%) amongst those who received a COMIRNATY booster. Furthermore, waning of protection was described for both, VAXZEVRIA and COMIRNATY third dose boosters, with reduction of protection with a booster of VAXZEVRIA to 37.2% (-44.1 to 72.6%) at 15 or more weeks after receiving the booster, as compared to 30.6% (26.8 to 34.3%) over the same period amongst those who received a third dose of COMIRNATY booster. Protection against symptomatic disease in those aged 65 years and older peaked at 66.1% (16.6 to 86.3%) and 68.5% (65.7 to 71.2%) among those who received VAXZEVRIA and COMIRNATY boosters, respectively, and waned to 44.5% (22.4 to 60.2%) and 54.1%(50.5 to 57.5%), respectively, after 5 to 9 weeks. VE against hospitalisation following infection with the SARS-CoV-2 Omicron variant peaked at 82.3% (64.2 to 91.3%) after an VAXZEVRIA booster and 90.9% after a third dose booster with (88.7 to 92.7%) booster. The authors noted differences between the population receiving VAXZEVRIA and the population receiving COMIRNATY, with those receiving 3 doses of VAXZEVRIA more likely to be in risk groups; this was also true for Andrews et al 2022b. While VAXZEVRIA-induced

concentrations of neutralising antibodies were lower against the Omicron variant than for other variants, no correlates of protection have been established, and clinical effectiveness of a VAXZEVRIA booster has been observed in real-world studies against COVID-19 due to the Omicron variant (Andrews et al 2022b, Kirsebom et al 2022), particularly against progression to severe disease, hospitalization, or death.

No information relevant to the benefit-risk assessment of VAXZEVRIA was identified from any other clinical trial or study sources, during the reporting period.

9.2 Vaccination errors

Case reports of vaccination error where no other AEs have been reported do not fulfil the criteria for inclusion in the tabulation in Appendix 2 but are included in the searches below.

The search strategy for vaccination errors includes the following MedDRA (version 25.0) PT's:

- PTs in the SMQ Medication errors and
- PT's: Device failure; Device deployment issue; Prescription drug used without a prescription; Device delivery system issue; Product advertising issue; Counterfeit product administered; Device mechanical issue; Device safety feature issue; Device environmental compatibility issue; Device data issue; Device temperature issue; Device user interface issue; Device signal transmission issue; Device wireless communication issue; Unevaluable device issue; Prosthetic cardiac valve malfunction; Device calibration failure; Product sterility issue.

Interval Period (29 December 2021 – 28 June 2022)

A total of 7728 case reports (7316 initial and 412 follow up), including 8104 vaccination error AEs, have been identified during the reporting period, which represents 42.5% of the cumulative cases (18164 case reports). Of those 7728 case reports, 560 were reported as serious (169 case reports were medically confirmed and 391 were consumer reports). In 5788 (75%) of the 7728 cases reports no associated AEs were reported in connection with the vaccination error. Other AEs were co-reported in the remaining 1940 (25%) case reports.

The frequently reported (>50) vaccination errors were Interchange of vaccine products (2329), Wrong product administered (2005), Expired product administered (1893), Inappropriate schedule of product administration (943), Product administered to patient of inappropriate age (892), Incorrect dose administered (809), Incomplete course of vaccination (198), Incorrect route of product administration (196), Product administration error (185), Medication error (171), Accidental exposure to product (141), Vaccination error (127), Incorrect product formulation administered (104), Product dose omission issue (84), Underdose (55) and Product administered at inappropriate site (53). The reported vaccination

error AEs have been grouped according to specific vaccination error groups suggested in the literature (Hibbs et al 2015), see Table 20.

Out of the 1940 cases with associated AEs, 523 (27%) cases were serious and 1417 (73%) were non-serious. Of the 1940 cases, 892 (45.97%) were medically confirmed and 1048 (54.02%) were non-medically confirmed. Out of 523 cases, the reported seriousness criteria were fatal/death in 27 case reports, hospitalisations in 177 cases and the remaining were medically important.

Out of 1940 case reports there were 10418 events (2335 serious and 8109 non-serious). More number of AEs were reported from the SOC of General disorders and administration site conditions (Table 18).

Table 18 Distribution of Adverse Events Associated with Vaccination Errors with VAXZEVRIA by MedDRA System Organ Class (SOC) from 29 December 2021 to 28 June 2022

MedDRA (SOC)	Serious	Non-Serious	Events Count (%)
General disorders and administration site conditions	373	1833	2197 (21.09)
Injury, poisoning and procedural complications	271	1653	1924 (18.47)
Nervous system disorders	417	772	1181 (11.34)
Surgical and medical procedures	58	979	1037 (9.95)
Musculoskeletal and connective tissue disorders	196	641	834 (8.01)
Investigations	85	692	776 (7.45)
Gastrointestinal disorders	103	295	398 (3.82)
Respiratory, thoracic and mediastinal disorders	130	203	333 (3.20)
Skin and subcutaneous tissue disorders	80	221	298 (2.86)
Infections and infestations	127	158	285 (2.74)
Psychiatric disorders	39	183	221 (2.12)
Vascular disorders	92	75	167 (1.60)
Cardiac disorders	68	49	117 (1.12)
Eye disorders	36	63	99 (0.95)
Ear and labyrinth disorders	32	56	88 (0.84)
Immune system disorders	33	47	80 (0.77)
Reproductive system and breast disorders	31	44	74 (0.71)
Blood and lymphatic system disorders	32	31	63 (0.60)
Renal and urinary disorders	30	24	54 (0.52)
Metabolism and nutrition disorders	17	36	53 (0.51)
Pregnancy, puerperium and perinatal conditions	35	6	41 (0.39)

Table 18 Distribution of Adverse Events Associated with Vaccination Errors with VAXZEVRIA by MedDRA System Organ Class (SOC) from 29 December 2021 to 28 June 2022

MedDRA (SOC)	Serious	Non-Serious	Events Count (%)
Social circumstances	12	26	38 (0.36)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	17	4	21 (0.20)
Hepatobiliary disorders	13	5	18 (0.17)
Endocrine disorders	6	5	11 (0.11)
Product issues	0	8	8 (0.08)
Congenital, familial and genetic disorders	2	0	2 (0.02)
Total	**2335**	**8109**	**10418 (100.00)**

MedDRA Medical Dictionary for Regulatory Activities, SOC System Organ Class

The co-reported AE counts are presented in Table 18.

Most commonly co-reported AEs (≥50) in these 1940 vaccination error cases were Headache (396), Pyrexia (376), Pain (247), Pain in extremity (228), Fatigue (202), Chills (193), Myalgia (163), Arthralgia (152), Malaise (142), Asthenia (141), COVID-19 (112), Nausea (101), Dizziness (96), Paraesthesia (90), Dyspnoea (68), Application site pain (63), Feeling abnormal (62), Injection site pain (60), Hypoaesthesia (58), Back pain (53), Vomiting (52), Diarrhoea (50).

During the reporting period there was one case each reported with Intradermal (ID), Intravesical (IB), Oral (PO) routes of administration that were associated with AE and 1 case each was reported with Intrameningeal (IMEN), Intraocular (IOC), Intrasynovial (ISYN) routes without AE. There were 2 cases each reported with Cutaneous (CU), Intra-articular (IJ), Subdermal (SD) routes that were associated with AE. Ten cases were reported with Transplacental (TPL) route, 11 cases were reported with Intracavernous (ICS) route that were associated with AE. There were 28 cases reported with Intravenous (IV) (with AE), 57 cases were reported with subcutaneous route (SQ) (55 with AE and 2 without AE) and 7593 cases were reported with intramuscular (1818 with AE and 5775 without AE). Additionally, there were 17 cases where the route of administration was unspecified of these, 9 were associated with AE and 8 without AE.

Cumulative Review (29 December 2020 – 28 June 2022)

A total of 18164 case reports, including 19593 vaccination error AEs, have been identified during the cumulative period. Of those 18164 case reports, 1644 were considered serious (429 case reports were medically confirmed and 1215 were consumer reports). In 13075

(72%) of the 18164 cases reports no other AEs were reported in connection with the vaccination error. Other AEs were co-reported in the remaining 5089 (28%) case reports.

The frequently reported (>50) vaccination errors were Interchange of vaccine products (3748), Wrong product administered (3347), Expired product administered (2753), Inappropriate schedule of product administration (2566), Incorrect dose administered (1558), Product administered to patient of inappropriate age (1541), Medication error (1467), Incorrect route of product administration (801), Product dose omission issue (530), Incomplete course of vaccination (527), Product storage error (481), Product temperature excursion issue (398), Product administration error (371), Vaccination error (349), Intercepted medication error (316), Underdose (286), Circumstance or information capable of leading to medication error (269), Accidental exposure to product (256), Intercepted product storage error (228), Overdose (186), Product administered at inappropriate site (166), Incorrect product formulation administered (129), Contraindication to vaccination (123), Product use issue (94), Extra dose administered (89) and Wrong technique in product usage process (63).

The reported vaccination error AEs have been grouped according to specific vaccination error groups suggested in the literature (Hibbs et al 2015, see Table 20.

Out of the 5089 cases with adverse events, 1559 (31%) cases were serious and 3530 (70%) were non-serious. Of the 5089 cases, 1555 (30%) were medically confirmed and 3534 (69%) were consumer reports Out of 1559 cases, the seriousness criteria were fatal/death in 58 case reports, hospitalisations in 508 cases and the remaining were medically important.

Out of 5089 case reports there were 27195 events (6218 serious and 21033 non-serious). More number of AEs were reported from the SOC of General disorders and administration site conditions (Table 19).

Table 19 Distribution of Adverse Events Associated with Vaccination Errors with VAXZEVRIA by MedDRA System Organ Class (SOC) through 28 June 2022

MedDRA (SOC)	Serious	Non-Serious	Events Count (%)
General disorders and administration site conditions	1164	5459	6607 (24.29)
Injury, poisoning and procedural complications	679	4840	5515 (20.28)
Nervous system disorders	1174	2300	3460 (12.72)
Musculoskeletal and connective tissue disorders	532	1808	2330 (8.57)
Surgical and medical procedures	105	1415	1520 (5.59)
Gastrointestinal disorders	321	894	1214 (4.46)
Investigations	190	1014	1203 (4.42)

Table 19 Distribution of Adverse Events Associated with Vaccination Errors with VAXZEVRIA by MedDRA System Organ Class (SOC) through 28 June 2022

MedDRA (SOC)	Serious	Non-Serious	Events Count (%)
Respiratory, thoracic and mediastinal disorders	308	527	834 (3.07)
Skin and subcutaneous tissue disorders	227	579	802 (2.95)
Infections and infestations	236	436	671 (2.47)
Psychiatric disorders	125	446	570 (2.1)
Vascular disorders	255	198	452 (1.66)
Eye disorders	128	216	344 (1.26)
Cardiac disorders	174	134	308 (1.13)
Reproductive system and breast disorders	82	148	229 (0.84)
Ear and labyrinth disorders	78	143	220 (0.81)
Blood and lymphatic system disorders	95	71	166 (0.61)
Metabolism and nutrition disorders	52	112	164 (0.6)
Immune system disorders	68	95	163 (0.6)
Social circumstances	41	68	109 (0.4)
Renal and urinary disorders	59	49	108 (0.4)
Pregnancy, puerperium and perinatal conditions	61	8	69 (0.25)
Product issues	3	49	52 (0.19)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	28	8	36 (0.13)
Hepatobiliary disorders	21	10	31 (0.11)
Endocrine disorders	6	6	12 (0.04)
Congenital, familial and genetic disorders	6	0	6 (0.02)
Total	**6218**	**21033**	**27195 (100)**

MedDRA Medical Dictionary for Regulatory Activities, SOC System Organ Class

The co-reported AE counts are presented in Table 19.

Most frequently co-reported AEs ≥ 50 within the 5089 case reports of vaccination error were Pyrexia (1342), Headache (1337), Pain (712), Fatigue (680), Chills (675), Pain in extremity (627), Myalgia (503), Arthralgia (431), Asthenia (416), Malaise (405), Dizziness (356), Nausea (337), Injection site pain (255), Paraesthesia (217), COVID-19 (215), Dyspnoea (195), Diarrhoea (187), Vomiting (187), Hypoaesthesia (172), Feeling abnormal (151), Application site pain (129), Cough (124), Back pain (120), Chest pain (119), Rash (119), Tremor (119), Pruritus (115), Vaccination site pain (112), Hyperhidrosis (107), Influenza like

illness (98), Insomnia (93), Peripheral swelling (93), Thrombosis (93), Abdominal pain (92), Decreased appetite (91), Limb discomfort (91), Erythema (90), Somnolence (89), Illness (85), Muscular weakness (85), Feeling cold (82), Hypersensitivity (82), Contusion (76), Nasopharyngitis (76), Syncope (76), Gait disturbance (73), Tinnitus (73), Heart rate increased (71), Muscle spasms (71), Oropharyngeal pain (70), Vision blurred (68), Body temperature increased (67), Palpitations (64), Abdominal pain upper (63), Neck pain (61), Anxiety (59), Discomfort (59), Injection site erythema (59), Maternal exposure during pregnancy (58), Eye pain (57), Feeling hot (57), Tachycardia (57), Therapy partial responder (56), Chest discomfort (55), Influenza (55), Migraine (55), Hypertension (54), Urticaria (54), Blood pressure increased (52), Burning sensation (50).

During the cumulative period, there was one case each reported with Gastroenteral (GE), Infiltration (IF), Intracardiac (IC), Intradiscal (intraspinal) (IS), Respiratory (inhalation) (IH), Subconjunctival (SCON) and Intravesical (IB) routes that were associated with AE. 2 cases each were reported with Auricular (otic) (EAR), Intravenous bolus (PU) and Nasal (IN) routes of administration which were associated with AE's and 2 cases were reported with Intrasynovial (ISYN) route (1 with AE and 1 without AE). There were 3 cases reported with Intra-articular (IJ), Transmammary (TM) route, Intrameningeal (IMEN) (1 with AE and 2 without AE), 4 cases with Subdermal (SD), 5 cases with Intraocular (IOC) (1 with AE and 4 without AE), 7 cases with Parenteral route (PAR), 11 cases with Transplacental (TPL), 12 cases with ICS, Oral (PO), CU route (11 with AE and 1 without AE) and 19 cases with Intradermal route of administration that were associated with AE. A total of 124 cases were reported with Intravenous (IV) route (121 with AE and 3 without AE) and 229 cases with subcutaneous (SQ) route (217 with AE and 12 without AE). There were 17640 cases reported with intramuscular route of administration (4634 with other co-reported AE and 13006 without AE). Additionally, there were 65 cases where the route of administration was unspecified of these, 19 were associated with AE and 46 without AE.

Table 20 Summary tabulation of Vaccination Error Adverse Events

Vaccination error group	Adverse Event (MedDRA PT)	With AE				Without AE				Total Cumulative
		Interval		Cumulative		Interval		Cumulative		
		Serious	Non-Serious	Serious	Non-Serious	Serious	Non-Serious	Serious	Non-Serious	
Accidental	Accidental exposure to product	13	10	21	21	3	115	7	207	256
	Accidental exposure to product packaging	0	0	0	1	0	0	0	0	1
	Accidental underdose	0	0	1	4	0	1	0	16	21
	Exposure to contaminated device	0	0	1	0	0	0	0	0	1
	Intercepted accidental exposure to product by child	0	0	0	0	0	0	0	1	1
Administration errors	Counterfeit product administered	0	0	0	0	0	0	0	1	1
	Drug administered in wrong device	0	0	0	0	0	0	1	1	2
	Drug monitoring procedure not performed	0	0	0	1	0	0	0	0	1
	Drug titration error	1	0	1	1	0	0	0	0	2
	Duplicate therapy error	0	0	0	0	0	0	0	3	3
	Inadequate aseptic technique in use of product	0	0	1	1	0	0	0	0	2
	Incorrect product formulation administered	0	0	0	1	1	103	3	125	129
	Incorrect product administration duration	1	0	1	6	0	0	0	13	20

Table 20 Summary tabulation of Vaccination Error Adverse Events

Vaccination error group	Adverse Event (MedDRA PT)	With AE				Without AE				Total Cumulative
		Interval		Cumulative		Interval		Cumulative		
		Serious	Non-Serious	Serious	Non-Serious	Serious	Non-Serious	Serious	Non-Serious	
	Incorrect route of product administration	5	154	51	653	0	37	0	97	801
	Lack of vaccination site rotation	0	0	1	0	0	0	0	0	1
	Product administration interrupted	0	0	0	2	0	0	0	0	2
	Product administered at inappropriate site	13	20	48	78	1	19	3	37	166
	Product administered to patient of inappropriate age	0	35	7	134	3	854	8	1392	1541
	Product administration error	4	148	18	202	1	32	2	149	371
	Product monitoring error	0	0	1	3	0	0	0	2	6
	Wrong route	0	0	0	2	0	0	0	0	2
	Wrong technique in device usage process	0	0	0	2	0	0	0	0	2
	Wrong technique in product usage process	5	7	10	28	0	14	1	24	63
Contraindication	Contraindication to vaccination	2	5	7	12	0	30	3	101	123
	Contraindicated product administered	0	1	3	4	0	1	0	2	9
	Contraindicated product prescribed	0	0	8	3	0	0	0	0	11

Table 20 Summary tabulation of Vaccination Error Adverse Events

Vaccination error group	Adverse Event (MedDRA PT)	With AE				Without AE				Total Cumulative
		Interval		Cumulative		Interval		Cumulative		
		Serious	Non-Serious	Serious	Non-Serious	Serious	Non-Serious	Serious	Non-Serious	
	Contraindication to medical treatment	0	0	0	1	0	0	0	0	1
	Documented hypersensitivity to administered product	0	0	0	0	0	0	0	2	2
	Labelled drug-drug interaction issue	2	0	2	1	0	0	0	0	3
	Labelled drug-drug interaction medication error	0	0	1	0	0	0	0	0	1
Equipment	Device use issue	0	0	1	0	0	0	0	0	1
	Device connection issue	0	0	0	0	0	0	0	3	3
	Device maintenance issue	0	0	0	0	0	0	0	1	1
	Device use confusion	0	0	0	1	0	0	0	0	1
	Device use error	0	1	0	1	0	0	0	1	2
	Device delivery system issue	0	1	0	1	0	0	0	0	1
	Injury associated with device	0	2	8	7	0	0	1	3	19
	Medical device monitoring error	0	0	0	0	0	0	0	1	1
	Needle issue	0	0	1	8	0	3	1	10	20
	Syringe issue	0	0	0	4	0	0	0	9	13
	Wrong device used	0	0	0	2	0	0	0	0	2
General error	Medication error	57	87	97	495	0	27	3	872	1467

Table 20 Summary tabulation of Vaccination Error Adverse Events

Vaccination error group	Adverse Event (MedDRA PT)	With AE				Without AE				Total Cumulative
		Interval		Cumulative		Interval		Cumulative		
		Serious	Non-Serious	Serious	Non-Serious	Serious	Non-Serious	Serious	Non-Serious	
	Occupational exposure to product	1	0	3	4	0	0	0	8	15
	Product use issue	5	27	12	63	0	4	0	19	94
	Vaccination error	1	22	12	69	0	104	0	268	349
Inappropriate schedule	Inappropriate schedule of product administration	41	249	52	920	2	651	3	1591	2566
	Wrong schedule	0	0	0	5	0	0	0	19	24
Incorrect dose	Accidental overdose	0	9	4	13	0	1	1	17	35
	Booster dose missed	0	0	0	9	0	0	0	23	32
	Dose calculation error	0	1	2	8	0	0	0	2	12
	Extra dose administered	0	1	3	16	0	9	0	70	89
	Incorrect dose administered by device	0	0	0	0	0	0	0	2	2
	Incorrect dose administered by product	0	0	0	1	0	0	0	0	1
	Incorrect product dosage form administered	0	0	1	1	0	0	0	0	2
	Incorrect dose administered	1	55	18	201	3	750	8	1331	1558
	Incomplete course of vaccination	4	66	11	215	1	127	2	299	527
	Incorrect dosage administered	0	8	0	11	0	2	0	30	41
	Overdose	1	36	54	92	0	3	0	40	186

Table 20 Summary tabulation of Vaccination Error Adverse Events

Vaccination error group	Adverse Event (MedDRA PT)	With AE				Without AE				Total Cumulative
		Interval		Cumulative		Interval		Cumulative		
		Serious	Non-Serious	Serious	Non-Serious	Serious	Non-Serious	Serious	Non-Serious	
	Prescribed overdose	0	0	0	1	0	0	0	0	1
	Prescribed underdose	2	1	2	3	0	0	0	1	6
	Product dose omission issue	22	35	26	268	0	27	0	236	530
	Product dose omission in error	0	1	0	17	0	0	1	11	29
	Underdose	1	6	2	24	0	48	4	256	286
Off-Label	Product use in unapproved indication	1	2	2	6	0	0	0	0	8
Potential errors	Circumstance or information capable of leading to device use error	0	0	0	0	0	0	0	2	2
	Circumstance or information capable of leading to medication error	0	16	4	93	0	4	1	171	269
	Intercepted product storage error	0	0	0	1	0	1	0	227	228
	Intercepted medication error	0	0	1	14	0	2	0	301	316
	Intercepted product preparation error	0	0	0	0	0	0	0	6	6
	Intercepted product dispensing error	0	0	0	0	0	1	0	1	1
	Intercepted product administration error	0	0	1	2	0	0	0	12	15
Preparation error	Product preparation error	0	3	0	3	0	2	0	24	27

Table 20 Summary tabulation of Vaccination Error Adverse Events

Vaccination error group	Adverse Event (MedDRA PT)	With AE				Without AE				Total Cumulative
		Interval		Cumulative		Interval		Cumulative		
		Serious	Non-Serious	Serious	Non-Serious	Serious	Non-Serious	Serious	Non-Serious	
	Product reconstitution quality issue	0	4	0	4	0	0	0	2	6
	Prescription drug used without a prescription	0	0	3	0	0	0	0	0	3
	Product preparation issue	1	2	1	7	0	0	0	14	22
Prescribing error	Transcription medication error	0	0	0	4	0	0	0	2	6
Product labelling/packaging	Product label confusion	0	0	0	1	0	0	0	3	4
	Product label issue	0	0	0	2	0	0	0	1	3
	Product name confusion	0	0	1	1	0	0	0	2	4
	Product packaging confusion	0	0	0	3	0	0	0	0	3
	Product packaging issue	0	0	0	0	0	0	0	1	1
	Product barcode issue	0	0	1	0	0	0	0	0	1
	Product confusion	0	0	0	1	0	0	0	2	3
	Product identification number issue	0	0	0	0	0	0	0	2	2
	Product lot number issue	0	0	0	0	0	0	0	6	6
Product quality	Poor quality product administered	0	0	4	2	0	18	0	43	49
	Product use complaint	0	0	0	0	0	0	0	2	2
Storage/dispensing	Device dispensing error	0	1	0	1	0	0	0	2	3
	Expired product administered	1	72	23	174	11	1809	12	2544	2753

Table 20 Summary tabulation of Vaccination Error Adverse Events

Vaccination error group	Adverse Event (MedDRA PT)	With AE				Without AE				Total Cumulative
		Interval		Cumulative		Interval		Cumulative		
		Serious	Non-Serious	Serious	Non-Serious	Serious	Non-Serious	Serious	Non-Serious	
	Product communication issue	0	1	0	3	0	0	0	7	10
	Product dispensing error	0	0	12	8	0	21	0	25	45
	Product dispensing issue	0	0	0	0	0	0	0	1	1
	Product prescribing error	0	0	1	6	0	0	0	16	23
	Product prescribing issue	0	0	0	1	0	0	0	2	3
	Product selection error	0	0	0	0	0	0	1	2	3
	Product substitution error	0	0	0	0	0	0	0	1	1
	Product storage error	0	2	0	34	0	4	0	447	481
	Product temperature excursion issue	0	0	0	7	0	2	0	391	398
Wrong vaccine	Wrong product administered	2	57	7	116	10	1936	21	3203	3347
	Interchange of vaccine products	63	1469	88	1893	4	793	6	1761	3748
	Unintentional use for unapproved indication	0	0	0	0	0	0	0	1	1
	Wrong dosage form	0	0	0	1	0	0	0	0	1
	Wrong dose	0	0	0	2	0	0	0	1	3
	Wrong drug	0	0	0	0	0	0	0	5	5
	Wrong patient received product	0	0	0	1	0	0	0	0	1
Other	Exposure via partner	0	0	1	0	0	0	0	0	1

Table 20 Summary tabulation of Vaccination Error Adverse Events

Vaccination error group	Adverse Event (MedDRA PT)	With AE				Without AE				Total Cumulative
		Interval		Cumulative		Interval		Cumulative		
		Serious	Non-Serious	Serious	Non-Serious	Serious	Non-Serious	Serious	Non-Serious	
	Exposure via direct contact	0	2	0	2	0	0	0	0	2
	Exposure via unknown route	0	0	0	1	0	0	0	0	1
Grand Total		**250**	**2619**	**642**	**6015**	**40**	**7555**	**93**	**16529**	**23279**

Seriousness was evaluated at the event level, which may differ from the seriousness assigned to the report level.

Cases with no reported AEs are also included.

In the above table 239 events were not included as these were considered invalid during interval period.

Case reports may include more than one vaccination error AE.

AE Adverse Event; MedDRA Medical Dictionary for Regulatory Activities; PT Preferred Term

Most frequently (>1000) reported vaccination error PTs were Interchange of vaccine products; Wrong product administered; Expired product administered; Inappropriate schedule of product administration; Incorrect dose administered; Product administered to patient of inappropriate age; and Medication error; most of the reports (72%) were not associated with other AEs apart from these medication errors. The above medications errors related to interchange, wrong product administered is related to interchange of vaccine (heterologous administration) for Dose1, Dose 2 and Dose 3 in many countries; and inappropriate schedule may be related to vaccine doses given at spacing intervals not aligned with the product information. Most of the reports were received from Brazil (52%), UK (10%), France (6%) and Germany (4%).

A review of the PT Interchange of vaccine products found that these medications errors were received mainly from following countries Brazil (45%), France (18%), Germany (9%), United Kingdom (6%) and Mexico (4%).

The vaccines most often interchanged with VAXZEVRIA included mRNA-PFIZER, CoronaVac, mRNA-Moderna, Janssen, mRNA-unspecified, Sputnik and Covaxin Vaccine.

CoronaVac, mRNA PFIZER, Janssen, and mRNA Moderna. vaccines were most often used in reports of the PT Wrong product administered. However, there was limited information available in narrative to interpret whether the vaccinees received wrong product/vaccine voluntarily or by mistake.

9.2.1 Fatal Cases Associated with Vaccination errors

The following request was places in the PRAC AR:

The MAH is requested to discuss all fatal cases associated with vaccination error in detail in next PSURs.

A review of cumulative vaccination error case reports with case level outcome of death/fatal are provided in Appendix 11. Interchange of vaccine products (n=21) and Incorrect route of product administration (n=14) were most frequently reported vaccination error events in these reports. Most of the reports with incorrect route of administration (intravenous, subcutaneous) were consumer reports and there was limited information on the actual medication error.

Most frequently reported AEs (≥3) in these reports were : Headache(7); Pyrexia(6); Cardiac arrest (6); Dyspnoea (6); Death(5); Cerebrovascular accident(5); Myalgia(4); Vomiting (4); Nausea(4); Dizziness(4); Loss of consciousness(4); Arthralgia(4); Myocardial infarction(4); Hypoaesthesia(4); Paraesthesia(4); Asthenia(4); Pain(3); Thrombosis(3); Immobile(3); Confusional state(3); Malaise(3); COVID-19(3); Exposure during pregnancy(3); and Hemiplegia(3).

Reported causes of death in these cases were Dyspnoea (3), Death (2), Thrombosis (2), Multiple organ dysfunction syndrome (1), Abortion spontaneous (1), Pulmonary embolism

(1), Confusional state (1), Loss of consciousness (1), Coronary artery occlusion (1), Nausea (1), Coronary artery thrombosis (1), Rash (1), COVID-19 (1), Cerebral thrombosis (1), Cardiac arrest (1), Dementia Alzheimer's type (1), Myocardial infarction (1), Diarrhoea (1), Skin discolouration (1), Pyrexia (1), Asthenia (1), Circulatory collapse (1), Vein rupture (1), Urosepsis (1), Haemorrhage intracranial (1), Vomiting (1), Headache (1) and Hypersensitivity (1).

Review of these fatal cases did not identify safety issues in relation to type of vaccination errors.

Summary and Conclusion

Most frequently reported vaccination errors along with other AEs included Inappropriate schedule of product administration, Incorrect route of product administration, Interchange of vaccine products, Medication error, Product dose omission issue, Incorrect dose administered, Incomplete course of vaccination, and Expired product administered; and 72% of the vaccination errors cases were not associated with other AEs. Most of the AEs reported for these vaccination errors were related to the reactogenicity events such as Pyrexia, Headache, Chills, Fatigue, Pain, Pain in extremity, Myalgia, Arthralgia, and Malaise. There was no clustering of AEs or AESI's with any of the vaccination error types.

A review of all the vaccination error AE reports received during interval and cumulative period did not demonstrate any medication error-emergent safety pattern associated with VAXZEVRIA. No new relevant patterns of vaccination errors or new safety concerns were identified during the reporting period.

Reports related to VAXZEVRIA vaccination errors will continue to be monitored by AstraZeneca through standard surveillance activities.

10 NON-CLINICAL DATA

There were no major safety findings from any AstraZeneca-sponsored non-clinical in vivo and in vitro studies of VAXZEVRIA ongoing or completed during the reporting period.

11 LITERATURE

AstraZeneca has reviewed the published non-clinical scientific literature relevant to VAXZEVRIA. No relevant new non-clinical safety information or information with potential impact on the benefit or risk evaluations, during the reporting period, were identified following review of literature.

AstraZeneca conducts comprehensive monitoring of peer-reviewed published scientific literature and unpublished manuscripts routinely on an ongoing basis. The search strategy includes VAXZEVRIA and other COVID-19 vaccines in order to identify potential class related findings.

Relevant literature articles containing new and significant safety findings relevant to VAXZEVRIA published during the review period were retrieved. Literature articles from clinical/observational/real world studies on vaccine effectiveness and booster dose are summarized in Section 9.1. Articles of interest related to event reviews completed as part of Health Authority requests, Important identified and Potential risks or Missing information have been included within the review of those safety concerns throughout section 15.2 and section 16. Other articles containing new and significant safety findings are summarized below.

Vaccine-related cutaneous manifestations (Avallone et al 2022)

Avallone et al 2022 conducted a systematic review of 229 articles according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. A search on MEDLINE, PubMed, Scopus, and Cochrane Library was conducted using the combination of the following keywords and medical subject heading (MeSH) terms: COVID vaccine, dermatology, rash, skin, cutaneous, BNT162, COMIRNATY, AstraZeneca, and mRNA-1273. The time range of our search was from 01 March 2020 to 04 November 2021.

Objective: To provide an extensive overview of all the vaccine-related cutaneous manifestations reported in the literature thus far.

Results: A total of 229 articles with data from 4649 patients with SARS-CoV-2 vaccine-related dermatological manifestations were included in the analysis. A total of 5941 SARS-CoV-2 vaccine-related dermatological manifestations were gathered. Local injection-site reactions were the most frequently observed, followed by rash/unspecified cutaneous eruption, urticarial rashes, angioedema, herpes zoster, morbilliform/maculopapular/erythematous macular eruption, pityriasis rosea and pityriasis rosea-like eruptions, and other less common dermatological manifestations. Flares of pre-existing dermatological conditions were also reported. Rash/Unspecified cutaneous eruption was the most common dermatological manifestation reported for AstraZeneca vaccine.

Overall conclusion as per author: Cutaneous adverse reactions following SARS-CoV-2 vaccine administration seem to be heterogeneous, rather infrequent, and not life-threatening. Vaccinated patients should be monitored for skin manifestations, and dermatological evaluation should be offered, when needed.

AstraZeneca comment

Cutaneous adverse events such as rash and urticaria and injections site reactions are listed in the VAXZEVRIA CDS. Cutaneous reactions are the most common form of ADRs, occurring in 2%–3% of inpatient and in approximately 2% of outpatient patients in general population. Also, a large majority of cutaneous reactions post vaccination were mild and self-limiting, and public health benefit of vaccination is considered to outweigh the rare occurrence of these events.

12 OTHER PERIODIC REPORTS

There have been no significant findings from other periodic reports provided by other parties during the reporting period.

13 LACK OF EFFICACY IN CONTROLLED CLINICAL TRIALS

During the reporting period one trial was completed (Study D8111C00002). In addition to one-year follow up results obtained from this study, the section below provides an update on data obtained on the variant of concern, Omicron.

As described in Section 7.2.1, Study D8111C00002 assessed the safety and immunogenicity of VAXZEVRIA in 256 participants in Japan across all age groups. After one year of follow up, it was observed that humoral responses against SARS-CoV-2 waned over time from previously reported peak responses post-second dose. At Day 365, anti-SARS-CoV-2 spike-binding (spike) and RBD mean antibody titers remained above Day 15 levels across all ages. Neutralizing antibody titers declined and were below detection levels in many participants by Day 365. Rates of unsolicited and serious adverse events were consistent with previous reports. Overall, VAXZEVRIA was well tolerated in Japanese adults across all age groups. Expected waning in humoral responses against SARS-CoV-2 were observed over the course of the one-year follow up; however, total spike and RBD mean antibody titers remained elevated above Day 15 levels.

Recent publications as described in Section 10 and Section 17 support the thesis that VAXZEVRIA confers good VE against symptomatic COVID-19 resulting from infection with the Omicron variant and it is particularly effective in preventing severe disease, hospitalizations and death.

No other data regarding lack of efficacy that would constitute a significant risk to the treated population were received during the reporting period.

Immunogenicty data on Omicron variant of concern

As described in the last PBRER, a collaborative work between ASTRAZENECA, the University of Oxford, and the UK Health Securities Agency (UKHSA) demonstrated that a 3rd booster dose of the VAXZEVRIA vaccine would increase the limited protection offered by a 2-primary immunization series of the VAXZEVRIA vaccine.

More recently, researchers at the University of Oxford have assessed neutralization of the emerging Omicron sub-lineages BA.4 and BA.5 (in addition to BA.2) by serum from individuals vaccinated with 3 doses of VAXZEVRIA or COMIRNATY **Tuekprakhon et al 2022**). Assays were performed using serum obtained 28 days following the 3rd dose. While BA.4/5 showed reduced neutralization compared with BA.1 and BA.2, the reductions were modest. For VAXZEVRIA, neutralization titers for BA.4/5 were reduced 2.1-fold compared with BA.1 ($p < 0.0001$) and 1.8-fold compared with BA.2 ($p < 0.0001$). For COMIRNATY, neutralization titers were reduced 3.1-fold ($p < 0.0001$) and 3.1-fold ($p < 0.0001$) compared

with BA.1 and BA.2, respectively. The authors concluded that although these reductions in titers may reduce the effectiveness of the vaccines at preventing infection, particularly at longer time points, it would be expected that protection would remain against severe disease.

CD8+ T cell responses have been identified as important mediators of COVID-19 disease in murine and non-human primate models of COVID-19, and are thought to be particularly important for the prevention of severe disease. T cell Receptors (TCR) sequencing analysis has identified that the immunodominant region of Spike recognised by CD8+ T cells (**Swanson et al 2021**) is not impacted by the Spike mutations present in the Omicron variant (including BA.4/BA.5 sublineages). T cell data are now available from the ongoing AstraZeneca-sponsored study D7220C00001, in which participants received a 3rd booster dose of VAXZEVRIA after a primary series of VAXZEVRIA or an mRNA vaccine. Analysis of spike peptide T-cell responses at Day 14 after a 3rd booster dose of VAXZEVRIA showed similar levels of CD4+ and CD8+ T cells against the ancestral SARS-CoV-2 strain or the Omicron variant. These data support the conclusion that protection would remain against severe disease caused by Omicron variant sub-lineages.

As described in Sections 9.1.4 and 17.2.4, real-world evidence has since supported the effectiveness of VAXZEVRIA in preventing infection, particularly severe infection leading to hospitalisation, by the Omicron variant.

14 LATE-BREAKING INFORMATION

After the data lock point of the PBRER (28 June 2022), VAXZEVRIA CDS updated on 01 July 2022 and 2 signals were validated, as mentioned below:

CDS Update

- VAXZEVRIA CDS was updated on 01 July 2022 (Version 19.0) to include Tinnitus as an ADR Section 4.8 (undesirable effects) with frequency of uncommon, see section 4, 16.2.5.2 and 16.3.4.2

Signal Evaluation

- **Immune thrombocytopenia (ITP):** The signal for ITP was re-opened based on well-documented case reports from the published literature. AstraZeneca internally validated the signal on 06 July 2022 and the topic is currently undergoing evaluation as per AstraZeneca's signal detection and evaluation processes. Conclusions and any recommended actions for this signal will be communicated in the next PBRER, or earlier as necessary
- **Cutaneous Vasculitis (CV):** The signal for cutaneous vasculitis was identified based on well-documented case series from published literature cases. Subsequently a request on the same topic was received from PRAC (Pharmacovigilance Risk Assessment Committee) Periodic Safety Update Report (PSUR) assessment report (see section 15.2). AstraZeneca internally validated the signal on 15 July 2022. Cumulative evaluation of this signal is presented in Appendix 16

  On 18 August 2022, upon further evaluation of this topic AstraZeneca considered that there is a reasonable possibility of causal relationship between VAXZEVRIA and

Cutaneous vasculitis. CDS Section 4.8 is in the progress to be updated to include cutaneous vasculitis as an ADR (frequency: not known). The updated CDS will be internally approved before the due date of this PBRER. Corresponding changes to local labels or product leaflets are also warranted. This revision is in the late stage of being finalized. Details of this signal evaluation are presented in Section 15.2.14 and Appendix 16

- **Literature**: An AstraZeneca co-authored article (Laffan et al 2022) regarding the risk of thrombosis with thrombocytopenia was published on-line on 19 August 2022. This article presents a review of ICSR case characteristics reported to AstraZeneca through to 28 December 2021. This article includes data and analyses already included in previous PBRERs/monthly summary reports, as well as in the cumulative review presented in section 16.3.2.1of this PBRER, and therefore presents no new, additional evidence. The article does not change the characterisation of this risk and is included in section 16.3.2.1 and 16.4.1.1 for information.

15 OVERVIEW OF SIGNALS (NEW, ONGOING OR CLOSED)

15.1 Overview of Validated Signals (New, Ongoing or Closed)

AstraZeneca are required to carry out pharmacovigilance on a routine basis according to the legislation. Routine pharmacovigilance is described in the pharmacovigilance system master file. However, a summary of signal identification is provided below.

Signals may be identified during:

- Review of individual case safety reports (ICSRs) arising from marketed use of the medicinal product or during clinical trials
- Regular analysis of aggregate ICSR data, including statistics of disproportionate reporting applied to the AstraZeneca global safety database and, as appropriate, publicly available databases of AEs (the US Food and Drug Administration (FDA) Adverse Event Reporting System, the World Health Organisation VigiBase and the Eudravigilance Data Analysis System (EVDAS) databases)
- Regular review of published biomedical articles and conference abstracts
- Review of results arising from AstraZeneca-sponsored trials and externally-sponsored scientific research (previously referred to as investigator-sponsored trials)
- Review of reports from the product complaints management system (ie, product quality complaints)

Safety-related enquiries from Health Authorities, healthcare professionals, and consumers are also considered a source of signals. Relevant findings from preclinical trials and new safety information on products with the same or similar modes of action to the medicinal product are also considered.

The above are considered the most likely sources of signals, however relevant information from other sources is not excluded from consideration.

In the analysis of aggregate ICSRs arising from marketed use of AstraZeneca products, qualitative and pre-defined quantitative criteria are applied to the data in order to identify signals for evaluation. Quantitative analysis includes the use of algorithms to generate statistics of disproportionate reporting, including significant changes in these statistics over time. The initial evaluation of identified signals may lead to a more detailed evaluation and if a potential new risk is identified, a detailed review is undertaken by a scientific and medical forum.

A tabulation of **validated** signals that were ongoing or closed during the reporting period is presented in Appendix 3.

There were three validated signals that were either ongoing or closed during the reporting period. The validated signals are provided in Table 21 along with a cross-reference, where applicable, to the sections of the PBRER where further detail is provided.

Table 21 Summary of the validated signals that were ongoing or closed during the reporting period

Validated Signal	Ongoing or Closed at the DLP of the PBRER	Section of the PBRER where additional detail is provided	Reference Regulatory Procedure Number
Guillain-Barré syndrome	Closed	Section 16.2.2.1 and Appendix 20	EMEA/H/C/005675/IB /0034 and IB/0044
Hypoaesthesia and Paraesthesia	Closed	Section 16.2.5.1	EMEA/H/C/PSUSA/00 010912/202112
Tinnitus[a]	Ongoing	Section 15.2.1 and 16.2.5.2	EMEA/H/C/PSUSA/00 010912/202112

[a] Signal of Tinnitus was closed after the data lock point on 01 July 2022.
DLP Data Lock Point

After the DLP the signals of cutaneous vasculitis and immune thrombocytopenia were validated. Please refer to further information in Section 15.2.14 (Cutaneous Vasculitis), Section 14 (Late-Breaking information) and Appendix 16.

15.2 Health Authority requests

AstraZeneca received the following requests from PRAC in the Assessment Report (AR) for PBRER (Procedure no.: EMEA/H/C/PSUSA/00010912/202112; period 29 June 2021 to 28 December 2021) and requested following Issues to be addressed in the next PSUR. The topics in question are presented in Table 22.

Table 22 List of Health Authority Requests

Topic	Section of the PBRER where additional detail is provided
Issues to be addressed in the next PSUR: Requests from PRAC Assessment Report (AR) for PBRER (Procedure no.: EMEA/H/C/PSUSA/00010912/202112 period 29 June 2021 to 28 December 2021)	

Table 22 List of Health Authority Requests

Topic	Section of the PBRER where additional detail is provided
Vaccination errors	Section 9.2
Tinnitus	Section 15.2.1
Hearing loss	Section 15.2.2
Booster dosing	Section 15.2.3
Menstrual disorders	Section 15.2.4
Myocarditis	Section 15.2.5
Sarcoidosis	Section 15.2.6
Subacute thyroiditis)	Section 15.2.7
Glomerulonephritis AND Nephrotic syndrome (including IgA Nephropathy	Section 15.2.8
Rhabdomyolysis	Section 15.2.9
Exacerbation of chronic conditions	Section 15.2.10
Exacerbations of type 1/type 2 mellitus diabetes	Section 15.2.10.1
Exacerbation of Adrenal insufficiency	Section 15.2.10.2
Exacerbation of hypertension	Section 15.2.10.3
PAM LEG 103: Review of pulmonary embolism (PE), coronary artery disease (CAD) including myocardial infarction (MI) and venous and arterial thromboses – Further data provision	Section 15.2.11
Viral reactivation (Non-Zoster)	Section 15.2.13
Cutaneous vasculitis	Section 15.2.14
The following topics were evaluated due to requests from Health Canada	
Acute Disseminated Encephalomyelitis	Section 15.2.12
Thrombosis With Thrombocytopenia syndrome (TTS)	Section 15.2.15

15.2.1 Tinnitus

Background

In the PRAC PAR *(EMEA/H/C/PSUSA/00010912/202112*) for the VAXZEVRIA PBRER (DLP: 28 December 2021), PRAC requested for further information to be presented in the next PBRER (28 June 2022): *The MAH is requested to discuss relevant literature on plausible mechanism of action.*

After the DLP of the PBRER (28 June 2022), VAXZEVRIA CDS (version 19.0, dated 01 July 2022) was updated to include Tinnitus (frequency: uncommon) in section 4.8 Undesirable effects.

Please refer to Section 4 and Section 16.3.5.2 for further information.

Literature

A literature search was conducted cumulatively through DLP 28 June 2022 from databases in Embase, InsightMeme and PubMed to identify articles that discuss a plausible mechanism for Tinnitus in association with VAXZEVRIA or with other COVID-19 vaccines.

The search retrieved 14 relevant articles, those were discussed and presented in the review below.

Based on the available literature, the precise mechanism of action is still not clear, however, some possible mechanisms of action were proposed by the authors, such as:

- A hypersensitivity reaction causing an abnormal autoimmune response; mediated by circulating immune complexes or cytotoxic vestibule-cochlear autoantibodies which can lead to a localised inflammation that damages the inner ear microvessels, or a vasculitic event with subsequent localised damage to the cochlea. (Ciorba et al 2018, Shamriz et al 2018, Oldstone 2014, Ahmed et al 2021, Parrino et al 2021, Garg and Paliwal 2021, Pisani et al 2022 and Di Mauro et al 2022).

- An immunisation anxiety-related reaction is also postulated, as anxiety has also been related to the severity and persistency of Tinnitus. (Elarbed et al 2021, Parrino et al 2021, Pisani et al 2022, Gold et al 2020).

- Molecular mimicry, considering a cross reactivity between anti-spike SARS-CoV-2 antibodies and otologic antigens, plus hepta-peptide resemblance between the coronavirus spike glycoprotein and human proteins. The anti-spike antibodies may potentially react with antigens anywhere along the auditory pathway and initiate an inflammatory reaction involving the tympanic membrane, ossicular chain, cochlea, cochlear vessels, organ of Corti, etc. (Kanduc and Shoenfeld 2020, Tseng et al 2021, Vojdani et al 2020, Ahmed et al 2021, Pisani et al 2022, Garg and Paliwal 2021, Wichova H et al 2021).

- Autoimmune inner ear disease also must be considered in the differential diagnosis, which may have increased the likelihood of a dysregulated autoimmune response, although it typically differs in clinical presentation. (Medina et al 2022, Parrino et al 2021, Ciorba et al 2018).

Despite these possible mechanisms of action, the authors have also suggested the review of pre-existing history of autoimmune disorder and anxiety which have been related to the severity and persistency of Tinnitus (Elarbed et al 2021, Pisani et al 2022, Ahmed et al 2021, Parrino et al 2021). This also includes underlying infections, such as COVID-19 (Di Mauro et al 2022), or a history of glaucoma, thrombosis, or vascular conditions (Ahmed et al 2021).

Conclusion

AstraZeneca performed a comprehensive literature review through DLP 28 June 2022 with focus on identifying articles that discuss a plausible mechanism. AstraZeneca acknowledges the authors' views and suggestions concerning the mechanism of action. However, any further exploration of the hypothesized mechanisms in mechanism-based studies or demonstration of a conclusive mechanism could not be identified and thereby any specific mechanism of action for Tinnitus following COVID-19 vaccination remains speculative. Following a recent signal evaluation, Section 4.8 of the VAXZEVRIA CDS was updated to include Tinnitus. It is AstraZeneca's opinion that this topic is adequately described in the updated VAXZEVRIA CDS and will no longer discuss it in future PBRERs, unless significant new safety information arises.

15.2.2 Hearing loss

In the assessment report received from the PRAC EMA (*PRAC PAR (EMEA/H/C/PSUSA/00010912/202112)* for the VAXZEVRIA (formerly AZD1222) PBRER (review period –29 December 2021 – 28 June 2022), further information on the topic of Hearing Loss is requested as follows: *The MAH is requested to present an updated cumulative review of all medically confirmed cases of Hearing loss, including an age-stratified analysis. A complete review of the literature, including a discussion on possible mechanism should also be provided.*

Global Patient Safety Database

Cumulative Period (DLP 28 June 2022)

A cumulative search until DLP (28 June 2022) of the AstraZeneca Global Safety Database for Hearing loss with VAXZEVRIA was performed using MedDRA version 25.0 with the High-Level Term (HLT): Hearing losses. The search retrieved a total of 1831 events of Hearing loss in 1719 case reports cumulatively, 301 events in 284 case reports were received during the reporting period (211 initial and 73 follow-up).

The case source distribution for Hearing loss cumulatively through DLP 28 June 2022 is presented in Table 23.

Table 23 Hearing loss case reports received with VAXZEVRIA cumulatively through DLP 28 June 2022 by reporting source and seriousness

Classification of case report source	Non-serious cases	Serious cases	Grand Total
Clinical trial	0	0	0
Spontaneous[a]	378	1307	1685
Literature	2	7	9
Non-interventional/post-marketing study	15	10	25
Grand Total	**395**	**1324**	**1719**

[a] Of the 1685 Spontaneous case reports, 1511 (89.7%) were from Regulatory source.

The following Table 24 presents number and percentage (%) of case reports with Hearing loss reported after respective doses.

Table 24 Number and percentage (%) of the case reports of Hearing loss reported after respective doses of VAXZEVRIA cumulatively through DLP 28 June 2022

No of Cases (After First Dose)	No of Cases (After Second Dose)	No of Cases (After First and Second Dose)	No of Cases (After Third Dose)	No of Cases (Dose number Unknown)
1547 (92.7%)	114 (6.8%)	4 (0.2%)	3 (0.2%)	50 (NA)

TTO was reported for 1668 case reports used to calculate the percentage and in 1 case report, the event occurred before the vaccine administration.

These case reports for Hearing loss were reported most frequently in the following countries: United Kingdom 859 (50%), Germany 195 (11.3%), Australia 97 (5.6%), France 62 (3.6%) and Brazil 57 (3.3%).

- Vaccinee age was reported in 1533 case reports and ranged from 18 to 93 years (mean: 53 years; median: 54 years). 1197 (69.6%) vaccinees were between age group of 18-<65 years of age (Adult), 360 (20.9%) vaccinees were >65 years (Elderly) of age, 1 (0.1%) vaccinee was pediatric and in 18 (6.3%) vaccinees the age was unknown
- Vaccinee gender was reported in 1668 case reports. Of these 1668 case reports, 35.5% (611) were male vaccinees and 61.5% (1057) were female vaccinees
- Two hundred eighty-one (281 [16.3%]) case reports were medically confirmed and 1438 (83.7%) non-medically confirmed (consumer reports)
- Of the total 1719 case reports, the time to onset (TTO) of Hearing loss from VAXZEVRIA administration was reported in 1234 case reports and ranged from 0 days to 224 days (mean: 13 days; median: 3 days)

TTO is further stratified in Table 25.

Table 25 TTO for Hearing loss case reports cumulatively through DLP 28 June 2022

TTO (Days)	No of Cases	Percentage (%)[a]
0 to 1	424	24.7
2 to 5	290	16.9
6 to 10	145	8.4
11 to 15	106	6.2
16 to 20	53	3.1
21 to 28	60	3.5
>28 days	156	9.1
Unknown	484	28.2

[a] TTO was reported for 1719 case reports used to calculate the percentage and in 1 case report, the event occurred before the vaccine administration.

A total of 1831 events pertaining to the searched term for Hearing loss was reported in 1719 cases, cumulatively. The 1831 events (PTs) reported in these cases is presented in the Table 26 below:

Table 26 Distribution of MedDRA PTs pertaining to Hearing Loss with VAXZEVRIA received cumulatively through 28 June 2022

MedDRA PT	Non-serious		Serious		Grand Total	
	All cases	Medically Confirmed	All cases	Medically Confirmed	All cases	Medically Confirmed
Deafness	640	69	0	0	640	69
Hypoacusis	300	57	290	46	590	103
Sudden hearing loss	199	31	79	12	278	43
Deafness unilateral	117	25	48	8	165	33
Deafness neurosensory	68	23	12	5	80	28
Deafness bilateral	38	5	0	0	38	5
Deafness transitory	8	3	11	6	19	9
Neurosensory hypoacusis	8	5	1	0	9	5
Mixed deafness	4	1	1	0	5	1
Conductive deafness	0	0	2	1	2	1
Presbyacusis	1	1	1	0	2	1
Alport's syndrome	1	0	0	0	1	0
Deafness congenital	1	0	0	0	1	0
Deafness traumatic	0	0	1	0	1	0
Total	**1385**	**220**	**446**	**78**	**1831**	**298**

PT Preferred Term

Tinnitus (n=595, 9.2%) and headache (n=425, 6.5%) were the most common events that were co-reported in these cases with Hearing loss:

- 1385 [75.6%] of the events were serious (220 medically confirmed and 1165 non-medically confirmed); reported seriousness criteria in these cases were medically important event (1113 [80.4%]), disability (412 [29.7%]), hospitalization (145 [10.5%]), life threatening (18 [1.3%]) and/or the event reportedly resulted in death (2 [0.1%]). An event may have met more than one criterion for seriousness. The remaining 446 (24.4%) events were non-serious (78 medically confirmed and 368 non-medically confirmed).
- Of the 1831 events, the outcome was reported in 28.9% (529/1831) as Recovered and/or Recovering, 3.8% (70/1831) recovered with sequelae, not recovered 53.2% (975/1831) and 0.1% (02) of the events as fatal. The outcome of the remaining 13.9 % (255 out of 1831) of events were reported as unknown.
- Amongst 340 events with reported outcome 'recovered' or 'recovered with sequelae,' the event duration was reported in 125 (36.8%) cases. Range was (0-348 days), Median and mean duration was 2 days and 16 days respectively. For 91 cases (26.8%), the event resolved within 7 days and for the remaining 34 (10%) cases the event resolved after 7 days.

Brighton Collaboration Classification Assessment

The Brighton Collaboration Classification (BCC) case definition (Carol Liu et al. 2020) for Hearing loss was used for the review of the data available in the case reports. Furthermore, causality assessment according to WHO-UMC criteria was completed for cases fulfilling BCC Level 1, 2 or 3.

Based on this approach, out of the 281 medically confirmed case reports retrieved cumulatively through DLP 28 June 2022, 8 (2.8%) cases fulfilled BCC Level 1 criteria, 4 (1.4%) fulfilled BCC Level 2 criteria, 6 (2.1%) fulfilled BCC Level 3 criteria, 260 (92.5%) fulfilled BCC Level 4 criteria and 3 (1.1%) fulfilled BCC Level 5 criteria. As Levels 1, 2 and 3 can be considered particularly relevant for fulfilling reasonable BCC diagnostic certainty for Hearing loss, these case report assessments are therefore presented in Table 27, Table 28 and Table 29 for each BCC Level accordingly.

Brighton Collaboration Classification Level 1

Of the 281 medically confirmed case reports, 8 (2.8%) case reports fulfilled BCC Level 1 criteria. These case reports are summarized in Table 27 below:

Table 27 Case reports of hearing loss with VAXZEVRIA fulfilling Brighton Collaboration Criteria Level 1 (N=8) reported cumulatively till 28 June 2022

Case ID/ Country/ Serious-Y/N / Medically confirmed - Y/N	Age (Years) /Gender (M/F)	Risk factors - Relevant comorbidities and concomitant medications	Adverse Events/ Co-reported events	Dose # / Time to Onset (days)	AE Outcome	WHO-UMC Causality Assessment	Case assessment / comment
[redacted] Y/ Y	34/ F	Not Reported/ Not Reported	Deafness unilateral, Deafness neurosensory/ Dyspnoea, Tinnitus, Pyrexia, Nausea, Headache	1st dose/ 1	Not recovered	Possible with limited information	Time to onset within the risk window. The WHO-UMC causality assessed as Possible with limited information, considering lack of details in medical history, concomitant medication, diagnosis, and etiology workup.
[redacted] Y/ Y	39/ M	Not Reported/ Not Reported	Deafness neurosensory/ Tinnitus	1st dose/ 11	Recovering	Possible with limited information	Time to onset within the risk window. The WHO-UMC causality assessed as Possible with limited information, considering lack of details in medical history, concomitant medication, diagnosis, and etiology workup.
[redacted] Y/ Y	43/ M	Not Reported/ Not Reported	Sudden hearing loss/ Tinnitus	1st dose/ 14	Not recovered	Possible with limited information	Time to onset within the risk window. The WHO-UMC causality assessed as Possible with limited information, considering lack of details in medical history, concomitant medication, diagnosis, and etiology workup.
[redacted] Y/ Y	44/ M	Not Reported/ Not Reported	Deafness neurosensory/ Tinnitus	1st dose/ 18	Recovering	Possible with limited information	Time to onset within the risk window. The WHO-UMC causality assessed as Possible with limited information, considering lack of details in medical history, concomitant medication, diagnosis, and etiology workup.

Table 27 Case reports of hearing loss with VAXZEVRIA fulfilling Brighton Collaboration Criteria Level 1 (N=8) reported cumulatively till 28 June 2022

Case ID/ Country/ Serious-Y/N / Medically confirmed - Y/N	Age (Years) /Gender (M/F)	Risk factors - Relevant comorbidities and concomitant medications	Adverse Events/ Co-reported events	Dose # / Time to Onset (days)	AE Outcome	WHO-UMC Causality Assessment	Case assessment / comment
[redacted] Y/ Y	72/ F	Not Reported/ No	Deafness/ Visual acuity reduced	1st dose/ 33	Recovering	Unlikely	Time to onset out the risk window. The WHO-UMC causality assessed as Unlikely. However, it is noted the missing information about medical history, concomitant medication, diagnosis, and etiology workup.
[redacted] Y/ Y	48/ F	No/ Not Reported	Deafness neurosensory/ Bell's palsy, Facial paralysis, Facial nerve disorder, Balance disorder, Tinnitus, Ear pain, Taste disorder	1st dose/ Unknown	Recovered with sequelae	Unassessable/ Unclassifiable	Due to unknown time to onset WHO-UMC causality assessed as Unassessable/Unclassifiable. It is noted missing information about medical history, concomitant medication, diagnosis, and etiology workup.
[redacted] N/ Y	61/ F	Hypertension, Dyslipidemia, Autoimmune thyroiditis/ Not Reported	Deafness neurosensory	2nd dose/ Unknown	Recovered	Unassessable/ Unclassifiable	Due to unknown time to onset WHO-UMC causality assessed as Unassessable/Unclassifiable. Medical history is noted as risk factor; however, more information is required. Limited information about concomitant medication, diagnosis, and etiology workup.

Table 27 Case reports of hearing loss with VAXZEVRIA fulfilling Brighton Collaboration Criteria Level 1 (N=8) reported cumulatively till 28 June 2022

Case ID/ Country/ Serious-Y/N / Medically confirmed - Y/N	Age (Years) /Gender (M/F)	Risk factors - Relevant comorbidities and concomitant medications	Adverse Events/ Co-reported events	Dose # / Time to Onset (days)	AE Outcome	WHO-UMC Causality Assessment	Case assessment / comment
[redacted] Y/ Y	57/ M	Not Reported/ Not Reported	Deafness neurosensory	1st dose/ 2	Unknown	Possible with limited information	Time to onset within the risk window. The WHO-UMC causality assessed as Possible with limited information, considering lack of details in medical history, concomitant medication, diagnosis, and etiology workup.

F Female, M Male, N No, Y Yes

Brighton Collaboration Classification Level 2

Of the 281 medically confirmed case reports, 4 (1.4%) case reports fulfilled BCC Level 2 criteria. These case reports are summarized in Table 28 below:

Table 28 Case reports of hearing loss with VAXZEVRIA fulfilling Brighton Collaboration Criteria Level 2 (N=4) reported cumulatively till 28 June 2022.

Case ID/ Country/ Serious-Y/N / Medically confirmed - Y/N	Age (Years) /Gender (M/F)	Risk factors - Relevant comorbidities and concomitant medications	Adverse Events/ Co-reported events	Dose # / Time to Onset (days)	AE Outcome	WHO-UMC Causality Assessment	Case assessment / comment
[redacted] Y/ Y	58/ F	No/ Not Reported	Hypoacusis	1st dose/ 13	Not recovered	Possible with limited information	Time to onset within the risk window. The WHO-UMC causality assessed as Possible with limited information, considering lack of details in medical history, concomitant medication, diagnosis, and etiology workup.
[redacted] Y/ Y	66/ M	Type 2 diabetes mellitus, Dyslipidemia, Hypertension, Age / No	Neurosensory hypoacusis/ Tinnitus	1st dose/ 45	Recovering	Unlikely	Time to onset outside the risk window. Medical history is risk factor; though, more information is required. The WHO-UMC causality assessed as Unlikely. However, it is noted the missing information about concomitant medication, diagnosis, and etiology workup.
[redacted] Y/ Y	Unknown/ M	No/ Not Reported	Deafness neurosensory	1st dose/ Unknown	Recovered	Unassessable/ Unclassifiable	Due to unknown time to onset WHO-UMC causality assessed as Unassessable/Unclassifiable. It is noted missing information about medical history, concomitant medication, diagnosis, and etiology workup.
[redacted] Y/ Y	74/ M	Elderly Age, Alcohol use, Head injury, Cerebral infarction,	Presbyacusis/ Atrial fibrillation, Dysarthria, Loss of consciousness, Brain stem auditory evoked response	1st dose/ Unknown	Unknown	Unassessable/ Unclassifiable	Due to unknown time to onset, WHO-UMC causality assessed as Unassessable/Unclassifiable. Medical history is risk factor; however, more information is required. It is noted missing

Table 28 Case reports of hearing loss with VAXZEVRIA fulfilling Brighton Collaboration Criteria Level 2 (N=4) reported cumulatively till 28 June 2022.

Case ID/ Country/ Serious-Y/N / Medically confirmed - Y/N	Age (Years) /Gender (M/F)	Risk factors - Relevant comorbidities and concomitant medications	Adverse Events/ Co-reported events	Dose # / Time to Onset (days)	AE Outcome	WHO-UMC Causality Assessment	Case assessment / comment
		Hypoxia, Hypotension / No	abnormal, Dyskinesia, Cerebrovascular accident, Hemiplegia, Cerebral thrombosis, Headache, Hypoaesthesia, Seizure, Syncope, Cerebral ischaemia, Ischaemic stroke, Essential hypertension, Thrombosis with thrombocytopenia syndrome, Gastrointestinal haemorrhage, Gait disturbance, Balance disorder, Paralysis, Coordination abnormal, Speech disorder, Paraesthesia, Hemiparesis				information about concomitant medication, diagnosis, and etiology workup.

F Female, M Male, N No, Y Yes

Brighton Collaboration Classification Level 3

Of the 281 medically confirmed case reports, 6 (2.1%) case reports fulfilled BCC Level 3 criteria. These case reports are summarized in Table 29 below:

Table 29 Case reports of hearing loss with VAXZEVRIA fulfilling Brighton Collaboration Criteria Level 3 (N=6) reported cumulatively till 28 June 2022

Case ID/ Country/ Serious-Y/N / Medically confirmed - Y/N	Age (Years) /Gender (M/F)	Risk factors - Relevant comorbidities and concomitant medications	Adverse Events/ Co-reported events	Dose # / Time to Onset (days)	AE Outcome	WHO-UMC Causality Assessment	Case assessment / comment
[redacted] Y/ Y	37/ M	Not Reported/ Not Reported	Deafness neurosensory/ Tinnitus	1st dose/ Unknown	Recovered	Unassessable/ Unclassifiable	Due to unknown time to onset WHO-UMC causality assessed as Unassessable/Unclassifiable. It is noted missing information about concomitant medication, diagnosis, and etiology workup.
[redacted] Y/ Y	61/ F	No/ No	Deafness neurosensory, Sudden hearing loss, Deafness bilateral/ Paraesthesia, burning feet syndrome, Hypoesthesia, Tinnitus, Blister, Urticaria, Contusion, Erythema, Pruritus, Swelling, Burning sensation	1st dose/ 1	Recovered/ Not recovered/ Not recovered	Possible with limited information	Time to onset within the risk window. The WHO-UMC causality assessed as Possible with limited information, considering lack of details in medical history, concomitant medication, diagnosis, and etiology workup.
[redacted] Y/ Y	56/ F	Not Reported/ Not Reported	Deafness neurosensory, Deafness unilateral	1st dose/ 2	Not recovered/ Not recovered	Possible with limited information	Time to onset within the risk window. The WHO-UMC causality assessed as Possible with limited information, considering lack of details in medical history, concomitant medication, diagnosis, and etiology workup.

Table 29 Case reports of hearing loss with VAXZEVRIA fulfilling Brighton Collaboration Criteria Level 3 (N=6) reported cumulatively till 28 June 2022

Case ID/ Country/ Serious-Y/N / Medically confirmed - Y/N	Age (Years) /Gender (M/F)	Risk factors - Relevant comorbidities and concomitant medications	Adverse Events/ Co-reported events	Dose # / Time to Onset (days)	AE Outcome	WHO-UMC Causality Assessment	Case assessment / comment
[redacted] Y/ Y	40/ F	No/ Not Reported	Sudden hearing loss, Deafness/ Embolism, Thrombocytopenia, Vascular occlusion, Sensory disturbance, Hypoesthesia, Tinnitus, Pain in extremity, Injection site pain, Tremor, Nausea, Diarrhea, Influenza like illness, Myalgia, Feeling cold	1st dose/ 3	Not recovered/ Not recovered	Possible with limited information	Time to onset within the risk window. The WHO-UMC causality assessed as Possible with limited information, considering lack of details in medical history, concomitant medication, diagnosis, and etiology workup.
[redacted] Y/ Y	68/ M	Not Reported/ Not Reported	Deafness unilateral/ Fatigue	1st dose/ 22	Unknown	Possible with confounder / risk factor	Time to onset within the risk window. The WHO-UMC causality assessed as Possible with confounder / risk factor, since patient age (+65yo) can be a predisposing factor.

Table 29 Case reports of hearing loss with VAXZEVRIA fulfilling Brighton Collaboration Criteria Level 3 (N=6) reported cumulatively till 28 June 2022

Case ID/ Country/ Serious-Y/N / Medically confirmed - Y/N	Age (Years) /Gender (M/F)	Risk factors - Relevant comorbidities and concomitant medications	Adverse Events/ Co-reported events	Dose # / Time to Onset (days)	AE Outcome	WHO-UMC Causality Assessment	Case assessment / comment
[redacted] Y/ Y	43/ F	Tinnitus, Anaphylactic reaction/ No	Deafness bilateral/ Hemiparesis, Tinnitus, Heavy menstrual bleeding, Palpitations, Vision blurred, Coordination abnormal, Muscle contractions involuntary, Mental fatigue, Muscle fatigue, Head discomfort, Dyspnea, Chills, Pyrexia, Headache, Paraesthesia, Feeling abnormal	1st dose/ Unknown	Unknown	Unassessable/ Unclassifiable	Due to unknown time to onset WHO-UMC causality assessed as Unassessable/Unclassifiable. However, medical history reported is noted to be a risk factor. There is missing information such as concomitant medication, diagnosis, and etiology workup.

Brighton Collaboration Level 4.

Of the total 281 medically confirmed case reports of Hearing loss with VAXZEVRIA reported, 260 (92.5%) fulfilled BCC Level 4 criteria. These case reports did not fulfil criteria for certainty levels 1, 2 and 3 as there was insufficient information to confirm the diagnosis or medical assessment of the case.

Brighton Collaboration Level 5.

Three cases (1.1%) of the 281 medically confirmed case reports fulfilled BCC Level 5 criteria excluded due to an alternative diagnosis and/or not consistent with Hearing loss.

Events with fatal outcome

Of the 1831 events of Hearing loss reported, 2 events of interest (deafness neurosensory, deafness) in 2 cases (0.1%) were reported with fatal outcome, of which 1 case was medically confirmed.

Case #1: [redacted]
The case was received from a physician via regulatory authority in United Kingdom (MHRA), regarding 35 years old female vaccinee with relevant medical history of sensorineural hearing loss, neuropathic pain, and epilepsy since unknown date. Patient received VAXZEVRIA (1st dose) on 4 February 2021, and an unknown date the patient experienced deafness neurosensory. Laboratory data included negative COVID-19 test, INR with 2.84, APTT prolonged 1.97, fibrinogen 1.1, platelet count 163, C-Reactive protein (CRP) 28, HCO3 8, lactate 16, potassium 3.5, blood glucose 7.5, oxygen saturation was 88, blood pressure 119/83, heart rate 112, chest X ray with right base opacification and raised left hemi diaphragm, ECG showing sinus tachycardia, CT head, chest, and abdomen without abnormalities, positive CTPA (Computed Tomography Pulmonary Angiogram) for pulmonary embolism was described. Patient died on 17 February 2021 An autopsy was performed, and the cause of death was provided as pulmonary embolism, acute cardiovascular failure (confirmed at autopsy), pulmonary thromboembolism, deep vein thrombosis, hypotensive, heel pain, afebrile, metabolic acidosis, CTPA no clot, platelet count greater than 150^109/l, acute chest syndrome, chest infection, sickle cell disease, pulmonary artery hypertension, sensorineural hearing loss, Hank's Balanced Salt Solution (HBBS), chest pain, cardiac arrest, unwell, sweating, sinus tachycardia, shortness of breath, crepitations, hypokalaemia, hypoglycaemia, hyperlactatemia, circulatory collapse and disseminated intravascular coagulation (DIC).

AstraZeneca comment: There is limited information on clinical manifestations, audiogram, tuning fork examination, otoacoustic emission, or auditory brainstem response and hence assessed as BCC4. Medical history includes sensorineural hearing loss, and epilepsy, however there is limited information about onset, duration, clinical progress, and baseline general condition. Treatment work-up was also not reported. There was conflicting information reported regarding finding of clot on CTPA. Due to unknown time to onset the

WHO-UMC causality was assessed as "Unassessable/Unclassified" with risk factors/confounders, ie, confounded by medical history of sensorineural hearing loss.

Case #2: [redacted]
The case was received from a consumer via regulatory authority in United Kingdom (MHRA), concerning a male vaccinee with unknown age. On unknown date patient received VAXZEVRIA (1st dose), and on an unspecified date the patient experienced deafness. On 13 October 2021 patient died, no details regarding autopsy, however cause of death was reported as deafness by narrative.

AstraZeneca comment: There is limited information for clinical manifestations, audiogram, tuning fork examination, otoacoustic emission, or auditory brainstem response and hence the case was assessed as BCC4. Treatment work-up was not reported within the narrative. Due to unknown time to onset the WHO-UMC causality is "Unassessable/Unclassified" with limited information, the lack of information being for medical history, concomitant medication, and aetiology workup.

Rechallenge / Recurrence case reports

Cumulatively through DLP 28 June 2022, in 4 (0.2%) out of 1719 case reports, the vaccinees experienced Hearing loss after the first dose, and a recurrence or worsening with the second dose of vaccination indicating potential recurrence/ rechallenge. All 4 cases were from spontaneous sources and one of 4 was medically confirmed.

One case report ([redacted] [25%]) was identified within the Risk Window TTO of 28 days (0-28) and therefore WHO-UMC causality was considered as "Possible". Alternative causal factors were noted in 2 (50%) out of 4 case reports, and a comprehensive causal attribution of other disease and drugs was not possible to identify for 2 (50%) cases, due to unknown TTO, insufficient information on laboratory investigations, baseline health condition, relevant medical history, and concomitant medications. These case reports are summarized in Table 30 below:

Table 30 WHO Causality assessment of Rechallenge/ Recurrence case reports for Hearing loss (N = 04) cumulatively through 28 June 2022

Case ID	TTO (Days) Dose 1	TTO (Days) Dose 2	Medical History/ Concomitant Medications	BCC level / WHO-UMC Causality assessment
[redacted]	Unknown	Unknown	Otitis externa; Ear pain	BCC level 4 / Unassessable/ Unclassifiable with risk factors/confounders
[redacted]	36	5	Deafness; Tinnitus	BCC level 3 / Possible with confounder / risk factor
[redacted]	>30	>30	Hearing impaired since childhood	BCC level 4 / Unlikely
[redacted]	Unknown	Unknown	Not Reported	BCC level 4 / Unassessable/ Unclassifiable with limited information

N Number, TTO Time to Onset. WHO World Health Organisation.

WHO-UMC causality analysis for medically confirmed cases

Of the total 1719 case reports, identified cumulatively through DLP 28 June 2022, 281 (16%) case reports were medically confirmed (214 serious and 67 non-serious), and WHO-UMC causality was further assessed as below within 0 to 28 days Risk Window.

Table 31 Overview of WHO-UMC Causality Assessment for medically confirmed case reports of Hearing loss with VAXZEVRIA reported cumulatively through 28 June 2022

WHO-UMC Causality category	WHO-UMC Causality assessment scale (AZ adapted)	Number of Cases
Certain	Certain	0
Probable-Likely	Probable-Likely	0
Possible	Possible with risk factors/confounders[a]	64
	Possible with limited information	132
Unlikely	Unlikely	31
Conditional / Unclassified	Conditional / Unclassified	0
Unassessable/Unclassifiable	Unassessable/Unclassifiable with risk factors/confounders[a]	21
	Unassessable/Unclassifiable with limited information	33
	Total	**281**

[a] Cases were considered to have "risk factors/confounders" where the event could also be explained by the vaccinee's diseases, or where relevant risk factors were present, or concomitant medications that could potentially contribute to the development of the event were reported.

Amongst 281 medically confirmed cases of Hearing loss, 85 (30.2%) cases were identified either with relevant risk or confounding factors. These are presented by the following categories for risk / confounding factors in descending order of frequency in Table 32.

Table 32 Relevant Risk factors / Confounders identified for medically confirmed case reports cumulatively through (28 June 2022)

Relevant Risk / Confounders	Number of reports	Percent of Total Number of Reports
Patient's age (Elderly age: ≥ 65 years)	65	66.3%
Chronic conditions (Hypertension/ Diabetes Mellitus, Thyroid disorders)	40	40.8%
Previous history of Hearing loss, auditory disorders, tinnitus	22	22.4%

Table 32 Relevant Risk factors / Confounders identified for medically confirmed case reports cumulatively through (28 June 2022)

Relevant Risk / Confounders	Number of reports	Percent of Total Number of Reports
Previous history/ comorbidity of other conditions – Infections, cancer, Alcohol use, Covid-19, head injury	10	10.2%
concomitant medications-Aminoglycosides, Atorvastatin, spironolactone	10	10.2%

In the remaining 183 (65.1%) out of 281 medically confirmed case reports, there was insufficient information with respect to either dose latency, medical history, or concomitant medication, clinical course and examination details for a comprehensive causal assessment.

Overall, the review of medically confirmed cases did not raise any new relevant safety information for VAXZEVRIA.

Observed Versus Expected (O/E) Analyses

Based on review of Truven Marketscan (2019), the background incidence rate(s) (IR) of Sensorineural Hearing Loss (SNHL) is estimated at 309.86 per 100,000 persons per annum.

AstraZeneca also conducted an observed versus expected analysis for the event of interest Hearing loss using the cumulative observed number of cases. The Risk Window of 0-28 days was derived upon review of Carol Liu et al. 2020.

An O/E analysis of hearing loss was conducted cumulatively through DLP 28 June 2022 and presented in Table 33. The OE analysis was conducted using risk window of 28 days and is stratified by age and gender in the EEA, UK, Brazil, and Australia.

Conservatively, the exposure for global reports (448306152) is based on doses administered in 13 markets as explained in Appendix 8.

Table 33 Observed versus expected cumulative analyses through 28 June 2022 for reports of hearing loss with risk windows of 28 days (Global reports)

Topic	Risk window	Background rates/100,000 PY	Exposure[a]	Observed number of cases	Expected number of cases	O/E ratio (95% CI)	Conclusion
Overall cases/ Global	28	309.86	448,306,152	1078	106491.99	0.01 (0.01 - 0.01)	Observed significantly < expected
Overall cases/ Global with Unknown TTO	28	309.86	448,306,152	1562	106491.99	0.01 (0.01 - 0.02)	Observed significantly < expected

[a] Exposure until 28 June 2022; Incidence rates for hearing loss are obtained from Truven Marketscan (2019); CI Confidence Interval, E Expected, O Observed

An observed versus expected analysis of cases stratified by age range, gender, and region (United Kingdom) is presented in Table 34.

Table 34 Observed versus expected cumulative analyses through 28 June 2022 for reports of hearing loss stratified by age and gender for United Kingdom region.

Topic / Country / Age group/ Gender	Risk window	Background rates	Exposure[a]	Observed number of cases	Expected number of cases	O/E ratio (95% CI)	Conclusion
UK/ 18-49 / Male	28	148.13	7,399,929	76	840.33	0.09 (0.07 - 0.11)	Observed significantly < expected
UK/ 50-59 / Male	28	396.82	6,915,956	54	2103.89	0.03 (0.02 - 0.03)	Observed significantly < expected
UK/ 60-69/ Male	28	682.95	5,160,658	26	2701.91	0.01 (0.01 - 0.01)	Observed significantly < expected
UK/ 70-79/ Male	28	1116.25	3,358,831	17	2874.26	0.01 (0 - 0.01)	Observed significantly < expected
UK/ 80+/ Male	28	1467.22	1,160,382	1	1305.19	0 (0 - 0)	Observed significantly < expected
UK/ 18-49/ Female	28	155.56	7,999,627	126	953.99	0.13 (0.11 - 0.16)	Observed significantly < expected
UK/ 50-59/ Female	28	357.52	6,280,795	72	1721.44	0.04 (0.03 - 0.05)	Observed significantly < expected
UK/ 60-69/ Female	28	554.28	4,996,322	62	2123.03	0.03 (0.02 - 0.04)	Observed significantly < expected
UK/ 70-79/ Female	28	827.41	3,688,886	21	2339.88	0.01 (0.01 - 0.01)	Observed significantly < expected

Table 34 Observed versus expected cumulative analyses through 28 June 2022 for reports of hearing loss stratified by age and gender for United Kingdom region.

Topic / Country / Age group/ Gender	Risk window	Background rates	Exposure[a]	Observed number of cases	Expected number of cases	O/E ratio (95% CI)	Conclusion
UK/ 80+/ Female	28	1196.6	1,864,578	7	1710.43	0 (0 - 0.01)	Observed significantly < expected

[a] Exposure until 28 June 2022; Incidence rates for hearing loss are obtained from Truven Marketscan (2019);

CI Confidence Interval, E Expected, O Observed, UK United Kingdom

An observed versus expected analysis of cases stratified by age range and regions (EU/ UK, Australia, and Brazil) are presented in Table 35.

Table 35 Observed versus expected cumulative analyses through 28 June 2022 for reports of hearing loss stratified by age for EU/ UK, Australia, and Brazil regions.

Topic / Country / Age group/ Gender	Risk window	Background rates	Exposure[a]	Observed number of cases	Expected number of cases	O/E ratio (95% CI)	Conclusion
EU, UK, Brazil, Australia/ 18-49	28	151.98	100,987,434	406	11766.04	0.03 (0.03 - 0.04)	
EU, UK, Brazil, Australia/ 50-59	28	376.09	56,425,075	223	16268.24	0.01 (0.01 - 0.02)	
EU, UK, Brazil, Australia/ 60-69	28	615.27	57,182,485	240	26971.52	0.01 (0.01 - 0.01)	
EU, UK, Brazil, Australia/ 70+	28	1084.08	31,869,628	109	26485.92	0 (0 - 0)	

[a] Exposure until 28 June 2022; Incidence rates for hearing loss are obtained from Truven Marketscan (2019);

CI Confidence Interval, E Expected, O Observed, UK United Kingdom EU European Union

Observed events were significantly less than the expected overall and by age and gender stratifications.

Literature

A literature search was conducted within the period of 29 December 2021 – 28 June 2022, from databases in Embase, InsightMeme and PubMed to review the occurrence of Hearing loss in association with VAXZEVRIA.

The search revealed 16 results, of which 8 relevant articles were discussed and presented in the review for Hearing loss below.

Study articles identified for presentation during the reporting period (29 December 2021 to 28 June 2022):

Pisani et al 2022 conducted, a systematic literature review of audio-vestibular events, such as sudden sensorineural hearing loss (SSNHL), tinnitus, dizziness, and vertigo after COVID-19 Vaccination. Objective was to evaluate the consistency of the reports, analyse their scientific value, express plausible supporting theories, and possibly identify a shared pathway for the management of the patients. Findings hypothesizes a possible autoimmune aetiology, according to the mechanism of cross-reaction. This hypothesis has been further corroborated by the collection of clinical data on patients. However, limitation of this thesis is the absence of RT-PCR testing which could rule out COVID-19 infection in these patients. In fact, if not clearly excluded from a negative nasopharyngeal swab, there is a reasonable suspicion that symptoms are due to a new SARS-CoV-2 infection, which is known to be characterized by high neural tropism with potential damage to the inner ear, even in mild forms.

AstraZeneca comment: There was no evidence of an increased risk of vaccination-related hearing loss, nor is there evidence of an association with VAXZEVRIA. There was lack of systematization and standardization in the collection of clinical information, as well as in patient management which makes it difficult to aggregate the cases and draw unambiguous conclusions.

Literature patient case reports identified during the reporting period 29 December 2021 to 28 June 2022:

Literature case reports describing the use of VAXZEVRIA identified through this literature review were discussed earlier in the previous review of case reports retrieved from the AstraZeneca Global Patient Safety Database Section (Case ID [redacted]). On review of the remaining case report articles, no new safety concerns including information relating to a conclusive mechanism was identified.

Mechanism of action articles review and summary during the reporting period 29 December 2021 to 28 June 2022:

The proposed mechanisms from published literature are provided below:

- Viral infection and vascular compromise eg, "viral infections and vascular compromise are the most accepted etio-pathogenic mechanisms" (Alcas O et al 2021, Yanir Y et al 2022, De Marco F et al 2018, Tsetsos N et al 2021) eg, "viral infection, vascular ischemia, and autoimmune response are known suspicious causes of SNHL regardless of vaccination" (Jeong J et al 2021). Since this mechanism has been established with the viral infection, there may be a possibility of such mechanism being attributed to the vaccine
- Auto-immunogenicity eg, "Both the mRNA payload and the lipid nanoparticle delivery vehicle have been suggested to be potential mechanisms of auto-immunogenicity''; "A mechanism for COVID-19 vaccine-associated hearing loss could be an autoimmune process involving molecular mimicry related to the vaccine's antigen, or bystander activation of autoreactive T-cells that may involve the vestibulocochlear nerve (vestibular nerve is involved in balance and equilibrium functions, and cochlear nerve in hearing function)" (Formeister et al 2022)
- Biological mechanisms eg, "Reports of recovery of SARS-CoV-2 RNA in the middle ear of individuals who died of COVID-19 and recent findings of the ability of SARS-CoV-2 to directly infect human vestibular hair and Schwann cells provide plausible biological mechanisms for COVID-19–associated hearing loss and may open avenues of investigation into immune mechanisms for COVID-19 vaccines in the inner ear'' (Formeister et al 2022)
- Effect of synthesis of Immunoglobulin G eg, "SSNHL occurring 10 to 14 days after vaccination, could coincide with the production of Immunoglobulin G at 10 to 14 days after Covid-19 vaccine administration" (Wichova H et al 2021)

AstraZeneca comment: There is no confirmed mechanism of action for SNHL with VAXZEVRIA. However, potential mechanisms such as auto-immunogenicity, biological mechanisms with COVID-19 associated hearing loss, effect of synthesis of immunoglobulin and viral reactivation were proposed by the authors.

Overall summary of all case reports

Sudden hearing loss is known to occur naturally at an incidence that increases with age, and with a range of acquired and inherited risk factors involved (Lin RJ et al 2012).

Of the 1719 hearing loss cases reported cumulatively through 28 June 2022, the TTO was within 28 days for 1078 (62.7%) of the case reports that reported TTO. 281 out of 1719 cases were medically confirmed. Underlying cause/confounding factors were noted in 34.9% of medically confirmed cases.

Cases were assessed by age, sex, type of event, and outcome. The characteristics of the events and of the individuals with events were as expected for the general population, including the observation of increased incidence in the elderly. No unusual trends or clusters were identified. None of the cases met WHO-UMC criteria for Certain or Probable/Likely.

Of the 1719 cases, there were 2 fatal cases, of which 1 case was medically confirmed. These cases either had limited information on the or there were presence of confounders for the occurrence of the event and fatal outcome.

Review of medically confirmed reports did not raise any new relevant safety information for VAXZEVRIA. Most of the case reports (196 [69.8%]) were considered "Possible" related to VAXZEVRIA based on the suggestive TTO. 132 (47%) case reports also had presence of other risk factors/ confounders and 64 (22.8%) cases had limited information for a complete assessment. The O/E analysis results showed observed cases of hearing loss to be significantly less than expected for all stratifications.

From the review of literature, there is no confirmed mechanism, pathway or mediator identified for the occurrence of hearing loss in association with VAXZEVRIA.

In summary, the review of available data from spontaneous reports regarding hearing loss did not identify an index case or other evidence of a new or emerging signal.

Conclusion

Based on the review of the currently available cumulative data, AstraZeneca considers that there is insufficient evidence to suggest a causal association between hearing loss and VAXZEVRIA. It is AstraZeneca's opinion that no changes to the CDS or RMP are warranted at this time. Hearing loss will continue to be monitored as part of AstraZeneca's routine surveillance activities for VAXZEVRIA. AstraZeneca will no longer discuss the topic future PBRERs, unless significant new safety information arises.

15.2.3 Booster dosing

Request

Following the last PBRER (DLP 28 December 2021), PRAC requested AstraZeneca to discuss any new information regarding Booster dosing in the next PSUR. The booster dose report in the previous PBRER had a DLP of 04 January 2022.

AstraZeneca's response to this request is provided below.

Review of Cases

A search of the AstraZeneca global safety database (MedDRA version 25.0) was conducted to identify any adverse event (AE) reports involving confirmed Dose 3 or 'booster' dose of VAXZEVRIA received cumulatively through 28 June 2022. Adverse event (AE) reports involving confirmed booster was defined as any AE report for VAXZEVRIA where Dose 3 was indicated in the Dose Text field in the AstraZeneca global safety database and where VAXZEVRIA was listed as a Suspect or Co-suspect medication.

Cumulatively, through 28 June 2022, a total of 1104 reports have been received of confirmed 'booster' dosing involving VAXZEVRIA. Of the 1104 reports received, 352 (31.9%) were reported as serious and 472 (42.8%) were medically confirmed.

The majority of the reports (477, 43.2%) originated from the United Kingdom. The global country distribution of these reports are presented in the following Table 36 by decreasing frequency:

Table 36 Global country distribution of confirmed 'booster' dosing involving VAXZEVRIA vaccine cumulatively till 28 June 2022

Country	Case count
United Kingdom	477
Brazil	262
Philippines	146
Mexico	125
France	18
Portugal	12
Argentina	8
India	6
Thailand	5
Chile	4
Costa Rica	4
Poland	4
Australia	3
Austria	3
Colombia	3
Ecuador	3
Germany	3
Malta	3
Belgium	2
Lithuania	2
Northern Ireland	2
Sweden	2
Czech Republic	1
Greece	1
Ireland	1
Italy	1
Latvia	1
New Zealand	1
United States	1
Grand Total	**1104**

Compared to the previous booster analysis (DLP 04 January 2022), 495 new reports were received cumulatively till 28 June 2022. Most of the 495 new reports were from Brazil (206), Philippines (135) and Mexico (118), which co-relates with the booster dose administration in these countries in the PBRER reporting interval.

One hundred and sixty one of the 1104 cases, did not include other AEs apart from the medication error events (off-label use, overdose, medication error, drug exposure during pregnancy, Drug dose administration interval too long, Incorrect route of product administration, Inappropriate schedule of vaccine administered, Inappropriate dose of vaccine administered, Wrong vaccine administered, Drug dose administration interval too short, Incomplete course of vaccination, Vaccination failure, Inappropriate route of vaccination, Unevaluable event, and unexpected benefit). There was one case identified from the United States (US), however, VAXZEVRIA is not approved in the US. This case concerned a consumer from the US who read about a report of VAXZEVRIA and reported the AE to AstraZeneca. Information regarding the origin of the vaccinee who experienced the event of Intracranial pressure increased is unknown.

Of these 1104 cases, vaccinee gender was reported in 1065 of the reports with 715 (64.8%) occurring in females and 350 (31.70%) occurring in males and gender was unknown in 39 (3.5%) cases. Vaccinee age was available in 818 of the reports and ranged from 4 to 97 years of age with a median of 46 years.

A total of 3741 AEs were reported within the 1104 reports of booster dosing with VAXZEVRIA through 28 June 2022. Of these 3741 AEs, 1228 (32.8%) were reported as serious due to the AE being considered as medially important (974, [79.3%]), the AE was reported to have resulted in disability (241 [19.6]), required hospitalization (262 [19.8]), was life threatening (85 [6.9]), and/or resulted in death (40 [3.3]). Cases may have met more than one criteria for seriousness. Cases may have met more than one criteria for seriousness.

Outcome was reported for 1931 of the 3741 AEs reported, as follows: Not recovered (730, 37.8%), Recovered (778, 40.2%), Recovering (339, 17.6%), Recovered with sequelae (44, 2.3%), and Death (40, 2.1%).

A distribution of the AEs reported with a frequency >10 is provided in Table 37. The most frequently reported AEs with VAXZEVRIA booster were listed AEs as per VAXZEVRIA CDS, such as Headache, Pyrexia, Fatigue, myalgia, asthenia, chills, arthralgia, nausea, dizziness etc. in terms of most frequently reported events, No usual trends or clusters were identified compared to the previously PBRER.

Table 37 Distribution of Adverse Events (>10) with Booster Reporting Involving VAXZEVRIA (Suspect) through 28 June 2022

Adverse Event (Preferred Term)	Non-Serious	Serious	Medically Confirmed Adverse Events	Total Adverse Events
Headache	227	54	122	281
Pyrexia	194	46	125	240
Fatigue	113	62	33	175
Myalgia	150	19	84	169
Asthenia	98	26	12	124
Chills	99	20	46	119
Pain	97	22	20	119
Off label use	80	15	28	95
Arthralgia	68	25	19	93
Nausea	57	33	36	90
Dizziness	52	24	16	76
Adverse event	66	4	5	70
Cough	40	15	21	55
Pain in extremity	30	23	9	53
Tenderness	53	0	0	53
Diarrhoea	32	17	16	49
Interchange of vaccine products	37	9	19	46
Malaise	38	8	30	46
Dyspnoea	13	30	13	43
Oropharyngeal pain	35	8	17	43
Vomiting	31	11	22	42
Abdominal pain	33	5	20	38
Rash	25	12	24	37
Chest pain	9	26	9	35
Pruritus	24	11	18	35
COVID-19	10	21	4	31
Palpitations	9	22	9	31
Paraesthesia	11	17	8	28
Application site pain	25	2	26	27
Vaccination site pain	26	1	25	27
Rhinorrhoea	18	7	0	25
Back pain	13	10	9	23
Irritability	21	1	0	22
Tachycardia	8	14	3	22

Blood pressure increased	18	2	18	20
Erythema	15	5	5	20
Hypoaesthesia	10	10	5	20
Lymphadenopathy	8	12	2	20
Wrong product administered	19	0	19	19
Menstruation delayed	10	8	0	18
Expired product administered	17	0	16	17
Incorrect dose administered	16	1	17	17
Nasopharyngitis	12	5	11	17
Peripheral swelling	6	11	3	17
Heavy menstrual bleeding	4	11	0	15
Hyperhidrosis	9	6	3	15
Inappropriate schedule of product administration	15	0	12	15
Limb discomfort	6	9	2	15
Syncope	2	13	4	15
Injection site pain	7	7	4	14
Abdominal pain upper	3	10	1	13
Inflammation	7	6	1	13
Influenza	4	8	2	12
Swelling	7	5	1	12
Body temperature increased	8	3	0	11
Influenza like illness	4	7	1	11
Insomnia	3	8	1	11
Oedema	10	1	3	11

Homologous/Heterologous Dosing Regimens

Of the 1104 reports, 889 specified the regimens used for each of the 3 recommended vaccinations and unknown in 215 case reports. Of these 889 reports, 500 indicated homologous dosing and 389 indicated heterologous dosing. Please note that for 2 cases ([redacted] and [redacted]), both homologous and heterologous dosing regimens were reported within the same case.

Homologous Dosing

Of the 889 reports specifying the vaccine regimens for all 3 vaccinations, 500 indicated homologous dosing where VAXZEVRIA was used for all three vaccinations. A total of 1920 AEs were received within these 500 reports. Of the 1920 AEs, 579 AEs (30.2%) were serious due to the AE being considered as medially important by the reporter (483 [83.4%]), the AE reportedly resulted in disability (86[14.9%]), AE reportedly required hospitalization (58 [10.0%]), AE was reported as life threatening (41 [7.1%]), and/or the AE reportedly resulted in death (13 [2.2%]). Cases may have met more than one criteria for seriousness. Of the 1920 AEs, outcomes were reported as: Unknown (1111 [57.9%]), Not recovered (373 [19.4%]), Recovered (242[12.6%]), Recovering (150[7.8%]), Recovered with sequelae (31 [1.6%]), and Death (13[0<1%]). Of the 500 homologous reports, 157 cases (31.4%) were medically confirmed.

A distribution of the AEs reported for homologous dosing where VAXZEVRIA was used for all three vaccinations with a frequency >10 is provided in Table 38. The most commonly reported AEs with VAXZEVRIA homologous booster were listed AEs as per current CDS (Section 4).

Table 38 Distribution of Adverse Events (n = 1920) with Frequency ≥10 with Homologous Booster dosing Reporting Involving VAXZEVRIA (Suspect or Co-Suspect) through 28 June 2022

AEs for Homologous dosing regimen	Non-serious	Serious	Total
Headache	119	21	140
Fatigue	75	29	104
Pyrexia	81	19	100
Asthenia	87	5	92
Myalgia	77	8	85
Pain	72	8	80
Chills	54	9	63
Adverse Event	60	1	61
Arthralgia	46	10	56
Off-Label use	49	1	50
Dizziness	34	13	47
Nausea	32	0	15
Tenderness	46	0	
Diarrhoea	20	11	31
Cough	22	6	28
Oropharyngeal pain	20	2	22
Rhinorrhoea	18	4	22
Dyspnoea	7	14	21
Abdominal pain	19	1	20
Irritablity	20		20

Table 38 Distribution of Adverse Events (n = 1920) with Frequency ≥10 with Homologous Booster dosing Reporting Involving VAXZEVRIA (Suspect or Co-Suspect) through 28 June 2022

AEs for Homologous dosing regimen	Non-serious	Serious	Total
Pain in extremity	10	9	19
COVID-19	7	10	17
Pruritus	13	4	17
Chest pain	0	16	16
Vomiting	10	6	16
Palpitations	2	12	14
Tachycardia	6	8	14
Expired product administered	13	0	13
Malaise	8	5	13
Rash	8	5	13
Erythema	9	2	11
Abdominal pain upper	1	9	10
Inflammation	6	4	10

Heterologous Dosing

Of the 889 reports specifying the vaccine regimens for all 3 vaccinations, 389 indicated heterologous dosing where VAXZEVRIA was used as part of a vaccination regimen with another COVID-19 vaccine. Please note that 2 cases ([redacted] and [redacted]) indicated both homologous and heterologous dosing regimens within the same case.

In 228 reports, information regarding which vaccine(s) were used as part of the heterologous dosing was not available. In the remaining 161 reports, 8 involved heterologous dosing with mRNA vaccines (7 with COVID-19 mRNA VACCINE BIONTECH/PFIZER, 1 with COVID-19 mRNA VACCINE MODERNA), 3 with COVIDSHIELD, 3 with CORONAVAC /BUTANTAN and 147 involved heterologous booster dosing with COVID-19 VACCINE (RECOMBINANT)-BIO-MANGUINHOS/FIOCRUZ.

A total of 1145 adverse events were received within these 389 reports. Of the 1145 AEs, 448 AEs (39.1%) were serious due to the AE being considered as medially important by the reporter (349 [77.9%]), the AE reportedly resulted in disability (123 [27.5%]), AE reportedly required hospitalization (89 [19.8%]), AE was reported as life threatening (34 [7.6%]), and/or the AE reportedly resulted in death (3 [<1%]). Cases may have met more than one criteria for seriousness. Of the 1145 AEs, outcomes were reported as: Unknown (521 [45.5%]), Not recovered (269 [23.5%]), Recovered (242 [21.1%]), Recovering (101 [8.8%]), Recovered with sequelae (9 [<1%]), and Death (3 [<1%]). Of the 389 heterologous reports, 180 cases (46.2%) were medically confirmed.

A distribution of the AEs reported for heterologous dosing where VAXZEVRIA was used as part of a vaccination regimen with another COVID-19 vaccine. with a frequency >10 is provided in Table 39. The most commonly reported AEs with VAXZEVRIA heterologous booster were listed AEs per the current CDS (Version 18.0, 11 May 2022).

Table 39 Distribution of Adverse Events (n = 1145) with Frequency ≥10 with Heterologous Booster dosing Reporting Involving VAXZEVRIA (Suspect or Co-Suspect) through 28 June 2022

AEs for Heterologous dosing regimen	Non-serious	Serious	Total
Headache	69	20	89
Pyrexia	60	19	79
Myalgia	55	5	60
Fatigue	31	22	53
Nausea	21	12	33
Chills	26	6	32
Interchange of vaccine products	30	2	32
Pain in extremity	20	10	30
Off label use	28	1	29
Pain	14	9	23
Application site pain	22	0	22
Arthralgia	12	9	21
Asthenia	11	8	19
Cough	11	6	17
Paraesthesia	6	11	17
Back pain	9	7	16
Abdominal pain	11	3	14
Vomiting	12	2	14
Oropharyngeal pain	10	3	13
COVID-19	5	7	12
Diarrhoea	8	4	12
Wrong product administered	11	0	11
Dyspnoea	3	7	10
Incorrect dose administered	9	1	10

Fatal Reports

Cumulatively through till 28 June 2022, there have been 20 reports involving 30 adverse events reporting a fatal outcome with a third booster dose of VAXZEVRIA. These 22 reports with fatal outcome are summarized below in Table 40.

Table 40 Summary tabulation of fatal cases (n = 20) with booster dosing reporting Involving VAXZEVRIA through 28 June 2022

Case ID	Source	Dosing regimen	Patient details (Age in years / Gender	Medically confirmed	Fatal AEs (PTs)	Time to Onset from last Dose (booster dose)	Company assessment
[redacted]	**Spontaneous**	**Unknown**	**40 / M**	**No**	**Death**	**Unknown**	**Case poorly documented, lacking details such as patient´s medical and family history, baseline health status before vaccination, etiological and diagnostic work up including autopsy report and cause of death.**
[redacted]	Regulatory	Homologous	60 / F	YES	Death	Unknown	Case poorly documented, lacking details such as patient´s medical and family history, baseline health status before vaccination, etiological and diagnostic work up including autopsy report and cause of death.
[redacted]	Spontaneous	Heterologous	49 / M	YES	Abdominal distension	1 day	The cause of death was further specified as abdominal distension. Concomitant use of CoronaVac/ butantan could be considered a co-suspect the event abdominal distension. Due to limited information on baseline health status of the patient before vaccination, circumstances leading to the event, relevant family history, concurrent conditions, concomitant medications, etiological and diagnostic work up the evaluation did not find evidence to suggest a causal relationship between the event and VAXZEVRIA vaccine.
[redacted]	Regulatory	Unknown	66 / M	No	Myocardial infarction / Eczema /	Unknown	The events Myocardial infarction, Cardiac arrest, Chest pain, Dyspnoea, Feeling cold and Asthenia

					Cardiac arrest / Cardiac death / Fatigue / Chest pain / Dyspnoea / Feeling cold / Asthenia		could be considered in association with each other. The elderly age of the patient and possible underlying hypercholesterolemia as suggested by the intake of concomitant statins could be considered as contributory factors to the events Myocardial infarction and Chest pain. The past and current medical history of eczema could be considered contributory to the event Eczema. The "certified cause" of death was reported as Acute left ventricular failure B non-ST elevation Myocardial Infarction with 2 hypoxic brain injuries. It was also reported that the patient died on an unspecified date. Due to limited information on the baseline health condition of the patient before vaccination, concurrent diseases, onset date of the events, circumstances leading to the events and fatal outcome, etiologic and diagnostic work up, and in the absence of an autopsy report, the evaluation did not find evidence to suggest a causal relationship between the events and VAXZEVRIA
[redacted]*	Regulatory	Unknown	NA / F	No	Asphyxia / Epilepsy	Unknown	Events reported: Asphyxia (fatal), Epilepsy (fatal), Cerebrovascular accident, Confusional state, Dementia, Mobility decreased, Anal incontinence, Aphasia may be in association with each other. Vaccinee's past medical history of epilepsy may be contributory to the event of epilepsy. Due to limited information on circumstances leading to the events, age of the patient, onset dates of all the events, etiological and diagnostic work up, the evaluation did not find evidence to suggest a

							causal relationship between the event and VAXZEVRIA.
[redacted] *	Spontaneous	Homologous	63 / F	YES	Pain / Dyspnoea / Cough / Cardiac arrest / Cyanosis	< 1 day	The events could be in association with each other. The events of dyspnoea, cough, cyanosis and pain occurred on the day of the third dose of vaccination while cardiac arrest occurred a day after. The patient died on an unspecified date. Due to limited information on the exact circumstances surrounding the events, medical history and concurrent conditions, concomitant medications, detailed etiological and diagnostic work-up, clinical course leading to demise and autopsy report if available, the evaluation did not find evidence to suggest a causal relationship between the events and VAXZEVRIA.
[redacted] *	Regulatory	Heterologous	88 / NA	No	Ischaemic stroke	3 months	Underlying past medical history of Diabetes mellitus and age could be considered as risk factors for the event. The cause of death was reported as ischaemic stroke. Due to limited information on clinical course, baseline health characteristics of the vaccinee before vaccination, relevant family history, concurrent disease, autopsy performed and detailed diagnostic (D-Dimer blood test, imaging studies, physical examination, neurological findings, complete blood count, blood laboratory tests, coagulation studies, anti-platelet factor 4 (PF4) antibodies, echocardiogram) and risk factors (high blood pressure, high cholesterol, diabetes, coagulopathies, trauma, cancer, obesity, smoking, immobility), the evaluation did not find evidence to suggest a causal relationship between the fatal event and VAXZEVRIA.

[redacted] *	Regulatory	Unknown	NA / NA	No	Drug ineffective	Unknown	The cause of death was reported as no drug effect. Due to limited information on patient demographics, baseline health status of the patient prior to vaccine administration, details and circumstances of the events, medical history, use of concomitant medications, and etiologic and diagnostic workup (Covid-19 polymerase chain reaction test, blood chemistry, D-dimer, arterial blood gas, chest radiograph, chest computed tomography, autopsy report), the evaluation did not find evidence to suggest a causal relationship between the events and VAXZEVRIA.
[redacted] *	Spontaneous	Homologous	NA / NA	No	Thrombosis	Unknown	The event could be possibly associated to reported listed event of platelet count decreased. Due to limited information on date of vaccine administration, onset date of event, exact date of death, circumstances leading to the event, event details, baseline health condition prior to vaccine administration, concurrent conditions, concomitant medications, relevant medical history, relevant diagnostic workup, the evaluation did not find evidence to suggest a causal relationship between the fatal event and VAXZEVRIA.
[redacted] *	Regulatory	Unknown	79 / F	No	Dyspnoea / Respiratory distress	Unknown	Patient´s age and past and current medical history of anteroseptal infarction could be possible contributory risk factors for the events. Due to limited information on circumstances leading to the events, baseline health condition prior to vaccine administration, concurrent conditions, concomitant medications, other relevant medical history, family history, risk factors (respiratory disease, infections, sepsis, COVID-19 infection,

							weakened immune system), detailed etiological and diagnostic workup and autopsy report, the evaluation did not find evidence to suggest a causal relationship between the fatal events and VAXZEVRIA.
[redacted] *	Regulatory	Unknown	62 / M	YES	Cardiac arrest	Unknown	Due to limited information on circumstances leading to the event that further resulted to death, relevant medical history (cardiovascular disease, diabetes mellitus), concurrent diseases, concomitant medications, risk factors, detailed etiological and diagnostic workup (electrocardiogram, echocardiogram, chest Xray, metabolic panel), autopsy report, the evaluation did not find evidence to suggest a causal relationship between the event and VAXZEVRIA.
[redacted] *	Regulatory	Homologous	81 / M	No	Neoplasm malignant	Unknown	The reported cause of death was cancer. Additionally, due to limited information on baseline health condition before vaccination, relevant medical history, relevant family history, concurrent diseases, concomitant medications, date of death, relevant medication history and details and circumstances surrounding the event, the evaluation did not find evidence to suggest a causal relationship between the event and VAXZEVRIA.
[redacted] *	Regulatory	Homologous	73 / F	No	Death	Unknown	Death was reported as fatal event, with no cause of death reported. Age of the vaccinee could be contributory to the event. Other AEs such as Cardiac murmur, Chest pain, Dyspnoea, Palpitations and Tachycardia were also reported. Due to limited information on baseline health condition before vaccination, relevant family history, concomitant medications, relevant

							medication history, details and circumstances surrounding the events and detailed diagnostic and etiologic workup (physical examination, neurological findings, complete blood count, blood laboratory tests, coagulation studies, platelet count, infection profile, electrocardiogram, echocardiogram, chest radiological studies and imaging and cranial radiological studies and imaging). The evaluation did not find evidence to suggest a causal relationship between the events and VAXZEVRIA.
[redacted] *	Regulatory	Heterologous	65 / M	No	Cerebral infarction	Unknown	This case concerns a 65-year-old male who experienced Cerebral infarction (fatal) / Cerebral artery thrombosis / Cerebrovascular accident / Rhinorrhoea / Nasal congestion / Condition aggravated / Fatigue. The rhinorrhoea and nasal congestion could be in association with each other. current medical history of atrial fibrillation could be a risk factor for the events of Cerebral infarction, Cerebral artery thrombosis and Cerebrovascular accident. current medical history of nasal polyps could be a confounding factor for the events of Rhinorrhoea and Nasal congestion. Due to limited information on onset date of all events, circumstances leading to the events, treatment given, clinical course, health status of vaccinee before vaccination, risk factors, date of death, autopsy details, detailed diagnostic work up (complete blood count, neurological work up, imaging studies, ear, nose, throat work up), the evaluation did not find evidence to suggest a

							reasonable possibility of a causal relationship between the events and VAXZEVRIA.
[redacted] *	Regulatory	Homologous	NA / F	No	Chronic kidney disease	Unknown	Underlying condition of immunodeficiency could be a confounding factor for events Renal failure, Chronic kidney disease. Due to limited information on autopsy details, complete demographic data of the vaccinee, baseline health condition before vaccination, relevant medical history, relevant family history, concomitant medications, event onset date, possible risk factors (high blood pressure, diabetes, dehydration) and detailed diagnostic and etiologic workup (complete blood analysis, renal workup, physical examination, infection profile and chest radiological studies and imaging), the evaluation did not find evidence to suggest a causal relationship between the events and VAXZEVRIA.
[redacted] *	Regulatory	Homologous	82 / F	YES	Death	Unknown	The cause of death is further not specified. Advance age of vaccinee and history of Septic Shock; Hypoxic Ischemic Encephalopathy; Covid-19 Pneumonia with Hypoxemia could be considered as confounding factors for the death. Due to limited information on circumstances leading to death, baseline health condition before vaccination, relevant medical history, concurrent condition, concomitant medications, autopsy details, possible risk factor, detailed diagnostic and etiologic workup, the evaluation did not find evidence to suggest a causal relationship between the fatal event and VAXZEVRIA.
[redacted]	Regulatory	Unknown	49/M	Yes	Pyrexia/	1 day	Pyrexia is listed in the company core data sheet of VAXZEVRIA, however, as the event is reported

					Upper respiratory tract infection		with the seriousness criterion of death, the event is considered unlisted. The cause of death was reported as Fever and Upper respiratory tract infection. The events could be in association with each other. Due to limited information on medical and family history, concomitant medications, details and circumstances surrounding the events, possible risk factors (lung disorders, weak immune system, smoking, diabetes) and detailed diagnostic and etiologic workup (physical examination, pulmonological findings, complete blood count, blood laboratory test and infection profile), autopsy report with confirmed final diagnosis, the evaluation did not find evidence to suggest a causal relationship between the event and VAXZEVRIA.
[redacted]	Regulatory	Unknown	33/M	No	Death	Unknown	The cause of death was unknown. Due to limited information on circumstances leading to the event, clinical course, concurrent diseases relevant family history, concomitant medications, specific risk factors (infection, trauma), etiological and complete diagnostic workup (complete blood count, complete physical assessment with imaging), autopsy report of performed, the evaluation did not find evidence to suggest a causal relationship between the event and VAXZEVRIA.
[redacted]	Regulatory	Unknown	73/M	Yes	Cough/ Oxygen saturation decreased	4 months	It is notable that vaccinee received JANSSEN COVID-19 VACCINE, which could be considered as co-suspect. The cause of death was specified as cough and oxygen desaturation. Due to limited information on risk factors, circumstances surrounding the events, concurrent

							conditions, concomitant medications, relevant medical history, detailed etiological and diagnostic work-up before death, autopsy report with confirmed diagnosis, the evaluation did not find evidence to suggest a causal relationship between the events and VAXZEVRIA.
[redacted]	Regulatory	Unknown	35/M	Yes	Hemiparesis / Vomiting/ Dysarthria	5 months	Fatal events of hemiparesis and dysarthria are not listed in the company core data sheet of VAXZEVRIA. Vomiting is listed adverse event for VAXZEVRIA. However, as the event is reported with the seriousness criterion of death, t<<Update/delete this default footnote as required.>>he event vomiting is considered unlisted. Hemiparesis could be considered as the confounding factor for dysarthria. The cause of death was reported as left side body weakness, vomiting and slurred speech. Due to limited information on circumstances leading to the events, baseline health condition before vaccination, relevant medical history, family history, concomitant medications, concurrent diseases, risk factors (previous episodes of stroke, head injury), autopsy details, detailed etiologic and diagnostic workup (neurology work up), the evaluation did not find evidence to suggest a causal relationship between the events and VAXZEVRIA.

***** = New cases and / or new FU information since the previous booster summary report indicated in **bold**

In general, the review of fatal cases demonstrated insufficient case details or the presence of confounders / risk factors for the reported fatal AEs, and there is currently insufficient evidence to suggest a reasonable possibility of a causal relationship between VAXZEVRIA and the fatal AEs.

Unlisted Adverse Events (AEs)

Of the total 3741 AEs reported with VAXZEVRIA booster through 28 June 2022, 1531 (40.9%) AEs unlisted as per the Company Core Data Sheet (CDS) version 17.0. Of the 1531 unlisted AEs, 669 (43.7%) unlisted AEs were serious, of which 494 (73.8%) were considered medically important by the reporter, 149 (22.3%) reportedly required hospitalization, 137 (20.5%) were reported to have resulted in disability, 55 (8%) were reported as life-threatening and 40 (6%) reportedly resulted in death. Cases may have met more than one criteria for seriousness. Of the 1531 unlisted AEs, 862 (56.3%) were nonserious.

Of the 1531 unlisted AEs, the outcomes have been reported as: Unknown (729 [47.6%]), Not recovered (366 [23.9%]), Recovered (227 [14.8%]), Recovering (146 [9.5%]), Recovered with sequelae (23 [1.5%]), and patient died (40 [2.6%]). Of the 767 cases with unlisted AEs, 265 (34.6%) were medically confirmed.

A distribution of the most frequently reported unlisted AEs for all VAXZEVRIA booster with a frequency ≥10 is provided in Table 41.

Table 41 Unlisted AEs for all VAXZEVRIA booster with a frequency ≥10

Unlisted AE terms (PT)	Non-serious Unlisted	Serious Unlisted	Total unlisted AEs
Off label use	93	2	95
Adverse event	69	1	70
Cough	41	14	55
Tenderness	53	0	53
Interchange of vaccine products	43	3	46
Dyspnoea	14	29	43
Oropharyngeal pain	35	8	43
Chest pain	9	26	35
COVID-19	12	19	31
Palpitations	9	22	31
Rhinorrhoea	18	7	25
Irritability	21	1	22
Tachycardia	8	14	22
Blood pressure increased	18	2	20
Wrong product administered	19	0	19

Table 41 Unlisted AEs for all VAXZEVRIA booster with a frequency ≥10

Unlisted AE terms (PT)	Non-serious Unlisted	Serious Unlisted	Total unlisted AEs
Menstruation delayed	10	8	18
Expired product administered	17	0	17
Incorrect dose administered	16	1	17
Nasopharyngitis	12	5	17
Peripheral swelling	6	11	17
Heavy menstrual bleeding	4	11	15
Inappropriate schedule of product administration	15	0	15
Limb discomfort	7	8	15
Syncope	3	12	15
Inflammation	7	5	13
Influenza	5	7	12
Insomnia	3	8	11
Chest discomfort	1	9	10
Dysmenorrhoea	5	5	10
Muscular weakness	7	3	10
SARS-CoV-2 antibody test negative	10	0	10

The most frequent reported AEs/PT of off-label use mostly involved vaccinees receiving 3rd dose of VAXZEVRIA in countries where use of the vaccine as a booster has or had not yet been approved. The reported AEs/PTs of "Adverse events" refer to unspecified AEs and are of no safety concern.

Serious Unlisted AEs

Of the total 1531 unlisted AEs reported with VAXZEVRIA booster through 28 June 2022, 669 (43.6%) unlisted AEs were serious in 282 cases. Of the 282 serious unlisted cases, 47 cases (16.6%) were medically confirmed. The 5 most frequently reported unlisted SAEs were Dyspnoea, Chest pain, Palpitations, COVID-19 and Cough (Please refer to Table 42).

Table 42 Distribution of Serious Unlisted Adverse Events (n = 669) (top 6 frequency) with Booster reporting Involving VAXZEVRIA (Suspect or Co-Suspect) through 28 June 2022

Unlisted SAE (PT)	Unlisted SAE count	% of total unlisted SAEs	Time to Onset from last dose (Range, Median)
Dyspnoea	29	4.33	3 AEs have TTO reported from last dose: range <1 day to 2 days / median 1 day
Chest pain	26	3.88	3 AEs have TTO reported from last dose: range < 1 to 3 days / median 1 day
Palpitations	22	3.28	2 AEs have TTO reported from last dose: range 1 to 2 days / median 2 days
COVID-19	19	2.84	5 AEs have TTO reported from last dose: range < 1 day to 90 days / median 5 days
Cough	14	2.09	1 AE had TTO reported from last dose < 1 day/ median 0 days
Tachycardia	14	2.09	1 AE had TTO reported from last dose: 45 days

The serious unlisted cases for booster dosing were poorly documented, and no abnormal trend was identified for the serious unlisted AEs in general.

Unlisted Adverse Events - Homologous/Heterologous Dosing Regimens

Of the 1531 AEs within 767 cases that were unlisted as per the Company CDS (Version 17.0), a total of 1264 AEs in 640 reports involved confirmed homologous and heterologous. Covid-19 vaccine booster through 28 June 2022.

Of 1264 unlisted AEs in 640 reports which involved confirmed homologous and heterologous Covid-19 vaccine booster through 28 June 2022, 775 AEs in 381 cases involved confirmed homologous dosing and 489 AEs in 259 cases involved heterologous confirmed. Please note, as stated before, it was identified that 2 cases ([redacted] and [redacted]) indicated both homologous and heterologous dosing regimens within the same case.

Unlisted Adverse Events - Homologous Dosing Regimen:

775 AEs in 381 cases involved confirmed homologous dosing in which a 2-dose regimen of VAXZEVRIA was used followed by a third booster dose of VAXZEVRIA through 28 June 2022. Of the 775AEs, 306 (39.5%) were serious and 469 (60.5%) were non-serious (please refer to Table 43 showing the distribution of the most frequently reported AEs ≥10 involving homologous dosing).

Table 43 Distribution of Unlisted Adverse Events (N = 775) with Frequency ≥10 with Booster Reporting Involving VAXZEVRIA (Suspect or Co-Suspect) with confirmed homologous dosing regimen through 28 June 2022

Unlisted AE (Preferred Term) - Homologous dosing	Homologous dosing - unlisted AE distribution		
	Non-serious	Serious	Total
Adverse event	61	1	62
Off label use	49	1	50
Tenderness	46	0	46
Cough	22	6	28
Oropharyngeal pain	20	2	22
Rhinorrhoea	18	4	22
Dyspnoea	7	14	21
Irritability	20		20
COVID-19	7	10	17
Chest pain	0	16	16
Palpitations	2	12	14
Tachycardia Blood pressure increased	6	8	14
Expired product administered	13	0	13
Inflammation	6	4	10

The most frequently reported serious unlisted SAEs (>10) with homologous dosing were Dyspnoea (14), Chest pain (16), Palpitations (12), COVID-19 (10).

Of these 381 homologous cases with unlisted AEs, 104 (27.3%) cases with 168 AEs were medically confirmed (please refer to Table 44 showing the distribution of the most frequently

reported medically confirmed unlisted AEs >3 involving homologous dosing). There were very few medically confirmed unlisted SAEs reported.

Table 44 Distribution of medically confirmed Unlisted Adverse Events (n = 168) with Frequency ≥3 with Booster Reporting Involving VAXZEVRIA (Suspect or Co-Suspect) with confirmed homologous dosing regimen through 28 June 2022

Medically confirmed Unlisted AE (Preferred Term) – Homologous dosing	Homologous dosing - Medically confirmed unlisted AE distribution		
	Non-serious	Serious	Total
Off label use	18	0	18
Expired product administered	13	1	13
SARS-CoV-2 antibody test negative	9	0	9
Wrong product administered	8	0	8
Incorrect dose administered	7	0	7
Interchange of vaccine products	6	0	6
Cough	4	1	5
Inappropriate schedule of product administration	5	0	5
COVID-19	1	3	4
Dyspnoea	1	3	4
Oropharyngeal pain	4	0	4
Blood pressure increased	2	1	3
Chest discomfort	0	3	3
Chest pain	0	3	3
Incomplete course of vaccination	3	0	3
Chest discomfort	0	3	3
Incomplete course of vaccination	3	0	3

Unlisted Adverse Events - Heterologous Dosing Regimen:

489 AEs in 259 cases involved heterologous dosing with VAXZEVRIA Of the 489 AEs, 241 (49.3%) were serious and 248 (50.7%) were non-serious (please refer to Table 45 showing the distribution of the most frequently reported unlisted AEs ≥3 involving heterologous dosing).

The most frequently reported unlisted SAEs with heterologous dosing were cough (6) and COVID-19 (6).

Table 45 Distribution of Unlisted Adverse Events (n = 489) with Frequency ≥3 with Booster Reporting Involving VAXZEVRIA (Suspect or Co-Suspect) with confirmed heterologous dosing regimen through 28 June 2022

Unlisted AE (Preferred Term) - Heterologous dosing	Heterologous dosing - unlisted AE distribution		
	Non-serious	Serious	Total
Interchange of vaccine products	30	2	32
Off label use	28	1	29
Cough	11	6	17
Oropharyngeal pain	10	3	13
COVID-19	65	7	12
Dyspnoea	3	8	11
Wrong product administered	11	0	11
Incorrect dose administered	9	1	10

Of these 259 cases, 103 (39.8%) cases with 138 AEs were medically confirmed (please refer to Table 46 showing the distribution of the most frequently reported medically confirmed unlisted AEs ≥3 involving heterologous dosing). Few medically confirmed unlisted SAEs were reported with Dermatitis bullous as the most frequently reported SAE (3).

Table 46 Distribution of medically confirmed Unlisted Adverse Events (n = 138) with Frequency ≥2 with Booster Reporting Involving VAXZEVRIA (Suspect or Co-Suspect) with confirmed heterologous dosing regimen through 28 June 2022

Medically confirmed Unlisted AE (Preferred Term) – Heterologous dosing	Heterologous dosing - Medically confirmed unlisted AE distribution		
	Non-serious	Serious	Total
Wrong product administered	11	0	11
Incorrect dose administered	9	1	10
Interchange of vaccine products	10	0	10
Oropharyngeal pain	10	0	10
Cough	8	0	8
Product administered to patient of inappropriate age	8	0	8
Inappropriate schedule of product administration	7	0	7
Application site warmth	5	0	5
Off label use	5	0	5
Rhinitis	5	0	5
Application site oedema	3	0	3
Dyspnoea	3	0	3
Expired product administered	3	0	3
Sneezing	3	0	3
Syncope	2	1	3
Antibody test abnormal	2	0	2
Contraindication to vaccination	2	0	2
Dermatitis bullous	0	2	2

Unlisted Adverse Events - Adverse Events of Special Interest (AESIs)

Of all 1531 unlisted AEs reported involving booster with VAXZEVRIA through 28 June 2022, a total of 122 unlisted AEs (7.9%) from reports are considered Adverse Events of Special Interest (AESIs) for VAXZEVRIA and are being closely monitored as part of AstraZeneca's ongoing surveillance activities. Please note that since the last report, paraesthesia and hypoaesthesia are now considered ADRs with VAXZEVRIA and, hence, no longer included as AESIs. Of the 122 unlisted AESIs, 98 (80.3%) AESIs were serious, of which 65 (53.3%) were considered medically important by the reporter, 40 (26.9%)

reportedly required hospitalization, 24 (19.7%) were reported to have resulted in disability, 21 (17.2%) were reported as life threatening by the reporter and 3 (2.5%) reportedly resulted in death. Cases may have met more than one criteria for seriousness. Of the 122 unlisted AESIs, outcome was reported, as follows: Not recovered (51 [41.8%]), Unknown (27 [22.3%]), Recovering (20 [16.4%]), Recovered (17 [13.9%]), Recovered with sequelae (4 [3.3%]), and patient died (3 [2.5%]).

Of the 122 unlisted AESIs identified cumulatively till 28 June 2022, 46 involved patients with confirmed heterologous dosing regimen, 49 involved homologous dosing regimen, and 27 involved an unknown dosing regimen. The overall distribution of the reported unlisted AESIs for all VAXZEVRIA booster is provided in Table 47.

Table 47 Distribution of Unlisted AESI (n = 122) with Booster Reporting Involving VAXZEVRIA (Suspect or Co-Suspect) through 28 June 2022

Unlisted AESI	Heterologous dosing regimen		Homologous dosing regimen		Unknown dosing regimen		AESI Total
	Nonserious	serious	Nonserious	serious	Nonserious	serious	
Peripheral swelling	1	6	2	4	3	1	17
Hypersensitivity	1	0	2	4	1	1	9
Deep vein thrombosis	0	3	0	3	0	2	8
Myocarditis	0	1	0	4	0	1	6
Neuralgia	1	0	2	2	0	1	6
Seizure	0	2	0	2	0	2	6
Cerebrovascular accident	0	2	0	2	0	1	5
Guillain-Barre syndrome	0	2	0	1	0	2	5
Ageusia	0	0	1	1	1	1	4
Anosmia	0	1	1	0	1	1	4
Facial paralysis	0	1	1	1	0	1	4
Hypotension	0	1	1	2	0	0	4
Myocardial infarction	0	1	0	0	0	2	3
Neuropathy peripheral	0	2	0	1	0	0	3
Paraesthesia	0	3	0	0	0	0	3
Pulmonary embolism	0	1	0	2	0	0	3
Cerebral venous thrombosis	0	2	0	0	0	0	2
Chronic fatigue syndrome	0	1	0	1	0	0	2

Table 47 Distribution of Unlisted AESI (n = 122) with Booster Reporting Involving VAXZEVRIA (Suspect or Co-Suspect) through 28 June 2022

Unlisted AESI	Heterologous dosing regimen		Homologous dosing regimen		Unknown dosing regimen		AESI Total
	Nonserious	serious	Nonserious	serious	Nonserious	serious	
Conjunctivitis	1	1	0	0	0	0	2
Laryngeal oedema	0	1	0	1	0	0	2
Pneumonia	0	1	0	1	0	0	2
Rheumatoid arthritis	1	1	0	0	0	0	2
Bell's palsy	0	0	0	0	0	1	1
Cardiac asthma	0	0	0	1	0	0	1
Cerebral artery thrombosis	0	1	0	0	0	0	1
COVID-19 pneumonia	0	0	0	1	0	0	1
Encephalitis	0	0	0	0	0	1	1
Immune thrombocytopenia	0	1	0	0	0	0	1
Immune-mediated encephalitis	0	0	0	0	0	1	1
Ischaemic stroke	0	1	0	0	0	0	1
Mechanical ventilation	0	0	0	0	0	1	1
Myelitis transverse	0	0	0	0	1	0	1
Oedema peripheral	0	0	1	0	0	0	1
Periarthritis	0	1	0	0	0	0	1
Peripheral vein thrombus extension	0	0	0	1	0	0	1
Renal failure	0	0	0	1	0	0	1
Right ventricular failure	0	1	0	0	0	0	1
Sensory loss	0	0	1	0	0	0	1
Transient ischaemic attack	0	1	0	0	0	0	1
Troponin increased	0	0	0	1	0	0	1
Grand Total	5	41	12	37	7	20	122

Peripheral swelling (17 [13.9]), Hypersensitivity (9 [7.4%]), Deep vein thrombosis (8 [6.6]), were the most commonly reported unlisted AESI AEs reported for each event till 28 June 2022. 11 AEs of peripheral swelling were serious and 6 were non serious, and only 3 were

medically confirmed. All DVT AEs were reported as serious, but none were medically confirmed. Five hypersensitivity cases were serious and four were non-serious, and only three were medically confirmed.

Table 48 Summary Tabulation of medically confirmed unlisted AESI Reported with VAXZEVRIA (Suspect or Co-Suspect) through 28 June 2022 (n = 21)

Case ID	Source	Dosing Regimen	Patient (age)	AESI PT	Seriousness	Time to Onset from last dose	AESI outcome
[redacted]	Regulatory	Homologous	Female, age unknown	Neuralgia	Not serious	Unknown	Recovering
[redacted]	Regulatory	Homologous	Female, 74 years	Pulmonary embolism	Life Threatening	Unknown	Not recovered
[redacted]	Regulatory	Homologous	Female, 70 years	Myocarditis Troponin increased	Hospitalisation / Medically Important Hospitalisation / Medically Important	< 1 day Unknown	Recovered with sequelae Recovered with sequelae
[redacted]	Spontaneous	Heterologous	Female, 52 years	Epilepsy / Cerebral venous thrombosis	Disability Disability	2 weeks 4 days 2 weeks 4 days	Unknown Unknown
[redacted]	Regulatory	Homologous	Female, 38 years	Hypersensitivity	Medically Important	Unknown	Recovering
[redacted]	Regulatory	Homologous	Female, 85 years	Neuropathy peripheral / Facial paralysis / Seizure	Life Threatening / Disability / Medically Important Life Threatening / Disability / Medically Important Life Threatening / Disability / Medically Important	Unknown Unknown Unknown	Not recovered Not recovered Not recovered
[redacted]	Regulatory	Unknown	Male, 36 years	Myocarditis	Hospitalisation / Medically Important	< 1 month	Unknown
[redacted]	Regulatory	Heterologous	Female, 47 years	Seizure	Hospitalisation	Unknown	Recovered

Table 48 Summary Tabulation of medically confirmed unlisted AESI Reported with VAXZEVRIA (Suspect or Co-Suspect) through 28 June 2022 (n = 21)

Case ID	Source	Dosing Regimen	Patient (age)	AESI PT	Seriousness	Time to Onset from last dose	AESI outcome
[redacted]	Spontaneous	Heterologous	Female, age unknown	Hypersensitivity	Not serious	< 1 day	Recovering
[redacted]	Spontaneous	Homologous	Female, age unknown	Laryngeal oedema	Hospitalisation	< 1 day	Unknown
[redacted]	Spontaneous	Homologous	Male, 27 years	Hypotension	Not serious	3 days	Unknown
[redacted]	Spontaneous	Unknown	Unknown	Ageusia/ Anosmia	Hospitalisation/ Hospitalisation	Unknown	Unknown Unknown
[redacted]	Regulatory	Homologous	Unknown	Myocarditis/ Chest pain/ Chest discomfort/ Mitral valve /incompetence/ Dyspnoea	Hospitalisation/ Hospitalisation/ Hospitalisation/ Hospitalisation	Unknown	Recovered with sequelae/ Unknown/ Unknown/ Unknown/ Unknown
[redacted]	Regulatory	Unknown	Unknown	Peripheral swelling/ Dyspnoea/ Palpitations	Not serious	Unknown	Recovered/ Recovered/ Recovered
[redacted]	Spontaneous	Heterologous	Unknown	Peripheral swelling/ Limb discomfort	Life Threatening	Unknown	Unknown/ Unknown
[redacted]	Spontaneous	Homologous	Unknown	Peripheral swelling/ Incorrect route of product /administration Off label use	Medically Important	Unknown	Unknown/ Unknown/ Unknown

Table 48 Summary Tabulation of medically confirmed unlisted AESI Reported with VAXZEVRIA (Suspect or Co-Suspect) through 28 June 2022 (n = 21)

Case ID	Source	Dosing Regimen	Patient (age)	AESI PT	Seriousness	Time to Onset from last dose	AESI outcome
[redacted]	Regulatory	Unknown	Unknown	Anosmia/ Ageusia/ Nasopharyngitis/ Cough/ Oropharyngeal pain	Not serious	Unknown	Recovered/ Recovered/ Recovered/ Recovered/ Recovered
[redacted]	Spontaneous	Homologous	Unknown	Peripheral vein thrombus extension	Hospitalisation	24 days	Unknown
	Spontaneous	Heterologous	Unknown	Laryngeal oedema	Medically Important	1 day	Recovered
	Regulatory	Unknown	Unknown	Guillain-Barre syndrome	Hospitalisation	Unknown	Recovered
[redacted]	Spontaneous	Homologous	Unknown	Hypersensitivity/ Inappropriate schedule of product administration	Not serious	77 days/78 days	Unknown Unknown

In comparison to the previous PBRER DLP 28 December 2021, the increase in types and number of AESIs aligned with the increase in overall AEs and did not indicate any new safety concerns.

In general, the medically confirmed unlisted AESI cases demonstrated insufficient case details or confounders / risk factors for the reported AESIs and was therefore not possible to confirm causality or are unlikely to be related to VAXZEVRIA.

Summary

Overall, the most frequently reported AEs with VAXZEVRIA booster use are consistent with the known safety profile of the vaccine, with the majority of AEs being non-serious (68.1%). The majority of unlisted AE profiling was also non-serious (56.3%), and the most frequently reported unlisted PT was “off-label use” (95) which mostly involved vaccinees receiving 3rd

dose of VAXZEVRIA in countries where use of the vaccine as a booster has or had not yet been approved, and the PT "Adverse event" (70), which refer to unspecified AEs. On review of unlisted clinical AEs, no abnormal trend was identified cumulative till 28 June 2022, and in general the cases were poorly documented which is further confirmed by the fact that only 34.6% of all unlisted cases were medically confirmed overall, and additionally only 15% of serious unlisted cases were medically confirmed. Although the majority of unlisted AESIs were serious, there were relatively few unlisted AESIs reported (7.9%), and medically confirmed (21.3%). No trends for AESIs were identified when compared with the AESIs reported with primary vaccination.

A review of booster reports involving homologous and heterologous dosing with VAXZEVRIA within the vaccination regimen did not identify any new safety concerns. The nature and severity of adverse events reported with homologous or heterologous dosing did not differ from the currently known safety profile of VAXZEVRIA.

It is AstraZeneca's opinion that no changes to the CDS or the Risk Management Plan (RMP) are warranted at this time. AstraZeneca will continue to monitor adverse event reports involving booster dosing with VAXZEVRIA as part of ongoing routine surveillance activities.

15.2.4 Menstrual Disorder

Background

In the assessment report received from the PRAC EMA (PRAC PAR (EMEA/H/C/PSUSA/00010912/202112) for the VAXZEVRIA PBRER (review period 29 June 2021 to 28 December 2021), further information on the topic of Menstrual disorder is requested as follows from AstraZeneca:

The MAH is requested to present an in-depth evaluation of all available data and recently published literature, including a discussion on possible mechanism should also be provided. The MAH is requested to present a refined review of cases of rechallenge.

AstraZeneca's response to these requests are provided in the subsections below.

Global Patient Safety Database

A cumulative search till 28 June 2022 of the AstraZeneca Global Safety Database for Menstrual disorder with VAXZEVRIA was performed using MedDRA version 25.0. The search was conducted at the level of MedDRA HLTs: Menstruation and uterine bleeding NEC, Menstruation with decreased bleeding, Menstruation with increased bleeding; and MedDRA PTs: vaginal haemorrhage, uterine haemorrhage, and postmenopausal haemorrhage. The search retrieved a total of 20994 case reports with 27145 events of Menstrual disorders. Cumulatively, a total 2148 cases (10.2%) were reported in women over 50 years of age.

The case source distribution for Menstrual disorder cumulatively through 28 June 2022 is presented in Table 49:

Table 49 Menstrual disorders reports received with VAXZEVRIA cumulatively through DLP by reporting source and seriousness

Classification of case report source	Non-serious cases	Serious cases	Grand Total
Spontaneous[a]	12618	7895	20513
Literature	3	1	4
Non-interventional/post-marketing study	413	64	477
Grand Total	**13034**	**7960**	**20994**

[a] Of the 20513 Spontaneous case reports, 19490 (95%) were from Regulatory source

The following Table 50 presents number and percentage (%) of case reports with Menstrual disorder reported after respective doses cumulatively.

Table 50 Number and percentage (%) of the case reports of Menstrual disorders reported after respective doses of VAXZEVRIA cumulatively through DLP

No of Cases (After First Dose)	No. of Cases (After Second Dose)	No. of Cases (After both First and Second Dose)	No. of Cases (After Third Dose)
11748 (68.3%)	5415 (31.5%)	1 (0.006%)	46 (0.27%)

These case reports for Menstrual disorder were reported most frequently in the following countries: United Kingdom (14844, 70.7%), Germany (1451, 6.9%), Netherlands (867, 4.1%), Spain (583, 2.8%) and Brazil (464, 2.2%).

The following observations were made from a review of the 20994 case reports pertaining to Menstrual disorder:

- Vaccinee age was reported in 18029 case reports and ranged 0 to 94 years (median: 41 years). Five cases were reported with age 0 years however based on the reported information they were adult vaccinees and all were received via regulatory source (3 from UK, 1 each from Germany and Netherlands).
- Vaccinee gender was reported in 20328 case reports. In 67 (0.3%) out of the 20328 case reports, gender was reported as male. A total 37 of the 67 cases were considered as event coding errors upon further review of reported term and narrative. In remaining 30 of the 67, the gender was reported as male, however based on the reported information, they were female vaccinees. Of these 67, 64 reports were received via regulatory authority.
- A total of 1323 (6.3%) case reports were medically confirmed and 19671 (93.7%) were non-medically confirmed.
- A total of 197 vaccinees were pregnant at the time of reporting of menstrual disorder event; and 80 vaccinees had co-reported event of abortion.

All the reported menstrual disorders MedDRA PTs were grouped into 9 different menstrual disorder categories as presented in Table 51 below.

Table 51 Menstrual disorder categories

Category	MedDRA PTs
Heavy menstrual blood loss	Heavy menstrual bleeding
Less menstrual blood loss	Hypomenorrhoea
Irregular blood loss	Polymenorrhoea, Menstruation irregular
Intermenstrual blood loss	Intermenstrual bleeding
Amenorrhoea/oligomenorrhoea	Menstruation delayed, Amenorrhoea, Oligomenorrhoea
Dysmenorrhoea	Dysmenorrhoea, Premenstrual pain, Premenstrual syndrome, Premenstrual headache, Premenstrual dysphoric disorder, Menstrual discomfort
Withdrawal blood loss abnormal	Abnormal withdrawal bleeding, Withdrawal bleed
Other	Anovulatory cycle, Menometrorrhagia, Menstrual disorder, Vaginal haemorrhage, Uterine haemorrhage, Abnormal uterine bleeding, Premature menarche, Retrograde menstruation, Delayed menarche, Bleeding anovulatory, Polymenorrhagia
Postmenopausal haemorrhage	Postmenopausal haemorrhage

MedDRA Medical Dictionary for Regulatory Activities, PT Preferred Term

The distribution of the 27145 events, based on the Menstrual disorder categories and event seriousness is presented in Table 52 below in descending order of frequency:

Table 52 Distribution of events based on Menstrual disorders categories and MedDRA PTs (n=27,145) reported with VAXZEVRIA

Menstrual disorder category MedDRA PTs	Serious AEs	Non-Serious AEs	Total
Heavy menstrual blood loss	**3116**	**3431**	**6547**
Heavy menstrual bleeding	3116	3431	6547
Amenorrhoea/oligomenorrhoea	**1688**	**3830**	**5518**
Amenorrhoea	363	920	1283
Menstruation delayed	1254	2589	3843
Oligomenorrhoea	71	321	392
Other	**1851**	**3527**	**5378**
Abnormal uterine bleeding	9	13	22
Anovulatory cycle	16	17	33
Bleeding anovulatory		1	1
Delayed menarche		2	2
Menometrorrhagia	20	56	76

Table 52 Distribution of events based on Menstrual disorders categories and MedDRA PTs (n=27,145) reported with VAXZEVRIA

Menstrual disorder category MedDRA PTs	Serious AEs	Non-Serious AEs	Total
Menstrual disorder	876	2362	3238
Polymenorrhagia		1	1
Premature menarche	4	13	17
Retrograde menstruation	1	4	5
Uterine haemorrhage	61	42	103
Vaginal haemorrhage	864	1016	1880
Irregular blood loss	**1443**	**3161**	**4604**
Menstruation irregular	1096	2299	3395
Polymenorrhoea	347	862	1209
Dysmenorrhoea	**1240**	**1144**	**2384**
Dysmenorrhoea	1095	947	2042
Menstrual discomfort	13	76	89
Premenstrual dysphoric disorder	5	5	10
Premenstrual headache	9	9	18
Premenstrual pain	66	48	114
Premenstrual syndrome	52	59	111
Intermenstrual blood loss	**402**	**1155**	**1557**
Intermenstrual bleeding	402	1155	1557
Less menstrual blood loss	**177**	**387**	**564**
Hypomenorrhoea	177	387	564
Postmenopausal haemorrhage	**262**	**292**	**554**
Postmenopausal haemorrhage	262	292	554
Withdrawal blood loss abnormal	**13**	**26**	**39**
Abnormal withdrawal bleeding	5	14	19
Withdrawal bleed	8	12	20
Grand Total	**10192**	**16953**	**27145**

MedDRA Medical Dictionary for Regulatory Activities, PT Preferred Term

- Out of 27145 events, 10192 (37.5%) of the events were serious; 617 (6.1%) of them medically confirmed and 9575(93.9%) were consumer reports); reported seriousness criteria were medically important event (9,493 [85.2%]), disability (1,026 [9.2%]), hospitalization (487 [4.4%]), congenital anomaly (36 [0.3%]), life threatening (91 [0.8%]) and/or the event reportedly resulted in death (2 [0.01%]). An event may have met more than one criterion for seriousness. The remaining 16953 (62.5%) events were non-serious (937 medically confirmed and 16016 consumer reports).

- Heavy menstrual blood loss (24%) was the most reported menstrual disorder followed by amenorrhoea/oligomenorrhoea (20%) and other (20%). These 3 menstrual disorders category are discussed in detail below. Although the reported menstrual events were categorized in 9 categories, many of the reports contained multiple menstrual events and fell into multiple categories. In 16421 (78.2%) only one menstrual disorder event was reported, in 3587 reports (17.1%) 2 menstrual disorder event and in 986 (4.7%) reports 3 to 5 menstrual disorder event was reported.

Events categories by age group are presented in below Table 53 the age group of 35-44 was the largest group (31.5%) followed by 25-34 (23.1%) and 45-54 (22.1%). Postmenopausal haemorrhage was reported in 45-54 (42.4%) followed by 55-64 (39%) years age group.

Table 53 Menstrual disorder category events by age group

Menstrual disorders categories	<25 yrs N (%)	25-34 N (%)	35-44 N (%)	45-54 N (%)	55-64 N (%)	>65 N (%)	Age unknown N (%)	Total N (%)
Heavy menstrual blood loss	274 (4.2)	1246 (19)	2221 (33.9)	1779 (27.2)	127 (1.9)	11 (0.2)	889 (13.6)	6547 (100)
Amenorrhoea/oligomenorrhoea	376 (6.8)	1504 (27.3)	1648 (29.9)	1053 (19.1)	34 (0.6)	9 (0.2)	894 (16.2)	5518 (100)
Other	285 (5.3)	1139 (21.3)	1592 (29.7)	1244 (23.2)	320 (6)	94 (1.8)	682 (12.7)	5356 (100)
Irregular blood loss	258 (5.6)	1163 (25.1)	1603 (34.7)	886 (19.2)	45 (1)	3 (0.1)	668 (14.4)	4626 (100)
Dysmenorrhoea	205 (8.6)	682 (28.6)	725 (30.4)	383 (16.1)	57 (2.4)	8 (0.3)	324 (13.6)	2384 (100)
Intermenstrual blood loss	98 (6.3)	380 (24.4)	531 (34.1)	330 (21.2)	51 (3.3)	12 (0.8)	155 (10)	1557 (100)
Less menstrual blood loss	24 (4.3)	139 (24.6)	204 (36.2)	108 (19.1)	18 (3.2)	1 (0.2)	70 (12.4)	564 (100)
Postmenopausal haemorrhage	2 (0.4)	1 (0.2)	15 (2.7)	235 (42.4)	216 (39)	32 (5.8)	53 (9.6)	554 (100)
Withdrawal blood loss abnormal	8 (20.5)	11 (28.2)	7 (17.9)	4 (10.3)	3 (7.7)	(0)	6 (15.4)	39 (100)
Grand Total	**1530 (5.6)**	**6265 (23.1)**	**8546 (31.5)**	**6022 (22.2)**	**871 (3.2)**	**170 (0.6)**	**3741 (13.8)**	**27145 (100)**

Time to onset of menstrual disorder events and by age group is presented in Table 54. In 26% of the events the time to onset after vaccination was unknown; among the events with TTO most of them (76%) occurred within 28 days post vaccination (0-2 days: 29%; 3-7 days: 17%; 8-14 days: 14% and 15-28 days: 17%).

Table 54 Time to onset for menstrual disorder events by age group

Menstrual disorder category/ Age group	0-2 Days N (%)	3-7 days N (%)	8-14 days N (%)	15-28 days N (%)	> 29 days N (%)	Unk N (%)	Grand Total N (%)
Heavy menstrual blood loss	1326 (20.3)	935 (14.3)	659 (10.1)	862 (13.2)	1153 (17.6)	1612 (24.6)	6547 (100)
Age - <25 Yrs	53 (19.3)	31 (11.3)	31 (11.3)	34 (12.4)	62 (22.6)	63 (23)	274 (100)
Age – 25-34 Yrs	247 (19.8)	148 (11.9)	117 (9.4)	181 (14.5)	236 (18.9)	317 (25.4)	1246 (100)
Age – 35-44 Yrs	438 (19.7)	361 (16.3)	243 (10.9)	305 (13.7)	405 (18.2)	469 (21.1)	2221 (100)
Age – 45-54 Yrs	431 (24.2)	300 (16.9)	186 (10.5)	228 (12.8)	312 (17.5)	322 (18.1)	1779 (100)
Age – 55-64 Yrs	26 (20.5)	13 (10.2)	11 (8.7)	21 (16.5)	24 (18.9)	32 (25.2)	127 (100)
Age - 65+ Yrs	(0)	3 (27.3)	(0)	(0)	4 (36.4)	4 (36.4)	11 (100)
Age Unk	131 (14.7)	79 (8.9)	71 (8)	93 (10.5)	110 (12.4)	405 (45.6)	889 (100)
Amenorrhoea/oligomenorrhoea	1037 (18.8)	475 (8.6)	548 (9.9)	725 (13.1)	959 (17.4)	1774 (32.1)	5518 (100)
Age - <25 Yrs	80 (21.3)	32 (8.5)	27 (7.2)	49 (13)	63 (16.8)	125 (33.2)	376 (100)
Age – 25-34 Yrs	290 (19.3)	129 (8.6)	156 (10.4)	187 (12.4)	314 (20.9)	428 (28.5)	1504 (100)
Age – 35-44 Yrs	310 (18.8)	165 (10)	177 (10.7)	249 (15.1)	309 (18.8)	438 (26.6)	1648 (100)
Age – 45-54 Yrs	234 (22.2)	108 (10.3)	119 (11.3)	141 (13.4)	197 (18.7)	254 (24.1)	1053 (100)
Age – 55-64 Yrs	5 (14.7)	1 (2.9)	4 (11.8)	5 (14.7)	3 (8.8)	16 (47.1)	34 (100)
Age - 65+ Yrs	(0)	(0)	(0)	(0)	1 (11.1)	8 (88.9)	9 (100)
Age Unk	118 (13.2)	40 (4.5)	65 (7.3)	94 (10.5)	72 (8.1)	505 (56.5)	894 (100)

Table 54 Time to onset for menstrual disorder events by age group

Menstrual disorder category/ Age group	0-2 Days N (%)	3-7 days N (%)	8-14 days N (%)	15-28 days N (%)	> 29 days N (%)	Unk N (%)	Grand Total N (%)
Other	1372 (25.6)	693 (12.9)	499 (9.3)	612 (11.4)	858 (16)	1322 (24.7)	5356 (100)
Age - <25 Yrs	69 (24.2)	37 (13)	25 (8.8)	31 (10.9)	50 (17.5)	73 (25.6)	285 (100)
Age – 25-34 Yrs	287 (25.2)	117 (10.3)	110 (9.7)	142 (12.5)	208 (18.3)	275 (24.1)	1139 (100)
Age – 35-44 Yrs	421 (26.4)	216 (13.6)	147 (9.2)	212 (13.3)	256 (16.1)	340 (21.4)	1592 (100)
Age – 45-54 Yrs	374 (30.1)	189 (15.2)	125 (10)	127 (10.2)	192 (15.4)	237 (19.1)	1244 (100)
Age – 55-64 Yrs	66 (20.6)	45 (14.1)	37 (11.6)	34 (10.6)	68 (21.3)	70 (21.9)	320 (100)
Age - 65+ Yrs	18 (19.1)	9 (9.6)	10 (10.6)	5 (5.3)	19 (20.2)	33 (35.1)	94 (100)
Age Unk	137 (20.1)	80 (11.7)	45 (6.6)	61 (8.9)	65 (9.5)	294 (43.1)	682 (100)
Irregular blood loss	909 (19.6)	626 (13.5)	503 (10.9)	588 (12.7)	838 (18.1)	1162 (25.1)	4626 (100)
Age - <25 Yrs	56 (21.7)	32 (12.4)	19 (7.4)	31 (12)	57 (22.1)	63 (24.4)	258 (100)
Age – 25-34 Yrs	220 (18.9)	134 (11.5)	124 (10.7)	144 (12.4)	251 (21.6)	290 (24.9)	1163 (100)
Age – 35-44 Yrs	339 (21.1)	245 (15.3)	182 (11.4)	240 (15)	290 (18.1)	307 (19.2)	1603 (100)
Age – 45-54 Yrs	201 (22.7)	142 (16)	116 (13.1)	104 (11.7)	148 (16.7)	175 (19.8)	886 (100)
Age – 55-64 Yrs	4 (8.9)	7 (15.6)	6 (13.3)	5 (11.1)	16 (35.6)	7 (15.6)	45 (100)
Age - 65+ Yrs	1 (33.3)	(0)	(0)	1 (33.3)	(0)	1 (33.3)	3 (100)
Age Unk	88 (13.2)	66 (9.9)	56 (8.4)	63 (9.4)	76 (11.4)	319 (47.8)	668 (100)
Dysmenorrhoea	441 (18.5)	293 (12.3)	260 (10.9)	329 (13.8)	437 (18.3)	624 (26.2)	2384 (100)

Table 54 Time to onset for menstrual disorder events by age group

Menstrual disorder category/ Age group	0-2 Days N (%)	3-7 days N (%)	8-14 days N (%)	15-28 days N (%)	> 29 days N (%)	Unk N (%)	Grand Total N (%)
Age - <25 Yrs	30 (14.6)	24 (11.7)	18 (8.8)	37 (18)	42 (20.5)	54 (26.3)	205 (100)
Age – 25-34 Yrs	132 (19.4)	76 (11.1)	70 (10.3)	100 (14.7)	139 (20.4)	165 (24.2)	682 (100)
Age – 35-44 Yrs	132 (18.2)	92 (12.7)	85 (11.7)	106 (14.6)	154 (21.2)	156 (21.5)	725 (100)
Age – 45-54 Yrs	80 (20.9)	66 (17.2)	56 (14.6)	45 (11.7)	53 (13.8)	83 (21.7)	383 (100)
Age – 55-64 Yrs	18 (31.6)	6 (10.5)	7 (12.3)	5 (8.8)	11 (19.3)	10 (17.5)	57 (100)
Age - 65+ Yrs	(0)	2 (25)	2 (25)	(0)	(0)	4 (50)	8 (100)
Age Unk	49 (15.1)	27 (8.3)	22 (6.8)	36 (11.1)	38 (11.7)	152 (46.9)	324 (100)
Intermenstrual blood loss	438 (28.1)	248 (15.9)	161 (10.3)	164 (10.5)	244 (15.7)	302 (19.4)	1557 (100)
Age - <25 Yrs	21 (21.4)	16 (16.3)	14 (14.3)	12 (12.2)	15 (15.3)	20 (20.4)	98 (100)
Age – 25-34 Yrs	101 (26.6)	58 (15.3)	36 (9.5)	46 (12.1)	72 (18.9)	67 (17.6)	380 (100)
Age – 35-44 Yrs	165 (31.1)	82 (15.4)	54 (10.2)	52 (9.8)	91 (17.1)	87 (16.4)	531 (100)
Age – 45-54 Yrs	104 (31.5)	62 (18.8)	37 (11.2)	33 (10)	44 (13.3)	50 (15.2)	330 (100)
Age – 55-64 Yrs	15 (29.4)	6 (11.8)	8 (15.7)	5 (9.8)	12 (23.5)	5 (9.8)	51 (100)
Age - 65+ Yrs	3 (25)	3 (25)	2 (16.7)	2 (16.7)	2 (16.7)	(0)	12 (100)
Age Unk	29 (18.7)	21 (13.5)	10 (6.5)	14 (9)	8 (5.2)	73 (47.1)	155 (100)
Less menstrual blood loss	142 (25.2)	67 (11.9)	59 (10.5)	69 (12.2)	99 (17.6)	128 (22.7)	564 (100)

Table 54 Time to onset for menstrual disorder events by age group

Menstrual disorder category/ Age group	0-2 Days N (%)	3-7 days N (%)	8-14 days N (%)	15-28 days N (%)	> 29 days N (%)	Unk N (%)	Grand Total N (%)
Age - <25 Yrs	4 (16.7)	5 (20.8)	2 (8.3)	2 (8.3)	5 (20.8)	6 (25)	24 (100)
Age – 25-34 Yrs	34 (24.5)	15 (10.8)	13 (9.4)	13 (9.4)	22 (15.8)	42 (30.2)	139 (100)
Age – 35-44 Yrs	57 (27.9)	28 (13.7)	25 (12.3)	32 (15.7)	31 (15.2)	31 (15.2)	204 (100)
Age – 45-54 Yrs	35 (32.4)	12 (11.1)	9 (8.3)	13 (12)	27 (25)	12 (11.1)	108 (100)
Age – 55-64 Yrs	3 (16.7)	1 (5.6)	3 (16.7)	4 (22.2)	4 (22.2)	3 (16.7)	18 (100)
Age - 65+ Yrs	(0)	(0)	(0)	(0)	(0)	1 (100)	1 (100)
Age Unk	9 (60)	6 (60)	7 (60)	5 (60)	10 (60)	33 (60)	70 (60)
Postmenopausal haemorrhage	90 (16.2)	68 (12.3)	54 (9.7)	69 (12.5)	136 (24.5)	137 (24.7)	554 (100)
Age - <25 Yrs	(0)	(0)	(0)	1 (50)	(0)	1 (50)	2 (100)
Age – 25-34 Yrs	(0)	(0)	1 (100)	(0)	(0)	(0)	1 (100)
Age – 35-44 Yrs	7 (46.7)	1 (6.7)	1 (6.7)	2 (13.3)	2 (13.3)	2 (13.3)	15 (100)
Age – 45-54 Yrs	40 (17)	21 (8.9)	27 (11.5)	28 (11.9)	63 (26.8)	56 (23.8)	235 (100)
Age – 55-64 Yrs	36 (16.7)	39 (18.1)	19 (8.8)	28 (13)	50 (23.1)	44 (20.4)	216 (100)
Age - 65+ Yrs	3 (9.4)	(0)	1 (3.1)	7 (21.9)	9 (28.1)	12 (37.5)	32 (100)
Age Unk	4 (7.5)	7 (13.2)	5 (9.4)	3 (5.7)	12 (22.6)	22 (41.5)	53 (100)
Withdrawal blood	11 (28.2)	6 (15.4)	5 (12.8)	4 (10.3)	6 (15.4)	7 (17.9)	39 (100)

Table 54 Time to onset for menstrual disorder events by age group

Menstrual disorder category/ Age group	0-2 Days N (%)	3-7 days N (%)	8-14 days N (%)	15-28 days N (%)	> 29 days N (%)	Unk N (%)	Grand Total N (%)
loss abnormal							
Age - <25 Yrs	3 (37.5)	1 (12.5)	2 (25)	1 (12.5)	1 (12.5)	(0)	8 (100)
Age – 25-34 Yrs	3 (27.3)	2 (18.2)	(0)	1 (9.1)	3 (27.3)	2 (18.2)	11 (100)
Age – 35-44 Yrs	1 (14.3)	1 (14.3)	2 (28.6)	1 (14.3)	1 (14.3)	1 (14.3)	7 (100)
Age – 45-54 Yrs	1 (25)	1 (25)	1 (25)	(0)	1 (25)	(0)	4 (100)
Age – 55-64 Yrs	1 (33.3)	(0)	(0)	1 (33.3)	(0)	1 (33.3)	3 (100)
Age Unk	2 (33.3)	1 (16.7)	(0)	(0)	(0)	3 (50)	6 (100)
Grand Total	**5766 (21.2)**	**3411 (12.6)**	**2748 (10.1)**	**3422 (12.6)**	**4730 (17.4)**	**7068 (26)**	**27145 (100)**

Co-reported AEs

In 10,382 (49.5%) case reports, the menstrual disorder event was reported without any co-reported AEs. In the remaining cases there were 34034 co-reported AEs along with menstrual disorder events. The events most commonly co-reported with Menstrual disorders are presented in Table 55. The most co-reported AEs were systemic AEs such as, headache, fatigue, pyrexia, chills, nausea, and myalgia. Some notable frequently co-reported ADRs are menstruation symptoms such as breast complaints (breast pain (149), breast swelling (27), breast tenderness (47), breast discomfort (10)), mood swings (71), depressed mood (95) and hot flushes (168). The latter can be related to menopause as well.

Table 55 Distribution of most frequently co-reported events (n ≥ 100) in case reports of Menstrual disorders

Adverse events (PT)	Number of events	Percentage (%)
Headache	2613	7.7
Fatigue	2143	6.3
Pyrexia	1925	5.7
Chills	1235	3.6
Nausea	1054	3.1

Table 55 Distribution of most frequently co-reported events (n ≥ 100) in case reports of Menstrual disorders

Adverse events (PT)	Number of events	Percentage (%)
Myalgia	1021	3
Haemorrhage	867	2.5
Dizziness	770	2.3
Malaise	761	2.2
Pain	756	2.2
Pain in extremity	689	2
Arthralgia	679	2
Muscle spasms	570	1.7
Injection site pain	434	1.3
Abdominal pain	389	1.1
Migraine	370	1.1
COVID-19	337	1
Vomiting	316	0.9
Back pain	308	0.9
Asthenia	287	0.8
Diarrhoea	286	0.8
Abdominal pain upper	286	0.8
Influenza like illness	269	0.8
Paraesthesia	268	0.8
Influenza	255	0.7
Dyspnoea	255	0.7
Maternal exposure during breast feeding	241	0.7
Epistaxis	231	0.7
Palpitations	208	0.6
Hyperhidrosis	208	0.6
Abdominal distension	194	0.6
Lymphadenopathy	185	0.5
Limb discomfort	185	0.5
Chest pain	181	0.5
Contusion	169	0.5
Rash	168	0.5
Hot flush	168	0.5
Hypoaesthesia	156	0.5
Decreased appetite	152	0.4
Tremor	151	0.4
Breast pain	149	0.4

Table 55 Distribution of most frequently co-reported events (n ≥ 100) in case reports of Menstrual disorders

Adverse events (PT)	Number of events	Percentage (%)
Thrombosis	146	0.4
Pruritus	138	0.4
Vaccination site pain	130	0.4
Anxiety	124	0.4
Feeling abnormal	122	0.4
Vision blurred	120	0.4
Lethargy	120	0.4
COVID-19 immunisation	113	0.3
Injection site swelling	111	0.3
Peripheral swelling	102	0.3
Insomnia	101	0.3

Concomitant medication

In 5699 out of 20994 cases there was at least 1 concomitant medication reported. In total there were 2242 drugs reported as concomitant. Table 56 shows an overview of the 50 most reported concomitant medication. The most common reported concomitant medications were paracetamol, sertraline, ibuprofen, levothyroxine and citalopram.

Table 56 Fifty most reported concomitant medication

Concomitant medication	Number of reports
PARACETAMOL	513
SERTRALINE	304
IBUPROFEN	285
LEVOTHYROXINE	274
CITALOPRAM	201
MIRENA	141
DESOGESTREL	122
AMITRIPTYLINE	116
TRANEXAMIC ACID	106
CERAZETTE	106
INFLUENZA VIRUS	105
RAMIPRIL	104
OMEPRAZOLE	104
FLUOXETINE	98
NAPROXEN	96
PROPRANOLOL	91

Table 56 Fifty most reported concomitant medication

Concomitant medication	Number of reports
FOLIC ACID	90
CERELLE	90
VENTOLIN	87
VITAMIN D	82
PROGESTERONE	78
SALBUTAMOL	77
AMLODIPINE	75
OMEPRAZOL	74
FEXOFENADINE	71
METFORMIN	70
FOSTAIR	68
IRON	66
THYROXINE	62
UTROGESTAN	58
SERTRALIN	58
LAMOTRIGINE	58
CLENIL MODULITE	58
LANSOPRAZOLE	57
CO-CODAMOL	53
CODEINE	53
PREGABALIN	51
FEMOSTON	50

Medical history

In 11201 out of 20994 cases there was at least 1 medical history was reported. In total there were 995 medical history reported. Table 57 shows an overview of the 50 most reported medical history. The most common reported medical history were Suppressed lactation, Suspected COVID-19, Pregnancy, Disease risk factor (unspecified), Asthma, and Immunodeficiency. Reports with medical history of suppressed lactation were received via MHRA, however based on communications with MHRA, suppressed lactation from medical history is being deleted.

Table 57 50 most reported medical history

Medical history	Number of reports
Suppressed lactation	7049
Suspected COVID-19	1717
Pregnancy	626

Table 57 50 most reported medical history

Medical history	Number of reports
Disease risk factor	488
Asthma	353
Immunodeficiency	335
Clinical trial participant	277
Breast feeding	248
COVID-19	176
Endometriosis	172
Steroid therapy	165
Migraine	135
Hypersensitivity	122
Polycystic ovaries	103
Rheumatoid arthritis	103
Menopause	99
Hypothyroidism	99
Anxiety	93
Fibromyalgia	91
Heavy menstrual bleeding	87
Seasonal allergy	86
Inflammatory bowel disease	82
Depression	82
Headache	80
Hypertension	77
Fatigue	75
Drug hypersensitivity	71
Pain	68
Haemorrhage	55
Uterine leiomyoma	53
Non-tobacco user	51
Coeliac disease	50
Abortion spontaneous	50
Diabetes mellitus	50
Anaemia	50

Heavy menstrual blood loss

A total of 6547 (24% out of 27145 events) heavy menstrual blood loss cases were reported and most of them (95%) were consumer reports, see Table 58. Similar to overall menstrual

disorders combined, the age group of 35-44 was the largest group (34%) followed by 45-54 (27%) and 25-34 years (19%). Most frequently reported MedDRA LLT was Heavy periods (2753), followed by Heavy menstrual bleeding (673), Bleeding menstrual heavy (571), Menorrhagia (420), and Prolonged heavy periods (403). For most women the duration of the bleeding was either unknown or the woman was not recovered yet (46%). However, in the medically confirmed reports 48% heavy menstrual blood loss events had resolved. Out of 1046 events with a known duration, 760 (73%) had a bleeding duration of less than 14 days. Additionally, no trend was observed in terms of concomitant medication or medical history specific to heavy menstrual blood loss events compared to overall menstrual disorder events.

Other menstrual disorder category events co-reported with heavy menstrual blood loss cases were Dysmenorrhoea (941), Irregular blood loss (922), Other (686), Amenorrhoea/oligomenorrhoea (641), and Intermenstrual blood loss (232).

Table 58 Overview of heavy menstrual blood loss reports after VAXZEVRIA

Heavy menstrual blood loss	Age - <25 Yrs	Age – 25-34 Yrs	Age – 35-44 Yrs	Age – 45-54 Yrs	Age – 55-64 Yrs	Age - 65+ Yrs	Age Unk	Grand Total
All events	274	1246	2221	1779	127	11	889	6547
Events by report type (consumer report & medically confirmed) and seriousness								
Consumer report	256	1168	2098	1708	121	10	864	6225
Serious AEs	93	510	1031	882	56	8	456	3036
Non-serious AEs	163	658	1067	826	65	2	408	3189
Medically confirmed	18	78	123	71	6	1	25	322
Serious AEs	4	24	29	13	2		8	80
Non-serious AEs	14	54	94	58	4	1	17	242
Outcome of heavy menstrual blood loss events by report type								
Consumer report	256	1168	2098	1708	121	10	864	6225
Not recovered	133	586	1027	710	29	2	417	2904
Recovered	50	241	460	484	49	2	175	1461
Recovered with sequelae	6	33	54	40	2	1	23	159
Recovering	31	151	286	273	27	2	109	879
Unknown	36	157	271	201	14	3	140	822
Medically confirmed	18	78	123	71	6	1	25	322
Not recovered	10	36	38	17	1		8	110
Recovered	2	17	54	33	2	1	6	115

Table 58 Overview of heavy menstrual blood loss reports after VAXZEVRIA

Heavy menstrual blood loss	Age - <25 Yrs	Age – 25-34 Yrs	Age – 35-44 Yrs	Age – 45-54 Yrs	Age – 55-64 Yrs	Age - 65+ Yrs	Age Unk	Grand Total
Recovered with sequelae		3						3
Recovering	3	11	9	9	2		3	37
Unknown	3	11	22	12	1		8	57

Amenorrhoea/oligomenorrhoea

A total of 5518 (20% out of 27145 events) amenorrhoea/oligomenorrhoea cases were reported and most of them (95%) were consumer reports, see Table 59. Similar to overall menstrual disorders combined, the age group of 35-44 was the largest group (30%) followed by 25-34 (27%) and 45-54 (19%) years. Most frequently reported MedDRA LLT was Late period (1636), Delayed period (1294), Absence of menstruation (850), Menstruation delayed (692), Menstrual cycle prolonged (362), and Amenorrhea (256). The majority of the events (52%) had not recovered at the time of reporting, 20% did resolve, 2% resolved with sequalae, and 11% of the events were resolving at the time of reporting. In 313 (46%) events of amenorrhoea/oligomenorrhoea out of 545 events, the reported duration was longer than 14 days. A total 230 of the women with amenorrhoea/oligomenorrhoea had history of pregnancy, 37 were pregnant at the time of vaccination or after vaccination, 64 women had history of breast feeding, 37 and 33 women had history of endometriosis and polycystic ovaries respectively.

Table 59 Overview of Amenorrhoea/oligomenorrhoea reports after VAXZEVRIA

Amenorrhoea/oligomenorrhoea	Age - <25 Yrs	Age – 25-34 Yrs	Age – 35-44 Yrs	Age – 45-54 Yrs	Age – 55-64 Yrs	Age - 65+ Yrs	Age Unk	Grand Total
All events	376	1504	1648	1053	34	9	894	5518
Events by report type (consumer report & medically confirmed) and seriousness								
Consumer report	345	1421	1577	1017	31	9	862	5262
Serious AEs	98	469	482	287	13	6	282	1637
Non-serious AEs	247	952	1095	730	18	3	580	3625
Medically confirmed	31	83	71	36	3		32	256
Serious AEs	9	17	15	2			8	51

Table 59 Overview of Amenorrhoea/oligomenorrhoea reports after VAXZEVRIA

Amenorrhoea/oligomenorrhoea	Age - <25 Yrs	Age – 25-34 Yrs	Age – 35-44 Yrs	Age – 45-54 Yrs	Age – 55-64 Yrs	Age - 65+ Yrs	Age Unk	Grand Total
Non-serious AEs	22	66	56	34	3		24	205
Outcome of Amenorrhoea/oligomenorrhoea events by report type								
Consumer report	345	1421	1577	1017	31	9	862	5262
Not recovered	205	785	787	518	9		468	2772
Recovered	51	269	326	231	8	3	161	1049
Recovered with sequelae	12	25	24	13			10	84
Recovering	32	145	202	121	6	3	90	599
Unknown	45	197	238	134	8	3	133	758
Medically confirmed	31	83	71	36	3		32	256
Not recovered	13	40	32	14			15	114
Recovered	3	17	21	17	1		4	63
Recovered with sequelae	1						1	2
Recovering	4	10	3	2	1		9	29
Unknown	10	16	15	3	1		3	48

Other

A total of 5356 (20% out of 27145 events) other menstrual disorder events were reported and most of them (92%) were consumer reports, see Table 60. Similar to overall menstrual disorders combined, the age group of 35-44 was the largest group (30%) followed by 45-54 (23%) and 25-34 (21%) years. Most frequently reported MedDRA PTs was Menstrual disorder (3238), Vaginal haemorrhage (1880), Uterine haemorrhage (103), Menometrorrhagia (76), and Anovulatory cycle (33). Most of the events (42%) had not recovered at the time of reporting, however 41% were resolved/resolving/resolved with sequalae. Out of 793 events with a known duration, 582 (73.4%) had resolved within 14 days of onset. A total 139 of the women with other menstrual disorder events had history of pregnancy, 66 were pregnant at the time of vaccination or after vaccination, 57 women had history of breast feeding, 38, 27 and 24 women had history of endometriosis, menopause and polycystic ovaries respectively.

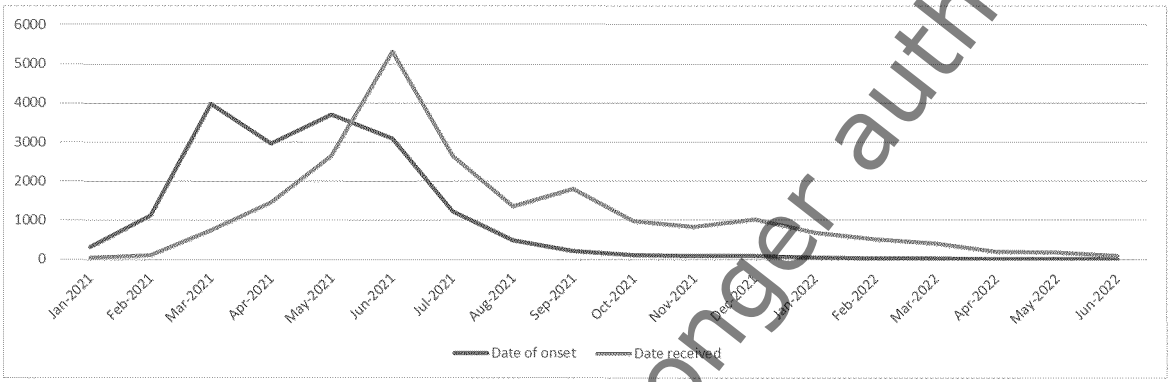
Table 60 Overview of other menstrual disorder reports after VAXZEVRIA

other menstrual disorder	Age - <25 Yrs	Age – 25-34 Yrs	Age – 35-44 Yrs	Age – 45-54 Yrs	Age – 55-64 Yrs	Age - 65+ Yrs	Age Unk	Grand Total
All events	285	1139	1592	1244	320	94	682	5356
Events by report type (consumer report & medically confirmed) and seriousness								
Consumer report	260	1045	1463	1169	298	77	628	4940
Serious AEs	60	298	475	470	129	42	241	1715
Non-serious AEs	200	747	988	699	169	35	387	3225
Medically confirmed	25	94	129	75	22	17	54	416
Serious AEs	11	33	30	19	8	8	18	127
Non-serious AEs	14	61	99	56	14	9	36	289
Outcome of other menstrual disorder events by report type								
Consumer report	260	1045	1463	1169	298	77	628	4940
Not recovered				1				1
Recovered	125	499	654	496	110	15	256	2155
Recovered with sequelae	60	227	310	348	110	33	129	1217
Recovering	5	22	19	18	5	4	7	80
Unknown	34	127	212	175	36	14	86	684
Medically confirmed	36	170	268	131	37	11	150	803
Not recovered	25	94	129	75	22	17	54	416
Recovered	10	24	35	24	3	1	11	108
Recovered with sequelae	6	35	44	27	9	9	14	144
Recovering	1	2	1	2		1	1	8
Unknown	4	17	18	6	5	2	9	61

Menstrual disorder cases over time

Anecdotal reports of the COVID-19 vaccines altering women's menstrual cycle have been circulating on the internet since the beginning of 2021. Menstrual disorder case reports were compared based on the case onset date and AstraZeneca initial receipt date. Figure 1 shows clear peaks for reports received date at times when menstrual disorders were discussed in the media (June/July 2021 to August 2021 and September/October 2021). However, the start dates of the menstrual disorder events shows no obvious peaks and seems to correlate with the vaccination program.

Figure 1 Peaks of reports received at times when Menstrual Disorders were discussed in media



The outcome based on the Menstrual disorder categories has been presented in Table 61. A total of 10012 events (37%) out of 27145, had resolved/resolved with sequelae/resolving. Overall, most women had not recovered at time of reporting (12974 events [48%]). However, in the medically confirmed reports 46% of the events were resolved/resolved with sequalae/resolving at the time of reporting.

Table 61 Outcome of the Menstrual disorder event categories

Outcome	Died N(%)	Not recovered N(%)	Recovered N(%)	Recovered with sequelae N(%)	Recovering N(%)	Unknown N(%)	Grand Total N(%)
Heavy menstrual blood loss	0 (0)	3014 (46)	1576 (24.1)	162 (2.5)	916 (14)	879 (13.4)	6547 (100)
Amenorrhoea/ oligomenorrhoea	0 (0)	2886 (52.3)	1112 (20.2)	86 (1.6)	628 (11.4)	806 (14.6)	5518 (100)
Other	1 (0)	2263 (42.3)	1361 (25.4)	88 (1.6)	745 (13.9)	898 (16.8)	5356 (100)
Irregular blood loss	0 (0)	2545 (55)	748 (16.2)	58 (1.3)	514 (11.1)	761 (16.5)	4626 (100)
Dysmenorrhoea	0 (0)	1164 (48.8)	454 (19)	57 (2.4)	344 (14.4)	365 (15.3)	2384 (100)
Intermenstrual blood loss	1 (0.1)	644 (41.4)	461 (29.6)	23 (1.5)	193 (12.4)	235 (15.1)	1557 (100)

Table 61 Outcome of the Menstrual disorder event categories

Outcome	Died N(%)	Not recovered N(%)	Recovered N(%)	Recovered with sequelae N(%)	Recovering N(%)	Unknown N(%)	Grand Total N(%)
Less menstrual blood loss	0 (0)	255 (45.2)	140 (24.8)	9 (1.6)	58 (10.3)	102 (18.1)	564 (100)
Postmenopausal haemorrhage	0 (0)	190 (34.3)	194 (35)	7 (1.3)	64 (11.6)	99 (17.9)	554 (100)
Withdrawal blood loss abnormal	0 (0)	13 (2.3)	10 (1.8)	(0)	4 (0.7)	12 (2.2)	39 (7)
Grand Total	**2 (0)**	**12974 (47.8)**	**6056 (22.3)**	**490 (1.8)**	**3466 (12.8)**	**4157 (15.3)**	**27145 (100)**

- Amongst 6546 events with reported outcome 'recovered' or 'recovered with sequelae,' the event duration was reported in 3559 [54%] events. The median duration of events 7 days (0-464 days), while 2032 (57%) had resolved within 8 days of onset.

Events with fatal outcome

Of the 27145 events of Menstrual disorder reported, 2 events (0.01%) in 2 cases were reported with fatal outcome cumulatively through DLP 28 June 2022, and both were consumer reports.

[redacted]: A 47 years old vaccinee with a medical history of asthma received VAXZEVRIA on an unknown date. At an unspecified time after vaccination, the vaccinee experienced pulmonary embolism which had a fatal outcome. Menstrual disorder was reported with no time to onset and with limited information.

AstraZeneca Comment: This report lacks information on the nature of the menstrual disorder, patient medical history including menstrual history, contraceptives or intrauterine devices used, platelet count, smoking, immobilisation and baseline health condition before the vaccination, etiological, diagnostic work up (clotting factors, coagulation panel, CT-angiogram, chest x-ray and CT-scan, full gynaecologic work up) and autopsy report. Death was attributed to pulmonary embolism and the TTO is not provided.

[redacted]: Female vaccinee of 41 years of age with a history of diabetes who had being vaccinated with VAXZEVRIA in February 2022. On 11 March 2022, approximately a month after receiving VAXZEVRIA, the patient experienced intermenstrual bleeding reported as spotting for one month, subsequently followed by blood clots in an unspecified site and died. The patient's previous history of any blood disorders is unknown. The other reported events included fatigue and abdominal pain. The cause of death was intermenstrual bleeding and thrombosis.

[redacted]: Female vaccinee of 41 years of age with a history of diabetes who had being vaccinated with VAXZEVRIA in February 2022. On 11 March 2022, approximately a month after receiving VAXZEVRIA, the patient experienced intermenstrual bleeding reported as spotting for one month, subsequently followed by blood clots in an unspecified site and died. The patient's previous history of any blood disorders is unknown. The other reported events included fatigue and abdominal pain. The cause of death was intermenstrual bleeding and thrombosis.

AstraZeneca Comment: There is limited information about the vaccinee's medical history including menstrual history, use of hormonal preparations such as contraceptives, smoking, baseline health status site of thrombosis, platelet count, anti-PF4, contraceptives, which precludes performing a complete assessment.

Rechallenge / Recurrence case reports

Cumulatively, 1 (0.005%) out of 20994 case reports of menstrual disorder had a rechallenge, the patient experienced abnormal uterine bleeding after the first dose, and a recurrence of abnormal uterine bleeding with the second dose of vaccination indicating potential recurrence/rechallenge. This case report was a medically confirmed report from regulatory source.

The report (case [redacted]) concerns a 45-year-old female of unknown ethnicity who experienced an unspecified abnormal uterine bleeding, 2 days after receiving first dose of VAXZEVRIA. The report described the re-administration of VAXZEVRIA (possibly dose 2) on an unknown date and the event of abnormal (unspecified) uterine bleeding recurred. There was no information on time to onset for the re-occurrence. At the time of reporting, the event was said to be ongoing.

AstraZeneca comment: In this report, there is limited information on the nature of the abnormal uterine bleeding for both episodes, patient medical history including menstrual history, gynaecologic disorders such as uterine fibroids or polyps, concomitant medications such as hormonal contraception, intrauterine devices, physical or mental stress, etiologic and diagnostic examination including gynaecological assessment. Also, there is no information on the dose timing in regards to the vaccinee's menstrual cycle, and the time interval between 2 doses and whether the in-between menstrual cycles were normal. This lacking information precludes performing a complete causal assessment.

Literature

A cumulative literature search of the databases in Embase, InsightMeme and PubMed was conducted on 28 June 2022 within the period of 29 December 2021 – 28 June 2022, DLP as 28 June 2022, using the following search criteria: PT of Vaginal haemorrhage, Uterine haemorrhage, and post-menopausal haemorrhage.

On using the above search criteria, 32 articles were identified. Of these, 7 articles were considered relevant for further discussion. All the seven articles reported multiple COVID-19 vaccines.

Von Woon et al 2022 conducted a prospective observational study to determine whether COVID-19 vaccination affects menstrual bleeding. Study included 79 menstruating women who logged at least three consecutive cycles, during which time they each received at least one dose of COVID-19 vaccine which included Pfizer (65 [82.3%]), Moderna (11 [14%]) and AstraZeneca (3 [3.8%]).

A dose of the COVID-19 vaccine was associated with a delay to start of menstruation in the subsequent period in spontaneously cycling participants (2.3 days after dose 1; 1.3 days after dose 2). Periods in inter-dose cycles and post-vaccination cycles occurred with a mean of 0.3 days late and 0.47 days early, respectively; these values were not significantly different from the pre-vaccination average. No change to timing was detected in those on hormonal contraception. No significant change was noted in self-reported menstrual flow in the period or withdrawal bleed following vaccination, either in spontaneously cycling participants, or in those taking hormonal contraception. Also, authors detected no association between menstrual changes and other commonly reported side effects of vaccination, such as sore arm, fever, and fatigue.

AstraZeneca comment: This was a prospective study design and therefore reduces selection bias. However, the cohort of subjects was small (79 patients), and very few patients received the VAXZEVRIA vaccine (3 [3.8%]). There was a delay in start of menstruation reported in spontaneously cycling participants, however this delay rapidly reversed. No change was noted in self-reported menstrual flow in the period or withdrawal bleed or no association between menstrual changes and other commonly reported side effects of vaccination.

Laganà et al 2022 evaluated menstrual irregularities after the first and second doses of the COVID-19 vaccine in Italy. A survey was available only in Italian language for 30 days (10 September 2021 to 10 October 2021) and distributed by social media, LinkedIn, Facebook and Twitter. The results of the study have been presented in Table 62 below.

Table 62 Analysis of frequency, length, and quantity of the menstrual cycle after the administration of first and second dose of the vaccine, stratified for the type of vaccine by Laganà et al 2022

Type of Vaccine	Type of event					
	Alterations in the frequency of the subsequent menstrual cycle		Alteration in the length of the subsequent menstrual cycle		Alteration in the quantity of the subsequent menstrual flow	
	Dose 1	Dose 2	Dose 1	Dose 2	Dose 1	Dose 2
VAXZEVRIA (AstraZeneca)	6 (66.7%)	6 (75%)	5 (55.6%)	4 (50%)	6 (66.7%)	5 (62.5%)
Cominarty (Pfizer-BioNtech)	75 (57.1%)	59 (52.2%)	55 (41.4%)	48 (42.5%)	62 (47.4%)	52 (46.9%)
Spikevax (Moderna)	9 (47.4%)	11 (78.6%)	10 (52.6%)	6 (42.9%)	10 (52.6%)	8 (64.3%)
Janssen (Johnson & Johnson)	1 (33.3%)	NA	2 (66.7%)	NA	2 (66.7%)	NA

Overall conclusion as per author: Approximately 50% to 60% of reproductive-age women who received the first dose of the COVID-19 vaccine reported menstrual cycle irregularities, regardless of the type of administered vaccine. The occurrence of menstrual irregularities seems to be slightly higher (60% to 70%) after the second dose. Menstrual irregularities after both the first and second doses of the vaccine were found to self-resolve in approximately half the cases within 2 months.

AstraZeneca comment: Although in order to limit confounders, women with gynaecological and non-gynaecological diseases, undergoing hormonal and non-hormonal treatments, in perimenopause or menopause, as well as who had irregular menstrual cycle in the last 12 months before vaccine administration were excluded, recall bias is a significant limitation. Also, from the methodological point of view, there is no control group, so the report is aimed only to offer a description of what was observed, without any possibility to infer cause-effect. Therefore, the information from the study is too limited to confirm causality.

The next two articles have published results of self-reported cross-sectional studies.

Baena-García et al 2022 used retrospective online survey to describe the prevalence of perceived premenstrual and menstrual changes after COVID-19 vaccine administration in Spain from June to September 2021. A total of 14153 women (mean age 31.5 ± 9.3 years old) who had received the full course of vaccination at least three months earlier were included in this cross-sectional study. The most predominant menstrual changes were more menstrual bleeding (43%), more menstrual pain (41%), delayed menstruation (38%), fewer days of menstrual bleeding (34.5%), and shorter cycle length (32%). The study concluded that women vaccinated against COVID-19 usually perceive mild menstrual and premenstrual changes and future studies are warranted to clarify the physiological mechanisms behind these widely reported changes.

Muhaidat et al 2022 investigated the prevalence and impact of menstrual abnormalities after the COVID-19 vaccination among females residing within the Middle East and North Africa in a cross-sectional online self-administered survey during July and August 2021. A total of 2269 females were included in the study, with a mean age of 34.3 ± 8.5 years and 66.3% reported having menstrual symptoms post-vaccination, thereof 46.7% after the first dose. They majority of the participants received COMIRNATY (48.4%), SINOPHARM (35.3%) and VAXZEVRIA (13.4%). Vaccine type did not significantly influence the incidence of abnormalities ($p < 0.05$). Among the participants, 75.1% had regular menstrual cycles before taking the vaccine for the last year, and 24.9% had irregular menstrual cycles. About a third (29.7%) of the participants were smokers, and 6.7% had a history of coagulation disorders (including bleeding, blood clots, thrombocytopenia, or taking coagulation medication). Among patients who complained of post-vaccination menstrual abnormalities, 77.6% had no previous COVID-19 infection. When comparing menstrual abnormalities among those with a previous history of infection and those without a history of infection there was no significant associations with post-vaccination menstrual abnormalities ($p = 0.136$); it was found that 66.8% had menstrual abnormalities among those who did not have previous COVID-19 infection or symptoms suspected of COVID-19 infection and did not test. Similarly, 67.5% of

those with confirmed previous COVID-19 infection had menstrual abnormalities. The post-vaccination menstrual abnormalities were significantly associated with the severity of previous COVID-19 infection (p = 0.006). The author's concluded that the study showed a possible link between the COVID-19 vaccine and menstrual abnormalities that have impacted vaccinees' quality of life

AstraZeneca comment: The cross-sectional design of these two studies limits the ability to determine causal relationships. In addition, self-reported data extraction has an increased likelihood of recall bias or self-selection as those with menstrual disorders might be more interested in participating in the study. The use of an internet-based survey might have underrepresented or overrepresented certain target groups, especially older populations with limited internet access or technological awareness. Therefore, the information from these two studies is too limited to assess causality.

Rogers et al 2022 reported on the incidence of adverse events (AEs), reactogenicity symptoms, menstrual changes and overall self-rated improvement in health and well-being after COVID-19 vaccination. Participants had registered through the study website (VAC4COVID Study 2022), 16 265 had consented to participate in the study. Overall rates of women aged 18–59 reporting menstrual symptoms in the 12 weeks after vaccination were low (0.3%). Unadjusted percentages of reporting menstrual symptoms, including menstrual cycle alteration or intermenstrual bleeding (12 events), heavy bleeding (11) or painful periods/cramping (5) within 12 weeks of vaccination were higher after COMIRNATY vaccinations (0.6% after first dose, 0.4% after second dose) than after ChAdOx1 (0.2% after first dose, 0.2% after second dose). However, there was no difference between vaccines after adjusting for age in a proportional hazards model and overall cumulative rates were low. Participants reported these events as 25% mild, 54% moderate and 21% severe; none resulted in hospitalisation. The study provides reassuring data on low rates of AEs after COVID-19 vaccination.

Nazir et al 2022 conducted a literature review using digital databases to systematically identify the studies reporting any menstrual abnormalities after the COVID-19 vaccine. A total of 78,138 vaccinated females were included in this review from 14 studies. Of these, 39,759 (52.05%) had some form of a menstrual problem after vaccination. Menorrhagia, metrorrhagia, and polymenorrhea were the most observed problems and the overall study-level rate of menstrual abnormality ranged from 0.83% to 90.9%. Age, history of pregnancy, systemic side-effects of COVID-19, smoking, and second dose of COVID-19 vaccine were predictors of menstrual problems after vaccination. Most of the cross-sectional studies reported in literature were unable to report causal relationship between menstrual irregularities and COVID-19 vaccination status. The studies reported were mainly questionnaire based cross-sectional studies and a causal relationship of the predictors with post vaccination menstrual irregularities requires further validation. The review concluded that further prospective cohort studies are needed to identify the temporal link between menstrual cycle changes.

AstraZeneca comment: The aetiologies of menstrual disorders are multifactorial and there could be an interplay of these factors in cases. AstraZeneca has not identified any increase in menstrual disorders with second dose.

Wang et al 2022 reported the associations of SARS-CoV-2 infection and COVID-19 vaccination with menstrual cycle characteristics. This was against the background of increasing public questions and mistrust about the potential adverse reproductive impacts of COVID-19 infection and vaccination. The study involved prospectively following 3858 pre-menopausal women in the Nurses' Health Study 3 (NHS3) living in the United States or Canada. In this analysis, participants who reported receiving the AstraZeneca vaccine (n=9) and participants who did not report vaccine type (n=6) were excluded. Logistic or multinomial logistic regression models were used to assess the associations between (1) SARS-CoV-2 infection and (2) COVID-19 vaccination and change in menstrual cycle characteristics. Authors concluded that COVID-19 vaccination may be associated with short-term changes in usual menstrual cycle length, particularly among women whose cycles were short, long or irregular before vaccination. These results underscore the importance of monitoring menstrual health in vaccine clinical trials. Future work should examine the potential biological mechanisms.

AstraZeneca comment: The study did not include VAXZEVRIA. The study population being healthcare workers with a high vaccination rate may limit generalizability to populations with a different pandemic experience including those who got access to vaccination later during the pandemic. However, the fact that there is some historical data from the participants allowed for comparison of pre and post vaccination menstrual cycle data and compare uninfected and unvaccinated. AstraZeneca will continue to closely monitor the topic of menstrual disorders.

Summary

Overall medical summary of all case reports

Menstrual disorders are very common and have high incidence rates regardless of vaccination; and stress (physical or psychological) is a common aetiology. There are 20994 reports of menstrual disorder reported globally for VAXZEVRIA. The number of reports is relatively low compared to both the number of people vaccinated (see 5.2.1.2) and the prevalence of menstrual disorders generally (Kwak et al 2019). The TTO median was 8 days and most of the reports (76%) were reported within 28 days post vaccination. Most of events (54.6%) were reported in menopausal age group (35-44 (31.5%) and 25-34 (23.1%)) and 45-54 (22.1%).

The most reported menstrual disorders were heavy menstrual blood loss, followed by amenorrhoea/oligomenorrhoea and other menstrual disorders. Menstrual disorders can be very diverse and different per individual. Although the reported menstrual events were categorised in 9 categories, many of the reports contained multiple menstrual events and fell into multiple categories.

The most frequent co-reported AEs were known systemic and local reactions. These are very common reactions and were to be expected. Other reactions that were frequently co-reported were reactions related to the menstrual cycle, such as breast changes and mood swings.

A total 48% of menstrual disorder events had not resolved at the time of reporting. It is possible that, women reported their complaints before they fully recovered which is understandable since menstrual disorders such as amenorrhoea and irregular menstrual cycle generally can take a longer time to recover.

Due to insufficient information available in these reports, these findings do not provide more insight on the possible relationship between VAXZEVRIA and menstrual disorders. In summary, the review of available data from spontaneous reports regarding menstrual disorders did not identify an index case or other evidence of a new or emerging signal.

Literature summary

As pointed out in **Von Woon et al 2022, Laganà et al 2022, Muhaidat et al 2022** articles there seems to be an association between COVID-19 vaccination (regardless of type) and menstrual disorders. The conclusion by Wang et al 2022 that is no link between menstrual disorders and COVID-19 infection but rather vaccination is plausible giving that both mRNA and adenovirus-vectored vaccines were both associated with menstrual change. Many of the literature available recommended future work to examine the potential biological mechanisms that may explain an association between COVID-19 vaccination and menstrual disorders. The design of most studies reviewed did not consider control groups, hence it is impossible to make causal inferences from them. The actual incidence rate of menstrual disorders with COVID-19 vaccination is still unclear due to problems of overestimating, underestimating and biases. However, there seem to be more calls for studies designed particularly to aid the determination of causal inference and also confirm biologic mechanisms that will adequately explain the effects of COVID vaccination on menstrual disorders.

Conclusion

Based on the review of the updated cumulative data, AstraZeneca considers that there is insufficient evidence to suggest a causal association between menstrual disorders and VAXZEVRIA. It is AstraZeneca's opinion that no changes to the CDS or RMP are warranted at this time. AstraZeneca will closely monitor safety information for Menstrual disorders as part of the ongoing safety surveillance activities for VAXZEVRIA.

15.2.5 Myocarditis

BACKGROUND

AstraZeneca received the following request in PRAC PSUR assessment report (review period: 29 June 2021 to 28 December 2021): In the next PBRER, AstraZeneca is requested to provide the following discussion for myocarditis:

- *A review of newly identified and cumulative cases;*
- *A causality assessment of myocarditis cases (not provided in the current review);*
- *A review of the literature for new publications on epidemiologic studies of interest and mechanistic discussions;*
- *A discussion on new evidence on an association between myocarditis and VAXZEVRIA*

AstraZeneca's responses to these requests are provided in subsections 15.2.6 below.

The BCC case definition (Myocarditis/Pericarditis Case Definition 2021) was used for the review of the data available in the case reports. Furthermore, causality assessment according to WHO-UMC criteria was completed for Myocarditis cases fulfilling BCC Level 1, 2 or 3.

AstraZeneca also conducted an observed versus expected analysis for Myocarditis using the cumulative observed number of cases and risk window of 2-42 days. Background incidence rates from Truven Marketscan (2019) have been used for O/E analyses. Background rates include hospitalized and non-hospitalized cases of myocarditis.

Global Patient Safety Database

A cumulative search (29 December 2020 to 28 June 2022) and periodic search (29 December 2021 to 28 June 2022) of the AstraZeneca Global Patient Safety Database for Myocarditis with VAXZEVRIA was performed for case reports from all sources (clinical, spontaneous, solicited reporting and literature) using MedDRA (version 25.0). The search strategy included the following MedDRA PTs: Myocarditis; Autoimmune myocarditis; Eosinophilic myocarditis; Giant cell myocarditis; Hypersensitivity myocarditis; Immune-mediated myocarditis; Lupus myocarditis, Myocarditis post infection; Chronic myocarditis; and Myopericarditis.

During the reporting interval (29 December 2021 to 28 June 2022), there were 266 case reports (214 initial reports [131 cases concerning Dose 1, 52 cases concerning Dose 2, 4 cases concerning dose 3 and in 27 cases dose information were unknown] and 52 follow-up reports [37 concerning Dose 1, 9 concerning Dose 2 and in 6 cases dose information were unknown]). Further analysis in this report is focused on the cumulative data.

Cumulative review through DLP 28 June 2022

The search retrieved a total of 763 events of Myocarditis from 761 case reports. Two cases reported with two PTs of Myocarditis (Myocarditis and Myopericarditis).

A split of myocarditis cases by seriousness and source is presented in Table 63.

Table 63 Distribution of the case reports of Myocarditis received with VAXZEVRIA cumulatively through 28 June 2022 by reporting source and report seriousness

Report Source	Non-serious cases	Serious cases	Grand Total
Clinical Trial	0	0	0

Table 63 Distribution of the case reports of Myocarditis received with VAXZEVRIA cumulatively through 28 June 2022 by reporting source and report seriousness

Report Source	Non-serious cases	Serious cases	Grand Total
Spontaneous[a]	0	740	740
Literature	0	18	18
Non-interventional/post-marketing study	0	3	3
Grand Total	**0**	**761**	**761**

[a] Of the 740 Spontaneous case reports, 675 (91.2%) were received via Regulatory authorities

Table 64 presents number and percentage (%) of Myocarditis case reports after respective doses.

Table 64 Number and percentage (%) of the case reports of Myocarditis reported after respective doses of VAXZEVRIA cumulatively through 28 June 2022

No of Cases (After Dose 1)	No of Cases (After Dose 2)	No of Cases (After Dose 1 and Dose 2)	No of Cases (After Dose 3)	No of Cases (Dose No Unknown)
495 (65.0%)	173 (22.7%)	0	6 (0.8%)	87 (11.4%)

Out of the 761 case reports, there were 397 (52.2%) from the United Kingdom, 93 (12.2%) from Australia, 83 (10.9%) from Germany, 27 (3.5%) from Brazil, 21 (2.8%) from France, 14 (1.8%) from Sweden, 13 (1.7%) from Austria, 12 (1.6%) from Italy, 11 (1.45) from Spain, 10 (1.3%) from Belgium, 9 (1.2%) from Ireland, 8 (1.1%) from Greece, 6 (0.8%) Mexico, 5 (0.7%) cases each from Poland and India, 4 (0.5%) from Canada, 3 (0.4%) cases each from Netherlands, Northern Ireland and Korea, Republic of, 2 (0.3%) cases each from Slovakia, Iceland, Iran, Argentina, Romania, Malaysia, Denmark, Costa Rica, Guatemala, and Thailand, and 1 (0.1%) case each from Kenya, Cyprus, Ukraine, United States, Slovenia, Mauritius, Taiwan, Portugal, Luxembourg, Norway, Estonia, Panama, Bahrain and Philippines.

The distribution of the 763 events of Myocarditis, by PT is presented in Table 65:

Table 65 Distribution of MedDRA PTs (n = 763) pertaining to Myocarditis with VAXZEVRIA received cumulatively through DLP 28 June 2022

MedDRA PT	Serious	Non-serious	Grand Total
Myocarditis	695	0	695
Myopericarditis	58	1	59
Autoimmune myocarditis	4	0	4
Giant cell myocarditis	2	0	2
Myocarditis post infection	1	0	1
Chronic myocarditis	1	0	1
Immune-mediated myocarditis	1	0	1

Table 65 Distribution of MedDRA PTs (n = 763) pertaining to Myocarditis with VAXZEVRIA received cumulatively through DLP 28 June 2022

MedDRA PT	Serious	Non-serious	Grand Total
Grand Total	**762**	**1**	**763**

MedDRA Medical Dictionary for Regulatory Activities, PT Preferred Term

Out of 761 case reports:

- Vaccinee age was reported in 671 (88.2%) case reports and ranged 10 to 95 years (mean: 48 years; median: 48 years). Out of 671 cases, 5 (0.7%) vaccinees were in the age group of 10 to 17 years, 220 (32.8%) vaccinees were in the age group of 18 to 40 years, 324 (48.3%) vaccinees were in the age group of 41 to 64 years, and 122 (18.2%) vaccinees were ≥ 65 years of age.
- Vaccinee gender was reported in 737 (96.8%) case reports. Of these case reports, 375 (50.9%) concerned male patients and 362 (49.1%) concerned female patients.
- A total of 221 (29.0%) case reports were medically confirmed and 540 (71.0%) were non-medically confirmed.
- Of the total 761 case reports for Myocarditis, the time to onset (TTO) from VAXZEVRIA administration to Myocarditis events was reported in 383 (50.3%) case reports and ranged from 0 to 344 days (median: 12 days).

This is further presented in the following Table 66 accordingly with respect to the risk window days 2-42 days.

Table 66 TTO for Myocarditis case reports cumulatively through 28 June 2022

TTO (Days)	No of Cases	Percentage (%) *
0 to 1	62	16.2%
2 to 5	76	19.8%
6 to 10	44	11.5%
10 to 15	32	8.4%
16 to 20	24	6.3%
21-30	57	14.9%
31-42	22	5.7%
>42	66	17.2%
Unknown	378	NA

*TTO was reported for 383 case reports (*total number of cases*) used to calculate the percentage.

763 Myocarditis events were reported in 761 cases:

- 762 (99.9%) of the events were reported as serious (222 medically confirmed and 540 non-medically confirmed). The seriousness criteria were reported as follows; 335 (44.0%) medically important event, 52 (6.8%) disability, 259 (34.0%) hospitalization, 95 (12.5%) life threatening, and 21 (2.8%) death. The remaining 1 (0.1%) event of Myocarditis was non-serious (non-medically confirmed).

- Of the 763 events of Myocarditis, the outcomes were reported as 95 (12.5%) of the events as recovered, 143 (18.7) of the events were recovering, 37 (4.8%) of the events were recovered with sequelae, 300 (39.3%) of the events were not recovered, and 21 (2.8%) of the events were fatal. The outcome of the remaining 167 (21.9%) events were reported as unknown.
- Amongst the 132 events with reported outcome of 'recovered' or 'recovered with sequelae,' the event duration was reported in 33 (25.0%) case reports. The median duration was 10 days. In 12 (36.4%) events, the events recovered within 7 days and for the remaining 21 (63.6%) the events recovered after 7 days.

Events with fatal outcome

Twenty-one (2.8%) cases in 761 case reports were reported with fatal outcome, of which 10 (47.6%) cases were medically confirmed and 11 (52.4%) were non-medically confirmed. In 13 (61.9%) cases Myocarditis was reported after the first dose, in 6 (28.6%) cases the event was reported after the second dose, and in 2 (9.5%) cases dose information was unknown. Four (4) out of 21 fatal case reports were within risk window of 2-42 days, 6 (28.6%) were outside the risk window, and in 11 (52.4%) TTO was unknown. Overall, the TTO of fatal events ranged from 0 to 195 days after receiving VAXZEVRIA. Of 21 fatal case reports, 2 (9.5%) cases fulfilled BCC level 1 criteria, 14 (66.7%) cases fulfilled BCC level 4 criteria, and 5 (19.0%) cases fulfilled BCC Level 5 criteria. WHO-UMC causality was assessed as "Possible" for 4 (23.8%) case reports, "Unlikely" for 7 (33.3%) case reports, and "Unassessable/Unclassifiable" for 10 (47.6%) case reports. Ten (10) (42.6%) of the 21 reports ([redacted]) had risk factors for myocarditis (presented in Table 67). Remaining 11 (52.4%) of the 21 cases lacked sufficient case details such as medical history, concomitant medications, etiological and diagnostic work-up, event start date, etc.

The summary of the fatal case reports is presented below in Table 67:

Table 67 Summary of case reports with fatal outcome for (N = 21) cumulatively through 28 June 2022

Sr. No.	Case ID / Country / Medically confirmed (Y/N) / Source	Age (Years) / Gender (M/F)	Medical History / Concomitant medications	Time to Onset (days) / Dose Information	Other reported conditions associated to the fatal outcome / Autopsy (Yes / No / Unk)	Brighton Collaboration classification	WHO-UMC Causality Assessment	Additional Comment
1	[redacted] Korea, Republic of / Y / Literature	63 / F	Endotracheal intubation; Mechanical ventilation; Balloon atrial septostomy; Heart transplant / Not Reported	0 / Dose 2	Not Reported / Unk	BCC1	Unlikely	TTO to chest pain is 0 days (outside risk window). Limited information on cardiac history, results of COVID test, WBC counts - infectious origin cannot be excluded. Alternative cause is immunocompromised state with heart transplant (acute cardiac failure)
2	[redacted] / United Kingdom / N / Spontaneous	36 / M	Type 1 diabetes mellitus; Hepatitis; Overweight / Albuterol; Fluticasone propionate, Salmeterol; Insulin lispro; Insulin detemir; Duloxetine; Metformin; Ramipril	159 / Dose 2	Type 1 diabetes mellitus, Dyspnoea, decreased blood sugar, circulatory collapse, Tremor, Foaming at mouth / Yes	BCC1	Unlikely	Conservatively BCC1 as it was mentioned autopsy was performed but no details provided. Outside of expected TTO; Alternative cause underlying autoimmune disease Type 1 diabetes mellitus
3	[redacted] / Korea,	Unk / Unk	Not Reported / Not Reported	Unknown / Dose 1	Not reported / No	BCC4	Unassessable / Unclassifiable	Unknown TTO, Limited information on medical history, concomitant drugs.

Table 67 Summary of case reports with fatal outcome for (N = 21) cumulatively through 28 June 2022

Sr. No.	Case ID / Country / Medically confirmed (Y/N) / Source	Age (Years) / Gender (M/F)	Medical History / Concomitant medications	Time to Onset (days) / Dose Information	Other reported conditions associated to the fatal outcome / Autopsy (Yes / No / Unk)	Brighton Collaboration classification	WHO-UMC Causality Assessment	Additional Comment
	Republic of / N / Spontaneous							
4	[redacted] France / N / Spontaneous	74 / F	Scleroderma; Raynaud's phenomenon / Not Reported	20 / Dose 1	Not reported / No	BCC4	Possible; with limited information	Limited work-up information reported, medical history or concomitant drugs
5	[redacted] United Kingdom / N / Spontaneous	56 / M	Colonoscopy; Tobacco user; Body mass index increased; Inguinal hernia repair; Smoking cessation therapy; Alcoholic / Not Reported	Unknown / Dose 1	The cause of death was [redacted] which was confirmed at autopsy. Agitation, staring, restlessness, depression suicidal, crying, nightmare, paranoia, anger, aggression and	BCC4	Unassessable / Unclassifiable	Psychiatric factors contributed to outcome of event; Tobacco user; Body mass index increased; limited diagnostic work up

Table 67 Summary of case reports with fatal outcome for (N = 21) cumulatively through 28 June 2022

Sr. No.	Case ID / Country / Medically confirmed (Y/N) / Source	Age (Years) / Gender (M/F)	Medical History / Concomitant medications	Time to Onset (days) / Dose Information	Other reported conditions associated to the fatal outcome / Autopsy (Yes / No / Unk)	Brighton Collaboration classification	WHO-UMC Causality Assessment	Additional Comment
					cardiomegaly / Yes			
6	[redacted] / United Kingdom / Y / Spontaneous	68 / M	Not Reported / Not Reported	Unknown / Dose 1	Limited information conditions associated to the death was reported / Unk	BCC4	Unassessable / Unclassifiable	Limited work-up information on medical history, concomitant medication, diagnostic work-up
7	[redacted] / United Kingdom / N / Spontaneous	48 / M	Not Reported / Not Reported	1 / Dose 2	Not reported / Unk	BCC4	Unlikely	Outside of expected TTO; Limited work-up information reported
8	[redacted] / United Kingdom / N / Spontaneous	Unk / Unk	Not Reported / Not Reported	1 / Dose 1	Not reported / Unk	BCC4	Unlikely	Lack of clarity on the course of event. Onset of symptoms was less than 24hrs which is not within expected TTO. Also, not clear if autopsy was performed, diagnosis seemed to be not a confirmed one. Limited info on medical history, diagnostic work-up

Table 67 Summary of case reports with fatal outcome for (N = 21) cumulatively through 28 June 2022

Sr. No.	Case ID / Country / Medically confirmed (Y/N) / Source	Age (Years) / Gender (M/F)	Medical History / Concomitant medications	Time to Onset (days) / Dose Information	Other reported conditions associated to the fatal outcome / Autopsy (Yes / No / Unk)	Brighton Collaboration classification	WHO-UMC Causality Assessment	Additional Comment
9	[redacted] / Mauritius / N / Spontaneous	40 / M	Not Reported / Not Reported	Unknown / Dose Unknown	Not reported / No	BCC4	Unassessable / Unclassifiable	TTO Unknown, Limited information on medical history and concomitant medications, support diagnosis
10	[redacted] / Germany / N / Spontaneous	70 / F	Not Reported / Not Reported	Unknown / Dose 1	Found dead in bed; in the autopsy noticeably many clot formations (coronary arteries, Cerebral arteries), clot vitality not certain no definite cause of death can be determined / Yes	BCC4	Unassessable / Unclassifiable	Elderly patient (≥65 years), unknown TTO. Limited information on medical history and concomitant medications No supportive diagnostic work up / course of event

Table 67 Summary of case reports with fatal outcome for (N = 21) cumulatively through 28 June 2022

Sr. No.	Case ID / Country / Medically confirmed (Y/N) / Source	Age (Years) / Gender (M/F)	Medical History / Concomitant medications	Time to Onset (days) / Dose Information	Other reported conditions associated to the fatal outcome / Autopsy (Yes / No / Unk)	Brighton Collaboration classification	WHO-UMC Causality Assessment	Additional Comment
11	[redacted] Germany / N / Spontaneous	Unk / F	Not Reported / Not Reported	Unknown / Dose 1	Not Reported / Yes	BCC4	Unassessable / Unclassifiable	Limited information on medical history and concomitant medications, work-up not reported. Unknown TTO. Fatal outcome after non-AZ vaccine (dose 2)
12	[redacted] / India / Y / Spontaneous	44 / F	Not reported / Not Reported	Unknown / Dose 1	Congestive heart failure / Unk	BCC4	Possible; with limited information	TTO to palpitations - 5 days. Missing medical history and concomitant drugs, results of investigations
13	[redacted] Sweden / Y / Spontaneous	82 / F	Ovarian cancer / Not Reported	195 / Dose 2	Spinal cord haemorrhage, Basal ganglia haemorrhage, Pneumonia, Myocarditis, Vasculitis / Yes	BCC4	Unlikely	Elderly patient (≥65 years), TTO outside risk window. Confounded by history of ovarian cancer. Missing concomitant drug, results of investigations.
14	[redacted] / Greece / Y /	50 / M	Not reported / Olanzapine Tablet	30 / Dose 1	Myocardial infarction / Yes	BCC4	Possible; with limited information	Missing diagnostic workup and medical history; Not clear if patient had underlying history of myocarditis

Table 67 Summary of case reports with fatal outcome for (N = 21) cumulatively through 28 June 2022

Sr. No.	Case ID / Country / Medically confirmed (Y/N) / Source	Age (Years) / Gender (M/F)	Medical History / Concomitant medications	Time to Onset (days) / Dose Information	Other reported conditions associated to the fatal outcome / Autopsy (Yes / No / Unk)	Brighton Collaboration classification	WHO-UMC Causality Assessment	Additional Comment
	Spontaneous							
15	[redacted] / Australia / N / Spontaneous	Unk / Unk	Not reported / Not Reported	Unknown / Dose Unknown	Not Reported / Unk	BCC4	Unassessable / Unclassifiable	TTO unknown, missing medical history, concomitant drugs and results of investigations
16	[redacted] / Brazil / Y / Spontaneous	23 / M	Rhinitis allergic; Appendicectomy; Bradycardia; Anxiety / Not Reported	Unknown / Dose 1	Autopsy (preliminary data, from macroscopy): lungs with edema, congestion and diffuse alveolar hemorrhage pattern; heart weighing 350g with red septal area; congested liver, with a	BCC4	Unassessable / Unclassifiable	Per macroscopic autopsy, there was involvement of multiple organ pathologies (Spleen, lungs, liver, etc) pointing to a multisystemic pathology, limited information on diagnostic myocarditis work up

Table 67 Summary of case reports with fatal outcome for (N = 21) cumulatively through 28 June 2022

Sr. No.	Case ID / Country / Medically confirmed (Y/N) / Source	Age (Years) / Gender (M/F)	Medical History / Concomitant medications	Time to Onset (days) / Dose Information	Other reported conditions associated to the fatal outcome / Autopsy (Yes / No / Unk)	Brighton Collaboration classification	WHO-UMC Causality Assessment	Additional Comment
					smooth, burgundy surface, with pale areas; wine spleen, congested; stomach occupied by extensive hemorrhage; diffuse cerebral edema with herniated cerebellar tonsils. Fragments of brain, spleen, liver, stomach, kidneys and pancreas were collected, necropsy showed			

Table 67 Summary of case reports with fatal outcome for (N = 21) cumulatively through 28 June 2022

Sr. No.	Case ID / Country / Medically confirmed (Y/N) / Source	Age (Years) / Gender (M/F)	Medical History / Concomitant medications	Time to Onset (days) / Dose Information	Other reported conditions associated to the fatal outcome / Autopsy (Yes / No / Unk)	Brighton Collaboration classification	WHO-UMC Causality Assessment	Additional Comment
					myocarditis/ Yes			
17	[redacted] United Kingdom / Y / Spontaneous	35 / F	Angina pectoris; Coagulopathy; Abortion spontaneous; Caesarean section; Amniotic cavity infection; Foetal vascular malperfusion; Gestational diabetes / Not Reported	1 / Dose 1	Cardiac arrest, Ventricular fibrillation, Bundle branch block left, Pneumonia aspiration, Brain oedema, Cardiogenic shock, Multi-organ failure, transthoracic ECHO (TTE) found evidence of severe LV failure (ejection fraction (EF) less than 20%), Elevated	BCC5	Unlikely	Alternative cause underlying coagulopathy disorder (previous miscarriages and history of foetal placental thrombosis) Death Certificate 1a:Bronchopneumonia; Aspiration pneumonia could be a consequence of cardiac arrest; cause of death seemed of cardiac origin, possibly related to a thrombotic coronary event or a myocardial autoimmune / inflammatory process / Alternative causal factors noted

Table 67 Summary of case reports with fatal outcome for (N = 21) cumulatively through 28 June 2022

Sr. No.	Case ID / Country / Medically confirmed (Y/N) / Source	Age (Years) / Gender (M/F)	Medical History / Concomitant medications	Time to Onset (days) / Dose Information	Other reported conditions associated to the fatal outcome / Autopsy (Yes / No / Unk)	Brighton Collaboration classification	WHO-UMC Causality Assessment	Additional Comment
					Troponin T and D dimer / No			
18	[redacted] United Kingdom / Y / Spontaneous	48 / M	Drug dependence; Tobacco user; Alcohol use; Drug abuse; Immunodeficiency; Anxiety; Depression; Psoriasis; Cardiac disorder; Hypertension / Diazepam; Insulin lispro; Methadone; Mirtazapine	Unknown / Dose 1	Drug abuse, enlargement heart, drug addiction (confirmed at autopsy) / Yes	BCC5	Unassessable / Unclassifiable	Alternative causality included multiple co morbidities (drug abuse, immunocompromised state, underlying cardiovascular disease). autopsy was performed. The cause of death was drug abuse, enlargement heart (confirmed at autopsy), drug addiction (confirmed at autopsy) and myocarditis / Alternative causal factors noted
19	[redacted] Belgium / N /	68 / M	Ex-tobacco user / Not Reported	Unknown / Dose 1	Limited information conditions associated to	BCC5	Unassessable / Unclassifiable	Elderly patient (≥65 years) with alternative cause infection process; limited work-up information reported;

Table 67 Summary of case reports with fatal outcome for (N = 21) cumulatively through 28 June 2022

Sr. No.	Case ID / Country / Medically confirmed (Y/N) / Source	Age (Years) / Gender (M/F)	Medical History / Concomitant medications	Time to Onset (days) / Dose Information	Other reported conditions associated to the fatal outcome / Autopsy (Yes / No / Unk)	Brighton Collaboration classification	WHO-UMC Causality Assessment	Additional Comment
	Spontaneous				the death was reported / Unk			onset of cardiac symptoms was before exposure to AZ vaccine
20	[redacted] Ireland / Y / Spontaneous	48 / F	Pyelonephritis; Oophorectomy; Nephrectomy / Not Reported	2 / Dose 2	Cardiac arrest, Coronary artery thrombosis/ Yes - (myocarditis, thrombotic myocardial infarction)	BCC5	Possible; with risk factors	Alternative cause confounders; thrombotic myocardial infarction, coronary artery atherosclerosis, acute myocardial infarct with myocardial rupture
21	[redacted] Sweden / Y / Spontaneous	79 / M	Hypertension; Coronary artery bypass; Cardiomegaly; Ischaemic cardiomyopathy; Hypothyroidism; Atrioventricular block complete; Cardiac assistance	30 / Dose 2	Lymphoid infiltrated into the lung, giant cells in the lung, foreign body giant cells in the lung, enlargement heart, coronary sclerosis and acute	BCC5	Unlikely	Elderly patient (≥65 years) with alternative cause underlying coronary artery bypass graft (started 2007), cardiovascular disease, hypertension (ongoing), enlargement heart, ischemic cardiomyopathy, hypothyroidism (ongoing), AV block third degree, artificial cardiac pacemaker user (ongoing), coronary sclerosis, glaucoma, renal failure, acute myocardial infarction, atrial fibrillation

Table 67 Summary of case reports with fatal outcome for (N = 21) cumulatively through 28 June 2022

Sr. No.	Case ID / Country / Medically confirmed (Y/N) / Source	Age (Years) / Gender (M/F)	Medical History / Concomitant medications	Time to Onset (days) / Dose Information	Other reported conditions associated to the fatal outcome / Autopsy (Yes / No / Unk)	Brighton Collaboration classification	WHO-UMC Causality Assessment	Additional Comment
			device user; Arteriosclerosis coronary artery; Glaucoma; Renal failure; Acute myocardial infarction; Atrial fibrillation; Left ventricular failure; COVID-19 immunisation / Apixaban		myocardial infarction / Yes			(ongoing) and left ventricular failure (ongoing), limited work up information

Unk, unknown; TTO, Time to onset; LV, Left Ventricular; EF, Ejection Fraction; CABG, coronary artery bypass graft; AV, Atrioventricular; F, Female; M, Male

Rechallenge / Recurrence case reports

There were no case reports identified for Myocarditis after the first dose with a recurrence or worsening with the second or third dose of vaccination.

Brighton Collaboration Classification (BCC) Assessment and Causality assessment as per WHO-UMC criteria

The Brighton collaboration of the myocarditis case definition criteria (Myocarditis/Pericarditis Case Definition 2021) were used for the review of the data available in the case reports. Based on this approach, out of the 761 case reports, 12 (1.6%) fulfilled level 1 criteria, 52 (6.8%) fulfilled level 2 criteria, none fulfilled level 3 criteria, 390 (51.2%) fulfilled level 4 criteria, and 307 (40.3%) case reports fulfilled level 5 criteria. Causality assessment for cases fulfilling BCC 1 to 3 were performed using WHO-UMC causality assessment criteria.

Brighton Collaboration Classification Level 1

Of the 761, 12 (1.6%%) case reports fulfilled Brighton collaboration level 1 criteria. These case reports are summarized in Table 68 below:

Table 68 Case reports of Myocarditis with VAXZEVRIA fulfilling Brighton Collaboration Criteria Level 1 (N=12) reported cumulatively till DLP 28 June 2022

Sr. No.	Case ID / Country / Serious (Y/N) / Medically Confirmed (Y/N)	Age (Years) / Gender (M/F)	Medical History / Concomitant medications	Time to Onset (days) / Dose #	Event / Outcome	WHO-UMC Causality Assessment	Case assessment / Comment
1	[redacted] Y / Y	Unk / M	Hepatic function abnormal / Bisoprolol; Ramipril	Unknown / Dose 1	Myocarditis / Not recovered	Unassessable / Unclassifiable	TTO Unknown, confounded by medical history of cardiac impairment which is supported by drug history as well. Conflicting info regarding underlying cardiac condition; Elevated troponin and ECHO finding of new unexplained regional wall abnormalities and new cardiac impairment, >1 cardiac symptom (chest pain and palpitation)
2	[redacted] Y / Y	46 / F	Asthma; Suppressed lactation / Beclometasone; Fexofenadine; Salbutamol	Unknown / Dose 1	Myocarditis / Recovered	Unassessable / Unclassifiable	TTO Unknown, > 1 ECHO (Severe global LV dysfunction and Pericardial effusion; elevated cardiac biomarker (troponin)
3	[redacted] Y / Y	18 / M	Pulmonary embolism; Myocarditis; Pericardial effusion / Not Reported	26 / Dose 1	Myocarditis / Recovered	Possible; with risk factors	TTO within risk window; cMRI findings of Myocardial inflammation; hyperaemia and late gadolinium myocardial enhancement; elevated cardiac biomarker (troponin). However, confounded by medical history of pulmonary embolism; pericardial effusion and myocarditis
4	[redacted] Y / N	39 / M	Not Reported / Not Reported	Unknown / Dose 1	Myocarditis / Unknown	Unassessable / Unclassifiable	Endocardial biopsy performed and result was demonstrating acute neutrophilic myocarditis (myocardial inflammation); alternative cause - confounder infectious process per biopsy result

Table 68 Case reports of Myocarditis with VAXZEVRIA fulfilling Brighton Collaboration Criteria Level 1 (N=12) reported cumulatively till DLP 28 June 2022

Sr. No.	Case ID / Country / Serious (Y/N) / Medically Confirmed (Y/N)	Age (Years) / Gender (M/F)	Medical History / Concomitant medications	Time to Onset (days) / Dose #	Event / Outcome	WHO-UMC Causality Assessment	Case assessment / Comment
5	[redacted] Y / N	30 / F	Obesity / Not Reported	2 / Dose 1	Myocarditis / Not recovered	Possible; with risk factors	ECHO finding of diffuse hypokinesia with EF 40 percent and elevated troponin; Underlying history of obesity could be risk factor.
6	[redacted] / Y / Y	63 / F	Endotracheal intubation; Mechanical ventilation; Balloon atrial septostomy; Heart transplant / Not Reported	0 / Dose 2	Myocarditis / Died	Unlikely	TTO to chest pain is 0 days (outside risk window). Limited information on cardiac history; results of COVID test; WBC counts - infectious nature cannot be excluded; History of Balloon atrial septostomy; Heart transplant (acute cardiac failure)
7	[redacted] Y / Y	30 / M	Not reported / Not Reported	Unknown / Dose 1	Myocarditis / Unknown	Conditional / Unclassified	TTO unknown; elevated troponin and Biopsy showing myocarditis; however, confounded by interchanging Moderna vaccine use; limited information on medical history and concomitant medications
8	[redacted] Y / Y	50 / M	Not reported / Not Reported	Unknown / Dose 1	Myocarditis / Unknown	Conditional / Unclassified	TTO unknown; elevated troponin and cardiac MRI abnormality; however, confounded by interchanging BioNTech vaccine use; limited information on medical history and concomitant medications
9	[redacted] Y / Y	55 / F	Essential hypertension; Hypercholesterolaemia / Not Reported	14 / Dose 2	Myocarditis / Recovered	Possible; with risk factors	TTO within risk window; elevated troponin and increased cMRI abnormalities present; however, confounded by history of essential hypertension and hypercholesterolemia

Table 68 Case reports of Myocarditis with VAXZEVRIA fulfilling Brighton Collaboration Criteria Level 1 (N=12) reported cumulatively till DLP 28 June 2022

Sr. No.	Case ID / Country / Serious (Y/N) / Medically Confirmed (Y/N)	Age (Years) / Gender (M/F)	Medical History / Concomitant medications	Time to Onset (days) / Dose #	Event / Outcome	WHO-UMC Causality Assessment	Case assessment / Comment
10	[redacted] Y / Y	68 / F	Acute myocardial infarction / Not Reported	Unknown / Dose 1	Autoimmune myocarditis / Unknown	Conditional / Unclassified	TTO Day 1; elevated troponin; C-reactive protein and cardiac MRI abnormality; however, confounded by history of coronary heart disease; elderly patient (≥65 years) could be risk factor
11	[redacted] Y / Y	23 / M	Dyspnoea; Tachycardia; Pleural effusion / Not Reported	Unknown / Dose 1	Myopericarditis / Recovered	Conditional / Unclassified	Increased Troponin; ECHO & cMRI findings; However, the presence of leukocytosis with neutrophil predominance and fever makes it highly suspicious of ongoing infectious process. Also, COVID 19 infection was not ruled out. The lack of information regarding the family history; laboratory work up and other possible differentials that could have been ruled out in this article; make it difficult to ascertain causal association of myopericarditis with pleuritis resulting from the use of VAXZEVRIA in this patient.
12	[redacted] Y / N	36 / M	Type 1 diabetes mellitus; Hepatitis; Overweight / Albuterol; Fluticasone propionate, Salmeterol; Insulin lispro; Insulin detemir; Duloxetine; Metformin; Ramipril	159 / Dose 2	Myocarditis / Died	Unlikely	Conservatively assessed as BCC1 as it was mentioned autopsy was performed but no details provided. Outside of expected TTO; alternative cause underlying type 1 diabetes mellitus; Overweight

LV, Left Ventricular; EF, Ejection Fraction; TTO, Time to onset; cMRI, Magnetic resonance imaging; ECHO, Echocardiography; Unk, Unknown; F, Female; M, Male

Brighton Collaboration Classification Level 2

Of the 761 case reports, 52 (6.8%) case reports fulfilled Brighton collaboration level 2 criteria. These case reports are summarized in Table 69 below:

Table 69 Case reports of Myocarditis with VAXZEVRIA fulfilling Brighton Collaboration Criteria Level 2 (N=52) reported cumulatively till DLP 28 June 2022

Sr. No.	Case ID / Country / Serious (Y/N) / Medically Confirmed (Y/N)	Age (Years) / Gender (M/F)	Medical History / concomitant medications	Time to Onset (days) / Dose #	Event / Outcome	WHO-UMC Causality Assessment	Additional Comment / Causality Assessment
1	[redacted] Y / N	54 / M	Not Reported / Not Reported	Unknown / Dose 1	Myocarditis / Unknown	Unassessable / Unclassifiable	TTO unknown; Chest pain with elevated Troponin; Limited information on medical history and concomitant medications.
2	[redacted] Y / Y	39 / M	Not Reported / Not Reported	4 / Dose 1	Myocarditis / Recovering	Possible; with risk factors	Patient had infection before prior to onset of related symptom; EKG+; CT pericardial effusion. Limited information on medical history and concomitant medications
3	[redacted] Y / N	44 / F	Not Reported / Amitriptyline; Fluoxetine	0 / Dose 1	Myocarditis / Not recovered	Unlikely	TTO - within hours of exposure; Cardiac symptoms with elevated Troponin; limited information on medical history
4	[redacted] Y / Y	61 / F	Tobacco user / Not Reported	1 / Dose 1	Myocarditis / Recovering	Unlikely	TTO was 1 day outside of risk window; chest pain with troponin increase; alternative cause - smoker
5	[redacted] Y / N	55 / M	Not Reported / Not Reported	Unknown / Dose 1	Myocarditis / Unknown	Unassessable / Unclassifiable	Chest pain with increased troponin; ECG and ECHO finding (widespread ST elevation; PR depression; EF 50% - low to normal); considering the associated symptoms and antibiotics treatment; more likely an infectious process

Table 69 Case reports of Myocarditis with VAXZEVRIA fulfilling Brighton Collaboration Criteria Level 2 (N=52) reported cumulatively till DLP 28 June 2022

Sr. No.	Case ID / Country / Serious (Y/N) / Medically Confirmed (Y/N)	Age (Years) / Gender (M/F)	Medical History / concomitant medications	Time to Onset (days) / Dose #	Event / Outcome	WHO-UMC Causality Assessment	Additional Comment / Causality Assessment
6	[redacted] Y / N	22 / M	Not Reported / Not Reported	3 / Dose 1	Myocarditis / Not recovered	Possible; with limited information	Cardiac symptom (Chest pain) with elevated Troponin and ECG findings were as follows: diffuse concave upward ST segment elevation); limited information on medical history and concomitant medications; limited work up info
7	[redacted] / Y / N	29 / M	Not Reported / Not Reported	7 / Dose 1	Myocarditis / Not recovered	Possible; with limited information	Chest pain with elevated Troponin; limited information on medical history and concomitant medications
8	[redacted] / Y / Y	20 / M	Not Reported / Not Reported	Unknown / Dose 1	Myocarditis / Not recovered	Unassessable / Unclassifiable	Cardiac symptom (tachycardia and chest pain); ECHO showed small pericardial effusion; limited information on medical history and concomitant medications; limited work up info
9	[redacted] / Y / N	27 / M	Not Reported / Not Reported	10 / Dose 1	Myocarditis / Recovering	Possible; with limited information	Chest pain with elevated Troponin; Limited information on medical history and concomitant medications
10	[redacted] Y / Y	Unk / M	Myalgia / Prednisolone	16 / Dose 1	Myocarditis / Unknown	Possible; with risk factors	Cardio symptom (chest pain and dyspnoea) with elevated Troponin; limited work up info; alternative cause; underlying autoimmune disease (use of steroid: prednisolone)
11	[redacted] Y / Y	41 / M	Nephrolithiasis; Asthma / beclometasone dipropionate, formoterol fumarate dihydrat; Loratadine	14 / Dose 2	Myocarditis / Recovering	Possible; with limited information	Chest pain with elevated Troponin; Limited info; limited work up info; medical history

Table 69 Case reports of Myocarditis with VAXZEVRIA fulfilling Brighton Collaboration Criteria Level 2 (N=52) reported cumulatively till DLP 28 June 2022

Sr. No.	Case ID / Country / Serious (Y/N) / Medically Confirmed (Y/N)	Age (Years) / Gender (M/F)	Medical History / concomitant medications	Time to Onset (days) / Dose #	Event / Outcome	WHO-UMC Causality Assessment	Additional Comment / Causality Assessment
12	[redacted] Y / Y	45 / F	Not Reported / Not Reported	18 / Dose 1	Myocarditis / Recovering	Possible; with limited information	Cardio symptom (dyspnoea, left ventricular hypokinesia and tachycardia) with Troponin T result found to be 77 nanogram per litre; ECHO result found to be hypokinesis of septum; inferior and posterior wall; limited information on medical history and concomitant medications
13	[redacted] Y / N	26 / M	Not Reported / Not Reported	7 / Dose 2	Myocarditis / Recovering	Possible; with limited information	Chest pain with elevated Troponin; limited information on medical history and concomitant medications
14	[redacted] Y / N	70 / F	Not Reported / Not Reported	3 / Dose 1	Myocarditis / Unknown	Possible; with risk factors	Chest discomfort with elevated Troponin; limited work up info; medical history; elderly patient (≥65 years could be risk factor); limited information on medical history and concomitant medications
15	[redacted] / Y / N	54 / M	Not Reported / Not Reported	Unknown / Dose 1	Myocarditis / Unknown	Unassessable / Unclassifiable	Chest pain with elevated Troponin; limited work up info; multiple risk factors - obesity; ex-smoker
16	[redacted] Y / N	48 / Unk	Depression / Not Reported	Unknown / Dose 1	Myocarditis / Unknown	Unassessable / Unclassifiable	Chest pain with elevated Troponin; Limited work up info
17	[redacted] Y / N	52 / F	Hospitalisation / Not Reported	14 / Dose 1	Myocarditis / Recovered	Possible; with limited information	Chest pain with elevated Troponin; Limited work up info

Table 69 Case reports of Myocarditis with VAXZEVRIA fulfilling Brighton Collaboration Criteria Level 2 (N=52) reported cumulatively till DLP 28 June 2022

Sr. No.	Case ID / Country / Serious (Y/N) / Medically Confirmed (Y/N)	Age (Years) / Gender (M/F)	Medical History / concomitant medications	Time to Onset (days) / Dose #	Event / Outcome	WHO-UMC Causality Assessment	Additional Comment / Causality Assessment
18	[redacted] Y / N	53 / M	Not Reported / Not Reported	Unknown / Dose 2	Myocarditis / Recovered	Unassessable / Unclassifiable	Chest pain with elevated Troponin; the timing of the vaccine exposure; onset of event and covid infection is not clear; limited information on medical history and concomitant medications
19	[redacted] / Y / Y	29 / F	Back pain / Pregabalin	5 / Dose 1	Myocarditis / Recovered	Possible; with limited information	Chest pain with elevated Troponin; ECG; showing in one of them bigeminism ventricular and in followed; ST depression accented in V3-V6; in the bottom wall and with supra-ST on the high lateral wall
20	[redacted] / Y / Y	22 / M	Not Reported / Not Reported	Unknown / Dose 1	Myocarditis / Unknown	Unassessable / Unclassifiable	Chest discomfort with elevated Troponin, Malaise, ECG finding slight concave ST1
21	[redacted] Y / Y	26 / M	Not Reported / Not Reported	11 / Dose 1	Myocarditis / Not recovered	Possible; with limited information	Chest pain with ejection fraction decreased and complete atrioventricular block; Limited information on medical history and concomitant medication
22	[redacted] Y / Y	Unk / M	Not Reported / Not Reported	11 / Dose 1	Myocarditis / Not recovered	Possible; with limited information	Chest pain with ejection fraction decreased and complete atrioventricular block; Limited information on medical history and concomitant medication
23	[redacted] Y / N	48 / M	Not Reported / Not Reported	30 / Dose 1	Myocarditis / Not recovered	Possible; with limited information	Chest pain with elevated Troponin; Limited information on medical history and concomitant medication

Table 69 Case reports of Myocarditis with VAXZEVRIA fulfilling Brighton Collaboration Criteria Level 2 (N=52) reported cumulatively till DLP 28 June 2022

Sr. No.	Case ID / Country / Serious (Y/N) / Medically Confirmed (Y/N)	Age (Years) / Gender (M/F)	Medical History / concomitant medications	Time to Onset (days) / Dose #	Event / Outcome	WHO-UMC Causality Assessment	Additional Comment / Causality Assessment
24	[redacted] / Y / Y	61 / F	Asthma; Eczema / Not Reported	Unknown / Dose 1	Myocarditis / Unknown	Unassessable / Unclassifiable	chest pain with elevated Troponin; Limited information on medical history and concomitant medication
25	[redacted] Y / Y	22 / M	Not Reported / Not Reported	9 / Dose 1	Myocarditis / Recovering	Possible; with limited information	Chest pain with elevated Troponin; Limited information on medical history and concomitant medication
26	[redacted] Y / Y	36 / M	Not Reported / Not Reported	13 / Dose 3	Myocarditis / Unknown	Possible; with limited information	chest pain, dyspnoea, palpitations and fatigue; Limited information on medical history and concomitant medication
27	[redacted] Y / Y	60 / F	Not Reported / Not Reported	171 / Dose 2	Myocarditis / Recovering	Unlikely	chest pain with elevated Troponin; Out of risk window; approx. 5 months after AZ vaccine exposure; however few days after Moderna vaccine exposure; This is unlikely due to Exposure to AZ vaccine. Limited information on medical history and concomitant medications
28	[redacted] Y / Y	50 / M	Hypertension; Deep vein thrombosis; Non-tobacco user; Pulmonary embolism / Amlodipine; Immunoglobulin; Atorvastatin; Doxazosin; Warfarin	Unknown / Dose Unknown	Myocarditis / Unknown	Unassessable / Unclassifiable	TTO Unknown; Chest pain with elevated Troponin; Patient had history of Hypertension; Deep vein thrombosis and Pulmonary embolism. alternative cause; patient had multiple confounders that could explain myocarditis - antiphospholipid syndrome; hepatitis acute; visceral venous thrombosis; haemorrhagic adrenal infarction; mesenteric arterial occlusion; aortitis; arteritis; intestinal

Table 69 Case reports of Myocarditis with VAXZEVRIA fulfilling Brighton Collaboration Criteria Level 2 (N=52) reported cumulatively till DLP 28 June 2022

Sr. No.	Case ID / Country / Serious (Y/N) / Medically Confirmed (Y/N)	Age (Years) / Gender (M/F)	Medical History / concomitant medications	Time to Onset (days) / Dose #	Event / Outcome	WHO-UMC Causality Assessment	Additional Comment / Causality Assessment
							dilatation; bowel ischaemia; sepsis NOS; catastrophic reaction and vasculitis
29	[redacted] Y / N	37 / M	Not Reported / Not Reported	249 / Dose 2	Myocarditis / Not recovered	Unlikely	Onset of symptoms was approx. 8 months after exposure to AZ vaccine; As reported all cardiac work up were ok; conflicting info regarding Troponin if it was done or not; conservatively a BCC2; Limited information on medical history and concomitant medications
30	[redacted] Y / N	19 / M	Not Reported / Not Reported	179 / Dose 2	Myocarditis / Unknown	Unlikely	Chest pain with elevated Troponin; ECG finding (ECG SR; widespread PR depression; high ST stake off in anterior leads. ECG (2): SR; concave STE in V2 (BER pattern); PR depression in leads V2-6); However Unlikely caused by AZ vaccine; TTO was not within risk window - approx. 4 months symptoms occurred immediately after exposure to m-RNA vaccine; Limited information on medical history and concomitant medications
31	[redacted] Y / Y	65 / F	Affective disorder; Hypertension / Metoprolol; Amlodipine; Sertraline	1 / Dose 2	Myocarditis / Recovered	Unlikely	Not within expected risk window; TTO 24hrs from exposure; Patient had underlying cardiac condition (Hypertension); Chest Pain + Dyspnoea; BCC2; elderly patient (≥65 years could be risk factor)

Table 69 Case reports of Myocarditis with VAXZEVRIA fulfilling Brighton Collaboration Criteria Level 2 (N=52) reported cumulatively till DLP 28 June 2022

Sr. No.	Case ID / Country / Serious (Y/N) / Medically Confirmed (Y/N)	Age (Years) / Gender (M/F)	Medical History / concomitant medications	Time to Onset (days) / Dose #	Event / Outcome	WHO-UMC Causality Assessment	Additional Comment / Causality Assessment
32	[redacted] / Y / Y	52 / M	Asthma; Hospitalisation; Benign prostatic hyperplasia / Formoterol W/Budesonide	6 / Dose 1	Myocarditis / Recovered	Possible; with limited information	Dyspnoea, with EKG and ECHO results; However, there was productive cough with no sputum culture to rule out infectious process; Limited work up info
33	[redacted] / Y / Y	60 / M	Not Reported / Tramadol	22 / Dose 1	Myocarditis / Recovering	Possible; with limited information	Raised Troponin. Limited information on medical history and concomitant medications; limited work up info
34	[redacted] / Y / Y	62 / F	Not Reported / Not Reported	2 / Dose 1	Myocarditis / Unknown	Possible; with limited information	Chest pain; raised troponin. Limited information on medical history and concomitant medications
35	[redacted] / Y / N	34 / F	Not Reported / Not Reported	5 / Dose 1	Myocarditis / Recovering	Possible; with limited information	Chest pain; palpitations; dyspnoea; raised troponin. Limited information on medical history and concomitant medications
36	[redacted] / Y / Y	50 / M	Obesity; Type 1 diabetes mellitus; Sleep apnoea syndrome / Not Reported	5 / Dose 2	Myocarditis / Recovered	Possible; with risk factors	Troponin; dyspnoea. Confounded by medical history of obesity; insulin-dependent diabetes mellitus; and chronic obstructive sleep apnoea syndrome
37	[redacted] / Y / N	39 / M	Not reported / Not Reported	25 / Dose 1	Myocarditis / Unknown	Possible; with limited information	TTO within risk window. Symptoms of angina pectoris and elevated troponin. Limited information on medical history and concomitant medications; limited work-up
38	[redacted] Y / N	77 / M	Stent placement; Food allergy; Non-tobacco user / Aspirin;	Unknown / Dose Unknown	Myocarditis / Not recovered	Unassessable / Unclassifiable	Raised Troponin and chest pain. Unknown TTO. Confounded by medical history of anginal

Table 69 Case reports of Myocarditis with VAXZEVRIA fulfilling Brighton Collaboration Criteria Level 2 (N=52) reported cumulatively till DLP 28 June 2022

Sr. No.	Case ID / Country / Serious (Y/N) / Medically Confirmed (Y/N)	Age (Years) / Gender (M/F)	Medical History / concomitant medications	Time to Onset (days) / Dose #	Event / Outcome	WHO-UMC Causality Assessment	Additional Comment / Causality Assessment
			Atorvastatin; Bisoprolol; Tamsulosin; Omeprazole				pain and stent placement; elderly patient (≥65 years could be risk factor)
39	[redacted] / Y / Y	48 / F	Hypothyroidism / Not Reported	81 / Dose 1	Giant cell myocarditis / Not recovered	Unlikely	Elevated troponin and abnormal ECHO; confounded by intentional product misuse (1st dose with VAXZEVRIA 2nd dose with Pfizer vaccine) and Interchange of vaccine products; history of Hypothyroidism
40	[redacted] Y / Y	49 / F	Drug hypersensitivity; Drug hypersensitivity; Hypothyroidism; Drug hypersensitivity / Synthroid (Levothyroxine Sodium)	56 / Dose 1	Myocarditis / Not recovered	Unlikely	Elevated troponin; abnormal ECHO and endomyocardial biopsy showing inflammation; confounded by intentional product misuse (1st dose with VAXZEVRIA 2nd dose with Pfizer vaccine) and interchange of vaccine; history of Hypothyroidism
41	[redacted] / Y / N	29 / M	Not reported / Not Reported	27 / Dose 1	Myocarditis / Recovered with sequelae	Possible; with limited information	TTO within risk window; elevated troponin and increased C-reactive protein; limited information on medical history and concomitant medications
42	[redacted] Y / Y	42 / M	Acute kidney injury / Not Reported	Unknown / Dose 1	Myopericarditis / Recovering	Unassessable / Unclassifiable	EKG finding; >1 myocardial biomarker; >1 cardiac symptom; history of acute kidney injury; Confounder -multiple organ failure
43	[redacted] Y / Y	Unk / F	Not Reported / Clarithromycin; Cyclizine	1 / Dose 1	Myopericarditis / Not recovered	Unlikely	Chest pain with elevated Troponin and lethargy; Limited work up info on medical history

Table 69 Case reports of Myocarditis with VAXZEVRIA fulfilling Brighton Collaboration Criteria Level 2 (N=52) reported cumulatively till DLP 28 June 2022

Sr. No.	Case ID / Country / Serious (Y/N) / Medically Confirmed (Y/N)	Age (Years) / Gender (M/F)	Medical History / concomitant medications	Time to Onset (days) / Dose #	Event / Outcome	WHO-UMC Causality Assessment	Additional Comment / Causality Assessment
44	[redacted] Y / Y	27 / M	Not Reported / Not Reported	107 / Dose 2	Myopericarditis / Recovering	Unlikely	Chest Pain with elevated Troponin, ECG result: saddle ST changes in lateral leads; limited information on medical history and concomitant medications
45	[redacted] Y / N	46 / M	Chest pain / Aspirin; Atorvastatin; Bisoprolol; Clopidogrel; Colchicine; Glyceryl Trinitrate; Lansoprazole	74 / Dose 2	Myopericarditis / Not recovered	Unlikely	Cardiac symptoms with elevated Troponin; Underlying cardiac condition; on anti-lipids could be risk factors
46	[redacted] / Y / Y	23 / M	Generalised anxiety disorder; Asthma / Not Reported	17 / Dose 1	Myopericarditis / Unknown	Possible; with limited information	ECG findings (slight axis shift to the right. After review by a cardiologist; BRD plus BAV 1 grade ECOTT), chest pain with elevated Troponin; limited work up info
47	[redacted] Y / N	38 / M	Not Reported / Not Reported	10 / Dose 1	Myopericarditis / Recovered with sequelae	Possible; with limited information	Palpitation, fatigue with increased Troponin; limited information on medical history and concomitant medications
48	[redacted] Y / N	47 / F	Not Reported / Not Reported	Unknown / Dose Unknown	Myopericarditis / Unknown	Unassessable / Unclassifiable	Chest Pain with elevated Troponin along with fatigue and palpitation; limited information on medical history and concomitant medications; Unknown TTO
49	[redacted] Y / Y	62 / M	Occupational exposure to dust; Asymptomatic COVID-19 / Not Reported	Unknown / Dose Unknown	Myopericarditis / Recovered	Conditional / Unclassified	Dyspnoea, weakness with elevated Troponin; The TTO for Myocarditis onset was not clear but seems to be out of expected risk window. Also, Patient had past history of covid infection prior to AZ exposure; other commodities -

Table 69 Case reports of Myocarditis with VAXZEVRIA fulfilling Brighton Collaboration Criteria Level 2 (N=52) reported cumulatively till DLP 28 June 2022

Sr. No.	Case ID / Country / Serious (Y/N) / Medically Confirmed (Y/N)	Age (Years) / Gender (M/F)	Medical History / concomitant medications	Time to Onset (days) / Dose #	Event / Outcome	WHO-UMC Causality Assessment	Additional Comment / Causality Assessment
							respiratory infection; pneumonitis with fibrosis on MRI; MRI result supports pneumonitis rather than Myocarditis
50	[redacted] / Y / Y	31 / M	Not reported / [redacted]	3 / Dose 1	Myocarditis / Recovering	Possible; with risk factors	Alternative cause [redacted] (This is [redacted] known to cause myocarditis)
51	[redacted] / Y / Y	36 / F	Psychomotor hyperactivity / Not Reported	208 / Dose 2	Myopericarditis / Recovering	Unlikely	Onset of symptom was few days after exposure to non-AZ vaccine; Also, alternative cause COVID-19
52	[redacted] N / N	16 / M	Not Reported / Not Reported	Unknown / Dose 1	Myopericarditis / Unknown	Unassessable / Unclassifiable	Unknown TTO. Limited information on medical history and concomitant medications

TTO, Time to onset; cMRI, Magnetic resonance imaging; ECG, electrocardiography; EKG, Electrocardiogram; EF, Ejection Fraction; CT, Computed tomography; ECHO Echocardiography; BAV, Bicuspid aortic valve; Unk, Unknown; F, Female; M, Male

Brighton Collaboration Classification Level 3

Of the 761, no case reports fulfilled Brighton collaboration level 3 criteria.

Brighton Collaboration Classification Level 4

Of the total 761 case reports, 390 (51.2%) fulfilled BCC Level 4 criteria. These case reports did not fulfil criteria for certainty levels 1, 2 and 3, as there was insufficient information to confirm the diagnosis or medical assessment of the case.

Brighton Collaboration Classification Level 5

A total of 307 (40.3%) of the 761 case reports of Myocarditis fulfilled BCC Level 5 criteria (ie, Myocarditis excluded due to an alternative diagnosis, hence a not a case of Myocarditis).

WHO-UMC causality analysis for BCC-1 to BCC-3 case reports

WHO-UMC causality assessment for Myocarditis was performed for BCC levels 1 (12 cases), 2 (52 cases) and 3 (none) cases for diagnostic certainty, these 64 cases are presented in Table 70:

Table 70 Overview of WHO-UMC Causality Assessment for BCC level 1 to BCC level 3 case reports of Myocarditis with VAXZEVRIA reported cumulatively through DLP 28 June 2022

WHO-UMC Causality category	WHO-UMC Causality assessment scale (AZ adapted)	Number of Cases
Certain	Certain	0
Probable-Likely	Probable-Likely	0
Possible	Possible; with risk factors/confounders[a]	8
	Possible; with Limited information	21
Unlikely	Unlikely	14
Conditional / Unclassified	Conditional / Unclassified	5
Unassessable/Unclassifiable	Unassessable/Unclassifiable with risk factors/confounders*	7
	Unassessable/Unclassifiable with limited information	9
Total		**64**

[a] Cases were considered to have "risk *factors/confounders" where the event could also be explained by the vaccinee's diseases, or where relevant risk factors were present, or concomitant medications that could potentially contribute to the development of the event were reported.*

Amongst 64 cases for Myocarditis, 22 (34.4%) were identified either with risk / confounding factors as presented in Table 71.These are categorised into the following groups and presented in descending order of frequency.

Table 71 Relevant Risk factors / Confounders identified for BCC-1 to BCC-3 case reports cumulatively through DLP 28 June 2022

Relevant Risk / Confounders	Number of reports	Percent of Total Number of Reports
Chronic conditions: (Hypertension, Type 1 diabetes mellitus, Hypothyroidism, Heart transplant, Pulmonary embolism, Hypercholesterolemia, Myocarditis, Coronary heart disease, Deep vein thrombosis, acute kidney injury, obesity etc)	17	21.9%
Patient's age (Elderly age: ≥ 65 years)	4[a]	6.3%
Concurrent infection	3	4.7%
Other factor: Interchange of vaccine products (1st dose with VAXZEVRIA 2nd dose with Pfizer vaccine)	2[a]	3.1%
Concomitant medications (cocaine and ecstasy).	1	1.6%

[a] In 5 cases more than 1 risk factors were reported (3 cases chronic condition + Elderly age: ≥ 65 years and 2 cases chronic condition + Intentional product misuse) hence the total is more than 22

In the remaining 42 (65.6%) case reports, there was insufficient information with respect to either time to onset, medical history/co-morbidities, concomitant medication details, and clinical course for a comprehensive causal assessment.

Overall, the review for case reports of Myocarditis did not raise any new relevant safety information for VAXZEVRIA.

Observed Versus Expected (O/E) Analyses

An O/E analysis of Myocarditis was conducted cumulatively through 28 June 2022 and presented in Table 72. The results are stratified by risk windows (7 days, 14 days, 21 days, and 42 days) age group (18--49 years, 50--59 years, 60--69 years, ≥ 70 years), gender and with dose (Dose 1 and Dose 2 for regions EEA, UK, Australia, Canada, Philippines, Argentina, Malaysia, New Zealand, Colombia, Taiwan, Brazil, and Thailand).

Background incidence rates from Truven Marketscan (2019) have been used for O/E analyses.

Conservatively, the exposure for global reports (448306152) is based on doses administered in 13 markets as explained in Appendix 8.

Table 72 Observed versus expected cumulative analyses through 28 June 2022 for reports of Myocarditis with risk windows of 2-42 days (7 days, 14 days, 21 days and 42 days)

Myocarditis / age groups (years) / gender / Dose	Risk window	BG rates	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
Myocarditis - All cases, all ages, medically confirmed and medically non-confirmed (RW 7, RW 14, RW 21, RW 42)							
Myocarditis - All cases, all ages MC and NC (RW 7)	7	9.62	448306152	103	826.55	0.12 (0.1 - 0.15)	Observed significantly < expected
Myocarditis - All cases, all ages MC and NC (RW 14)	14	9.62	448306152	150	1653.09	0.09 (0.08 - 0.11)	Observed significantly < expected
Myocarditis - All cases, all ages MC and NC (RW 21)	21	9.62	448306152	181	2479.64	0.07 (0.06 - 0.08)	Observed significantly < expected
Myocarditis - All cases, all ages MC and NC (RW 42)	42	9.62	448306152	255	4959.27	0.05 (0.05 - 0.06)	Observed significantly < expected
Myocarditis - All cases, all ages, medically confirmed and medically non-confirmed (RW 7, RW 14, RW 21, RW 42 + Unknown)							
Myocarditis - All cases, all ages MC and NC (RW 7 + Unk)	7	9.62	448306152	481	826.55	0.58 (0.53 - 0.64)	Observed significantly < expected
Myocarditis - All cases, all ages MC and NC (RW 14 + Unk)	14	9.62	448306152	528	1653.09	0.32 (0.29 - 0.35)	Observed significantly < expected
Myocarditis - All cases, all ages MC and NC (RW 21 + Unk)	21	9.62	448306152	559	2479.64	0.23 (0.21 - 0.24)	Observed significantly < expected
Myocarditis - All cases, all ages MC and NC (RW 42 + Unk)	42	9.62	448306152	633	4959.27	0.13 (0.12 - 0.14)	Observed significantly < expected
Myocarditis - all ages, medically confirmed (RW 7, RW 14, RW 21, RW 42)							
Myocarditis - all ages MC (RW 7)	7	9.62	448306152	54	826.55	0.07 (0.05 - 0.09)	Observed significantly < expected

Table 72 Observed versus expected cumulative analyses through 28 June 2022 for reports of Myocarditis with risk windows of 2-42 days (7 days, 14 days, 21 days and 42 days)

Myocarditis / age groups (years) / gender / Dose	Risk window	BG rates	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
Myocarditis - all ages MC (RW 14)	14	9.62	448306152	76	1653.09	0.05 (0.04 - 0.06)	Observed significantly < expected
Myocarditis - all ages MC (RW 21)	21	9.62	448306152	89	2479.64	0.04 (0.03 - 0.04)	Observed significantly < expected
Myocarditis - all ages MC (RW 42)	42	9.62	448306152	112	4959.27	0.02 (0.02 - 0.03)	Observed significantly < expected
Myocarditis - all ages, medically confirmed (RW 7, RW 14, RW 21, RW 42 + Unknown)							
Myocarditis - all ages MC (RW 7 + Unk)	7	9.62	448306152	118	826.55	0.14 (0.12 - 0.17)	Observed significantly < expected
Myocarditis - all ages MC (RW 14 + Unk)	14	9.62	448306152	140	1653.09	0.08 (0.07 - 0.1)	Observed significantly < expected
Myocarditis - all ages MC (RW 21 + Unk)	21	9.62	448306152	153	2479.64	0.06 (0.05 - 0.07)	Observed significantly < expected
Myocarditis - all ages MC (RW 42 + Unk)	42	9.62	448306152	176	4959.27	0.04 (0.03 - 0.04)	Observed significantly < expected
Myocarditis - EU / UK / Brazil / Australia, medically confirmed and medically non-confirmed (RW 7)							
Myocarditis (MC and NC)- 18 to 49, EU / UK / Brazil / Australia (RW 7)	7	8.19	100987434	50	158.51	0.32 (0.23 - 0.42)	Observed significantly < expected
Myocarditis (MC and NC)- 50 to 59, EU / UK / Brazil / Australia (RW 7)	7	9.5	56425075	16	102.73	0.16 (0.09 - 0.25)	Observed significantly < expected
Myocarditis (MC and NC)- 60 to 69, EU / UK / Brazil / Australia (RW 7)	7	13.33	57182485	21	146.09	0.14 (0.09 - 0.22)	Observed significantly < expected
Myocarditis (MC and NC)- Over 70, EU / UK /	7	18.66	31869628	8	113.97	0.07 (0.03 - 0.14)	Observed significantly < expected

Table 72 Observed versus expected cumulative analyses through 28 June 2022 for reports of Myocarditis with risk windows of 2-42 days (7 days, 14 days, 21 days and 42 days)

Myocarditis / age groups (years) / gender / Dose	Risk window	BG rates	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
Brazil / Australia (RW 7)							
Myocarditis - EU / UK / Brazil / Australia, medically confirmed and medically non-confirmed (RW 14)							
Myocarditis (MC and NC)- 18 to 49, EU / UK / Brazil / Australia (RW 14)	14	8.19	100987434	68	317.03	0.21 (0.17 - 0.27)	Observed significantly < expected
Myocarditis (MC and NC)- 50 to 59, EU / UK / Brazil / Australia (RW 14)	14	9.5	56425075	25	205.47	0.12 (0.08 - 0.18)	Observed significantly < expected
Myocarditis (MC and NC)- 60 to 69, EU / UK / Brazil / Australia (RW 14)	14	13.33	57182485	29	292.17	0.1 (0.07 - 0.14)	Observed significantly < expected
Myocarditis (MC and NC)- Over 70, EU / UK / Brazil / Australia (RW 14)	14	18.66	31869628	12	227.95	0.05 (0.03 - 0.09)	Observed significantly < expected
Myocarditis - EU / UK / Brazil / Australia, medically confirmed and medically non-confirmed (RW 21)							
Myocarditis (MC and NC)- 18 to 49, EU / UK / Brazil / Australia (RW 21)	21	8.19	100987434	81	475.54	0.17 (0.14 - 0.21)	Observed significantly < expected
Myocarditis (MC and NC)- 50 to 59, EU / UK / Brazil / Australia (RW 21)	21	9.5	56425075	26	308.2	0.08 (0.06 - 0.12)	Observed significantly < expected
Myocarditis (MC and NC)- 60 to 69, EU / UK / Brazil / Australia (RW 21)	21	13.33	57182485	35	438.26	0.08 (0.06 - 0.11)	Observed significantly < expected

Table 72 Observed versus expected cumulative analyses through 28 June 2022 for reports of Myocarditis with risk windows of 2-42 days (7 days, 14 days, 21 days and 42 days)

Myocarditis / age groups (years) / gender / Dose	Risk window	BG rates	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
Myocarditis (MC and NC)- Over 70, EU / UK / Brazil / Australia (RW 21)	21	18.66	31869628	16	341.92	0.05 (0.03 - 0.08)	Observed significantly < expected
Myocarditis - EU / UK / Brazil / Australia, medically confirmed and medically non-confirmed (RW 42)							
Myocarditis (MC and NC)- 18 to 49, EU / UK / Brazil / Australia (RW 42)	42	8.19	100987434	115	951.08	0.12 (0.1 - 0.15)	Observed significantly < expected
Myocarditis (MC and NC)- 50 to 59, EU / UK / Brazil / Australia (RW 42)	42	9.5	56425075	42	616.4	0.07 (0.05 - 0.09)	Observed significantly < expected
Myocarditis (MC and NC)- 60 to 69, EU / UK / Brazil / Australia (RW 42)	42	13.33	57182485	47	876.52	0.05 (0.04 - 0.07)	Observed significantly < expected
Myocarditis (MC and NC)- Over 70, EU / UK / Brazil / Australia (RW 42)	42	18.66	31869628	21	683.84	0.03 (0.02 - 0.05)	Observed significantly < expected
Myocarditis - UK Females (RW 7), medically confirmed and medically non-confirmed							
Myocarditis (MC and NC) - Female 18 to 29 UK (RW 7)	7	5.91	1221578	1	1.38	0.72 (0.02 - 4.04)	Observed < expected
Myocarditis (MC and NC) - Female 30 to 39 UK (RW 7)	7	5.68	2028622	2	2.21	0.9 (0.11 - 3.27)	Observed < expected
Myocarditis (MC and NC) - Female 40 to 49 UK (RW 7)	7	5.5	4749427	2	5.01	0.4 (0.05 - 1.44)	Observed < expected

Table 72 Observed versus expected cumulative analyses through 28 June 2022 for reports of Myocarditis with risk windows of 2-42 days (7 days, 14 days, 21 days and 42 days)

Myocarditis / age groups (years) / gender / Dose	Risk window	BG rates	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
Myocarditis (MC and NC) - Female 50 to 59 UK (RW 7)	7	7.5	6280795	4	9.03	0.44 (0.12 - 1.13)	Observed < expected
Myocarditis (MC and NC) - Female 60 to 69 UK (RW 7)	7	12.21	4996322	0	11.69	0 (0 - 0.32)	Observed significantly < expected
Myocarditis (MC and NC) - Female 70 to 79 UK (RW 7)	7	18.88	3688886	1	13.35	0.07 (0 - 0.42)	Observed significantly < expected
Myocarditis (MC and NC) - Female 80 plus UK (RW 7)	7	13.81	1864578	0	4.94	0 (0 - 0.75)	Observed significantly < expected
Myocarditis - UK Males (RW 7), medically confirmed and medically non-confirmed							
Myocarditis (MC and NC) - Male 18 to 29 UK (RW 7)	7	11.79	907479	4	2.05	1.95 (0.53 - 5)	Observed > expected
Myocarditis (MC and NC) - Male 30 to 39 UK (RW 7)	7	10.67	1537246	2	3.14	0.64 (0.08 - 2.3)	Observed < expected
Myocarditis (MC and NC) - Male 40 to 49 UK (RW 7)	7	10.14	4955204	4	9.63	0.42 (0.11 - 1.06)	Observed < expected
Myocarditis (MC and NC) - Male 50 to 59 UK (RW 7)	7	11.73	6915956	5	15.55	0.32 (0.1 - 0.75)	Observed significantly < expected
Myocarditis (MC and NC) - Male 60 to 69 UK (RW 7)	7	14.57	5160658	1	14.41	0.07 (0 - 0.39)	Observed significantly < expected
Myocarditis (MC and NC) - Male 70 to 79 UK (RW 7)	7	21.39	3358831	1	13.77	0.07 (0 - 0.4)	Observed significantly < expected

Table 72 Observed versus expected cumulative analyses through 28 June 2022 for reports of Myocarditis with risk windows of 2-42 days (7 days, 14 days, 21 days and 42 days)

Myocarditis / age groups (years) / gender / Dose	Risk window	BG rates	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
Myocarditis (MC and NC) - Male 80 plus UK (RW 7)	7	13.09	1160382	0	2.91	0 (0 - 1.27)	Observed < expected
Myocarditis - UK Females (RW 14), medically confirmed and medically non-confirmed							
Myocarditis (MC and NC) - Female 18 to 29 UK (RW 14)	14	5.91	1221578	1	2.77	0.36 (0.01 - 2.01)	Observed < expected
Myocarditis (MC and NC) - Female 30 to 39 UK (RW 14)	14	5.68	2028622	2	4.42	0.45 (0.05 - 1.63)	Observed < expected
Myocarditis (MC and NC) - Female 40 to 49 UK (RW 14)	14	5.5	4749427	5	10.01	0.5 (0.16 - 1.17)	Observed < expected
Myocarditis (MC and NC) - Female 50 to 59 UK (RW 14)	14	7.5	6280795	9	18.06	0.5 (0.23 - 0.95)	Observed significantly < expected
Myocarditis (MC and NC) - Female 60 to 69 UK (RW 14)	14	12.21	4996322	3	23.38	0.13 (0.03 - 0.37)	Observed significantly < expected
Myocarditis (MC and NC) - Female 70 to 79 UK (RW 14)	14	18.88	3688886	1	26.7	0.04 (0 - 0.21)	Observed significantly < expected
Myocarditis (MC and NC) - Female 80 plus UK (RW 14)	14	13.81	1864578	0	9.87	0 (0 - 0.37)	Observed significantly < expected
Myocarditis - UK Males (RW 14), medically confirmed and medically non-confirmed							
Myocarditis (MC and NC) - Male 18 to 29 UK (RW 14)	14	11.79	907479	5	4.1	1.22 (0.4 - 2.85)	Observed > expected
Myocarditis (MC and NC) - Male	14	10.67	1537246	3	6.29	0.48 (0.1 - 1.39)	Observed < expected

Table 72 Observed versus expected cumulative analyses through 28 June 2022 for reports of Myocarditis with risk windows of 2-42 days (7 days, 14 days, 21 days and 42 days)

Myocarditis / age groups (years) / gender / Dose	Risk window	BG rates	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
30 to 39 UK (RW 14)							
Myocarditis (MC and NC) - Male 40 to 49 UK (RW 14)	14	10.14	4955204	7	19.26	0.36 (0.15 - 0.75)	Observed significantly < expected
Myocarditis (MC and NC) - Male 50 to 59 UK (RW 14)	14	11.73	6915956	7	31.1	0.23 (0.09 - 0.46)	Observed significantly < expected
Myocarditis (MC and NC) - Male 60 to 69 UK (RW 14)	14	14.57	5160658	2	28.82	0.07 (0.01 - 0.25)	Observed significantly < expected
Myocarditis (MC and NC) - Male 70 to 79 UK (RW 14)	14	21.39	3358831	1	27.54	0.04 (0 - 0.2)	Observed significantly < expected
Myocarditis (MC and NC) - Male 80 plus UK (RW 14)	14	13.09	1160382	0	5.82	0 (0 - 0.63)	Observed significantly < expected
Myocarditis - UK Females (RW 21), medically confirmed and medically non-confirmed							
Myocarditis (MC and NC) - Female 18 to 29 UK (RW 21)	21	5.91	1221578	1	4.15	0.24 (0.01 - 1.34)	Observed < expected
Myocarditis (MC and NC) - Female 30 to 39 UK (RW 21)	21	5.68	2028622	2	6.63	0.3 (0.04 - 1.09)	Observed < expected
Myocarditis (MC and NC) - Female 40 to 49 UK (RW 21)	21	5.5	4749427	7	15.02	0.47 (0.19 - 0.96)	Observed significantly < expected
Myocarditis (MC and NC) - Female 50 to 59 UK (RW 21)	21	7.5	6280795	9	27.08	0.33 (0.15 - 0.63)	Observed significantly < expected

Table 72 Observed versus expected cumulative analyses through 28 June 2022 for reports of Myocarditis with risk windows of 2-42 days (7 days, 14 days, 21 days and 42 days)

Myocarditis / age groups (years) / gender / Dose	Risk window	BG rates	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
Myocarditis (MC and NC) - Female 60 to 69 UK (RW 21)	21	12.21	4996322	5	35.08	0.14 (0.05 - 0.33)	Observed significantly < expected
Myocarditis (MC and NC) - Female 70 to 79 UK (RW 21)	21	18.88	3688886	1	40.04	0.02 (0 - 0.14)	Observed significantly < expected
Myocarditis (MC and NC) - Female 80 plus UK (RW 21)	21	13.81	1864578	0	14.81	0 (0 - 0.25)	Observed significantly < expected
Myocarditis - UK Males (RW 21), medically confirmed and medically non-confirmed							
Myocarditis (MC and NC) - Male 18 to 29 UK (RW 21)	21	11.79	907479	5	6.15	0.81 (0.26 - 1.9)	Observed < expected
Myocarditis (MC and NC) - Male 30 to 39 UK (RW 21)	21	10.67	1537246	4	9.43	0.42 (0.12 - 1.09)	Observed < expected
Myocarditis (MC and NC) - Male 40 to 49 UK (RW 21)	21	10.14	4955204	7	28.89	0.24 (0.1 - 0.5)	Observed significantly < expected
Myocarditis (MC and NC) - Male 50 to 59 UK (RW 21)	21	11.73	6915956	7	46.64	0.15 (0.06 - 0.31)	Observed significantly < expected
Myocarditis (MC and NC) - Male 60 to 69 UK (RW 21)	21	14.57	5160658	2	43.23	0.05 (0.01 - 0.17)	Observed significantly < expected
Myocarditis (MC and NC) - Male 70 to 79 UK (RW 21)	21	21.39	3358831	1	41.31	0.02 (0 - 0.13)	Observed significantly < expected
Myocarditis (MC and NC) - Male 80 plus UK (RW 21)	21	13.09	1160382	0	8.73	0 (0 - 0.42)	Observed significantly < expected

Table 72 Observed versus expected cumulative analyses through 28 June 2022 for reports of Myocarditis with risk windows of 2-42 days (7 days, 14 days, 21 days and 42 days)

Myocarditis / age groups (years) / gender / Dose	Risk window	BG rates	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
Myocarditis - UK Females (RW 42), medically confirmed and medically non-confirmed							
Myocarditis (MC and NC) - Female 18 to 29 UK (RW 42)	42	5.91	1221578	3	8.3	0.36 (0.07 - 1.06)	Observed < expected
Myocarditis (MC and NC) - Female 30 to 39 UK (RW 42)	42	5.68	2028622	5	13.25	0.38 (0.12 - 0.88)	Observed significantly < expected
Myocarditis (MC and NC) - Female 40 to 49 UK (RW 42)	42	5.5	4749427	9	30.04	0.3 (0.14 - 0.57)	Observed significantly < expected
Myocarditis (MC and NC) - Female 50 to 59 UK (RW 42)	42	7.5	6280795	11	54.17	0.2 (0.1 - 0.36)	Observed significantly < expected
Myocarditis (MC and NC) - Female 60 to 69 UK (RW 42)	42	12.21	4996322	6	70.15	0.09 (0.03 - 0.19)	Observed significantly < expected
Myocarditis (MC and NC) - Female 70 to 79 UK (RW 42)	42	18.88	3688886	2	80.09	0.02 (0 - 0.09)	Observed significantly < expected
Myocarditis (MC and NC) - Female 80 plus UK (RW 42)	42	13.81	1864578	0	29.61	0 (0 - 0.12)	Observed significantly < expected
Myocarditis - UK Males (RW 42), medically confirmed and medically non-confirmed							
Myocarditis (MC and NC) - Male 18 to 29 UK (RW 42)	42	11.79	907479	7	12.3	0.57 (0.23 - 1.17)	Observed < expected
Myocarditis (MC and NC) - Male 30 to 39 UK (RW 42)	42	10.67	1537246	5	18.86	0.27 (0.09 - 0.62)	Observed significantly < expected
Myocarditis (MC and NC) - Male	42	10.14	4955204	10	57.78	0.17 (0.08 - 0.32)	Observed significantly < expected

Table 72 Observed versus expected cumulative analyses through 28 June 2022 for reports of Myocarditis with risk windows of 2-42 days (7 days, 14 days, 21 days and 42 days)

Myocarditis / age groups (years) / gender / Dose	Risk window	BG rates	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
40 to 49 UK (RW 42)							
Myocarditis (MC and NC) - Male 50 to 59 UK (RW 42)	42	11.73	6915956	10	93.29	0.11 (0.05 - 0.2)	Observed significantly < expected
Myocarditis (MC and NC) - Male 60 to 69 UK (RW 42)	42	14.57	5160658	3	86.46	0.03 (0.01 - 0.1)	Observed significantly < expected
Myocarditis (MC and NC) - Male 70 to 79 UK (RW 42)	42	21.39	3358831	2	82.62	0.02 (0 - 0.09)	Observed significantly < expected
Myocarditis (MC and NC) - Male 80 plus UK (RW 42)	42	13.09	1160382	0	17.47	0 (0 - 0.21)	Observed significantly < expected
Myocarditis - EU / UK / Australia / Canada / Philippines / Argentina / Malaysia / New Zealand / Colombia / Taiwan / Brazil / Thailand cases, all ages, Dose 1 and Dose 2, medically confirmed and medically non-confirmed (RW 7)							
Dose 1, All cases, all ages MC and NC, EU / UK / Australia / Canada / Philippines / Argentina / Malaysia / New Zealand / Colombia / Taiwan / Brazil / Thailand (RW 7)	7	9.62	184481881	83	340.13	0.24 (0.19 - 0.3)	Observed significantly < expected
Dose 1, All cases, all ages MC and NC, EU / UK / Australia / Canada / Philippines / Argentina / Malaysia / New Zealand / Colombia /	7	9.62	184481881	289	340.13	0.85 (0.75 - 0.95)	Observed significantly < expected

Table 72 Observed versus expected cumulative analyses through 28 June 2022 for reports of Myocarditis with risk windows of 2-42 days (7 days, 14 days, 21 days and 42 days)

Myocarditis / age groups (years) / gender / Dose	Risk window	BG rates	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
Taiwan / Brazil / Thailand (RW 7 + Unk)							
Dose 2, All cases, all ages MC and NC, EU / UK / Australia / Canada / Philippines / Argentina / Malaysia / New Zealand / Colombia / Taiwan / Brazil / Thailand (RW 7)	7	9.62	178903868	15	329.85	0.05 (0.03 - 0.08)	Observed significantly < expected
Dose 2, All cases, all ages MC and NC, EU / UK / Australia / Canada / Philippines / Argentina / Malaysia / New Zealand / Colombia / Taiwan / Brazil / Thailand (RW 7 + Unk)	7	9.62	178903868	88	329.85	0.27 (0.21 - 0.33)	Observed significantly < expected
Myocarditis - EU / UK / Australia / Canada / Philippines / Argentina / Malaysia / New Zealand / Colombia / Taiwan / Brazil / Thailand cases, all ages, Dose 1 and Dose 2, medically confirmed and medically non-confirmed (RW 14)							
Dose 1, All cases, all ages MC and NC, EU / UK / Australia / Canada / Philippines / Argentina / Malaysia / New Zealand / Colombia / Taiwan / Brazil /	14	9.62	184481881	109	680.26	0.16 (0.13 - 0.19)	Observed significantly < expected

Table 72 Observed versus expected cumulative analyses through 28 June 2022 for reports of Myocarditis with risk windows of 2-42 days (7 days, 14 days, 21 days and 42 days)

Myocarditis / age groups (years) / gender / Dose	Risk window	BG rates	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
Thailand (RW 14)							
Dose 1, All cases, all ages MC and NC, EU / UK / Australia / Canada / Philippines / Argentina / Malaysia / New Zealand / Colombia / Taiwan / Brazil / Thailand (RW 14 + Unk)	14	9.62	184481881	315	680.26	0.46 (0.41 - 0.52)	Observed significantly < expected
Dose 2, All cases, all ages MC and NC, EU / UK / Australia / Canada / Philippines / Argentina / Malaysia / New Zealand / Colombia / Taiwan / Brazil / Thailand (RW 14)	14	9.62	178903868	31	659.69	0.05 (0.03 - 0.07)	Observed significantly < expected
Dose 2, All cases, all ages MC and NC, EU / UK / Australia / Canada / Philippines / Argentina / Malaysia / New Zealand / Colombia / Taiwan / Brazil /	14	9.62	178903868	104	659.69	0.16 (0.13 - 0.19)	Observed significantly < expected

Table 72 Observed versus expected cumulative analyses through 28 June 2022 for reports of Myocarditis with risk windows of 2-42 days (7 days, 14 days, 21 days and 42 days)

Myocarditis / age groups (years) / gender / Dose	Risk window	BG rates	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
Thailand (RW 14 + Unk)							
Myocarditis - EU / UK / Australia / Canada / Philippines / Argentina / Malaysia / New Zealand / Colombia / Taiwan / Brazil / Thailand cases, all ages, Dose 1 and Dose 2, medically confirmed and medically non-confirmed (RW 21)							
Dose 1, All cases, all ages MC and NC, EU / UK / Australia / Canada / Philippines / Argentina / Malaysia / New Zealand / Colombia / Taiwan / Brazil / Thailand (RW 21)	21	9.62	178903868	135	989.54	0.14 (0.11 - 0.16)	Observed significantly < expected
Dose 1, All cases, all ages MC and NC, EU / UK / Australia / Canada / Philippines / Argentina / Malaysia / New Zealand / Colombia / Taiwan / Brazil / Thailand (RW 21 + Unk)	21	9.62	178903868	341	989.54	0.34 (0.31 - 0.38)	Observed significantly < expected
Dose 2, All cases, all ages MC and NC, EU / UK / Australia / Canada / Philippines / Argentina / Malaysia / New Zealand / Colombia / Taiwan / Brazil /	21	9.62	184481881	34	1020.39	0.03 (0.02 - 0.05)	Observed significantly < expected

Table 72 Observed versus expected cumulative analyses through 28 June 2022 for reports of Myocarditis with risk windows of 2-42 days (7 days, 14 days, 21 days and 42 days)

Myocarditis / age groups (years) / gender / Dose	Risk window	BG rates	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
Thailand (RW 21)							
Dose 2, All cases, all ages MC and NC, EU / UK / Australia / Canada / Philippines / Argentina / Malaysia / New Zealand / Colombia / Taiwan / Brazil / Thailand (RW 21 + Unk)	21	9.62	184481881	107	1020.39	0.1 (0.09 - 0.13)	Observed significantly < expected
Myocarditis - EU / UK / Australia / Canada / Philippines / Argentina / Malaysia / New Zealand / Colombia / Taiwan / Brazil / Thailand cases, all ages, Dose 1 and Dose 2, medically confirmed and medically non-confirmed (RW 42)							
Dose 1, All cases, all ages MC and NC, EU / UK / Australia / Canada / Philippines / Argentina / Malaysia / New Zealand / Colombia / Taiwan / Brazil / Thailand (RW 42)	42	9.62	178903868	184	1979.08	0.09 (0.08 - 0.11)	Observed significantly < expected
Dose 1, All cases, all ages MC and NC, EU / UK / Australia / Canada / Philippines / Argentina / Malaysia / New Zealand / Colombia / Taiwan / Brazil /	42	9.62	178903868	390	1979.08	0.2 (0.18 - 0.22)	Observed significantly < expected

Table 72 Observed versus expected cumulative analyses through 28 June 2022 for reports of Myocarditis with risk windows of 2-42 days (7 days, 14 days, 21 days and 42 days)

Myocarditis / age groups (years) / gender / Dose	Risk window	BG rates	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
Thailand (RW 42 + Unk)							
Dose 2, All cases, all ages MC and NC, EU / UK / Australia / Canada / Philippines / Argentina / Malaysia / New Zealand / Colombia / Taiwan / Brazil / Thailand (RW 42)	42	9.62	184481881	58	2040.78	0.03 (0.02 - 0.04)	Observed significantly < expected
Dose 2, All cases, all ages MC and NC, EU / UK / Australia / Canada / Philippines / Argentina / Malaysia / New Zealand / Colombia / Taiwan / Brazil / Thailand (RW 42 + Unk)	42	9.62	184481881	131	2040.78	0.06 (0.05 - 0.08)	Observed significantly < expected

MC, medically confirmed; NC, medically non-confirmed; Unk, Unknown; RW, risk window

The observed versus expected analysis for all reported cases of myocarditis with stratifications by risk windows age group, gender and dose suggested that observed cases occurred less frequently than expected, except for age group 18-29 in UK males with risk window 7 and 14 days (where observed cases were more than expected without being statistically significant). However, when a qualitative review was conducted for 5 case reports from 18-29 years age UK males with risk window 7 and 14 days, 1 case had met the BCC level 2 with WHO-UMC causality as possible; however there were limited information on medical history, concomitant medications precluding a proper assessment to determine causal relationship. The remaining 4 case reports were BCC 4/5, as there was insufficient information to confirm the diagnosis or medical assessment of the case. The O/E analysis does not take account of potential confounders for the event, which could provide an alternative explanation.

Literature Review

A search of the literature was performed to review the reports of Myocarditis in association with VAXZEVRIA and other COVID-19 vaccines during the reporting period 29 December 2021 to 28 June 2022.

The searches yielded 469 articles, of these, 68 articles were considered relevant for further review and presentation which included: 19 articles concerning to VAXZEVRIA and 49 articles concerning to other COVID vaccines (mRNA vaccine). These 68 articles were further categorized into (article may be considered in multiple categories);

- 8 articles concerned systematic literature reviews/meta-analyses,
- 50 articles providing information on hypothesized mechanisms leading to Myocarditis after vaccination
- 17 articles concerned myocarditis case reports after vaccination with VAXZEVRIA.

No epidemiological articles with relevant new safety information were identified during the reporting period 29 December 2021 to 28 June 2022.

Systematic reviews/Meta-analyses articles identified during the reporting period 29 December 2021 to 28 June 2022

The search yielded 8 relevant articles from systematic reviews/meta-analyses during the reporting period 29 December 2021 to 28 June 2022 are presented in Table 73 below.

Table 73 Systematic reviews/Meta-analyses articles identified during the reporting period 29 December 2021 to 28 June 2022

Author and article title	Type of study / Objectives / Results	AstraZeneca assessment
Al-Ali D et al 2021 / Cardiovascular and haematological events post COVID-19 vaccination: A systematic review	Study type Systematic review Objective Putting together all the reported cardiovascular and haematological events post COVID-19 vaccination in published literature and to suggest possible mechanisms to explain these rare phenomena Results A total of 50 CI events were reported after receiving Pfizer vaccine (32 myocarditis, 3 myocardial infarction (MI), 11 myopericarditis and 4 others, including 2 pericarditis, 1 acute coronary syndrome (ACS) and 1 stress cardiomyopathy). Twenty-five cases of cardiac events were detected in individuals post Moderna vaccination (24 myocarditis and 1 MI). Seventy-four cardiac events were reported in individuals who received the AstraZeneca vaccine (23 MI, 46 ischemic heart disease and 5 others, including 1 heart strain, 1 cardiac arrest and 3 ACS). These results revealed that more myocarditis and myopericarditis events were reported after the mRNA vaccines, Pfizer and Moderna, while more MI and ischemic heart disease were mainly reported following the VAXZEVRIA vaccination. Overall conclusion as per author The frequency of cardiovascular events in general was higher following the VAXZEVRIA, but more myocarditis and pericarditis cases were reported following mRNA vaccines. Some of the attributes to the use of vaccines may not be true as mechanisms supports more of anaphylactic reaction	Key findings and strength Although cardiac injury, hypertension, hemorrhage, thrombosis and thrombocytopenia were reported as adverse events, reported that the benefits of vaccination outweigh the potential risks Weakness Bias in terms of publishing report (Not the same doses were given in all vaccines reported, as such it is difficult to compare against each other in terms of prevalence) (Another limitation was the lack of evidence that any of the reported events were associated with or induced by the vaccines) • 93 out of the 99 included studies were case reports/case series (many limitations: inability to assess causality particularly in incidental events, lack of generalisability, no denominator data, no comparison group, lack of information on known confounders, high risk of residual confounding, high risk of misclassification, publication bias, etc.) • Age not reported in approx. half the cases who received AZ vaccine, limiting inferences about age-specific risk Conclusion Almost all of the studies included in this review were case reports/case series with the above-mentioned limitations including potential confounding by recognized risk factors such as comorbidities, etc., which were not taken in to consideration. Thus, available information is insufficient to suggest a causal relationship between VAXZEVRIA and cardiovascular events,.

Table 73 Systematic reviews/Meta-analyses articles identified during the reporting period 29 December 2021 to 28 June 2022

Author and article title	Type of study / Objectives / Results	AstraZeneca assessment
Fatima M et al 2022 / Development of myocarditis and pericarditis after COVID-19 vaccination in adult population: A systematic review.	Study type Systematic review Objective The aim of this systematic review is to explore the incidence, clinical presentation, management, and association between myocarditis and pericarditis after covid-19 vaccination. Results Out of the 97, most of the patients received Pfizer-BioNTech (n = 67, 69%) and rest of the patients received 25 (25.7%) Moderna (n = 67, 69%), Janssen Johnson & Johnson (n = 4, 4.1%) and **AstraZeneca (n = 1, 1.03%).** A total of 79 (81.4%) patients developed acute myocarditis, 9 (9.2%) myopericarditis or perimyocarditis, 3 (3%) acute pericarditis, 4 (4.1%) fulminant myocarditis, 1 (1.03%) each with fulminant pericarditis and lymphohistiocytic myocarditis. Overall conclusion as per author Myocarditis and pericarditis after the COVID-19 vaccine occur most commonly in adult males after the second dose of mRNA vaccines (Pfizer and Moderna) especially after the second dose. Viral vector vaccines may be a better alternative for patients with a history of cardiac diseases.	Key findings and strength 5 cohort studies with relatively large sample sizes (15,585,309 participants) and describing Covid-19 vaccine -associated myocarditis/ pericarditis with mean onset of symptoms after vaccine administration of 3.8 ± 4.5 days and 75% of 97 reported cases developing symptoms after the second dose Weakness Although, quality assessment of included studies (methodological strength) was performed. However, the results of this assessment was not presented in main text/discussion. According to the author, "the main limitation of this review is that no large-scale (only from 2 countries; USA and Israel) clinical trial investigating the risk factors, clinical presentation, and prognosis of patients developing myocarditis and pericarditis following COVID-19 vaccination has been conducted so far so only case reports, case series, and cohort studies have been included in the review" Conclusion Of the 5 studies described in the article, cases involving VAXZEVRIA was lower (1.03%) when compared to other mRNA vaccines. The review, however, should still be considered regarding involvement of other mRNA vaccines that exhibit similar complications.

Table 73 Systematic reviews/Meta-analyses articles identified during the reporting period 29 December 2021 to 28 June 2022

Author and article title	Type of study / Objectives / Results	AstraZeneca assessment
Ahmed S K et al 2022 / Global reports of myocarditis following COVID-19 vaccination: A systematic review and meta-analysis	Study type Systematic review and Meta-analysis Objective The main objective is to clarify the potential occurrence of myocarditis associated with COVID-19 vaccination and elaborate on the demographic and clinical characteristics of COVID-19 vaccinated individuals who develop myocarditis and how many cases have been reported in the literature Results Sixty-two studies, including 218 cases, participated in the current systematic review. The median age was 29.2 years; 92.2% were male and 7.8% were female. 72.4% of patients received the Pfizer-BioNTech (COMIRNATY) vaccine, 23.8% of patients received the Moderna COVID-19 Vaccine (mRNA-1273), and the rest of the 3.5% received other types of COVID-19 vaccine. Furthermore, most myocarditis cases (82.1%) occurred after the second vaccine dose, after a median time interval of 3.5 days. The most frequently reported symptoms were chest pain, myalgia/body aches and fever. Troponin levels were consistently elevated in 98.6% of patients. The admission ECG was abnormal in 88.5% of cases, and the left LVEF was lower than 50% in 21.5% of cases. Most patients (92.6%) resolved symptoms and recovered, and only three patients died Overall conclusion as per author The findings may help public health policy to consider myocarditis in the context of the benefits of COVID-19 vaccination.	Key findings and strength Demographics of included studies is very broad. 62 studies, including 218 cases each, from the United States, Italy, Israel, Germany, Poland, France, Korea, Brazil, Japan, Mexico, Spain, New Zealand, Portugal, Germany, Iraq Turkey and Iran participated in this systematic review. Weakness • Most of the studies were case reports/case series (many limitations: inability to assess causality particularly in incidental events, lack of generalisability, no denominator data, no comparison group, lack of information on known confounders, high risk of residual confounding, high risk of misclassification, publication bias, etc.) Percentage of myocarditis cases involving individuals who received VAXZEVRIA was not specified as compared to other vaccines eg, 72.4% of patients received the Pfizer-BioNTech (COMIRNATY) vaccine, 23.8% of patients received the Moderna COVID-19 Vaccine (mRNA-1273). Conclusion Although findings from the review suggests a male predisposition and multiple dosing as risk factors, incidence of Myocarditis post Covid-19 vaccination still similar to typical myocarditis cases. The quality of the included study finding do not contribute new safety information regarding causal relationship of event Myocarditis with VAXZEVRIA.

Table 73 Systematic reviews/Meta-analyses articles identified during the reporting period 29 December 2021 to 28 June 2022

Author and article title	Type of study / Objectives / Results	AstraZeneca assessment
Ilonze OJ et al 2022 / Myocarditis following COVID-19 vaccination in adolescents and adults: a cumulative experience of 2021	Study type Systematic review Objective Aimed at describing a systematic literature review of myocarditis associated with the COVID-19 vaccine in all patients reported globally. Results Myocarditis occurred most commonly after the Pfizer-BioNTech mRNA vaccine (n = 183; 76.45) and after the second dose (n = 182; 80%). Symptoms started 3.95 ± 4.5 days after vaccination. The commonest symptom was chest pain (n = 221; 93%) Overall conclusion as per author Histopathologically, lymphocytic myocarditis is present in the majority of cases. Patients are predominantly males of young age, but all ages and both sexes, as well as all types of vaccines, are represented. Women develop post-vaccine myocarditis at an older age and have longer hospital stay.	Key findings and strength Review represents large international cohort of myocarditis that occurred within 60 days following COVID-19 vaccine. Females who presented with myocarditis post-vaccination were older than men (41.3 ± 21.5 vs 25.7 ± 14 years, p = 0.001), were hospitalized for a longer duration (13.6 ± 21.7 days vs 3.9 ± 3.2 days, p = 0.02), and had a trend towards longer time between the vaccination and onset of symptoms (6.5 ± 7.2 days vs 3.7 ± 4.2 days in males, p = 0.08). Older patients also had a longer duration between the last dose of the vaccine and symptoms onset (4.8 days ± 5.5 days vs 3.0 ± 3.3 days, p = 0.04) Weakness Most of the studies were case reports/case series. 60% of cases reported in North America, but in absence of denominator data we cannot really compare countries -very few cases received VAXZEVRIA, and the denominators are unknown so cannot draw any conclusions comparing vaccines According to the author, "Several cases published in 2022 were not included in the analysis as reported cases were limited to 2021". Per Author, "due to inadequate data in some patients, some may have had concomitant pericarditis (myopericarditis) which may have a variable presentation from frank myocarditis." Conclusion The information available in this review is insufficient to suggest a causal association as risk factors such as medical history, confounders, etc was not ascertained. Review was rather generalized for all vaccines as opposed to specific to VAXZEVRIA.

Table 73 Systematic reviews/Meta-analyses articles identified during the reporting period 29 December 2021 to 28 June 2022

Author and article title	Type of study / Objectives / Results	AstraZeneca assessment
Lane S et al 2021/ Systematic review of spontaneous reports of myocarditis and pericarditis in transplant recipients and immunocompromised patients following COVID-19 mRNA vaccination	Study type Systematic review Objective To determine whether spontaneous reporting rates of myocarditis and pericarditis differed in immunocompromised patients compared to the whole population overall, and in terms of demographics, vaccine dose, and time-to-onset. Results There were 106 reports of myocarditis and pericarditis amongst immunocompromised individuals overall. Seriousness was comparable between the immunocompromised and overall populations in both databases. No trends in age or sex were observed amongst immunocompromised individuals. Most reports (54.4%) to VAERS followed a second vaccine dose and 70.2% of events occurred within 14 days. The frequency of reporting was similar to the wider population (PRR=1.36 [95% CI= 0.89-1.82] for VAERS population). Overall conclusion as per author Myocarditis and pericarditis following COVID-19 vaccination are very rare, and benefits of COVID-19 vaccination continue to outweigh any perceived risks. Reporting rates of myocarditis and pericarditis were similar in immunocompromised individuals, however defining characteristics differed compared to the whole population; therefore, continued monitoring of adverse events following vaccination remains vital to understand differences between population subgroups.	Key findings and strength - This is the first study to investigate the frequency and characteristics of reported events of myocarditis and pericarditis in immunocompromised individuals compared with the population as a whole, bringing together data from two regions (Europe, the United States, and the UK). - Results from this study demonstrate that myocarditis and pericarditis are not more frequently reported following COVID-19 mRNA vaccines for immunocompromised individuals as compared to the general population Weakness - Per authors: As with all analyses using spontaneously reported data, results may have been subject to underreporting and missing information, including information on comorbidities and concomitant medications. It is possible that some immunocompromised were incorrectly classified as immunocompetent. Further biases may have influenced results, including differences in vaccination strategies between the two regions examined, differences in data collected via spontaneous reporting systems, and serious events more likely to be reported. - Per authors: It is not possible to estimate incidence rates using spontaneous reports due to a lack of data on the exposed population, and there is no unexposed comparison group. Conclusion Current information was too limited to confirm causal relationship with VAXZEVRIA
Ling R R et al 2022 / Myopericarditis following COVID-19	Study type Systematic review and Meta-analysis	Key findings and strength

Table 73 Systematic reviews/Meta-analyses articles identified during the reporting period 29 December 2021 to 28 June 2022

Author and article title	Type of study / Objectives / Results	AstraZeneca assessment
vaccination and non-COVID-19 vaccination: a systematic review and meta-analysis.	Objective To characterize the incidence of myopericarditis following COVID-19 vaccination and compare this with non-COVID-19 vaccination. Results Overall incidence of myopericarditis from 22 studies (405 272 721 vaccine doses) was 33·3 cases (95% CI 15·3–72·6) per million vaccine doses, and did not differ significantly between people who received COVID-19 vaccines (18·2 [10·9–30·3], 11 studies [395 361 933 doses], high certainty) and those who received non-COVID-19 vaccines (56·0 [10·7–293·7], 11 studies [9 910 788 doses], moderate certainty, p=0·20 Overall conclusion as per author This meta-analysis of more than 400 million doses of vaccines suggests that the overall incidence of myopericarditis following COVID-19 vaccination is similar to that in the published literature on its incidence after influenza vaccination, and is lower than the incidence after live smallpox vaccination	- Younger males who received a second dose of mRNA COVID-19 vaccine were at increased risk for myopericarditis - Large sample size (approximately 400 million vaccine doses) - Robust and clearly presented methodology, including restriction to observational studies where temporal relationship between exposure and outcome could be assumed (with some exceptions). Also, literature screening, data extraction, and quality assessment were carried out independently by three reviewers. - Assessment of study quality as well as grading of evidence using standard tools. - Statistical synthesis: the authors conducted random effects meta-analysis to estimate the pooled incidence of myopericarditis following vaccination, including COVID-19 vaccines, with appropriate assessment and reporting of heterogeneity. Also, sensitivity analyses were carried out to assess the impact of intra-study risk of bias, and publication bias was assessed using standard methods. - The risk was estimated by the type of vaccine (COVID-19 vs. non-COVID-19 vaccines, as well as mRNA COVID-19 vaccine vs. non-mRNA COVID-19 vaccines) as well as age-stratified subpopulations (adults vs. paediatrics). - Appropriate assessment of the effect of covariates on the incidence of myopericarditis, including the type of COVID-19 vaccine (mRNA vs. non-mRNA), the dose of vaccine, age, sex. Weakness

Table 73 Systematic reviews/Meta-analyses articles identified during the reporting period 29 December 2021 to 28 June 2022

Author and article title	Type of study / Objectives / Results	AstraZeneca assessment
		- From AZ's POV: the main weakness is that the effect of Vaxzveria was not assessed as it was grouped in the "non-mRNA" group. - Some data sources included registries with their inherent risk of misclassification as well as the lack of longitudinal data. - Potentially confounded comparisons between vaccines as this was carried out indirectly across studies which were carried at different time points. - Marked heterogeneity and imprecision across studies of non-COVID-19 vaccines, which was evident in the wide confidence intervals around the estimated measures thereof. - No data on patients younger than 12 years receiving vaccination against COVID-19. - An umbrella term, "myopericarditis", was used by the authors to mitigate the marked heterogeneity across studies. However, this may not be useful if the outcome of interest is either condition. <u>Conclusion</u> The review provides compelling evidence of an increased of myopericarditis in younger males post dose two. However, information was too limited to assess the association with VAXZEVRIA.

Table 73 Systematic reviews/Meta-analyses articles identified during the reporting period 29 December 2021 to 28 June 2022

Author and article title	Type of study / Objectives / Results	AstraZeneca assessment
Park DY et al 2022/ Myocarditis after COVID-19 mRNA vaccination: A systematic review of case reports and case series	Study type Systematic review and Meta-analysis Objective To delineate the demographics and clinical characteristics of vaccine-associated myocarditis. Results A total of 57 studies containing 275 cases of COVID-19 vaccine-associated myocarditis were catalogued. Mean age was 26.7 years and male to female ratio was 14:1. For 86.9% of patients, myocarditis occurred after the second dose. Average time to onset and length of hospitalization were 3.7 and 3.9 days, respectively. Prognosis was largely benign, but there was a 1.1% reported mortality. Chest pain (95.2%), elevation of troponin (100%), and ST elevation on electrocardiography (68.5%) were common. Nonsteroidal anti-inflammatory drugs (81.4%) were the most used medication, followed by colchicine (33.1%) Overall conclusion as per author Patients with COVID-19 vaccine-associated myocarditis are usually younger males presenting with chest pain 3-4 days after receiving their second dose of COVID vaccine.	Key findings and strength Consistent with previous studies, myocarditis following mRNA COVID-19 vaccines appeared to occur at a greater frequency in younger males, mostly following dose two. Weakness - From AZ's POV: the main weakness is the exclusion of cases associated with non-mRNA COVID-19 vaccines, including VAXZEVRIA. - All of the 57 included studies were case reports/series, with all the limitations thereof which are listed in assessments of similar reviews above. Indeed, the authors listed several limitations that are specific to these study designs, including heterogeneity across studies with respect to clinical evaluations, selective reporting and publication bias. - The analysis was descriptive in nature and thus cannot assess causal association, with the inability to adjust for potential confounding. Conclusion This review reiterates the reported association of mRNA COVID-19 vaccines and myocarditis in younger males, mostly following dose two. However, the review does not provide any information relevant to VAXZEVRIA, and therefore, the information provided do not contribute new safety information regarding causal relationship of event Myocarditis with VAXZEVRIA.

Table 73 Systematic reviews/Meta-analyses articles identified during the reporting period 29 December 2021 to 28 June 2022

Author and article title	Type of study / Objectives / Results	AstraZeneca assessment
Ghoshouni H et al 2022 / Unraveling the Mystery of covid-19 Postvaccination Myocarditis: A Systemic Review of Current Cases.	Study type Systematic review Objective To better understand whether there is a link between COVID-19 vaccination and one of the most devastating complications, cardiac Inflammation. Results Overall incidence of myopericarditis from 22 studies (405 272 721 vaccine doses) was 33·3 cases (95% CI 15·3–72·6) per million vaccine doses, and did not differ significantly between people who received COVID-19 vaccines (18·2 [10·9–30·3], 11 studies [395 361 933 doses], high certainty) and those who received non-COVID-19 vaccines (56·0 [10·7–293·7], 11 studies [9 910 788 doses], moderate certainty, p=0·20 Overall conclusion as per author In conclusion, postvaccination adverse events need close monitoring to gain a more realistic view of possible complications and how best to approach them.	Key findings and strength Consistent with previous studies, myocarditis following mRNA COVID-19 vaccines appeared to occur at a greater frequency in younger males, mostly following dose two. Weakness - This review was strictly restricted to case reports, and thus, all of the aforementioned limitations thereof apply. Counter-intuitively, the authors argued that the reason they applied such criterion was to "portray a better association between different factors and the risk of postvaccination myocarditis". This goes against the conventional epidemiologic wisdom that case reports are the least reliable design with respect to assessing causal associations. Conclusion The review was restricted to case reports and did not provide information to enable an assessment of any potential association between VAXZEVRIA and myocarditis.

Literature patient case reports

Literature case reports describing the use of VAXZEVRIA identified through this literature review were discussed in the above section ([redacted].

Mechanism of action articles review and summary identified during the reporting period 29 December 2021 to 28 June 2022

The proposed mechanism from published literature is provided below:

- Molecular mimicry as potential mechanism eg, "antibodies against a part of the SARS-CoV-2's spike protein that the mRNA encodes for, cross-react with structurally similar host proteins in the heart. (Perez Y et al 2021, Tsilingiris D et al 2021, Truong D T et al 2022, Kaul R et al 2021, Kiblboeck D et al 2022, Klamer TA et al 2022, Chouchana L et al 2021, Christophe A et al 2021, Sharbatdaran A et al 2022, Lee CH et al 2022, Mengesha B et al 2022, Wang AYL 2022, Chellapandian SB et al 2022, Power JR et al 2022, Perna F et al 2022, Alami A et al 2022, Chou OHI et al 2022, O'Leary ST et al 2021, Park S et al 2022, Rafaniello C et al 2022, Parra-Lucares A et al 2021, Kang DH et al 2022, Hassanzadeh S et al 2022, Soraci L et al 2022, Cau R et al 2022, Bews H et al 2022, Gluckman T J et al 2022, Cerne D et al, Kittichokechai P et al, Pillay J et al 2022, Marsukjai A et al 2022 and Bollano E et al 2022)
- Hypersensitivity as potential mechanism -hypersensitivity myocarditis resulting from an inflammatory response to the vaccine (Scheuermeyer FX et al 2022, Nakanishi Y et al 2022, Sexson Tejtel SK et al 2022, Chouchana L et al 2021, Won T et al 2022, Jamie S Y et al 2021, Bews H et al 2022, Moosmann J et al 2022 and Ahmed S K et al 2022)
- Hyper immune/inflammatory response, via exposure to spike protein, mRNA strand, or unknown trigger as potential mechanism eg, "The immune system may detect genes in the vaccine as antigens, thereby activating proinflammatory cascades and immune pathways that may play a role in the development of myocarditis" (Murakami Y et al 2021, Tsilingiris D et al 2021, Gomez Martín AM et al 2022, Wang M et al 2022, Cau R et al 2022, Parra-Lucares A et al 2021, Ohayon A et al and Park S et al 2022)
- Dysregulated micro-RNA response as potential mechanism "pre-existing dysregulated pathways in certain individuals with predisposition, resulting in a polyclonal B-cell expansion, immune complex formation, and inflammation" (Dursun AD et al 2022, Chin SE et al 2022)
- Sex steroid hormones as potential mechanism eg, "The association of myocarditis with male sex and younger age could be attributed to sex hormones which may account for a more intense inflammatory response. As suggested by experimental studies on myocarditis in mice, testosterone may be implicated in the inhibition of anti-inflammatory cells and the stimulation of immune responses mediated by Th1-lymphocytes" (Lazaros G et al 2021, Bricoli S et al 2021).
- Maladaptive innate immune response activation triggered by mRNA vaccination against SARS-CoV2 (neutrophil infiltration and natural killer cells) as potential mechanism (Kawano H et al 2022).

- Deposition of immune complex in cardiac pericyte due to expression of ACE2 as potential mechanism for myocarditis. "A more likely mechanism is where the vaccine lipid nanoparticles leak from the injection site and enter circulation where injection practices are not very well observed. Then they reach the heart and can be endocytosed by cardiac tissue including cardiac muscle, pericytes, endothelial cells, and macrophages. Local production of spike protein on the surface of cardiac cells and/or its shedding along with detached cell membranes may recruit neutrophils that also express ACE2 on their surface. Spike-activated neutrophils produce neutrophil extracellular traps that subsequently activate alternative pathway of complement in situ, damaging cardiac endothelial cells." (Kadkhoda K 2021)
- Antibody-mediated mechanisms characterized by elevated titres of serum anti-Spike antibody may be responsible for acute cardiac events following COVID-19 vaccination (Singh R et al 2021).

Literature overview

On review during the reporting period 29 December 2021 to 28 June 2022, 68 articles were further assessed, of which 19 articles describing VAXZEVRIA versus 49 articles describing use of all other COVID vaccines (mRNA vaccine). No epidemiological articles with relevant new safety information were identified during the reporting period 29 December 2021 to 28 June 2022. According to the Fatima M et al 2022 article, mean onset of symptoms after vaccine administration was 3.8 ± 4.5 days and 75% of 97 reported cases developed symptoms after the second dose. This was also buttressed in Ahmed S K et al 2022 article which also demonstrates a strong male predominance for both conditions (Myocarditis and Myopericarditis). However, it was noted that females who presented with Myocarditis post-vaccination were older than men (41.3 ± 21.5 vs 25.7 ± 14 years, p = 0.001 according to Ilonze OJ et al 2022 article. In addition and according to Ling RR et al 2022 article, incidence of myopericarditis in association with COVID-19 vaccines (mRNA vaccines) from 22 studies (405 272 721 vaccine doses) was 33·3 cases (95% CI 15·3–72·6) per million vaccine doses and did not differ significantly between people who received COVID-19 vaccines (18·2 [10·9–30·3], 11 studies [395 361 933 doses], high certainty) and those who received non-COVID-19 vaccines (56·0 [10·7–293·7], 11 studies [9 910 788 doses], moderate certainty, p=0·20. 17 of 19 articles describing VAXZEVRIA in association with Myocarditis were discussed in the previous review of ICSRs retrieved from the AstraZeneca Global Patient Safety Database and remaining two articles was not a case report and did not contain any relevant safety information. On review of remaining 49 of 68 articles for all other COVID -19 vaccines (mRNA vaccine) no new safety concerns regarding Myocarditis and association with VAXZEVRIA including information relating to a conclusive mechanism of action were identified. Of the 50 articles corresponding to Myocarditis, most frequent mechanism postulated was molecular mimicry (32), followed by hypersensitivity/inflammatory response (17), dysregulated micro-RNA response (2), sex predilection due to sex steroid hormones (2), maladaptive innate immune response activation (1), deposition of immune complex in cardiac pericyte due to expression of ACE2 (1) and Antibody-mediated mechanisms (1) amongst others.

Overall Summary

Of 761 Myocarditis cases, no gender preponderance was noted between males (50.9%) and females (49.1%). The majority of events (48.3%) were for vaccinees between the ages 40 to 64 years. The majority (65.0%) of cases were reported after Dose 1 as compared to Dose 2 (22.7%) and Dose 3 (0.8%). Out of 763 events from 761 reports, 99.9% events were serious with 2.8% resulting in death. There have been 266 (214 initial reports and 52 follow-up) additional case reports of Myocarditis compared to previous PBRER (with DCO December 2021 that discussed 593 cases). Of 761 case reports, 1.6% fulfilled BCC 1 criteria, 6.8% fulfilled BCC 2 criteria, no case fulfilled BCC 3 criteria, 51.2% fulfilled BCC 4, and 40.3% fulfilled BCC 5 criteria. WHO-UMC causality assessment for Myocarditis was performed for 64 cases (BCC levels 1, 2 and 3 cases), and none of the cases met WHO-UMC criteria for "Probable" (Likely) or "Certain". A total of 45.3% were considered as possibly related, 21.9% were considered as unlikely related, 25.0% were considered as Unassessable/Unclassifiable and 7.9% were considered as Conditional/Unclassified. In addition, 34.4% were identified with relevant risk/confounding factors and 65.6% cases had limited information for a comprehensive causal assessment. There were no case that reported a recurrence/worsening of myocarditis with a subsequent dose of VAXZEVRIA. There were no index cases identified from review of case reports. Observed vs expected analysis suggests that observed number of cases regardless of age, gender, dose and various risk windows did not exceed the expected number of cases. A review of literature suggests various hypothesized mechanisms for development of Myocarditis mainly in association with mRNA vaccines.

Conclusion

From the data identified during the reporting period and also taking into account the cumulative experience, it is AstraZeneca's opinion that currently there is insufficient evidence of a causal association between myocarditis and VAXZEVRIA. AstraZeneca did not find evidence of a new or emerging signal for Myocarditis to suggest a need to update the VAXZEVRIA CDS or RMP. Myocarditis is an AESI for VAXZEVRIA and will continue to be kept under close surveillance by AstraZeneca.

15.2.6 Sarcoidosis

Background

In the assessment report received from the PRAC EMA (PRAC PAR (EMEA/H/C/PSUSA/00010912/202112) for the VAXZEVRIA PBRER (review period 29 June 2021 – 28 December 2021)), further information on the topic of Sarcoidosis is requested as follows:

- *The MAH is requested to provide a cumulative review of sarcoidosis cases (HLT "Acute and chronic sarcoidosis") from all available sources, including details of the underlying condition(s), time to onset, duration, outcome and an assessment of the causal relationship with the vaccine. Depending on the results of this review, the MAH should also discuss the need for any potential amendment to the product information, as appropriate.*

Global Patient Safety Database

A cumulative search till DLP 28 June 2022 of the AstraZeneca Global Safety Database for Sarcoidosis with VAXZEVRIA was performed using MedDRA 25.0. The search strategy included the HLT: Acute and chronic sarcoidosis which has the following PTs: Cutaneous Sarcoidosis, Heerfordt's syndrome, Liver Sarcoidosis, Loefgren syndrome, Muscular Sarcoidosis, Neurosarcoidosis, Ocular sarcoidosis, Pulmonary sarcoidosis, Sarcoidosis, Cardiac Sarcoidosis, and Sarcoidosis of Lymph node.

The search retrieved a total of 68 case reports of Sarcoidosis with 75 events.

The case source distribution for Sarcoidosis is presented in Table 74:

Table 74 Case reports of Sarcoidosis received with VAXZEVRIA by reporting source and seriousness

Classification of case report source	Non-serious cases	Serious cases	Total (Percentage %)
Spontaneous[a]	9	54	63 (92.6%)
Literature	1	4	5 (7.4%)
Non-interventional/post-marketing study	0	0	0 (0%)
Total	**10**	**58**	**68**

[a] Of the 63 Spontaneous case reports, 57 (90%) were from Regulatory source

The following Table 75 presents number and percentage (%) of case reports with sarcoidosis reported after respective doses:

Table 75 Number and percentage (%) of the case reports of Sarcoidosis reported after respective doses of VAXZEVRIA cumulatively through DLP 28 Jun 2022

No of Cases (After First Dose)	No of Cases (After Second Dose)	No of Cases (After both First and Second Dose)	No of Cases (After Third Dose)	No of Cases (Dose number Unknown)
46 (67.6%)	7 (10.3%)	0	0	15 (22.1%)

These case reports of Sarcoidosis were reported most frequently from the following countries: United Kingdom 40 (58.8%), Germany 11 (16.2%), France 3 (4.4%), Netherlands 3 (4.4%), 2 (2.9%) each from Denmark, India, Ireland, and 1 (1.5%) each from Austria, Canada, Sweden, Lithuania, and Greece.

The following observations were made from a review of the 68 case reports:

- Vaccinee age was reported in 65 case reports and ranged from 21 to 67 years (median: 49 years).
- Vaccinee gender was reported in 67 case reports. Of these case reports, 29 (42.6%) concerned male patients and 38 (55.9%) concerned female patients.

- 21 (31.8%) case reports were medically confirmed and 47 (68.2%) were non-medically confirmed.
- Of the total 68 case reports, the time to onset (TTO) from VAXZEVRIA administration to the onset of Sarcoidosis was reported in 36 case reports and ranged 0 days to 175 days (median: 21 days).

TTO is further presented in the following Table 76 accordingly with respect to the risk window of 0-180 days.

Table 76 TTO for Sarcoidosis case reports cumulatively through 28 June 2022

TTO (Days)	No of Cases	Percentage (%)[a]
0 to 1	5	13.9 %
2-5	6	16.7%
6 to 10	0	0
10 to 15	3	8.3%
16 to 20	3	8.3%
20-28	3	8.3%
29 - 42	6	16.7%
43 – 60	2	5.6%
61 – 90	5	13.9%
91 – 180	3	8.3%
Unknown	32	

[a] TTO was reported for 36 case reports (*total number of cases- 68*) used to calculate the percentage.

The distribution of the preferred event term for Sarcoidosis is presented in Table 77 below in descending order of frequency:

Table 77 Distribution of MedDRA PTs for events (n = 75) pertaining to Sarcoidosis with VAXZEVRIA received cumulatively through 28 Jun 2022

MedDRA PT	Serious	Non serious	Grand Total	Total events (Percentage %)
Sarcoidosis	48	9	57	76.0%
Pulmonary sarcoidosis	4	1	5	6.7%
Neurosarcoidosis	5	0	5	6.7%
Loefgren syndrome	3	0	3	4.0%
Cardiac sarcoidosis	2	0	2	2.7%
Cutaneous sarcoidosis	1	1	2	2.7%
Ocular Sarcoidosis	1	0	1	1.3%
Grand Total	**64**	**11**	**75**	**100.0%**

MedDRA Medical Dictionary for Regulatory Activities, PT Preferred Term

Of 68 cases reported, 75 events were reported, and the following observations were made cumulatively through DLP 28 June 2022:

64 (85.3%) of the events were serious (17 medically confirmed and 47 non-medically confirmed) and reported seriousness criteria were medically important event (45 [60.0%]), disability (15 [20.04%]), hospitalization (22 [29.3%]), life threatening (3 [4.0%]). An event may have met more than one criterion for seriousness. The remaining 11 (14.6%) events were non-serious (5 medically confirmed and 6 non-medically confirmed).

- Of the 75 events, the outcome was reported as resolved or recovering 16 (21.3%), recovered/resolved with sequelae 8 (10.7%), not recovered/ not resolved 35 (46.7%) and none of the events is reported as fatal. The outcome of the remaining events were reported as unknown or not reported and that accounts for 16 (21.3%).
- Amongst 8 events with reported outcome 'recovered' or 'recovered with sequelae, only one had the event duration of one day reported.

Rechallenge / Recurrence case reports

There were no case reports indicating potential recurrence / rechallenge cumulatively through DLP 28 June 2022. Worsening of sarcoidosis and or its subtypes was reported in 2 case reports, however the two cases had previous medical history of sarcoidosis.

WHO-UMC causality analysis for cases

WHO-UMC causality assessment for the 68 case reports are provided below considering a risk window of 0-180 days.

Table 78 Overview of WHO-UMC Causality Assessment case reports of Sarcoidosis with VAXZEVRIA reported

WHO-UMC Causality category	WHO-UMC Causality assessment scale (AZ adapted)	Number of Cases
Certain	Certain	0
Probable-Likely	Probable-Likely	0
Possible	Possible with risk factors/confounders[a]	20 (29.4)
	Possible with Limited information	24 (35.3%)
Unlikely	Unlikely	0
Conditional / Unclassified	Conditional / Unclassified	0
Unassessable/Unclassifiable	Unassessable/Unclassifiable with risk factors/confounders*	5 (7.4%)
	Unassessable/Unclassifiable with limited information	19 (27.9%)
	Total	**68**

[a] Cases were considered to have "risk factors/confounders" where the event could also be explained by the vaccinee's diseases, or where relevant risk factors were present, or concomitant medications that could potentially contribute to the development of the event were reported. Some of the cases are with limited information on medical history, concomitant medication, and lack of detailed investigations. Few of the cases were considered unassessable /unclassifiable due to unknown TTO.

Amongst 68 cases for sarcoidosis, 19 (27.9%) were identified with relevant risk / confounding factors as presented in Table 79. These are presented into the following categories for risk / confounding factors in descending order of frequency.

Table 79 Relevant Risk factors / Confounders identified case reports cumulatively

Relevant Risk / Confounders	Number of reports	Percent of Total Number of Reports
History of Sarcoidosis	11	61.1%
Immunodeficiency	4	22.2 %
Hypertension	2	11.1 %
Neoplasm/Cancer	2	11.1 %

Overall, the cumulative review of cases did not identify an index case or a safety signal for VAXZEVRIA. A review of the post-marketing cases did not identify any index case or a safety signal. The cases provided insufficient information or were confounded by alternative aetiologies which precluded a proper causality assessment.

Observed Versus Expected (O/E) analysis

The background incidence rate(s) of sarcoidosis in the general population were obtained from literature articles from population based studies conducted in EU and South Korea. The literature is as analysed by Arkemer et al 2020 which have been used for this O/E analysis. This includes medically confirmed cases.

AstraZeneca conducted an observed versus expected analysis for the event of sarcoidosis using the cumulative observed number of cases. The risk window of 7 - 180 days was derived upon review of Arkemer et al 2020

An O/E analysis of sarcoidosis was conducted cumulatively through DLP 28 June 2022. The results were provided in line with 180 days risk windows for EEA and UK case reports, including unknown TTO. Please refer to Appendix 8 for the methodology of the O/E analyses and Appendix 9 for any additional sensitivity analysis.

The O/E analysis for the cumulative cases of sarcoidosis with risk window of 180 days, is presented with results in Table 80 below.

Conservatively, the exposure for global reports (448306152) is based on doses administered in 13 markets as explained in Appendix 8.

Table 80 Observed versus expected analyses through 28 June 2022 for reports of sarcoidosis

Topic / Sarcoidosis	Risk window (days)	Background rates/100,000 PY	Exposure	Observed number of cases	Expected number of cases	O/E ratio (95% CI)	Conclusion
Overall EEAUK only RW 7-180	7-180	11.5	117692071	34	6670.16	0 (0 - 0.01)	Observed significantly < expected
Overall EEAUK only RW 7-180 and including Unk TTO	7-180	11.5	117692071	64	6670.16	0.01 (0.01 - 0.01)	Observed significantly < expected

The O/E analysis has been restricted to EEA/UK data because 95.5% of the cases were reported in the EEA and UK. The incidence rate has been based on Arkemer et al 2020). Observed events were significantly less than the expected events using the risk window of 7-180 days.

Literature

A cumulative literature search through 28 June 2022 of the databases in Embase, InsightMeme and PubMed was conducted using the following search criteria. The following search terms were used: Cutaneous Sarcoidosis; Heerfordt's syndrome; Liver Sarcoidosis; Loefgren syndrome; Muscular Sarcoidosis; Neurosarcoidosis; Ocular sarcoidosis; Pulmonary sarcoidosis; Cardiac sarcoidosis, Sarcoidosis; Sarcoidosis of Lymph node.

The search retrieved 9 articles of which contained no relevant new safety information regarding Sarcoidosis and its association with VAXZEVRIA. None of the 9 articles provided relevant hypothesised mechanism of action for Sarcoidosis in association with mRNA or VAXZEVRIA

Discussion on Biological Plausibility and Possible Mechanisms

Sarcoidosis is an immunologically mediated disorder. Pathogenesis is believed to be a two-step process, requiring: (1) an initial exposure to an antigen that is presented to CD4+ T lymphocytes by antigen-presenting cells (human leukocyte antigen [HLA] class II molecules); and (2) an inflammatory milieu in which the antigen presentation can take place. Following antigen presentation, there is upregulation of the immune response, with activation of alveolar macrophages and dendritic cells, and development of memory for the causal antigen (sensitization) (Oliver and Zarnke 2021). Sarcoidosis is associated most strongly with HLA class II molecules on chromosome 6. The HLA-DRB1□11:01 allele is associated with increased risk for sarcoidosis in African-American and White subjects. HLA-DRB1□11:01

and occupational exposure to insecticides have been shown to interact in a positive manner to increase the risk for sarcoidosis ($p < 0.10$) and to increase risk for extrapulmonary sarcoidosis ($p < 0.05$), indicating the importance of both genetic and environmental factors (Oliver and Zarnke 2021).

However, as already mentioned, there is no hypothesised mechanism for the development of sarcoidosis in association with VAXZEVRIA.

In conclusion, a cumulative literature review through 28 June 2022 did not identify any article with significant safety information relating to VAXZEVRIA and sarcoidosis.

Summary

Cumulatively through DLP 28 June 2022, a total of 68 case reports of sarcoidosis with the use of VAXZEVRIA have been received using a broad search strategy, of which 85.3% of the reported events were serious and 14.6% were non-serious. The age range was 21years to 67 years and median age was reported as and 49.4 years.30.8% of cases were medically confirmed and 69.1% were not medically confirmed.

The most common PTs reported were Cutaneous Sarcoidosis 2 (2.7%), Loefgren syndrome 3 (4.0%), Neurosarcoidosis 5 (6.7%), Pulmonary sarcoidosis 5 (6.7%), Cardiac sarcoidosis 2 (2.7%), Sarcoidosis 57 (76.0%) and Ocular sarcoidosis 1 (1.3%).

Amongst 75 events reported for sarcoidosis received cumulatively through 28 June 2022, 35 (46.7%) had a reported outcome not recovered, 16 (21.3%) for recovering/resolved, 8 (10.7%) recovered with sequeale and 16 (21.3%) had outcome unknown.

OE analysis showed that observed cases were significantly less than expected cases.

WHO UMC case causality analysis conducted for all case reports, the majority of the case reports (24 [35.3%]) were considered possible with limited information, possible with confounder (20 [29.4%]) and unassesable/unclassifiable with limited information (19 [27.9%]) related to VAXZEVRIA.

Overall, the clinical pattern of case presentation and numbers of reports are broadly consistent with what might be expected from the natural epidemiology of sarcoidosis, and no specific biological mechanism through which VAXZEVRIA vaccine could cause or contribute to the development of sarcoidosis has been identified.

Conclusion

Based on the review of the updated cumulative data, AstraZeneca considers that there is insufficient evidence to suggest a causal association between sarcoidosis and VAXZEVRIA. It is AstraZeneca's opinion that no changes to the CDS or RMP are warranted at this time. The topic will continue to be closely monitored as part of AstraZeneca's ongoing surveillance

activities. AstraZeneca will no longer discuss the topic future PBRERs, unless significant new safety information arises.

15.2.7 Subacute Thyroiditis

Background

Following review of the PBRER (reporting period 29 June 2021 to 28 December 2021) (EMEA/H/C/PSUSA/00010912/202112) AstraZeneca was requested to address Subacute thyroiditis in the next PBRER as follows:

- *A review and discussion of the available literature on the relationship between subacute thyroiditis and vaccination with VAXZEVRIA.*
- *A review of the medically confirmed cases with a formal causality assessment using WHO-UMC criteria, and case description that allows to reproduce the assessment.*

AstraZeneca's responses to these requests are provided in the subsections below.

Global Patient Safety Database

A cumulative search of the AstraZeneca Global Safety Database for Subacute thyroiditis with VAXZEVRIA was performed using MedDRA version 25.0 for the period 29 December 2020 to 28 June 2022. The search strategy included the following PTs: Subacute thyroiditis which include Autoimmune thyroiditis; Immune-mediated thyroiditis; Silent thyroiditis; Thyroiditis; Thyroiditis acute; and Thyroiditis subacute

Cumulatively, the search retrieved a total of 187 events of Subacute thyroiditis in 178 case reports.

The case source and seriousness distribution for Subacute thyroiditis received cumulatively through DLP 28 June 2022 is presented in Table 81:

Table 81 Distribution of the case reports of Subacute thyroiditis received with VAXZEVRIA cumulatively up to 28 June 2022 by reporting source and report seriousness

Classification of case report source	Non-serious cases	Serious cases	Grand Total
Spontaneous[a]	58	106	164
Literature	5	6	11
Non-interventional/post-marketing study	0	3	3
Total	**63**	**115**	**178**

[a] Of the 178 Spontaneous case reports, 141 (%) were from Regulatory source.

Table 82 presents number and percentage (%) of case reports with Subacute thyroiditis reported after respective doses.

Table 82 Number and percentage (%) of the case reports of subacute thyroiditis reported after respective doses of VAXZEVRIA cumulatively through DLP 28 June 2022

No of Cases (After First Dose)	No of Cases (After Second Dose)	No of Cases (After First and Second Dose)	No of Cases (After Third Dose)	No of Cases (Dose number Unknown)
104 (58.4%)	20 (11.2%)	0	0	54 (30.9%)

These case reports for subacute thyroiditis were reported most frequently in the following countries: 52 (29.2%) from the United Kingdom; 30 (16.9%) from Germany; 19 (10.7%) from Italy; 12 (6.7%) from Australia; 9 (5.1%) from Sweden; 7 (3.9%) from France; 6 cases each (3.4%) from Brazil, Netherland, and Spain; 4 cases (2.2%) from Greece; 3 case reports each (1.7%) from Hungary, India, and Mexico; 2 cases each (1.1%) from Estonia and Finland; and 1 case report each (0.6%) from Denmark, Costa Rica, Canada, Colombia, Austria, Albania, Bulgaria, Portugal, Romania, Slovenia, and Thailand.

The distribution of the 187 case reports and 178 events of Subacute thyroiditis are presented in Table 83 and Table 84 below:

Table 83 Distribution of MedDRA PTs of Events (n = 187) pertaining to Subacute thyroiditis with VAXZEVRIA received cumulatively through 28 June 2022

MedDRA PT for Events	Serious	Percentage
Autoimmune Thyroiditis	49	26.2%
Thyroiditis	60	32.1%
Thyroiditis subacute	56	29.9%
Thyroiditis acute	22	11.8%
Total	**187**	**100%**

MedDRA Medical Dictionary for Regulatory Activities, PT Preferred Term

The following observations were made from a review of these 178 cases:

- Vaccinee age was reported in 163 (91.2%) case reports and ranged 19 to 84 years (median: 50 years).
- Vaccinee gender was reported in 173 case reports. Of these case reports, 138 (79.8%) concerned female patients and 35 (20.2%) concerned male patients.
- 52 (29.2%) case reports were medically confirmed and 126 (70.8%) were non-medically confirmed.

Of the 52 medically confirmed cases, 32 (61.5%) cases were serious while 20 (38.5%) were non-serious. The reported seriousness criteria were; medically important event in 28 (87.5%), disability 1 (3.1%), hospitalisation 6 (18.8%) cases reportedly required. An event may have

met more than one criterion for seriousness. The time to onset was available in 116 case reports out of the 178 case reports. The elaborate TTO information is further presented in the following Table 84 accordingly with respect to the risk window.

Table 84 TTO for Subacute thyroiditis case reports cumulatively through DLP 28 June 2022

TTO (Days)	No of Cases	Percentage (%) [a]
0 to 1	22	18.6%
2 to5	22	18.6%
6 to 10	10	8.5%
11 to 15	7	5.9%
16 to 20	9	7.6%
21 to30	15	12.7%
31 to42	10	8.5%
>42 days	23	19.5%
Unknown	60	-
Total	**178**	**100%**

[a] TTO was reported for 118 case reports used to calculate the percentage.

- Of the 187 events, the outcome was reported for 155 (82.9%) of the events, and 32 (17.1%) events had their outcome reported as unknown. Of the 155 events, 71 events (45.8%) had the outcome reported as resolved or resolving, in 9 (5.8%) of the events the outcome was recovered with sequelae, and in 75 (48.4%) of the events the outcome was not recovered.

WHO-UMC causality analysis for medically confirmed cases

Of the total 178 case reports identified cumulatively through DLP 28 June 2022, 52 (29.2%) case reports were medically confirmed (32 serious and 20 non-serious), and WHO-UMC causality was further assessed and is presented in Table 85. A listings of medically confirmed Subacute Thyroiditis case reports received with VAXZEVRIA received cumulatively through DLP 28 June 2022 is provided in Appendix 19.

Table 85 Overview of WHO-UMC Causality Assessment for medically confirmed case reports of Subacute thyroiditis with VAXZEVRIA reported cumulatively through DLP 28 June 2022

WHO-UMC Causality category	WHO-UMC Causality assessment scale (AZ adapted)	Number of Cases
Certain	Certain	0
Probable-Likely	Probable-Likely	0
Possible	Possible with risk factors/confounders[a]	5 (9.6%)
	Possible with Limited information	33 (63.5%)

Table 85 Overview of WHO-UMC Causality Assessment for medically confirmed case reports of Subacute thyroiditis with VAXZEVRIA reported cumulatively through DLP 28 June 2022

WHO-UMC Causality category	WHO-UMC Causality assessment scale (AZ adapted)	Number of Cases
Unlikely	Unlikely	6 (11.5%)
Conditional / Unclassified	Conditional / Unclassified	0
Unassessable/Unclassifiable	Unassessable/Unclassifiable with risk factors/confounders*	0
	Unassessable/Unclassifiable with limited information	**8 (15.4%)**
	Total	**52**

[a] Cases were considered to have "risk factors/confounders" where the event could also be explained by the vaccinee's diseases, or where relevant risk factors were present, or concomitant medications that could potentially contribute to the development of the event were reported.

Amongst 52 medically confirmed cases for subacute thyroiditis, 5 case reports (9.61%) were identified either with relevant risk / confounding factors as presented in Table 85 above. These are presented into the following categories for risk / confounding factors in descending order of frequency.

The confounders included Hashimoto's thyroiditis (2), thyroid nodule (1), Basedow's disease (1), and thyroid disorder (1).

In the remaining 47 (90.4%) out of 52 case reports, there was insufficient information with respect to either dose latency, medical history, laboratory values or concomitant medication details required for a comprehensive causal assessment.

Overall, the review of medically confirmed cases did not identify any new relevant safety information or an index case for VAXZEVRIA.

Rechallenge / Recurrence case reports

There were no case reports identified for Subacute thyroiditis after the Dose 1, with a recurrence or worsening of subacute thyroiditis with the Dose 2/Dose 3 of vaccination indicating potential recurrence / positive rechallenge cumulatively through DLP 28 June 2022.

Observed Versus Expected (O/E) Analyses

An O/E analysis of subacute thyroiditis was conducted cumulatively through 28 June 2022. The results were provided including all cases reported within 0 to 60 days risk window, including those with unknown TTOs.

Background incidence rates from Fatourechi et al 2003 have been used for O/E analyses. These include hospitalised and non-hospitalised cases subacute thyroiditis cases.

The O/E analysis for the cumulative cases of subacute thyroiditis with risk window of 60 days is presented with results in Table 86:

Conservatively, the exposure for global reports (448306152) is based on doses administered in 13 markets as explained in Appendix 8.

Table 86 Observed versus expected cumulative analyses through DLP 28 June 2022 with risk windows of 60 days.

Subacute thyroiditis	Risk window in days	Background rate/100,000 PY	Exposure	Observed number of cases	Expected number of cases	O/E ratio (95% CI)	Conclusion
All cases within RW of 60 days	60	3.6	448306152	101	2651.23	0.04 (0.03 - 0.05)	Observed significantly < expected
All cases within RW of 60 days + cases with unknown TTO	60	3.6	448306152	163	2651.23	0.06 (0.05 - 0.07)	Observed significantly < expected

CI, Confidence Interval; O/E, Observed versus Expected ratio; PY, Person-Years; RW, risk window; TTO, Time to Onset

Observed events were significantly less than the expected events provided using the risk window of 0 to 60 days.

Review and discussion of the literature case reports, received cumulatively

Cumulatively, 11 literature case reports were received for the event pertaining to sub-acute thyroiditis and is presented in the below Table 87.

Table 87 Analysis of literature case reports received cumulatively for VAXZEVRIA and the event pertaining to searched term of Subacute thyroiditis

Case ID / Gender / Age / Country / Dose number / TTO (days)	Clinical Features	Relevant laboratory Findings	Treatment / Outcome	WHO-UMC	Confounders
[redacted] 55, F, [redacted] Dose 1, 21	Presenting features of neck pain, swelling, headache, sore throat, generalized aches and palpitations	At treatment Biochemical hyperthyroidism, TPO Ab - negative CRP - increased, ESR - increased USG (Thyroid) - Enlarged thyroid gland with heterogeneous echotexture Doppler - showing reduced vascular flow in right thyroid lobe At 6 weeks biochemical hypothyroidism At 12 weeks - TRAb - negative, TgAb - increased	Beta-blocker for palpitations. NSAIDs for neck pain Levothyroxine at 6 weeks, Reversal of thyroid state at 6 weeks Clinical resolution after 12 weeks but with new TgAb increase	Possible (limited info)	Unk
	Comments: *Presenting features of clinical hyperthyroidism, neck pain with biochemical hyperthyroidism and clinical course with initial hyperthyroidism to progression into biochemical hypothyroidism in 6 weeks which is in line with the known natural history for subacute thyroiditis. Exclusion of any viral or respiratory illness, no family history.* *TTO of 3 weeks may be reasonable to vaccination. However, detection of new onset TRAb after about 15 weeks after vaccination (while other thyroid antibodies (TRAb, TPO Ab) remained non-detectable in the 12 week follow up) cannot be considered to have a temporal relationship to vaccine. Also progression of initial hyperthyroidism to hypothyroidism despite no immunosuppressant therapy precludes any singular vaccine immune etiopathogenesis.*				
[redacted] 26, F, [redacted] Dose 1, 14	Presented with worsening cervical pain that radiated to both ears.	Biochemical euthyroidism (Free T3 mild increase), TPOAb, TRAb, TgAb - negative CRP - increased, WBC - increased USG (thyroid) normal size, heterogeneous echogenicity and bilateral hypoechoic areas Doppler - reduced vascular flow FNAC - consistent with subacute thyroiditis (mononuclear lymphocytic infiltrate and multinucleated giant cells) Cervical LN - enlarged	NSAIDs Prednisolone Clinical and biochemical resolution after 6 weeks	Possible (limited info)	Unk
	Comments: *Presenting features of cervical pain with USG findings, FNAC findings and inflammatory markers is suggestive of thyroiditis. Duration of 6 weeks may be in line with subacute presentation. However, there was concurrent clinical euthyroidism (mild T3 increase with normal TSH) and non-detectable thyroid antibodies (TRAb, TPO Ab, TgAb).* *TTO of 2 weeks may be reasonable to vaccination.*				

Table 87 Analysis of literature case reports received cumulatively for VAXZEVRIA and the event pertaining to searched term of Subacute thyroiditis

Case ID / Gender / Age / Country / Dose number / TTO (days)	Clinical Features	Relevant laboratory Findings	Treatment / Outcome	WHO-UMC	Confounders
	Past medical history for thyroid diseases or recent upper respiratory tract infections were ruled out and there was no family history of thyroid disorders. However, there is limited information on exclusion of other systemic infections, neoplasms, other autoimmune diseases. *WHO-UMC causality assessed as Possible with limited information based on TTO of initial presentation which may be reasonable. Role of prednisolone therapy for event resolution suggesting an immune based pathology cannot be conclusively confirmed as thyroid antibodies (TRAb, TPO Ab, TgAb) was non-detectable from the initial presenting phase.*				
[redacted] 20, F, [redacted] Dose 1, Unk	Presenting features of drug-refractory headache 10 days and unilateral calf pain	TPOAb - increased MRI - CVST D-dimer - increased USG (leg) - subacute thrombophlebitis of the small right saphenous vein. Beta-2-glycoprotein-IgG titer elevated Cardiolipin antibodies and lupus anticoagulant - normal Heterozygous MTHFR A1298C mutation vaccine-specific cellular immunity seen (flow-cytometric analysis of the specific T-cell reactivity after whole blood stimulation with overlapping peptides from the SARS-CoV-2 spike protein)	LMW heparin later replaced by phenprocoumon, not reported	Unassessable with confounder	ethinylestradiol Past drug therapy of rivaroxaban for pulmonary embolism Heterozygous MTHFR A1298C mutation
	Comments: *Clinico-radiological features of CVST. TPOAb and diagnosis of Hashimoto's thyroiditis was an incidental finding.* *Concomitant ethinylestradiol therapy, medical history of pulmonary embolism and heterozygous MTHFR A1298C mutation are confounders for thromboembolic events. MTHFR A1298C mutation is also a common co-association for Hashimoto's thyroiditis.* *WHO-UMC causality for thyroid events cannot be comprehensively assessed in view of limited information on previous thyroid status.*				
[redacted] 39, F, [redacted] Dose 1, 21	Abnormalities of TFTs detected incidentally on routine regular work-up	Biochemical hyperthyroidism, TPO Ab - increased Inflammatory markers normal Thyroid scintigraphy - Thyroid scintigraphy showed decreased uptake Viral workup - negative; CMV and EBV workup suggested immunity USG (Thyroid) - diffuse hypoechoic echotexture of the thyroid gland Doppler - reduced blood flow COVID-19 - negative	Methyl prednisolone, Clinical and biochemical resolution in 2 months	Possible with alternate explanation	Maternal medical history of Hashimoto thyroiditis

Table 87 Analysis of literature case reports received cumulatively for VAXZEVRIA and the event pertaining to searched term of Subacute thyroiditis

Case ID / Gender / Age / Country / Dose number / TTO (days)	Clinical Features	Relevant laboratory Findings	Treatment / Outcome	WHO-UMC	Confounders
	Comments: *Incidental detection of biochemical hyperthyroidism on routine monitoring. This along with decreased isotope intake on thyroid scintigraphy, correlated USG & Doppler picture and duration of 2 months may be suggestive of subacute thyroiditis.* *TTO of 3 weeks for vaccine dose 1 may be reasonable to vaccination.* *Maternal medical history of Hashimoto thyroiditis can also suggest a genetic basis for the current event and increased TPOAb. Clinical resolution duration of 2 months despite methylprednisolone use suggest natural history of clinical course than a temporary immune challenge.* *WHO-UMC causality assessed as Possible with alternate explanation.*				
[redacted] 76, M, [redacted] Dose 1, 60	Presenting features of weight loss, arthralgia, myalgia, irritability, and tachycardia.	not reported	Beta-blocker not reported	Unlikely	Unk
	Comments: *Presenting features of clinical hyperthyroidism. However there was no information on relevant investigations, medical history, concomitant medications and etiological workup.* *The TTO of 60 days for vaccine dose 1 is considered unlikely.*				
[redacted] 47, F, [redacted] Dose 1, 21	Presenting features of fever, neck pain (tender goitre), tachycardia, restlessness, difficulty in swallowing and weight loss of 3 kg	Biochemical hyperthyroidism (thyrotoxicosis), TPO Ab, TRAb, TgAb - negative CRP - increased, ESR - increased Thyroid scintigraphy - no uptake of 99mTc-pertechnetate) Viral workup - negative; CMV and EBV workup suggested immunity USG (Thyroid) - Enlarged thyroid gland with hypoechoic nodules (1.5×1.0 cm in the right and 0.8×0.5 cm in the left lobe) without any cystic changes, calcifcation or increased vascularity Doppler - showing reduced vascular flow in right thyroid lobe FNAC (right-sided suspicious nodule) - granulomatous inflammation	Beta-blocker, clinical, radiological and biochemical resolution at follow-up of 8 weeks	Possible (limited info)	Unk
	Comments: *Presenting features of thyrotoxicosis, neck pain. Scintigraphy, USG (thyroid), FNAC and disease duration consistent with subacute thyroiditis.*				

Table 87 Analysis of literature case reports received cumulatively for VAXZEVRIA and the event pertaining to searched term of Subacute thyroiditis

Case ID / Gender / Age / Country / Dose number / TTO (days)	Clinical Features	Relevant laboratory Findings	Treatment / Outcome	WHO-UMC	Confounders
	TTO of 21 days for vaccine dose 1 may be reasonable to vaccination. *No information on medical history, concomitant medications and etiological work-up.* *WHO-UMC causality assessed as Possible with limited information based on TTO of initial presentation which may be reasonable. An immune based pathology cannot be conclusively confirmed based on no perturbation in thyroid antibodies (TRAb, TPO Ab, TgAb).*				
[redacted] 65, M, [redacted] Dose 1, 3	Presenting features of malaise, pain in the thyroid region, hoarseness and tachycardia Thyroid gland was slightly enlarged and palpable without tenderness Weight loss of eight kilograms	Biochemical hyperthyroidism, TPO Ab, TRAb - negative, TgAb - increased CRP - increased, ESR - increased, mild normochromic normocytic anemia USG (Thyroid) - slightly enlarged thyroid gland with hypoechogenic texture; enlarged nonsuspicious lymph nodes COVID-19 rapid antigen test was negative	No special treatment was required because of the regressive symptoms, clinical, radiological and biochemical resolution (except anemia)	Possible with limited information	
	Comments: *Presenting features of mixed clinical hyperthyroidism (tachycardia, weight loss) and clinical hypothyroidism (malaise, hoarseness) but with biochemical hyperthyroidism and thyroid area tenderness. Based on USG findings and increase in inflammatory markers with above symptoms, a thyroiditis cannot be excluded. There was no history of thyroid disease, neither in the patient nor in their family. No information on exact pre-vaccination medical history, concomitant medications and etiological work-up.* *TTO within 4 days may not be considered a subacute presentation to vaccination administration. Normochromic anaemia and weight loss of 8 kgs suggest chronic pathology inconsistent with chronology following vaccine administration. Also a mixed thyroid clinical picture is unlikely to be attributed to a singular vaccine based pathogenesis.* *WHO-UMC causality assessed as Possible with alternate explanation.*				
[redacted] 52, F, [redacted] Dose 1, 7	Presenting features of painful anterior neck swelling	Biochemical hyperthyroidism, TRAb - within normal range CRP increased USG (thyroid) - heterogeneous features of thyroiditis. A neck Doppler ultrasound Doppler - increased Doppler flow COVID-19 - negative	Beta-blocker, Clinical and biochemical resolution (week 18)	Possible (limited info)	Unk
	Comments: *Presenting features of painful anterior neck swelling with biochemical hyperthyroidism.* *TTO of 7 days for vaccine dose 1 may be reasonable to vaccination.*				

Table 87 Analysis of literature case reports received cumulatively for VAXZEVRIA and the event pertaining to searched term of Subacute thyroiditis

Case ID / Gender / Age / Country / Dose number / TTO (days)	Clinical Features	Relevant laboratory Findings	Treatment / Outcome	WHO-UMC	Confounders
	No preceding history of thyroid disease; patient was otherwise well and took no regular medication. However, there is limited information on exclusion of other infections, neoplasms, other autoimmune diseases. *WHO-UMC causality assessed as Possible with limited information based on TTO of initial presentation which may be reasonable. An immune based pathology cannot be conclusively confirmed based on non-detectable thyroid antibodies (TRAb).*				
[redacted] 19, M, [redacted] Dose 2, 5	reported as hypothyroidism (acute rhabdomyolysis with a pericardial effusion, and a very high level of thyroid stimulating hormone, decreased free thyroxin and higher level of peroxidase and thyroglobulin thyroid autoantibody)	Biochemical hypothyroidism, TPOAb - increased, TgAb - increased	Levothyroxine, Biochemical resolution in 1 week (of creatine kinase, kidney function and thyroid functions)	Possible (limited info)	Unk
	Comments: *Clinical features of clinical and biochemical hypothyroidism with concurrent rhabdomyolysis and pericardial effusion. Thyroid antibodies were increased (TRAb, TgAb)* *TTO of 5 days for vaccine dose 2 may be reasonable to vaccination.* *However, there is limited information on exclusion of infections, neoplasms, other autoimmune diseases, medical history, scintigraphy & USG of thyroid, concomitant medications and clinical course following 1st vaccination dose.* *WHO-UMC causality assessed as Possible with limited information based on TTO of initial presentation which may be reasonable.*				

Table 87 Analysis of literature case reports received cumulatively for VAXZEVRIA and the event pertaining to searched term of Subacute thyroiditis

Case ID / Gender / Age / Country / Dose number / TTO (days)	Clinical Features	Relevant laboratory Findings	Treatment / Outcome	WHO-UMC	Confounders
[redacted] 55, F, [redacted] Dose 2, 14	Presenting features of fever, dyspnea, chest pain, neck pain, weight loss, tachycardia.	Biochemical hyperthyroidism, TPOAb, TRAb, TgAb - negative High-sensitivity cardiac troponin I - increased CRP and ESR - normal COVID-19 PCR - negative. USG (thyroid) - normal thyroid gland size, homogeneous parenchyma Doppler - increased Doppler flow Iodine-131 uptake study - very low thyroid uptake, consistent with thyroiditis. Transthoracic echocardiography - normal Cardiac magnetic resonance imaging - suggestive of recent myocarditis	Beta-blocker, Clinical and biochemical resolution in 3 weeks	Possible (limited info)	Unk
	Comments: *Clinical features of clinical and biochemical hypothyroidism, neck pain with concurrent myocarditis. Thyroid function tests along with neck pain and very low thyroid isotope uptake, and disease duration may be suggestive of with thyroiditis. Thyroid antibodies were within normal range (TPOAb, TRAb, TgAb).* *TTO of 14 days for vaccine dose 2 may be reasonable to vaccination. Essential hypertension and hypercholesterolemia may point to an undiagnosed underlying thyroid dysfunction.* *There is limited information on exclusion of infections, neoplasms, other autoimmune diseases, medical history, clinical course following 1st vaccination dose and concomitant medications.* *WHO-UMC causality assessed as Possible with limited information based on TTO of initial presentation which may be reasonable. An immune based pathology cannot be conclusively confirmed based on non-detectable thyroid antibodies (TPOAb, TRAb, TgAb).*			
[redacted] 53, M, [redacted] Unk, 3	Unknown	Biochemical hyperthyroidism CRP and ESR - increased	Prednisolone Beta blocker, Recovered	Possible with limited information	
	Comments: *Subacute thyroiditis after 3 days following unspecified type and dose number of COVID-19 vaccine.* *Biochemical hyperthyroidism and raised inflammatory markers.* *However, there is limited information on latency to vaccine administration, exclusion of infections, neoplasms, other autoimmune diseases, medical history, vaccination type, vaccination dose and concomitant medications for a comprehensive causal assessment.*				

CRP – C Reactive protein; FNAC – Fine needle aspiration cytology; ESR – Erythrocyte sedimentation rate; MRI – Magnetic resonance imaging; TgAb – Thyroglobulin antibody; TPOAb – Thyroid peroxidase antibody; TRAb – Thyroid stimulating hormone receptor antibody; TTO – Time to onset; USG - Ultrasonography

On review of the 11 literature case reports, majority of cases were concerning female gender (n = 7; 64%) which is in line with known gender distribution on subacute thyroiditis cases (**Rothacker 2016, Oyibo 2021, Stasiak and Lewiński 2021**). The age distribution ranged from 19 to 76 years (median 49.5 years). The VAXZEVRIA dose details were reported in 10 cases with dose 1 in 8 cases (80%) and dose 2 in 2 cases (20%). The TTO varied from 3 to 30 days for events after dose 1 (median = 21 days) with majority within 0 to 21 days (6 out of 7 cases). Although only 2 cases were reported following dose 2, the reported TTO of 5 days and 14 days varied widely precluding any singular etiopathogenesis.

The presentation of subacute thyroiditis in the general population is usually characterised by severe pain, swelling, and tenderness in the thyroid region accompanied by malaise, fatigue, myalgia, and arthralgia with an initial thyrotoxic phase with raised inflammatory markers, followed by a hypothyroid phase and then a recovery phase (**Stasiak and Lewiński 2021**). An important differentiating factor with other immune mediated thyroid disorders may be low radioactive iodine or isotope intake test (**Sriphrapradang 2016**). Of the 11 literature case reports, in 5 case reports the case information on presenting clinical thyroid status, neck pain, low isotope intake, and disease duration were suggestive of sub-acute thyroiditis. In 2 cases ([redacted]), there was clinical presentation of hypothyroidism, while in 2 cases ([redacted]) the thyroid status was seen incidentally without any thyroid specific features. In the remaining 2 cases there was insufficient information to confirm a subacute thyroiditis. In summary, the clinical presentation of subacute thyroiditis was too varied to suggest a singular vaccine based etiopathogenesis.

In all 10 cases, clinical and/or biochemical resolution was reported. Thyroiditis specific treatment was reported in 10 cases comprised of beta-blocker therapy (6 cases), prednisolone with beta-blocker (2 cases), prednisolone (1 case), and spontaneous regression (in 1 case, [redacted]). As beta-blockers are not directed to underlying etiology of subacute thyroiditis, most cases can be considered to have resolved spontaneously. This precluded any trend of vaccine induced immune etiopathogenesis.

The WHO-UMC causality was assessed as Possible with confounders in 1 case (MTHFR A1298C mutation, family history of Hashimoto's disease), possible with limited information in 8 cases (based on temporal association only in backdrop of limited etiological workup), and unlikely in 1 case (due to implausible TTO). In the remaining 1 case, due to insufficient information on latency to vaccine administration, a comprehensive causal assessment was not possible.

To summarize, an analysis of the 11 cases either have limited information or do not present any significant trend to confirm a causal role of VAXZEVRIA COVID-19 vaccination.

Literature review analysis:

A cumulative literature search through 28 Jun 2022 of Embase, InsightMeme, and PubMed databases was conducted using the following search criteria:

The key terms used in the searches include Autoimmune thyroiditis; Immune-mediated thyroiditis; Silent thyroiditis; Thyroiditis; Thyroiditis acute; Thyroiditis subacute.

Of the 48 articles, 15 articles were considered relevant for further evaluation and discussion based on mechanism of action for all COVID-19 vaccines.

Of the 48 articles, 15 articles were considered relevant for further evaluation and discussion based on mechanism of action for all COVID-19 vaccines.

Articles suggesting hypothesized mechanisms for the development of sub-acute thyroiditis post COVID-19 Vaccination

Summary of the potential mechanisms from literature is provided below:

- Molecular mimicry as potential mechanism for autoimmune thyroiditis for eg, SARS-CoV-2 spike protein, nucleoprotein, and membrane proteins all cross-reacted with thyroid peroxidase (TPO) (Sozen, M et al. 2021, Vasileiou et al 2021, Khan et al 2022, Capezzone M et al 2022, Bostan et al. 2022, Adelmeyer et al 2022, Marsukjai A et al 2022 and Pla Peris et al. 2022)
- Autoimmune/inflammatory syndrome induced by adjuvants (ASIA) as potential mechanism for autoimmune thyroiditis as an entity that incorporates diverse autoimmune conditions induced by the exposure to various adjuvants (Khan et al 2022, Adelmeyer et al 2022, Uzoma et al. 2022, Alkis et al. 2022, El Haddad et al 2022 and Pla Peris et al. 2022) postulated.

Increased blood viscosity induced by vaccine which might contribute to thyrotoxicosis (Mungmunpuntipantip and Wiwanitkit 2022). The association between hyperviscosity and thyrotoxicosis is proposed. An increasing of blood viscosity is due to rapid increased level of antibody after vaccination and the viscosity will decrease when there is a decline of antibody level. Finally, if thyroid hormone test is based on immunoassay, an interference, a false aberration of hormone level might be induced by a high blood viscosity. However, the article did not present evidence for this hypothesis.

AZ comment: Regarding molecular mimicry, cross-reactivity between the coronavirus spike protein produced after vaccination and thyroid cell antigens is suggested as an underlying mechanism. However, the molecular basis of the structural similarity between these antigens was not described further. The authors proposed that subacute thyroiditis is a phenomenon of autoimmune inflammatory syndrome induced by adjuvants (ASIA). It was suggested that in genetically predisposed individuals, the administration of adjuvants may trigger an autoimmune response which might lead to subacute thyroiditis. The authors suggest that the vaccine may induce increase in blood viscosity due to increased antibody level after vaccination and that there is an association between hyper viscosity and thyrotoxicosis. It was not elaborated how increased blood viscosity might lead to thyrotoxicosis.

This cumulative review of literature has not identified any new safety information on the association of subacute thyroiditis with VAXZEVRIA.

Summary

Cases were assessed by age, sex, type of event, and outcome. Of the 178 case reports of subacute thyroiditis with the use of VAXZEVRIA have been received, of which 64.6% of the reported events were serious and 35.4% were non-serious. The age range was 19 to 83 years and mean and median age was reported as 51 years and 50 years, respectively. The case reports were reported more in females 138 (77.5%) compared to males 35 (19.7%). 29.2% of cases were medically confirmed and 70.8% were not medically confirmed. Subacute thyroiditis is generally reported in the 3rd to 5th decade, and is 1.9 to 6 times more frequent in females (Fatourechi et al 2003). For the event of subacute thyroiditis, the most common PTs reported were Autoimmune thyroiditis (49), Thyroiditis (60), Thyroiditis acute (22), and Thyroiditis subacute (56).

Amongst 178 case reports for subacute thyroiditis received cumulatively through DLP 28 June 2022, 64 events had a reported outcome of recovered or recovering, the outcome of recovered with sequelae was reported in 7 case reports, and the case outcome of Not recovered was reported in 88 of the case reports. No fatal event pertaining to searched term of 'Subacute thyroiditis' was reported. The TTO was varied and ranged from 0 to 1 day to more than 42 days and there was no trend or pattern seen. Of the 178 Subacute thyroiditis cases reported globally and included in AstraZeneca's post-marketing database, there were 118 case reports in which the TTO was within the risk window of 42 days. Underlying cause/confounding factors were noted in 9.6% of these cases.

The characteristics of the events and of the individuals with events were as expected for the general population, including the observation of increased incidence in the elderly. No usual trends or clusters were identified. None of the cases met WHO-UMC criteria for Certain or Probable/Likely. Of the 178 cases, there were no fatal cases.

The O/E analysis results for subacute thyroiditis showed observed cases to be significantly less than expected.

The majority of non-medically confirmed case reports had limited information. Of the total number of case reports, 52 (29.2%) were medically confirmed. WHO-UMC case causality assessment for majority 32 (61.5%) medically confirmed case reports was "Possible" with limited information; these cases lacked information about medical history, concomitant medications, or laboratory values and no trend was seen. However, 4 (7.7%) case reports demonstrated possible risk factors/confounders and were assessed as possible with confounders. In 6 (11.5%) cases the time to onset was outside the risk window of 42 days and therefore assessed as unlikely related to VAXZEVRIA. In 10 (19.2%) cases the time to onset was unknown and were assessed as "Unassessable".

Overall, none of the case reports raised any new relevant safety concerns for subacute thyroiditis cumulatively until DLP 28 June 2022 during the reporting period. Also, in summary, the review of available data from spontaneous reports regarding of Subacute thyroiditis did not identify an index case or other evidence of a new or emerging signal.

Conclusion

Based on the review of the available cumulative data, AstraZeneca considers that currently there is insufficient evidence of a causal association between subacute thyroiditis and VAXZEVRIA. It is AstraZeneca's opinion that no changes to the VAXZEVRIA CDS or RMP are warranted at this time. Subacute thyroiditis is an AESI for VAXZEVRIA and will continue to be closely monitored as part of AstraZeneca's ongoing surveillance activities. AstraZeneca will no longer discuss the topic future PBRERs, unless significant new safety information arises.

15.2.8 Glomerulonephritis AND Nephrotic syndrome (including IgA Nephropathy)

In the assessment report received from the PRAC EMA (PRAC PAR EMEA/H/C/PSUSA/00010912/202112) for the VAXZEVRIA PBRER (review period 29 June 2021 – 29 December 2021), further information on the topic of Glomerulonephritis AND Nephrotic syndrome (including IgA Nephropathy) is requested from AstraZeneca as follows:

The MAH is requested to submit:
• a cumulative review of cases based on search conducted at the level of HLT "glomerulonephritis and nephrotic syndrome";
• causality assessments of the cases;
• a review of articles published during the PSUR reporting period;
• a discussion on the need for updating product information and/or risk management plan, and submit proposal as required.
AstraZeneca's response to these requests are provided in the subsection below.

Additional note to the MAH: Published cases should be submitted to Eudravigilance and attempts should be made to follow up on poorly documented spontaneous cases.

AstraZeneca Response: 14 cases were identified in the literature and have been submitted to EudraVigilance. The spontaneous cases are followed up where reporter contact details are available and consent to follow-up has been provided. As much information as possible is obtained when the AE report is first received. Further active follow-up is performed to obtain the necessary data to allow appropriate medical evaluation of the case. Glomerulonephritis is kept under close surveillance thus maximum number of follow-up attempts are made according to the AstraZeneca process, ie, 3 contacts with reporter.

Glomerulonephritis Background

Glomerulonephritis is the term applied to a group of diseases characterised by inflammatory changes in glomerular capillaries and accompanying signs and symptoms of an acute nephritic syndrome; particularly haematuria, proteinuria, and diminished renal function in some cases associated with fluid retention, hypertension, and oedema (Couser 1999). The aetiological description refers to primary (aetiology unknown, generally thought to be a

manifestation of autoimmunity) or secondary (associated with one of several autoimmune, infectious, malignant, or metabolic diseases) forms of glomerulonephritis (Chadban & Atkins 2005). The major pathological types of glomerulonephritis are IgA nephropathy (IgAN), membranous nephropathy (MN), membrano-proliferative glomerulonephritis (MPGN), mesangial proliferative glomerulonephritis, minimal change disease (MCD), focal segmental glomerulosclerosis (FSGS), post-infectious glomerulonephritis, idiopathic crescentic proliferative glomerulonephritis, ANCA-associated necrotising crescentic glomerulonephritis, anti-glomerular basement membrane disease (Kazi and Hashmi 2022, KDIGO 2012). The underlying pathogenetic mechanism common to all of these different varieties of glomerulonephritis (GN) is immune-mediated (humoral as well as cell-mediated pathways may be active) followed by consequent inflammatory response, whether restricted to the kidney, or if associated with systemic immune-mediated disease. The principles of management of GN also involves immunosuppression alongside management of complications (blood pressure, proteinuria, control edema, and nephrotic syndrome) and removal of insult (KDIGO 2012). Kidney biopsy is mandatory for diagnosis (KDIGO 2012).

IgA Nephropathy (or Berger's disease) is the most common of all glomerulonephritis. IgA is an antibody that plays a crucial part in mucosal immunity (Lai et al, 2016). The name of IgAN originates from predominant IgA immune complex deposition in the glomerular mesangium on biopsy (including immunofluroescence) which is also the only confirmatory diagnosis (Farooq et al 2021; Lai et al, 2016). It is characterized by deposition (or possibly in situ formation) of pathogenetic polymeric IgA1 immune complexes (occasionally with IgG and IgM) in the glomerular mesangium, proliferation of mesangial cells, increased synthesis of extracellular matrix and variable infiltration of macrophages, monocytes and T cells. IgA and IgG that recognize the autoantigen IgA1 in IgAN are typically also reactive against antigens from extrinsic microorganisms involved in recurrent upper respiratory and gastrointestinal mucosal infections; the nephritogenic IgA1 molecules are produced by B cells following mucosal infections, particularly tonsillitis (Lai et al, 2016). IgAN can also be seen in the transplanted kidney and it points to a systemic immunochemical abnormality (Chailimpamontree et al, 2009; Lai et al, 2016). IgAN can occur in either sporadic (90–95%) or familial (5–10%) patterns (Lai et al, 2016). Although a consistent definition of secondary IgAN in the literature however systemic disorders associated with secondary IgA nephropathy - Gastrointestinal and Liver disorders (cirrhosis, Inflammatory bowel diseases), Infections (chronic mucosal infections, lyme disease, chlamydia, hepatitis B, Hepatitis C, Human Immuno deficiency Virus etc), Autoimmune disorders (Henoch-Schonlein purpura, IgA vasculitis, etc), Respiratory tract disorders, Neoplasms (may be causal such as IgA myeloma, lymphomas and solid malignancies) and genetic associations (Saha et al 2018; Kiryluk et al, 2012;; Kiryluk et al, 2014; Pouria and Bharratt 2008).

The age standardized rates in 2019 for incidence of acute glomerulonephritis per 100,000 population were 9.45 (95% uncertainty interval, 7.72 to 11.55) and the mortality rate was 0.13(95% uncertainty interval, 0.10 to 0.16) (Guo et al 2021). IgA Nephropathy (or Berger's disease) is the most common of all glomerulonephritis with an incidence estimated to be 2.5 per 100,000 patient years (Sethi et al 2016; McGrogan 2011). It is characterised by immune

complex deposition in the glomerular mesangium on biopsy (including immunofluroescence) which is also the only confirmatory diagnosis (Farooq et al 2021; Lai et al, 2016).

Nephrotic syndrome (NS) represents the clinical manifestations of several kidney diseases, characterized clinically by the presence of peripheral edema, heavy proteinuria, hypoalbuminemia, and hypercholesterolemia. Most adult patients with NS have primary glomerular diseases, including FSGS, MN, and MCD) (Kodner 2016; Hull and Goldsmith, 2008; Oth and Ritz 1998). Although the population incidence of NS is estimated to be approximately 3 per 100,000 person-years (Gao et al 2021).

Global Patient Safety Database

A cumulative search up to 28 June 2022 of the AstraZeneca Global Safety Database for Glomerulonephritis AND Nephrotic syndrome (Including IgA Nephropathy) with VAXZEVRIA was performed using the MedDRA (version 25.0) HLT "glomerulonephritis and nephrotic syndrome".

The cumulative search retrieved a total of 115 case reports containing 130 events of Glomerulonephritis AND Nephrotic syndrome (including IgA Nephropathy).

The distribution of these 115 cases split by case source and seriousness is presented in Table 88:

Table 88 Distribution of case reports by source and seriousness

Classification of case report source	Non-serious cases	Serious cases	Grand Total
Spontaneous[a]	13	88	101
Literature	2	12	14
Grand Total	**15**	**100**	**115**

[a] Of the 101 Spontaneous case reports, 91 (90%) were from Regulatory source

The distribution of the 130 events of interest are presented in Table 89 below in descending order of frequency:

Table 89 Distribution of MedDRA PTs (n=130) pertaining to Glomerulonephritis AND Nephrotic syndrome (including IgA Nephropathy) with VAXZEVRIA

MedDRA PT	Serious	Non-serious	Grand Total
Nephrotic syndrome	35	8	43
Glomerulonephritis minimal lesion	14	2	16
IgA nephropathy	10	3	13
Granulomatosis with polyangiitis	11	0	11
Glomerulonephritis	9	0	9
Focal segmental glomerulosclerosis	7	0	7

Table 89 Distribution of MedDRA PTs (n=130) pertaining to Glomerulonephritis AND Nephrotic syndrome (including IgA Nephropathy) with VAXZEVRIA

MedDRA PT	Serious	Non-serious	Grand Total
Glomerulonephritis membranous	4	1	5
Glomerulonephritis rapidly progressive	5	0	5
Microscopic polyangiitis	4	0	4
Glomerulonephritis membranoproliferative	3	0	3
Goodpasture's syndrome	3	0	3
C3 glomerulopathy	2	0	2
Henoch-Schonlein purpura nephritis	1	1	2
Alagille syndrome	1	0	1
Alport's syndrome	1	0	1
Anti-glomerular basement membrane disease	1	0	1
Glomerulonephritis acute	0	1	1
Glomerulonephritis chronic	1	0	1
Glomerulonephritis proliferative	1	0	1
Mesangioproliferative glomerulonephritis	1	0	1

MedDRA Medical Dictionary for Regulatory Activities, PT Preferred Term

The following Table 90 presents number and percentage (%) of case reports with Glomerulonephritis AND Nephrotic syndrome (including IgA Nephropathy) reported after respective doses cumulatively through DLP 28 June 2022.

Table 90 Dose-wise distribution of case reports

No. of cases (115)			
After First Dose	After Second Dose	After both First and Second Dose	After Third Dose
95 (82.6%)	16 (14%)	4 (3.4%)	0

These case reports for Glomerulonephritis and Nephrotic syndrome (including IgA Nephropathy) were reported most frequently from the following countries United Kingdom (41, 35.6%), Germany (17, 14.7%), France (15, 13%), Italy (6, 5.2%), and India (5, 4.3%)

The following observations were made from a review of the 115 case reports pertaining to Glomerulonephritis and Nephrotic syndrome (including IgA Nephropathy).

- Vaccinee age was reported in 110 (95.6%) case reports and ranged 19 to 95 years (median: 58 years).
- There was no specific gender predilection; 58 (50.4%) males and 57 (49.6%) females.

- A total 66 (57.4%) case reports were medically confirmed and 49 (42.6%) were consumer reports. Of the total 115 case reports, the time to onset (TTO) from VAXZEVRIA administration to Glomerulonephritis AND Nephrotic syndrome (including IgA Nephropathy) was reported in 76 case reports and ranged 0 days to 333 days (median: 14 days). A breakdown of the TTO for these cases with respect to the risk widow of 42 days is presented in Table 91.

Table 91 TTO for Glomerulonephritis AND Nephrotic syndrome (including IgA Nephropathy) case reports

TTO (Days)	No of Cases	Percentage (%)[a]
0 to 1	9	12%
2 to 5	15	20%
6 to 10	6	8%
11 to 15	11	14%
16 to 20	4	5%
21 to 30	7	9%
31 to 42	8	11%
>42 days	16	21%
Unknown	39	NA

[a] TTO was reported for 76 case reports used to calculate the percentage.

The events commonly co-reported with Glomerulonephritis and Nephrotic syndrome (including IgA Nephropathy) are presented in Table 92:

Table 92 Co-reported events (≥2%) with Glomerulonephritis and Nephrotic syndrome (including IgA Nephropathy)

Adverse events (PT)	Number of Cases	Percentage (%)
Pyrexia	9	2.2%
Proteinuria	9	2.2%
Haematuria	8	2%
Joint swelling	7	2%
Oedema	6	2%
Condition aggravated	6	2%
Oedema peripheral	6	2%
Headache	6	2%
Fatigue	6	2%

- One hundred and twelve (86.2%) of the events were serious and the reported seriousness criteria were medically important event (53 [35.3%]), disability (14 [9.3%]), hospitalization (73 [48.7%]), life threatening (9 [6%]) and/or death (1 [0.8%]). An event may have met

more than one criterion for seriousness. The remaining 18 (13.8%) events were non-serious (6 medically confirmed and 13 non-medically confirmed).

- Of the 130 events, the outcome was reported in 37 (28.5%) of the events as favorable (resolved or resolving), 8 (6.2%) of the events was recovered/resolved with sequelae, 56 (43.1%) of the events was not recovered/ not resolved and 1 (0.8%) of the events as fatal. The outcome of the remaining 28 (21.6%) of events were reported as unknown or not reported.
- Amongst 42 cases with reported outcome 'recovered' or 'recovered with sequelae,' the event duration was reported in 3 (7%) cases. In 1 case (33.3%), the event resolved within 7 days and for the remaining 2 (66.7%) cases the event resolved after 7 days.
- Of the 115 cases, 39 cases (34%) had information on medical history and concomitant medications. The confounders identified in these cases in decreasing order of frequency were pre-existing renal conditions (13%; such as previous episodes, chronic glomerulonephritis, renal cyst, poor corticocentral differentiation of the kidney, etc.), infections (11%; COVID-19, pneumonia, recurrent UTI, polyp, and diverticulitis, etc.), pre-existing dyslipidemia, diabetes mellitus (9%), neoplasms (6%; breast cancer, lymphoma, glioma) and auto-immune disorders (7%).
- WHO-UMC causality assessment was performed for the 115 case reports and is as follows: "Possible" with limited information for 48 (42%) case reports, "Possible" with confounders for 18 (16%) case reports, "Unlikely" for 22 (19%) case reports, "Unassessable/Unclassified" with limited information for 15 (13%) case reports, and "Unassessable/Unclassified" with confounders for 12 (10%) case reports.

Events with fatal outcome

Of the 130 events of Glomerulonephritis and Nephrotic syndrome (including IgA Nephropathy), 1 (0.8%) event of glomerulonephritis proliferative was reported with fatal outcome, and is summarized below.

The case [redacted] received from a health professional from India regarding a 78 year old male patient who experienced pneumonia, emphysema, alveolar proteinosis, interstitial lung disease and glomerulonephritis proliferative after an unspecified time post unknown dose of VAXZEVRIA. The cause of death was reported as lobar pneumonia, emphysema, pulmonary alveolar proteinaceous, interstitial lung disease and proliferative glomerulonephritis.

AstraZeneca comment: Pneumonia could be the infectious trigger for glomerulonephritis. The events of pneumonia, interstitial lung disease, emphysema and alveolar proteinosis can also explain the fatality in the backdrop of advanced age of the patient. The event of emphysema usually have a chronic clinical course. However, due to insufficient information on onset latency of the events, baseline health condition including renal status, clinical course, etiological workup, renal biopsy, autopsy, concomitant medication and corrective therapy, a comprehensive causal assessment could not be performed.

Rechallenge / Recurrence case reports

Cumulatively through 28 June 2022, of the 115 cases in 3 cases (2.6%) the patient experienced the events after the first dose, and had a recurrence or worsening of the event with the second dose. Of the 3 case reports, 1 (33%) case report was medically confirmed and the remaining 2 were consumer reports. The review of these cases is presented in Table 93.

Table 93 Assessment of cases with recurrence/worsening with subsequent dose

Case #/ Age/Gender/ Country/ Medically Confirmed/ Source	PT / Seriousness Criteria / Outcome	Clinical features of recurrence	Time to onset (in days) / Dose number	Previous history	Relevant Comorbidities	Relevant investigations	AZ Assessment as per WHO-UMC scale
[redacted] Not medically confirmed Regulatory Authority	Nephrotic syndrome / Hospitalization / Not recovered	swelling started getting worse and painful	5/dose 1 Unk/dose 2	Not reported	Not reported	Insufficient information Renal Biopsy: not reported	Possible; with limited information
	Comments: *TTO of nephrotic syndrome of 5 days following VAXZEVRIA Dose 1. It was reported that following the 2nd vaccination, the swelling started getting worse and painful. There was no information on medical history, clinical features, laboratory results including biopsy findings, any improvement prior to 2nd dose, exact clinical course following 2nd dose, any treatment taken, concomitant medications, etiological workup for a comprehensive causal assessment. The WHO-UMC causality is assessed as possible based only on temporal association of onset.*						
[redacted] Not medically confirmed Regulatory authority	Granulomatosis with polyangiitis / Hospitalization / Unknown	Acute kidney injury (AKI)	66 (for AKI) / AZ dose 1 Unk / AZ dose 2 Unk / Influenza vaccine Unk / mRNA COVID-19 vaccine	Multiple flares of Granulomatosis with polyangiitis	Multiple flares of Granulomatosis with polyangiitis	As reported 'Blood tests had not shown a flare or alternatively an infection for the first time in his medical history. Consultants had assumed a flare' Renal Biopsy: not reported	Unlikely

Table 93 Assessment of cases with recurrence/worsening with subsequent dose

Case #/ Age/Gender/ Country/ Medically Confirmed/ Source	PT / Seriousness Criteria / Outcome	Clinical features of recurrence	Time to onset (in days) / Dose number	Previous history	Relevant Comorbidities	Relevant investigations	AZ Assessment as per WHO-UMC scale
	Comments: *As reported the patient experienced a flare after each of the four vaccinations and that the underlying Granulomatosis with polyangiitis has progressively worsened. After the VAXZEVRIA dose 1, the patient experienced Acute kidney injury (AKI) after 66 days. Therafter flares were experienced after VAXZEVRIA dose 2, Influenza vaccine, 3rd COVID-19 vaccine (mRNA), however exact latency was not reported. On workup, blood tests had not shown a flare or alternatively an infection. The patient has previously had four major flares and a number of minor flares mostly caused by infections or operations such as his cholecystectomy or ERCP. The patient was on Rituximab infusions as required.* The patient had been on past drug therapy of cyclophosphamide, steroids and azathioprine, however the exact duration since discontinuation was not reported. *The TTO of first flare of renal symptom (AKI) following COVID-19 vaccination of 66 days is considered unduly prolonged. A vaccine induced flare would have been expected to manifest in much shorter timeframe considering its immunological response. Moreover, considering the onset of past and current flares to infections, operations, different vaccine types, the contributory role of VAXZEVRIA is considered unlikely.*						
[redacted] Medically confirmed Literature	Glomerulonephritis minimal lesion / Medically significant / Unknown	Edema	7 / dose 1 Unk / dose 2	Not reported	Not reported	As per the authors, 'secondary etiologies, such as, drugs and malignancies, were ruled out'. (unspecified tests)	Possible; with limited information
	Comments: *TTO of MCD within 1 week of VAXZEVRIA vaccination. Patient was started on prednisolone on an unknown date and prednisolone was withheld at the time of 2nd vaccine dose. Recurrent edema after the second dose. Thus recurrence is confounded by prednisolone interruption. On etiological work-up, drugs and malignancies were ruled out. However there was insufficient information on exclusion of infections (especially COVID-19) and on patient's medical history for a comprehensive causal assessment.*						

AKI Acute Kidney Injury; AZ AstraZeneca; MCD Minimal Change Disease; PT Preferred Term; TTO Time To Onset; WHO-UMC World Health Organization Uppsala Monitoring Centre

On review of the 3 cases reporting recurrence / worsening, the AEs of nephrotic syndrome, Granulomatosis with polyangiitis and Glomerulonephritis minimal lesion were singularly reported, and no trend was seen. The TTO of the events of interest after 1st dose (5 days, 7 days, 66 days) presented a widely varied picture, precluding possibility of any specific etiopathogenesis. In all the 3 cases, an exact clinical course of the events were not reported. Corrective therapy was reported in only 1 case [redacted] as corticosteroids which was interrupted before 2nd vaccine dose. Interruption of prednisolone could possibly confound the recurrence. In 1 case [redacted], recurrence (of Granulomatosis with polyangiitis) was reported to multiple stimuli like infections, major operations and vaccines (irrespective of type) during an extended course, thus precluding any direct causality to a specific vaccine type.

One additional case ([redacted], medically confirmed) reported information of ongoing resolution of the event of granulomatosis with polyangiitis despite administration of 2nd vaccine dose. The initial event had a TTO of 36 days after 1st dose of COVID-19 vaccination. The case was assessed as per WHO-UMC causality as possible only based on temporal association. There was insufficient information on medical history, concomitant medications and etiological workup.

In summary, a review of the cases of recurrence / worsening did not identify any specific trends to events, vaccine type, onset latency and any patient susceptibility. The recurrence was confounded in one case while there was insufficient information on clinical course and concomitant medications in the remaining two cases for a comprehensive assessment.

WHO-UMC causality assessment for medically confirmed cases

Of the total 115 case reports identified cumulatively through DLP of 28 Jun 2022, 66 (57.4%) case reports comprising 75 events of interest were medically confirmed (63 serious and 3 non-serious).

Out of 66 medically confirmed cases pertaining to Glomerulonephritis AND Nephrotic syndrome (including IgA Nephropathy), 7 case reports reported a relapse or flare-up of pre-existing condition [redacted]

- The reported PTs were Nephrotic syndrome (n=4; [redacted], Glomerulonephritis minimal lesion (n=2; [redacted], Microscopic polyangiitis (n=1; [redacted]).
- On review of 4 cases of nephrotic syndrome, the underlying renal disease was reported in 2 cases (minimal change disease, FSGS). Three out of 4 cases of nephrotic syndrome reported relapses or flare-up following 1st COVID-19 vaccination (TTO of 3 days, 7 days, 14 days) while 1 case reported after 2nd COVID-19 vaccination (unspecified TTO). None of the 4 cases of Nephrotic syndrome reported renal biopsy findings.
- On review of 2 cases of Glomerulonephritis minimal lesion, both cases presented with frothy urine within 1 day of 1st dose of COVID-19 vaccine administration. No renal biopsy findings were reported.

- The event of Microscopic polyangiitis was reported 13 days after 2nd COVID-19 vaccination, however no renal symptoms or renal biopsy findings were specified.
- Overall, there was insufficient information on baseline clinical status of the underlying renal pathologies. The pre-existing treatment details was reported only in 2 out of 7 cases (tacrolimus therapy), however there was insufficient information on any action taken with the tacrolimus prior to COVID-19 vaccination.
- Out of the 7 cases of relapse / flare-up, confounders for flare-up was identified in 4 cases (COPD, hypertension, mild renal impairment eGFR, neoplasm, previous history of relapses of nephrotic syndrome, severely high BMI of 45.5 kg/m^2 and concomitant sulfamethoxazole). In the remaining 2 out of 7 cases, there was insufficient information on any action taken with the immunosuppressants (tacrolimus) prior to COVID-19 vaccination.
- In summary on review of medically confirmed case reports of a relapse or flare-up of pre-existing condition, no trend was seen on temporal association based on widely varied TTO and some presenting only after 2nd vaccination. This also precludes any singular immune mediated hypothesis (non-specific or adaptive immune response). Moreover, majority of cases had confounders.

Causality assessment was performed based on WHO-UMC criteria and a risk window of 42 days risk window days and provided in Table 94.

Table 94 Overview of WHO-UMC Causality Assessment for medically confirmed case reports.

WHO-UMC Causality category	WHO-UMC Causality assessment scale (AZ adapted)	Number of Cases
Certain	Certain	0
Probable-Likely	Probable-Likely	0
Possible	Possible with risk factors/confounders[a]	13
	Possible with Limited information	27
Unlikely	Unlikely	13
Conditional / Unclassified	Conditional / Unclassified	0
Unassessable/Unclassifiable	Unassessable/Unclassifiable with risk factors/confounders[a]	6
	Unassessable/Unclassifiable with limited information	7
	Total	**66**

[a] Cases were considered to have "risk factors/confounders" where the event could also be explained by the vaccinee's diseases, or where relevant risk factors were present, or concomitant medications that could potentially contribute to the development of the event were reported.

WHO-UMC World Health Organization Uppsala Monitoring Centre

Amongst 66 medically confirmed cases pertaining to Glomerulonephritis and Nephrotic syndrome (including IgA Nephropathy), 25 (38%) were identified either with relevant risk / confounding factors as presented in Table 95. These are presented into the following categories for risk / confounding factors in descending order of frequency.

Table 95 Relevant Risk factors / Confounders identified for medically confirmed case reports

Relevant Risk / Confounders	Number of reports
Infections (COVID-19, pneumonia, recurrent UTI, polyp and diverticulitis)	5
Neoplasms (breast cancer, lymphoma, glioma)	5
Pre-existing dyslipidemia, diabetes mellitus	5
Pre-existing renal conditions (previous relapses, chronic glomerulonephritis, renal cyst, poor corticocentral differentiation of the kidney)	4
Concomitant medication [penicillin, sulfa drugs, acetylsalicylic acid, amiodarone (for vasculitis), letrozole (for edema)]	4
Risk allele (APOl1 G1/G0)	1
Autoimmune disorders	1

UTI Urinary Tract Infection

In the remaining 41 (62%) out of 66 case reports, there was insufficient information with respect to either dose latency, medical history or concomitant medication details for a comprehensive causal assessment.

Overall, the review of medically confirmed cases did not raise any new relevant safety information for VAXZEVRIA.

Nephrotic syndrome

Out of the 130 events pertaining to searched topics of Glomerulonephritis AND Nephrotic syndrome (including IgA Nephropathy), 46 PTs of Nephrotic syndrome in 43 cases were identified, cumulatively till 28 June 2022.

Out of the 46 events of Nephrotic syndrome, 36 were serious and 10 were non-serious. The TTO was reported in 27 (62.8%) cases. The mean and median TTO was 39 days (mean) and 18 days (median) respectively. The distribution of most frequently co-reported renal events in 4 case reports for Nephrotic syndrome were Glomerulonephritis minimal lesion (4 cases), 2 cases each of Glomerulonephritis membranous, FSGS, AKI and singular case of Chronic kidney disease-mineral and bone disorder. Thus, in majority of cases the underlying renal

pathology for the presentation of nephrotic syndrome was not reported. Also, the co-reported renal events do not show any particular trend with VAXZEVRIA vaccine.

Amongst 46 events, 14 events had a reported outcome of recovered or recovered with sequelae. The majority of events had a reported outcome of not recovered (45.6%) at the time of reporting and were mostly reported via regulatory source. Amongst 14 cases with reported outcome 'recovered' or 'recovered with sequelae,' the event duration was reported in 1 (7.1%) case (232 days). No event of fatal Nephrotic syndrome was reported.

On review of 23 medically confirmed cases pertaining to Nephrotic syndrome, 18 (78%) cases were assessed on WHO-UMC causality scale as 'Possible' based on temporal association only with confounders identified in 5 out of 18 cases (28%). Three cases (17%) were assessed as 'Unlikely' based on unreasonable time relationship of event to vaccination and presence of alternate explanations. The remaining 2 cases could not be comprehensively assessed due to insufficient information on vaccine latency and clinical course of the event. Four case reports reported a relapse or flare-up of pre-existing nephrotic syndrome were identified. However, no trend was seen on temporal plausibility based on varied TTO (3, 7 and 14 days, and unspecified after 2nd vaccination), one case ( ) presenting only after 2nd vaccination, and three cases ( ) presenting only after 1st vaccination. The two underlying renal pathologies were singularly reported. This also precludes any singular etiopathogenesis. Amongst 23 medically confirmed cases pertaining to Nephrotic syndrome, 8 (35%) were identified either with relevant risk / confounding factors [pre-existing dyslipidemia, diabetes mellitus (3 cases); pre-existing renal conditions (previous relapses, poor corticocentral differentiation of the kidney) 2 cases; concurrent infection (polyp and diverticulitis) in 1 case; neoplasms in 1 case; and concomitant medication of amiodarone (for vasculitis), letrozole (for edema) in 1 case].

Overall, none of the case reports raised any new relevant safety concerns for the event of VAXZEVRIA and nephrotic syndrome.

IgA Nephropathy

Out of the 130 events pertaining to searched term of Glomerulonephritis AND Nephrotic syndrome (including IgA Nephropathy), 13 PTs of IgA Nephropathy in 13 cases were identified, cumulatively till 28 June 2022 (

The majority of the IgA nephropathy events were serious (9 out of 13 events, 69%). No events were reported with a fatal outcome. The seriousness criteria of one event was life-threatening, however, the basis for life-threatening nature was not specified in the case narratives. The presenting features of the IgAN as reported only in 38.5% of the cases (n=5 out of 13) was gross hematuria. Although, the clinical presentation of IgAN is varied from asymptomatic microscopic haematuria to a rapidly progressive form of glomerulonephritis, macroscopic haematuria may not be an infrequent initial presentation of IgAN (Lai et al, 2016). Proteinuria

was reported in 3 cases ([redacted]) but not as a presenting symptom but was reported at a later date and thus a conclusive confirmation as manifestation of IgA nephropathy could not be made. Hypertension was reported in one case ([redacted]), however it was not considered a de novo clinical feature secondary to IgAN as the patient had a medical history of the same. The commonly co-reported events were IgAN (haematuria), or concurrent IgA vasculitis (Henoch-Schonlein purpura) which could be in association with IgAN, listed events (myalgia, pyrexia) and concurrent influenza. Owing to very few cases of Henoch-Schonlein purpura (3 cases), no significant trends in predisposition to underlying IgA pathogenesis can be comprehensively made. Although, none of the cases reported acute kidney injury, one case ([redacted]) reported serum creatinine levels of 1.4 (unspecified units). Information on renal biopsy was available in only 5 cases with biopsy confirmation of IgAN in 3 case, while in 2 cases only a clinical diagnosis was done and renal biopsy not performed. None of the cases had information on immunotyping of IgA deposits (such as IgA1), correlation with serum IgA levels, correlation with vaccine immunogenicity (such as spike IgG Ab, neutralizing antibodies), other immunological determinants in renal biopsy (such as complements). Majority of cases (6 out of 13) did not report any etiological work-up such as gastrointestinal and liver disorders, infections, autoimmune disorders, neoplasms or genetic associations, while in 2 cases the relevant investigations were limited to radiology of kidney, ureter, bladder and of abdomen. Possible concurrent mucosal infections as suggested by UTI, influenza with oropharyngeal pain, use of benzathine penicillin was reported in 3 out of 13 cases and may contribute to IgA immune response.

The medical history was reported in 7 out of 13 cases (54%) out of which majority (4 cases out of 7; 57%,) had reported a past history of IgAN. Out of these 4 cases reporting past history of IgAN, the TTO to current IgAN was reported in 2 cases as same day and 1 day ([redacted]) respectively. However, possible confounders such as concurrent UTI, and Crohn's disease were also identified. A co-morbidity of Henoch Schonlein purpura was reported in two cases ([redacted]), however in these two cases possible confounders were also identified (eg, Crohn's disease, use of benzathine penicillin suggesting a systemic infection).

The latency of the presenting symptom of IgAN (or to the diagnosis of IgAN) to COVID-19 vaccine administration was reported in 10 out of 13 cases and all 10 cases were reported following first vaccine dose. In majority of the cases (6 out of 13 cases), the TTO of vaccine administration to the presenting symptom of IgAN (or to the diagnosis of IgAN) ranged between 0-3 days [redacted]. In 2 out of these 6 cases, a medical history of IgAN was reported [redacted]. In 1 case, there was concurrent IgA vasculitis [redacted]). This short TTO may be possibly explained by innate non-specific immunity or pre-existing disease pathogenesis rather than adaptive immunity to vaccine. In 3 out of these 6 cases, possible confounders for IgAN could be identified such as concurrent infections (UTI, use of benzathine penicillin) and renal cyst [redacted]. In one case, although both vaccine doses were administered, there were no similar complaints of recurrence and /or worsening after second dose [redacted].

In view of reasonable TTO but limited insufficient information on exact clinical course of IgAN, diagnostic and etiological work up and corrective treatment, the assessment as per WHO-UMC scale for VAXZEVRIA was considered as Possible with limited information in 7 out of 13 cases [redacted]. In one case, although the TTO was reasonable, the event of IgAN could also be explained by concurrent infection and hence considered Possible with confounders identified [redacted]. In the 1 case, the TTO to clinical suspicion of IgAN was 284 days, however it was reported that the patient had been given subsequent doses of COVID-19 vaccine but there was no information on vaccine types and vaccination dates [redacted]. In the remaining 4 cases, although confounder for IgAN were identified (such as concurrent influenza with oropharyngeal pain, concurrent chronic kidney disease, medical history of IgAN in the backdrop of pre-existing Crohn's disease), based on insufficient information on TTO a comprehensive causal assessment was not possible. In summary, on cumulative review of 13 cases pertaining to IgA nephropathy, based on insufficient case details (on medical history, concomitant medications, etiological work-up) for a comprehensive causal assessment or based on confounders, there is unsubstantiated evidence to support a causal relationship of IgA nephropathy to VAXZEVRIA.

Observed Versus Expected (O/E) Analyses for Glomerulonephritis AND Nephrotic syndrome (including IgA Nephropathy)

An O/E analysis of Glomerulonephritis and Nephrotic syndrome (including IgA Nephropathy) was conducted cumulatively through DLP 28 June 2022. The results were provided including case reporting within 0-42 days risk window, also cases with unknown TTOs were included. Please refer to Appendix 8 for the methodology of the O/E analyses and Appendix 9 for any additional sensitivity analysis.

The background incidence rate (IR) was based on Go et al 2021 for Glomerulonephritis / Nephrotic syndrome and McQuarrie et al 2014. for IgA nephropathy.

The Risk Window of 42 days was considered based on Diebold et al 2022.

The O/E analysis for the cumulative cases pertaining to events of interest of Glomerulonephritis with risk window of 42 days is presented with results in Table 96 below.

Conservatively, the exposure for global reports (448306152) is based on doses administered in 13 markets as explained in Appendix 8.

Table 96 Observed versus expected cumulative analyses through DLP 28 June 2022 for reports of Glomerulonephritis and Nephrotic syndrome with risk windows of 42 days

Topic	Risk window (days)	Background rates/100,000 PY	Exposure	Observed number of cases	Expected number of cases	O/E ratio (95% CI)	Conclusion
All	42	1.3	448306152	60	670.17	0.09 (0.07 - 0.12)	Observed significantly < expected
All incl UNK TTO	42	1.3	448306152	102	670.17	0.15 (0.12 - 0.18)	Observed significantly < expected

DLP Data Lock Point, TTO Time To Onset; CI Confidence Interval; O/E Observed Versus Expected

The O/E analysis for the cumulative cases of IgA Nephropathy with risk window of 42 days is presented with results in Table 97:

Table 97 Observed versus expected cumulative analyses through DLP 28 June 2022 for reports of IgA Nephropathy with risk windows of 42 days.

Topic	Risk window	Background rates	Exposure	Observed number of cases	Expected number of cases	O/E ratio (95% CI)	Conclusion
All	42	1.33	448306152	6	685.64	0.01 (0 - 0.02)	Observed significantly < expected
All incl UNK TTO	42	1.33	448306152	11	685.64	0.02 (0.01 - 0.03)	Observed significantly < expected

DLP Data Lock Point, TTO Time To Onset; CI Confidence Interval; O/E Observed Versus Expected

Observed events for Glomerulonephritis and Nephrotic syndrome (including IgA Nephropathy) were significantly less than the expected events provided using the risk window of 42 days.

Literature

In line with PRAC's request, a literature search of the databases - Embase, InsightMeme and PubMed was conducted for the reporting period (29 December 2021 – 28 June 2022) using the following search terms:

'sars-cov-2 vaccine'/exp/mj OR 'covid-19 vaccine':ti,ab OR 'sars-cov-2 vaccine*' OR 'bnt162'/exp OR 'ad5 ncov'/exp OR 'gam-covid-vac'/exp OR 'mrna-1273 vaccine'/exp OR 'nvx-cov2373 vaccine'/exp OR JCOVDEN vaccine'/exp OR 'covid 19 vaccine*' OR 'sputnik v vaccine'/exp OR 'tozinameran'/exp OR 'comirnaty'/exp OR 'azd-1222' OR 'azd 1222' OR

'azd1222' OR 'covid-19 vaccine astrazeneca' OR 'vaxzevria' OR 'chadox1 ncov 19'/exp OR 'chadox1 ncov 19' OR 'covishield' OR ('astrazeneca' NEAR/2 'covid-19 vaccine') OR 'chadox1-s'.

'glomerulonephritis'/exp OR 'alagille syndrome'/exp OR 'alport syndrome'/exp OR 'anti-glomerular basement membrane disease' OR 'anti-lrp2 nephropathy' OR 'thin basement membrane nephropathy'/exp OR 'benign familial hematuria' OR 'c1q nephropathy'/exp OR 'c1q nephropathy' OR 'c3 glomerulopathy'/exp OR 'c3 glomerulopathy' OR 'chronic autoimmune glomerulonephritis' OR 'congenital nephrotic syndrome'/exp OR 'denys drash syndrome'/exp OR 'fibrillary glomerulonephritis'/exp OR 'fibrillary glomerulonephritis' OR 'focal segmental glomerular sclerosis'/exp OR 'focal segmental glomerular sclerosis' OR 'frasier syndrome'/exp OR 'acute glomerulonephritis'/exp OR 'chronic glomerulonephritis'/exp OR 'membranous glomerulonephritis'/exp OR 'glomerulonephritis minimal lesion' OR 'proliferative glomerulonephritis'/exp OR 'rapidly progressive glomerulonephritis'/exp OR 'goodpasture syndrome'/exp OR 'wegener granulomatosis'/exp OR 'henoch schoenlein purpura nephritis'/exp OR 'henoch schoenlein purpura nephritis' OR 'hepatitis virus-associated nephropathy' OR 'hiv associated nephropathy'/exp OR 'ig a nephropathy' OR 'ig m nephropathy' OR 'immunotactoid glomerulonephritis'/exp OR 'immunotactoid glomerulonephritis' OR 'membranous-like glomerulopathy with masked igg-kappa deposits' OR 'mesangiolipidosis' OR 'membranoproliferative glomerulonephritis'/exp OR 'microscopic polyangiitis'/exp OR 'nephritis'/exp OR 'nephritic syndrome' OR 'immune complex nephritis'/exp OR 'nephrotic syndrome'/exp OR 'nephrotic syndrome' OR 'paraneoplastic glomerulonephritis' OR 'paraneoplastic nephrotic syndrome' OR 'post infection glomerulonephritis' OR 'allergic glomerulonephritis'/exp OR 'primary coenzyme q10 deficiency' OR 'pulmonary renal syndrome'/exp OR 'pulmonary renal syndrome'.

Search results during the reporting period:

The search identified a total of 90 relevant abstracts comprising 65 published case reports / series, 15 conference abstracts (with limited study details such as baseline characteristics, full statistical analysis plan), and 10 observational studies or reviews in the reporting period of the PBRER (29 December 2021 to 28 Jun 2022).

Out of the 90 articles, 56 concerned mRNA Covid-19 vaccines, 13 concerned multiple COVID-19 vaccines [including VAXZEVRIA (n=5)], 10 concerned vector based vaccines and 5 concerned inactivated COVID-19 vaccine. Of the 19 IgA Nephropathy articles, 15 concerned mRNA covid-19 vaccines, 3 concerned to multiple COVID-19 vaccines and 1 was reported to inactivated COVID-19 vaccine. All but one article were case reports or case series. Three relevant articles with an observational controlled study design and consensus review is summarized in Table 98 below:

Table 98 Study articles identified during the reporting period [29 December 2021 to 28 June 2022]

Author et al year	Type of study / Objectives / Results	Overall medical assessment (AstraZeneca Comments)
Diebold et al 2022	Study type Nationwide retrospective cohort and case-cohort design Objective To test whether SARS-CoV-2 mRNA vaccines increase the incidence of several types of glomerulonephritis (GN) or the temporal associations can be attributed to a by-chance-effect by comparing the observed incidence of GN in Switzerland during the vaccination campaign in 2021 to the expected incidence based on a baseline period (2015 to 2019). Results The observed incidence during the vaccination campaign was not different from the expected incidence (incidence rate ratio 0.86, 95%-credible interval 0.73–1.02). The estimated RR for the development of new-onset biopsy-proven GN was 0.97 (95% CI 0.66–1.42, *P*=0.95) in vaccinated vs. unvaccinated individuals. Patients with GN manifesting within 4 weeks after vaccine did not differ clinically from the rest of the cohort. Results were consistent across all types of glomerulonephritis with the possible exception of minimal change disease (MCD). Overall conclusion as per author Vaccination against SARS-CoV-2 was not associated with new-onset GN. Most temporal associations between SARS-CoV-2 vaccination and GN are likely coincidental	Key findings and strength Inclusion of biopsy proven glomerulonephritis Inclusion of comparison group matched for age and time-point No significant increase in observed rates versus expected rates. Weakness Pre-print article, not peer-reviewed Data from single country Only extrapolated to new onset GN Part questionnaire based study design Specific to mRNA vaccine Conclusion Real-world evidence of nationwide renal biopsy confirmed comparative observational study design showing no significant increase in observed rates versus expected rates. Findings to be correlated with similar studies from other countries and COVID-19 vaccines.
Stevens et al 2022	Study type	Key findings and strength

Table 98 Study articles identified during the reporting period [29 December 2021 to 28 June 2022]

Author et al year	Type of study / Objectives / Results	Overall medical assessment (AstraZeneca Comments)
	Review article and summary of consensus from Immunonephrology Working Group (IWG) of the European Renal Association (ERA) and the European Vasculitis Society (EUVAS) Objective Review summary of reported cases of de novo GN or a relapse/flare of the established disease. Consensus summary on vaccine efficacy in patients with immune-mediated kidney diseases (IMKD). Results Until the end of December 2021, 45 cases of IgAN, 36 cases of MCD, 20 of AAV, 11 of membranous nephropathy, 7 of anti-GBM-disease and AIN, 5 of FSGS, 3 with lupus nephritis, 2 of IgA vasculitis and 1 each of proliferative GN, IgG4-related disease and scleroderma renal crisis were received. Most IMKD relapsed/flared were diagnosed after the second dose of the COVID-19 vaccine, with the exception of MCD, which was usually found after the first dose. These findings warrant confirmation in independent cohorts, but the benefits of vaccination far outweigh this small, theoretical risk. Rechallenge on heterologous vaccine dosing was also seen. Most disease onset or relapse/flare of immune-mediated kidney disease can be successfully treated in a standard manner. Overall conclusion as per author Patients with immune-mediated kidney diseases should be prioritized to receive booster doses according to national implementation as early as possible, as reduced vaccine response is anticipated in many cases. Reported side effects (including recurrence of disease or de novo glomerulonephritis) are rare and large population-based investigations	IMKDs are rare in frequency and true association to COVID-19 vaccines not proven. Consensus from Immunonephrology Working Group (IWG) of the European Renal Association (ERA) and the European Vasculitis Society (EUVAS) Weakness Review article Strength of evidence recommendations not provided Literature search criteria not provided Conclusion Although a temporal association was reported in the cases, there is insufficient evidence of causal association due to the above-mentioned limitations.

Table 98 Study articles identified during the reporting period [29 December 2021 to 28 June 2022]

Author et al year	Type of study / Objectives / Results	Overall medical assessment (AstraZeneca Comments)
	are necessary to provide evidence of a true association. The benefits of COVID-19 vaccines clearly outweigh the potential risks.	
Zan et al 2022	Study type: Longitudinal design, single centre Objective: Longitudinal follow-up of patients with pre-existing biopsy confirmed IgA nephropathy or IgA vasculitis nephritis who received a COVID-19 vaccination, in a single hospital centre in Peking. Results: A total of 202 patients with IgAN or IgA vasculitis nephritis received at least 1-dose vaccination and had blood and urine tests within 3 months before and after vaccination. There was no significant difference between the baseline and postvaccination proteinuria (0.59 [interquartile range, 0.30– 0.98] vs. 0.54 [0.33–0.92] g/d; P = 0.52) and hematuria (25.1 [8.9–72.2] vs. 25.4 [9–59.2]/ml; P = 0.47). Estimated glomerular filtration had a mild but statistically significant difference (68.39 [23.18] vs. 67.33 [23.53] ml/min per 1.73 m2; P - 0.03) from prevaccination to postvaccination. Overall conclusion as per author Overall, the absolute incidence of adverse events was low, and COVID-19 vaccine was well tolerated in patients with IgAN, especially to those having relatively stable disease. Although glomerular filtration rate decline was observed in a few patients, the change was temporary.	Key findings and strength Included patients with pre-existing IgAN or IgA vasculitis nephritis each of the 202 patients served as their self-control for the analysis of renal parameters Weakness Single -centre study Efficacy parameters of the inactivated vaccine not reported Conclusion Patients with pre-existing IgAN or IgA vasculitis nephritis although had perturbation in renal parameters, however, did not show any statistically difference in renal parameters post-vaccination compared to pre-vaccination. The limitation of this study are that it is a single centre study, undertaken with inactivated COVID-19 vaccines with limited information on vaccine efficacy parameters. Hence, an extrapolation of study findings to all COVID-19 vaccines cannot be reliably made.

AIN Acute Interstitial Nephritis, FSGS Focal Segmental Glomerulosclerosis, GN Glomerulonephritis, IgAN IgA Nephropathy, IMKD with immune-mediated kidney diseases, MCD Minimal Change Disease, RR Risk Ratio

Potential Mechanism of action

The various mechanisms hypothesized by the authors for glomerulonephritis and nephrotic syndrome were:

- Abnormal T cell mediated glomerular damage (Leclerc et al 2021, Biradar et al 2022, Neves et al 2022, Schaubschlager et al 2022, Timmermans et al 2022)
  - For the mechanism of abnormal T cell mediated glomerular damage, the authors referenced to mouse models of nephrotic syndrome wherein imbalance in T-cell, especially circulating CD8+T suppressor cells aggravates nephrotic syndrome by directly inducing foot process infusion (Wang et al 2001; van den Berg and Weening 2004). As per the authors, VAXZEVRIA also has the potential to stimulate CD8+ T cells and the resultant Th2-type responses can potentially cause immunological adverse effects (Bordon 2021). Neves et al 2022 proposed the role of VAXZEVRIA induced innate immune stimulation (especially interferons) which in turn would amplify T cell mediated podocytopathy. This would also explain the short latency after COVID-19 vaccination. This mechanism was also proposed for mRNA vaccine (Bomback et al 2021)
- B cell pathway mediated podocytopathy (Timmermans et al 2022)
  - For the mechanism of B cell pathway mediated podocytopathy, in the case series presented by Timmermans et al 2022), there was also evidence seen for polyclonal IgG deposits but no electron deposits on kidney biopsy
- Molecular mimicry between SARS CoV-2 spike protein and self -antigens on the podocytes (Leclerc et al 2021) – the self-antigens were unspecified
- Aberrant activation of the immune system in predisposed individuals (Leclerc et al 2021)
  - For the mechanism of Aberrant activation of the immune system in predisposed individuals, as per Leclerc et al 2021, because IFN pathways have an important role in the pathogenesis of CG, notably in patients homozygous for APOL1 high-risk variants, their stimulation by SARS-CoV-2 immunization could be a potential second-hit triggering CG development, especially among genetic susceptible patients

<u>Specific mechanisms for IgA Nephropathy</u>

- anti-glycan antibodies that cross-react with pre-existing under- galactosylated IgA1 (Abramson et al 2021; Kudose et al, 2021; Park et al 2021; Roberts 2021) and increase of pathogenic IgA production post vaccination similar to the influenza vaccine (Abramson et al 2021; Carr et al 2021; Farooq et al 2021; Li NL et al 2021; Nihei 2022; Negrea and Rovin 2021; Wu et al 2021)
  - For the proposed mechanism of increase of pathogenic IgA production post vaccination, Nihei 2022 provided a chronologic correlation of increased IgA1 levels with clinical symptoms in a single case report with a mRNA vaccination. It was observed that the urine Gd-IgA1 level was highest at the onset of gross hematuria. For the proposed mechanism of mRNA based production of aberrant glycosylated IgA via Toll-like receptors (TLRs) signalling, Matsuzaki et al, 2021 provided reference to previous studies (mechanism based studies in animals) which demonstrated the

association with TLR9with single-stranded Deoxyribonucleic Acid (DNA) containing unmethylated CpG motifs, and the synthesis of these IgA (Suzuki et al, 2008; Makita et al, 2020). Zheng et al, 2020 recently showed that TLR7, which recognizes endogenous or exogenous single-stranded RNAs is also involved in the production of aberrantly glycosylated IgA1, indicating that there might be some link between TLR signalling and the pathogenesis of IgAN.

- robust T-helper and B cell response in the germinal centre by mRNA vaccination (Abramson et al 2021; Chan et al 2022)
- subclinical IgAN becoming apparent (Abramson et al 2021; Acharya et al 2021; Chan et al 2022) ; Fujita et al, 2022; Hanna et al, 2021; Klomjit et al 2021; Lo and Chan 2021)
  - For the proposed mechanism of subclinical IgAN becoming apparent after COVID-19 vaccination, Klomjit et al 2021 explored it further on a previously preserved nephrectomy sample (preserved at the time of diagnosis of renal cell carcinoma) and it revealed evidence of pre-existing subclinical IgAN. Although this is a unique case, further studies will be required to explore the possibility of presence of subclinical IgAN in patients manifesting with new-onset IgAN post COVID-19 vaccination. Rahim et al 2021, Klomjit et al 2021 presented cases of inconsistent IgAN relapses to multiple previous vaccinations to the current mRNA COVID-19 vaccination (inconsistently seen with annual influenza vaccinations or other previous vaccinations). Also, in the longitudinal follow up of 202 patients with pre-existing IgAN, Zan et al 2022 did not observe any significant increase in renal parameters, post COVID-19 vaccination. Although different vaccines (Influenza vaccine, Shingrix vaccine, mRNA COVID-19 vaccine) may have common excipients (eg, Polysorbate 80), due to inconsistent association of relapse of IgAN or IgA pathology with various vaccines, extrapolation of results of one vaccine to others cannot be comprehensively done.
- potent stimulation of immune response from mRNA-based vaccine compared to other vaccines (Abramson et al 2021; Acharya et al 2021),
- stimulation of Gut-associated lymphoid tissue and other mucosal tissues (Chan et al 2022; Hamza and Beers, 2021) or aberrant mucosal immunity response (Roberts 2021)
- molecular mimicry (Fujita et al, 2022; Kanamori 2022)
- delayed type hypersensitivity (Rahim et al 2021; Plasse et al 2021)
- systemic cytokine-mediated flare (Kudose et al, 2021; Park et al 2021)
- mRNA based production of aberrant glycosylated IgA via Toll-like receptors (TLRs) signalling (Matsuzaki et al, 2021).

***AstraZeneca Comments**: The review of mechanisms proposed by the authors included both vaccine type specific and vaccine non-specific mechanisms. For IgAN, the mechanism of presence of subclinical IgA pathology was explored further, however, an inconsistent association of IgAN flare/reactivation with patient receiving multiple vaccine types was observed. The remaining mechanisms are hypothesis and further evidence on the pathway or*

mediators leading to the glomerular injury are lacking. Thus, there is insufficient comprehensive evidence for a conclusive mechanism for glomerulopathies following VAXZEVRIA vaccination and that evidence from other vaccine types cannot be comprehensively extrapolated to all other vaccines.

Summary

Overall medical summary of all case reports

Of the 115 case reports of Glomerulonephritis AND Nephrotic syndrome (including IgA Nephropathy) reported globally and included in AstraZeneca's post-marketing database, the TTO was within 42 days for 60 of the case reports that reported TTO. Underlying cause/confounding factors were noted in 39 cases (34%) of cases.

Cases were assessed by age, sex, type of event, and outcome. The characteristics of the events and of the individuals with events were as expected for the general population, including the observation of increased incidence in the elderly. No unusual trends or clusters were identified. None of the cases met WHO-UMC criteria for Certain or Probable/Likely.

Of the 130 events of Glomerulonephritis AND Nephrotic syndrome (including IgA Nephropathy) reported, 1 event of glomerulonephritis proliferative in 1 case (0.8%) was reported with fatal outcome cumulatively through 28 June 2022. However, due to insufficient information on onset latency of the events, clinical course, etiological workup, renal biopsy, autopsy, concomitant medication and corrective therapy, a comprehensive causal assessment of the fatal outcome of glomerulonephritis proliferative is not possible.

Out of 115 cases, 3 cases reported recurrence / worsening with the PTs of nephrotic syndrome, Granulomatosis with polyangiitis and Glomerulonephritis minimal lesion. A review of the cases of recurrence / worsening did not identify any specific trends to events, vaccine type, onset latency and any patient susceptibility. The recurrence was confounded in one case while there was insufficient information on clinical course and concomitant medications in the remaining two cases for a comprehensive assessment.

On review of 66 medically confirmed cases pertaining to Glomerulonephritis AND Nephrotic syndrome (including IgA Nephropathy), 40 (61%) cases were assessed on WHO-UMC causality scale as 'Possible' based on temporal association only with confounders identified in 13 out of 40 cases (33%). Thirteen cases (20%) were assessed as 'Unlikely' based on unreasonable time relationship of event to vaccination and presence of alternate explanations. The remaining 13 cases could not be comprehensively assessed due to insufficient information on vaccine latency and clinical course of the event. Seven case reports reported a relapse or flare-up of pre-existing glomerulonephritic condition were identified. However, no trend was seen on temporal plausibility based on widely varied TTO and some presenting only after 2nd vaccination. This also precludes any singular immune mediated hypothesis (non-specific or adaptive immune response). Moreover, majority of cases had confounders. Additionally, amongst 66 medically confirmed cases pertaining to Glomerulonephritis AND

Nephrotic syndrome (including IgA Nephropathy), 25 (38%) were identified either with relevant risk / confounding factors. Overall, the review of medically confirmed cases did not raise any new relevant safety information for VAXZEVRIA.

The O/E analysis results pertaining to Glomerulonephritis AND Nephrotic syndrome (including IgA Nephropathy) showed observed cases to be significantly less than expected cases.

In summary, the review of available data from spontaneous reports regarding Glomerulonephritis AND Nephrotic syndrome (including IgA Nephropathy) did not identify an index case or other evidence of a new or emerging signal.

Literature summary:

An analysis of the three relevant literature articles did not find any evidence of increased observed frequency of glomerulopathies compared to expected rates in general population. The review of mechanisms proposed by the authors included both vaccine type specific and vaccine non-specific mechanisms. However, there was insufficient evidence for a conclusive mechanism for glomerulopathies following VAXZEVRIA vaccination and that evidence from mRNA vaccine types cannot be comprehensively extrapolated to all other vaccines.

Conclusion

Based on the review of the currently available data, AstraZeneca considers that there is insufficient evidence to suggest a causal association between VAXZEVRIA and Glomerulonephritis AND Nephrotic syndrome (including IgA Nephropathy). It is AstraZeneca's opinion that no updates to CDS or RMP are warranted at this time.

AstraZeneca will continue to monitor safety information for Glomerulonephritis AND Nephrotic syndrome (including IgA Nephropathy) as part of routine safety surveillance activities and take further actions as deemed necessary.

15.2.9 Rhabdomyolysis

BACKGROUND

In the assessment report received from the PRAC EMA (EMEA/H/C/PSUSA/00010912/202112) for the VAXZEVRIA PBRER (review period 29 June 2021 – 28 December 2021), further information on the topic of rhabdomyolysis is requested as follows: *The MAH is requested to comment on the WHO-UMC identified signal of Rhabdomyolysis and to provide a cumulative review of cases reported with VAXZEVRIA. A discussion on the need to update the PI should be included. Rhabdomyolysis was actively monitored in UMC's signal detection activities for COVID-19 vaccines due to it being marked as an adverse event of special interest (AESI).*

Clinical Study data

There were no reports of rhabdomyolysis in the Oxford clinical studies

In the US Study (D8110C00001), data cut-off 30 July 2021. 5 cases of Rhabdomyolysis were reported in the AZD1222 arm and 1 subject in the placebo and all cases were assessed as not related to study intervention by the principal investigator. WHO-UMC assessment was unlikely for 3 cases, and possible with confounders for 2 cases. Five cases in the AZD1222 arm are presented in Table 99.

Table 99 Data from Clinical study database (DCO-3 Study)

Subject ID / Age / Sex / Seriousness (criteria)	AE Preferred Term	TTO for event / Event after dose 1 or Dose 2	Corrective treatment provided / Outcome of event	AE Intensity / AE Duration	Co-reported events at the same time	Concomitant medications / Medical history	WHO-UMC causality assessment	AstraZeneca Comment
[redacted] 54 / F / Non-serious	Rhabdomyolysis	133 days / Dose 2	Yes / Recovered	Moderate / 2 days	None	NR / None	Unlikely	Rhabdomyolysis was reported 133 days post Dose 2. Subject was treated with acetaminophen, ibuprofen and methylprednisolone and she recovered.
[redacted] 67 / F / Serious (Hospitalisation)	Rhabdomyolysis	16 days/ Dose 1	Yes / Recovered	Potentially Life-threatening / 6 days	Fall; Pneumonia; Sepsis; Thrombocytopenia; Acute respiratory distress syndrome	Atorvastatin, Sertaline / Hyperlipidaemia, Colon cancer, [redacted] Depression, Chronic hepatitis B	Possible; with confounder	Subject with medical history of [redacted], hepatitis B, colon cancer, Depression experienced syncope and fall, pneumonia, sepsis, thrombocytopenia, and respiratory distress along with rhabdomyolysis. Rhabdomyolysis most likely due to concurrent fall, infections and underlying risk factors and subject was immobile. Subject was treated with antibiotics and recovered.
[redacted] 66 / M / Non-serious	Rhabdomyolysis	178 days / Dose 2	No / Recovered	Severe/ 6 days	Suicide attempt, chronic kidney disease, cough	Rosuvastatin, Sertraline / Hyperlipidaemia, Depression, [redacted] obesity	Unlikely	The event of rhabdomyolysis was reported approximately 6 months after Dose 2. Concurrent chronic kidney disease, history of [redacted] and concomitant mediations statins and sertraline could explain the event.

Table 99 Data from Clinical study database (DCO-3 Study)

Subject ID / Age / Sex / Seriousness (criteria)	AE Preferred Term	TTO for event / Event after dose 1 or Dose 2	Corrective treatment provided / Outcome of event	AE Intensity / AE Duration	Co-reported events at the same time	Concomitant medications / Medical history	WHO-UMC causality assessment	AstraZeneca Comment
[redacted] 49 /M / Serious (Hospitalisation)	Rhabdomyolysis	39 days / Dose 2	No / Recovered	Severe / 5 days	None	None / Obesity	Possible; with confounder	The subject has a history of obesity and experienced the event on rhabdomyolysis 39 days after Dose 2 and was hospitalised. The event resolved within 5 days.
[redacted] 30 / M / Serious (Hospitalisation)	Rhabdomyolysis	134 days/ Dose 2	Yes / Recovered	Severe / 4	Acute psychosis; Hypomagnesaemia	NR / Tobacco user	Unlikely	The subject experienced acute psychosis secondary to schizophrenia disorder bipolar type and akathisia, severe rhabdomyolysis and hypomagnesemia. Subject was treated with IV fluids and antipsychotics and he recovered.

AE Adverse Event, F Female, M Male, TTO Time to Onset, WHO-UMC World Health Organization Uppsala Monitoring Centre

Global Patient Safety Database

A cumulative search of the AstraZeneca Global Safety Database for reports of Rhabdomyolysis with VAXZEVRIA until DLP 28 June 2022 was performed.

The search strategy included the following MedDRA PTs (version 25.0): Muscle necrosis; Myoglobin blood increased; Myoglobin blood present; Myoglobin urine present; Myoglobinaemia; Myoglobinuria; Myopathy; Myopathy toxic; Necrotising myositis; Rhabdomyolysis; Thyrotoxic myopathy and Muscle infarction.

The search retrieved a total of 92 case reports with 95 events of Rhabdomyolysis. The case report source is presented in Table 100:

Table 100 Distribution of the case reports of Rhabdomyolysis by reporting source and report seriousness

Report Source	Non-serious cases	Serious cases	Grand Total
Clinical	0	0	0
Spontaneous[a]	10	77	87
Literature	0	5	5
Non-interventional/post-marketing study	0	0	0
Grand Total	**10**	**82**	**92**

[a] Of the 87 Spontaneous case reports, 73 (79.3%) were received via Regulatory authorities.

Table 101 presents number and percentage (%) of case reports with Rhabdomyolysis reported after respective doses.

Table 101 Dose-wise distribution of case reports of Rhabdomyolysis with VAXZEVRIA

No. of cases {N (%)}				
After First Dose	After Second Dose	After First and Second Dose	After Third Dose	Dose number Unknown
71 (77.2%)	13 (14.1%)	0	0	8 (8.7%)

Out of the 92 case reports, 20 (21.7 %) were from Germany, 18 (19.6%) from United Kingdom, 10 (10.9%) from Australia, 7 (7.6%) from Brazil, 6 (6.5%) cases each from Austria and Italy, 4 (4.3%) from Netherlands, 3 (3.3%) cases each from Greece, France and Mexico, 2 (2.2%) cases each from Portugal, Taiwan and India and 1 (1.1%) case each from Spain, Sweden, Chile, Luxembourg, Norway and Japan. Out of 92 case reports:

- Vaccinee age was reported in 86 (93.5%) case reports and ranged from 10 to 92 years (median: 54 years). Out of 86 case reports, 21 (24.4%) vaccinees were between the age

group of 18 to 40 years, 41 (47.7%) vaccinees were between the age group of 41 to 64 years and 24 (27.9%) vaccinees were ≥ 65 years of age.

- Vaccinee gender was reported in 91 (98.9%) case reports. Of these case reports, 38 (41.8%) were male patients and 53 (58.2%) female patients.
- 43 (46.7%) case reports were medically confirmed and 49 (53.3%) were non-medically confirmed (consumer reports).
- Of the total 92 case reports, the time to onset (TTO) identified from VAXZEVRIA administration to Rhabdomyolysis events was available in 63 (68.5%) case reports and ranged from 0 days to 266 days (median: 3 days). Where multiple events/TTOs were present in a case, the most conservative TTO was taken (usually the shortest).

A breakdown of cases by TTO is presented in Table 102.

Table 102 TTO for Rhabdomyolysis case reports with VAXZEVRIA

Shortest TTO (Days)	No of Cases	Percentage (%)[a]
<1	10	15.9%
1 to 5	26	41.3%
6 to 10	7	11.1%
10 to 15	8	12.7%
16 to 20	2	3.2%
21-30	5	7.9%
31-42	3	4.8%
>42	2	3.2%
Unknown	29	NA

[a] TTO was reported for 63 case reports used to calculate the percentage in case [redacted] TTO from vaccine administration was unknown, but the patient died on day 22 after dose 1.

Ninety Five Rhabdomyolysis events were reported in 92 cases. The distribution of these 95 events of Rhabdomyolysis are presented in Table 103 below in descending order of frequency:

Table 103 Distribution of MedDRA PTs (n = 95) pertaining to Rhabdomyolysis

MedDRA PT	Serious	Non-serious	Grand Total
Rhabdomyolysis	54	0	54
Myopathy	19	12	31
Muscle necrosis	6	0	6
Myopathy toxic	2	0	2
Myoglobin blood increased	1	0	1
Necrotising myositis	1	0	1
Total	**83**	**12**	**95**

The events commonly co-reported with Rhabdomyolysis are presented in Table 104:

Table 104 Distribution of most frequently co-reported events (for example ≥ 5%) in case reports for Rhabdomyolysis

Adverse events (PT)	Number of Cases	Percentage (%)
Myalgia	25	26.3%
Arthralgia	16	16.8%
Pain in extremity	16	16.8%
Fatigue	14	14.7%
Muscular weakness	14	14.7%
Pain	12	12.6%
Pyrexia	11	11.6%
Asthenia	11	11.6%
Acute kidney injury	10	10.5%
Peripheral swelling	9	9.5%
Headache	9	9.5%
Myositis	9	9.5%
Muscle spasms	8	8.4%
Malaise	7	7.4%
Paraesthesia	7	7.4%
Hypoaesthesia	7	7.4%
Oedema peripheral	6	6.3%
Dyspnoea	6	6.3%
Chills	6	6.3%
Blood creatine phosphokinase increased	5	5.3%
Gait disturbance	5	5.3%
Dizziness	5	5.3%
Fibrin D dimer increased	5	5.3%
Back pain	5	5.3%

MedDRA Medical Dictionary for Regulatory Activities, PT Preferred Term

Ninety Five Rhabdomyolysis events were reported in 92 cases:

- 83 (87.4%) of the events were serious. The reported seriousness criteria were reported as follows; 29 (34.9%) medically important event, 6 (7.2%) disability, 33 (39.8%) hospitalization, 10 (12.0%) life threatening and 5 (6.0%) death. The remaining 12 (14.5%) events were non-serious (non-medically confirmed).
- Of the 95 events of Rhabdomyolysis, the reported outcomes were recovered 20 (21.1%), recovering 23 (24.2%), recovered with sequelae 3 (3.2%), not recovered 24 (25.3%) and fatal in 5 (5.3%) events. The outcome in the remaining 20 (21.1%) events was unknown.

- Amongst 23 events with reported outcome 'recovered' or 'recovered with sequelae,' the event duration was reported in 11 (47.8%) cases. The median duration was 11 days. For 5 (45.5%) cases, the event recovered within 7 days and for the remaining 6 (54.5%) cases the event recovered after 7 days.

Events with fatal outcome

5 out of 95 events (from 4 case reports) were reported as fatal. Of the 4 cases, 3 cases were medically confirmed and 1 was consumer report. The 5 reported fatal events (PTs) were rhabdomyolysis (4) and myoglobin blood increased (1). In all 4 fatal cases, the events were reported after Dose 1. The TTO of fatal events ranged from 2 to 25 days after receiving VAXZEVRIA. All 4 fatal case reports were assessed as Possible as per WHO-UMC causality. Of 4 fatal case reports, 2 case reports [redacted] and [redacted] had concomitant medications such as mirtazapine and simvastatin which are known to cause rhabdomyolysis. In one case report [redacted], it was described that based on the hypothesis of a multiple acyl-CoA dehydrogenase deficiency (MADD), an exome sequence analysis detected a heterozygous variant c.233C>T (p.Thr78Met), confirmed by Sanger sequencing, in caveolin 3 (CAV3) gene. Furthermore, a c.800-1G>A in MYH3 gene, encoding for Myosin heavy chain-embryonic (MyHC-emb) molecule, a skeletal muscle specific contractile protein, was also documented. Genomic sequencing identified 2 genes (CAV 3 and MYH3) known to be potentially associated with an increased risk of Rhabdomyolysis. Remaining one case report [redacted] lacked sufficient case details such as medical history, concomitant medications, autopsy details (if performed or not), etiological and diagnostic work-up.

An overview of the fatal case reports is presented in the below Table 105:

Table 105 Summary of case reports with fatal outcome for Rhabdomyolysis (N = 4)

Sr. No.	Case ID / Country / Medically confirmed (Y/N) / Source	Age (Years) / Gender (M/F)	Medical History / Concomitant Medications	Time to Onset (days) / Dose Information	Event PTs	Other reported conditions associated to the fatal outcome / Autopsy (Yes / No / Unk)	WHO-UMC Causality Assessment	Comment
1	[redacted] United Kingdom / N / Spontaneous	Unk / F	Asthma / Mirtazapine	Within 22 days / Dose 1	Rhabdomyolysis	None / Unk	Possible; with risk factor	TTO within risk window of 01-42 days. Confounder: Mirtazapine. COVID-19 test negative
2	[redacted] Italy / Y / Spontaneous	68 / M	Not Reported / Not Reported	25 / Dose 1	Rhabdomyolysis / Myoglobin blood increased	Acute kidney injury, Transaminases increased, Hyperkalaemia, Fibrin D dimer increased / Unk	Possible; with limited information	TTO within risk window of 01-42 days. Limited information on medical history, concomitant medications, etiologic and diagnostic work up as well on autopsy details.
3	[redacted] Brazil / Y / Spontaneous	75 / F	Not Reported / Simvastatin	2 / Dose 1	Rhabdomyolysis	Not reported / Unk	Possible; with risk factor	TTO within risk window of 01-42 days. Confounder: Simvastatin

4	[redacted] Italy / Y / Literature	68 / M	Not Reported / Not Reported	9 / Dose 1	Rhabdomyolysis	Multiple organ failure / Unk	Possible; with risk factor	TTO within risk window of 01-42 days. Based on the hypothesis of a multiple acyl-CoA dehydrogenase deficiency (MADD), an exome sequence analysis targeted at 19 genes associated with mitochondrial fatty acid b-oxidation disorders was performed, and no genetic variations were detected. However, a heterozygous variant c.233C>T (p.Thr78Met), confirmed by Sanger sequencing, in caveolin 3 (CAV3) gene was found. Furthermore, a c.800-1G>A in MYH3 gene, encoding for Myosin heavy chain-embryonic (MyHC-emb) molecule, a skeletal muscle specific contractile protein, was also documented. Genomic sequencing identified 2 genes (CAV 3 and MYH3) known to be potentially associated with an increased risk of Rhabdomyolysis.

TTO, Time to onset; Unk, Unknown; F, Female; M, Male, WHO-UMC World Health Organization Uppsala Monitoring Centre

Rechallenge / Recurrence case reports

There were no case reports identified for Rhabdomyolysis after the first dose, with a recurrence or worsening with the second dose of vaccination indicating potential recurrence / rechallenge.

WHO-UMC causality assessment

The clinical presentation of rhabdomyolysis varies, ranging from an asymptomatic increase in serum levels of enzymes released from the damaged muscles to severe muscle pain and conditions such as hypovolaemia, metabolic and electrolyte abnormalities as well as acute kidney injury. Typically, the urine is dark due to the release of myoglobin. Diagnosis is confirmed by serum creatine phosphokinase (CPK) levels above 1,000 U/L or five times above the normal upper limit. The thresholds for upper limits of normal CPK-values differ for men and women and are considered to range between 39-308 U/L for men and 26-192 U/L for women, with some variation between ethnicities. The elevation of CPK could be considered the hallmark of rhabdomyolysis and usually rises within 12 hours after the onset of muscle injury and peaks within one to three days. Other important diagnostic tests include serum myoglobin, urinalysis for myoglobinuria and serum electrolyte abnormalities Torres PA et al 2015, Nance JR et al 2015

After review of 92 case reports of Rhabdomyolysis, in 3 (3.3%) cases the CPK value was less than 1000 U/L without reported PT of Rhabdomyolysis, and in 33 (35.9%) cases the CPK value was unknown without reported PT of Rhabdomyolysis. Hence, these 36 cases were unlikely to meet the case definition of Rhabdomyolysis. 54 (58.7%) case reports were reported with PT of Rhabdomyolysis and in 2 (2.2%) case reports the CPK value were more than 1000 U/L with PT Muscle necrosis and Myopathy along with additional symptoms of muscle pain and muscle weakness. Based on these factors, a total of 56 cases, were considered for WHO-UMC causality assessment.

AstraZeneca considered 56 cases of Rhabdomyolysis for WHO-UMC causality assessment using a Risk Window of 1-42 days which is presented in Table 106 below:

Table 106 Overview of WHO-UMC Causality Assessment of Rhabdomyolysis with VAXZEVRIA

WHO-UMC Causality category	WHO-UMC Causality assessment scale (AZ adapted)	Number of Cases
Certain	Certain	0
Probable-Likely	Probable-Likely	0
Possible	Possible with risk factors/confounders[a]	15
	Possible with limited information	20
Unlikely	Unlikely	8
Conditional / Unclassified	Conditional / Unclassified	1
Unassessable/Unclassifiable	Unassessable/Unclassifiable with risk factors/confounders[a]	7
	Unassessable/Unclassifiable with limited information	5
Total		**56**

[a] Cases were considered to have "risk factors/confounders" where the event could also be explained by the vaccinee's diseases, or where relevant risk factors were present, or concomitant medications that could potentially contribute to the development of the event were reported.

Amongst 56 cases for Rhabdomyolysis, 26 (46.4%) cases were identified either with relevant risk/confounding factors (Torres PA et al 2015 and Nance JR et al 2015) as presented in Table 107. These are presented into the following categories for risk / confounding factors in descending order of frequency.

Table 107 Relevant Risk factors / Confounders identified for case reports

Relevant Risk / Confounders	Number of reports	Percent of Total Number of Reports
Chronic conditions (such as Diabetes mellitus; Depression; Personality disorder; Chronic kidney disease; Obesity; Urinary tract infection; Bipolar disorder; Deep vein thrombosis; Basedow's disease; Carntine palmityl deficiency; Breast cancer; nicotine abuse; Cervical conisation; Psychotic disorder; Parkinson's disease; arthrosis; Rhabdomyolysis; Pulmonary embolism with thrombocytopenia; Schizophrenia; Sjogren's syndrome; Secondary progressive multiple sclerosis; Hypothyroidism; tendon disorder; Immunodeficiency; and Antiphospholipid syndrome)	17	65.4%
Concomitant medications (ezetimibe, levetiracetam, prednisolone, sodium Valproate, atorvastatin, pregabalin, clozapine, mirtazapine, simvastatin, febuxostat, lurasidone, lamivudine + zidovudine, and venlafaxine hydrochloride)	12*	46.2%
Patient's age (Elderly age: ≥ 80 years)	5*	19.2%
Suspected COVID-19	2*	7.7%
Other: CAV 3 gene and MYH3 gene can be associated with rhabdomyolysis	1	3.8%

*In 11 case reports, more than 1 risk factor was reported (6 cases chronic condition + concomitant medications, 2cases: chronic condition + elderly age: ≥ 80 years and 2 cases chronic condition + suspected COVID-19), hence the total is more than 26

In the remaining 30 (53.6%) out of 56 case reports of Rhabdomyolysis, there was insufficient information with respect to either dose latency, medical history or concomitant medication details for a comprehensive causal assessment.

Observed Versus Expected (O/E) Analyses

In addition to the case review requested, AstraZeneca also conducted an observed versus expected analysis for Rhabdomyolysis using cumulative observed cases. The background incidence rate (IR) from McKenna MC et al 2019 has been used for O/E analysis. With regards to the Risk Window of 1-42 days, as there is a lack of specific literature or a postulated biological mechanism and/or precedent for investigation of this as a postulated Adverse Event Following Immunization (AEFI), a risk window of 1-42 days was chosen to align with the broad concept of this being a suitable risk window for possible immune-mediated AEFIs (Rowhani-Rahbar A et al 2012).

An O/E analysis of Rhabdomyolysis was conducted cumulatively through DLP 28 June 2022 are presented in Table 108. The results were provided for 42 days risk windows for all global and regional (EU/UK) reports. The background incidence rate (IR) from McKenna MC et al 2019 has been used for O/E analysis.

Conservatively, the exposure for global reports (448306152) is based on doses administered in 13 markets as explained in Appendix 8.

Table 108 Observed versus expected cumulative for reports of Rhabdomyolysis with risk window of 1-42 days

Rhabdomyolysis	Risk window	BG rates	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
Rhabdomyolysis - All cases (RW 42)	42	59	448306152	51	29691.3	0 (0 - 0)	Observed significantly < expected
Rhabdomyolysis - All cases (RW 42 + Unk)	42	59	448306152	80	29691.3	0 (0 - 0)	Observed significantly < expected
Rhabdomyolysis – EU/UK (RW 42)	42	59	117692071	40	7794.74	0.01 (0 - 0.01)	Observed significantly < expected
Rhabdomyolysis – EU/UK (RW 42 + Unk)	42	59	117692071	55	7794.74	0.01 (0.01 - 0.01)	Observed significantly < expected

Unk, Unknown; RW Risk window.

Observed events were significantly less than the expected events using the Risk Window (RW) of 42 days for all global and regional (EU/UK) reports, and also including those events with unknown TTO.

Summary

Rhabdomyolysis was actively monitored in UMC's signal detection activities for COVID-19 vaccines due to it being marked as an AESI. WHO identified signal of rhabdomyolysis for COVID-19 vaccines.

The incidence of Rhabdomyolysis in general population is unknown. On literature review McKenna MC et al 2019 is concerned with the incidence rate in hospitalised patients. Rhabdomyolysis is known to occur naturally at an overall annual incidence of 59 cases per 100,000 persons (McKenna MC et al 2019) per annum. The natural aetiology is multifactorial but includes traumatic injury, exertion, medicines, infections and metabolic causes. The classic presentation is of muscle pain, weakness, pigmenturia, and a marked elevation of serum CPK five to ten times above the upper limit of normal (ULN) serum levels (Chavez L O et al 2016).

Ninety-two (92) Rhabdomyolysis cases were reported globally and included in AstraZeneca's post-marketing database. Cases were assessed by age, sex, type of event, and outcome. The characteristics of the events and of the individuals with events were as expected for the general population, including the observation of increased incidence in the elderly. No usual trends or clusters were identified. The time to onset (TTO) was available in 63 (68.5%) case reports and ranged from 0 days to 266 days (median: 3 days). Of 63 cases, 51 (81.0%) cases were within TTO range of 1-42 days.

Of 92 cases, 54 (58.7%) cases were reported with PT of Rhabdomyolysis and in 2 (2.2%) cases the CPK value were more than 1000 U/L with PT Muscle necrosis and Myopathy along with additional symptoms of muscle pain and muscle weakness. In 33 cases, Rhabdomyolysis was not reported as a PT (with CPK value not stated) and in 3 cases CPK was less than 1000 U/L without Rhabdomyolysis reported. Hence these 36 cases were unlikely to meet the definition of Rhabdomyolysis. Of 92 cases, 56 cases were considered for WHO-UMC causality. None of the cases met WHO-UMC criteria for Certain or Probable/Likely. 62.5% were considered as Possible, 14.3% were considered as Unlikely, 1.8% were Conditional/Unclassified and 21.4% were considered as Unassessable/Unclassifiable related to VAXZEVRIA. Amongst 56 cases, 46.4% were identified with relevant risk/confounding factors and 53.6% cases had limited information for a comprehensive causal assessment.

Of 92 cases, there were 4 fatal cases which were assessed as Possible as per WHO-UMC causality (3 cases had relevant confounders and 1 case had limited information).

The O/E analysis results for rhabdomyolysis showed observed cases to be significantly less than expected for all age and Global and EU/UK reports.

In summary, the review of available data from spontaneous reports regarding rhabdomyolysis did not identify an index case or other evidence of a new or emerging signal.

Conclusion

Based on the currently available cumulative data, AstraZeneca considers that there is insufficient evidence to suggest a causal relationship between VAXZEVRIA and Rhabdomyolysis. It is AstraZeneca's opinion that no update to the CDS or RMP is warranted at this time.

Rhabdomyolysis is an AESI for VAXZEVRIA and will continue to be kept under close surveillance by AstraZeneca. AstraZeneca will no longer discuss the topic in future PBRERs, unless significant new safety information arises.

15.2.10 Exacerbation of Diabetes, Adrenal Insufficiency and Hypertension

Background

In the assessment report received from the PRAC EMA (EMEA/H/C/PSUSA/00010912/202112) for the VAXZEVRIA PBRER (review period 29 June 2021 to 28 December 2021), further information on the topic of Exacerbation of Diabetes Mellitus (eDM), Adrenal Insufficiency and Hypertension is requested as follows:

The MAH is requested to comment on the WHO-UMC identified signal of exacerbation of these health issues and provide a cumulative review of cases reported with VAXZEVRIA. A discussion on the need to update the PI should be included.

15.2.10.1 Exacerbations of type 1/type 2 mellitus diabetes

A cumulative search till DLP (28 June 2022) of the AstraZeneca Global Safety Database with VAXZEVRIA was performed using the following MedDRA Preferred Term(s) (version 25.0): Diabetes mellitus inadequate control; Diabetes with hyperosmolarity; Diabetic hyperglycaemic coma; Diabetic hyperosmolar coma; Diabetic ketoacidosis; PTs related to increased blood glucose; Blood glucose fluctuation; Blood glucose increased; Glucose tolerance impaired; Glycosylated haemoglobin abnormal; Glycosylated hemoglobin increased; Diabetic ketoacidotic hyperglycaemic coma; Diabetic ketosis; Diabetic metabolic decompensation; Hyperglycaemic hyperosmolar nonketotic syndrome; Hyperglycaemic seizure; Hyperglycaemic unconsciousness; Hyperosmolar state; Ketoacidosis; Hyperglycaemia; Increased insulin requirement.

The search retrieved a total of 1087 cases, of them DM was coded incorrectly in 9 cases, which were removed from further analysis. Of the remaining 1078 cases, diabetes mellitus (DM) was reported as medical history in 383 cases, these cases are considered to be exacerbation of DM and are further analysed. A total of 409 events of eDM were reported in the 383 cases.

The case source distribution for eDM cumulatively through DLP [28 June 2022] is presented in Table 109. Most cases of eDM were received from regulatory and spontaneous sources, 307 and 71, respectively.

Table 109 Distribution of the case reports of eDM received with VAXZEVRIA cumulatively through DLP by reporting source and report seriousness

Classification of case report source	Non-serious cases	Serious cases	Grand Total
Clinical trial	0	2	2
Spontaneous[a]	178	199	377
Literature	2	2	4
Grand Total	180	203	383

[a] Of the 378 spontaneous case reports, 307 (81.2%) were from Regulatory source.

The following Table 110 presents number and percentage (%) of case reports with eDM reported after respective doses cumulatively through DLP [28 June 2022]. In most cases (73.3%) eDM was reported following the first dose of VAXZEVRIA.

Table 110 Number and percentage (%) of the case reports of eDM reported after respective doses of VAXZEVRIA cumulatively through DLP by reporting source and report seriousness

No of Cases (After First Dose)	No of Cases (After Second Dose)	No of Cases (After both First and Second Dose)	No of Cases (After Third Dose)	No of Cases (Dose number Unknown)
280 (73.1%)	11 (2.9%)	0 (0%)	0 (0%)	92 (24.0%)

These case reports for eDM were reported most frequently (>5%) in the following countries; UK 130 (33.9%), France 60 (15.6%), Netherlands 25 (6.5%), and Spain 20 (5.2%) cumulatively through DLP (28 June 2022).

The distribution of the 409 events of interest [eDM] by MedDRA PT are presented in Table 111 below in alphabetical order: The most frequently reported events of interest were Blood glucose increased and Hyperglycaemia, 166 and 115 events, respectively.

Table 111 Distribution of MedDRA PTs (n = 409) pertaining to eDM with VAXZEVRIA received cumulatively through DLP [28 June 2022]

MedDRA PT	Serious	Non-serious	Grand Total
Blood glucose fluctuation	15	23	38
Blood glucose increased	57	109	166
Diabetes mellitus inadequate control	27	21	48
Diabetic ketoacidosis	20	0	20
Diabetic ketosis	3	0	3

Table 111 Distribution of MedDRA PTs (n = 409) pertaining to eDM with VAXZEVRIA received cumulatively through DLP [28 June 2022]

MedDRA PT	Serious	Non-serious	Grand Total
Diabetic metabolic decompensation	7	1	8
Glucose tolerance impaired	1	0	1
Hyperglycaemia	66	49	115
Hyperglycaemic hyperosmolar nonketotic syndrome	1	0	1
Hyperosmolar state	1	0	1
Increased insulin requirement	1	6	7
Ketoacidosis	1	0	1

MedDRA Medical Dictionary for Regulatory Activities, PT Preferred Term

The following observations were made from a review of the 409 events in 383 case reports pertaining to eDM cumulatively through the DLP (28 June 2022):

- Vaccinee age was reported in 346 case reports and ranged from 20 to 89 (mean: 54.5 years; median: 57 years). 244 (63.8%) reports referred to adult and 113 (29.4%) to elderly vacinees, in 26 case reports age group was not available.
- Vaccinee gender was reported in 382 case reports. Of these case reports, 233 (60.8%) were in female patients and 149 (38.9%) were in male patients. In one (0.3%) case report gender was not reported.
- 117 (30.5%) case reports were medically confirmed and 266 (69.5%) were non-medically confirmed.
- 203 (53.0%) of the cases were serious (62 medically confirmed and 141 were consumer reports)
- Serious criteria in the 203 cases were Fatal 12 (5.9%), Life threatening 26 (13.2%), Hospitalisation 53 (26.0%), Disability 22 (10.8%), and Medically important 158 (77.5%). An event may have met more than one criteria for seriousness. The remaining 180 (46.9%) events were non-serious (55 medically confirmed and 125 consumer reports).
- Amongst 118 cases with reported outcome Recovered or Recovered with sequelae, the event duration was reported in 43 [36.1%] cases. The mean duration was 7 days. In 36 (83.7%) cases, the event resolved within 7 days and in the remaining 7 (16.3%) cases the event resolved between 8 and 77 days after onset.
- Of the total 383 case reports, the time to onset (TTO) identified from VAXZEVRIA administration to eDM (0 days) was reported in 348 case reports and ranged from 0 to 213 days (mean: 4.0 days; median: 0 days). Most of the cases occurred in the initial 5 days of vaccination. This is further presented in the following Table 112 accordingly with respect to the risk window days:

Table 112 TTO for eDM case reports cumulatively through DLP (28 June 2022)

Shortest TTO (Days)	No of Cases	Percentage (%)[a]
0-5	315	82.0
6-10	8	2.3
11-15	4	1,0
16-20	2	0.5
21-25	2	0.5
26-30	3	0.8
31-35	3	0.8
36-42	1	0,3
>42	10	2.6
Unknown	35	9.1

[a] TTO was reported for 349 case reports (384) used to calculate the percentage, and if there were multiple TTOs are present in a case, the most conservative TTO for the relevant event is chosen.

Events with fatal outcome

Of the 383 cases of eDM reported, 12 (3.1%) were reported with fatal outcome cumulatively through DLP [28 June 2022], of which 5 (41.7%) were medically confirmed and 7 (58.3%) were consumer reports. The fatal PTs pertaining to eDM is presented in Table 113 below.

Table 113 Fatal AEs (PTs) pertaining to eDM reported in fatal case reports received cumulative though DLP [28 June 2022]

MedDRA / PT	Grand Total
Diabetic ketoacidosis	5
Blood glucose increased	3
Hyperglycaemia	3
Hypermolar state	1
Diabetic metabolic decompensation	1
Grand Total	**13**

MedDRA Medical Dictionary for Regulatory Activities, PT Preferred Term

One fatal case contained two fatal events of interest, Diabetic ketoacidosis and Hyperglycaemia.

The assessment of the fatal case reports identified cumulatively till DLP (28 June 2022) is presented in the below Table 114:

Table 114 Summary of case reports with fatal outcome for eDM (N=12) cumulatively through DLP [28 June 2022].

Case ID/ Country/ Age/Gender/Medically confirmed (Y/N)/ Source	Shortest TTO	PT of interest/Other reported conditions associated with the fatal outcome/ Autopsy (Y/N)	WHO UMC Causality Assessment/ Additional Comment	AstraZeneca medical comment
[redacted]/United Kingdom/88 (years)/Female/Y/Regulatory	4	Diabetic ketoacidosis/No/Unknown	Possible with risk factors/confounders	Confounders/risk factors for diabetic ketoacidosis: Poorly controlled T2DM, palliative care, recent infection, advanced age.
[redacted]/United Kingdom/20 (years)/Male/Y/Regulatory	2	Diabetic ketoacidosis; Hyperglycaemia/No/Unknown	Possible with risk factors/confounders	Confounded by poor compliance with insulin regime and a history of several admissions with DKA in the previous year.
[redacted]/United Kingdom/Unknown (years)/Female/N/Regulatory	2	Diabetic ketoacidosis/Death/Unknown	Possible with risk factors/confounders	Confounders: concurrent pneumonia, concomitant atorvastatin and tacrolimus, both known for dysregulating glycaemic control, ongoing history of peripheral vascular disease, diabetic nephropathy and IHD, previous history of renal transplant. Concurrent fatal acute myocardial infarction is a confounding factor for the fatal outcome.
[redacted]United Kingdom/63 (years)/Female/Y/Regulatory	3	Diabetic ketoacidosis/Circulatory collapse/Unknown	Possible with risk factors/confounders	Confounded by circulatory collapse, dyspnoea and malaise that were developed two days before; ongoing medical history of hypertension, peripheral vascular disease, status post renal transplantation. The outcome is confounded by concurrent fatal acute myocardial infarction and circulatory collapse.
[redacted]/United Kingdom/71 (years)/Male/Y/Regulatory	38	Hyperosmolar state/Autoimmune encephalopathy; Myocardial ischaemia; Diabetes mellitus; Hypertension/No	Unlikely	TTO outside risk window. Fatal outcome is confounded by concurrent fatal events of autoimmune encephalopathy (direct cause of death), ischaemic heart disease and hypertension and concomitant steroid treatment.
[redacted]/United Kingdom/65	Unknown	Blood glucose increased /Cerebrovascular accident;	Unassessable/Unclassifiable with limited information	Unknown TTO. Confounders: concomitant amlodipine, ongoing history of hypertension, concurrent events of acute cerebrovascular

Table 114 Summary of case reports with fatal outcome for eDM (N=12) cumulatively through DLP [28 June 2022].

Case ID/ Country/ Age/Gender/Medically confirmed (Y/N)/ Source	Shortest TTO	PT of interest/Other reported conditions associated with the fatal outcome/ Autopsy (Y/N)	WHO UMC Causality Assessment/ Additional Comment	AstraZeneca medical comment
(years)/Male/N/Regulatory		COVID-19 pneumonia/Unknown		accident and COVID-19 pneumonia. The direct causes of death were reported as cerebrovascular accident and COVID-19 pneumonia.
[redacted]/United Kingdom/61 (years)/Female/Y/Regulatory	19	Hyperglycaemia/Myocardial ischaemia/Unknown	Unlikely	TTO is outside risk window. Missing: baseline blood glucose, control of diabetes. The patient died from the event of myocardial ischemia. Fatal outcome is confounded by concurrent fatal acute renal failure. Hyperglycaemia is confounded by obesity.
[redacted]/United Kingdom/38 (years)/Male/N/Regulatory	1	Diabetic ketoacidosis/Arterial thrombosis; Chest pain; Myocardial infarction; Vomiting/No	Possible with risk factors/confounders	It was not reported if patient's type 2 DM was adequately controlled. Diabetic ketoacidosis is confounded by concurrent vomiting. The outcome is confounded by concurrent fatal events of myocardial infarction, chest pain and vomiting.
[redacted]Czech Republic/76 (years)/Female/N/Regulatory	80	Diabetic metabolic decompensation/Sudden death; Diplegia; Pulmonary embolism; Peripheral venous disease; Cardiac failure; Pneumonia; Hypertrophic cardiomyopathy; Hypertension; Nephrosclerosis; Arteriosclerosis; Brain oedema; Basal ganglion degeneration; Desmoid tumour; Type 2 diabetes mellitus; Bronchitis chronic; Ecchymosis; Atrial fibrillation; Obesity; Hydrothorax; Pulmonary embolism/Yes	Unlikely	TTO is outside risk window. Diabetic metabolic decompensation is a non-fatal event, confounded by ongoing medical history of arterial hypertension, hypertensive angiosclerosis, concurrent infection and AKI, concomitant telmisartan, hydrochlorothiazide, linagliptin, furosemide sodium. Missing information: if patient's type 2 DM was adequately controlled, relevant workup. Fatal outcome is attributed to sudden death, paralysis, lung embolism, venous stasis, cardiac insufficiency, bilateral bronchopneumonia, hypertrophic heart disease, arterial hypertension, nephrosclerosis arteriolar, arteriosclerosis, brain swelling, basal ganglion degeneration, fibromatosis, type II diabetes mellitus, chronic bronchitis, ecchymoses, fibrillation atrial, adipositas and hydrothorax and embolism lung.

Table 114 Summary of case reports with fatal outcome for eDM (N=12) cumulatively through DLP [28 June 2022].

Case ID/ Country/ Age/Gender/Medically confirmed (Y/N)/ Source	Shortest TTO	PT of interest/Other reported conditions associated with the fatal outcome/ Autopsy (Y/N)	WHO UMC Causality Assessment/ Additional Comment	AstraZeneca medical comment
[redacted]/United Kingdom/70 (years)/Female/N/Regulatory	Unknown	Blood glucose increased/Myocardial infarction/Unknown	Unassessable/Unclassifiable with limited information	TTO is unknown. Non-fatal event of Blood glucose increased is confounded by chronic kidney disease and immunodeficiency. The fatal outcome is attributed to heart attack (the cause of death) and confounded by ongoing medical history of chronic kidney disease, immunodeficiency, recent stroke.
[redacted]/United Kingdom/78 (years)/Male/N/Regulatory	213	Blood glucose increased/Tuberculosis/Unknown	Unlikely	TTO is outside the risk window. Limited information on onset dates of blood sugar increased, breathlessness, lethargic, tiredness, night sweats, fever, appetite lost and abnormal loss of weight. The fatal outcome is attributed to tuberculosis (the cause of death).
[redacted]Brazil/83 (years)/Male/N/Spontaneous	14	Hyperglycaemia/Respiratory failure; Pneumonia bacterial; Ischaemic stroke; Dementia Alzheimer's type/Unknown	Unlikely	TTO is outside the risk window. Hyperglycaemia is confounded by ongoing medical history of Alzheimer's disease and recent fall. Fatal outcome is attributed to respiratory failure, bacterial pneumonia, ischemic stroke and Alzheimer's disease.

Of the 12 fatal case reports (eDM) cumulatively till the DLP (28 June 2022), 5 (41.7%) were medically confirmed. Overall, the TTO was reported for 10 of the 12 fatal events and ranged from 0 to 213 days after receiving vaccine. The risk window for TTO was considered to be between 0 and 7 days, inclusive. Of the 12 fatal case reports the WHO-UMC causality was considered possibly related in 5 (41.7%) cases, unlikely related in 5 (41.7%) cases due to TTO being outside the risk window, and in 2 (16.7%) cases it was considered to be unassessable due to unknown TTO. Diabetic ketoacidosis was reported in all cases assessed as possibly related, all the cases contained strong confounding factors: inadequate control or compliance in 2 cases, concurrent pneumonia, recently developed circulatory collapse and myocardial infarction. All remaining fatal cases also reported confounding factors or alternative explanation. In 6 cases fatal outcome was attributed to other events: autoimmune encephalopathy, acute cerebrovascular accident and COVID-19 pneumonia, myocardial ischemia, heart attack, tuberculosis, and to respiratory failure, bacterial pneumonia, ischemic stroke and Alzheimer's disease. In the remaining fatal case, the fatal outcome was attributed to a number of conditions, including sudden death and type II diabetes mellitus.

Rechallenge / Recurrence case reports

There were no case reports indicating potential recurrence / rechallenge cumulatively through DLP.

WHO-UMC causality analysis

Of the total 383 case reports of eDM identified cumulatively through DLP (28 June 2022), 117 (30.5%) case reports were medically confirmed (62 serious and 55 non-serious), and 266 (69.5%) case reports were not medically confirmed. The WHO-UMC causality was further assessed below with 0 to 7 days risk window.

Table 115 Overview of WHO-UMC Causality Assessment for cases of eDM with VAXZEVRIA reported cumulatively through DLP (28 June 2022).

WHO-UMC Causality category	WHO-UMC Causality assessment scale (AZ adapted)	Number of Cases
Possible	Possible with limited information	169 (44.1%)
	Possible with risk factors/confounders*	97 (25.3%)
Unassessable/ Unclassifiable	Unassessable/Unclassifiable with limited information	70 (18.3%)
	Unassessable/Unclassifiable with risk factors/confounders*	8 (2.1%)
Unlikely	Unlikely	39 (10.2%)
Total		**383**

Cases were considered to have "risk factors/confounders" where the event could also be explained by the vaccinee's diseases, or where relevant risk factors were present, or concomitant medications that could potentially contribute to the development of the event were reported.

Amongst 383 cases of eDM, no case was assessed as Certain or probable/likely related to VAXZEVRIA. Most cases, 266 (69.5%) were assessed as possibly related to VAXZEVRIA, followed by unassessable/unclassifiable cases, 78 (20.4%). 39 (10.2%) cases were unlikely related to VAXZEVRIA since the time to onset exceeded the risk window.

Of the 383 cases 239 (69.5%) had insufficient information for medical evaluation, and 105 (30.5%) cases were identified either with relevant risk/confounding factors.

Analysis of confounding factors for all cases of eDM is presented in Table 116.

Table 116 Relevant Risk factors / Confounders identified cumulatively through DLP (28 June 2022).

Relevant Risk / Confounders	Total	Percent of Total
Concomitant medication (Polypharmacy, Statins, Calcium channel blockers, Beta blockers, Immunosuppressants, Steroids)	66	33.3
Concurrent AE (Vomiting, Diarrhoea, Thrombosis, Circulatory collapse Hypertensive crisis, Pyrexia, Hypothermia, Gastrointestinal disturbance, Angioedema, pancreatic/thyroid pathology)	31	15.7
Advanced Age	13	6.6
Other (Alzheimer's disease, Anxiety, Depression, Post-traumatic stress disorder, developmental delay, PCOS, Hypothyroidism, Osteoporosis, Palliative care, Pancreas transplant rejection, Sarcoidosis, Heart disease)	12	6.1
Poorly controlled diabetes	11	5.6
Influenza/Influenza-like illness	9	4.5
Hypertension	8	4.0
Obesity	8	4.0
Infection	8	4.0
Renal disease (failure, impairment, transplant)	6	3.0
Immunodeficiency	6	3.0
COVID-19/COVID-19 pneumonia	5	2.5
Occlusive disease	5	2.5
Myocardial infarction	4	2.0
Stroke	4	2.0
History of Diabetic ketoacidosis	2	1.0
Total	198	100

Of the 383 cases, 132 contained risk factors/confounders for eDM. In the remaining 251 (65.5%) case reports cumulatively through DLP, there was insufficient information with respect to either dose latency, medical history or concomitant medication details for a comprehensive causal assessment.

Overall, the review of eDM cases did not raise any new relevant safety information for VAXZEVRIA.

Literature

A cumulative literature search through DLP 28 June 2022 of the databases in Embase, InsightMeme and PubMed was conducted using the following search terms: Diabetes mellitus inadequate control, Diabetes with hyperosmolarity, Diabetic hyperglycaemic coma, Diabetic hyperosmolar coma, Diabetic ketoacidosis, Blood glucose fluctuation, Blood glucose increased, Glucose tolerance impaired, Glycosylated haemoglobin abnormal, Glycosylated hemoglobin increased, Diabetic ketoacidotic hyperglycaemic coma, Diabetic ketosis, Diabetic metabolic decompensation, Hyperglycaemic hyperosmolar nonketotic syndrome, Hyperglycaemic seizure, Hyperglycaemic unconsciousness, Hyperosmolar state, Ketoacidosis, Hyperglycaemia for VAXZEVRIA

On using the above search criteria, 15 articles were identified. None of these, 15 articles were considered relevant for further evaluation and presentation.

Summary

Overall medical summary of all case reports

Cumulatively through DLP (28 June 2022), a total of 383 reports of eDM with the use of VAXZEVRIA have been received, of which 53.0% of the reported cases were serious and 46.9% were non-serious. 12 fatal events were reported, all of them were confounded by pre-existing inadequate control of DM, or by other strong confounding factors or were not the direct cause of death. The age range was 20 to 89 years and mean and median age was reported as 54.5 years and 57 years, respectively. More cases were reported for adult patients compared to the elderly, 63.8% and 29.4%, respectively, and more cases were reported for female that for male vaccinees, 60.8% and 38.9%, respectively. 30.5% of cases were medically confirmed and 69.5% were consumer reports.

Most of the cases were reported after the first dose of VAXZEVRIA, 280 (73.3%). 11 (2.9%) cases occurred after the second dose, and none after the third dose. There were no case reports identified for eDM after the first dose, with a recurrence or worsening of eDM with the second dose of vaccination indicating potential recurrence / rechallenge cumulatively through DLP.

Of the serious cases, the most were medically important, 77.5%, followed by hospitalization, 26.0%, life threatening, 13.2%, disability, 10.8% and fatal, 5.9%.

For eDM, the most common PTs reported were Blood glucose increased (166), Hyperglycaemia (116), Diabetes mellitus inadequate control (48), Blood glucose fluctuation (38) and Diabetic ketoacidosis (20).

The most commonly co-reported events were Pyrexia (25.8%) and Headache (28.4%).

Cumulatively through DLP (28 June 2022) of the 383 case reports, the TTO was reported in 348 (90.8%) cases. The mean and median TTO was 4.0 days (mean) and 0 days (median) respectively. TTO ranged from 0 to 213 days, and was unknown in 35 (9.1%) case reports..

- Amongst 383 cases received cumulatively through DLP (28 June 2022) 118 had a reported outcome recovered or recovered with sequelae. The majority of the events were reported as recovered at time of reporting, and the different case report source was as followed: Clinical trial (2); Spontaneous (377); and Literature (4). Amongst 1188 cases with reported outcome Recovered or Recovered with sequelae, the event duration was reported in 43 [36.1%] cases. The mean duration was 7.0 days.
- For 36 cases (83.7% of the events with reported duration), the events of interest resolved within 7 days and for the remaining 7 (16.3%) cases the events resolved between 8 and 77 days after onset.
- 30.5% of cases were medically confirmed and 69.5% were consumer reports.

The majority of case reports cumulatively through DLP (28 June 2022), 62.4% contained insufficient information to confirm causality assessment. A total of 30.5% of eDM cases included relevant risk/confounding factors.

On further WHO UMC case causality analysis conducted for case reports of eDM, none were considered as certain or probable and 10.2% were considered unlikely related to VAXZEVRIA. About, 69.5% case reports were assessed as possibly related to VAXZEVRIA, however these cases had either limited information or presence alternate etiologies.

Overall, none of the case reports raised any new relevant safety concerns for eDM cumulatively till DLP, and we are not aware of any specific biological mechanism through which VAXZEVRIA vaccine could cause eDM.

Discussion and Conclusion

AstraZeneca was requested to provide a cumulative review on exacerbations of type 1/type 2 mellitus diabetes in vaccinees who received VAXZEVRIA based on the corresponding signal identified by WHO UMC. WHO UMC identified 90 case reports of exacerbation of diabetes, that includes 22 cases for VAXZEVRIA. However, lack of information available in the reports precluded any conclusions on the impact of the hyperglycaemia exacerbation. The report also included cases and case series published in the literature, a hypothetical mechanism of such toxicity, and recommendations from medical societies, which contained no official recommendations regarding the use of vaccines in patients with diabetes. WHO-UMC concluded that these findings do not amount to a contraindication of COVID-19 vaccination in patients with these conditions. On review of the WHO UMC signal report, AstraZeneca have found that the report does not contain definitive evidence on causal association between VAXZEVRIA and exacerbation of diabetes.

Based on the currently available cumulative data, AstraZeneca considers that there is insufficient evidence to suggest a causal relationship between eDM and VAXZEVRIA. It is the opinion of AstraZeneca that no changes to the CDS or RMP are warranted at this time.

AstraZeneca will continue to monitor safety information for eDM as part of the routine safety surveillance activities for VAXZEVRIA. AstraZeneca will not discuss the topic future PBRERs, unless significant new safety information arises.

15.2.10.2 Exacerbation of Adrenal insufficiency

A cumulative search of the AstraZeneca Global Safety Database up to the DLP of 28 June 2022 for Exacerbation of Adrenal Insufficiency with VAXZEVRIA was performed using MedDRA version 25.0. Preferred Terms: Addison's disease; Adrenal insufficiency; Adrenal insufficiency neonatal; Adrenal suppression; Adrenocortical insufficiency acute; Adrenocortical insufficiency neonatal; Immune-mediated adrenal insufficiency; Primary adrenal insufficiency; Secondary adrenocortical insufficiency; Tertiary adrenal insufficiency.

The search retrieved a total of 86 case reports, cumulatively, of which 25 (29.1%) case reports had pre-existing medical history of adrenal disease suggesting Exacerbation of Adrenal Insufficiency.

All of the 25 (100%) cases reports were from spontaneous sources, and were serious.

The following Table 117 presents number and percentage (%) of case reports with exacerbation of Adrenal Insufficiency reported after respective doses cumulatively through DLP [28 June 2022]. In most cases (72%) exacerbation of Adrenal insufficiency the dose number was unknown.

Table 117 Number and percentage (%) of the case reports of exacerbation of Adrenal Insufficiency reported after respective doses of VAXZEVRIA cumulatively through DLP (28 June 2022)

No of Cases (After First Dose)	No of Cases (After Second Dose)	No of Cases (After both First and Second Dose)	No of Cases (After Third Dose)	No of Cases (Dose number Unknown)
6 (24%)	1 (4%)	0	0	18 (72%)

These case reports for exacerbation of Adrenal Insufficiency were reported in the following countries: United Kingdom 23 (92%), Sweden 1 (4%) and Thailand 1 (4%).

The distribution of the 26 events of exacerbation of Adrenal Insufficiency in the 25 case reports by MedDRA PT are presented in Table 118.

Table 118 Distribution of MedDRA PTs (n = 26) pertaining to exacerbation of Adrenal Insufficiency with VAXZEVRIA received cumulatively through DLP [28 June 2022]

MedDRA PT	Case Count
Adrenocortical insufficiency acute	15 (57.7%)
Adrenal insufficiency	10 (38.5%)
Addison's disease	1 (3.8%)
Total	26

MedDRA Medical Dictionary for Regulatory Activities, PT Preferred Term

The following observations were made from a review of the 25 case reports pertaining to Exacerbation of adrenal insufficiency:

- Vaccinee age was reported in 24 (96%) case reports and ranged 18 to 78 years (mean: 56 years; median: 58.5 years).
- Vaccinee gender was reported in 24 (96%) case reports. Of these case reports, 7 (29.2%) concerned males and 17 (70.8%) concerned females.
- All 25 (100%) cases were serious (7 [28%] were medically confirmed and 18 [72%] were consumer reports).
- Of the total 25 cases of exacerbation, 23 (92%) were from United Kingdom and the remaining 2 cases (8%) were from Thailand and Sweden.
- Of the total 25 case reports, the TTO identified from VAXZEVRIA administration to Exacerbation of Adrenal Insufficiency was available in 13 (52%) case reports and ranged from 0 to 30 days (mean: 4.7 days; median: 0 day) as presented in Table 119.

Table 119 TTO for Exacerbation of Adrenal Insufficiency case reports cumulatively through 28 June 2022

TTO (Days)	No of Cases	Percentage (%)
0 to < 1 day	7	28
1-14 days	5	20
15-30 days	1	4
Undefined (missing)	12	48
Total	**25**	**100**

TTO, time to onset.

- The baseline status of the adrenal insufficiency at the time of vaccination was provided in only one of the 25 case reports. In this one case, it was mentioned that the patient had suffered with adrenal fatigue for several years. Status of therapy with steroids in this case was not reported. However, the patient had started to feel better prior to vaccination. Since vaccination the patient had relapsed and had felt nausea, head pressure and extreme fatigue.
- Twenty- two of the 25 patients with history of adrenal insufficiency had steroid therapy in their history or were concomitantly treated with steroids at the time of the vaccination.

Information on whether steroid therapy was interrupted or if dose was reduced at the time of vaccination was not provided in any of the 22 cases.

- In 22 of the 25 case reports the description of the exacerbation after vaccination was reported. Patients reported symptoms such as headache, dizziness, nausea, chills, feeling unwell, hypotension, fatigue, headache, fever, vomiting, abdominal pain etc. during the exacerbation. In 11 of the 25 cases, the patient's steroid doses were increased to treat the exacerbation. In the remaining 14 cases, the status of steroid therapy post exacerbation was not reported.
- The 25 case reports had 26 relevant conditions reported in medical history that suggested an exacerbation of pre-existing adrenal insufficiency. The distribution of the events of Adrenal insufficiency in medical history are presented in Table 120 below in descending order of frequency.

Table 120 Distribution of medical history of Adrenal disease PTs

Medical History PTs	Case count (%)
Adrenal insufficiency	11 (42.3)
Addison's disease	7 (26.9)
Adrenocortical insufficiency acute	5 (19.2)
Adrenal suppression	2 (7.7)
Adrenocorticotropic hormone deficiency	1 (3.8)
Total	**26**

PT, preferred term.

The 25 cases reported 26 events of interest, and the following observations were made from their review:

- All 26 (100%) events were serious (7 medically confirmed and 19 consumer reports) due to the event being considered as medically important event (19 [73.0%]) by the reporter, the event reportedly resulted in disability (5 [19.2%]), event reportedly required hospitalization (7 [26.9%]), the event considered as life threatening by the reporter (6 [23.1%]). None of the events resulted in death. An event may have met more than one criterion for seriousness.
- Of the 26 events, the outcome was reported as follows: 46.1% (12/26) of the events were favourable (resolved or resolving), 7.8% (2/26) of the events was not recovered/not resolved. The outcome of the remaining 46.1% (12/26) of events were reported as unknown or not reported.

WHO-UMC causality analysis for cases of Exacerbation of Adrenal Insufficiency

For total 25 case reports identified cumulatively through 28 June 2022 WHO-UMC causality was further assessed below with a 42-day risk window (Table 121).

Table 121 Overview of WHO-UMC Causality Assessment for case reports of Exacerbation Adrenal Insufficiency with VAXZEVRIA reported cumulatively through DLP 28 June 2022

WHO-UMC Causality category	WHO-UMC Causality assessment scale (AZ adapted)	Number of Cases
Possible	Possible with risk factors/confounders*	17
	Possible with Limited information	0
Unassessable/Unclassifiable	Unassessable/Unclassifiable with risk factors/confounders*	8
	Unassessable/Unclassifiable with limited information	0
	Total	25

Cases were considered to have "risk factors/confounders" where the event could also be explained by the vaccinee's diseases, or where relevant risk factors were present, or concomitant medications that could potentially contribute to the development of the event were reported.
AZ, AstraZeneca; WHO-UMC; World Health Organization Upsala Monitoring Committee.

Of the 25 case reports, none were classified as Certain or Probable/ likely related to VAXZEVRIA. 17 cases were assessed as possible and 8 cases were unassessable or unclassifiable. 22 of the 25 cases for exacerbation of Adrenal insufficiency were identified with relevant risk/confounding factors as presented in Table 122. These are presented into the following categories for risk/confounding factors in descending order of frequency.

Table 122 Relevant Risk factors/Confounders identified case reports of Exacerbation of Adrenal Insufficiency cumulatively through 28 June 2022

Relevant Risk/Confounders	Number of reports[a]	Percent of Total Number of Reports (%)[b]
History of endocrine disorders (hypothyroidism, growth hormone deficiency, panhypopituitarism, type1 and 2 diabetes mellitus, diabetes insipidus, cCushings syndrome etc)	12	48
History of infections (Tuberculosis, Colitis, aseptic meningitis, COVID-19 etc.)	6	24
Genetic disorders (degenerative mitochondrial disorder, kearns-sayre syndrome, hypokalemic periodic paralysis and Klinefelter syndrome)	3	12
Other Vaccines such as influenza vaccine	2	8

[a] Each case may have had more than one risk factor. Each report may have had more than one risk factor from a case.
[b] Percentages were calculated based on a total of 25 cases.

In the remaining 3 out of 25 case reports, there was insufficient information with respect to either medical history or, concomitant medication or other details for a comprehensive causal assessment.

Literature

A cumulative literature search through 28 June 2022 of the Embase, InsightMeme, and PubMed databases was conducted using the following search terms: Addison disease, adrenal insufficiency, adrenal insufficiency neonatal, adrenal suppression, adrenocortical insufficiency acute, adrenocortical insufficiency neonatal, immune-mediated adrenal insufficiency, primary adrenal insufficiency, primary adrenal insufficiency, secondary adrenocortical insufficiency and tertiary adrenal insufficiency for VAXZEVRIA.

On using the above search criteria, 5 articles were identified. Of these, 2 articles (Maguire et al 2021 and Varona et al 2021) were considered relevant for further evaluation and presentation as they described the use of vector-based vaccines. These were literature case reports with VAXZEVRIA (Case IDs [redacted] and [redacted]. On review of the case report articles, no new safety concerns including information relating to a conclusive mechanism was identified.

Mechanism of action articles review and summary cumulatively through 28 June 2022:

Zhao and Wu 2022 summarized the influence of COVID-19 vaccines on the endocrine system and explored the pathogenic mechanisms. The authors hypothesised that autoimmune/inflammatory syndrome induced by vaccine adjuvants (ASIA) could be one of the possible mechanisms. Adjuvants have been widely used in human vaccines to enhance the immune response to vaccination. The authors speculated that in genetically susceptible individuals, ASIA may develop by disrupting the immunological balance of the host, by molecular mimicry, triggering polyclonal activation of B lymphocytes or other similar etiopathogenetic mechanisms. The authors claim that, previously, type 1 diabetes mellitus, primary ovarian failure, adrenal insufficiency, and thyroiditis (mostly subacute thyroiditis) have been reported to be related to ASIA syndrome after human papillomavirus, hepatitis B virus (HBV), and influenza vaccination. The authors also suggested that, for the COVID-19 vaccines, aluminium salts, emulsions, oils, toll-like receptors, AS01B, four lipids of the mRNA vaccine and polyethylene glycol might induce an immune response in susceptible individuals.

AZ Comment:

ASIA remains a speculative hypothesis and the paper by Zhao and Wu 2022 provides no specific new evidence. VAXZEVRIA does not have adjuvants, hence the link to ASIA is

unlikely. Literature review cumulatively though 28 June 2022 did not identify any new clinical data or other evidence to support a causal association between VAXZEVRIA and Exacerbation of Adrenal Insufficiency.

Summary

Overall medical summary of all case reports

Cumulatively through 28 June 2022, a total of 86 case reports of Adrenal insufficiency were reported. Of the 86 case reports, 25 (29.1%) case reports had 26 pre-existing medical history PTs of adrenal disease indicating Exacerbation of Adrenal Insufficiency. All 25 cases were from spontaneous sources and were serious. 7 were medically confirmed. 23 of the 25 case reports were from United Kingdom. The age range in these cases was between 18 to 78 years with a mean of 56 years. 70.8% of these cases were reported in females. TTO ranged between 0 to 30 days and the mean was 4.7 days. Overall, 57.7 % of the 25 cases had a PT of Adrenal insufficiency acute reported. 46.1% had a favorable outcome (resolved/resolving). Of the 25 cases 17 were assessed as possibly related to VAXZEVRIA using the WHO-UMC causality assessment. However, all cases were found to have risk factors/confounders which could also explain the exacerbation

Cumulatively through 28 June 2022, a total of 86 case reports of Adrenal insufficiency were reported. Of the 86 case reports, 25 (29.1%) case reports had 26 pre-existing medical history PTs of adrenal disease indicating Exacerbation of Adrenal Insufficiency. All 25 cases were from spontaneous sources and were serious. 7 were medically confirmed. 23 of the 25 case reports were from United Kingdom. The age range in these cases was between 18 to 78 years with a mean of 56 years. 70.8% of these cases were reported in females. TTO ranged between 0 to 30 days and the mean was 4.7 days. Overall, 57.7 % of the 25 cases had a PT of Adrenal insufficiency acute reported. 46.1% had a favorable outcome (resolved/resolving). Of the 25 cases 17 were assessed as possibly related to VAXZEVRIA using the WHO-UMC causality assessment. However, all cases were found to have risk factors/confounders which could also explain the exacerbation

Overall, none of the case reports raised any new safety concerns for Exacerbation of Adrenal Insufficiency cumulatively through 28 June 2022, and the company is not aware of any confirmed biological mechanism through which VAXZEVRIA vaccine could cause an exacerbation of adrenal insufficiency.

Literature summary:

Two literature case reports of Adrenal insufficiency were identified, of which, both are linked with case reports in the AstraZeneca Global Safety Database.

Literature review cumulatively though 28 June 2022 did not establish a definitive causal association between VAXZEVRIA and Exacerbation of Adrenal Insufficiency.

Conclusion

Based on the currently available data, AstraZeneca considers that there is insufficient evidence of a causal association between Exacerbation of Adrenal insufficiency and VAXZEVRIA. It is AstraZeneca's opinion that no changes to the CDS or RMP are warranted at this time..

AstraZeneca will continue to monitor safety information regarding Exacerbation of Adrenal Insufficiency as part of the routine safety surveillance activities for VAXZEVRIA. AstraZeneca will not discuss the topic future PBRERs, unless significant new safety information arises.

15.2.10.3 Exacerbations of Hypertension

Global Patient Safety Database

A cumulative search till DLP (28 June 2022) of the AstraZeneca Global Safety Database for the Preferred term (MedDRA version 25.0): 'Hypertension' in association with VAXZEVRIA. A total of 4859 cases were retrieved with this search cumulatively. The Lower Level terms (LLTs) of 'Hypertension aggravated'; 'Hypertension exacerbated'; 'Hypertension not adequately controlled'; 'Hypertension worsened'; and 'Uncontrolled hypertension' were used to explore the reports of patients with a presumed pre-existing hypertension with exacerbation after receiving VAXZEVRIA. The search with aforementioned LLTs retrieved a total of 129 case reports of exacerbation of hypertension reporting 129 events.

All 129 case reports for exacerbation of hypertension were received from spontaneous sources, 112 (87%) were from Regulatory authorities. Seventy (70) case reports were serious and 59 were non-serious.

The following Table 123 presents number and percentage (%) of case reports with exacerbation of hypertension reported after respective doses cumulatively through DLP (28 June 2022):

Table 123 Number and percentage (%) of the case reports of exacerbation of hypertension reported after respective doses of VAXZEVRIA cumulatively through DLP (28 June 2022)

No of Cases (After First Dose)	No of Cases (After Second Dose)	No of Cases (After both First and Second Dose)	No of Cases (After Third Dose)
115(89%)	8(6%)	1 (0.7%)	1(0.7%)

These case reports of exacerbation of hypertension were reported most frequently in the following countries France (28%), United Kingdom (17%), Sweden (10%), Austria (5%) and Brazil (4.7%), Mexico and Italy (4.5%) each cumulatively till DLP (28 June 2022).

The following observations were made from a review of the 129 case reports pertaining to exacerbation of hypertension cumulatively through DLP (28 June 2022):

- Vaccinee age was reported in 119 case reports and ranged 33 to 94 years (mean: 63 years; median: 63.5 years). Of the 129 case reports, 102 (79%) cases concerned patients >50 years old.
- Vaccinee gender was reported in 127 case reports. Of these case reports, 27% (34) concerned male patients and 73% (93) concerned female patients.
- Fifty-four (42%) case reports were medically confirmed and 75 (58%) were non-medically confirmed.
- Of the total case reports (129), the time to onset (TTO) identified from VAXZEVRIA administration to the exacerbation of hypertension was reported in 105 case reports and ranged from 0 days to 254 days (mean: 127 day; median: 12 day).

This is further presented in the following Table 124:

Table 124 TTO for exacerbation of hypertension case reports cumulatively through DLP (28 June 2022)

TTO (Days)	No of Cases	Percentage (%)[a]
0 to 1	47	36%
2 to 5	30	23%
6 to 10	8	6%
11 to 15	7	5%
16 to 20	2	2%
21 to 28	1	0.7%
>28 days	10	8%
Unknown	24	19%

[a] TTO was reported for 129 case reports used to calculate the percentage. Where multiple TTOs are present in a case, the most conservative TTO for the relevant event is chosen

- Of the 129 cases reported cumulatively through DLP (28 June 2022), the following observations were made. Sixty-six (51%) of the events were serious (23 medically confirmed and 43 non-medically confirmed) due to the event being considered as medically important event (39 [59%]) by the reporter, event reportedly resulted in disability (6 [9%]), event reportedly required hospitalization (23[35%]), event reported to have congenital anomaly (0 [0%]), event considered as life threatening by the reporter (3 [5%]) and/or the event reportedly resulted in death (1 [2%]). An event may have met more than one criterion for seriousness. The remaining 63 (49%) events were non-serious (31 medically confirmed and 32 non-medically confirmed).
- Of the 129 cumulative events, the outcome was reported in 49% (63/129) of the events as favorable (resolved or resolving), 1% (2/129) of the events was recovered/resolved with sequelae, 25% (32/129) of the events was not recovered/ not resolved and 0.7% (1/129) of the events as fatal. The outcome of the remaining 24 % (31/129) of events were reported as unknown or not reported.

Events with fatal outcome

Of the 129 events of the exacerbation of hypertension, 1 event in a case (0.7%) was reported with fatal outcome cumulatively through DLP [28 June 2022]. This non-medically confirmed case [redacted]) pertaining to a 74-year-old female patient from United Kingdom with past and current medical history of hypertension, whooping cough, steroid therapy (for recurring chest infections suffered after each vaccine), atherosclerosis, COPD. After unknown period of both first and second dose patient experienced lower respiratory tract infection, COPD and hypertension. The patient experienced exacerbation of hypertension after the first dose, and a recurrence of exacerbation of hypertension with the second dose of vaccination indicating potential recurrence / rechallenge. Approximately 4 months after the second dose of VAXZEVRIA patient was found dead. The post-mortem concluded she died from COPD and high blood pressure. Blood pressure values were not provided.

AZ Comment: The case lacks adequate information such as time to onset, clinical course, baseline general condition and disease control status, compliance to antihypertensive therapy around the time of vaccination, serial blood pressure measurements, etc. The event and outcome can be attributed to the patient's comorbidities including advanced age, obesity, atherosclerosis, and COPD; concomitant medications including unknown steroid and antibiotic treatments for recurring chest infections, albuterol and formoterol; concurrent lower respiratory tract infection and polypharmacy. WHO-UMC Causality Assessment for this case is Unassessable/ Unclassifiable with risk factors/confounders due to lack of abovementioned details.

Rechallenge / Recurrence case reports

Cumulatively through DLP [28 June 2022], in 1 (0.7%) out of 129 case report, the patient experienced exacerbation of hypertension after the first dose, and a recurrence of exacerbation of hypertension with the second dose of vaccination indicating potential recurrence / rechallenge. This case report was consumer report received from regulatory authority. Fatal outcome was present in this case [redacted], which is described in fatal cases above. WHO-UMC Causality Assessment for this case is Unassessable/ Unclassifiable with risk factors/confounders.

WHO-UMC causality analysis:

Of the total 129 case reports identified cumulatively through 28 June 2022, 53 (41%) case reports were medically confirmed (22 Serious and 31 Non-Serious) and 76 (59%) case reports were consumer reports (46 serious and 30 non-serious). WHO-UMC causality was further assessed below (Table 125).

Table 125 Overview of WHO-UMC Causality Assessment for medically confirmed case reports of Exacerbation of Hypertension with VAXZEVRIA reported cumulatively through DLP 28 June 2022

WHO-UMC Causality category	WHO-UMC Causality assessment scale (AZ adapted)	Number of Cases
Possible	Possible with risk factors/confounders*	95
	Possible with Limited information	13
Unassessable/Unclassifiable	Unassessable/Unclassifiable with risk factors/confounders*	15
	Unassessable/Unclassifiable with limited information	6
Total		**129**

Cases were considered to have "risk factors/confounders" where the event could also be explained by the vaccinee's diseases, or where relevant risk factors were present, or concomitant medications that could potentially contribute to the development of the event were reported.

AZ, AstraZeneca; DLP, data lock point; WHO-UMC; World Health Organization Upsala Monitoring Committee.

Amongst the 129 cases for Exacerbation of Hypertension, 110 (85%) were identified with relevant risk/confounding factors as presented in Table 126. These are presented into the following categories for risk/confounding factors are presented by categories in descending order of frequency. None of these cases were classified as Certain or Probable or likely related to VAXZEVRIA.

Table 126 Relevant Risk factors/Confounders identified for case reports cumulatively through 28 June 2022

Relevant Risk/Confounders	Number of reports[a]	Percent of Total Number of Reports (%)[b]
Advanced age	54	42
Obesity/Overweight	49	38
Concomitant medications that could potentially contribute/polypharmacy	19	15
History of Cardiovascular disease	16	12
History of Diabetes Mellitus	11	9

[a] Each report may have had more than one risk factor from a case.

[b] Percentages were calculated based on a total of 129 cases.

[c] Confirmed past medical history of pre-existing hypertension.

In the remaining 19/129 (15%) case reports, there was insufficient information with respect to either dose latency, medical history or, concomitant medication or other details for a comprehensive causal assessment.

Literature

A cumulative literature search through DLP [28 June 2022] of the databases in Embase, InsightMeme and PubMed was conducted using the following search criteria: Hypertension aggravated; Hypertension exacerbated; Hypertension not adequately controlled; Hypertension worsened; Uncontrolled hypertension for VAXZEVRIA

On using the above search criteria, 12 articles were identified. None of these 12 articles were considered relevant for further evaluation and presentation, as they discussed either non-hypertension related adverse events or mRNA based vaccine events.

Summary

Overall medical summary of all case reports

Cumulatively through DLP (28 June 2022), a total of 129 reports of exacerbation of hypertension with the use of VAXZEVRIA have been received, of which 54% were serious and 46% were non-serious. The age range was 33 to 94 years and mean and median age was reported as 63 years and 63.5 years, respectively. Forty two (42%) of cases were medically confirmed and 58% were consumer reports.

Cumulatively through DLP (28 June 2022) of the 129 cases, the TTO was reported in 105 (81%) cases. The mean and median TTO was 12 days and 127 days respectively.

Amongst 129 events received cumulatively through DLP (28 June 2022), 65 (50%) events had a reported outcome recovered or recovered with sequelae.

One event in 129 case reports (0.7%) was reported with fatal outcome cumulatively through DLP [28 June 2022], which was non-medically confirmed. There was insufficient information on the baseline control status and clinical course of hypertension, and the fatal outcome is likely due to the multiple co-morbidities.

Cumulatively through DLP (28 June 2022), of the 129 case reports reporting the exacerbation of hypertension with VAXZEVRIA use, there was 1 (0.7%) case report with potential recurrence/rechallenge.

These 129 case reports received cumulatively through DLP (28 June 2022) were analysed by AstraZeneca and found to have limited information (including information on baseline control of hypertension, prior/ongoing therapy and treatment information) and/or are confounded by alternative aetiologies including the possibility of a concurrent COVID-19 infection.

Upon further WHO-UMC case causality analysis conducted for the 129 case reports, the majority of case reports (108 [84%]) were considered possibly related to VAXZEVRIA. However, 95 of these 108 (88%) case reports also demonstrated possible risk factors/confounders and 13 of these 108 (12%) cases had limited information to confirm causality assessment.

Literature summary:

A cumulative literature search through DLP [28 June 2022] of the databases in Embase, InsightMeme and PubMed was conducted using the following search terms: Hypertension aggravated; Hypertension exacerbated; Hypertension not adequately controlled; Hypertension worsened; Uncontrolled hypertension for VAXZEVRIA

From the above search, 12 articles were identified. None of these 12 articles were considered relevant for further evaluation and presentation as they discussed either non-hypertension related adverse events or mRNA based vaccine events.

Literature review cumulatively though 28 June, 2022 did not identify any article elucidating a possible pathogenic mechanism leading to exacerbation of hypertension with VAXZEVRIA.

Conclusion

Based on the currently available data, AstraZeneca considers that there is currently insufficient evidence of a causal association between Exacerbation of hypertension and VAXZEVRIA.It is AstraZeneca's opinion that no changes to the CDS or RMP are warranted at this time.. AstraZeneca will continue to monitor safety information for Exacerbation of hypertension as part of the ongoing safety surveillance activities for VAXZEVRIA. AstraZeneca will not discuss the topic future PBRERs, unless significant new safety information arises.

15.2.11 Post-Authorisation Measure LEG 103: Review of pulmonary embolism (PE), coronary artery disease (CAD) including myocardial infarction (MI) and venous and arterial thromboses - Further data provision

Following submission of the EMA LEG procedure (Post-Authorisation Measure LEG 103) PRAC requested that the following data should be included in this PBRER:

1. A review of the literature for new publications on epidemiologic studies of interest related to these safety endpoints, including a presentation of a cumulative overview table of all epidemiological studies (similar to table 17 of the assessment report)
2. O/E analysis of the safety endpoints using data where age and age/gender stratified analysis are possible with reliable estimates of vaccine exposure (ie, UK and EEA data). Background rates used should be clearly and explicitly documented, including information that may be useful for interpretation: countries, databases, time period, population. The MAH should discuss the comparability between the populations and systems that give rise to the observed and expected cases and discuss potential biases giving limitations in the comparability. If the source comes from a systematic

review/meta-analysis, then reporting ranges and 95% CIs of the estimates can also be useful to assess the heterogeneity and precision of the estimates.

Literature Review

After careful review five articles discussing the association between VAXZEVRIA and thromboembolism were summarised and added to the previous summary of seven for the EMA LEG procedure. The five new articles are presented first in Table 127.

Table 127 Design overview of large population-based studies and AstraZeneca's comments

Reference, Country	Data source	Time period	Design	Comparator	AstraZeneca comments
Berild et al, 2022, Denmark, Norway and Finland	The Norwegian Immunization Register SYSVAK, the Finnish National Vaccination Register, and the Danish Vaccination Register (exposure) and the national patient registers (outcome)	January 1, 2020, to May 16, 2021.	Self-controlled case series	The risk period was 28 days postvaccination. The control period was January 1, 2020 to 14 days prior to vaccination, or COVID infection.	• Nationwide registers including the whole populations used. However, less severe cases from primary care not included. • Patient acted as their own control; therefore, time invariant confounding was controlled for. • Selection effect by including only those with outcome • Control period included 2020 to allow adjustment for seasonal variability, this may have introduced a bias, since access to health care may have been affected by the pandemic. • A pre-risk period of 14-days was used to ensure events did not influence subsequent exposures.
Rahman et al, 2022, Malaysia.	Malaysia Vaccine Administration System (MyVAS) database and the Malaysian Data Warehouse (MyHDW), a national health data repository that collects data from public and private hospitals in Malaysia	1 February 2021 to 30 September 2021	Self-controlled case series	The risk period was 21 days postvaccination. The control period was between 1 February 2021 and 30 September 2021, except a 14-day pre vaccination risk window and the vaccination day (day 0).	• Nationwide registers including the whole populations used. About 8% were vaccinated with VAXZEVRIA. • Less severe cases from primary care not included. • Patient acted as their own control; therefore, time invariant confounding was controlled for. • A pre-risk period of 14-days was used to ensure events did not influence subsequent exposures. • Selection effect by including only those with outcome. • Due to the vaccination roll out the sample have a large proportion of frontline health workers, elderly, and risk groups.

Table 127 Design overview of large population-based studies and AstraZeneca's comments

Reference, Country	Data source	Time period	Design	Comparator	AstraZeneca comments
					• Opt-in stream for the ChAdOx1-S vaccine was introduced in May 2021-due to high demand it was reintroduced to regular roll out.
Chen et al, 2022, multicountry	Pubmed, Embase, Cochrane COVID-19 Study Register, Cochrane Library, Chinese National Knowledge Infrastructure, Wanfang Data Knowledge Service Platform (Wanfang) and SinoMed.	Published 1 January 2020 to 20 October 2021.	Systematic review and meta-analysis	Unvaccinated population or population that received placebo	• Much heterogeneity among the studies, the I^2 (a test of heterogeneity) of most AEs was above 90%. • Grouped viral vector vaccines: JCOVDEN, ChAdOx1 and Sputnik V. • Study population in some studies are comprised of patient groups such as transplant recipients or cancer patients, while some includes health care workers, health care workers with previous severe allergic diseases, and the general population. • The adverse event rates of venous and arterial thrombosis would differ between these populations and to meta-analyse them makes interpretation difficult.
Corrao et al, 2022, Lombardy, Italy	The Regional Health Service (RHS) management, the registry of patients with a confirmed diagnosis of SARS-CoV-2 infection and the COVID-19 vaccination registry	27 December 2020 to 3 May 2021	Cohort study	Unvaccinated or pre-vaccination person time, matched on sex and age 1:10	• The outcomes were measured in a hospital setting, so they did not include milder cases treated in primary care. • A large number of health conditions were considered as confounders and adjusted for. • Residual confounding still probable. • Population-based but only include one region.
Hviid et al, 2022, Denmark	The Danish vaccination register and the Danish National Patient Register	27 December 2020 to 13 April 2021	Cohort study	Unvaccinated risk time from all individuals starting on 27 December 2020. Those who were still unvaccinated after 28 days	• Only included frontline personnel: health care and social services workers. • Adjusted for several confounding including comorbid conditions associated with risk for severe COVID-19 using inverse probability weights.

Table 127 Design overview of large population-based studies and AstraZeneca's comments

Reference, Country	Data source	Time period	Design	Comparator	AstraZeneca comments
				then contributed with another 28-day observation period, and so forth until any vaccination, event, or censoring, whichever came first.	• Outcomes measured in a hospital setting- milder cases not included. • The median age at study start was 44 years, and 82% of participants were female-results are not generalisable to other groups.
Whitely et al 2022, England	Primary care (GPES), covid and vaccination (NIMS, GDPPR), secondary care (HES, SUS) pharmacy (NHS BSA), and death registrations.	8 December 2020 to 18 March 2021	Cohort study	Unvaccinated or pre-vaccination person time	• Adjusted for several confounding factors. • End date before diagnostic effort was expected to be concentrated in people receiving VAXZEVRIA. • Unmeasured confounding and misclassification of confounding factors is probable.
Hippisley-Cox et al 2021 England	COVID and vaccination (NIMS, GDPPR), secondary care (HES, SUS), and death registrations.	1 December 2020 to 24 April 2021.	Self-controlled case series (SCCS)	Exposed time periods (after vaccination or SARS-CoV-2 infection) compared with unexposed baseline periods in people with the outcome of interest (excluding the pre-risk interval)	• SCCS method widely used in vaccine research. Robustness of the findings for most outcomes. • Detailed data for risk periods after vaccine exposure. • Less severe cases from primary care not included. • Selection bias by including only those with outcome.
Botton et al 2022, France	SNDS (France), hospital discharge diagnoses linked to vaccination files, 18 to 74 years old	06 February 2021 to 20 July 2021 for VAXZEVRIA.	Self-controlled case series (SCCS)	Three weeks following the first dose, and if applicable the second and third doses. All other observation periods were considered reference periods.	• Large study population representing the population of France with high vaccine exposure. • SCCS design widely used in vaccine research • Crude case definitions used for thrombosis. • A case-only analysis risks selection bias by including only those individuals pre-disposed to experiencing thrombotic events.

Table 127 Design overview of large population-based studies and AstraZeneca's comments

Reference, Country	Data source	Time period	Design	Comparator	AstraZeneca comments
Andrews et al 2022, England	Vaccination (NIMS), secondary care (SUS), and death registrations.	30th November 2020 to 18th April 2021	Cohort study	Unvaccinated period with an offset for population at risk (person days).	• Less severe cases not included. • Vaccinated cohort was compared to an unvaccinated cohort, but only for few confounders were adjusted for, not including health relevant comorbidities. This may have led to an overestimation of RIs.
Burn et al 2021a, UK	CPRD (primary care medical records)	8 December 2020 to 6 March 2021. Follow up time was 28 days from their first vaccination.	Cohort study with historical controls	A general population background cohort, followed from a primary care visit or contact between 1 January 2017 and 31 December 2019 to 31 December 2019.	• Differences in study periods when using historical controls can lead to confounding. • Primary care data, possible underestimation of outcomes diagnosed in hospital. • Adjusted for age and sex only, thus risk of residual confounding.
Burn et al 2021b, Spain	SIDIAP, Catalonia, Spain	27 December 2020 to 19 May 2021	Cohort study with historical controls	Historical controls present in the database 1 January 2017 followed until 31 December 2019	• Differences in study periods when using historical controls can lead to confounding. • Historical general population cohort were younger and healthier, compared to vaccinated cohorts, reflecting vaccination guidelines adjusted for age and sex only, thus risk of residual confounding.
Laporte et al 2021, Spain	CMBD register (discharge diagnoses), Catalonia, Spain	01 January 2021 to 18 April 2021.	Cohort study with historical controls	General population in Catalonia on 1 January 2019 with follow up to 31 December 2019	• Differences in study periods when using historical controls can lead to confounding. • Adjusted for age and sex only, thus risk of residual confounding.

Table 128 Summary of large population-based studies on relative risk or risk difference of studied events

Reference, Country	Design (time window)	Relative risk (95% Confidence interval)					
		MI	CVST	PE	VTE	ATE	IS
Berild et al, 2022, Denmark, Norway and Finland	Self-controlled case series (28-days)	0.92 (0.82-1.03) (CAD including angina and atherosclerotic heart disease)			1.83 (1.56 to 2.15)	2.99 (1.74-5.13)	1.21 (1.05-1.40) (Cerebral thromboembolic events)
Rahman et al, 2022, Malaysia	Self-controlled case series (21-days)	1.02 (0.69, 1.51)			2.22 (1.17 to 4.21)		1.14 (0.80, 1.63)
Chen et al, 2022, multicountry.	Systematic review and meta-analysis (Differed between studies)				1.128 (1.023 to 1.1244) NOTE: viral vector vaccines	1.167 (1.103 to 1.234) NOTE: viral vector vaccines	
Corrao et al, 2022, Lombardy, Italy.	Cohort study (1-28 days)				Women: <50: 2.43 (1.05 to 5.63) 50–59: 1.53 (0.54 to 4.38) 60–69: 0.78 (0.28 to 2.18) 70–79: 0.39 (0.21 to 0.72) 80+(no cases) Men <50: 0.29 (0.04–2.12) 50–59: 1.12 (0.34–3.69) 60–69: 0.81 (0.39–1.68) 70–79: 0.40 (0.24–0.69) 80+: 1.18 (0.14–9.88)		

Table 128 Summary of large population-based studies on relative risk or risk difference of studied events

Reference, Country	Design (time window)	Relative risk (95% Confidence interval)					
		MI	CVST	PE	VTE	ATE	IS
Hviid et al, 2022, Denmark	Cohort study (0-28 days) **NOTE: risk difference per 100 000 vaccinations**		1.68 (-0.64 to 4.00)	0.93 (-2.35 to 4.21)	Splanchnic vein thrombosis: 0.84 (-0.80 to 2.48) DVT (risk difference): 8.35 (0.21 to 16.49)	<3 events: Not estimable	
Whiteley et al 2022, England	Cohort study (fully adjusted rates 1-28 days)	<70 years : 0.88 (0.83–0.94), 70+years: 0.76 (0.71–0.81)		<70 years: 0.95 (0.85–1.05), 70+years: 0.54 (0.48–0.61)	<70 years: 0.97 (0.90–1.05), 70+years: 0.58 (0.53–0.63)	<70 years: 0.90 (0.86–0.95), 70+years: 0.76 (0.73–0.79)	<70 years: 0.90 (0.84–0.96), 70+years: 0.77 (0.73–0.82)
Hippisley-Cox et al 2021, England	SCCS (8-14 days)		4.01, (2.08 to 7.71)		1.10 (1.02 to 1.18)	1.02 (0.98 to 1.06)	1.07 (1.00 to 1.14)
Botton et al 2022, France	SCCS (8-14 days only the treatment studied)	1.28 (1.12–1.47)		1.30 (1.04–1.62)			1.10 (0.93–1.31)
Andrews et al 2022, England	Cohort study (4-13 days fully adjusted rates)				15-39 years: 2.2 (1.7-3.0), 40-64 years: 1.3 (1.1-1.4), 65+ years: 0.9 (0.8-1.0)		
Burn et al 2021a, UK	Cohort study, adjusted age/ sex	0.84 (0.76 to 0.94)	2.32 (0.97 to 5.58)	1.23 (1.09 to 1.39)	1.07 (0.98 to 1.18)	0.81 (0.73 to 0.89)	0.75 (0.60 to 0.95)
Burn et al 2021b, Spain	Cohort study, adjusted age/ sex	0.98 (0.70–1.37)		1.01 (0.60–1.71)	1.15 (0.83–1.58)	0.98 (0.79 to 1.21)	0.96 (0.72–1.27)

Table 128 Summary of large population-based studies on relative risk or risk difference of studied events

Reference, Country	Design (time window)	Relative risk (95% Confidence interval)					
		MI	CVST	PE	VTE	ATE	IS
Laporte et al 2021, Spain	Cohort study, adjusted age/ sex		0.42 (0.09 to 2.01)		3.68 (2.27-6.01)		

ATE Arterial thromboembolism, CVST Cerebrovascular venous and sinus thrombosis, MI Myocardial Infarction, VTE Venous thromboembolism, PE pulmonary embolism

.

Arterial thrombosis (ATE), ischaemic stroke (IS) and myocardial infarction (MI):

Six studies assessed the association between VAXZEVRIA and MI. Three (Berild et al, 2022,; Burn et al 2021a; Rahman et al, 2022) found no association and two (Burn et al 2021b; Whiteley et al 2022) found there was a decreased risk and only one study found an increased risk of MI post vaccination (Botton et al 2022).

Seven studies assessed the association between VAXZEVRIA and IS (Table 123). Four found no statistically significant associations (Rahman et al, 2022, Hippisley-Cox et al 2021, Botton et al 2022, Burn et al 2021b) and two studies found a decreased risk Whiteley et al 2022, Burn et al 2021a) and one found an increased risk of IS post vaccination (Berild et al, 2022).

Six studies assessed the association between VAXZEVRIA and ATE (table 123). Two studies found no association (Hippisley-Cox et al 2021; Burn et al 2021b). Two studies found a decreased risk (Whiteley et al 2022, Burn et al 2021a) and two studies found an increased risk of ATE post vaccination (Berild et al, 2022, Chen et al, 2022), one of the studies was a meta-analysis assessing all viral vector vaccines (Chen et al, 2022).

Based on these varied results AstraZeneca cannot draw any conclusions on an association between VAXZEVRIA vaccination and arterial thrombosis, IS or MI.

Venous thromboembolism (VTE), pulmonary embolism (PE) and Cerebrovascular venous and sinus thrombosis (CVST):

Four studies assessed the association between VAXZEVRIA and CVST (Table 123), one of which reported a statistically significant association (Hippisley-Cox et al 2021). Five studies assessed the association between VAXZEVRIA and PE, two of which found no association, one reported a decreased risk in those 70 or over, and two found an increased risk after VAXZEVRIA vaccination. Eleven studies assessed the association between VAXZEVRIA and VTE, two reported no statistically significant association and one reported a decreased risk in those 70 or older, one reported a decreased risk for those 70-79 and an increased risk for woman younger than 50 and eight reported an increased risk after VAXZEVRIA vaccination.

The majority of the studies assessing the association between VAXZEVRIA and VTE did report an association between exposure to AZD1222 and an increased risk of VTE. The associations were found in both SCCS studies that compare post vaccination time to control time in those with the outcome, and cohort studies using non-vaccinated or historical controls. In the studies that presented results stratified by sex and age the increased risk was higher, or only present in younger age groups and in women (Andrews et al 2022; Corrao et al, 2022). Relative risks by sex and age group can be found in Appendix 2, for the studies where they were available. The highest relative risk was found in Laporte et al 2021, who found those

vaccinated with VAXZEVRIA had 3.68 times higher risk of VTE compared to historical controls. This study only adjusted for sex and age, and did not exclude participants with history of study outcomes, making confounding likely. Other studies reported between a 10% (corresponding to 66 excess case per 1 million vaccinations, Hippisley-Cox et al 2021) and a 2.43 times increased risk (corresponding to 23,207 citizens vaccinated per one harmful event among women <50, Corrao et al, 2022) and a risk difference of 8.35 cases (95% CI 0.21 to 16.49) of DVT per 100 000 vaccinations in frontline health care personnel consisting mainly of younger women (Hviid et al, 2022). Though residual confounding may still be present in the studies reviewed, a suggestion of a modest potential association between VAXZEVRIA and VTE, especially in younger women, requires further review of new evidence.

Observed Versus Expected Analysis

Background rates for O/E analysis

The background rates for VTE, ATE and CAD were obtained from the ACCESS study (see Appendix for details about the ACCESS rates)., a random-effect meta-analysis was performed using the ACCESS rates from the Danish (DCE-AU), Spanish (BIFAP, FISABIO, SIDIAP), Italian (ARS), Netherlands (PHARMO) and the United Kingdom (CPRD) Registries. The rates for CVA came from the literature and PE rates were from MarketScan 2019 (see appendix for more details).

Updated OE analyses are provided in appendix 9.

Sensitivity graphs are also provided in Appendix 9 so that results can be considered for when background incidence rates or reporting fractions are reduced.

Arterial thromboembolism (ATE)

The O/E analysis results for ATE without thrombocytopenia (TCP) showed observed cases to be significantly less than expected for all stratifications and all risk windows.

When considering the sensitivity graphs in Appendix 9 for global reports, when the background incidence rate was reduced to the lower limit of the 95% confidence interval, observed cases are still less than expected.

Venous thromboembolism (VTE)

The O/E analysis results for VTE without thrombocytopenia showed observed cases to be significantly less than expected for all stratifications and all risk windows.

When considering the sensitivity graphs in Appendix 9, for global reports, when the background incidence rate was reduced to the lower limit of the 95% confidence interval, observed cases are still less than expected.

Pulmonary embolism (PE)

The O/E analysis results for PE without thrombocytopenia showed observed cases to be significantly less than expected or less than expected for all stratifications and all risk windows.

When considering the sensitivity graphs in Appendix 9, for global reports, when the background incidence rate was reduced to the lower limit of the 95% confidence interval, observed cases are still less than expected.

Coronary Artery Disease including Myocardial Infarction

The O/E analysis results for Coronary Artery Disease including Myocardial Infarction showed observed cases to be either less or significantly less than expected for all stratifications and for all risk windows except for Females aged 18-29 years in the UK for risk windows 21 and 28 days, when cases with unknown time to onset were included, where observed cases were more than expected. This result was not significant however, and the case numbers for these stratifications were small.

When considering the sensitivity graphs in Appendix 9, for global reports, when the background incidence rate was reduced to the lower limit of the 95% confidence interval, observed cases are still less than expected.

Cerebrovascular Accident (CVA)

The O/E analysis results for CVA without thrombocytopenia showed observed cases to be either less or significantly less than expected for all stratifications, except for females 18 to 39 years of age in the UK (risk window 21), and, 28, and 42 days (when unknown TTO was included), females in UK 40-49 years (risk window 21 days when unknown TTO included), and male 18-39 years (risk window 21 days when unknown TTO was included) where observed cases were more than expected. This result was only significant for females 18-39 (risk window 21 days), females 30-39 (risk window 28 days) and females 40-49 (risk window 21 days), and then only when cases with unknown TTO were included. It should be noted that results including unknown TTO potentially may overestimate the number of relevant cases.

In the previous EMA LEG response the O/E analysis results for CVA without thrombocytopenia showed observed cases to be either less or significantly less than expected for all stratifications, except for females 30 to 39 years of age in the UK where observed cases were more than expected. However, the result was not statistically significant.

When considering the sensitivity graphs in Appendix 9, for global reports, when the background incidence rate was reduced to the lower limit of the 95% confidence interval, observed cases are still less than expected.

Limitations of the O/E analysis

The O/E analyses provided is based on the most recent and available data but there is a level of assumption made and any change in the data would impact the results. The following are some of the limitations/assumptions of the data used:

- Doses administered for determination of exposure: Currently only exposure data from certain countries are available, but these countries generate the majority of cases reported to AstraZeneca.
- The background incidence rate used for the calculation is the same as the population vaccinated: The identification of incidence rates can vary depending on the source of the data.
- The number of observed events is spontaneously reported: Spontaneously reported events may only represent a fraction of the events that have actually occurred. Both under-reporting for certain events, and conversely, over-reporting for certain events may be a factor.
- The risk period reflects the period of time an event would occur post- vaccination: Over-estimating the risk window would increase the Person-Years at Risk period and include events that are outside the actual period of time a true event would occur. Under-estimating the risk window will result in reduced sensitivity making it difficult to reach statistical significance.

The OE analyses does not account for confounding/risk factors which might be present in the cases, such as seasonal effects on the occurrence of certain events, or for example the effect of COVID which may also contribute.

Under-reporting in the context of O/E analysis

Regarding the results of O/E analysis, the PRAC assessor commented that it might be useful to explore the level of under-reporting, which might have impacted the results:

AZ comment:

O/E analysis is a signal detection tool which is inherently associated with a range of uncertainty and requires certain assumptions and sensitivity analyses to be applied. The most significant area of uncertainty for any O/E analysis based on passive surveillance is the level of under-reporting of suspected ADRs. The level of under-reporting, as a general rule, is likely to be highly variable across products, over time, across regions and is also subject to influences such as publicity and awareness of a given safety topic. Although several studies have been performed to evaluate and quantify the level of spontaneous under-reporting to

different pharmacovigilance systems, such as the study by Bäckström et al (2004) quoted in the PRAC AR which found 86% under-reporting of possible drug-induced thromboembolic events, it is very unlikely that any single estimate of under-reporting fraction can be applied to any given situation or safety topic, as this is likely to be variable across time and across countries/systems. To take one example that is relevant to the current pandemic situation, in the 2009/10 swine flu pandemic 14 cases of Guillain Barre Syndrome were reported to the UK MHRA as suspected ADRs within 6 weeks of Pandemrix vaccine, which signaled an O/E excess at every under-reporting fraction, except 0% (ie, assuming 100% reporting) (see Swine_flu_vaccines_and_antiviral_medicines_UK_post-pandemic_safety_review.pdf (publishing.service.gov.uk). A subsequent epidemiological study, which ascertained all diagnosed cases of Guillain-Barré syndrome (GBS) within 6 weeks of the vaccine in England during the same immunisation campaign, identified only 9 GBS cases and no evidence of an increased risk following vaccination (Guillain-Barré syndrome and H1N1 (2009) pandemic influenza vaccination using an AS03 adjuvanted vaccine in the United Kingdom: self-controlled case series - PubMed (nih.gov)). This therefore suggested that the reporting fraction was, in fact, closer to 100%. In that pandemic situation, there was increased awareness in the UK amongst health professionals and patients of GBS being a 'potential' risk (based on swine flu vaccines used in 1976) which likely contributed to very high reporting rates (and likely over-reporting of unconfirmed GBS).

It is therefore a possibility that a high level of awareness amongst health professionals and patients of the reports of thromboembolic events following VAXZEVRIA vaccination has led to higher levels of suspected ADR reporting, and it cannot be assumed that high under-reporting fractions are necessarily a plausible reflection of the current reality based on past surveys of under-reporting for other drugs. However, it is not possible to quantify or estimate this to any extent at present and under-reporting is likely to vary across countries and pharmacovigilance systems. Therefore, AstraZeneca considers the best approach for O/E analysis, where this is required, is to continue to consider a range of under-reporting fractions (as well as conservative background incidences and more refined estimates of stratified exposure) as has presented in our O/E analyses so far, as a way of taking account of the range of uncertainty and applying case by case judgement on potential signals.

This said, it should also be considered that O/E analysis is a signal detection tool, and such analysis is not designed or intended to confirm or quantify any causal associations. It could be argued that, as the potential signal of thromboembolic events has already been detected, the continuation or extension of O/E analysis has less value as more robust sources of evidence start to emerge and so more evidence-based analysis to further evaluate the signal should be considered. Therefore, AstraZeneca considers that ongoing appraisal of the relative strengths and weaknesses of the available and emerging pharmacoepidemiological studies on this topic should be the focus of continuing review.

Conclusion on O/E analysis

Both embolic and thrombotic events and CAD including MI occur in all ages and are more common as age advances. AstraZeneca did not find evidence of a new or emerging signal from review of the O/E analysis.

15.2.12 Acute Disseminated Encephalomyelitis

In June 2022, AstraZeneca received the following request from the Therapeutic Goods Administration (TGA) to include 'Acute disseminated encephalomyelitis' (ADEM) to Section 4.4 Special Warnings and Precautions for Use and Section 4.8 Adverse Effects (Undesirable Effects) of the Australian Product Information (PI). It was also mentioned that ADEM is a very serious, life-threatening condition and while a causal relationship with VAXZEVRIA has not been established to date, listing ADEM in the PI would increase awareness of this potential reaction, supporting rapid diagnosis and effective treatment.

The assessment of the risk of acute disseminated encephalomyelitis (ADEM) with VAXZEVRIA vaccination included the review of nine cases by the TGA's Medicines and Vaccines Investigation and Surveillance (MaVIS) Section of the Pharmacovigilance Branch (PB). Based on the review, TGA (MaVIS) concluded that there are sufficient safety grounds to update the PI for VAXZEVRIA regarding this risk, in particular, the fatal case of a 63-year-old man ([redacted] in AstraZeneca safety database), where it was considered that the vaccination was the likely cause of ADEM in this individual given the lack of evidence for alternative causes and the short period between vaccination and symptom onset.

AstraZeneca also received a similar request from Health Canada in June 2022 for assessment of ADEM with VAXZEVRIA. It was requested to include analyses of all cases, stratified by age, gender, doses administered, time to onset, and any other relevant information along with an observed-to-expected analysis including the appropriate risk window and a provision of appropriate case definition including a causality assessment.

ADEM is an acute monophasic demyelinating condition. ADEM is a part of the important potential risk - Immune-mediated neurological conditions -presented in the core RMP Version7 dated 22 February 2022. This AESI is being kept under close surveillance by AstraZeneca. As per the section 4.4 (Special warnings and special precautions for use) of the current CDS for VAXZEVRIA, very rare events of demyelinating disorders, including GBS, have been reported following vaccination with VAXZEVRIA. A causal relationship has not been established. As with other vaccines, the benefits and potential risks of vaccinating individuals with VAXZEVRIA should be considered. Therefore, the Company conducted a review of all data sources available to the Company to evaluate the risk of ADEM with VAXZEVRIA.

Background (Acute Disseminated Encephalomyelitis)

Acute disseminated encephalomyelitis (ADEM) is an acute multifocal demyelinating disease of the central nervous system (CNS) that typically follows an infectious illness. The prototypical disease was 1st reported in the year 1790, occurring in a 23-year-old-woman who presented with lower-extremity weakness and bladder retention 1 week after a measles rash (Croft, 1969). Later, it became apparent that several different viruses, mainly exanthematous, could produce febrile encephalopathy shortly after the infection.

Risk Factors

ADEM is an autoimmune disease resulting from para- or post-infectious complications (Croft, 1969). Between 55% to 86% of pediatric ADEM cases have preceding symptoms of systemic viral illness (Cole et al 2019; Pohl et al 2004; Menge et al 2007; Tenembaum et al 2002). A known association following vaccine preventable infections was about 1/1000 wild type measles or varicella and 1/5000 rubella (Sejvar et al 2007 as cited in Law B 2021 [B]). Only proven association with vaccine is with the now unavailable Semple rabies vaccine derived from sheep or mouse brains (Sejvar et al 2007; Hemachudha et al 1987 [A]; Law B 2021 [B]).

Infections preceding ADEM include: Streptococcus; *Borrelia burgdorferi*; Legionella; *Mycoplasma pneumoniae*; Tetanus; Salmonella; Measles; Mumps; Rubella; Smallpox; Coxsackie; Rabies; Coronavirus; Herpes (herpes simplex virus, human herpesvirus-6, varicella zoster virus (VZV), Epstein-Barré virus, cytomegalovirus (CMV); Influenza A and B; Hepatitis A and B; Human T-lymphotropicvirus-1; HIV; Japanese encephalitis virus; Dengue virus; Smallpox; Yellow fever; Rickettsia rickettsia; Chlamydia; Pertussis; Campylobacter; and Leptospira. Vaccinations preceding ADEM include those for: Measles, Mumps, Rubella (MMR); Oral Polio; Rabies (Semple type); Smallpox; Japanese B Encephalitis; Hepatitis B; Diphtheria-Tetanus-Polio (DPT); and Influenza (Garg 2003; Bennetto and Scolding 2004; Menge et al 2005; Tenembaum et al 2007).

Manzano et al 2021 in their systematic review analyzed cases of ADEM and acute hemorrhagic leukoencephalitis (AHLE) following infection with COVID-19. They found differences between the reported post–COVID-19 ADEM and AHLE cases; morbidity was high despite the use of standard ADEM treatments and mortality was common with relatively short follow up. Their findings lend plausibility to COVID-19 acting as a viral trigger for ADEM and AHLE, as has been postulated with other pathogens in the past, including coronaviruses (MERS and OC43).

Epidemiology

ADEM is an uncommon illness and hence epidemiologic studies are complicated by small case series from limited centres. ADEM can occur at any age, with higher frequency in

children than adults. Predominant age of occurrence in children is 5 to 8 years (Hynson et al 2001; Tenembaum et al 2002; Anlar et al 2003) and in adults is 19 to 61 years (Schwarz et al 2001). In children, there appears to be no gender predominance (Dale et al 2000; Leake et al 2004), although some studies have reported a slight male incidence (Murthy et al 2002; Tenembaum et al 2002). The diagnosis of ADEM is usually made in the setting of a viral illness or vaccination. Hence, the incidence of disease varies with the triggering infectious agent. A higher occurrence of ADEM has been described in the winter and spring months in small studies, but the illness can occur throughout the whole year (Murthy et al 2002; Leake et al 2004). The reported incidence of ADEM in all age groups is about 0.15 /100 000/year (Willame et al 2021). Worldwide distribution of ADEM is unknown, in part because regional cases of ADEM are often linked to specific vaccinations. Incidence of ADEM after measles is 1:1000, vaccination 1:63 to 1:300,000, varicella 1:10,000, and rubella 1:20 000 (Gibbons 1956; Spillane and Wells 1964). A recent United States (US) vaccine safety data link study found a possible association of ADEM following the tetanus, diphtheria, and pertussis vaccine (DTaP), but the excess risk was no more than 1.16 cases/million vaccine doses administered (Baxter et al 2016).

Clinical Features and Etiopathogenesis

The clinical course of ADEM is classically monophasic with acute or subacute presentation, with most patients (70% to 77%) reporting an antecedent infection or vaccination (Amit et al 1986 Hynson et al 2001; Tenembaum et al 2002). In children, clinical manifestations of ADEM can be pleotropic. Symptoms can range from non-specific, such as malaise and fatigue, to fulminant, progressing rapidly to obtundation and coma. In adults, clinical manifestations of ADEM are slightly different from the pediatric population. In contrast to children, fever (15%), meningism (15%), loss of consciousness (19%), and seizures (4%) are uncommon (Schwarz et al 2001). Other symptoms and their frequency of occurrence include motor (77%), sensory (65%), brainstem (62%), ataxia (38%), spinal (15%), and aphasia (8%). The median age of onset is 33 (range 19 to 61), with slight female predominance (65%) (Schwarz et al 2001).

Diagnosis

Magnetic resonance imaging (MRI) is the imaging of choice for evaluating patients for possible ADEM. Since ADEM evolves over several days, initial MRI may be normal if performed at the onset of prodromal symptoms (Bennetto and Scolding 2004; Menge et al 2007). During the progressive course of the disease, T2 MRI sequences show several lesions scattered throughout the brain involving both white- and gray-matter structures, such as cerebral cortices, thalamus, basal ganglia, brainstem, and cerebellum (Schwarz et al 2001; Menge et al 2007). Most lesions show contrast enhancement.

In addition to the brain, spinal cord can also be affected in ADEM, occurring in about 11% to 28% of cases (Dale et al 2000; Hynson et al 2001; Tenembaum et al 2002; Anlar et al 2003). Spinal cord lesions are typically large and appear edematous on MRI. Often there is a predilection for the thoracic cord, but lesions can occur at any level.

Serial MRI after the initial episode plays a vital role in establishing the diagnosis of ADEM. In monophasic ADEM, MRI obtained at least 6 months after the initial episode should show resolving lesions and, more importantly, no evidence of any new lesions. Further specificity for the diagnosis of ADEM can be obtained by continual MRI follow-up over 2 to 3 years. If there is accrual of additional T2 lesions over time, then patients need to be evaluated for possible multiple sclerosis.

The diagnosis of ADEM can only be confirmed by biopsy. The hallmark of ADEM is multifocal perivascular inflammation, with infiltration of lymphocytes and macrophages into the parenchyma. Adjacent to the areas of inflammation, myelin loss occurs with relative axonal sparing. There is proliferation of endothelial cells and fibrin deposits are seen within the vascular lumens. Plasma cells and granulocytes are only rarely seen in ADEM. Most lesions are seen in the white matter, but gray matter is also involved in many cases (Behan et al 1972, Behan et al 1973).

The pathogenesis of ADEM has most resemblance to the animal model experimental autoimmune encephalomyelitis (EAE), which is an acute monophasic inflammatory demyelinating disease induced by immunization of animals with myelin protein products (Rivers et al 1933). Analogous to EAE, in humans, ADEM cases have been observed after immunization with Semple rabies vaccine, a live attenuated vaccine that in the past was contaminated with rabbit or goat CNS tissue (Hemachudha et al 1987 [B]). Since EAE is a T-cell-mediated disease, as demonstrated by adoptive transfer of the disease through T-cells and not through serum factors to recipient animals, it is likely that ADEM is also a T-cell-mediated disease by its close resemblance to the EAE model (Paterson 1960). The distinguishing features between the 2 illnesses of encephalitis and ADEM is usually a rather abrupt and fulminant course with acute encephalitis as opposed to ADEM, which usually has a subacute onset and greater white-matter involvement (Hartung and Grossman 2001).

Differential Diagnosis for ADEM

ADEM usually presents with subacute encephalopathy, which has a broad differential. The antecedent history, temporal course of the illness, neuroimaging, cerebrospinal fluid (CSF) analysis, and probably repeat imaging during remission are most important in arriving at the diagnosis and excluding other causes of encephalopathy. In the differential diagnosis, conditions to consider and rule out relevant to treatment and prognosis are multiple sclerosis and neuromyelitis optica (NMO); vascular strokes; cerebral autosomal dominant arteriopathy with sub-cortical infarcts and leukoencephalopathy; amyloid angiopathy; posterior reversible

encephalopathy syndrome; eclampsia; infectious viral or bacterial encephalitis, HIV encephalopathy; progressive multifocal leukoencephalopathy; abscess; toxic inhaled heroin; carbon monoxide autoimmune multiple sclerosis; neurosarcoidosis; Behcet's disease; primary CNS angiitis; vasculitis due to connective tissue diseases such as lupus and Sjogren's Disease; metabolic mitochondrial diseases (mitochondrial encephalomyopathy or Leber's hereditary optic neuropathy); adrenoleukodystrophy, central and extrapontine myelinolysis; iatrogenic methotrexate, tacrolimus, cyclosporine; neoplastic neoplasms; metastasis; paraneoplastic syndromes, lactic acidosis, and stroke-like episodes (Hartfield et al 1999; Suwa et al 1999).

Treatment and Prognosis

Due to rarity of ADEM, acute presentation, and urgency of treatment, no clinical trials of therapeutic agents have been systematically studied. Treatment of choice is high-dose glucocorticoid administered systemically for 3 to 5 days, followed by an extended oral steroid taper over 6 to 8 weeks. Recrudescences are fewer when this regimen is employed compared to a short steroid taper, strongly suggesting a benefit from glucocorticoid treatment, as might be expected for a T-cell-mediated process. A good response to therapy has been observed in most studies (Wang et al 1996; Apak et al 1999; Schwarz et al 2001; Tenembaum et al 2002). There are cases of ADEM or even fulminant presentation such as acute hemorrhagic leukoencephalitis (AHL), where steroids alone are not sufficient for suppressing inflammation and improving clinical findings. Plasma exchange, intravenous immunoglobulin (IvIg), and immunosuppressive drugs have been used with some success (Seales and Greer 1991; Stricker et al 1992; Rodriguez et al 1993; Markus et al 1997; Pradhan et al 1999; Sahlas et al 2000). Plasma exchange or intravenous Ig is usually the 2nd step in recalcitrant cases. Of the immunosuppressive agents, cyclophosphamide has been more often used in ADEM after steroid failure. Its use is rather reserved, often as a 3rd-line agent after inadequate response from plasma exchange or intravenous Ig.

The prognosis of ADEM has significantly improved from former times. This is probably due to a drastic decrease in wild-type measles infections and the use of safer and more efficient vaccinations. Also, there is a widespread use of steroids once ADEM is diagnosed, which has been found to be beneficial in limiting clinical symptoms. Full recovery occurs in many patients and improvement with minor residual symptoms occurs in up to 70% to 90% of patients (Shahar et al 2002; Gupte et al 2003; Menge et al 2005). However, mortality from ADEM may still be as high as 5%. This may be the case particularly in patients with more ominous clinical presentation, such as those with infratentorial lesions and large spinal cord lesions. In the case of AHL, the mortality can be as high as 50% (Borlot et al 2011). A greater percentage of pediatric patients recover completely from ADEM compared to adults (60% to 80% versus 46%, respectively), implying greater recovery potential of the developing CNS in children (Schwarz et al 2001).

Biological Plausibility

Several theories have been postulated to explain how infections or vaccinations prime T-cell responses against myelin antigens in the CNS such as molecular mimicry (Fujinami and Oldstone 1985), bystander activation of naturally occurring autoreactive T-cells by "superantigens" (Burns et al 1992; Jorens et al 2000), or inhibition of suppressor T-lymphocytes (Sakaguchi et al 1995; Grant et al 2008), and activation of previously primed immune cells through reinfection (Merkler et al 2006). It is likely that more than one immune mechanism is involved in triggering ADEM in susceptible patients. However, more comprehensive studies need to be carried out worldwide in order to understand fully the epidemiology of ADEM, as it may be relevant to shedding light on triggering factors, pathogenesis of the disease, and possibly preventive measures (Javed and Khan 2014). The Institute of Medicine (IOM) reviewed evidence for a link between MMR, VZV, influenza, hepatitis A/B, human papillomavirus, DTaP, meningococcal vaccines, and ADEM and concluded evidence was inadequate to accept or reject a causal relationship (IOM 2011). They noted that immune mediated mechanisms included autoantibodies, T-cells, and molecular mimicry (IOM 2011). An updated review of evidence published since the 2011 IOM report for the same vaccines had a similar conclusion to IOM regarding no evidence to accept/reject causality (Dudley et al 2020).

Risk Window

The recommended risk window for ADEM as a vaccine product-related reaction (Rowhani-Rahbara et al 2012 as cited in Law B 2021 [B]) for inactivated or subunit vaccines is 2 to 42 days.

Clinical Studyand Pre-clinicalStudy DataLive attenuated vaccines: this should be based on the incubation period for the vaccine strain, adding as above, 5 to 28 days for primary analysis and 2 to 42 days for secondary analysis following the end of the incubation period.

A search was conducted in the AstraZeneca Clinical database for adverse event (AE) reports with a Preferred Term (PT) of 'Acute disseminated encephalomyelitis' (MedDRA version 23.1) following use of AZD1222 (data cut-off of 30 July 2021 for the US Study D8110C00001; data cut-off of 07 December 2020 for the Oxford pooled studies).

There were no AEs of 'Acute disseminated encephalomyelitis' reported in the AstraZeneca US Study (D8110C00001) and in the Oxford pooled studies (COV001, COV002, COV003, and COV005).

Pre-clinical Data

No ADEM-related safety findings were identified in the in vitro or in vivo non-clinical studies with AZD1222.

AstraZeneca Global patient Safety Database

A cumulative search up to 28 June 2022 of the AstraZeneca Global Patient Safety Database for the of PT 'Acute disseminated encephalomyelitis' with VAXZEVRIA was performed using MedDRA version 25.0.

The cumulative search retrieved a total of 83 events of ADEM in 83 cases in vaccinees who received VAXZEVRIA. Of the 83 cases, 3 cases ([redacted] and [redacted] were found to be duplicates and, therefore, not included for further review, resulting in a total of 80 serious cases. During the reporting period of the PBRER (29 December 2021 – 28 June 2022) a total of 37 events of ADEM in 37 cases of VAXZEVRIA were received.

The ADEM case source and seriousness for the 80 cases, received cumulatively are presented below in Table 129.

Table 129 Cases of ADEM Received with VAXZEVRIA by Reporting Source and Report Seriousness

Classification of Case Report source	Non-Serious Cases	Serious Cases	Grand Total
Clinical	0	0	0
Spontaneous	0	57	57
Literature	0	23	23
Non-Interventional/ Post-Marketing Study	0	0	0
Grand Total	0	80	80

ADEM=acute disseminated encephalomyelitis.

Table 130 presents the number and percentage of cases of ADEM reported after respective doses.

Table 130 Number and Percentage (%) of the Cases of ADEM Reported After Respective Doses

Dose 1[a]	Dose 2	Dose 1 and Dose 2	Dose 3/Booster Dose
74 (92.5%)	6 (7.5%)	0	0

[a] 19 cases with dose number unknown were conservatively considered as after Dose 1.
ADEM-acute disseminated encephalomyelitis.

The 80 cases of ADEM were reported in the following countries: 16 (20.0%) each were from India and the United Kingdom (UK); 12 (15.0%) were from Australia; 9 (11.3%) were from Germany; 5 (6.3%) were from Italy, 4 (5.0%) were from Spain; 3 (3.8%) were from Brazil; 2 (2.5%) each were from France and Greece; 1 (1.3%) each were from Argentina, Belgium, Croatia, Finland, Hungary, Ireland, Republic of Korea, Latvia, Poland, Sweden, and the US. One case ([redacted]) was received via a [redacted] from a physician in US concerning a fatal outcome of ADEM with dizziness in a 63-year old male vaccinee. No further information was available and VAXZEVRIA is not marketed in the US. However, this case may be a potential duplicate of case reported from TGA Australia.

The events most commonly co-reported with ADEM are presented in Table 131.

Table 131 Distribution of Most Frequently Co-Reported Events in Cases for ADEM

Preferred Term	Number of Cases	Percentage (%)
Headache	8	10.0%
Pyrexia	8	10.0%
Asthenia	7	8.8%
Ataxia	5	6.3%
Gait disturbance	5	6.3%
Paraesthesia	5	6.3%

[a] ADEM=acute disseminated encephalomyelitis.

The following observations were made after a review of the 80 cases of ADEM:

- Vaccinee age was reported in 76 cases and ranged from 22 to 90 years (median 53 years).
- Vaccinee gender was reported in 79 cases. Of these cases, approximately 36 (46%) cases concerned male patients and approximately 43 (54%) cases concerned female patients.
- Fifty-six (56; 70%) cases were medically confirmed and 24 (30%) were non-medically confirmed.
- The time to onset (TTO) identified from VAXZEVRIA administration to ADEM was reported in 50 (62.5%) cases and ranged from same day to 186 days (median 8 days).

This is further presented in the Table 132 accordingly with respect to the risk window days.

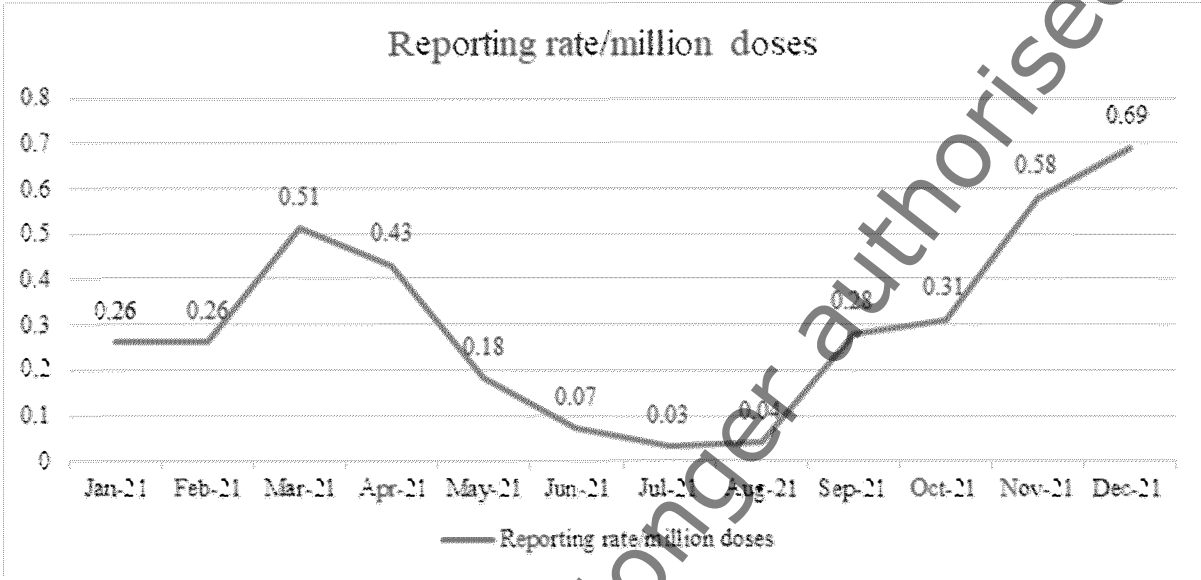
Table 132 TTO for ADEM Cases

TTO (Days)	Number of Cases	Percentage (%)[a]
0 to 2	14	28%
3 to 14	24	48%
15 to 30	5	10%
31 to 42	1	2%
> 42	6	12%

[a] TTO was reported for 50 case reports (total number of cases) used to calculate the percentage.
ADEM=acute disseminated encephalomyelitis; TTO=time to onset.

- All the 80 events pertaining to ADEM was serious with the event seriousness was considered as follows: medically important event 45 (56.3%), 15 (18.8%) events resulted in disability, 46 (57.5%) events required hospitalization, 13 (16.3%) events were considered life threatening, and 5 (6.3%) events resulted in death. Note that some events reported > 1 seriousness criteria.
- Eighteen out of 80 cases(22.5%) had information on anti-MOG antibody status. Of the 18 cases, 8 (44.4%) cases were anti-MOG positive, 9 (50%) cases were anti-MOG negative and in 1 case (5.6%) the anti MOG status was unknown. Thus, no specific trend with respect to MOG antibody positive status ADEM in individuals vaccinated with VAXZEVRIA was seen on review of safety database.
- Of the 80 events, outcomes were reported in 27 (33.8%) events as resolved or resolving, 2 (2.5%) events as recovered/resolved with sequelae, 25 (31.3%) events as not recovered/not resolved, 5 (6.3%) events as fatal, and the remaining 21 (26.3%) events as unknown or not reported.
- A trend analysis was performed for reporting rates of ADEM events per million doses of VAXZEVRIA administered in the UK, EU, Brazil, Canada, and Australia (as monthly dose administration data is available from these countries; Figure 2). Event rate over time was calculated based on the case onset date which was available in 57 out of 80 cases, and the remaining cases unknown onset date were excluded from reporting rate calculation. On review of reporting rate trends of ADEM post VAXZEVRIA vaccination, a peak which was seen in the months of March to April and November to December of 2021. However, the peak vaccine exposure was seen in the months of May and June of 2021. The peaks of reporting rate of ADEM could be considered to be more coinciding with COVID-19 pandemic peaks, especially in Europe, south-east Asia and Western Pacific (WHO COVID-19 Dashboard), rather than coinciding with trends in vaccine exposure, although this is not a direct comparison. Additionally, the observed increase in reporting rates in November and December, 2021 could be possibly explained by emergent strains in circulation and onset of winter season.

Figure 2 **Reporting Rate per Million Doses Administered for ADEM from UK, EU, Brazil, Canada, Australia**



ADEM, Acute disseminated encephalomyelitis; EU, European Union; UK, United Kingdom.

Nine (9) cases ([redacted] and [redacted]) were mentioned in the TGA request. Of these 9 cases, 6 fulfilled the BCC level 1 to 3 criteria and are presented in below. The remaining 3 cases were assessed as BCC level 4 and BCC level 5. Four of the 9 cases were assessed as "Possible" using the World Health Organization-Uppsala Monitoring Centre (WHO-UMC) causality assessment criteria (3/4 had limited information [such as medical history, comorbidities, or investigations]; and 1/4 case [[redacted]; BCC level 2] had confounders such as Bickerstaff encephalitis, GBS, presumed sepsis and treatments with succinyl choline and midazolam). Two of the nine cases were assessed as "Unlikely" as these occurred outside the risk window of ADEM. The remaining 3/9 cases were assessed as "Unassessable" or "Unclassifiable" as the TTO was unknown; in which 1/3cases [redacted] was classified as BCC level 4 using the BCC criteria for ADEM.

ADEM cases by BCC

The Brighton collaboration criteria (BCC) (Law B 2021 [B]) was used for the case level of certainty assessment based on the data available in the cases. The strongest level of certainty was 1, with levels of certainty 2 and 3 being less strong. Level of certainty 4 was reached for cases where the diagnosis was named but not supported with history, clinical findings, clinical course or diagnostic tests. Level of certainty 5 was the designation for cases where another diagnosis was noted. Based on this approach, of the 80 cases, 3 cases fulfilled level 1 criteria, 26 cases fulfilled level 2 criteria, 5 cases fulfilled level 3 criteria, 27 cases fulfilled level 4

criteria, and 19 cases fulfilled level 5 criteria. In addition to the BCC, the published Brighton Case Definition for ADEM (Law B 2021 [A]) was also referenced during the review of the cases for the assessment of evidence related to associated risk factors (eg, malignancy, infections, use of vaccines, or surgery).

Brighton Collaboration Criteria Level 1

Three (3) of the 80 cases fulfilled BCC level 1 according to classification by clinical course, examination features, and/or level of certainty, and are presented in Table 133.

Table 133 Cases of Acute Disseminated Encephalomyelitis Fulfilling BCC Level 1

Case ID/ Country/ Serious- (Y/N) Age (Years)/ Gender (M/F)	Co-Report-ed PTs	Relevant Comorbidities and Concomitant Medications	TTO (days)/ Dose #	MRI/ CSF Findings	Diagnostic Workup/Other Investigations	Treatment/ Outcome	WHO-UMC Causality Assessment	Additional Comment
[redacted] Y/ 45/ Unk	Malfor-mation venous	Unk	0.5/1st dose	MRI: Medullary revealed a T2 hyperintense lesion, without mass effect, extending from D10 to the cone, without contrast enhancement. CSF: 43 cells, hyperproteinorrachia (406 mg/L), normal glycorrachia, absence of oligoclonal bands MRI: Brain revealed hyperintense T2 / FLAIR lesions in subcortical area, gray/white matter and a venous malformation in the frontal area	CSF and Serum microbiology - negative. Autoimmune workup negative. anti-AQP4 antibodies negative, anti-MOGs were positive CRP (8.44 mg/L). COVID test negative	Steroid treatment / Recovering	Unlikely	Unlikely, due to rapid TTO (within 12 hours of vaccination) consistent with pre-existing predisposition prior to vaccination. Infectious work up performed; however, medical history, family history, potential genetic sources for CNS vascular malformation and past history not available. As the follow up was less than 3 months, a relapse/remission cannot be comprehensively ruled out, thus making the diagnosis less reliable. This case will be reassessed if further follow-up information for 3 months is received.
[redacted] Y/ 63/ M	NA	Medical history: Subarachn oid hemorrhag e. vertigo, IDDM; MI; AF; Cardiac pacemaker insertion	12/1st dose	MRI: Head Non-contrast MRI: Brain and cervical spine numerous bilateral foci (more than 20) of high T2 and FLAIR signal in the cerebral white matter, with both periventricular and juxtacortical involvement.	Serology for antivoltage gated K+ channel, anti-NMDA receptor, anti-LGI-1, anti-CASPR2, anti-NMO, anti-MOG and anti-neuronal antibodies were negative; open biopsy of a right	Corticoste-roids and plasmaphe-resis/Fatal	Possible with limited information	The case was assessed as BCC level 1 based on clinical features, MRI findings, ante mortem biopsy and autopsy. Ongoing evaluation of pre-existing vertiginous and non-vertiginous dizziness, (pre-existing foci in white matter) and presenting symptom of vertigo could also point to

Table 133 Cases of Acute Disseminated Encephalomyelitis Fulfilling BCC Level 1

Case ID/ Country/ Serious-(Y/N) Age (Years)/ Gender (M/F)	Co-Report-ed PTs	Relevant Comorbidities and Concomitant Medications	TTO (days)/ Dose #	MRI/ CSF Findings	Diagnostic Workup/Other Investigations	Treatment/ Outcome	WHO-UMC Causality Assessment	Additional Comment
		Concomitant medications: apixaban, bisoprolol, irbesartan, empagliflozin, metformin, Novomix-30 (insulin aspart-insulin aspart-protamine), rosuvastatin, and pantoprazole.		Radiological differential diagnoses included a demyelinating condition (such as ADEM) and CNS lymphoma. MRI: Head stable lesions, but also merging of previously separate lesions. A diagnosis of ADEM was favored over CNS lymphoma CSF: leukocyte count of $8x10^6$/L (mononuclear cells without polymorphs or eosinophils). The culture and cytology were unremarkable and flow cytology did not show any abnormal lymphoid populations. PCR was negative for Neisseria meningitides, Oligoclonal bands in CSF were present. CT: multifocal hypodensities in the brain, 50% proximal right vertebral artery stenosis.	frontal lesion: white matter edema with areas of pallor in a perivascular distribution. Small focal perivascular hemorrhages, with no destructive vasculitis or vascular necrosis. Luxol fast blue stain showed perivascular demyelination with axonal preservation (demonstrated by neurofilament stain). Autopsy: Based on the ante mortem medical records and the results of the post-mortem investigation, the cause of death was registered as 'Acute disseminated encephalomyelitis'			possible ongoing immune response to an unknown preexisting brain pathology. The patient's condition and fatality thereof could also be complicated by underlying significant cardiac (heart disease with ischemic cardiac events) and metabolic issues (ketoacidosis and mitochondrial dysfunction) as increased lactate levels were seen in CSF even post ketoacidosis correction with no increased leucocytic pleocytosis. There was limited information on post-mortem autopsy of other organs. Limited etiologic work-up was presented, including infectious and cell type assessment on the biopsy sample.

Table 133 Cases of Acute Disseminated Encephalomyelitis Fulfilling BCC Level 1

Case ID/ Country/ Serious-(Y/N) Age (Years)/ Gender (M/F)	Co-Report-ed PTs	Relevant Comorbidities and Concomitant Medications	TTO (days)/ Dose #	MRI/ CSF Findings	Diagnostic Workup/Other Investigations	Treatment/ Outcome	WHO-UMC Causality Assessment	Additional Comment
					in the setting of recent VAXZEVRIA vaccination. COVID test unk			
[redacted] Y/ 49/F	NA	Unk	21/ 2nd dose	MRI: Brain favored a diagnosis of tumefactive demyelination. FLAIR sequences showed hyper intense lesion in the left posterior temporal region with other similar hyper-intense lesions in the right temporal and basal ganglion nucleus. CSF: protein 29 mg%, glucose 85 mg% (corresponding blood sugar 118 mg%) without any cells. Cytology was negative for atypical cells. An infective panel for bacteria, viruses and fungi was negative. Anti-NMOSD panel including AQP4 and MOG antibodies was negative. Multiple sclerosis	B_{12} levels were on the lower limit of normal. Vasculitis work up negative Autoimmune workup negative VEP showed marginal increase in P100 latencies bilaterally. Hemogram was normal. CRP was negative. Procalcitonin was normal. Blood, urine, and CSF cultures did not show growth of any organisms. COVID test negative	Steroids/ Recovering	Possible with limited information	Follow up for ≥ 3 months showed some fluctuation during the 3 months (unusual for ADEM), but resolution after 3 months. CSF glucose perturbation without pleocytosis suggested a possible metabolic etiology. Past medical history and family history are unk; general work up for the present illness was negative without specific negatives for infectious exposures being noted.

Table 133 Cases of Acute Disseminated Encephalomyelitis Fulfilling BCC Level 1

Case ID/ Country/ Serious-(Y/N) Age (Years)/ Gender (M/F)	Co-Report-ed PTs	Relevant Comorbidities and Concomitant Medications	TTO (days)/ Dose #	MRI/ CSF Findings	Diagnostic Workup/Other Investigations	Treatment/ Outcome	WHO-UMC Causality Assessment	Additional Comment
				evaluation panel revealed no evidence of oligoclonal bands or intrathecal IgG synthesis.				

ADEM-acute disseminated encephalomyelitis; AF-Atrial fibrillation; AQP4-aquaporin-4; BCC-Brighton Collaboration Criteria; CASPR2-contactin-associated protein-like 2; CNS-central nervous system; CRP-C-reactive protein; CSF-cerebrospinal fluid; CT-computed tomography; F-female; FLAIR-Fluid attenuated inversion recovery; ID-identification; IDDM-Insulin dependent diabetes mellitus; Ig-immunoglobulin; M-male; MI-myocardial ischemia; MOG-myelin oligodendrocyte glycoprotein; MRI-magnetic resonance imaging; N-no; NA-not applicable; NMDA-N-methyl-D-aspartate; NMO-neuromyelitis optica; NMOSD-neuromyelitis optica spectrum disorder; PCR-polymerase chain reaction; PT-preferred term; TTO-time to onset; WHO-UMC-World Health Organization-Uppsala Monitoring Centre; Unk-unknown; VEP-Visual Evoked Potential; Y-yes.

Of the 3 cases, 1 case was reported in female vaccinee, 1 case was reported in a male vaccinee and in 1 case the gender was unknown. The ages of the vaccinees were 45, 49 and 63 years. The TTO for the 3 cases were the same day (dose 1), 12 days (dose 1), and 21 days (dose 2). The outcome in 1 case was fatal; however, the fatality was confounded by pre-existing ischemic heart disease, atrial fibrillation, recurrent vertiginous and non-vertiginous dizziness and diabetes. In the remaining 2 cases, the outcome was recovering. Of the 3 cases fulfilling BCC level 1, 2 cases were assessed as "Possible" with limited information and 1 case was assessed as "Unlikely" per the WHO UMC causality assessment criteria.

Brighton Collaboration Criteria Level 2

Twenty-six (26) of the 80 cases fulfilled BCC level 2. The cases fulfilled this classification by clinical course, examination features, and confirmatory tests and are presented in Table 134.

Table 134 Cases of Acute Disseminated Encephalomyelitis Fulfilling BCC Level 2

Case ID/ Country/ Serious- (Y/N) Age (Years) /Gender (M/F)	Co-Reported PTs	Relevant Comorbidities and Concomitant Medications	TTO (days)/ Dose #	MRI/ CSF Findings	Diagnostic Workup / Other Investigations	Treatment/ Outcome	WHO-UMC Causality Assessment	Additional Comment
[redacted] Y/25/F	NA	Unk	9/1st dose	MRI: Spinal longitudinal edema throughout the thoracic spinal cord exhibiting mild contrast enhancement as well as focal central hemorrhages MRI: Cranial bihemispheric white matter lesions with focal contrast enhancement CSF: granulocytic pleocytosis and a highly elevated CSF/serum quotient for albumin. Intrathecal IgM synthesis, flow cytometry analysis revealed a mildly increased B cell proportion among lymphocytic populations in pink-tinged CSF	CSF and Serum microbiology – negative. Moreover, glial-, neuronal-targeting-, and paraneoplastic-autoantibodies (CBA for AQP4-, and MOG-, immunofluorescence) – negative, Autoimmune workup negative. COVID test negative	Steroid + Plasma exchange / Recovering	Possible with limited information	Infectious work up performed; however, limited information due to medical history, family and past history not available. Evidence of blood brain barrier breakdown, CSF increased B lymphocyte population and granulocytic pleocytosis. Elevated granulocytes, B cells and intrathecal IgM synthesis consistent with intrathecal inflammatory/ infectious process; could be early marker of multiple sclerosis or CNS infection versus ADEM. Lacking diagnostic workup for intrathecal IgM synthesis.
[redacted] /Y /Unk/F	Ataxia Nausea Dizziness	Anxiety Depression Psoriasis (chronic immune mediated	Unk/ 1st dose	MRI: reported as ADEM	Not reported Covid test negative	Not reported/ Not Recovered	Unassessable/Unclassifia-ble	Limited information; unk TTO; unk age. Follow up limited, less than 3 months. Association of CNS inflammation/ multiple sclerosis with psoriasis

Table 134 Cases of Acute Disseminated Encephalomyelitis Fulfilling BCC Level 2

Case ID/ Country/ Serious- (Y/N) Age (Years) /Gender (M/F)	Co-Reported PTs	Relevant Comorbidities and Concomitant Medications	TTO (days)/ Dose #	MRI/ CSF Findings	Diagnostic Workup / Other Investigations	Treatment/ Outcome	WHO-UMC Causality Assessment	Additional Comment
		cutaneous disease associated with CNS inflammation, multiple sclerosis)						
[redacted] /Y /37/F	Headache Myelopathy Pyrexia Ataxia Lymphocytosis Sensory disturbance	Unk relevant risks and/or concomitant medications	8/1st dose	MRI: brain and spine revealed high signal in the grey and white matter of the brain and spinal cord. CSF: lymphocytosis with slightly raised protein	Not reported Covid test negative	Not reported/ Not Recovered	Possible with limited information	9-day TTO. Lymphocytosis in CSF suggested a possible infective etiology, but no specifics were given. Possible with limited information. No past or family or current medical history or exposures.
[redacted] Y/38/F	Headache Urinary retention Asthenia Demyelination Paraesthesia Sensory loss Pyrexia	Suspected COVID-19, urinary retention, demyelination, nystagmus, acute tonsillitis, acne vulgaris,	8/1st dose	MRI: Spine appearances most likely represent demyelinating plaques involving the cervical and upper dorsal spine.	Investigations for NMOSD or MOG negative Covid test negative	Not reported/ Recovering	Possible with limited information	Given the diagnosis of ADEM. Pathology is primarily indicative of longitudinally extensive transverse myelitis. MRI is consistent with transverse myelitis; multiple infectious etiologies; fever, tonsillitis, otitis media; suspected COVID; improvement without immunotherapy. Possible due to TTO. Limited information on work up, or exposures.

Table 134 Cases of Acute Disseminated Encephalomyelitis Fulfilling BCC Level 2

Case ID/ Country/ Serious- (Y/N) Age (Years) /Gender (M/F)	Co-Reported PTs	Relevant Comorbidities and Concomitant Medications	TTO (days)/ Dose #	MRI/ CSF Findings	Diagnostic Workup / Other Investigations	Treatment/ Outcome	WHO-UMC Causality Assessment	Additional Comment
	Nausea Nystag-mus							
[redacted] Y/ 63/ F	Pyrexia Cough Dyspno-ea Muscular weakness Ataxia Confusi-onal state Back pain Gait disturba-nce	CNS neoplasm and another vaccination	7/1st dose	MRI Brain: severe diffuse bilateral white matter oedema with extension to bilateral basal ganglian and brainstem CSF: leukocytes 856, polymorphs 632, mononuclear cells 224. Glucose 4.4, protein 1.22. No viral or bacterial growth.	Blood cultures, Pneumococcal antigen and Viral PCR negative TSH 0.63, CRP 120, eGFR 41, WBC 25.2, Neutrophils 24.3 (high), lymphocytes 0.3 (low), platelets 130, Cryptococcus antigen negative, HIV Neg, PCT 0.25 (H), Syphilis, Rickettsia, and JC virus negative. CSF: CSF antibodies Not detected. total leucocytes 856 10^6/L, Total erythrocytes 45 10^6/L, polymorphs 632 10^6/L, mononuclears	Azithrom-ycin, Steroids, Plasma exchange/ Not Recovered	Possible with confounders	Dates are incorrect in the beginning of the narrative. Onset about 14 to 15 days after flu vaccine, as likely etiology. AZ vaccine was several weeks prior with only normal reactogenicity post AZ vaccine. Exam shows possible evidence of neoplasm in the lung and potential metastasis to brain; however, pathology not available. Confounded by diagnoses of possible CNS neoplasm and another vaccination in close proximity to the onset of symptoms as well as seizures.

Table 134 Cases of Acute Disseminated Encephalomyelitis Fulfilling BCC Level 2

Case ID/ Country/ Serious- (Y/N) Age (Years) /Gender (M/F)	Co-Reported PTs	Relevant Comorbidities and Concomitant Medications	TTO (days)/ Dose #	MRI/ CSF Findings	Diagnostic Workup / Other Investigations	Treatment/ Outcome	WHO-UMC Causality Assessment	Additional Comment
					224 10^6/L, glucose 4.4 mmol/L (high), protein 1.22 g/L (high) Covid test unk			
[redacted] Y/ 53/ M	NA	Unk relevant risks and/or concomitant medications	Same day as vaccination/ 1st dose	MRI: showed possible ADEM in cervical and thoracic cord	Not reported Covid test unk	Not reported/ Not Recovered	Unlikely	No other work up noted. No information on past or present infections, pre-existing conditions, diagnoses, other medications, or other pertinent brain findings. Complaints of weakness after 1st dose and different changes after 2nd dose of vaccine, weakness noted to be subjective. Scan of brain suggested ADEM. Reported weakness within 1 day after 2nd dose of AZ vaccine (very early TTO). Rechallenge and repeated symptoms not confirmed.
[redacted] Y/ 71/ M	NA	Unk relevant risks and/or concomitant medications	49/unk	MRI: brain and cervical spine revealed changes that could be in keeping with either metastasis of an unk primary cancer of demyelination. Lumbar puncture did not reveal any malignant cells.	Not reported Covid test unk	Not reported/ Fatal	Unlikely	49-day TTO. Improvement on MRI and improvement in patient complaints; however, narrative suggests patient may have died. Conflicting information in narrative.

Table 134 Cases of Acute Disseminated Encephalomyelitis Fulfilling BCC Level 2

Case ID/ Country/ Serious-(Y/N) Age (Years) /Gender (M/F)	Co-Reported PTs	Relevant Comorbidities and Concomitant Medications	TTO (days)/ Dose #	MRI/ CSF Findings	Diagnostic Workup / Other Investigations	Treatment/ Outcome	WHO-UMC Causality Assessment	Additional Comment
[redacted] Y/ 51 /F	NA	Unk relevant risks and/or concomitant medications	14/unk	MRI: showed enhancing T2 hyperintense lesions in the spinal cord with longitudinal extension, in the midbrain and in the optic nerves bilaterally. CSF: lymphocyte pleocytosis (50 cells/L), negative oligoclonal bands, normal synthesis rate and positivity for anti-MOG-IgG antibody. Borrelia IgM antibodies positive in serum but Borrelia PCR negative in serum and CSF.	Not reported Covid test negative	Steroids/ Recovering	Possible with confounders	Autoimmunity associated with Borrelia infection is a confounder leading to or associated with MOG antibody disease; confounded by clinical presentation as NMOSD with MRI findings and MOG antibodies.
[redacted] Y/ 22/ M	Myelitis transverse	Unk relevant risks and/or concomitant medications	16/unk	MRI: Cervico-Dorsal Spine was performed with galodino and diffusion, result showed lesion evident from C2 metamere to conus medullar-is, compatible with transverse myelitis. MRI: Brain performed with gadolinium and diffusion, result showed multiple lesions of	Not reported Covid test unk	Intraveno-us human Ig/ unk	Possible with limited information	Clinical features are consistent with transverse myelitis. Despite MRI lesions throughout the spinal cord and in the brain, acute signs and symptoms relate only to spinal cord deficits. Possible determination is based on TTO within 42 days. Limited etiology evaluation did rule out limited viral etiologies, but other common viral, bacterial, and parasitic causes were not evaluated. Underlying medical conditions,

Table 134 Cases of Acute Disseminated Encephalomyelitis Fulfilling BCC Level 2

Case ID/ Country/ Serious- (Y/N) Age (Years) /Gender (M/F)	Co-Reported PTs	Relevant Comorbidities and Concomitant Medications	TTO (days)/ Dose #	MRI/ CSF Findings	Diagnostic Workup / Other Investigations	Treatment/ Outcome	WHO-UMC Causality Assessment	Additional Comment
				anarchic arrangement in both cerebral hemispheres and brainstem.				family history, or other neurological conditions were not addressed, or evaluated or noted and thus a comprehensive assessment is not possible.
[redacted] Y/ 43/ F	Myelin oligoden-drocyte glycopro-tein antibody-associated disease	Migraine	9/1st dose	MRI: Spinal revealed T2 hyperintense lesions involving C6 to T1 as well as T3 and T4, consistent with transverse myelitis. CSF: extensive predominant granulocytic pleocytosis of 545 cells, elevated lactate, and CSF protein as well as a reduced CSF to serum glucose ratio. Oligoclonal bands were negative and no other Ig abnormalities were detected.	Antibodies against MOG in CSF and serum with titers of 1:32 and 1:1000, respectively. Slightly increased antinuclear antibody titer of 1:320; however, anti-extractable nuclear antigens tested negative. IgG antibodies against AQP4, GFAP, NMDA receptor, GABA-B were neither detectable in CSF nor serum. Covid test unk	Steroids Ceftriaxone ampicillin, and plasma exchange/ Recovering	Possible with confounders	Narrative shows some evidence of autoimmune connective tissue disorder, MOG antibodies, CSF consistent with infection, early fluctuating or variable clinical course, low immunity to SARS COV (despite recent vaccination) with suggestion of immune unresponsiveness, possible immune dysfunction. No etiology noted for the event, which had features consistent with both ADEM and meningitis (fever, CSF findings).
[redacted] Y/	Gait, balance disturba-nce, proprioc-	Unk relevant risks and/or concomita	6/1st dose	MRI: confluent brain lesions, extensive cord lesions.	Not reported Covid test unk	Not Reported/ Not Recovered	Possible with limited information	Limited information on past medical history, concomitant medications, WHO-UMC, possible with limited information.

Table 134 Cases of Acute Disseminated Encephalomyelitis Fulfilling BCC Level 2

Case ID/ Country/ Serious- (Y/N) Age (Years) /Gender (M/F)	Co-Reported PTs	Relevant Comorbidities and Concomitant Medications	TTO (days)/ Dose #	MRI/ CSF Findings	Diagnostic Workup / Other Investigations	Treatment/ Outcome	WHO-UMC Causality Assessment	Additional Comment
Unk/ F	eption loss. CSF: positive oligo clonal bands, elevated protein and wbc Belt-like sensory disturb-ance Asthenia Influenza like illness	nt medicatio ns						
[redacted] Y/ 61/ M	Apallic syndro-me	hypothyroidism and polymyalgia rheumatica	2/ 1st dose	MRI: bilateral confluent cortical and subcortical FLAIR hyperintense lesions with hemorrhagic involvement of the basal ganglia. CSF: normal cell counts and cell subsets (1 leukocyte per µL. No CSF-specific oligoclonal bands or intrathecal	Laboratory testing for bacterial and viral infectious agents of the CNS via serology and PCR (CSF and/or serum) remained negative. No AQP4 or myelin oligodendrocyte glycoprotein antibodies.	High dose steroid followed by plasma exchange/ Unk	Possible with confounders	Confounded by hypothyroidism and polymyalgia rheumatica (underlying autoimmune disorder).

Table 134 Cases of Acute Disseminated Encephalomyelitis Fulfilling BCC Level 2

Case ID/ Country/ Serious-(Y/N) Age (Years) /Gender (M/F)	Co-Reported PTs	Relevant Comorbidities and Concomitant Medications	TTO (days)/ Dose #	MRI/ CSF Findings	Diagnostic Workup / Other Investigations	Treatment/ Outcome	WHO-UMC Causality Assessment	Additional Comment
				IgG/-A/-M-synthesis. were detected.	Screening for antinuclear antibodies, antineutrophil cytoplasmic antibodies, antiphospholipid antibodies, neuronal and paraneoplastic antibodies were negative.			
[redacted] Y/ 36/ F	Optic neuritis	Unk relevant risks and/or concomitant medications	Unk/ unk	MRI: multiple T2/ FLAIR lesions in subcortical white matter, posterior limbs internal capsules, pons,left middle cerebellar peduncle. Multiple punctate foci of gadolinium enhancement.	Biochemical analysis normal. Serum and CSF AQP4 antibodies negative. Serum MOG antibody negative Covid test negative	Unk/ Recovering	Unassessable/unclassifia-ble	Missing relevant information. MRI scan and optic nerve scans abnormal. No information on relevant medications, co-factors, confounders, infections, etiology, past or current medical history, or family history. Early multiple sclerosis is possible differential due to optic neuritis and age. Unassessable due to unknown TTO.
[redacted] Y/ 33/ F	NA	Unk relevant risks and/or concomitant medications	14/1st dose	MRI: Brain showed T2/ FLAIR hyperintensity in frontoparietal regions. CSF: 105 cells lymphocytic predominant, protein 28.12 mg/dL, glucose 70.4 mg/dL, serum	Not Reported Covid test unk	Steroids and Acyclovir/Unk	Possible with limited information	Comprehensive assessment of causality not possible due to lack of information regarding the patient's medical history, family history, and concomitant medications, etc. Work up for viral or bacterial infections is absent.

Table 134 Cases of Acute Disseminated Encephalomyelitis Fulfilling BCC Level 2

Case ID/ Country/ Serious-(Y/N) Age (Years) /Gender (M/F)	Co-Reported PTs	Relevant Comorbidities and Concomitant Medications	TTO (days)/ Dose #	MRI/ CSF Findings	Diagnostic Workup / Other Investigations	Treatment/ Outcome	WHO-UMC Causality Assessment	Additional Comment
				MOG was strongly positive				
[redacted] Y/ 35/ F	NA	Unk relevant risks and/or concomitant medications	9/1st dose	MRI: showed T2/ FLAIR hyperintensities in mid brain, pons, left MCP, bilateral posterior limbs internal capsule, thalamus, bilateral centrum semiovale, and LETM from cervical cord to conus. CSF: 58 cells lymphocyte, protein 47.4 mg/dL, glucose was 106 mg/dL.	CRP was positive. ANA profile, ANCA, VDRL test, and RF were negative. Serum MOG was positive. VEP, BERA, and SSEP were normal. Covid test unk	Steroids/ Unk	Possible with limited information	Comprehensive assessment of causality is hampered due to lack of information regarding patient's medical history, family history, and concomitant medications, etc. Infectious viral or bacterial source work up unk.
[redacted] Y/ 52/ F	NA	Unk relevant risks and/or concomitant medications	35/1st dose	MRI: brain showed tumefactive demyelination in left frontal hemisphere with insular involvement along with left > right midbrain involvement. CSF: unremarkable (2 cells, protein 40.5 mg/dL and glucose 56 mg/dL.)	ESR was 18 and CRP was positive; ANA, ANCA, and VDRL were negative. Serum NMO and MOG were negative.	Steroids, plasmapheresis, wysolone (prednisolone) and rituximab/ Unk	Possible with limited information	Infectious work up for causality not known. Comprehensive assessment of causality is additionally hampered due to lack of information regarding patient's medical history, family history, and concomitant medications, etc.

Table 134 Cases of Acute Disseminated Encephalomyelitis Fulfilling BCC Level 2

Case ID/ Country/ Serious- (Y/N) Age (Years) /Gender (M/F)	Co-Reported PTs	Relevant Comorbidities and Concomitant Medications	TTO (days)/ Dose #	MRI/ CSF Findings	Diagnostic Workup / Other Investigations	Treatment/ Outcome	WHO-UMC Causality Assessment	Additional Comment
[redacted] Y/ 45/ M	NA	Unk relevant risks and/or concomitant medications	10/1st dose	MRI: Brain and spine showed hyperintensities in brainstem, cervicodorsal cord and supratentorial regions with central cord swelling. CSF: 44 cells- 44% lymphocytes, protein 90.9 mg/dL, glucose 68 mg/dL, rabies CSF PCR was negative	ANA showed U1RNP 1+ and ANCA was negative. Serum MOG was strongly positive and Serum NMO was negative Covid test unk	Steroids, plasmaph-eresis, wysolone and mycophe-nolate mofetil/ Unk	Possible with limited information	U1RNP suggests mixed connective tissue disease. Additional infectious workup not comprehensive. Causality assessment is hampered by lack of info on past, current, or family histories.
[redacted] Y/ 60/ M	NA	Unk relevant risks and/or concomitant medications	14/2nd dose	MRI: Brain showed multiple focal lesions in right pons, midbrain, medial temporal lobes, splenium of corpus callosum, high parietal lobe with tumefaction and peripheral enhancement. CSF: 9 cells 90% lymphocytes, protein 68.3 mg/dL, glucose 132 mg/dL, CSF OCB negative	ANA, vitamin B_{12}, homocysteine, VDRL and ANCA were negative, ACE was normal, serum NMO and serum MOG were negative and VEP was normal. Covid test unk	Steroids and mycoph-enolate mofetil/ Unk	Possible with limited information	Infectious work up for causality not known. Comprehensive assessment of causality is additionally hampered due to lack of information regarding patient's medical history, family history, and concomitant medications, etc.

Table 134 Cases of Acute Disseminated Encephalomyelitis Fulfilling BCC Level 2

Case ID/ Country/ Serious- (Y/N) Age (Years) /Gender (M/F)	Co-Reported PTs	Relevant Comorbidities and Concomitant Medications	TTO (days)/ Dose #	MRI/ CSF Findings	Diagnostic Workup / Other Investigations	Treatment/ Outcome	WHO-UMC Causality Assessment	Additional Comment
[redacted] Y/ 55/ F	Brainst-em haemorr-hage	Unk relevant risks and/or concomitant medications	9/1st dose	MRI: Brain revealed multiple FLAIR hyperintense and hemorrhagic lesions in the right parietal and temporal lobes, bilaterally in frontotemporal distribution as well as in the right occipital lobe and left fronto-basal region. There were no signs of cerebral sinus vein thrombosis. CSF: mixed granulocytic and lymphocytic pleocytosis and a normal CSF/ serum quotient for albumin. No CSF-specific oligoclonal bands were detected. Intrathecal IgM, IgA, and IgG synthesis was detected, while flow cytometry analysis revealed an increased B cell proportion among lymphocytic populations (56% CD4+ T-cells,	Laboratory testing for infectious agents via serology (in serum) and PCR (in CSF and/or serum), proved negative. Both autoimmune (AQP4-, MOG-autoantibodies), and paraneoplastic antibodies were negative. brain cortex biopsy from the affected right temporal lobe revealed perivascular predominantly granulocytic infiltrates and hemorrhages. Covid test negative	Steroids/ Not recovered	Possible with limited information	Timeline and clinical course consistent with ADEM versus acute haemorrhagic encephalomyelitis (no demyelination noted), bilateral white matter lesions, fulminant cerebral edema, increased ICP, fatal swelling. Work up for causality performed; missing current history of medical diagnoses just prior to events.

Table 134 Cases of Acute Disseminated Encephalomyelitis Fulfilling BCC Level 2

Case ID/ Country/ Serious- (Y/N) Age (Years) /Gender (M/F)	Co-Reported PTs	Relevant Comorbidities and Concomitant Medications	TTO (days)/ Dose #	MRI/ CSF Findings	Diagnostic Workup / Other Investigations	Treatment/ Outcome	WHO-UMC Causality Assessment	Additional Comment
				27% CD8+ T-cells, 5% CD14+ monocytes, 6% CD19+ B cells, and 1% CD56+ NK cells).				
[redacted] Y/ 46/ M	Thromb-octopen-ia	Unk relevant risks and/or concomitant medications	4/1st dose	MRI: extensive supratentorial, infratentorial and long segment spinal cord hyperintensities. CSF: 63 cells/ mm^3, protein 52 mg/dL, sugar 93 mg/dL, CSF encephalitis panel negative.	Serum NMO, MOG, and ANCA negative Covid test negative	Steroids followed by plasma exchange/ Recovered	Possible with limited information	Thrombocytopenia is not consistent; Work up not fully performed.
[redacted] Y/ 64/ M	NA	lymphocytic pleocytosis	20/2nd dose	MRI: showed multifocal cord hyperintensities and bilateral hemispheric corticospinal tract hyperintensities	Not Reported Covid test unk	Rituximab/ Recovered	Possible with limited information	Etiology work up not available. Past medical history and family history, not available.
[redacted] Y/ 45/ M	NA	Allergic asthma triggered by pollen, controlled by inhaled corticosteroids plus	7/1st dose	MRI: Spinal cord revealed a central non-expansive STIR signal lesions extended to spinal cord from D10 to conus; CSF: 43 cells (cut off < 25) associated with	Complete blood count, metabolic panel, thyroid testing, and inflammatory marker negative. Neutrophil-dominant	Antibiotics Steroids/ Unk	Possible with confounder	No current medical history except preceding several hour episode of vertigo 2 months prior to vaccination and the reported event. A brain MRI 16 days after vaccination showed a complicated picture of multiple poorly defined hyperintense T2-weighted and

Table 134 Cases of Acute Disseminated Encephalomyelitis Fulfilling BCC Level 2

Case ID/ Country/ Serious- (Y/N) Age (Years) /Gender (M/F)	Co-Reported PTs	Relevant Comorbidities and Concomitant Medications	TTO (days)/ Dose #	MRI/ CSF Findings	Diagnostic Workup / Other Investigations	Treatment/ Outcome	WHO-UMC Causality Assessment	Additional Comment
		short acting beta 2 agonist drugs		mild hyperproteinorachia (406 mg/L; cut off 305) and normal glycorrhachia and oligoclonal bands.	leukocytosis at 80.7% (cut off 74%). Mild increase of CRP 8.44 mg/L (cut off less than 5 mg/L). Serological panel was negative for recent infections. A positivity of IgG was found for adenovirus, herpes simplex 1, HHV6, cytomegalovirus, EBV VCA, EBNA, parvovirus B19, toxoplasma, and VZV. AQP4 antibodies were negative. A positivity to anti-MOG was confirmed with a titer of 1:2560 (positive :160). Covid test negative			FLAIR bilateral subcortical/cortical gray-white matter lesions, and a frontal venous malformation. Not clear if lesions are at gray-white junction versus both gray and white matter. Transverse myelitis features. Positive IgG for multiple viruses known to produce latent infection is considered a possible confounder.
[redacted]	Fronto-temporal dementia	Unk relevant risks	3/ 1st dose	MRI: Brain had revealed diffusion restriction and patchy and fair	Hematological and biochemical parameters were	Not reported/ Recovering	Possible with limited information	Limited etiological work up.

Table 134 Cases of Acute Disseminated Encephalomyelitis Fulfilling BCC Level 2

Case ID/ Country/ Serious-(Y/N) Age (Years) /Gender (M/F)	Co-Reported PTs	Relevant Comorbidities and Concomitant Medications	TTO (days)/ Dose #	MRI/ CSF Findings	Diagnostic Workup / Other Investigations	Treatment/ Outcome	WHO-UMC Causality Assessment	Additional Comment
Y/ 45/ M		and/or concomitant medications		hyperintensity in bilateral frontal subcortical and deep white matter without any contrast uptake. CSF: unremarkable including a panel for common regional etiologies of viral encephalitis.	normal. Thyroid profile, [redacted] vasculitis workup, anti-TPO, autoimmune and paraneoplastic panel workup, USG abdomen, and X-ray chest were normal. Covid test unk			
[redacted] Y/ 40/ F	NA	Hypertension treated with amlodipine	14/ 1st dose	MRI: Spine: acute anterior horn hypoperfusion/ischemia at T3-T11 level with hyperintense signals at T9-T11 cord likely cytotoxic edema or hypoperfusion. owls eye sign suggestive of anterior horn ischemia extending over 6 thoracic segments on post-gadolinium contrast-enhanced images with restricted diffusion in some of these segments on DWI. MRI: Brain revealed a swelling with altered	To rule out autoimmune encephalitis NMDA-NR1, AMPA-GluR1, AMPA-GluR2, GABA-B receptor antibody, LGi-1 antibody, CASPR2 antibody in CSF, and serum were sent but were negative. Anti-double-stranded DNA, ENA panel and MOG antibodies were also negative in serum. Her C3	Steroids, Immuno-globulin/ Fatal	Possible with limited information	Area of brain involvement can explain symptoms. Pathology would be useful to determine the pathological process: multiple sclerosis versus ADEM.

Table 134 Cases of Acute Disseminated Encephalomyelitis Fulfilling BCC Level 2

Case ID/ Country/ Serious- (Y/N) Age (Years) /Gender (M/F)	Co-Reported PTs	Relevant Comorbidities and Concomitant Medications	TTO (days)/ Dose #	MRI/ CSF Findings	Diagnostic Workup / Other Investigations	Treatment/ Outcome	WHO-UMC Causality Assessment	Additional Comment
				signal in the visualized cervical cord-medulla and another juxtacortical lesion in the right temporal lobe on T2 and FLAIR scan suggestive of demyelinating pathology likely ADEM. CSF: acellular with normal protein content (48 mg/dL) with no oligoclonal bands. Gram stain and culture, fungal smear, gene-Xpert, cryptococcal antigen, TB-gene-Xpert, AFB, CSF-EBV PCR, CSF CMV PCR, CSF VZV, and CSF VDRL were all negative.	and C4 levels were normal. Covid test negative			
[redacted] Y/ 67/ M	Guillain-Barré syndrome Encephalitis	Conmeds: midazolam hydrochloride Suxamethonium Immunoglobulin	14/unk	MRI: neuroaxis showed. changes in keeping with florid ADEM.	Not Reported Covid test unk	Steroids, Plasma exchange/ Not Recovered	Possible with confounders	Confounders: multiple diagnoses Bickerstaff encephalitis, GBS, ADEM, presumed sepsis. Confounding treatments were succinyl choline and midazolam. Past or current or family histories not known. Etiologic Work up not provided.

Table 134 Cases of Acute Disseminated Encephalomyelitis Fulfilling BCC Level 2

Case ID/ Country/ Serious-(Y/N) Age (Years) /Gender (M/F)	Co-Reported PTs	Relevant Comorbidities and Concomitant Medications	TTO (days)/ Dose #	MRI/ CSF Findings	Diagnostic Workup / Other Investigations	Treatment/ Outcome	WHO-UMC Causality Assessment	Additional Comment
		Methylpredn-isolone sodium succinate.						
[redacted] Y/ 67/ F	NA	Unk relevant risks and/or concomitant medications	14/unk	MRI: Brain showed multiple nodular/ oval T2/ FLAIR hyperintensities involving the deep and periventricular cerebral white matter asymmetrically, corpus callosum, subcortical regions, bilateral middle cerebellar peduncles, bilateral cerebellar hemisphere, and left basal ganglia without any mass effect. Few lesions showed peripheral diffusion restriction and incomplete ring and complete ring enhancement after contrast administration. MRI: Cervical spine was unremarkable.	The patient underwent extensive blood and CSF investigations to rule out any infective, paraneoplastic, connective tissue disorder, or inflammatory disorder. The laboratory results showed a marginally increased WBC count of 10.40 thousand [normal range 4-10000] with an increased absolute neutrophil count of 8.30 thousand/mm^3 [normal 2-7]. The rest of the blood profile was normal.	Steroids/ Recovering	Possible with limited information	Possible with limited information. Past history, current medications, and current diagnoses not known.

Table 134 Cases of Acute Disseminated Encephalomyelitis Fulfilling BCC Level 2

Case ID/ Country/ Serious-(Y/N) Age (Years) /Gender (M/F)	Co-Reported PTs	Relevant Comorbidities and Concomitant Medications	TTO (days)/ Dose #	MRI/ CSF Findings	Diagnostic Workup / Other Investigations	Treatment/ Outcome	WHO-UMC Causality Assessment	Additional Comment
				CSF: positive for oligoclonal bands with mildly raised glucose levels.	Covid test negative			

[a] ACE-angiotensin converting enzyme; ADEM-acute disseminated encephalomyelitis; AFB-acid fast bacilli; AMPA-α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; ANA-antinuclear antibodies; ANCA-antineutrophil cytoplasmic antibodies; AQP4-aquaporin-4; BCC-Brighton Collaboration Criteria; BERA-brain evoked response auditory; CASPR2-contactin-associated protein-like 2; CBA-cell-based assays; CD-cluster of differentiation; CMV-cytomegalovirus; CNS-central nervous system; CRP-C-reactive protein; CSF-cerebrospinal fluid; DNA-deoxyribonucleic acid; DWI-diffusion weighted imaging; EBNA-Epstein-Barré nuclear antigen; EBV-Epstein-Barré virus; EBV VCA-Epstein-Barré virus viral capsid antigen; eGFR-estimated glomerular filtration rate; ENA-extractable nuclear antigen; ESR-electron spin resonance; F-female; FLAIR-Fluid attenuated inversion recovery; GABA-B-γ-aminobutyric acid B; GFAP-glial fibrillary acidic protein; HHV6-human herpesvirus 6; HIV-human immunodeficiency virus; ID-identification; ICP-Intracranial pressure; Ig-immunoglobulin; JC-John Cunninghman virus; LETM-longitudinally extensive transverse myelitis; M-male; MCP-middle cerebellar peduncle; MOG-myelin oligodendrocyte glycoprotein; MRI-magnetic resonance imaging; N-no; NA-not applicable; NMDA-N-methyl-D-aspartate; NK-natural killer; NMO-neuromyelitis optica; NMOSD-neuromyelitis optica spectrum disorder; OCB-oligoclonal band; PCR-polymerase chain reaction; PCT-procalcitonin; PT-preferred term; RF-rheumatoid factor; SARS-COV-severe acute respiratory syndrome coronavirus; SSEP-somatosensory evoked potential; STIR-Short Tau Inversion Recovery; TB-tuberculosis; TPO-thyroid peroxidase; TSH-thyroid stimulating hormone; TTO-time to onset; WHO-UMC-World Health Organization-Uppsala Monitoring Centre; U1RNP-U1 Ribonucleoprotein; UK-United Kingdom; Unk-unknown; USG-ultrasonogram; VDRL-venereal disease research laboratory; VEP-Visual Evoked Potential; VZV-varicellazoster virus; WBC-white blood cell; Y-yes.

Fifteen (15) cases were reported in female vaccinees and 11 were reported in male vaccinees. The age range was 22 to 71 years with mean and median of 47.3 years and 45.5 years, respectively. The TTO ranged between the same day to 49 days and the median TTO was 9 days. Two cases ([redacted] and [redacted]) had a fatal outcome. The outcome was not recovered in 7 cases, recovered in 2 cases, recovering in 7 cases, and unknown in 8 cases. Nineteen (19) cases occurred after the 1st dose, 2 cases after the 2nd dose, and in 5 cases the dose information was unknown. Out of the 26 cases fulfilling BCC level 2, 22 cases were assessed as "Possible" as they occurred within the risk window of 2 to 42 days, 2 cases were "Unassessable" as the TTO was unknown, and 2 cases were "Unlikely" as they were outside the risk window per the WHO-UMC causality assessment criteria. Of the 26 cases, possible confounders or alternate explanations could be identified in 9 (35%) cases, which were infections (n=3; Borrelia infection, suspected COVID-19, and positive IgG for multiple viruses [adenovirus, herpes simplex 1, HHV6, cytomegalovirus, EBV VCA, EBNA, parvovirus B19, toxoplasma, and VZV]), autoimmune conditions (n=2; autoimmune connective tissue disorder, polymyalgia rheumatica, and hypothyroidism), CNS neoplasm (n=1), Bickerstaff encephalitis and GBS (n=1) and features suggestive of multiple sclerosis (n=2; concurrent optic neuritis and intrathecal IgM synthesis). Seventeen (17) cases had limited information regarding medical history or comorbidities, or investigations.

Brighton Collaboration Criteria Level 3

Five (5) of the 80 cases fulfilled BCC level 3. The cases fulfilled this classification by clinical course, examination features, and confirmatory tests, and are presented in Table 135.

Table 135 Cases of Acute Disseminated Encephalomyelitis Fulfilling BCC Level 3

Case ID/ Country/ Serious- (Y/N) Age (Years /Gender (M/F)	Co-Reported PTs	Relevant Comorbidities and Concomitant Medications	TTO (days)/ Dose #	MRI/ CSF Findings	Diagnostic Workup / Other Investigations	Treatment/ Outcome	WHO-UMC Causality Assessment	Additional Comment
[redacted] Y/ 45/ F	Diplegia Blindness Rhinitis allergic Headache	Unk relevant risks and/or concomitant medications	Unk/ unk	Not reported	Not reported COVID test unk	Not reported/ Unk	Unassessable/Unclassifia-ble	Unknown TTO. Suggested preceding upper respiratory illness; this could be causative
[redacted] Y/ 55/ M	Hypo-aesthesia, Neuralgia Pain in extremity Fatigue, Arthralgia Bell's palsy Inflammation Visual impair-ment	Conmeds: Omeprazole, Prednisolone, Paracetamol, Colecalciferol	6/1st dose	Not reported	Not reported COVID test unk	Not reported/ Unk	Possible with limited information	Results of CT scans not available; given 5-day infusion, improved except for fatigue, cranial nerve 7 Palsy, non-specific numbness; no cerebral signs. Myelitis, encephalomyelitis seem likely, same BCC level 3. Possible due to TTO, no work up for exposures, preceding medical conditions, or past history. Limited information.
[redacted] Y/ 64/ F	Gait disturban-ce Memory impair-ment	Unk relevant risks and/or concomitant	Unk/ unk	Diffuse bilateral white matter oedema with extension to bilateral basal ganglia and brainstem.	Not reported COVID test unk	Ceftriaxone + azithromycin; Steroids/ Not recovered	Unassessable/Unclassifia-ble	Patient received 2 vaccines, influenza and AZ vaccine; 51-day TTO after AZ vaccine. MRI scan showed disseminated lesions in lungs as well as brain. Dry cough was present. lumbar puncture shows low glucose, very high cell count

Case ID/ Country/ Serious-(Y/N) Age (Years /Gender (M/F)	Co-Reported PTs	Relevant Comorbidities and Concomitant Medications	TTO (days)/ Dose #	MRI/ CSF Findings	Diagnostic Workup / Other Investigations	Treatment/ Outcome	WHO-UMC Causality Assessment	Additional Comment
	Cough Asthenia	medications		CSF: leukocytes 856, polymorphonuclear 632, monocular 224, protein 1.2, glucose 4.4. CSF NMDA, CASPR2, LG1, GABA-B, DPPX, IgLON negative. CSF PCR negative.				consistent with neoplastic CNS process. Pan-fungal cultures not finalized. WHO-UMC: Unassessable due to TTO. Confounded by possible neoplasm or disseminated infection and an additional vaccine.
[redacted] Y/ 63/ F	Balance disorder Asthenia Diplopia	Unk relevant risks and/or concomitant medications	43/1st dose	Not reported	Not reported COVID test negative	Not reported/ Recovered with sequelae	Unlikely	TTO is considered unlikely
[redacted] Y/ Unk/ F	Paraparesis Urinary hesitation Disturbance in attention Headache	Unk relevant risks and/or concomitant medications	30/unk	Not reported	CSF anti-MOG autoantibodies (Serum: 1:1000, liquor, 1:32), allowed the diagnosis of MOG antibody positive COVID test unk	Not reported /Unk	Possible with limited information	Although unk TTO, it falls within the range of expected TTO. BCC acute sensorimotor paraparesis (PT: Paraparesis) + progressive reduction in vigilance (PT: Disturbance in attention) + neurocognitive deficits and ataxia. WHO UMC - Possible but limited information

[a] AZ-AstraZeneca; BCC-Brighton Collaboration Criteria; CASPR2-contactin-associated protein-like 2; CNS-central nervous system; CSF-cerebrospinal fluid; CT-computed tomography; DPPX-dipeptidyl-peptidase–like protein-6; F-female; GABA-B-γ-aminobutyric acid B; M-male; MOG-myelin oligodendrocyte glycoprotein; MRI-magnetic resonance imaging; N-no; NMDA-N-methyl-D-aspartate; PCR-polymerase chain reaction; PT-preferred term; TTO-time to onset; WHO-UMC-World Health Organization-Uppsala Monitoring Centre; Unk-unknown; Y-yes.

Brighton Collaboration Criteria Level 4

Twenty-seven of the 80 cases fulfilled BCC level 4. These cases did not fulfil criteria for a level 3, 2 or 1 certainty as there was insufficient information (pertaining to exclusion of alternate diagnosis for illnesses such as neoplasm, vascular disorder, infection and toxic/ metabolic encephalopathy) to confirm the diagnosis or medical assessment of the case as ADEM. Out of the 27 cases 17 were assessed as possible, 5 cases were assessed as unassessable, and 5 cases were assessed as unlikely per the WHO-UMC causality assessment criteria.

Brighton Collaboration Criteria Level 5

Nineteen of the 80 cases fulfilled BCC level 5 and, therefore excluded due to an alternative diagnosis such as GBS, Neuromyelitis Optica Spectrum disorder (NMOSD), microhaemorrhages in brain, MS and infectious encephalitis. Out of the 19 cases, 9 were assessed as possible, 8 were un-assessable, and 2 were assessed as unlikely per the WHO-UMC causality assessment criteria.

The WHO-UMC causality assessment for all the 80 cases is summarized in Table 136.

Table 136 Overview of WHO-UMC Causality Assessment for Case Reports of ADEM With VAXZEVRIA

WHO-UMC Causality Category	WHO-UMC Causality Assessment Scale (AstraZeneca Adapted)	Number of cases
Certain	Certain	0
Probable	Probable	0
Possible	Possible with risk factors/confounders[a]	26
	Possible with Limited information	26
Unlikely	Unlikely	11
Conditional / Unclassified	Conditional / Unclassified	0
Unassessable/ Unclassifiable	Unassessable/Unclassifiable with risk factors/confounders[a]	6
	Unassessable/Unclassifiable with limited information	11
	Total	80

WHO-UMC Causality Assessment - Medically Confirmed, Brighton Collaboration Criteria Level 1 to 3 Cases

Of the 80 cases identified, 56 (70%) cases were medically confirmed, all of which were serious. The BCC (Law B 2021 [B]) were used for the review of the data available in these cases and WHO-UMC causality was further assessed with a 2 to 42 day risk window. Of the 56 cases that were medically confirmed, 25 cases met BCC level 1 to 3 based on clinical course, examination features, and confirmatory tests (Table 137).

Table 137 Overview of WHO-UMC Causality Assessment for Medically Confirmed Case Reports of ADEM With VAXZEVRIA Reported for Cases of Diagnostic Certainty (BCC Levels 1, 2, and 3)

WHO-UMC Causality Category	WHO-UMC Causality Assessment Scale (AstraZeneca Adapted)	Number of Cases
Certain	Certain	0
Probable	Probable	0
Possible	Possible with risk factors/confounders[a]	12
	Possible with Limited information	6
Unlikely	Unlikely	4
Conditional / Unclassified	Conditional / Unclassified	0
Unassessable/Unclassifiable	Unassessable/Unclassifiable with risk factors/confounders[a]	1
	Unassessable/Unclassifiable with limited information	2
	Total	**25**

[a] Cases were considered to have "risk factors/confounders" where the event could also be explained by the vaccinee's diseases, or where relevant risk factors were present, or concomitant medications that could potentially contribute to the development of the event were reported.

[b] ADEM-acute disseminated encephalomyelopathy; BCC-Brighton collaboration criteria; WHO-UMC-World Health Organization-Uppsala Monitoring Centre.

Amongst 56 medically confirmed cases for ADEM, 24 (42.9%) were identified either with relevant risk/confounding factors as presented in Table 138.

Table 138 Relevant Risk factors / Confounders Identified for Medically Confirmed Case Reports[a]

Relevant Risk / Confounders	Number of Reports	Percent of Total Number of Reports
Chronic conditions such as hypertension, diabetes Mellitus type 1 and 2, and hypercholesterolemia	8	33.3%
Autoimmune conditions, endocrine, and metabolic conditions	5	20.8%
Para- or post infectious conditions and other vaccines	0	0
History of neurological disease	6	25.0%
Personal history such as history of tobacco use, allergies, and being overweight	5	20.8%

Relevant Risk / Confounders	**Number of Reports**	**Percent of Total Number of Reports**
Other conditions suggestive of possible symptoms of organic brain disorder, cancers, immunological conditions: anxiety, depression, psoriasis, urinary retention, overactive bladder, back pain, nystagmus, migraine, sub arachnoid hemorrhage, lymphocytic pleocytosis, breast cancer, bowel cancer	7	29.2%

[a] Some cases have more than 1 relevant risk/confounding factors.

In the remaining 32 (57.1%) of the 56 cases, there was insufficient information with respect to either dose latency, medical history, or concomitant medication details for a comprehensive causal assessment.

Overall, the review of medically confirmed cases did not raise any new relevant safety information for VAXZEVRIA.

Rechallenge/Recurrence Case Reports

There were no cases identified for ADEM after Dose 1, with a recurrence or worsening of ADEM with the Dose 2/Dose 3 of vaccination indicating potential recurrence/positive rechallenge.

Events with Fatal Outcome

Of the 80 cases of ADEM, 5 cases (6.3%) were reported with a fatal outcome, all of which were medically confirmed. The assessment of the fatal events identified is presented in Table 139.

Table 139 Summary of Cases with Fatal Outcome for ADEM (N=5)

Case ID/ Country/ Age (Years)/ Gender/ Medically Confirmed (Y/N)/Source	BCC Level	Dose/ TTO (Days)	Relevant Medical History/Concomitant Medications (Risk Factors)	Other Reported Conditions Associated with the Fatal Outcome/ Autopsy (Y/N)	WHO-UMC Causality Assessment/ Additional Comment	AZ Comment
[redacted] [redacted] Australia/ 71/M/Y/Spontaneous	2	Unk/49	Unk relevant risks and/or concomitant medications	Improvement on MRI and improvement in patient complaints; however, narrative suggests patient may have died. / Unknown	Unlikely	The case was assessed as BCC level 2 based on pattern of initial MRI picture suggestive of several lesions scattered throughout the brain correlating with acute presentation of neurological features, Serial MRI showed resolving lesions with no evidence of new lesions. However, a comprehensive assessment of the fatal ADEM could not be made due to insufficient information on the complete clinical course especially after radiological resolution and discharge of the patient, and on any corrective therapy, any autopsy, medical history and any etiological workup. The WHO-UMC was assessed as unlikely based on temporal association.
[redacted] [redacted] United States/ 63/ M/ Y/ Spontaneous	4	1st dose/ Unk	Unk relevant risks and/or concomitant medications	Poorly responsive, vertigo, abdominal pain, and fatigue /No	Unassessable/ Unclassifiable	The case was assessed as BCC level 4 as there was limited information to assess ADEM. Additionally, due to lack of autopsy and insufficient information on TTO, clinical course, any corrective therapy, medical history, diagnostic workup and any etiological workup, a comprehensive causal assessment was not possible

Case ID/ Country/ Age (Years)/ Gender/ Medically Confirmed (Y/N)/Source	BCC Level	Dose/ TTO (Days)	Relevant Medical History/Concomitant Medications (Risk Factors)	Other Reported Conditions Associated with the Fatal Outcome/ Autopsy (Y/N)	WHO-UMC Causality Assessment/ Additional Comment	AZ Comment
[redacted] Brazil/ 90/ M/ Y/ Spontaneous	4	1st dose/ same day	Concomitant medications included enalapril maleate and doxasozin mesilate	Elderly age (90 years) /Unknown.	Unlikely	The case was assessed as BCC level 4 as there was limited information to assess ADEM. Additionally, due to the rapid onset on the day of vaccination, it is likely a pre-existing predisposition to ADEM was present before vaccination and the vaccine is unlikely to be the cause of the ADEM. Further, no information on autopsy, complete clinical course, any corrective therapy, medical history, diagnostic workup and any etiological workup was available.

Case ID/ Country/ Age (Years)/ Gender/ Medically Confirmed (Y/N)/Source	BCC Level	Dose/ TTO (Days)	Relevant Medical History/Concomitant Medications (Risk Factors)	Other Reported Conditions Associated with the Fatal Outcome/ Autopsy (Y/N)	WHO-UMC Causality Assessment/ Additional Comment	AZ Comment
[redacted] Australia/ 63/ M/ Y/ Literature	1	1st dose/ 12	Medical history: recurrent vertiginous and non-vertiginous dizziness (after a small traumatic subarachnoid hemorrhage after a fall with head strike 3 years prior), which at times had orthostatic/head posture/exertional exacerbation, ischemic heart disease, atrial fibrillation, cardiac pacemaker in situ. Concomitant medications: apixaban, bisoprolol, irbesartan, empagliflozin, metformin, Novomix-30 (insulin aspart-insulin aspart protamine), rosuvastatin, and pantoprazole.	Ketoacidosis and silent myocardial infarction /Yes	Possible with limited information	The case was assessed as BCC level 1 based on clinical features, MRI findings, ante mortem biopsy and autopsy. Ongoing evaluation of pre-existing vertiginous and non-vertiginous dizziness, (pre-existing foci in white matter) and presenting symptom of vertigo could also point to possible ongoing immune response to an unknown preexisting brain pathology. The patient's condition and fatality thereof could also be complicated by underlying significant cardiac (heart disease with ischemic cardiac events) and metabolic issues (ketoacidosis and mitochondrial dysfunction) as increased lactate levels were seen in CSF even post ketoacidosis correction with no increased leucocytic pleocytosis. There was limited information on post-mortem autopsy of other organs. Limited etiologic work-up was presented, including infectious and cell type assessment on the biopsy sample.

[redacted] [redacted] India/ 40/ F/ Y/ Literature	2	1st dose/ 14	Medical history: hypertension treated with amlodipine and spinal cord ischemia	None /Unknown	Possible with confounders	The case was assessed as BCC level 2 per the Brighton Collaboration algorithm based on the clinical features of encephalopathy, changed mentation, upper motor neuron signs (increased reflexes, bilateral Babinski,) acute onset and multi-focal features on MRI suggesting demyelination in the cerebrum. Potential infectious and auto-immune causes were potentially ruled out, however there was an unevaluated acute episode of self-resolving myalgia just prior to COVID-19 vaccination. Additionally, there was a description of anterior horn spinal cord ischemia/hypoperfusion or possible infarction on MRI suggesting a vascular/vasculitic pathology and noted paradoxical breathing was consistent with spinal cord pathology causing diaphragm paralysis. Limited or no information on any biopsy or autopsy, exact causes of death, work up for possible malignancies, paraneoplastic syndromes, and hematological investigations were not available. Hypertensive encephalopathy or acute fulminant multiple sclerosis would also be in the differential. Based on reasonable time relationship of the neurological event, onset to vaccine administration, the WHO-UMC was assessed as Possible with confounders of hypertension and spinal cord ischemia.

[a] ADEM-acute disseminated encephalomyelitis; BCC-Brighton Collaboration Criteria; CNS-central nervous system; F-female; ID-identification; M-male; MI-myocardial infarction; MRI-magnetic resonance imaging; N-no; TTO-time to onset; unk-unknown; WHO-UMC-World Health Organization-Uppsala Monitoring Centre; Y-yes.

Of the 80 cases, 5 had a fatal outcome. The case fatality rate of 6.3% is in line with previously document case fatality rates in ADEM (5% to 50%; Borlot et al 2011). Two (2) cases were from literature sources and 3 cases from spontaneous sources. The TTO was reported in 4 of 5 cases (same day, 12 days, 14 days, and 49 days) and all cases were reported or considered to be following 1st vaccine dose. The time to fatal outcome was reported in 2 of 5 cases (7 days and 20 days). Sufficient information to classify the reported ADEM event as BCC level 1 to 3 was available only in 3 of 5 cases (BCC level 2 in 2 cases and BCC level 1 in 1 case). Reasonable information to rule in a possible confounding role of other diseases for fatal outcome was identified in 1 case in which the patient's underlying significant cardiac (heart disease with ischemic cardiac events) and metabolic (ketoacidosis) issues. The remaining 4 of 5 cases had insufficient information on medical history, autopsy, any corrective therapy, medical history, or comprehensive etiological work-up (eg, work up for possible malignancies or paraneoplastic syndromes).

In summary no significant safety concerns were seen on review of ADEM cases with fatal outcome.

Observed Versus Expected Analysis

An observed versus expected (O/E) analysis of 'Acute disseminated encephalomyelitis' was conducted cumulatively to 28 June 2022. The results were stratified by 3 risk windows (14, 30 and 42 days) for all global reports, stratified by age in the European Union (EU), UK, Brazil, and Australia, and by age and gender. The risk window of 2 to 42 days was included from the Brighton case definition (Law B 2021 [B]). In order to provide an accurate incidence rate for this rare event, a meta-analysis using random-effect model was performed based on data from years 2017 to 2019 from databases (ES_BIFAP_PC, ES_BIFAP_PCHOSP, ES_FISABIO, ES_SIDIAP_PC (Spain Information System for the Development of Research in Primary Care), ES_SIDIAP_PCHOSP, and IT_ARS, UK_CPRD) presented in the revised ACCESS protocol (Willame et al 2021). Please refer to Appendix 8 for the methodology of the O/E analyses.

The O/E analysis for the cumulative cases of 'Acute disseminated encephalomyelitis' with risk windows of 14, 30, and 42 days is presented with results in Table 140.

Conservatively, the exposure for global reports (448306152) is based on doses administered in 13 markets as explained in Appendix 8.

Table 140 Observed Versus Expected Analysis for all Reports of ADEM (Global

Adverse Events	Risk Window (Days)	Background Rates/ 100,000 PY	Exposure	Observed Number of Cases	Expected Number of Cases	O Over E Ratio (95% CI)	Conclusion
Overall (global) ACCESS IR ADEM	14	0.15	448306152	37	25.78	1.44 (1.01-1.98)	Observed significantly > expected

Table 140 Observed Versus Expected Analysis for all Reports of ADEM (Global

Adverse Events	Risk Window (Days)	Background Rates/ 100,000 PY	Exposure	Observed Number of Cases	Expected Number of Cases	O Over E Ratio (95% CI)	Conclusion
	30	0.15	448306152	42	55.23	0.76 (0.55-1.03)	Observed < expected
	42	0.15	448306152	43	77.33	0.56 (0.4-0.75)	Observed significantly < expected
Overall (global) ACCESS IR including cases with an unknown time to onset	14	0.15	448306152	68	25.78	2.64 (2.05-3.34)	Observed significantly > expected
	30	0.15	448306152	73	55.23	1.32 (1.04-1.66)	Observed significantly > expected
	42	0.15	448306152	74	77.33	0.96 (0.75-1.2)	Observed < expected

[a] IR = 0.15/100,000 person years.

[b] ADEM-acute disseminated encephalomyelitis; CI-confidence interval; E-expected; IR-incidence rate; O-Observed; PY-patient years.

[c] Source: Willame et al 2021 (Meta-analysis IR from 2017-2019 ADEM-Narrow).

An O/E analysis of cases meeting case definition according to BCC Level 1, 2, or 3, based on clinical course, examination such as brain histopathology, focal/multifocal CNS abnormalities, brain MRI or recurrence or relapse of illness since the symptomatic nadir, and no alternative etiology (Law B 2021 [B]) are presented in Table 141.

Table 141 Observed Versus Expected Analysis for Cases for ADEM Meeting BCC Level 1, 2 or 3 (Global Reports)

Adverse Events	Risk Window (Days)	Background Rates/ 100,000 PY	Exposure	Observed Number of Cases	Expected Number of Cases	O Over E Ratio (95% CI)	Conclusion
Overall (global) ACCESS IR ADEM BCC levels 1 to 3	14	0.15	448306152	15	25.78	0.58 (0.33-0.96)	Observed significantly < expected
	30	0.15	448306152	17	55.23	0.31 (0.18-0.49)	Observed significantly < expected
	42	0.15	448306152	17	77.33	0.22 (0.13-0.35)	Observed significantly < expected
Overall (global) ACCESS IR ADEM	14	0.15	448306152	30	25.78	1.16 (0.79-1.66)	Observed > expected
	30	0.15	448306152	32	55.23	0.58 (0.4-0.82)	Observed significantly < expected

Table 141 Observed Versus Expected Analysis for Cases for ADEM Meeting BCC Level 1, 2 or 3 (Global Reports)

Adverse Events	Risk Window (Days)	Background Rates/ 100,000 PY	Exposure	Observed Number of Cases	Expected Number of Cases	O Over E Ratio (95% CI)	Conclusion
BCC levels 1 to 3 including cases with an unknown TTO	42	0.15	448306152	32	77.33	0.41 (0.28-0.58)	Observed significantly < expected

[a] IR = 0.15/100,000 person years.

[b] ADEM=acute disseminated encephalomyelitis; BCC=Brighton collaboration criteria; CI=confidence interval; E=expected; IR=incidence rate; O=Observed; PY=patient years; TTO=time to onset.

[c] Source: Willame et al 2021 (Meta-analysis from revised ACCESS protocol IR from 2017-2019 ADEM-Narrow)

Additionally, the O/E analysis is presented with stratification by age for the EU, UK, Brazil, and Australia regions based on the available exposure data, this is presented in Table 142.

Table 142 Observed Versus Expected Analysis for ADEM Cases Stratified by Age for the EU, UK, Brazil, and Australia Regions

AEs	Risk Window (Days)	IR[a] / 100,000 PY	Exposure[b]	Observed Number of Cases	Expected Number of Cases	O Over E Ratio (95% CI)	Conclusion
Age 18 to 49	14	0.15	100987434	16	5.81	2.75 (1.57-4.47)	Observed significantly > expected
	30	0.15	100987434	17	12.44	1.37 (0.8-2.19)	Observed > expected
	42	0.15	100987434	17	17.42	0.98 (0.57-1.56)	Observed < expected
Age 50 to 59	14	0.07	56425075	5	1.51	3.31 (1.08-7.73)	Observed significantly > expected
	30	0.07	56425075	6	3.24	1.85 (0.68-4.03)	Observed > expected
	42	0.07	56425075	6	4.54	1.32 (0.48-2.88)	Observed > expected
Age 60 to 69	14	0.16	57182485	8	3.51	2.28 (0.98-4.49)	Observed > expected
	30	0.16	57182485	8	7.51	1.07 (0.46-2.1)	Observed > expected
	42	0.16	57182485	8	10.52	0.76 (0.33-1.5)	Observed < expected
Age over 70	14	0.08	31869628	3	0.98	3.06 (0.63-8.95)	Observed > expected
	30	0.08	31869628	4	2.09	1.91 (0.52-4.9)	Observed > expected
	42	0.08	31869628	5	2.93	1.71 (0.55-3.98)	Observed > expected

[a] Source: Willame et al 2021 (Meta-analysis estimates of ACCESS from 2017-2019 ADEM-Narrow).

[b] Exposure till 26 June 2022.

[c] ADEM-acute disseminated encephalomyelitis; AE-adverse events; CI-confidence interval; E-expected; EEA-European Economic Area IR-incidence rate; O-Observed; PY-Patient years, TTO-time to onset; UK-United Kingdom

An O/E analysis of cases meeting case definition according to BCC Level 1, 2 or 3 stratified by age for the EU, UK, Brazil, and Australia regions is presented in Table 143.

Table 143 Observed Versus Expected Analysis for ADEM Cases Meeting BCC Level 1, 2 or 3 and Stratified by Age for EU, UK, Brazil, and Australia Regions

Age group	Risk Window (Days)	IR[a] / 100,000 PY	Exposure[b]	Observed Number of Cases	Expected Number of Cases[a]	O Over E Ratio (95% CI)	Conclusion
Age 18-49 (BCC 1 to 3)	14	0.15	100987434	5	5.81	0.86 (0.28-2.01)	Observed < expected
	30	0.15	100987434	5	12.44	0.4 (0.13-0.94)	Observed significantly < expected
	42	0.15	100987434	5	17.42	0.29 (0.09-0.67)	Observed significantly < expected
Age 50-59 (BCC 1 to 3)	14	0.07	56425075	2	1.51	1.32 (0.16-4.78)	Observed > expected
	30	0.07	56425075	2	3.24	0.62 (0.07-2.23)	Observed < expected
	42	0.07	56425075	2	4.54	0.44 (0.05-1.59)	Observed < expected
Age 60-69 (BCC 1 to 3)	14	0.16	57182485	4	3.51	1.14 (0.31-2.92)	Observed > expected
	30	0.16	57182485	4	7.51	0.53 (0.15-1.36)	Observed < expected
	42	0.16	57182485	4	10.52	0.38 (0.1-0.97)	Observed significantly < expected
Age over 70 (BCC 1 to 3)	14	0.08	31869628	0	0.98	0 (0-3.76)	Observed < expected
	30	0.08	31869628	0	2.09	0 (0-1.77)	Observed < expected
	42	0.08	31869628	0	2.93	0 (0-1.26)	Observed < expected

[a] Source: Willame et al 2021 (meta-analysis estimates of ACCESS from 2017-2019 ADEM-Narrow)

[b] Exposure until 26 June 2022.

[c] ADEM-acute disseminated encephalomyelitis; BCC-Brighton collaboration criteria; CI-confidence interval; E-expected; EEA-European Economic Area; IR-incidence rate; O-Observed; PY-Patient years, UK-United Kingdom.

An O/E analysis of cases meeting case definition according to BCC Level 1, 2 or 3 stratified by age and gender for UK is presented in Table 144.

Table 144 Observed Versus Expected Analysis for ADEM Cases Meeting BCC Level 1, 2 or 3 and Stratified by Age and Sex for the UK

Age group BCC Level Sex	Risk Window (Days)	IR[a] / 100,000 PY	Exposure[b]	Observed Number of Cases	Expected Number of Cases[a]	O Over E Ratio (95% CI)	Conclusion
Age 18 to 49 (BCC 1 to 3) Female	14	0.07	7999627	2	0.21	9.52 (1.15-34.4)	Observed significantly > expected
	30	0.07	7999627	2	0.46	4.35 (0.53-15.71)	Observed > expected
	42	0.07	7999627	2	0.64	3.12 (0.38-11.29)	Observed > expected
Age 50 to 59 (BCC 1 to 3) Female	14	0.05	6280795	0	0.12	0 (0-30.74)	Observed < expected
	30	0.05	6280795	0	0.26	0 (0-14.19)	Observed < expected
	42	0.05	6280795	0	0.36	0 (0-10.25)	Observed < expected
Age 60 to 69 (BCC 1 to 3) Female	14	0.12	4996322	0	0.23	0 (0-16.04)	Observed < expected
	30	0.12	4996322	0	0.49	0 (0-7.53)	Observed < expected
	42	0.12	4996322	0	0.69	0 (0-5.35)	Observed < expected
Age 70 to 79 (BCC 1 to 3) Female	14	0.09	3688886	0	0.13	0 (0-28.38)	Observed < expected
	30	0.09	3688886	0	0.27	0 (0-13.66)	Observed < expected
	42	0.09	3688886	0	0.38	0 (0-9.71)	Observed < expected
Age over 80 (BCC 1 to 3) Female	14	0.02	1864578	0	0.01	0 (0-368.89)	Observed < expected
	30	0.02	1864578	0	0.03	0 (0-122.96)	Observed < expected
	42	0.02	1864578	0	0.04	0 (0-92.22)	Observed < expected
Age 18 to 49 (BCC 1 to 3) Male	14	0.21	7399929	0	0.6	0 (0-6.15)	Observed < expected
	30	0.21	7399929	0	1.28	0 (0-2.88)	Observed < expected
	42	0.21	7399929	0	1.79	0 (0-2.06)	Observed < expected

Table 144 Observed Versus Expected Analysis for ADEM Cases Meeting BCC Level 1, 2 or 3 and Stratified by Age and Sex for the UK

Age group BCC Level Sex	Risk Window (Days)	IR[a] / 100,000 PY	Exposure[b]	Observed Number of Cases	Expected Number of Cases[a]	O Over E Ratio (95% CI)	Conclusion
Age 50 to 59 (BCC 1 to 3) Male	14	0.07	6915956	1	0.19	5.26 (0.13-29.32)	Observed > expected
	30	0.07	6915956	1	0.4	2.5 (0.06-13.93)	Observed > expected
	42	0.07	6915956	1	0.56	1.79 (0.05-9.95)	Observed > expected
Age 60 to 69 (BCC 1 to 3) Male	14	0.12	5160658	0	0.24	0 (0-15.37)	Observed < expected
	30	0.12	5160658	0	0.51	0 (0-7.23)	Observed < expected
	42	0.12	5160658	0	0.71	0 (0-5.2)	Observed < expected
Age 70 to 79 (BCC 1 to 3) Male	14	0.09	3358831	0	0.12	0 (0-30.74)	Observed < expected
	30	0.09	3358831	0	0.25	0 (0-14.76)	Observed < expected
	42	0.09	3358831	0	0.35	0 (0-10.54)	Observed < expected

[a] Source: Willame et al 2021 (meta-analysis estimates of ACCESS from 2017-2019 ADEM-Narrow)
[b] Exposure until 26 June 2022.
[c] ADEM-acute disseminated encephalomyelitis; BCC-Brighton collaboration criteria; CI-confidence interval; E-expected; IR-incidence rate; O-Observed; PY-Patient years, UK-United Kingdom.

The O/E analysis of all cases of ADEM suggested that the observed cases of ADEM cases were less than the number of expected cases in the 30-day risk and the 42-day risk windows, while for the 14-day risk window the analysis suggested that the observed cases of ADEM were significantly more than the number of expected cases. As a conservative approach all cases with time to onset within 0 to 42 days and all cases with unknown time to onset were included in the O/E analysis. The vaccine exposure by doses administered for O/E analysis were only considered from few countries where the data were available. Fifteen cases were reported with the ADEM onset within 0 to 5 days of VAXZEVRIA vaccination. A latency of ADEM within 0 to 5 days of immunization is considered too short and cases less than 5 days from vaccination would be questionable in any causative association and may be possibly indicative of pre-existing infection or underlying condition. While immunization with the Semple rabies vaccine, which has a proven association with ADEM (Sejvar et al 2007; Hemachudha et al 1987 [A], has been shown to be associated with a peak interval of 1 to 2 weeks between immunization and onset of ADEM's neurologic symptoms among some vaccine recipients (Hemachudha et al 1987 [B]). Leake et al 2004, in an epidemiologic study of 64 ADEM cases also reported 93% of ADEM patients had one or more of the following symptoms or signs of infection within the preceding 21 days: fever, cough, rhinorrhea; vomiting; or diarrhoea. Of the 37 cases within 14 days TTO, there were 15 reports of ADEM

reported within the risk window of 0-5 days; if the 15 reports are excluded the observed cases are less than expected Also, there is a possibility of reporting bias for increased reporting of cases with a shorter risk window for the passive event reporting of rare diseases. When cases with unknown TTO were added to the observed numbers, observed cases were significantly more than expected for the 14-day and 30-day risk windows. However, an O/E analysis of cases meeting BCC levels 1 to 3 showed that the observed number ADEM cases fulfilling case definition were less and/or significantly less than number of expected cases in all risk windows except the 14-day risk window including cases with unknown TTO.

When O/E analyses are stratified by age in EU, UK, Australia, and Brazil, and different risk windows (14, 30, and 42 days), numbers of cases become very small resulting in observed as greater than expected for most age groups. The O/E analysis for cases meeting the BCC level 1, 2 or 3 and stratified by age group with different risk windows (14, 30, and 42 days) suggested that observed cases were less than expected for most age groups. Also, there is too much variability in these data to make an assessment.

When O/E analysis are stratified by age and gender in the UK for cases meeting BCC level 1, 2, or, 3 the observed numbers were significantly greater or greater than expected in females aged 18 to 49 and males aged 50 to 59 in all risk windows. The observed numbers were less than expected in other age and sex stratifications.

Further review of cases in these groups where observed were above expected showed that most cases had insufficient information to make any causality assessment. Of the 80 cases reported during the reporting period, only 34 cases met BCC level 1 to 3.

The O/E analyses provided is based on the most recent and available data, but there is a level of assumption made and any change in the data would impact the results. The following are some of the limitations/assumptions of the data used:

- Doses administered for determination of exposure: Currently only exposure data from certain countries are available, but these countries generate the majority of cases reported to AstraZeneca.
- The background incidence rate used for the calculation is the same as the population vaccinated: The identification of incidence rates can vary depending on the source of the data.
- Most of the observed events are spontaneously reported: Spontaneously reported events may only represent a fraction of the events that have actually occurred. Both under-reporting for certain events, and conversely, over-reporting for certain events could have played a role.
- The risk period reflects the period of time an event would occur post-vaccination: Over-estimating the risk window would increase the "Person-Years at Risk" period and include events that are outside the actual period of time a true event would occur. Under-estimating the risk window will result in reduced sensitivity making it difficult to reach statistical significance.

The O/E analyses does not account for confounding/risk factors which might be present in the cases, such as seasonal effects on the occurrence of certain events, or for example the effect of COVID which may also contribute. Also, when stratified by age/gender, there are small numbers of cases in each stratification, which should be considered when interpreting the significance of the results.

Literature Review

A cumulative literature search to 28 June 2022 of the databases in Embase, InsightMeme, and PubMed was conducted using the following search terms for ADEM with VAXZEVRIA: 'acute disseminated encephalomyelitis'/exp OR 'acute disseminated encephalomyelitis' OR 'ADEM'.

The literature search resulted in 126 articles. After medical review of all the articles, 15 articles (which includes 23 cases) were considered relevant and are discussed in the section below and in the Section 2.6 AstraZeneca Global Patient Safety Database. These relevant articles are as follows: Escolà et al 2022 ( ); Garg et al 2022 ( ); Ancau et al 2022 ( ); Kumar et al 2022 ( ); Li et al 2022 ( ); Maramattom et al 2022( ); Mumoli et al 2021 ( ); Nagaratnam et al 2022( ); Netravathi et al 2022 ( ); Rinaldi et al 2022( ); Simone et al 2021 ( ); Sivji et al 2022( ); Tapdia et al 2022 ( ); Permezel et al 2022 ( ); and an article reference that was redacted in the source document ( ). The remaining 111 articles were considered to be not relevant as these did not describe ADEM or did not identify any safety concerns with ADEM following VAXZEVRIA vaccination.

Netravathi et al 2022 described an observational comparative analysis study, case series (over a period from May 2021 to December 2021) of patients with different neurological manifestations of CNS demyelination presenting within 6 weeks of vaccination against SARS-CoV-2 versus controls, from a neuropsychiatric tertiary university hospital in India.

A total of 116 patients with CNS demyelination were assessed during the study period, of whom 29 met the inclusion criteria for post-vaccine demyelination and the rest were taken as controls as either they were already diagnosed with 1 of the disorders with CNS demyelination or were not vaccinated within 6 weeks of the demyelination.

The inclusion criteria for post-vaccine demyelination comprised a) receipt of a SARS-CoV-2 vaccine, either 1st or 2nd dose within the past 42 days; b) no recent history of COVID-19 infection within the past 3 months; and c) evidence of CNS demyelination based on clinical and radiological features. The exclusion criterion was presence of other precipitating factors besides SARS-CoV-2 vaccine as a cause for demyelination in the last 3 months.

In addition to patient history, clinical examination, and routine hematological investigations, the following investigations were performed: CSF analysis, serum and/or CSF NMO antibodies, MOG antibodies (testing done with IgG1), MRI of the brain and/or spine, evoked potentials (visual evoked potentials, brainstem auditory evoked response, somatosensory evoked potential) and ancillary investigations to exclude alternative etiologies: serum antinuclear antibodies (ANA) profile, C-reactive protein, and antineutrophil cytoplasmic antibodies.

Out of the 29 cases, 27 received ChAdOx1-S vaccine, while 2 were vaccinated with BBV152. Most patients (n=22; 75.9%) developed the symptoms after the 1st vaccination dose and none of them had prior history of demyelination. The timing of presentation for neurological symptoms after vaccine exposure ranged from 1 to 42 days.

The CSF cell count (excluding singular case of traumatic CSF picture) was reported in 25 of 29 (86%) cases with pleocytosis seen in 15 (60%) cases and normal counts seen in 10 (40%) cases. For controls, the CSF cell count was reported in 61 of 87 (70%) controls with pleocytosis seen in 19 (22%) controls; however, there was insufficient information on proportion of normal CSF counts. The CSF protein was raised in 12 of 25 (48%) cases and normal counts seen in 13 (52%) cases. For controls, the CSF protein was raised in 11 of 59 (18.6%) controls; however, there was insufficient information on proportion of normal CSF protein.

Information on CSF oligoclonal bands was available in 10 of 29 (34%) cases and 47 of 87 (54%) controls and no significant difference was seen in its frequency (60% in cases and 68% in controls; p=0.6293). Information on ANA positivity was available in all 29 of cases and 74 of 87 (85%) controls and no significant difference was seen in its frequency (20.7% in cases and 16.2% in controls; p=0.5903).

Information on myelin oligodendrocyte glycoprotein (MOG) positivity and aquaporin-4 (AQP4) positivity was available in all 29 cases and 69 of 87 (79.3%) controls. Ten of 29 (34.5%) cases and 10 of 69 (14.5%) controls were found to be positive for MOG antibodies (p=0.0257). Out of 10 cases, 4 presented with optic neuritis (ON), 3 with ADEM, 2 with longitudinally extensive myelitis, and 1 with simultaneous ON and myelitis. Two (2) patients were diagnosed with AQP4-positive NMOSD in this post-vaccine period while 1 patient was diagnosed with McDonald's definite multiple sclerosis. The rest of the patients were seronegative for both AQP4 and MOG antibodies. The ANA profile showed antibody positivity in 4 patients. A paraneoplastic profile was performed in 1 patient, and it was positive for anti-recoverin antibody with no evidence of malignancy on computed tomography (CT) of the chest and abdomen. The majority of patients in the control group had the diagnosis of multiple sclerosis (48 of 87 [55.2%]) followed by AQP4-positive NMOSD (11 of 87 [12.6%]).

Significant improvement was seen in most (96.5%) patients with medical management (intravenous methylprednisolone followed by oral steroids, plasmapheresis, intravenous Ig, mycophenolate mofetil, and rituximab). One (1) patient with ADEM with tumefactive

demyelinating lesions remained critically ill, requiring invasive ventilation, and died after a prolonged intensive care unit (ICU) stay and superimposed infection. Two (2) patients received a 2nd ChAdOx1-S vaccine dose while taking 20 mg of oral prednisone and did not show neurological worsening. One (1) patient received an alternative BBV152 vaccination after a primary ChAdOx1-S vaccine dose without any adverse events.

All the cases were suggested by the authors to have a probable causality label. This was in view of temporal association of symptoms occurring within 6 weeks of administration of COVID-19 vaccination without an alternative reason.

The authors concluded that it was difficult to establish a causal relationship between vaccination and neurological adverse events such as demyelination. The temporal association with the vaccination and the presence of MOG antibodies raises the possibility of an immunogenic process triggered by the vaccine in susceptible individuals.

AstraZeneca Comment

This study was based on chart review from a tertiary care centre in India. There was no information on the expected frequency of CNS demyelination in the tertiary hospital in India to assess the trend of observed frequency of the 116 CNS demyelination cases.

The controls comprising of patients already diagnosed with 1 of the disorders with CNS demyelination or those who were not vaccinated within 6 weeks of the demyelination is not considered a suitable comparison group for case-control analysis. It was not reported whether the patients with pre-existing demyelination were on any concurrent immunosuppressive therapy, which might have confounded the current presentation, especially the immunological parameters.

Out of a total of 116 patients with CNS demyelination, 61 patients received ChAdOx1 NCoV-19 vaccination (27 in the cases and 34 in the controls). Thus, in the majority of the ChAdOx1 NCoV-19 vaccinated patients presenting with CNS demyelination, either a pre-existing underlying demyelination was identified or TTO of the adverse event following vaccination was considered unreasonable. Also, since this study was based on chart review rather than actual patient monitoring, the authors could not flawlessly estimate the occurrence of COVID-19 infection in the study population (as highlighted as a limitation of this study). These limitations preclude a comprehensive causal assessment beyond a temporal association.

Additionally, CSF investigation parameters were not consistently reported for all patients in cases and controls and, therefore, any consistent association could not be comprehensively assessed. No significant difference was seen in the patterns of CSF oligoclonal bands between cases and controls to signify any particular pathogenesis.

Similarly, MOG antibody parameters were not consistently reported for all patients in the control group (reported in 79.3% of controls versus 100% in cases) and hence a comparison regarding it in the cases and controls could not be comprehensively made.

In the article, there was insufficient information on background characteristics and matching of the complete cohort. Hence, the cohort of the 'susceptible' individuals as reported by the authors could not be further assessed.

On review of the 80 cases of ADEM in the AstraZeneca global safety database, 18 (22.5%) cases had information on anti-MOG antibody status. Of the 18 cases, 8 (44.4%) cases were anti-MOG positive, 9 (50%) cases were anti-MOG negative and in 1 case (5.5%) the anti-MOG status was unknown.
On review of the global safety database, no specific trend with respect to MOG antibody positive status ADEM in individuals vaccinated with VAXZEVRIA was seen.

Mechanism of Action

On review of the proposed mechanisms for COVID-19 vaccines, the mechanisms were discussed mainly for demyelinating events, as a whole, rather than to ADEM in particular. The various mechanisms hypothesized by the authors were:

- Molecular mimicry of viral proteins to myelin (Ismail and Salama 2022; Matsumoto et al 2022; Lee et al 2022)
- Immunological triggering or unmasking of pre-existing pathology by vaccine adjuvants, adenovirus vector, and messenger ribonucleic acid (mRNA) (acting as both antigen and adjuvant) (Ismail and Salama 2022; Lee et al 2022)
- Bystander activation eg, autoreactive lymphocytes (Fujinami et al 2006; Matsumoto et al 2022 ; Lee et al 2022)
- Susceptible patients (Ismail and Salama 2022; Lee et al 2022)

These mechanisms are described in detail below
The proposed mechanism of molecular mimicry was mainly predicted based on cross-reactions between human host and SARS-CoV-2 proteins (Yapici-Eser et al 2021; Vojdani and Kharrazian 2020). Using a computational model, Yapici-Eser et al 2021 predicted the possible interaction of SARS-CoV-2 proteins (approximately 11 proteins) with proteins involved in synaptic vesicle trafficking, endocytosis, axonal transport, neuronal transmission, thrombosis, inflammation, and the mitochondrial and blood brain barrier as well as protein growth factors. However, the authors acknowledged the limitations of in silico models and suggested further exploration using in vitro and in vivo models. In an experimental in vitro study reported as a letter to the editor, Vojdani and Kharrazian 2020 tested commercially available mouse monoclonal antibody against recombinant SARS coronavirus spike protein (anti SARS-CoV-2 spike antibody) and rabbit monoclonal antibody made against SARS coronavirus nucleoprotein to 50 different human tissue antigens (autoimmune epitopes) using enzyme-linked immunosorbent assay. The authors reported strong reactions against transglutaminase 3, transglutaminase 2, anti-extractable nuclear antigen, myelin basic protein, mitochondria, nuclear antigen, α-myosin, and thyroid peroxidase among others. However, as this study was reported as a letter to the editor with insufficient information on methodology, inter-species antigenic variability, in vitro design,

any correlation with observed frequency of autoimmunity with COVID-19, and any correlation with rare autoimmune reactions following vaccination to allow any further extrapolation of the study findings to clinical settings is not possible. In summary, there is lack of conclusive clinical evidence for molecular mimicry, especially for ADEM.

The proposed mechanism of triggering pre-existing immune pathology by vaccines was hypothesized to the adjuvants or viral vector (eg, adenovirus vector), or the mRNA itself (Ismail and Salama 2022). However, there was insufficient information linking proof of mechanism in either a mechanism-based study or further exploration of mechanism in the same case.

The proposed mechanism of bystander activation is ascribed mainly to activation of antigen presenting cells to local dying cells in areas of tissue destruction and inflammation and thereby stimulation, activation and proliferation of autoreactive T- or B-cells eg, myelin oligodendrocyte antibody (Fujinami et al 2006; Matsumoto et al 2022; Ismail and Salama 2022). This mechanism is considered to be non-specific to any immune stimulant type.

The authors also hypothesize a possible role of immunological and genetic susceptibility in combination to vaccine-related factors as described above for the demyelination events (Ismail and Salama 2022; Lee et al 2022). However, there is insufficient information on any identification of immunological and genetic susceptibility to date.

AstraZeneca comment for mechanisms of action

The review of mechanisms proposed by the authors suggests both vaccine-specific and patient susceptibility factors. However, no conclusive evidence linking proof of mechanism in either a mechanism-based study or further exploration of mechanism in the same case was identified. No new safety signals were identified from review of literature.

Other sources

The EVDAS was used to look for any signals of disproportionate reporting (SDR). The reporting odds ratio (RoR) was evaluated on the available data up to and including 15 June 2022 (run on 21 June 2022) and a SDR (EVDAS ROR 1.06) was identified for VAXZEVRIA (ChAdOx1 NCoV 19) and 'Acute disseminated encephalomyelitis'. ADEM is a rare and serious event and when this event is compared against the drugs in EVDAS, especially in the context of global rollout of COVID-19 vaccines, it is expected to show a disproportionality. Additionally, the RoR scoring is susceptible to a number of scoring biases. Some common biases encountered with ROR scoring includes dictionary structure, notoriety bias, reporting bias and masking or cloaking. Some of these biases can be corrected by data stratification techniques but are not employed through RoR scoring. The differing regional scoring attempts to lessen some of these effects

On review of other COVID-19 vaccine labels (Summary of Product Characteristics (SmPC) and PI), none of the labels had information on PT 'Acute disseminated encephalomyelitis'.

Summary and Discussion

ADEM is an acute autoimmune multifocal demyelinating disease. Viral illnesses and vaccinations have been reported in association to ADEM It may have a life-threatening severity. Although no specific criteria exist for diagnosing ADEM, it has a broad differential and thereby the antecedent history, temporal course of the illness, neuroimaging, CSF analysis, and probably repeat imaging during remission are most important in arriving at the diagnosis and excluding other causes of encephalopathy.

On review of AstraZeneca's Global Safety Database cumulatively to 28 June 2022, a total of 80 cases of ADEM with the use of VAXZEVRIA have been received. All of the reported cases were serious. Fifty-seven (57) of the 80 cases were reported from spontaneous sources. The majority of the cases were reported after the 1st dose. None of the cases that occurred after the 1st dose were identified to have positive rechallenge or worsened after the 2nd/3rd dose. The age range was 22 to 90 years with a median of 53 years. This was well within the age range (19 to 61 years) mentioned by Schwarz et al 2001. Gender was reported in 79 cases, of which 43 (54%) cases were reported in female vaccinees suggesting a slight female preponderance.

Overall, 56 (70%) of the 80 cases were medically confirmed. In 46 (57.5%) cases, ADEM was reported to cause hospitalization and in 45 (56.3%) cases ADEM was considered a medically important event. In 27 (33.8%) cases the events had a favorable outcome ie, recovering/resolving/resolved. Five (5; 6.3%) cases had a fatal outcome. In the 5 fatal cases, the WHO-UMC causality was considered as "Possible" with limited information in 1 case, "Possible" with confounders in 1 case, "Unlikely" in 2 cases, and "Unassessable" in 1 case. Two (2) cases met BCC level 2 and 1 case met BCC level 1. No significant safety concerns were seen on review of ADEM cases with fatal outcome. In 25 (31.3%) cases the outcome was not recovered. The case fatality rate of 6.3% is in line with previously document case fatality rates in ADEM (5% to 50%; Borlot et al 2011).

Out of the 80 cases, 3 (3.8%) fulfilled BCC level 1, 26 (32.5%) fulfilled BCC level 2, 5 (6.3%) fulfilled BCC level 3, which fulfilled the diagnostic criteria for certainty. Of the 3 cases fulfilling BCC level 1, 2 cases were assessed as "Possible" with limited information and 1 case was assessed as "Unlikely" per the WHO-UMC causality assessment criteria.

Of the 80 cases, TTO was reported in 50 (62.5%) cases and the median TTO was 8 days. The O/E analysis of all ADEM cases suggested that there was insufficient information to make any causality assessment from the groups where observed cases were above expected. On review of the 56 (70%) medically confirmed cases, 25 (44.6%) cases met BCC level 1 to 3 and the WHO-UMC causality was assessed as "Possible" with confounders in 12 (48%) cases, "Possible" with limited information in 6 (24%) cases and "Unlikely" in 4 (16%) cases. The remaining 3 cases (12%) had insufficient case details for a comprehensive causal assessment. Amongst 56 medically confirmed cases for ADEM, 24 (42.9%) were identified either with relevant risk/confounding factors.

There were no events of Acute disseminated encephalomyelitis' from the pre-clinical and clinical studies. The O/E analysis of all ADEM cases suggested that overall, the observed numbers were significantly less than the expected numbers in the 42-day risk windows. The observed numbers were greater than expected in a few sub group stratifications and may be explained by reporting bias for increased reporting of cases with a shorter risk window for the passive event reporting of rare diseases. Review of cases in these subgroups where observed numbers were above expected showed that most cases had insufficient information to make any causality assessment. On review of the PT 'Acute disseminated encephalomyelitis' in EudraVigilance database (EVDAS), it exceeded the disproportionality assessment threshold. ADEM is a rare and serious event and when this event is compared against the drugs in EVDAS, especially in the context of global rollout of COVID-19 vaccines, it is expected to show a disproportionality. Therefore, this finding is not considered significant. A trend analysis was conducted of case reports over time. The analysis identified a peak in reporting in March/April and November/December 2021, which may be due to the prevalence of COVID-19 infection in the community as it coincided with COVID-19 pandemic peaks rather than with vaccine exposure. AstraZeneca does not consider the trend analysis to be suggestive of increased risk due to VAXZEVRIA.

On cumulative review of the literature to 28 June 2022, there is insufficient evidence to establish a causality or any conclusive mechanism of action, and in addition, did not identify any new safety information for ADEM and VAXZEVRIA The review of mechanism of action articles and case reports found no conclusive evidence linking proof of mechanism in either a mechanism-based study or further exploration of mechanism in the same case were identified. No new safety signals were identified from review of literature.

AstraZeneca's review of the cases in the safety database, O/E analysis, clinical and pre-clinical databases, external databases, and competitor labels does not bring any new information that will alter the current benefit-risk profile for the event 'Acute disseminated encephalomyelitis' in association with VAXZEVRIA. As is already stated in Section 4.4 of the CDS that neurological events, which includes demyelinating disorders, are very rare events reported following vaccination with VAXZEVRIA. A causal relationship has not been established. As with other vaccines, the benefits and potential risks of vaccinating individuals with VAXZEVRIA should be considered. AstraZeneca's review of the cases in the safety database, O/E analysis, clinical and pre-clinical databases, external databases, and competitor labels does not bring any new information that will alter the current benefit-risk profile for the event 'Acute disseminated encephalomyelitis' in association with VAXZEVRIA. As is already stated in Section 4.4 of the CDS that neurological events, which includes demyelinating disorders, are very rare events reported following vaccination with VAXZEVRIA. A causal relationship has not been established. As with other vaccines, the benefits and potential risks of vaccinating individuals with VAXZEVRIA should be considered.

Conclusion

AstraZeneca's review of the cases in the safety database, O/E analysis, clinical and pre-clinical databases, literature and external databases does not bring any new information that will alter the current benefit-risk profile for the event 'Acute disseminated encephalomyelitis' in association with VAXZEVRIA. As is already stated in Section 4.4 of the CDS that neurological events, which includes demyelinating disorders such as Guillain-Barré Syndrome (GBS), are very rare events reported following vaccination with VAXZEVRIA. A causal relationship has not been established. As with other vaccines, the benefits and potential risks of vaccinating individuals with VAXZEVRIA should be considered. Therefore, AstraZeneca considers that no updates to CDS or RMP are required.

ADEM will continue to be closely monitored as part of AstraZeneca's ongoing surveillance efforts for the important potential risk of nervous system disorders, including immune-mediated neurological conditions.

15.2.13 Viral reactivation (Non-Zoster)

In the assessment report received from the Pharmacovigilance Risk Assessment Committee (PRAC) EMA (EMEA/H/C/PSUSA/00010912/202112) for the VAXZEVRIA PBRER (review period 29 June 2021 – 28 Dec 2021), further information on the topic of Viral reactivation (non-Zoster) is requested as follows:

The MAH is asked to provide:
• An overview cumulative review of viral reactivation (in the HLGT "Viral infectious disorders") from all available sources in the next PSUR, including details of the underlying condition(s), concomitant treatments, time to onset, duration, outcome and an assessment of the causal relationship with the vaccine
• A discussion on the need for any potential amendment to the product information, as appropriate or other risk minimisation measures

Also 4 confirmed serious cases of Viral reactivation (Non-Zoster) highlighted by PRAC were referenced in the assessment report. These cases have been summarised in Table 149.

Global Patient Safety Database

A cumulative search till DLP 28 Jun 2022 of the AstraZeneca Global Safety Database for Viral Infectious Disorders with VAXZEVRIA was performed using MedDRA version 25.0 in the AE High Level Group Term "Viral Infectious Disorders". The search retrieved a total of 53,252 events of viral infections occurring post vaccine and included 152 PTs. The PTs were reviewed to only include cases with viruses (viral infections) that have the potential to cause both latent and lytic cycles of replication, and to exclude zoster viruses (herpes zoster infections).

Based on this strategy 98 PTs were excluded and the following 54 PTs were included as part of the search which yielded 935 cases: Herpes virus infection; Herpes simplex; Genital herpes; Infectious mononucleosis; Herpes ophthalmic; Nasal herpes; Skin papilloma; Meningitis viral; Herpes simplex reactivation; Epstein-Barr virus (EBV) infection; Mumps;

Epstein-Barr virus infection reactivation; Exanthema subitum ; Encephalitis viral; Eczema herpeticum; Herpes dermatitis; Anogenital warts; Viral myocarditis; Cytomegalovirus infection; Ophthalmic herpes simplex; Viral pericarditis; Papilloma viral infection; Meningoencephalitis viral; Hepatitis viral; Herpes simplex meningitis; Genital herpes simplex; Meningoencephalitis herpetic; Herpes simplex encephalitis; Herpetic radiculopathy; Epstein Barr virus positive mucocutaneous ulcer; Meningitis coxsackie viral; Adenovirus infection; Progressive multifocal leukoencephalopathy; Cytomegalovirus infection reactivation; Hepatitis C; Hepatitis infectious mononucleosis; T-cell lymphoma; Human herpesvirus 6 infection reactivation; Colitis herpes; Cervix warts; Herpes pharyngitis; Epstein-Barr viraemia; Parvovirus B19 infection; Viral myelitis; Kaposi's sarcoma; Pneumonia adenoviral; Keratitis viral; T-cell type acute leukaemia; Coxsackie viral infection; Herpes simplex hepatitis; Erythema infectiosum; Cytomegalovirus hepatitis; Chronic hepatitis B; and Encephalitis cytomegalovirus.

55 of 935 cases were assessed as Viral Reactivation (Non-Zoster) based on the medical history, laboratory data (eg, Polymerase chain reaction for HSV) and other relevant information (eg, clinical course of the event).

One additional case from literature by Tang et al 2021 (case ID [redacted]) (assessed as Viral Reactivation (Non-Zoster)) was identified and included in the review, hence the total cases are 56.

Clinical Study Data

A search was conducted in the AstraZeneca Clinical database for serious adverse events (SAEs) of viral reactivation excluding zoster viruses in association with the use of VAXZEVRIA (formerly AZD1222) reported from all completed and ongoing clinical studies with data cut-off 29 June 2022 for ongoing studies. The search utilized the Medical Dictionary for Regulatory Activities (MedDRA; version 25.0) with the above-mentioned PTs. An additional search was conducted in the AstraZeneca Clinical database for participants with a medical history of viral reactivation with the same search strategy.

Although a total of 750 subjects had a medical history of viral diseases in the clinical trials with the use of VAXZEVRIA (formerly AZD1222), the search yielded 5 cases of SAEs in which patients experienced viral infection; however, none of them were assessed as viral reactivation.

Non-clinical data

Data from the VAXZEVRIA pre-clinical safety database was searched and no information of the viral reactivation was found.

Post-Marketing

The case source distribution for Viral reactivation (Non-Zoster) cumulatively through DLP 28 June 2022 is presented in Table 145:

Table 145 Case reports of Viral reactivation (Non-Zoster) received with VAXZEVRIA cumulatively through DLP by reporting source and seriousness

Classification of case report source	Non-serious cases	Serious cases	Grand Total
Clinical Trial	0	0	0
Spontaneous[a]	2	46	48
Literature	2	5	7
Non-interventional/post-marketing study	0	1	1
Grand Total	**4**	**52**	**56**

[a] Of the 48 Spontaneous case reports, 47 (98%) were from Regulatory source.

The following Table 146 below presents number and percentage (%) of case reports of Viral reactivation (Non-Zoster) after respective doses cumulatively through DLP (28 June 2022):

Table 146 Number and percentage (%) of the case reports of Viral reactivation (Non-Zoster) after respective doses of VAXZEVRIA cumulatively

No of Cases (After First Dose)	No of Cases (After Second Dose)	No of Cases (After both First and Second Dose)	No of Cases (After Third Dose)	No of Cases (Dose number Unknown)
14 (25%)	5 (8.9%)	1 (1.8%)	0 (0.0%)	36 (64.3%)

These case reports were reported most frequently in the following countries: 33 (58.9%) were from the United Kingdom, 7 (12.5%) from France, 4 (7.1%) from Germany, 2 (3.6%) from Iran, 2 (3.6%) from Italy - 1 (1.9%) each from Australia, Brazil, Estonia, Iran, Luxembourg, Spain and the United States.

The following observations were made from a review of the 56 case reports pertaining to Viral reactivation (Non-Zoster):

- Vaccinee age was reported in 52 case reports and ranged 22 to 88 years (median: 51 years).
- Vaccinee gender was reported in 54 case reports. Of these case reports, 41 % (23) were male and 55% (31) were female.
- 18 (32%) case reports were medically confirmed and 38 (67.9%) were non-medically confirmed (consumer reports).
- 44 of the 56 cases had information of time to onset (TTO) and ranged 0-85 days (median: 4 days).

  TTO is further presented in the following Table 147 accordingly:

Table 147 TTO for Viral reactivation (Non-Zoster) cumulatively through DLP 28 June 2022

TTO (Days)	No of Cases	Percentage (%) *
0 to 1	15	29.4
2 to 5	13	25.5
6 to 11	10	19.6
12 to 16	5	9.8
17 to 21	4	7.8
>21 days**	4	7.8
Unknown	5	9.8

*TTO was reported for 51 case reports (*total number of cases*) used to calculate the percentage.** Risk window for Viral reactivation (Non Zoster) is 21 days.
Where multiple TTOs in a case were present, the shortest TTO was taken.

In the 56 cases, 67 events of interest were reported. The adverse events PTs reported for Viral reactivation (Non-Zoster) cumulatively through DLP 28 June 2022 are presented in Table 148 below:

Table 148 Distribution of most frequently reported events of interest in case reports for Viral reactivation (Non-Zoster) cumulatively

Adverse events (PT)	Non -serious	Serious	Total number of Cases	Percentage (%)
Meningitis viral	0	10	10	14.9
Epstein-Barr virus infection reactivation	2	6	8	11.9
Genital herpes	0	7	7	10.4
Herpes ophthalmic	0	7	7	10.4
Herpes simplex	1	4	5	7.5
Herpes simplex reactivation	1	4	5	7.5
Oral herpes	0	4	4	6.0
Encephalitis viral	0	3	3	4.5
Viral pericarditis	0	3	3	4.5
Encephalitis	0	2	2	3.0
Mumps	0	2	2	3.0
Chronic hepatitis B	0	1	1	1.5
Cytomegalovirus infection reactivation	0	1	1	1.5
Epstein-Barr Virus Test positive	0	1	1	1.5
Hepatitis E	0	1	1	1.5
Herpes simplex encephalitis	0	1	1	1.5

Table 148 Distribution of most frequently reported events of interest in case reports for Viral reactivation (Non-Zoster) cumulatively

Adverse events (PT)	Non -serious	Serious	Total number of Cases	Percentage (%)
Keratitis	0	1	1	1.5
Meningitis	0	1	1	1.5
Noninfective gingivitis	0	1	1	1.5
Ophthalmic herpes simplex	0	1	1	1.5
Pericarditis	0	1	1	1.5
Viral myocarditis	0	1	1	1.5

Upon review of these cases, the following observations made cumulatively through DLP 28 June 2022:

- 63 (94.0%) of the events were reported as serious (23 medically confirmed and 44 non-medically confirmed) The seriousness criteria were reported as follows: medically important event (41 [65.0%]), disability (7 [11.1%]), hospitalization (23 [36.5%]), life threatening (3 [4.8%]) and death (1 [1.6%]). No event had seriousness criteria of congenital anomaly. An event may have met more than one criterion for seriousness. The remaining 4 (6.2%) events were non-serious (2 medically confirmed and 2 non-medically confirmed).
- Of the 67 events, the outcome was reported as recovered or recovering (32 [47.8%]), not recovered (14 [20.9]) and fatal (1 [1.5%]). The outcome of the remaining events (20 [30%]) were reported as unknown or not reported.
- Amongst 11 events with reported outcome 'recovered' the event duration was reported in (3 [27.3%]) events. The mean duration was eight days. One (9.0%) event resolved within 7 days and the remaining 2 (18.2%) events resolved after 7 days.

Cases highlighted by PRAC reported to the [redacted] pharmacovigilance system

PRAC highlighted 10 confirmed case reports of viral reactivation (except zoster virus): [redacted] and [redacted]. The case [redacted] was not in the AstraZeneca Global Safety Database at the time of the DLP. And the case [redacted] (case ID [redacted]) was suppressed as not an AstraZeneca Product. Of the remaining 8 cases 4 cases were reported as non-serious and 4 cases were reported as serious and medically confirmed. Serious medically confirmed cases have been summarized below with AstraZeneca assessment.

Table 149 Summary of Serious Viral Reactivation (Non-Zoster) cases highlighted by PRAC in the assessment report

No	WWI/Case ID/Medically confirmed - Y/N	Age (Years)/Gender (M/F)	Risk factors - Relevant comorbidities and concomitant medications	Dose # / Time to Onset (days)	Event / Outcome	WHO-UMC Causality Assessment	AstraZeneca comment
1	[redacted] / Y	62/ M	Dental surgery, myocardial infarction	Unknown/ 1	EBV infection reactivation/ Recovering	Possible; with limited information	The patient had a history of dental surgery and myocardial infarction. No concomitant medications were reported. The reactivation of the EBV infection was reported on the next day of vaccination, however, the information about the previous EBV infection, baseline status, and/or confirming lab data were not provided.
2	[redacted] / Y	82/ F	Autoimmune hypothyroidism, Lupus erythematosis disseminated, Antiphospholipid syndrome, Pyelonephritis, Chronic cystitis, Capsulitis of shoulder	Unknown/ 12	EBV infection reactivation/ Recovering	Possible; with alternate cause or confounders	The patient had a history of multiple autoimmune and infectious diseases; however, no relevant concomitant medications were reported. The reactivation of the EBV infection was reported, however, the information about the previous EBV infection, baseline status, and/or confirming lab data were not provided.
3	[redacted] / Y	60/ M	Unknown/Unknown	Unknown/Unknown	Hepatitis E/ Recovering	Unassessable/ Unclassifiable with limited information	TTO unknown, lack of information on relevant medical history and concomitant medications.
4	[redacted] Y	64/ M	Unknown/Unknown	Unknown/ 9	Hepatitis E/ Not recovered	Possible; with limited information	The patient had a history of type 2 diabetes; however, no relevant concomitant medications were reported. The reactivation of the Hepatitis E infection was reported, however, the information about the previous Hepatitis E infection and/or confirming lab data were not provided.

Fatal

Of the 56 cases reporting Viral reactivation (Non-Zoster), there was one case of death however the outcome of the event under review (PT: Chronic hepatitis B) was reported as unknown. This case which was medically confirmed is summarized below.

Case [redacted]: A spontaneous serious and medically confirmed case from Estonia (EMA) where a 31-old male patient with a medical history of chronic hepatitis B (HBV), type 2 diabetes mellitus (T2DM), hypertension and migraine died from the event of disseminated intravascular coagulation, ischaemic stroke (confirmed at autopsy), ten days after vaccination with VAXZEVRIA. A CT scan preformed on 27 February 2021 showed: thrombosis of arteria carotis interna (ACI) and arteria cerebri media (ACM). The patient has been tested negative for COVID 19 virus. On 01 March 2021, the platelet count was Thrombocytopaenia up to 5 E9/L. Other diagnostic tests performed were P-HBV DNA QN 492 IU/ml, HBsAg positive, HBsAb QN negative, HBsAb 2 IU/L, HBc IgM negative, HBcAb positive, HBeAg negative, HBeAB positive. The reporter assessed the events disseminated intravascular coagulation, ischaemic stroke, severe thrombocytopenia, severe headache, chronic hepatitis b, brain edema, fever, pyrexia, as serious medical condition that required hospitalization and ischemic stroke to be serious due to seriousness criteria of death. The outcome was fatal for the events of ischemic stroke and disseminated intravascular coagulation.

AstraZeneca comment: In this case although the P-HBV DNA QN level of 492 IU/ml was indicted, a viral reactivation could not be comprehensively confirmed as there was insufficient information on previous HBV DNA status (patient had chronic Hepatitis B). The case was assessed as Possible (with limited information) according to WHO-UMC criteria.

Rechallenge / Recurrence case reports

Cumulatively through 28 June 2022, 1 (1.8%) of 56 case reports was reported as rechallenge/recurrence case.

Pedrazini et al 2022 **Case** [redacted]: This case is a 60-year-old patient who experienced Herpes simplex type I reactivation after the first dose, and a positive recurrence or worsening of Herpes simplex type I reactivation with the second dose of vaccination indicating potential positive recurrence / rechallenge. The case was medically confirmed, non-serious report from a literature. The case was identified within the risk window of 21 days. The patient's medical history included latent HHV-1. The author stated the patient presented with herpetic labial lesion after 7 days of the first and second dose, in the same location as previous episodes 2 year before the vaccine. The outcome was reported as recovering (patient has had a remission).

AstraZeneca comment: There was no further information on investigations to confirm lytic phase of the virus (eg: DNA copies). The patient's immune status, relevant medical history or concomitant medications, surgical procedures, or any exposure to close contacts are unknown

to preclude a proper assessment. The case was assessed as Possible (with limited information) according to WHO-UMC causality.

WHO-UMC causality analysis

Of the total 56 case reports identified cumulatively through 28 June 2022, 18 (28.3%) case reports were medically confirmed (16 serious and 2 non-serious), and WHO-UMC causality was further assessed below with 21 days risk window.

Table 150 Overview of WHO-UMC Causality Assessment of Viral reactivation (Non-Zoster) cases with VAXZEVRIA reported cumulatively through 28 June 2022

WHO-UMC Causality category	WHO-UMC Causality assessment scale (AZ adapted)	Number of Cases
Certain	Certain	0
Probable-Likely	Probable-Likely	1
Possible	Possible with risk factors/confounders*	13
	Possible with Limited information	38
Unlikely	Unlikely	4
Conditional /Unclassified	Conditional / Unclassified	0
Unassessable/Unclassifiable	Unassessable/Unclassifiable with risk factors/confounders*	0
	Unassessable/Unclassifiable with limited information	**0**
	Total	**56**

Cases were considered to have "risk factors/confounders" where the event could also be explained by the vaccinee's diseases, or where relevant risk factors were present, or concomitant medications that could potentially contribute to the development of the event were reported.

For 13 cases assessed as Possible (with risk factors/confounders) the following relevant risk / confounding factors were identified: autoimmune hypothyroidism, lupus erythematosus disseminated, pyelonephritis, chronic cystitis, capsulitis of shoulder, orthotopic heart transplantation, tooth abscess, end-stage renal disease, haemodialysis, immunosuppressants, type 2 diabetes, viral encephalitis, viral meningitis, radiotherapy, breast cancer, eczema, vitiligo, and Hashimoto's thyroiditis.

There was one report (case no. [redacted]) assessed as Probable-likely according to WHO-UMC criteria. The case was from literature and is summarised below:

Literature case [redacted] (Marlene et al 2021), *also highlighted by PRAC*: A case report concerns a 67-years-old female patient. The patient had a past medical history of atrial fibrillation, hypertension, obesity, degenerative knee joint disease, and no documented history of COVID-19 infection. Patient received first dose of ChAdOx1 nCoV-19 vaccination

(TTO of 14 days). The patient had no allergies, no history of immune deficiency, or recent infectious disease. Patient denied the use of illicit drug. Two weeks after vaccination, the patient suffered from fever, weakness and arthralgia of the knees, hips and shoulders. Because both, antibiotic treatment with piperacillin/tazobactam and steroids did not improve clinical symptoms with persistent fever and weakness, the patient was hospitalized with stable vital parameters and normal physical examination. CT scans of the chest and abdomen revealed reactive mediastinal lymphadenopathy and hepatic steatosis. A repeat nasopharyngeal swab for Sars-Cov-2 RNA testing by polymerase chain reaction (PCR) was negative. Serological examination excluded HBV, hepatitis C virus (HCV), hepatitis E virus (HEV) infection, and HIV. Cardiac magnetic resonance imaging (MRI) confirmed diagnosis of pericarditis with circumferential thickening and contrast enhancement of the entire pericardium at late gadolinium enhancement. Based on these imaging findings, heart involvement with viral pericarditis was suspected. EBV serology was compatible with past infection (anti-EBV-VCA-IgG: positive, anti-EBV-IgM: negative), confirmed by PCR with no detectable EBV-DNA. However, serology of CMV was compatible with active CMV infection (anti-CMV-IgG: greater than 250 IU/mL, anti-CMVIgM: positive), confirmed by PCR with detectable CMV viremia (415 IU/mL). The patient recovered from the events of reactivation of cytomegalovirus infection and pericarditis. Authors Comment: The clinical course of a patient with CMV reactivation and pericarditis in temporal association with ChAdOx1 nCoV-19 vaccination against SARSCoV-2.

AstraZeneca comment: Patient had viral serology findings suggesting past infection of EBV and CMV. Both these viruses are known to have latent and lytic phases. However, reactivation of only one virus was seen (CMV). This can also be explained by viral derived factors (such as its known natural history). In addition, it's known that this elderly patient has a history of obesity and degenerative knee joint disease, however, at the time of the event there is a limited information about her concomitant medications. It is also unknown how long the patient took antibacterial and steroid therapy, which can lead to suppression of immunity before her admission to the hospital and serological testing. Based on WHO-UMC classification, the causality assessment is Probable. Association between the event and VAXZEVRIA cannot be ruled out.

Overall, the review of medically confirmed cases did not raise any new relevant safety information for VAXZEVRIA.

Literature

AstraZeneca conducted a cumulative search of the literature to identify any articles in Embase, InsightMeme, and PubMed published from 29 December 2020 to 28 June 2022 identifying literature of viral reactivation in association with VAXZEVRIA and other COVID-19 vaccines using the following search terms:

Herpes virus infection; Herpes simplex; Genital herpes; Infectious mononucleosis; Herpes ophthalmic; Nasal herpes; Skin papilloma; Meningitis viral; Herpes simplex reactivation; Epstein-Barr virus infection; Mumps; Epstein-Barr virus infection reactivation; Exanthema

subitum ; Encephalitis viral; Eczema herpeticum; Herpes dermatitis; Anogenital warts; Viral myocarditis; Cytomegalovirus infection; Ophthalmic herpes simplex; Viral pericarditis; Papilloma viral infection; Meningoencephalitis viral; Hepatitis viral; Herpes simplex meningitis; Genital herpes simplex; Meningoencephalitis herpetic; Herpes simplex encephalitis; Herpetic radiculopathy; Epstein Barr virus positive mucocutaneous ulcer; Meningitis coxsackie viral; Adenovirus infection; Progressive multifocal leukoencephalopathy; Cytomegalovirus infection reactivation; Hepatitis C; Hepatitis infectious mononucleosis; T-cell lymphoma; Human herpesvirus 6 infection reactivation; Colitis herpes; Cervix warts; Herpes pharyngitis; Epstein-Barr viraemia; Parvovirus B19 infection; Viral myelitis; Kaposi's sarcoma; Pneumonia adenoviral; Keratitis viral; T-cell type acute leukaemia; Coxsackie viral infection; Herpes simplex hepatitis; Erythema infectiosum; Cytomegalovirus hepatitis; Chronic hepatitis B; Encephalitis cytomegalovirus.

On using the above search criteria, 765 articles were identified. Of these, 758 articles were considered irrelevant for further discussion and presentation based on the topic of interest "virus reactivation in association with VAXZEVRIA and other COVID19 vaccines" and strength of evidence: study type (systematic reviews / meta-analyses / randomized controlled trials), study population, size and design, limitations, overall impact, and conflict of interest.

Seven literature case reports and case series describing the use of VAXZEVRIA identified through this literature review were also registered within the Global Safety Database. One of these 7 cases assessed as Probable-likely according to WHO-UMC assessment was discussed above in respective subsection. One of the remaining 6 has been discussed under Rechallenge / Recurrence case reports section. The remaining 5 cases are discussed below.

Ardalan M et al 2022 **(case ID** [redacted]**)** In this case report authors describe a 28- year-old man, with no systemic disease, presented with herpes-like skin lesions on his right upper eyelid 2 days following the first dose of ChAdOx1 nCoV-19 vaccine. The patient reported a post-trauma history of a herpes simplex virus (HSV) infection of the right eye in his childhood. According to the patient, he has experienced periods of cold sore (herpes simplex labialis) ever since. Treatment was started based on the diagnosis of recurrent HSV lesion of the upper eyelid. Seven days after the onset of the lesion, signs and symptoms disappeared.

AstraZeneca comment: There is limited information on patient concomitant medications, medical history, and presence of any alternate viral reactivation triggers that precluded a proper assessment. The case was assessed as Possible (with limited information) according to WHO-UMC criteria.

Ashod Kherlopian and Gayle Fischer 2022 **(case ID** [redacted]**)** In this case series report of HSV infection following COVID-19 vaccination. HSV status was confirmed by PCR of lesioned skin swabs. Demographic and clinical characteristics were assessed, which include age, ethnicity, time between COVID-19 vaccination and the development of mucocutaneous HSV infection and relevant comorbidities. The onset of cutaneous changes due to occult HSV infection occurred between 1 to 7 days following COVID-19 vaccination. In 2 patients, the COVID-19 vaccine received was the Pfizer (Comirnaty) vaccine, whilst in the other the

vaccine administered was VAXZEVRIA. All three patients were treated with antivirals, made a full recovery and were subsequently discharged home.

AstraZeneca comment: There is limited information on event details, patient concomitant medications, medical history, and presence of any alternate viral reactivation triggers that precluded a proper assessment. The case was assessed as Possible (with limited information) according to WHO-UMC criteria.

Moslemi, Mohammadreza, et al 2022 **(case ID [redacted])** In this case report article authors present a case of herpes simplex encephalitis (HSE) in a 27-year-old male patient with no underlying systemic conditions and no prior history of herpes simplex virus (HSV) and COVID-19 infection who received his first dose of ChAdOx1 nCoV-19 COVID-19 vaccine (AZD1222) 8 days prior to being referred to the clinic. Neurological examination revealed altered mental status and decreased level of consciousness, and disorientation. Following examination revealed elevated temperature of 38.9 ºC (102.02 °F) and leukocytosis (12,900/mm3). Laboratory tests were all in normal ranges. However, antiviral therapy was started based on patient clinical symptoms and his medical history. Decreased protein levels (3.05 mg/dl) in CSF analysis with the predominance of lymphocyte, and normal glucose levels were suggestive of a viral encephalitis. The final diagnosis was made after polymerase chain reaction (PCR) showed a positive result for HSV in the CSF. The patient was discharged with clinical improvement on the 21st day. However, authors concluded that regarding the correlation of the ChAdOx1 nov-19 vaccine and herpes simplex encephalitis is unattainable due to scarcity of similar evidence. Author's proposed potential Mechanism of action when the vaccine can initiate cytokine release and an immune response cascade in a similar fashion to viral infections of SARS-CoV-2 itself and further upregulation of NKG2D ligands and reactivation of the HSV from its latent phase and development of the clinical signs and symptoms of herpetic infections.

AstraZeneca comment: There is a limited information on patient concomitant medications, patient comorbidities, inflammatory and/or infectious disease, sinus surgery, ophthalmic or dental invasive procedures before vaccination which could be one of the triggers of developing HSE. A possible mechanism was also described within this article. However, this hypothesis has not been verified. To date, no conclusive mechanism of action leading to viral reactivation after COVID-19 vaccination has been identified. Furthermore, the mechanism as applicable to AZD1222 remains unclear. The case was assessed as Possible (with limited information) according to WHO-UMC criteria.

Singh et al 2022 **(case ID [redacted])** In this case report article authors present a case of herpes simplex (HSV) retinitis in 29-year-old male two days following the first dose of the Covishield vaccine. Since the blood serologies were all negative, a diagnostic vitrectomy was performed and the vitreous sample for viral PCR came positive for HSV-1. At 6-week follow-up, the patient improved with a near-complete resolution of retinitis after the course of antiviral therapy.

AstraZeneca comment: There is a limited information on patient concomitant medications, medical history, and presence of any alternate viral reactivation triggers that precluded a proper assessment. The case was assessed as Possible (with limited information) according to WHO-UMC criteria.

Tang et al 2021 **(case ID** [redacted]**)** In this article authors report a case of a heart transplant recipient who presented with a rapidly growing Epstein-Barr virus–positive, diffuse large B-cell lymphoma in a 51-year-old man 7 days after receiving the first dose of the ChAdOx1 nCoV-19 vaccine. He had been diagnosed with idiopathic dilated cardiomyopathy and received an orthotopic heart transplantation on [redacted], 2014. He developed end-stage renal disease and required haemodialysis in December 2018. His recent immunosuppressant regimen included tacrolimus and mycophenolate mofetil. Authors are not able to exclude the coincidence of COVID-19 vaccination and the development of posttransplant lymphoproliferative disorder (PTLD) in this case.

AstraZeneca comment: As authors have confirmed the pathogenesis of PTLD is closely associated with infection or reactivation of EBV in the context of chronic immunosuppression as the main predisposing factor. At the time of admission, the patient was on complex immunosuppressants and hemodialysis, which may predispose to the growth of lymphoma. EBV PCR of serum was negative 2 months before patient's admission to the clinic. There is limited information on circumstances leading to events, patient´s baseline health status prior vaccination, the evaluation did not find evidence to suggest a causal relationship between EBV contamination and vaccine. The case was assessed as Possible (has alternative explanations, risk factors) according to WHO-UMC criteria.

Summary

Overall medical summary of all case reports

Cumulatively through DLP 28 June 2022 a total of 56 reports of Viral reactivation (Non-Zoster) with the use of VAXZEVRIA have been received, of which 92.9% of the reported events were serious. The age range was 22 to 88 years and mean and median age was reported as 51 years and 49.5 years, respectively. The cases were predominantly in females (55.4%).

Of the 56 reports, 25.0% of cases of Viral reactivation (Non-Zoster) occurred after the first dose and 8.9% after the second dose. The dose number was unknown in 64.3% of cases.

One case (1.8%) was reported with a fatal outcome, however, the cause of death confirmed by autopsy was an ischaemic stroke, co-reported hepatitis B assessed by reporter as serious due to hospitalization, ischemic stroke was also assessed as a life-threatening event, a viral reactivation could not be comprehensively confirmed as there was insufficient information on previous HBV DNA status. Two more events were reported as life threatening. The first event of hepatitis E was reported as a life threatening, however, a viral reactivation could not be comprehensively confirmed as there was insufficient information on previous hepatitis E

history. The second event of herpes simplex encephalitis was reported by consumer as a life threatening, however, there is a limited information on patient concomitant medications and comorbidities that precluded a proper assessment.

Of the 56 cases, 38 (67.9%) were assessed as "Possible with Limited information" and 13 (23.2%) as "Possible with risk factors/confounders". One case (1.8%) was considered "Probable-Likely". Although the patient had viral serology findings suggesting past infection of EBV and CMV, both viruses are known to have latent and lytic phases. Reactivation of only one virus was seen (CMV) and can be explained by viral derived factors (such as its known natural history). The remaining four cases (7.1%) were assessed as "Unlikely".

Of the four serious cases highlighted by PRAC reported to the French pharmacovigilance system, two were assessed as "Possible; with limited information", one as "Possible; with alternate cause or confounders", and one as "Unassessable/Unclassifiable with limited information".

Overall, none of the case reports raised any new relevant safety concerns for Viral Reactivation (Non-zoster) cumulatively till 28 June 2022.

Literature summary

AstraZeneca performed a cumulative review of the literature in Embase, InsightMeme, and PubMed published from 29 December 2020 to 28 June 2022 identifying literature of viral reactivation in association with VAXZEVRIA and other COVID19 vaccines and 765 articles were identified. Of these, 758 articles were considered irrelevant for further evaluation and presentation based on the topic of interest "virus reactivation in association with VAXZEVRIA and other COVID19 vaccines".

Seven literature case reports of viral reactivation were identified; the cases were reviewed as part of Global Safety Database review. On review of any remaining case report articles, no new safety concerns were identified.

Conclusion

Based on the review of the currently available cumulative data, AstraZeneca considers that there is insufficient evidence to suggest a causal association with VAXZEVRIA.It is AstraZeneca's opinion that no changes to the CDS or RMP on this topic are warranted at this time. Viral reactivation will continue to be monitored as part of AstraZeneca's routine surveillance activities. AstraZeneca will no longer discuss the topic future PBRERs, unless significant new safety information arises.

15.2.14 Cutaneous Vasculitis

The MAH is requested to submit:

- *A cumulative review of the cases of cutaneous vasculitis published in the literature after vaccination with VAXZEVRIA. The literature search should update the list of articles already retrieved by EMA. The search strategy should be explained.*
- *A cumulative review of the reported cases of cutaneous vasculitis.*
- *A discussion on the possible mechanisms of action that could lead to Cutaneous vasculitis after vaccination with VAXZEVRIA.*
- *A discussion on the need to update VAXZEVRIA product information for Cutaneous vasculitis.*

Complete evaluation of signal of Cutaneous vasculitis is presented in Appendix 16 and conclusions are presented in Section 14.

15.2.15 Thrombosis with Thrombocytopenia Syndrome

AstraZeneca received the following requests from Health Canada on thrombosis with thrombocytopenia syndrome:

As part of Health Canada's efforts to minimize health risk factors to Canadians while maximizing the safety provided by the regulatory system for health products, the Marketed Health Products Directorate (MHPD) is conducting a comprehensive review on thrombosis with thrombocytopenia syndrome to determine whether there is a need for additional risk minimization measures in Canada for the VAXZEVRIA *COVID-19 Vaccine (ChAdOxS-1 [Recombinant]).*
In accordance with the Risk Management Plan Terms and Conditions, imposed under Section C.01.014.21 (1.1) of the Food and Drug Regulations, AstraZeneca Canada Inc. is required to submit the following information:

Question 1

Provide a Cumulative Review of thrombosis with thrombocytopenia syndrome including causality assessment of all individual reports from clinical trials, post-market use, and literature.

a. *Review of data from ongoing clinical trials and observational studies stratified by age and gender, if possible.*
b. *Review of data from post-authorization use from all available sources including MAH safety database and published literature by age strata (18-29, 30-39, 40-49, 50-64, ≥65 years), sex, dose received, different dose interval, time to onset, outcomes, and any other relevant descriptive information.*
c. *Brighton collaboration Case Definition and CDC Case Definition should be considered.*
d. *Use the WHO-UMC system for standardized case causality assessment.*
e. *Update of the Observed versus Expected analyses by age strata (18-29, 30-39, 40-49, 50-64, ≥65 years), and sex.*

AstraZeneca's Response

a. There were no TTS events observed in the ongoing/completed VAXZEVRIA clinical trials (see section 7). Observational studies are discussed in Appendix 18, data from these studies showed increased risk of TTS following vaccination with the first dose of VAXZEVRIA. The highest relative risk is observed in younger age groups (Andrews et al 2022; Higgins et al 2021). However, the risk associated with AZD1222 was much lower than following SARS-CoV-2 infection.

b. AstraZeneca has conducted a cumulative review of events of TTS in the AstraZeneca Global Patient Safety Database from post-authorization use and is presented in section 16.3.2.1. The analysis is stratified by age group (18-29, 30-39, 40-49, 50-64, ≥65 years), sex, dose. TTS case reports are classified by MHRA and CDC case definitions. Also O/E analysis with the requested age stratifications and reporting rate is provided. There are limitations of using data from post-marketing passive safety surveillance systems for the definitive adjudication of TTS cases. Such data are dependent on spontaneous case reports and the information provided by the reporter; access to follow-up data is typically very limited. It is therefore difficult to apply the criteria established for clinical purposes (eg, the UK Expert Haematology Panel criteria or the Brighton Collaboration's TTS definition) to these spontaneous post-marketing reports.

c. The Brighton collaboration Case Definition, CDC Case Definition and the case definition proposed by MHRA (which is described below in item "d") have been used in the review of this topic. As the MHRA case definition results in a larger number of cases being at least possible cases compared to the CDC definition, we consider this to be the most conservative and suitable definition to use in this context. We have not additionally applied the Brighton collaboration Case Definition as the O/E analysis includes all reported cases within the relevant risk window regardless of diagnostic certainty.

d. With regard to the request to provide a cumulative review of TTS case reports using the WHO-UMC system for standardized case causality assessment, instead, AstraZeneca has an agreed approach with the MHRA to judge individual case assessments based on the criteria in the table below, which is combined with an observed vs expected analysis (which also includes all cases regardless of diagnostic certainty). This has also been applied in our routine updates on the topic to EMA.

Figure 3 Medicines and Healthcare products Regulatory Agency (MHRA) case definition for thrombosis in combination with thrombocytopenia

Confirmed	Any venous/arterial thrombosis +	Platelet count <150 x 10^9/L +	D-dimer >4000ng/mL +	Anti-PF4 Abs
Probable	Any venous/arterial thrombosis +	Platelet count <150 x 10^9/L +	D-dimer >4000ng/mL	
Possible	Any venous/arterial thrombosis +	Platelet count <150 x 10^9/L OR wording compatible with platelet count decreased		
Unlikely	Criteria met for any of the above BUT alternative diagnosis more likely to explain the event			
Criteria Not met	One or none of the criteria are met			

Although assessment of individual case definition for TTS is independent from assessment of individual case causality, we consider this approach to be a more suitable and evidence-based approach to evaluate and quantify the risk of TTS (and, as noted above, applying the MHRA definition results in a more conservative assessment than the CDC definition). We therefore have utilized this approach, rather than the WHO-UMC causality criteria, to foster a more aligned regulatory assessment on this topic.

e. Please refer to item "b" for the Observed versus Expected analyses by age strata (18-29, 30-39, 40-49, 50-64, ≥65 years), and sex.

Question 2

Discuss new information about mechanism of action, clinical definition, risk factors, at risk groups, long-term sequelae, clinical management, fatality rate, and risk minimization.
AstraZeneca's Response

Mechanism of action: The exact mechanism of thrombosis with thrombocytopenia syndrome (TTS) following immunisation with VAXZEVRIA is unknown. New information on biological mechanism of TTS was discussed in the EMA workshop on thrombosis with thrombocytopenia syndrome EMA 2022.

Cohen 2022 (AstraZeneca) hypothesized that ChAdOx1-PF4 complexes are recognized by pre-existing B-cell clones encoding "pathogenic" anti-PF4 IgG. The boosted production of TTS inducing anti-PF4 antibodies (IgG) subsequently triggers thrombosis via activation of platelets and neutrophils. Also, vaccination with VAXZEVRIA does not increase anti-PF4 levels in healthy vaccine recipients. This is in line with the in vitro binding data between PF4 and ChAdOx1 reported by Baker et al 2021. The anti-PF4 IgG will then lead to the downstream activation cascade as it has been shown that IgG from TTS patients is capable of activating platelets and neutrophils and inducing thrombosis in a murine model (hFcγRIIa/hPF4) Chong et al 2021.

Baker et al 2021, demonstrated the binding of three adenoviruses (Ad5, ChadOx1 and Ad26) to PF4. Computational modelling and Brownian dynamic simulations indicated that the interactions are not randomly distributed over the virion surface but mainly occur at the interfaces between hexons. Othman et al 2022 discuss possible mechanisms of how adenoviral vectors may cause rare VITT. (1): Adenovirus leaks into bloodstream following intramuscular injection of the vaccine, directly binds to platelet via Coxsackie and adenovirus receptor (CAR), and/or secondary receptors present on platelets, inducing platelet activation and triggering coagulation as well as liver clearance of activated platelets and thrombocytopenia. (2). The binding of adenovirus to coagulation factors such as factor X (FX), their potential activation thus triggering clot formation. (3). "Vaccine induced COVID mimicry" resulting from vaccine induced secretion of mis-spliced, C-terminal truncated spike protein into the blood, activating endothelial cells through ACE2. This initiates vascular inflammation and damage with consequent platelet activation, thrombotic events and platelet factor 4 (PF4) release. (4). Binding of adenovirus capsid to PF4. The adenovirus/PF4 complex stimulates pre-existing memory B cells against PF4, the IgG/PF4 complex then binds to Fcγ-receptor IIA (FcγRIIa) and stimulates platelet activation, and clot formation. (5). PF4-adenovirus complexes are internalized by B cells that recognize PF4. These B cells present adenoviral peptides via major histocompatibility complex class II, which are recognized pre-existing anti-vector CD4+ T cells that in turn provide T cell help to B cells, and drive their production of anti-PF4 antibodies that can stimulate platelets via FcγRIIa. (6). Impurities of human or non-structural viral proteins in vaccine preparation triggering autoantibodies such as anti-PF4m which stimulates platelet activation and clot formation. (7). Acute infection with SARS-CoV-2 following vaccine administration, modified/atypical COVID-19, presented with thrombosis and thrombocytopenia.

Huynh et al 2021demonstrated that the binding of anti-PF4 antibodies from patients with VITT was restricted to eight surface amino acids on PF4, all of which were located within the heparin-binding site, and that the binding was inhibited by heparin. By contrast, antibodies from patients with HIT bound to amino acids that corresponded to two different sites on PF4. Authors demonstrated that VITT antibodies are distinct from HIT antibodies, despite the apparent phenotypical similarity of the two diseases. These results provide an explanation for VITT-antibody-induced platelet activation that could contribute to thrombosis. For more details see section 16.3.

Clinical Case definition and clinical management guidelines: Consensus on the definition of TTS is needed to enable consistent analysis and interpretation of existing and emerging data. Currently available clinical definitions and treatment guidelines are provided in below Table 151.

Table 151 References for clinical definitions and treatment guidelines

Sponsor Agency	(Version) Date Updated	Source
ISTH	20/04/2021	https://cdn.ymaws.com/www.isth.org/resource/resmgr/ISTH_VITT_Guidance_2.pdf
AHA/ASA [3]	29/04/2021	https://www.ahajournals.org/doi/full/10.1161/STROKEAHA.121.035564
World Health Organization	(2021.1) (19/07/2021)	https://www.who.int/publications/i/item/WHO-2019-nCoV-TTS-2021.1
United Nations	11/08/2021	https://www.un.org/sites/un2.un.org/files/coronavirus_vipitguidance.pdf
UK Expert Haematology Panel	(v2.2) 31/08/2021	https://b-s-h.org.uk/media/20075/guidance-version-22-20210903.pdf
European Stroke Organisation [4]	06/09/2021	https://journals.sagepub.com/doi/10.1177/23969873211030842
Brighton Collaboration	(2b draft) 11/11/2021	https://brightoncollaboration.us/wp-content/uploads/2021/11/TTS-Updated-Brighton-Collaboration-Case-Defintion-Draft-Nov-11-2021.pdf
THSANZ	18/12/2021	https://www.thanz.org.au/documents/item/591
UK NICE	(v4.6) 27/01/2022	https://www.nice.org.uk/guidance/ng200/resources/covid19-rapid-guideline-vaccineinduced-immune-thrombocytopenia-and-thrombosis-vitt-pdf-51036811744
American Society of Hematology	(v1.8) 28/01/2022	https://www.hematology.org/covid-19/vaccine-induced-immune-thrombotic-thrombocytopenia
Australian Government	(v3) 28/02/2022	https://www.health.gov.au/sites/default/files/documents/2022/03/covid-19-vaccination-primary-care-approach-to-thrombosis-with-thrombocytopenia-syndrome-after-covid-19-astrazeneca-vaccine.pdf

TTS Thrombosis With Thrombocytopenia syndrome

Risk factors and risk groups: currently there are no known risk factors or groups for TTS/VITT. Studies are being conducted by AstraZeneca and other public health organisations to identify any potential risk factors including genetic risk factors involved in the etiology of TTS/VITT.

Long-term sequelae: A literature search was carried out, however, no information was available on long-term sequelae.

Fatality rate: Fatality rate stratified by month/year, age, gender and region are presented in Table 14 and Figure 2 in Section 16.3.2.1.

Risk minimization: there are no additional risk minimization measures for TTS during the reporting interval. Routine risk minimisation measures are considered appropriately discussed in section 4.3, 4.4 and 4.8 of the CDS and RMP.

Question 3

Provide an assessment of the benefits and the risks, stratified by sex and age, for the use of the VAXZEVRIA vaccine in the current Canadian context, taking into consideration disease projections and the epidemiology of circulating variants, and post-market reports of rare thrombotic events associated with thrombocytopenia.

AstraZeneca's Response

AstraZeneca conducted a targeted benefit-risk analysis presented below, which is based on real-world COVID-19 case, hospitalization, and death rates publicly available from the CDC, external published estimates of AZD1222 vaccine effectiveness against the Omicron and Delta variants, and AstraZeneca data regarding occurrences of TTS after AZD1222 administration. The results indicate that when administered as a 2-dose primary series, the benefits of AZD1222 continue to outweigh the serious (albeit rare) risks of TTS. While this favourable benefit: risk profile was seen across all groups 18 years of age and older, it is particularly evident in individuals 65 years of age and older.

Analysis Methods and Assumptions

Benefit

To evaluate the expected benefits of AZD1222 vaccination, the primary analysis estimates numbers of symptomatic COVID-19 cases, COVID-19 hospitalisations, and COVID-19 deaths that would be prevented over a 6-month period if 1 million adults received 2 priming doses of AZD1222. Benefits were estimated separately in adults ≥ 18, ≥ 30, ≥ 50 and ≥ 65 years of age, with the proportion of adults in each age group reflective of the age-structure of the US population (ACS 2020).

To model the benefits of primary vaccination with AZD1222 during an Omicron or Delta wave, the period when Omicron was dominant (01 January 22 – ongoing) and the period when Delta was dominant (01 July 21 – 15 December 21) were identified (GISAID 2022).

Average, age-specific event rates (cases, hospitalizations, deaths) were then calculated for each period. Rates for cases and deaths were obtained from Data.CDC.gov (CDC 2022). Hospitalization rates were obtained from COVID-NET (COVID-NET 2022).

Due to data availability, hospitalization and death rates were reported up to 26 February 2022 and case rates were reported up to 19 March 2022. Thus the period used to derive average event rates for an Omicron wave began on 01 January 2022 and ended on 19 March 2022 (though in fact the current Omicron wave is ongoing). Given that Omicron was trending upwards in March 2022, hospitalizations and death rates associated with Omicron may be underestimated relative to symptomatic cases overall.

An independent meta-analysis of clinical trials and real-world studies conducted by IHME (IHME 2022) provided the estimates of vaccine effectiveness used in our model. For a complete, two-dose primary series of AZD1222, the VE estimates assuming an Omicron wave (and regardless of age threshold) were 36% against symptomatic COVID-19 and 71% against severe COVID-19. For a Delta wave, the VE estimates were 69% against symptomatic COVID-19 and 94% against severe COVID-19. Numbers of prevented cases were calculated as follows:

Number of Deaths / Hospitalizations / Cases prevented =
Rate of COVID-19 deaths/hospitalizations/cases in unvaccinated individuals
X Estimated VE against severe disease (for deaths and hospitalizations) or symptomatic COVID-19 (for cases) X 6 months X 1 million persons.

Sensitivity analyses were conducted to account for:

- Potentially lower VE in older adults (we assumed 10% lower VE in adults ≥ 65 years of age),
- Waning of VE over six months (we assumed a 20% reduction in estimated VE against symptomatic COVID-19 and a 10% reduction in estimated VE against severe COVID-19), and
- Extreme waning of VE over six months (we assumed an 85% reduction in estimated VE against symptomatic COVID-19 and a 20% reduction in estimated VE against severe COVID-19).

Risk

Estimates of the expected risks of TTS, TCP/ITP, TM, and GBS for adults ≥ 18, ≥ 30, ≥ 50 and ≥ 65 years of age were based on events reported to and vaccines administered in the UK, EU, Brazil, and Australia up to 15 March 2022.

- TTS was defined according to CDC criteria, tiers 1 and 2 (CDC 2021)

As the risk of TTS has been observed to vary by dose (Bhuyan et al 2021), rates were reported separately per million first and second doses. Risk rates for TTS were calculated as:

(Reported events / Number of VAXZEVRIA doses administered) X 1 million first or second doses.

When reporting fatal TTS, the date of death was conservatively assumed to be the same as the date of the corresponding event onset.

Where the categorization of vaccination exposures by age in a data set did not align with the thresholds presented above (eg, 350,000 vaccination exposures for the category 25 – 34 years of age), the exposures were assumed to be evenly distributed (eg, 35,000 vaccinations per age-year) and only the relevant exposures (eg, 175,000 vaccinations for the age-years 30 through 34) included in the relevant (eg, ≥ 30 years) analysis threshold.

Age was unknown for a small number of individuals in the UK and EU data sets (0.3% and 2.9%, respectively). For all benefit and risk calculations, these individuals were included in all age thresholds.

Results

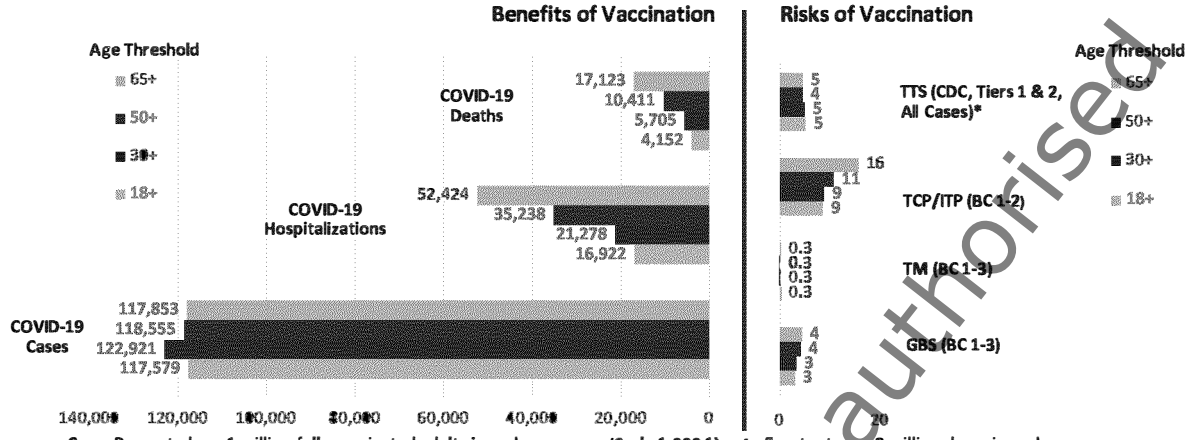
Primary Analysis

Results of the benefit:risk analysis assuming the Omicron variant predominates are presented in Figure 4. The number of COVID-19 cases averted after receiving the full vaccination series of AZD1222 was similar for all age thresholds. However, the number of COVID-19 hospitalizations prevented increased from 16,922 when the age threshold was ≥ 18 years to 52,424 when the age threshold was ≥ 65 years. Similarly, the number of COVID-19 deaths prevented increased from 4,152 when the age threshold was ≥ 18 years to 17,123 when the age threshold was ≥ 65 years. Hence the benefits of receiving a primary series of AZD1222 were overwhelmingly most evident when the age threshold was ≥ 65 years.

The risk of vaccination-associated TTS did not increase with age. Across the age spectrum, the number of TTS cases after AZD1222 vaccination (using the CDC definition) was 4-5.

Based on these findings on the Omicron variant, AstraZeneca concludes that the benefits of VAXZEVRIA outweigh the risks across all ages, with particular benefits observed in those over the age of 65.

Figure 4 **Benefit:Risk of Primary AZD1222 Vaccination Over 6 Months Assuming the Omicron Variant Predominates (All Age Thresholds)**



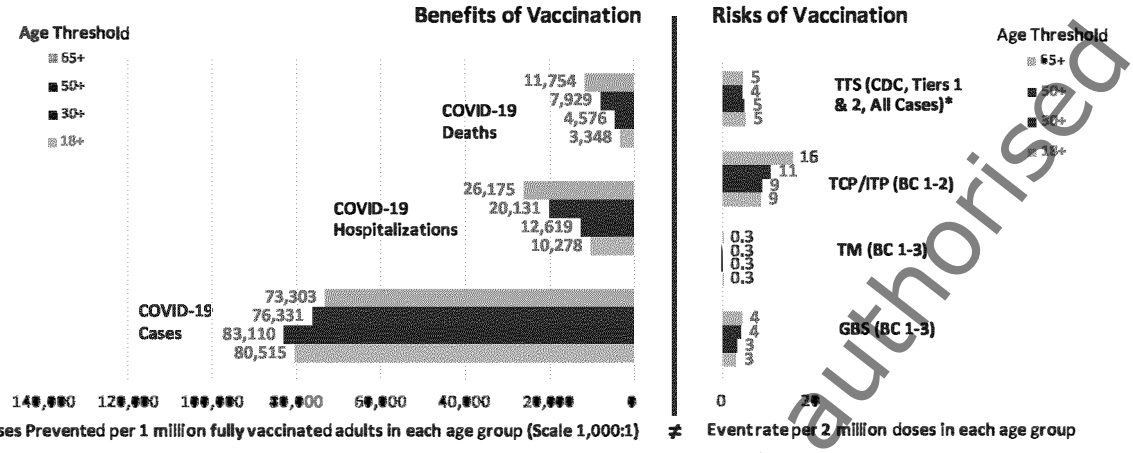
Benefits and Risks over 6 months after fully vaccinating 1 million individuals (2 million doses), assuming average rates of infection during the Omicron wave. Benefit assessment is based on a model that incorporates data on average age-specific rates of COVID-19 cases, COVID-19 hospitalisations, and COVID-19 deaths in unvaccinated individuals during the Omicron wave, and vaccine effectiveness estimates against symptomatic disease (VE = 36%) and severe disease (VE = 71%) caused by the Omicron variant from real-world studies.

CDC = Centers for Disease Control; BC = Brighton Collaboration; GBS = Guillain-Barré syndrome; TCP = idiopathic thrombocytopenia purpura; TM = transverse myelitis;
TTS = thrombotic thrombocytopenic syndrome

*TTS rates differ after the 1st and 2nd doses; this is accounted for by adding reported rates per million 1st doses to reported rates per million 2nd doses. All other rates are per observed two million doses without regard to order.

With the Delta variant predominating (Figure 5), benefit:risk analysis yields results similar to those described for Omicron, even though the Delta variant is associated with a lower average event rate and higher VE estimates. Based on these findings on the Delta variant, AstraZeneca concludes that the benefits of VAXZEVRIA outweigh the risks across all ages, with particular benefits observed in those over the age of 65.

Figure 5 **Benefit:Risk of Primary AZD1222 Vaccination Over 6 Months Assuming the Delta Variant Predominates (All Age Thresholds)**



Benefits and Risks over 6 months after fully vaccinating 1 million individuals (2 million doses), assuming average rates of infection during the Delta wave. Benefit assessment is based on a model that incorporates data on average age-specific rates of COVID-19 cases, COVID-19 hospitalisations, and COVID-19 deaths in unvaccinated individuals during the Delta wave, and vaccine effectiveness estimates against symptomatic disease (69%) and severe disease (94%) caused by the Delta variant from real-world studies.

CDC = Centers for Disease Control; BC = Brighton Collaboration; GBS = Guillain-Barré syndrome; TCP = idiopathic thrombocytopenia purpura; TM = transverse myelitis; TTS = thrombotic thrombocytopenic syndrome

*TTS rates differ after the 1st and 2nd doses; this is accounted for by adding reported rates per million 1st doses to reported rates per million 2nd doses. All other rates are per observed two million doses without regard to order.

Sensitivity Analyses

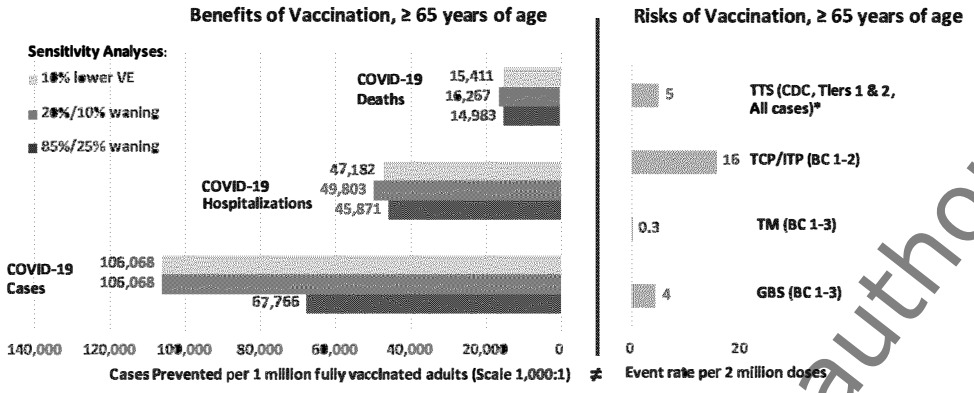
When sensitivity analyses were performed to evaluate the potential impacts on vaccination benefit of:

- 10% lower estimated VE in individuals ≥ 65 years of age,
- Waning of estimated VE over 6 months by 20% (cases) and 10% (severe disease), and
- Extreme waning of estimated VE over 6 months by 85% (cases) and 20% (severe disease),

fewer cases of symptomatic disease were prevented but there was little impact on prevention of hospitalizations or deaths in any age threshold.

Results for the threshold ≥ 65 years of age are shown in Figure 6 (assuming predominance of the Omicron variant) and in Figure 7 (assuming predominance of the Delta variant).

Figure 6 **Sensitivity Analyses of the Benefit:Risk of Primary AZD1222 Vaccination Over 6 Months, Assuming the Omicron Variant Predominates (Age Threshold ≥ 65 years)**

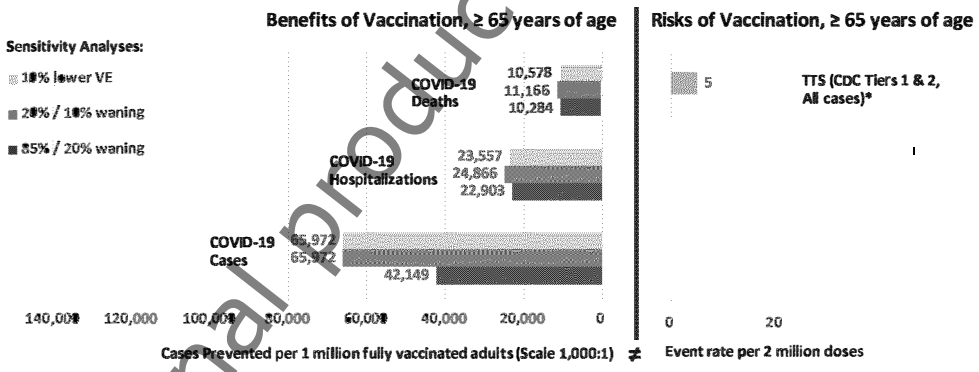


Benefits and Risks over 6 months after fully vaccinating 1 million individuals (2 million doses), assuming average rates of infection during the Omicron wave. Benefit assessment is based on a model that incorporates data on average age-specific rates of COVID-19 cases, COVID-19 hospitalisations, and COVID-19 deaths in unvaccinated individuals during the Omicron wave. Sensitivity Analyses assume (a) 10% lower VE in individuals ≥ 65 years of age; (b) waning of VE over 6 months (20% for symptomatic disease; 10% for severe disease); (c) extreme waning of VE over 6 months (85% for symptomatic disease; 20% for severe disease) as compared with the VE estimates for the primary analysis (36% against symptomatic disease; 71% against severe disease).

CDC = Centers for Disease Control; BC = Brighton Collaboration; GBS = Guillain-Barré syndrome; TCP = idiopathic thromobocytopenia purpura; TM = transverse myelitis;
TTS = thrombotic thrombocytopenic syndrome

*TTS rates differ after the 1st and 2nd doses; this is accounted for by adding reported rates per million 1st doses to reported rates per million 2nd doses. All other rates are per observed two million doses without regard to order.

Figure 7 **Sensitivity Analyses of the Benefit:Risk of Primary AZD1222 Vaccination Over 6 Months, Assuming the Delta Variant Predominates, (Age Threshold ≥ 65 years)**



Benefits and Risks over 6 months after fully vaccinating 1 million individuals (2 million doses), assuming average rates of infection during the Delta wave. Benefit assessment is based on a model that incorporates data on average age-specific rates of COVID-19 cases, COVID-19 hospitalisations, and COVID-19 deaths in unvaccinated individuals during the Delta wave. Sensitivity Analyses assume (a) 10% lower VE in individuals ≥ 65 years of age; (b) waning of VE over 6 months (20% for symptomatic disease; 10% for severe disease); (c) extreme waning of VE over 6 months (85% for symptomatic disease; 20% for severe disease) as compared with the VE estimates for the primary analysis (69% against symptomatic disease; 94% against severe disease).

CDC = Centers for Disease Control; BC = Brighton Collaboration; GBS = Guillain-Barré syndrome; TCP = idiopathic thromobocytopenia purpura; TM = transverse myelitis;
TTS = thrombotic thrombocytopenic syndrome

*TTS rates differ after the 1st and 2nd doses; this is accounted for by adding reported rates per million 1st doses to reported rates per million 2nd doses. All other rates are per observed two million doses without regard to order.

Conclusion

Based on a modelling approach using real world data and conservative VE estimates from an external source (IHME 2022), the expected benefits of a 2-dose primary series of

VAXZEVRIA continue to outweigh the risk of TTS in individuals 65 years of age and older. The benefits were seen whether the model assumed predominance of the Omicron or the Delta variant, and persisted when reduced estimates of VE were used (10% reduction for all individuals ≥ 65 years of age, waning over 6 months by 20% (cases) and 10% (severe disease), or extreme waning over 6 months by 85% (cases) and 20% (severe disease). Therefore, AstraZeneca concludes that the benefits of VAXZEVRIA outweigh the risks across all ages, with particular benefits observed in those over the age of 65.

Question 4

Conduct a comprehensive root-cause analysis of the risk of thrombosis with thrombocytopenia syndrome. The analysis should include the potential mechanism action, biological plausibility, risk factors (including the role of exercise) and the impact of the vaccination interval (booster dose).

AstraZeneca's Response

The exact mechanism/ biological plausibility/risk factors of thrombosis with concurrent thrombocytopenia following immunisation with VAXZEVRIA are unknown, please see Question 2 AstraZeneca response for more details. Analysis of booster dose is presented in Section 16.3.2.1.

Question 5

Include a discussion of the background rate of thrombosis with thrombocytopenia syndrome as well as a discussion of this condition following COVID-19 disease.

AstraZeneca's Response

The background incidence of TTS used in our O/E and other analysis of the topic is derived from the data sources outlined below from the pre-pandemic period. We have not identified a suitable data source from which to derive an overall background incidence of TTS in the pandemic period (ie, during 2020 prior to use of the vaccine) or a specific incidence of TTS following COVID-19 infection or disease. Whilst there is a body of evidence regarding the risk of thrombosis and/or thrombocytopenia following COVID-19 disease (eg, Iba and Levy 2022) these studies have not specifically evaluated TTS as per the relevant case definition used in our analyses.

In the context of our O/E analyses on this topic, we consider that use of the pre-pandemic background incidence is suitably conservative, since any pandemic period incidence, if different, is more likely to be higher rather lower than the pre-pandemic incidence.

Background rates for thrombosis with thrombocytopenia syndrome: Data on background rates are available from internal analyses conducted by AstraZeneca and from literature.

AstraZeneca study using US claims data (Mullerova et al; Soboleva et al 2022): Pre-pandemic background TTS rates were generated via secondary data analysis using a cohort design in the IBM Truven MarketScan® US health insurance claims database, from 1 January to 31 December 2019. No single diagnosis code for TTS exists, TTS was defined based on thrombocytopenia and thrombotic/ thromboembolic claims. Thrombotic/thromboembolic

events included all venous and arterial thrombotic events and pulmonary embolism except acute myocardial infarction or overall "stroke". Two algorithms were applied: thrombocytopenia occurring ±7 days (algorithm 1) or occurring 1 day prior to ≤14 days after the thrombotic/thromboembolic event (algorithm 2) (Soboleva et al 2022).

In this analysis, pre-pandemic background TTS incidence was estimated as 9.8–11.1 per 100,000 person-years. When standardised to a 21-day risk window, incident TTS event rates (95% CI) with algorithms 1 and 2 were 5.6 (5.3 to 6.0) and 6.4 (6.0 to 6.8) per 1M persons/21-days, respectively (Table 152). Event rates were higher in males and increased with age. Similar patterns were observed with both algorithms.

Literature

Published event rates for TTS by specific thrombotic/thromboembolic sites show substantial heterogeneity. For example, across 7 databases from 5 European countries, Burn et al.2022. reported pre-pandemic background rates (per 100 000 person-years) of 1.0–8.5 for DVT with thrombocytopenia, 0.5–20.8 for PE with thrombocytopenia, 0.1–2.5 for SVT with thrombocytopenia, and 1.0–43.4 for myocardial infarction or ischemic stroke with thrombocytopenia. This heterogeneity may be due to different methods of estimating background event rates between studies and/or differences in diagnostic or recording patterns in selected countries/regions. Variability in case definitions, their coding, and timeframes covered by the databases used were also likely contributing factors. None of the published studies provided an overall TTS event rate, but instead reported individual types of acute thrombosis/thromboembolism in combination with thrombocytopenia. (Burn et al.2022; Laporte et al 2021; Willame et al 2021) TTS cases may present with multiple thrombotic/thromboembolic sites, a single case could be counted several times in each of the thrombotic/thromboembolic event analyses, confounding an observed to expected analysis.

Table 152 Incident and prevalent background overall TTS event rates and by type of thrombosis/thromboembolism in adults aged ≥18 years in the Truven MarketScan database (2019: pre-pandemic)

	Algorithm 1			Algorithm 2		
Thrombosis type*	**Events**	**Event rate per 100K PY (95% CI)**	**Event rate per 1M person-21-days (95% CI)**	**Events**	**Event rate per 100K PY (95% CI)**	**Event rate per 1M person-21-days (95% CI)**
Incident events						
All thrombotic/thromboembolic events	902	9.8 (9.2 to 10.4)	5.6 (5.3 to 6.0)	1028	11.1 (10.5 to 11.8)	6.4 (6.0 to 6.8)
CVST	22	0.2 (0.2 to 0.4)	0.1 (0.1 to 0.2)	24	0.3 (0.2 to 0.4)	0.15 (0.1 to 0.2)
DVT	613	6.6 (6.1 to 7.2)	3.8 (3.5 to 4.1)	715	7.8 (7.2 to 8.3)	4.5 (4.1 to 4.8)
Intra-abdominal	124	1.3 (1.1 to 1.6)	0.8 (0.6 to 0.9)	129	1.4 (1.2 to 1.7)	0.8 (0.7 to 1.0)
PE	363	3.9 (3.5 to 4.4)	2.3 (2.0 to 2.5)	408	4.4 (4.0 to 4.9)	2.5 (2.3 to 2.8)
Prevalent events						
All thrombotic/thromboembolic events	1783	19.3 (18.4 to 20.2)	11.1 (10.6 to 11.6)	1971	21.3 (20.4 to 22.3)	12.2 (11.7 to 12.8)
CVST	32	0.4 (0.2 to 0.5)	0.2 (0.1 to 0.3)	35	0.4 (0.3 to 0.5)	0.2 (0.15 to 0.3)
DVT	1188	12.8 (12.1 to 13.6)	7.4 (7.0 to 7.8)	1327	14.3 (13.6 to 15.1)	8.2 (7.8 to 8.7)
Intra-abdominal	267	2.9 (2.6 to 3.3)	1.7 (1.5 to 1.9)	282	3.1 (2.7 to 3.4)	1.75 (1.6 to 2.0)
PE	596	6.4 (5.9 to 7.0)	3.7 (3.4 to 4.0)	657	7.1 (6.6 to 7.7)	4.1 (3.8 to 4.4)

Incident event counts exclude patients with thrombosis that occurred in 365 days prior to first thrombosis in 2019. Prevalent event counts include these patients. The first encounter in 2019 with thrombosis was categorised by subtype. Patients who had more than one subtype during this encounter were counted in each contributing type, but only once in the overall count; hence the counts of events by subtype exceed the overall count.
*All occurring with thrombocytopenia following the criteria for the algorithm used.
1M, 1 million; CI, confidence interval; CVST, Cerebrovascular venous and sinus thrombosis; DVT, deep vein thrombosis; PE, pulmonary embolism; PY, person-years; TTS, THROMBOSIS WITH thrombocytopenia syndrome.

Question 6

Provide an assessment of the need for and propose any additional risk minimization measures that could be applied in the Canadian context.

AstraZeneca's Response

There are no additional risk minimisation measures proposed, as the current routine risk minimisation measures are sufficient to manage the safety concern of TTS following immunisation with VAXZEVRIA.

16 SIGNAL AND RISK EVALUATION

16.1 Summary of safety concerns

At the beginning of the reporting period, the VAXZEVRIA safety specification (presented in the global AstraZeneca Core Risk Management Plan, Version no. 5.0, dated 09 December 2021included the following important identified risks, important potential risks, and missing information (see Table 153):

Table 153 Summary of safety concerns – AstraZeneca Core Risk Management Plan for VAXZEVRIA (Version no. 5.0, dated 09 December 2021)

Risk category	Safety concern
Important identified risks	Thrombosis in combination with thrombocytopenia
Important potential risks	Cerebrovascular venous sinus thrombosis without thrombocytopenia
	Immune mediated neurological conditions
	Vaccine-associated enhanced disease (VAED)
Missing information	Use of VAXZEVRIA in pregnant and breastfeeding women
	Use of VAXZEVRIA in subjects with severe immunodeficiency
	Use of VAXZEVRIA in subjects with severe and/or uncontrolled underlying disease
	Use of VAXZEVRIA with other vaccines

16.2 Signal evaluation

Two validated signals were closed during the reporting period, Hypoaesthesia and Paraesthesia and Guillain-Barré syndrome. One signal, Tinnitus, was validated during the reporting period and closed after the DLP for the report. A summary of the signal evaluation is provided below.

Two signals were validated after the DLP, please refer to Section 14 (Late-breaking information).

16.2.1 Closed and rejected/refuted signals

There were no closed and rejected/refuted signals during the reporting period. However, the signal of Guillain-Barré syndrome (GBS) was closed during the reporting period, and VAXZEVRIA CDS section 4.4 Warnings and Precautions was updated to include GBS (see section 5).

16.2.2 Closed signals categorised as important potential risks

There was one closed signal, Guillain-Barré syndrome (GBS), that was categorized as Important potential risk during the reporting period, see details in Table 154. (Please refer to Appendix 20 for GBS Signal Evaluation and Supporting Document for CDS Changes).

16.2.2.1 Guillain-Barré syndrome (GBS)

Table 154 Guillain-Barré syndrome (GBS)

Characterisation	**Summary**
Source of the signal	Regulatory Authority. Following evaluation of GBS in 2nd PBRER for VAXZEVRIA a signal was validated.
Date detected	24 January 2022
Date closed	13 May 2022
Reference document(s)	Appendix 20
Regulatory Procedure Reference	EMEA/H/C/005675/IB/0034 and IB/0044
Search criteria	SMQ narrow Guillain-Barré syndrome
Method(s) of evaluation	Comprehensive cumulative review of clinical and post-marketing reports and the literature (including case reviews and epidemiological studies). Medical review according to Brighton collaboration and causality assessment according to WHO-UMC causality criteria. Quantitative Signal Detection System (Observed versus expected analysis), stratified by age, gender, dose and using different risk windows with incidence rates from ACCESS protocol.
Outcome of the evaluation	AstraZeneca clarified the existing language on demyelinating disorders in Section 4.4 of CDS with inclusion of GBS specifically. In line with this, the relevant text on GBS was added to the CPIL. AstraZeneca believes that this may help the vaccinees seek early medical care irrespective of the underlying aetiology of GBS.

Table 154 Guillain-Barré syndrome (GBS)

Characterisation	Summary
Conclusions	Although AstraZeneca's position is that a reasonable possibility of a causal association does not exist between VAXZEVRIA and GBS at this time, AstraZeneca acknowledges the 1432 case reports in our Safety database, the published evidence, and the increased O/E ratio in some categories amidst the complexities including the role of COVID-19 possibly causing GBS in the background. However, the available data on GBS is mainly from spontaneously reported cases, which are voluntary and often have limited information or have predisposing / confounding factors for GBS. Four (4) out of 1432 cases were considered "Probable" according WHO-UMC criteria, despite having some missing information as explained above. The incidence rates that are used for the O/E analyses are conservative, as other reliable sources have higher rates. In addition, the rates are since pre-pandemic times and not accounting for the COVID-19 pandemic in the background. Although there are epidemiological articles describing a temporal association to the first dose of VAXZEVRIA, the risk was approximately 4 times greater after a COVID-19 infection. Therefore, there are still gaps in understanding on the incidence rate of GBS in the context of the effect of COVID-19 pandemic in the background. Taking this into consideration, AstraZeneca will continue to closely monitor GBS as part of our surveillance activities and take further actions as deemed necessary.

GBS Guillain-Barré syndrome.

16.2.3 Closed signals categorised as important identified risks

There were no closed signals categorised as important identified risks during the reporting period.

16.2.4 Closed signals that are potential risks not categorised as important

There were no closed signals that are potential risks not categorised as important during the reporting period.

16.2.5 Closed signals that are identified risks not categorised as important

There were two signals (Hypoaesthesia and Paraesthesia and Tinnitus) that were closed during or shortly after the reporting interval, please refer to Table 155 and Table 156.

A review for Tinnitus is provided in Section 15.2.1.

16.2.5.1 Hypoaesthesia and Paraesthesia

Table 155 Hypoaesthesia and Paraesthesia

Characterisation	Summary
Source of the signal	Regulatory Authority. A safety observation was made on 01 December 2021 by Australian Therapeutic Goods Administration (TGA).

Table 155 Hypoaesthesia and Paraesthesia

Characterisation	Summary
Date detected	01 December 2021
Date closed	02 March 2022
Reference document(s)	Refer to section 16.3.4.3
Regulatory Procedure Reference	EMEA/H/C/PSUSA/00010912/202112
Search criteria	PTs (MedDRA 24.1); Hypoaesthesia; Paraesthesia
Method(s) of evaluation	Comprehensive cumulative review of clinical and post-marketing reports and the literature (including case reviews and epidemiological studies). Quantitative data review using the reporting odds ratio (ROR) from EVDAS data.
Outcome of the evaluation	VAXZEVRIA CDS Section 4.8 (undesirable effects) updated with 'Hypoaesthesia' and 'Paraesthesia'
Conclusions	Based on the evaluation of currently available information from all available sources, with particular focus on post-market data, AstraZeneca considers that there is a reasonable possibility of a causal association between VAXZEVRIA and hypoaesthesia and paraesthesia. Many of these events were co-reported with reactogenicity events. The information regarding hypoaesthesia and paraesthesia will be added to the CDS and the company will continue to conduct routine pharmacovigilance activities on this safety topic.

MedDRA Medical Dictionary for Regulatory Activities, PT Preferred Term, TGA Australian Therapeutic Goods Administration.

16.2.5.2 Tinnitus

Table 156 Tinnitus

Characterisation	Summary
Source of the signal	Regulatory Authority – Request in preliminary assessment report for 3rd PBRER (DLP 28 Jun 2022) to include "Tinnitus" in section 4.8 of the EU SmPC
Date detected	11 May 2022
Date closed	01 July 2022
Reference document(s)	Section 16.3.4.2
Regulatory Procedure Reference	EMEA/H/C/PSUSA/00010912/202112
Search criteria	MedDRA PT Tinnitus
Method(s) of evaluation	Comprehensive cumulative review of clinical and post-marketing reports and the literature (including case reviews and epidemiological studies). Medical review and causality assessment according to WHO-UMC causality criteria for medically confirmed cases. Quantitative Signal Detection System using EVDAS data and observed versus expected analysis), stratified by age and risk window 0-42 days, with incidence rates from Stohler et al 2019.
Outcome of the evaluation	Update to include "Tinnitus" in section 4.8 in VAXZEVRIA CDS with frequency "uncommon" based on clinical trial data and section 4 of PIL

Table 156 Tinnitus

Characterisation	Summary
Conclusions	Based on the evaluation of currently available information from various sources, AstraZeneca considers that there is a reasonable possibility of a causal association between VAXZEVRIA and tinnitus. VAXZEVRIA CDS Section 4.8 (undesirable effects) was updated (post DLP) to include 'Tinnitus'. When used in accordance with the revised prescribing information, the benefits of VAXZEVRIA continue to outweigh the risks.

MedDRA Medical Dictionary for Regulatory Activities, PT Preferred Term

16.3 Evaluation of risks and new information

This section presents data from the AstraZeneca global safety database obtained using search strategies inclusive of all available data in the database. Numbers presented here may differ from those presented in the Appendix 2 summary tabulations (also from the AstraZeneca global safety database), where the search strategies are specific to the requirements for the summary tabulations.

Period data may include case reports which have been received prior to this period but where follow-up information have been obtained during the reporting period. New information on important potential risks

16.3.1 New information on important potential risks

All important potential risks included in Section 16.1 are kept under close surveillance by AstraZeneca.

16.3.1.1 Cerebrovascular venous and sinus thrombosis without thrombocytopenia

Global Patient Safety Database

A cumulative search (29 December 2020 to 28 June 2022) and period search (29 December 2021 to 28 June 2022) of the AstraZeneca Global Patient Safety Database was conducted using the following MedDRA (v25.0) HLT: Cerebrovascular venous and sinus thrombosis (CVST). To identify the cases of CVST without co-reported thrombocytopenia, the following were excluded from the search results described above: any cases with events from the HLT: Thrombocytopenia, SMQ: Hematopoietic thrombocytopenia (Narrow), or cases with platelet values less than 150,000 per microliter.

Reporting period (29 December 2021 – 28 June 2022)

After applying the above exclusion criteria, 89 cases (53 initial and 36 follow-up) of CVST without thrombocytopenia were retrieved. Out of the 89 case reports, 1 case was from the clinical trial ([redacted]- insignificant follow up information was received during the reporting period, case presented in previous PBRER dated (29 June 2021 – 28 December 2021), 5 literature cases and 83 cases are from spontaneous sources.

The adverse events (PTs) reported for 89 cases included: Cerebral venous sinus thrombosis (53), Cerebral venous thrombosis (CVT) (34), Transverse sinus thrombosis (3), Superior sagittal sinus thrombosis (1) and Cavernous sinus thrombosis (1).

All the 89 cases were serious. Out of 89 cases 49 were medically confirmed. The reported seriousness criteria for the 89 serious cases of CVST without thrombocytopenia included: death (13), life-threatening (21), hospitalization or prolongation of existing hospitalization (54), persistent or significant disability or incapacity (2) and medically significant (44). A single case may have met more than one criterion for serious.

A majority of the cases, 33 (37%), were reported from Germany; followed by the UK with 11 (12%) cases. A total of 62 (70%) case reports were reported in females, 26 (29%) were reported in males, and in the remaining 1 (1%) the gender was not reported. The median age was 45.5 years, with a range of 20 to 90 years. Of 89 reported cases, 64 (72%) occurred in adults (18 to 64 years of age), 12 (13%) in elderly (≥ 65 years of age) and in the remaining 13 (15%) the age was not reported.

Of the 89 cases, time to onset from the administration of vaccine to the onset of the CVST event was available in 60 (67%) cases as follows: 0 to 7 days in 18 (20%); 8 to 14 days in 15 (17%); 15 to 21 days in 4 (4%); 22 to 28 days in 3 (3%); 29 to 42 days in 8 (9%) and, greater than 42 days in 12 (14%) cases. Time to onset was not reported in the remaining 29 (33%) cases. Time to onset ranged from 0 to 301 days, with a median of 12.5 days.

The outcomes of the 89 CVST without thrombocytopenia cases were as follows: 26 (29.2%) were not recovered; 20 (22.4%) were recovering, 14 (15.8%) recovered; 6 (6.7%) recovered with sequelae; 13 (14.6%) died; and the remaining 10 cases (11.3%) had unknown outcomes.

Of the 89 case reports, 13 (14.6%) cases had a reported fatal outcome (7 initial and 6 follow-up cases). There were 7 medically confirmed cases and 6 non-medically confirmed cases with a fatal outcome. Age/gender and fatal reports are presented in Table 157.

Table 157 CVST Without Thrombocytopenia Case Reports by age/gender, and fatality

Age Group	Female N (Fatal cases)	Male N (Fatal cases)	Unknown N (Fatal cases)	Total N (Fatal cases)
Age - 18-29 Years	8 (0)	4 (0)	0 (0)	12 (0)
Age - 30-39 Years	9 (2)	5 (0)	0 (0)	14 (2)
Age - 40-49 Years	11 (0)	4 (0)	0 (0)	15 (0)
Age - 50-59 Years	9 (0)	3 (0)	0 (0)	12 (0)
Age - 60-69 Years	10 (2)	6 (0)	0 (0)	16 (2)
Age - 70-79 Years	1 (1)	2 (0)	0 (0)	3 (1)
Age - 80+ Years	3 (1)	1 (0)	0 (0)	4 (1)
Age Unknown	11 (6)	1 (0)	1 (1)	13 (7)
Grand Total	62 (12)	26 (0)	1 (1)	89 (13)

CVST Cerebrovascular venous and sinus thrombosis, N, Number of cases.

The 13 cases of CVST without thrombocytopenia related PTs with a fatal outcome in order of frequency were as follows: Cerebral venous thrombosis (10), Cerebral venous sinus thrombosis (2) and Cavernous sinus thrombosis (1).

Of the 13 fatal outcome cases, the reported causes of death were: Cerebral venous thrombosis (5), Syncope (4), Death (2), Cerebral haemorrhage (2), Cerebral venous sinus thrombosis (1), Brain injury (1), Subarachnoid haemorrhage (1), Cavernous sinus thrombosis (1). Four cases had > 1 reported cause of death.

Of the 89 cases, there were 76 cases in which the vaccinee received first dose of vaccine and the event occurred post dose 1. A majority of these cases, 56 (73.6%) out of 76, occurred in the 20 to 65 age group (median 43 years), and 55 (72.3%) of the 76 cases were in female vaccinees. The time to onset was available in 52 case reports with a median of 11 days (Range: 0-284 days). The time to onset from the administration of dose 1 to the event onset was: 0 to 21 days in 36 (69.2%), 22 to 28 days in 2 (3.8%), 29 to 42 days in 6 (11.5%), and greater than 42 days in 8 (15.3%) of cases. Time to onset was not reported in 24 cases.

Of the 89 cases, there were 12 cases in which the vaccinee received 2 doses of vaccine and the event occurred post 2nd dose. A majority of these cases, 10 (83.3%) out of 12, occurred in the 28 to 65 age group (median 43.5 years), and 7 (58.3%) of the 12 cases were in female vaccinees. The time to onset was available in 8 case reports (Range: 2-301 days). The time to onset from the administration of dose 2 to the event onset was: 0 to 21 days in 1 (12.5%), 22 to 28 days in 1 (12.5%), 29 to 42 days in 2 (25%), and greater than 42 days in 4 (50%) of cases. Time to onset was not reported in 4 cases.

Out of the 11 cases in vaccinees who developed CVST after Dose 2, 1 case reported a fatal outcome. Reported age in fatal case was 63 years and the cause of death was reported as Cavernous sinus thrombosis, Subarachnoid haemorrhage and Cerebral haemorrhage. The time to onset for the fatal case was 41 days.

Out of the 11 cases, in 1 case patient received COVID-19 messenger RNA (mRNA) Vaccine Biontech (tozinameran) as the second dose and experienced a CVST event after receiving the second dose ([redacted]) is discussed below:

- [redacted]: A spontaneous report has been received from the regulatory authority in [redacted] (EMA) regarding a 62-year-old female patient who was reported to have received VAXZEVRIA Dose 1 and 98 days after Dose 1, patient received Dose 2 (COVID-19 VACCINE PFIZER). Approximately 5 months after, Dose 2 (COVID-19 VACCINE PFIZER), the vaccinee experienced cerebral venous sinus thrombosis. No information on treatment provided and the event was ongoing at the time of the report was received.

AZ Comment: The time to onset from the VAXZEVRIA dose was 8 months (240 days), which is clearly outside of the risk window of 42 days. AstraZeneca considers a causal relationship between VAXZEVRIA and the event as unlikely. In addition, there are missing information of medical history and concomitant medication.

In another case the vaccinee reported to have received COVID-19 messenger RNA (mRNA) Vaccine Biontech (tozinameran) as the second dose and third dose with the CVST related event occurring on an unknown exact date. This case is described below:

- [redacted]: A spontaneous report has been received from a physician via the regulatory authority in [redacted] (EMA) regarding a 52-year-old male patient who was reported to have received VAXZEVRIA Dose 1 on 06 March 2021, after 84 days from Dose 1, patient received Dose 2 (COVID-19 VACCINE PFIZER) on 29 May 2021 and received Dose 3 (COVID-19 VACCINE PFIZER) on 10 December 2021. On an unknown date in 2021, the vaccinee experienced cerebral venous sinus thrombosis.

AZ Comment: The time to onset is unknown in this case. AstraZeneca considers the case unassessable with limited information. Missing information are those of medical history and concomitant medication.

There were no cases with a recurrence noted (after the first and second dose of the vaccine). Twenty two (24.2%) cases out of 89 had radiological confirmation of CVST, and 14 (15.7%) of the 22 cases were medically confirmed.

Of the 89 cases, 10 cases had co-reported cerebrovascular events (such as Cerebral haemorrhage (5), Cerebrovascular accident (4), Subarachnoid haemorrhage (1)

There was information available on confounding comorbidities, other medical confounders or risk factors and confounding medications reported in 21 (23.5%) of the 89 cases. Out of the remaining 68 cases, 38 cases had no information on confounding/risk factors and in 30 cases, although with various risk factors, but none was assessed to be particular or pertinent to the occurrence of cerebrovascular pathology. A single case may have more than one risk/confounding factor. Details of the WHO-UMC causality assessment are provided in Table 158**.**

The confounding factors reported for the cases were concomitant use of contraceptives, cancer/neoplasms, deep vein thrombosis, history of thrombosis, COVID-19 illness prior to vaccine, hypertension, fibromyalgia, cerebrovascular accident. None of the cases met WHO-UMC criteria as 'Certain' and 'Probable-Likely'.

Cumulative review (29 December 2020 - 28 June 2022)

Cumulatively, 573 cases with CVST without thrombocytopenia were received from vaccinees who received VAXZEVRIA. Out of the 573 case reports, 1 case was from the clinical trial, 25 literature cases, 3 cases from non-interventional/post-marketing and 544 cases are from spontaneous sources.

Of the 573 case reports, 566 were reported as serious and 7 were reported as non-serious; 340 were medically confirmed. The seriousness criteria for the 573 serious cases of CVST without thrombocytopenia included: death (46), life-threatening (127), hospitalization or prolongation of existing hospitalization (360), Congenital anomaly (1), persistent or significant disability or incapacity (38), and medically significant (300). A single case may have met more than one criterion for serious.

A majority of the cases, 194 (34%) were reported from Germany and 154 (27%) cases were reported from UK. A total of 350 (61%) case reports were reported in females, 203 (35%) were reported in males, and in 20 (4%) the gender was not reported. The median age was 51 years with a range of 18 to 98 years. Out of 573 reported cases, 388 (68%) occurred in adults (18-64 years of age), 123 (21%) in elderly (≥ 65 years of age), and in 62 (11%) the age was not reported.

The reported CVST PTs from the 573 cases were: Cerebral venous sinus thrombosis (359), Cerebral venous thrombosis (160), Superior sagittal sinus thrombosis (28), Transverse sinus thrombosis (32) and Cavernous sinus thrombosis (15).

Of the 573 case reports, 46 (8%) cases had a reported fatal outcome; of which 26 were medically confirmed. and 23 (50%) occurred in the age group of 18-49.

Reported outcomes in the remaining 527 non-fatal case reports of CVST without thrombocytopenia were: Not Recovered 212 (36.9%), Recovered 68 (11.8%), Recovering 113 (19.7%), Recovered with Sequelae 18 (3.1%), and Unknown/missing 116 (20.2%).

Table 158 WHO-UMC Causality Assessment for Reporting Period and Overall CVST without Thrombocytopenia Cases

WHO-UMC Causality assessment	Case Count (Cumulative)	Case Count (Reporting period)
Probable/Likely	1	0
Possible with Confounders	141	10
Possible with limited information	219	37
Unassessable with limited information	116	23
Unassessable with Confounders	38	5
Unlikely	57	13
Conditional/Unclassified	1	1
Total	**573**	**89**

None of the cases met WHO-UMC criteria as 'Certain'.

There was available information on confounding comorbidities, other medical confounders or risk factors and confounding medications reported in 199 (34.7%) of the 573 cases. Out of the remaining 374 cases, 322 cases had no information on any confounding/risk factor and in 52 cases there were no relevant risk factors identified. A single case may have more than one risk/confounding factor.

The confounding factors reported for the cases were concomitant use of contraceptives, cancer/neoplasms, history of obesity, deep vein thrombosis, history of thrombosis, COVID-19 illness prior to vaccine, Factor V Leiden mutation, hypertension, pulmonary embolism, immunodeficiency, fibromyalgia, and autoimmune thyroiditis.

Review of Literature (29 December 2021 – 28 June 2022)

AstraZeneca performed a search for the period 29 December 2021 to 28 June 2022 of PubMed, Embase and InsightMeme databases to identify literature of CVST with COVID-19 vaccines, including VAXZEVRIA.

A total of 285 articles were retrieved from the search of which 29 were duplicates and 256 were unique articles. Of the 256 articles, 5 articles included 5 literature cases of CVST without Thrombocytopenia with VAXZEVRIA included in the review above ([redacted],

[redacted]). The remaining 251 articles were not considered as relevant and therefore will not be discussed (as they discussed CVST in the context of VITT, TTS, or CVST with thrombocytopenia; contained information on unspecified COVID-19 vaccines; or did not provide sufficient information to make a meaningful assessment).

Observed versus Expected Analysis

Please refer to Appendix 8 for the methodology of the O/E analyses and Appendix 9 for any additional sensitivity analysis.

The observed versus expected analyses for all cases of CVST without thrombocytopenia are carried out using incidence rates from ACCESS: SIDIAP PCHOSP and Truven MarketScan (2019). The observed versus expected analysis for all cases of CVST without thrombocytopenia is presented with different risk windows (21 days, 30 days and 42 days) for all global reports in Table 159 and stratified by age for the EEA, UK, Australia and Brazil regions in Table 160 and by age and gender in UK (Table 161 and Table 162). Global analysis also included cases with an unknown time to onset, as a conservative approach. The incidence rates used were from SIDIAP_PCHOSP (Willame et al 2021 [B]), as that rate was used by the EMA, and this would permit a comparison of the O/E analysis conducted by EMA and AstraZeneca.

SIDIAP PCHOSP is a data source containing 5.7 million (80% of the population) in Catalonia and includes General Practitioner (GP) medical records, communication from specialists and hospitalization discharge diagnoses. SIDIAP PCHOSP is representative of the general population in terms of age, sex, and geographic distribution. Since CVST is a very rare event, a larger database was used in addition to SIDIAP PCHOSP. Truven MarketScan (US) was chosen since is a longitudinal database capturing outcomes from in- and outpatient visits and pharmaceuticals and contains almost 230 million unique patients. Moreover, it includes both commercial employer-based insurance and government-based insurance. In addition to its large sample size Truven MarketScan was used for consistency with background rates for TTS generated using MarketScan.

As a comparison to the above, the same observed versus expected analyses are carried out using incidence rates from Truven MarketScan. Those analyses for CVST are presented with different risk windows (21 days, 30 days and 42 days) for all global reports in Table 163, stratified by age in the EEA, UK, Australia and Brazil in Table 164 and by age and gender in the UK (Table 165 and Table 166).

Conservatively, the exposure for global reports (448306152) is based on doses administered in 13 markets as explained in Appendix 8.

Table 159 Observed versus expected analysis for CVST without thrombocytopenia (using SIDIAP_PC HOSP incident rate) for global reports

Age group	IR [a]	Exposure [b]	Risk Window 21 Days				Risk Window 30 Days				Risk Window 42 Days			
			Observed number of cases [c]	Expected number of cases	O over E ratio (95% CI)	Conclusion	Observed number of cases [c]	Expected number of cases	O over E ratio (95% CI)	Conclusion	Observed number of cases [c]	Expected number of cases	O over E ratio (95% CI)	Conclusion
Overall (Global)	0.72	44830615 2	278	185.59	1.5 (1.33 - 1.68)	Observed significantly > expected	319	265.12	1.2 (1.07 - 1.34)	Observed significantly > expected	365	371.17	0.98 (0.89 - 1.09)	Observed < expected
Overall (Global) plus cases Unk TTO	0.72	44830615 2	434	185.59	2.34 (2.12 - 2.57)	Observed significantly > expected	475	265.12	1.79 (1.63 - 1.96)	Observed significantly > expected	521	371.17	1.4 (1.29 - 1.53)	Observed significantly > expected

a Incidence rate Source: Willame et al 2021, from ES_SIDIAP_PCHOSP

b Exposure is to DLP 28 June 2022.

c All cases up to DLP 28 June 2022.

Only cases observed within 0-21, 0-30 and 0-42 days were included; Risk window: 21, 30 and 42 days.

CI Confidence Interval, CVST Cerebrovascular venous and sinus thrombosis, E Expected; IR Incidence Rate; O Observed; TTO Time To Onset; Unk Unknown

Table 160 Observed versus expected analysis for CVST without thrombocytopenia (using SIDIAP_PC HOSP incident rates) stratified by age in the EEA +UK +Australia +Brazil

Age group	IR [a]	Exposure [b]	Risk Window 21 Days				Risk Window 30 Days				Risk Window 42 Days			
			Observed number of cases [c]	Expected number of cases	O over E ratio (95% CI)	Conclusion	Observed number of cases [c]	Expected number of cases	O over E ratio (95% CI)	Conclusion	Observed number of cases [c]	Expected number of cases	O over E ratio (95% CI)	Conclusion
EEA+UK+Brazil+Australia Data														

18-49 Years	0.27	100987434	121	15.68	7.72 (6.4 - 9.22)	Observed significantly > expected	133	22.4	5.94 (4.97 - 7.04)	Observed significantly > expected	151	31.35	4.82 (4.08 - 5.65)	Observed significantly > expected
50-59 Years	1.57	56425075	53	50.93	1.04 (0.78 - 1.36)	Observed > expected	63	72.76	0.87 (0.67 - 1.11)	Observed < expected	71	101.87	0.7 (0.54 - 0.88)	Observed significantly < expected
60-69 Years	0.68	57182485	56	22.36	2.5 (1.89 - 3.25)	Observed significantly > expected	63	31.94	1.97 (1.52 - 2.52)	Observed significantly > expected	75	44.71	1.68 (1.32 - 2.1)	Observed significantly > expected
Over 70 Years	0.34	31869628	35	6.23	5.62 (3.91 - 7.81)	Observed significantly > expected	41	8.9	4.61 (3.31 - 6.25)	Observed significantly > expected	46	12.46	3.69 (2.7 - 4.92)	Observed significantly > expected

a Incidence rate Source: Willame et al 2021 [B], from ES_SIDIAP_PCHOSP

b Exposure is to DLP 28 June 2022.

c All cases to DLP 28 June 2022.

Only cases observed within 0-21, 0-30 and 0-42 days were included; Risk window: 21, 30 and 42 days.

CI Confidence Interval; E Expected; IR Incidence Rate; O Observed; TTO Time to onset; UK United Kingdom; EEA European economic area

Table 161 Observed versus expected analysis for CVST without thrombocytopenia (using SIDIAP_PC HOSP incident rates) stratified by age and gender (FEMALE) in the UK

Age group/ Gender	IR [a]	Exposure [b]	Risk Window 21 Days				Risk Window 30 Days				Risk Window 42 Days			
			Observed number of cases [c]	Expected number of cases	O over E ratio (95% CI)	Conclusion	Observed number of cases [c]	Expected number of cases	O over E ratio (95% CI)	Conclusion	Observed number of cases [c]	Expected number of cases	O over E ratio (95% CI)	Conclusion
Female 40-49	0.77	4749427	12	2.1	5.71 (2.95 - 9.98)	Observed significantly > expected	12	3	4 (2.07 - 6.99)	Observed significantly > expected	13	4.21	3.09 (1.64 - 5.28)	Observed significantly > expected

Female over 80	1.67	1864578	1	1.79	0.56 (0.01 - 3.11)	Observed < expected	1	2.56	0.39 (0.01 - 2.18)	Observed < expected	3	3.58	0.84 (0.17 - 2.45)	Observed < expected

a Incidence rate Source: Willame et al 2021 [B]' from ES_SIDIAP_PCHOSP

b Exposure is to DLP 28 June 2022.

c All cases to DLP 28 June 2022.

Only cases observed within 0-21, 0-30 and 0-42 days were included; Risk window: 21, 30 and 42 days.

CI Confidence Interval; E Expected; IR Incidence Rate; O Observed; TTO Time to onset; UK United Kingdom; EEA European economic area

Table 162 Observed versus expected analysis for CVST without thrombocytopenia (using SIDIAP_PC HOSP incident rates) stratified by age and gender (MALE) in the UK

Age group/ Gender	IR [a]	Exposure [b]	Risk Window 21 Days				Risk Window 30 Days				Risk Window 42 Days			
			Observed number of cases [c]	Expected number of cases	O over E ratio (95% CI)	Conclusion	Observed number of cases [c]	Expected number of cases	O over E ratio (95% CI)	Conclusion	Observed number of cases [c]	Expected number of cases	O over E ratio (95% CI)	Conclusion
Male 18-29	1.27	907479	2	0.66	3.03 (0.37 - 10.95)	Observed > expected	2	0.95	2.11 (0.25 - 7.6)	Observed > expected	4	1.33	3.01 (0.82 - 7.7)	Observed > expected
Male 40-49	0.72	4955204	5	2.05	2.44 (0.79 - 5.69)	Observed > expected	6	2.93	2.05 (0.75 - 4.46)	Observed > expected	7	4.1	1.71 (0.69 - 3.52)	Observed > expected
Male 50-59	0.9	6915956	6	3.58	1.68 (0.62 - 3.65)	Observed > expected	8	5.11	1.57 (0.68 - 3.08)	Observed > expected	12	7.16	1.68 (0.87 - 2.93)	Observed > expected
Male 60-69	2.49	5160658	4	7.39	0.54 (0.15 - 1.39)	Observed < expected	4	10.55	0.38 (0.1 - 0.97)	Observed significantly < expected	6	14.78	0.41 (0.15 - 0.88)	Observed significantly < expected
Male 70-79	1.68	3358831	3	3.24	0.93 (0.19 - 2.71)	Observed < expected	3	4.63	0.65 (0.13 - 1.89)	Observed < expected	3	6.49	0.46 (0.1 - 1.35)	Observed <

Table 162 Observed versus expected analysis for CVST without thrombocytopenia (using SIDIAP_PC HOSP incident rates) stratified by age and gender (MALE) in the UK

Age group/ Gender	IR [a]	Exposure [b]	Risk Window 21 Days				Risk Window 30 Days				Risk Window 42 Days			
			Observed number of cases [c]	Expected number of cases	O over E ratio (95% CI)	Conclusion	Observed number of cases [c]	Expected number of cases	O over E ratio (95% CI)	Conclusion	Observed number of cases [c]	Expected number of cases	O over E ratio (95% CI)	Conclusion
														expected
Male over 80	2.81	1160382	1	1.87	0.53 (0.01 - 2.98)	Observed < expected	1	2.68	0.37 (0.01 - 2.08)	Observed < expected	1	3.75	0.27 (0.01 - 1.49)	Observed < expected

a Incidence rate Source: Willame et al 2021 [B] from ES_SIDIAP_PCHOSP

b Exposure is to DLP 28 June 2022.

c All cases to DLP 28 June 2022.

Only cases observed within 0-21, 0-30 and 0-42 days were included; Risk window: 21, 30 and 42 days.

CI Confidence Interval; E Expected; IR Incidence Rate; O Observed; TTO Time to onset; UK United Kingdom; EEA European economic area

Table 163 Observed versus expected analysis for CVST without thrombocytopenia (using Truven 14 incident rates) for global reports

Age group	IR [a]	Exposure [b]	Risk Window 21 Days				Risk Window 30 Days				Risk Window 42 Days			
			Observed number of cases [c]	Expected number of cases	O over E ratio (95% CI)	Conclusion	Observed number of cases [c]	Expected number of cases	O over E ratio (95% CI)	Conclusion	Observed number of cases [c]	Expected number of cases	O over E ratio (95% CI)	Conclusion
Overall (Global)	1.5	448306152	278	386.64	0.72 (0.64 - 0.81)	Observed significantly < expected	319	552.34	0.58 (0.52 - 0.64)	Observed significantly < expected	365	773.27	0.47 (0.42 - 0.52)	Observed significantly < expected
Overall (Global) plus cases	1.5	448306152	434	386.64	1.12 (1.02 - 1.23)	Observed significantly > expected	475	552.34	0.86 (0.78 - 0.94)	Observed significantly < expected	521	773.27	0.67 (0.62 - 0.73)	Observed significantly < expected

Table 163 Observed versus expected analysis for CVST without thrombocytopenia (using Truven 14 incident rates) for global reports

Age group	IR [a]	Exposure [b]	Risk Window 21 Days				Risk Window 30 Days				Risk Window 42 Days			
			Observed number of cases [c]	Expected number of cases	O over E ratio (95% CI)	Conclusion	Observed number of cases [c]	Expected number of cases	O over E ratio (95% CI)	Conclusion	Observed number of cases [c]	Expected number of cases	O over E ratio (95% CI)	Conclusion
Unk TTO														

a Incidence Rate (per/100,000 PY) from Truven Market Scan database (2019)

b Exposure is to DLP 28 June 2022.

c All cases to DLP 28 June 2022.

Only cases observed within 0-21, 0-30 and 0-42 days were included; Risk window: 21, 30 and 42 days.

CI Confidence Interval; E Expected; IR Incidence Rate; O Observed; TTO Time to onset; UK United Kingdom; EEA European economic area

Table 164 Observed versus expected analysis for CVST without thrombocytopenia (using Truven 14 incident rates) for EEA+UK+Australia+Brazil

Age group	IR [a]	Exposure [b]	Risk Window 21 Days				Risk Window 30 Days				Risk Window 42 Days			
			Observed number of cases [c]	Expected number of cases	O over E ratio (95% CI)	Conclusion	Observed number of cases [c]	Expected number of cases	O over E ratio (95% CI)	Conclusion	Observed number of cases [c]	Expected number of cases	O over E ratio (95% CI)	Conclusion
EEA+UK+Brazil+Australia Data														
18-49 Years	1.55	100987434	121	90	1.34 (1.12 - 1.61)	Observed significantly > expected	133	128.57	1.03 (0.87 - 1.23)	Observed > expected	151	180	0.84 (0.71 - 0.98)	Observed significantly < expected

Table 164 Observed versus expected analysis for CVST without thrombocytopenia (using Truven 14 incident rates) for EEA+UK+Australia+Brazil

Age group	IR [a]	Exposure [b]	Risk Window 21 Days				Risk Window 30 Days				Risk Window 42 Days			
			Observed number of cases [c]	Expected number of cases	O over E ratio (95% CI)	Conclusion	Observed number of cases [c]	Expected number of cases	O over E ratio (95% CI)	Conclusion	Observed number of cases [c]	Expected number of cases	O over E ratio (95% CI)	Conclusion
50-59 Years	0.86	56425075	53	27.9	1.9 (1.42 - 2.48)	Observed significantly > expected	63	39.86	1.58 (1.21 - 2.02)	Observed significantly > expected	71	55.8	1.27 (0.99 - 1.6)	Observed > expected
60-69 Years	1.65	57182485	56	54.25	1.03 (0.78 - 1.34)	Observed > expected	63	77.5	0.81 (0.62 - 1.04)	Observed < expected	75	108.5	0.69 (0.54 - 0.87)	Observed significantly < expected
Over 70 Years	0.9	31869628	35	16.49	2.12 (1.48 - 2.95)	Observed significantly > expected	41	23.56	1.74 (1.25 - 2.36)	Observed significantly > expected	46	32.98	1.39 (1.02 - 1.86)	Observed significantly > expected

a Incidence Rate (per 100,000 PY) from Truven Market Scan database (2019)

b Exposure is to DLP 28 June 2022.

c All cases to DLP 28 June 2022.

Truven 14: CVST (I63.6 or I67.6) inpatient without TCP within -1/14 days (incident)

Only cases observed within 0-21, 0-30 and 0-42 days were included; Risk window: 21, 30 and 42 days.

CI Confidence Interval; E Expected; IR Incidence Rate; O Observed; TTO Time to onset; UK United Kingdom; EEA European economic area

Table 165 Observed versus expected analysis for CVST without thrombocytopenia (using Truven 14 incident rates) stratified by age and gender (Female) in the UK

Age group/ Gender	IR [a]	Exposure [b]	Risk Window 21 Days				Risk Window 30 Days				Risk Window 42 Days			
			Observed number of cases [c]	Expected number of cases	O over E ratio (95% CI)	Conclusion	Observed number of cases [c]	Expected number of cases	O over E ratio (95% CI)	Conclusion	Observed number of cases [c]	Expected number of cases	O over E ratio (95% CI)	Conclusion
Female 18-29	2.46	1221578	3	1.73	1.73 (0.36 - 5.07)	Observed > expected	4	2.47	1.62 (0.44 - 4.15)	Observed > expected	4	3.46	1.16 (0.31 - 2.96)	Observed > expected
Female 30-39	2.23	2028622	3	2.6	1.15 (0.24 - 3.37)	Observed > expected	3	3.72	0.81 (0.17 - 2.36)	Observed < expected	5	5.2	0.96 (0.31 - 2.24)	Observed < expected
Female 40-49	1.84	4749427	12	5.02	2.39 (1.24 - 4.18)	Observed significantly > expected	12	7.18	1.67 (0.86 - 2.92)	Observed > expected	13	10.05	1.29 (0.69 - 2.21)	Observed > expected
Female 50-59	0.82	6280795	6	2.96	2.03 (0.74 - 4.41)	Observed > expected	8	4.23	1.89 (0.82 - 3.73)	Observed > expected	9	5.92	1.52 (0.7 - 2.89)	Observed > expected
Female 60-69	1.41	4996322	2	4.05	0.49 (0.06 - 1.78)	Observed < expected	4	5.79	0.69 (0.19 - 1.77)	Observed < expected	5	8.1	0.62 (0.2 - 1.44)	Observed < expected
Female 70-79	0.71	3688886	3	1.51	1.99 (0.41 - 5.81)	Observed > expected	4	2.15	1.86 (0.51 - 4.76)	Observed > expected	4	3.01	1.33 (0.36 - 3.4)	Observed > expected
Female over 80	9.32	1864578	1	9.99	0.1 (0 - 0.56)	Observed significantly < expected	1	14.27	0.07 (0 - 0.39)	Observed significantly < expected	3	19.98	0.15 (0.03 - 0.44)	Observed significantly < expected

a Incidence Rate (per/100,000 PY) from Truven Market Scan database (2019)

b Exposure is to DLP 28 June 2022.

c All cases to DLP 28 June 2022.

Truven 14: CVST (163.6 or I67.6) inpatient without TCP within -1/14 days (incident)

Only cases observed within 0-21, 0-30 and 0-42 days were included; Risk window: 21, 30 and 42 days.

Table 166 Observed versus expected analysis for CVST without thrombocytopenia (using Truven 14 incident rates) stratified by age and gender (Male) in the UK

Age group/ Gender	IR [a]	Exposure[b]	Risk Window 21 Days				Risk Window 30 Days				Risk Window 42 Days			
			Observed number of cases[c]	Expected number of cases	O over E ratio (95% CI)	Conclusion	Observed number of cases[c]	Expected number of cases	O over E ratio (95% CI)	Conclusion	Observed number of cases[c]	Expected number of cases	O over E ratio (95% CI)	Conclusion
Male 18-29	1.1	907479	2	0.57	3.51 (0.42 - 12.67)	Observed > expected	2	0.82	2.44 (0.3 - 8.81)	Observed > expected	4	1.15	3.48 (0.95 - 8.91)	Observed > expected
Male 30-39	0.69	1537246	2	0.61	3.28 (0.4 - 11.84)	Observed > expected	2	0.87	2.3 (0.28 - 8.3)	Observed > expected	2	1.22	1.64 (0.2 - 5.92)	Observed > expected
Male 40-49	0.86	4955204	5	2.45	2.04 (0.66 - 4.76)	Observed > expected	6	3.5	1.71 (0.63 - 3.73)	Observed > expected	7	4.9	1.43 (0.57 - 2.94)	Observed > expected
Male 50-59	0.91	6915956	6	3.62	1.66 (0.61 - 3.61)	Observed > expected	8	5.17	1.55 (0.67 - 3.05)	Observed > expected	12	7.24	1.66 (0.86 - 2.9)	Observed > expected
Male 60-69	1.92	5160658	4	5.7	0.7 (0.19 - 1.8)	Observed < expected	4	8.14	0.49 (0.13 - 1.26)	Observed < expected	6	11.39	0.53 (0.19 - 1.15)	Observed < expected
Male 70-79	2.49	3358831	3	4.81	0.62 (0.13 - 1.82)	Observed < expected	3	6.87	0.44 (0.09 - 1.28)	Observed < expected	3	9.62	0.31 (0.06 - 0.91)	Observed significantly < expected
Male over 80	6.64	1160382	1	4.43	0.23 (0.01 - 1.26)	Observed < expected	1	6.33	0.16 (0 - 0.88)	Observed significantly < expected	1	8.86	0.11 (0 - 0.63)	Observed significantly < expected

a Incidence Rate (per/100,000 PY) from Truven Market Scan database (2019)

b Exposure is to DLP 28 June 2022.

c All cases to DLP 28 June 2022.

Truven 14: CVST (I63.6 or I67.6) inpatient without TCP within -1/14 days (incident)

Only cases observed within 0-21, 0-30 and 0-42 days were included; Risk window: 21, 30 and 42 days.

When an overall rate of 0.72/100,000 person years from SIDIAP_HOSP is used, observed cases of CVST without thrombocytopenia are significantly more than expected for all risk windows except for risk window of 42 days. Observed cases were significantly more than expected for all risk windows when an unknown time to onset was included.

In comparison, when Truven 14 IR are used, observed cases are significantly less than expected for all the risk windows, when cases with unknown TTO are excluded. When cases with an unknown TTO are included to all risk windows as a conservative approach, observed cases are significantly more than expected for risk window 21 days, however observed cases were significantly less than expected for 30- and 42-days risk window (Table 167).

When the observed versus expected analysis was stratified by age in the EEA, UK, Australia and Brazil region using SIDIAP_HOSP rates, observed cases were less than expected for age groups 50-59 (for risk window 30 and 42 days). For all other age stratifications and risk windows of 21, 30 and 42 days in EEA, UK, Australia and Brazil region using SIDIAP_HOSP rates observed cases were either more or significantly more than expected (Table 168).

In comparison, when observed versus expected analysis was stratified by age in the EEA, UK, Australia and Brazil region using Truven 14 IRs, observed cases are more or significantly more than expected in all age groups from 18-69 and over 70 years for risk windows 21 days. In risk window of 30 days, observed cases are more or significantly more than expected in age groups from 18-59 and in age group over 70 years and observed cases are less than expected in age group 60-69 years for risk window of 30 days. For risk window of 42 days, observed cases were significantly less than expected for age groups of 18-49, 60-69 and observed cases were either more or significantly more than expected for age groups 50-59 and over 70 years (Table 168).

When stratified by age and gender in the UK, using Truven 14 IRs (Table 169), the observed cases divided between males and females as follows:

For females, observed cases were more or significantly more than expected for the age groups 18-59 and 70-79 years and observed cases were less or significantly less than expected for the age groups 60-69 and over 80 for 21 days risk window. Observed cases were more or significantly more than expected for the age groups 18-29, 40-49, 50-59, 70-79 years and observed cases were less or significantly less than expected for the age groups 30-39, 60-69 and over 80 years for 30 and 42 days risk window.

For males, observed cases were less or significantly less than expected for age groups 60-69, 70-79 and over 80 years age group for all risk windows (21, 30 and 42 days). For all other age stratifications observed cases were either more or significantly more than expected for all risk windows (21, 30 and 42 days).

Observed versus expected analyses for CVST without thrombocytopenia (with known normal platelet count)

Information on normal platelets was available in 111 of the 573 cases. In the remaining 462 of the 573 cases the post-vaccination platelet count was unknown, however no thrombocytopenia-related

PTs were reported. The 111 cases were used for observed versus expected analysis in order to represent the dataset with known normal thrombocytes.

The observed versus expected analysis for all 111 cases of CVST without thrombocytopenia is presented with different risk windows (21 days, 30 days and 42 days) for global reports in Table 167 and stratified by age in the EEA, UK, Australia and Brazil region in Table 168 and age groups in UK Table 169. The incidence rates used were from SIDIAP PCHOSP (Willame et al 2021 [B]), as that rate was used by the EMA, and this would permit a comparison of the O/E analysis conducted by EMA and AstraZeneca. All stratifications are provided with and without cases that have an unknown time to onset.

The O/E analysis for CVST without thrombocytopenia (with known normal thrombocytes) showed that the number of observed cases were significantly lower than expected when overall cases were considered. With the stratified O/E analysis by age and gender, there were certain age and gender groups where the observed number was higher than expected. However, when a qualitative review was conducted, many of the cases were missing information such as medical history, concomitant medications, precluding a proper assessment to determine causal relationship.

Table 167 Observed versus expected analysis for CVST without thrombocytopenia (with known normal platelet count) (using SIDIAP_PC HOSP incident rate) for global reports

Age group/ Gender	IR [a]	Exposure[b]	Risk Window 21 Days				Risk Window 30 Days				Risk Window 42 Days			
			Observed number of cases[c]	Expected number of cases	O over E ratio (95% CI)	Conclusion	Observed number of cases[c]	Expected number of cases	O over E ratio (95% CI)	Conclusion	Observed number of cases[c]	Expected number of cases	O over E ratio (95% CI)	Conclusion
Overall (Global)	0.72	448306152	47	185.59	0.25 (0.19 - 0.34)	Observed significantly < expected	61	265.12	0.23 (0.18 - 0.3)	Observed significantly < expected	73	371.17	0.2 (0.15 - 0.25)	Observed significantly < expected
Overall (Global) plus cases Unk TTO	0.72	448306152	72	185.59	0.39 (0.3 - 0.49)	Observed significantly < expected	86	265.12	0.32 (0.26 - 0.4)	Observed significantly < expected	98	371.17	0.26 (0.21 - 0.32)	Observed significantly < expected

a Incidence rate Source: Willame et al 2021 [B], from ES_SIDIAP_PCHOSP

b Exposure is to DLP 28 June 2022.

c All cases to DLP 28 June 2022.

Only cases observed within 0-21, 0-30 and 0-42 days were included; Risk window: 21, 30 and 42 days.

CI Confidence Interval; E Expected; IR Incidence Rate; O Observed; TTO Time to onset; UK United Kingdom; EEA European economic area

Table 168 Observed versus expected analysis for CVST without thrombocytopenia (using SIDIAP_PC HOSP incident rates) (with known normal platelet count) stratified by age in the EEA +UK +Australia +Brazil

Age group/ Gender	IR [a]	Exposure [b]	Risk Window 21 Days				Risk Window 30 Days				Risk Window 42 Days			
			Observed number of cases [c]	Expected number of cases	Over E ratio (95 % CI)	Conclusion	Observed number of cases [c]	Expected number of cases	Over E ratio (95 % CI)	Conclusion	Observed number of cases [c]	Expected number of cases	Over E ratio (95 % CI)	Conclusion
EEA+UK+Brazil+Australia Data														
18-49 Years	0.34	100987434	19	19.74	0.96 (0.58 - 1.5)	Observed < expected	21	28.2	0.74 (0.46 - 1.14)	Observed < expected	23	39.48	0.58 (0.37 - 0.87)	Observed significantly < expected
50-59 Years	1.57	56425075	12	50.93	0.24 (0.12 - 0.41)	Observed significantly < expected	17	72.76	0.23 (0.14 - 0.37)	Observed significantly < expected	19	101.87	0.19 (0.11 - 0.29)	Observed significantly < expected
60-69 Years	0.68	57182485	6	22.36	0.27 (0.1 - 0.58)	Observed significantly < expected	9	31.94	0.28 (0.13 - 0.53)	Observed significantly < expected	12	44.71	0.27 (0.14 - 0.47)	Observed significantly < expected
Over 70 Years	0.34	31869628	7	6.23	1.12 (0.45 - 2.32)	Observed > expected	10	8.9	1.12 (0.54 - 2.07)	Observed > expected	13	12.46	1.04 (0.56 - 1.78)	Observed > expected

Table 168 Observed versus expected analysis for CVST without thrombocytopenia (using SIDIAP_PC HOSP incident rates) (with known normal platelet count) stratified by age in the EEA +UK +Australia +Brazil

Age group/ Gender	IR [a]	Exposure[b]	Risk Window 21 Days				Risk Window 30 Days				Risk Window 42 Days			
			Observed number of cases[c]	Expected number of cases	Over E ratio (95 % CI)	Conclusion	Observed number of cases[c]	Expected number of cases	Over E ratio (95 % CI)	Conclusion	Observed number of cases[c]	Expected number of cases	Over E ratio (95 % CI)	Conclusion
18-49 Years plus cases Unk TTO	0.34	100987434	26	19.74	1.32 (0.86 - 1.93)	Observed > expected	28	28.2	0.99 (0.66 - 1.44)	Observed < expected	30	39.48	0.76 (0.51 - 1.08)	Observed < expected
50-59 Years plus cases Unk TTO	1.57	56425075	16	50.93	0.31 (0.18 - 0.51)	Observed significantly < expected	21	72.76	0.29 (0.18 - 0.44)	Observed significantly < expected	23	101.87	0.23 (0.14 - 0.34)	Observed significantly < expected
60-69 Years plus cases Unk TTO	0.68	57182485	8	22.36	0.36 (0.15 - 0.7)	Observed significantly < expected	11	31.94	0.34 (0.17 - 0.62)	Observed significantly < expected	14	44.71	0.31 (0.17 - 0.53)	Observed significantly < expected
Over 70 Years plus cases Unk TTO	0.34	31869628	12	6.23	1.93 (1 - 3.36)	Observed > expected	15	8.9	1.69 (0.94 - 2.78)	Observed > expected	18	12.46	1.44 (0.86 - 2.28)	Observed > expected

a Incidence rate Source: Willame et al 2021[B], from ES_SIDIAP_PCHOSP

b Exposure is to DLP 28 June 2022.

c All cases to DLP 28 June 2022.

Table 169 Observed versus expected analysis for CVST without thrombocytopenia (using SIDIAP_PC HOSP incident rates) (with known normal platelet count) stratified by age in the UK

Age group	IR [a]	Exposure [b]	Risk Window 21 Days				Risk Window 30 Days				Risk Window 42 Days			
			Observed number of cases [c]	Expected number of cases	O over E ratio (95% CI)	Conclusion	Observed number of cases [c]	Expected number of cases	O over E ratio (95% CI)	Conclusion	Observed number of cases [c]	Expected number of cases	O over E ratio (95% CI)	Conclusion
18-49 UK	0.34	15400733	12	3.01	3.99 (2.06 - 6.96)	Observed significantly > expected	13	4.3	3.02 (1.61 - 5.17)	Observed significantly > expected	15	6.02	2.49 (1.39 - 4.11)	Observed significantly > expected
50-59 UK	1.57	13197033	9	11.91	0.76 (0.35 - 1.43)	Observed < expected	12	17.02	0.71 (0.36 - 1.23)	Observed < expected	14	23.83	0.59 (0.32 - 0.99)	Observed significantly < expected
60-69 UK	0.68	10157100	3	3.97	0.76 (0.16 - 2.21)	Observed < expected	5	5.67	0.88 (0.29 - 2.06)	Observed < expected	7	7.94	0.88 (0.35 - 1.82)	Observed < expected
70-79 UK	0.67	7047791	4	2.71	1.48 (0.4 - 3.78)	Observed > expected	5	3.88	1.29 (0.42 - 3.01)	Observed > expected	5	5.43	0.92 (0.3 - 2.15)	Observed < expected
Over 80 UK	1.49	3024979	1	2.59	0.39 (0.01 - 2.15)	Observed < expected	1	3.7	0.27 (0.01 - 1.51)	Observed < expected	3	5.18	0.58 (0.12 - 1.69)	Observed < expected
18-49 UK plus cases Unk TTO	0.34	15400733	15	3.01	4.98 (2.79 - 8.22)	Observed significantly > expected	16	4.3	3.72 (2.13 - 6.04)	Observed significantly > expected	18	6.02	2.99 (1.77 - 4.73)	Observed significantly > expected

Table 169 Observed versus expected analysis for CVST without thrombocytopenia (using SIDIAP_PC HOSP incident rates) (with known normal platelet count) stratified by age in the UK

Age group	IR [a]	Exposure [b]	Risk Window 21 Days				Risk Window 30 Days				Risk Window 42 Days			
			Observed number of cases [c]	Expected number of cases	O over E ratio (95% CI)	Conclusion	Observed number of cases [c]	Expected number of cases	O over E ratio (95% CI)	Conclusion	Observed number of cases [c]	Expected number of cases	O over E ratio (95% CI)	Conclusion
50-59 UK plus cases Unk TTO	1.57	13197033	13	11.91	1.09 (0.58 - 1.87)	Observed > expected	16	17.02	0.94 (0.54 - 1.53)	Observed < expected	18	23.83	0.76 (0.45 - 1.19)	Observed < expected
60-69 UK plus cases Unk TTO	0.68	10157100	5	3.97	1.26 (0.41 - 2.94)	Observed > expected	7	5.67	1.23 (0.5 - 2.54)	Observed > expected	9	7.94	1.13 (0.52 - 2.15)	Observed > expected
70-79 UK plus cases Unk TTO	0.67	7047791	5	2.71	1.85 (0.6 - 4.31)	Observed > expected	6	3.88	1.55 (0.57 - 3.37)	Observed > expected	6	5.43	1.1 (0.41 - 2.41)	Observed > expected
Over 80 UK plus cases Unk TTO	1.49	3024979	2	2.59	0.77 (0.09 - 2.79)	Observed < expected	2	3.7	0.54 (0.07 - 1.95)	Observed < expected	4	5.18	0.77 (0.21 - 1.98)	Observed < expected

a Incidence rate Source: Willame et al 2021 [B], from ES_SIDIAP_PCHOSP

b Exposure is to DLP 28 June 2022.

c All cases to DLP 28 June 2022.

Only cases observed within 0-21, 0-30 and 0-42 days were included; Risk window: 21, 30 and 42 days.

CI Confidence Interval; E Expected; IR Incidence Rate; O Observed; TTO Time to onset; UK United Kingdom; EEA European economic area.

As a comparison to the above, the same observed versus expected analyses are carried out using incidence rates from Truven MarketScan. That approach is aligned with incidence rates routinely used for TTS O/E monitoring. In particular, the time window for exclusion of patients with TCP (either -7/+7 or-1/+14) was consistent with the one used for TTS. In this analysis, a conservative approach in terms of ICD10 codes for CVST (I63.6 and I67.6) was used. Also, the analysis included only incident (no CVST claims within 12 months prior to index) inpatient claims. Those analyses for CVST are presented with different risk windows (21 days, 30 days, and 42 days) for all global reports in Table 170, stratified by age in the EEA, UK, Australia and Brazil region in Table 171, stratified by age in UK in Table 172and gender (Female and Male) in the UK Table 173 and Table 174. All stratifications also included cases with an unknown TTO, as a conservative approach.

The O/E analysis for CVST without thrombocytopenia (with known normal thrombocytes) using incidence rates from Truven MarketScan showed that the number of observed cases were significantly lower than expected when overall and also cases from EEA, UK, Brazil and Australia were considered. With the stratified O/E analysis by age and gender, there were certain age and gender groups (50-59 years in UK for all risk windows including unknown TTO, 18-49 years in UK for risk window of 21 days, only when unknown TTO is considered) where the observed number was higher than expected. However, when a qualitative review was conducted, many of the cases were missing information such as medical history, concomitant medications, precluding a proper assessment to determine causal relationship.

Table 170 Observed versus expected analysis for CVST without thrombocytopenia (with known normal platelet count) (using Truven 14 incident rates) for global reports

Age group	IR [a]	Exposure [b]	Risk Window 21 Days				Risk Window 30 Days				Risk Window 42 Days			
			Observed number of cases [c]	Expected number of cases	O over E ratio (95% CI)	Conclusion	Observed number of cases [c]	Expected number of cases	O over E ratio (95% CI)	Conclusion	Observed number of cases [c]	Expected number of cases	O over E ratio (95% CI)	Conclusion
Overall (Global)	1.5	448306152	47	386.64	0.12 (0.09 - 0.16)	Observed significantly < expected	61	552.34	0.11 (0.08 - 0.14)	Observed significantly < expected	73	773.27	0.09 (0.07 - 0.12)	Observed significantly < expected
Overall (Global) plus cases Unk TTO	1.5	448306152	72	386.64	0.19 (0.15 - 0.23)	Observed significantly < expected	86	552.34	0.16 (0.12 - 0.19)	Observed significantly < expected	98	773.27	0.13 (0.1 - 0.15)	Observed significantly < expected

a Incidence Rate (per/100,000 PY) from Truven Market Scan database (2019)

b Exposure is to DLP 28 June 2022.

c All cases to DLP 28 June 2022.

Truven 14: CVST (I63.6 or I67.6) inpatient without TCP within -1/14 days (incident)

Only cases observed within 0-21, 0-30 and 0-42 days were included; Risk window: 21, 30 and 42 days.

Table 171 Observed versus expected analysis for CVST without thrombocytopenia (with known normal platelet count) (using Truven 14 incident rates) for EEA+UK+Australia+Brazil

Age group	IR [a]	Exposure[b]	Risk Window 21 Days				Risk Window 30 Days				Risk Window 42 Days			
			Observed number of cases[c]	Expected number of cases	O over E ratio (95% CI)	Conclusion	Observed number of cases[c]	Expected number of cases	O over E ratio (95% CI)	Conclusion	Observed number of cases[c]	Expected number of cases	O over E ratio (95% CI)	Conclusion
EEA+UK+Brazil+Australia Data														
18-49 Years	1.55	100987434	19	90	0.21 (0.13 - 0.33)	Observed significantly < expected	21	128.57	0.16 (0.1 - 0.25)	Observed significantly < expected	23	180	0.13 (0.08 - 0.19)	Observed significantly < expected
50-59 Years	0.86	56425075	12	27.9	0.43 (0.22 - 0.75)	Observed significantly < expected	17	39.86	0.43 (0.25 - 0.68)	Observed significantly < expected	19	55.8	0.34 (0.21 - 0.53)	Observed significantly < expected
60-69 Years	1.65	57182485	6	54.25	0.11 (0.04 - 0.24)	Observed significantly < expected	9	77.5	0.12 (0.05 - 0.22)	Observed significantly < expected	12	108.5	0.11 (0.06 - 0.19)	Observed significantly < expected
Over 70 Years	0.9	31869628	7	16.49	0.42 (0.17 - 0.87)	Observed significantly < expected	10	23.56	0.42 (0.2 - 0.78)	Observed significantly < expected	13	32.98	0.39 (0.21 - 0.67)	Observed significantly < expected
18-49 Years plus cases Unk TTO	1.55	100987434	26	90	0.29 (0.19 - 0.42)	Observed significantly < expected	28	128.57	0.22 (0.14 - 0.31)	Observed significantly < expected	30	180	0.17 (0.11 - 0.24)	Observed significantly < expected
50-59 Years plus cases	0.86	56425075	16	27.9	0.57 (0.33 - 0.93)	Observed significantly < expected	21	39.86	0.53 (0.33 - 0.81)	Observed significantly < expected	23	55.8	0.41 (0.26 - 0.62)	Observed significantly < expected

Table 171 Observed versus expected analysis for CVST without thrombocytopenia (with known normal platelet count) (using Truven 14 incident rates) for EEA+UK+Australia+Brazil

Age group	IR [a]	Exposure[b]	Risk Window 21 Days				Risk Window 30 Days				Risk Window 42 Days			
			Observed number of cases[c]	Expected number of cases	O over E ratio (95% CI)	Conclusion	Observed number of cases[c]	Expected number of cases	O over E ratio (95% CI)	Conclusion	Observed number of cases[c]	Expected number of cases	O over E ratio (95% CI)	Conclusion
Unk TTO														
60-69 Years plus cases Unk TTO	1.65	57182485	8	54.25	0.15 (0.06 - 0.29)	Observed significantly < expected	11	77.5	0.14 (0.07 - 0.25)	Observed significantly < expected	14	108.5	0.13 (0.07 - 0.22)	Observed significantly < expected
Over 70 Years plus cases Unk TTO	0.9	31869628	12	16.49	0.73 (0.38 - 1.27)	Observed < expected	15	23.56	0.64 (0.36 - 1.05)	Observed < expected	18	32.98	0.55 (0.32 - 0.86)	Observed significantly < expected

a Incidence Rate (per/100,000 PY) from Truven Market Scan database (2019)

b Exposure is to DLP 28 June 2022.

c All cases to DLP 28 June 2022.

Truven 14: CVST (I63.6 or I67.6) inpatient without TCP within -1/14 days (incident)

Only cases observed within 0-21, 0-30 and 0-42 days were included; Risk window: 21, 30 and 42 days

Table 172 Observed versus expected analysis for CVST (Cerebrovascular venous and sinus thrombosis) without thrombocytopenia (with known normal platelet count) (using Truven 14 incident rates) stratified by age in the UK

Age group	IR [a]	Exposure [b]	Risk Window 21 Days				Risk Window 30 Days				Risk Window 42 Days			
			Observed number of cases [c]	Expected number of cases	O over E ratio (95% CI)	Conclusion	Observed number of cases [c]	Expected number of cases	O over E ratio (95% CI)	Conclusion	Observed number of cases [c]	Expected number of cases	O over E ratio (95% CI)	Conclusion
18-49 UK	1.55	15400733	12	13.72	0.87 (0.45 - 1.53)	Observed < expected	13	19.61	0.66 (0.35 - 1.13)	Observed < expected	15	27.45	0.55 (0.31 - 0.9)	Observed significantly < expected
50-59 UK	0.86	13197033	9	6.53	1.38 (0.63 - 2.62)	Observed > expected	12	9.32	1.29 (0.67 - 2.25)	Observed > expected	14	13.05	1.07 (0.59 - 1.8)	Observed > expected
60-69 UK	1.65	10157100	3	9.64	0.31 (0.06 - 0.91)	Observed significantly < expected	5	13.77	0.36 (0.12 - 0.85)	Observed significantly < expected	7	19.27	0.36 (0.15 - 0.75)	Observed significantly < expected
70-79 UK	1.53	7047791	4	6.2	0.65 (0.18 - 1.65)	Observed < expected	5	8.86	0.56 (0.18 - 1.32)	Observed < expected	5	12.4	0.4 (0.13 - 0.94)	Observed significantly < expected
Over 80 UK	8.21	3024979	1	14.28	0.07 (0 - 0.39)	Observed significantly < expected	1	20.4	0.05 (0 - 0.27)	Observed significantly < expected	3	28.56	0.11 (0.02 - 0.31)	Observed significantly < expected
18-49 UK plus cases Unk TTO	1.55	15400733	15	13.72	1.09 (0.61 - 1.8)	Observed > expected	16	19.61	0.82 (0.47 - 1.32)	Observed < expected	18	27.45	0.66 (0.39 - 1.04)	Observed < expected

Table 172 Observed versus expected analysis for CVST (Cerebrovascular venous and sinus thrombosis) without thrombocytopenia (with known normal platelet count) (using Truven 14 incident rates) stratified by age in the UK

Age group	IR [a]	Exposure[b]	Risk Window 21 Days				Risk Window 30 Days				Risk Window 42 Days			
			Observed number of cases[c]	Expected number of cases	O over E ratio (95% CI)	Conclusion	Observed number of cases[c]	Expected number of cases	O over E ratio (95% CI)	Conclusion	Observed number of cases[c]	Expected number of cases	O over E ratio (95% CI)	Conclusion
50-59 UK plus cases Unk TTO	0.86	13197033	13	6.53	1.99 (1.06 - 3.4)	Observed significantly > expected	16	9.32	1.72 (0.98 - 2.79)	Observed > expected	18	13.05	1.38 (0.82 - 2.18)	Observed > expected
60-69 UK plus cases Unk TTO	1.65	10157100	5	9.64	0.52 (0.17 - 1.21)	Observed < expected	7	13.77	0.51 (0.2 - 1.05)	Observed < expected	9	19.27	0.47 (0.21 - 0.89)	Observed significantly < expected
70-79 UK plus cases Unk TTO	1.53	7047791	5	6.2	0.81 (0.26 - 1.88)	Observed < expected	6	8.86	0.68 (0.25 - 1.47)	Observed < expected	6	12.4	0.48 (0.18 - 1.05)	Observed < expected
Over 80 UK plus cases Unk TTO	8.21	3024979	2	14.28	0.14 (0.02 - 0.51)	Observed significantly < expected	2	20.4	0.1 (0.01 - 0.35)	Observed significantly < expected	4	28.56	0.14 (0.04 - 0.36)	Observed significantly < expected

a Incidence Rate (per/100,000 PY) from Truven Market Scan database (2019)

b Exposure is to DLP 28 June 2022.

c All cases to DLP 28 June 2022.

Truven 14: CVST (163.6 or I67.6) inpatient without TCP witbin -1/14 days (incident)

Table 173 Observed versus expected analysis for CVST (Cerebrovascular venous and sinus thrombosis) without thrombocytopenia (with known normal platelet count) (using Truven 14 incident rates) stratified by gender (Female) in the UK

Age group/ Gender	IR [a]	Exposure [b]	Risk Window 21 Days				Risk Window 30 Days				Risk Window 42 Days			
			Observed number of cases[c]	Expected number of cases	Over E ratio (95% CI)	Conclusion	Observed number of cases[c]	Expected number of cases	Over E ratio (95% CI)	Conclusion	Observed number of cases[c]	Expected number of cases	Over E ratio (95% CI)	Conclusion
Female 18-29	2.46	1221578	1	1.73	0.58 (0.01 - 3.22)	Observed < expected	1	2.47	0.4 (0.01 - 2.26)	Observed < expected	1	3.46	0.29 (0.01 - 1.61)	Observed < expected
Female 30-39	2.23	2028622	2	2.6	0.77 (0.09 - 2.78)	Observed < expected	2	3.72	0.54 (0.07 - 1.94)	Observed < expected	2	5.2	0.38 (0.05 - 1.39)	Observed < expected
Female 40-49	1.84	4749427	4	5.02	0.8 (0.22 - 2.04)	Observed < expected	4	7.18	0.56 (0.15 - 1.43)	Observed < expected	5	10.05	0.5 (0.16 - 1.16)	Observed < expected
Female 50-59	0.82	6280795	4	2.96	1.35 (0.37 - 3.46)	Observed > expected	5	4.23	1.18 (0.38 - 2.76)	Observed > expected	6	5.92	1.01 (0.37 - 2.21)	Observed > expected
Female 60-69	1.41	4996322	1	4.05	0.25 (0.01 - 1.38)	Observed < expected	3	5.79	0.52 (0.11 - 1.51)	Observed < expected	4	8.1	0.49 (0.13 - 1.26)	Observed < expected
Female 70-79	0.71	3688886	2	1.51	1.32 (0.16 - 4.78)	Observed > expected	3	2.15	1.4 (0.29 - 4.08)	Observed > expected	3	3.01	1 (0.21 - 2.91)	Observed < expected
Female over 80	9.32	1864578	0	9.99	0 (0 - 0.37)	Observed significantly < expected	0	14.27	0 (0 - 0.26)	Observed significantly < expected	2	19.98	0.1 (0.01 - 0.36)	Observed significantly < expected
Female 18-29 plus cases	2.46	1221578	1	1.73	0.58 (0.01 - 3.22)	Observed < expected	1	2.47	0.4 (0.01 - 2.26)	Observed < expected	1	3.46	0.29 (0.01 - 1.61)	Observed < expected

Table 173 Observed versus expected analysis for CVST (Cerebrovascular venous and sinus thrombosis) without thrombocytopenia (with known normal platelet count) (using Truven 14 incident rates) stratified by gender (Female) in the UK

Age group/ Gender	IR [a]	Exposure [b]	Risk Window 21 Days				Risk Window 30 Days				Risk Window 42 Days			
			Observed number of cases[c]	Expected number of cases	O over E ratio (95% CI)	Conclusion	Observed number of cases[c]	Expected number of cases	O over E ratio (95% CI)	Conclusion	Observed number of cases[c]	Expected number of cases	O over E ratio (95% CI)	Conclusion
Unk TTO														
Female 30-39 plus cases Unk TTO	2.23	2028622	2	2.6	0.77 (0.09 - 2.78)	Observed < expected	2	3.72	0.54 (0.07 - 1.94)	Observed < expected	2	5.2	0.38 (0.05 - 1.39)	Observed < expected
Female 40-49 plus cases Unk TTO	1.84	4749427	6	5.02	1.2 (0.44 - 2.6)	Observed > expected	6	7.18	0.84 (0.31 - 1.82)	Observed < expected	7	10.05	0.7 (0.28 - 1.44)	Observed < expected
Female 50-59 plus cases Unk TTO	0.82	6280795	5	2.96	1.69 (0.55 - 3.94)	Observed > expected	6	4.23	1.42 (0.52 - 3.09)	Observed > expected	7	5.92	1.18 (0.48 - 2.44)	Observed > expected
Female 60-69 plus cases Unk TTO	1.41	4996322	3	4.05	0.74 (0.15 - 2.16)	Observed < expected	5	5.79	0.86 (0.28 - 2.02)	Observed < expected	6	8.1	0.74 (0.27 - 1.61)	Observed < expected

Table 173 Observed versus expected analysis for CVST (Cerebrovascular venous and sinus thrombosis) without thrombocytopenia (with known normal platelet count) (using Truven 14 incident rates) stratified by gender (Female) in the UK

Age group/ Gender	IR [a]	Exposure [b]	Risk Window 21 Days				Risk Window 30 Days				Risk Window 42 Days			
			Observed number of cases[c]	Expected number of cases	Over E ratio (95% CI)	Conclusion	Observed number of cases[c]	Expected number of cases	Over E ratio (95% CI)	Conclusion	Observed number of cases[c]	Expected number of cases	Over E ratio (95% CI)	Conclusion
Female 70-79 plus cases Unk TTO	0.71	3688886	2	1.51	1.32 (0.16 - 4.78)	Observed > expected	3	2.15	1.4 (0.29 - 4.08)	Observed > expected	3	3.01	1 (0.21 - 2.91)	Observed < expected
Female over 80 plus cases Unk TTO	9.32	1864578	1	9.99	0.1 (0 - 0.56)	Observed significantly < expected	1	14.27	0.07 (0 - 0.39)	Observed significantly < expected	3	19.98	0.15 (0.03 - 0.44)	Observed significantly < expected

a Incidence Rate (per/100,000 PY) from Truven Market Scan database (2019)

b Exposure is to DLP 28 June 2022.

c All cases to DLP 28 June 2022.

Truven 14: CVST (163.6 or I67.6) inpatient without TCP within -1/14 days (incident)

Only cases observed within 0-21, 0-30 and 0-42 days were included; Risk window: 21, 30 and 42 days.

Table 174 Observed versus expected analysis for CVST (Cerebrovascular venous and sinus thrombosis) without thrombocytopenia (with known normal platelet count) (using Truven 14 incident rates) stratified by gender (Male) in the UK

Age group/ Gender	IR [a]	Exposure[b]	Risk Window 21 Days				Risk Window 30 Days				Risk Window 42 Days			
			Observed number of cases[c]	Expected number of cases	O over E ratio (95% CI)	Conclusion	Observed number of cases[c]	Expected number of cases	O over E ratio (95% CI)	Conclusion	Observed number of cases[c]	Expected number of cases	O over E ratio (95% CI)	Conclusion
Male 18-29	1.1	907479	1	0.57	1.75 (0.04 - 9.77)	Observed > expected	1	0.82	1.22 (0.03 - 6.79)	Observed > expected	2	1.15	1.74 (0.21 - 6.28)	Observed > expected
Male 30-39	0.69	1537246	1	0.61	1.64 (0.04 - 9.13)	Observed > expected	1	0.87	1.15 (0.03 - 6.4)	Observed > expected	1	1.22	0.82 (0.02 - 4.57)	Observed < expected
Male 40-49	0.86	4955204	3	2.45	1.22 (0.25 - 3.58)	Observed > expected	4	3.5	1.14 (0.31 - 2.93)	Observed > expected	4	4.9	0.82 (0.22 - 2.09)	Observed < expected
Male 50-59	0.91	6915956	5	3.62	1.38 (0.45 - 3.22)	Observed > expected	7	5.17	1.35 (0.54 - 2.79)	Observed > expected	8	7.24	1.1 (0.48 - 2.18)	Observed > expected
Male 60-69	1.92	5160658	2	5.7	0.35 (0.04 - 1.27)	Observed < expected	2	8.14	0.25 (0.03 - 0.89)	Observed significantly < expected	3	11.39	0.26 (0.05 - 0.77)	Observed significantly < expected
Male 70-79	2.49	3358831	2	4.81	0.42 (0.05 - 1.5)	Observed < expected	2	6.87	0.29 (0.04 - 1.05)	Observed < expected	2	9.62	0.21 (0.03 - 0.75)	Observed significantly < expected
Male over 80	6.64	1160382	1	4.43	0.23 (0.01 - 1.26)	Observed < expected	1	6.33	0.16 (0 - 0.88)	Observed significantly < expected	1	8.86	0.11 (0 - 0.63)	Observed significantly < expected
Male 18-29 plus cases	1.1	907479	1	0.57	1.75 (0.04 - 9.77)	Observed > expected	1	0.82	1.22 (0.03 - 6.79)	Observed > expected	2	1.15	1.74 (0.21 - 6.28)	Observed > expected

Table 174 Observed versus expected analysis for CVST (Cerebrovascular venous and sinus thrombosis) without thrombocytopenia (with known normal platelet count) (using Truven 14 incident rates) stratified by gender (Male) in the UK

Age group/ Gender	IR [a]	Exposure[b]	Risk Window 21 Days				Risk Window 30 Days				Risk Window 42 Days			
			Observed number of cases[c]	Expected number of cases	O over E ratio (95% CI)	Conclusion	Observed number of cases[c]	Expected number of cases	O over E ratio (95% CI)	Conclusion	Observed number of cases[c]	Expected number of cases	O over E ratio (95% CI)	Conclusion
Unk TTO														
Male 30-39 plus cases Unk TTO	0.69	1537246	1	0.61	1.64 (0.04 - 9.13)	Observed > expected	1	0.87	1.15 (0.03 - 6.4)	Observed > expected	1	1.22	0.82 (0.02 - 4.57)	Observed < expected
Male 40-49 plus cases Unk TTO	0.86	4955204	4	2.45	1.63 (0.44 - 4.18)	Observed > expected	5	3.5	1.43 (0.46 - 3.33)	Observed > expected	5	4.9	1.02 (0.33 - 2.38)	Observed > expected
Male 50-59 plus cases Unk TTO	0.91	6915956	8	3.62	2.21 (0.95 - 4.35)	Observed > expected	10	5.17	1.93 (0.93 - 3.56)	Observed > expected	11	7.24	1.52 (0.76 - 2.72)	Observed > expected
Male 60-69 plus cases Unk TTO	1.92	5160658	2	5.7	0.35 (0.04 - 1.27)	Observed < expected	2	8.14	0.25 (0.03 - 0.89)	Observed significantly < expected	3	11.39	0.26 (0.05 - 0.77)	Observed significantly < expected

Table 174 Observed versus expected analysis for CVST (Cerebrovascular venous and sinus thrombosis) without thrombocytopenia (with known normal platelet count) (using Truven 14 incident rates) stratified by gender (Male) in the UK

Age group/ Gender	IR [a]	Exposure[b]	Risk Window 21 Days				Risk Window 30 Days				Risk Window 42 Days			
			Observed number of cases[c]	Expected number of cases	O over E ratio (95% CI)	Conclusion	Observed number of cases[c]	Expected number of cases	O over E ratio (95% CI)	Conclusion	Observed number of cases[c]	Expected number of cases	O over E ratio (95% CI)	Conclusion
Male 70-79 plus cases Unk TTO	2.49	3358831	3	4.81	0.62 (0.13 - 1.82)	Observed < expected	3	6.87	0.44 (0.09 - 1.28)	Observed < expected	3	9.62	0.31 (0.06 - 0.91)	Observed significantly < expected
Male over 80 plus cases Unk TTO	6.64	1160382	1	4.43	0.23 (0.01 - 1.26)	Observed < expected	1	6.33	0.16 (0 - 0.88)	Observed significantly < expected	1	8.86	0.11 (0 - 0.63)	Observed significantly < expected

a Incidence Rate (per/100,000 PY) from Truven Market Scan database (2019)

b Exposure is to DLP 28 June 2022.

c All cases to DLP 28 June 2022.

Truven 14: CVST (I63.6 or I67.6) inpatient without TCP within -1/14 days (incident)

Only cases observed within 0-21, 0-30 and 0-42 days were included; Risk window: 21, 30 and 42 days.

Summary:

AstraZeneca continued to review the safety information for CVST without thrombocytopenia from sources including clinical trials, post-marketing reports, and the published literature for the reporting period.

There were no reports of CVST without thrombocytopenia related AEs in the Oxford pooled studies. There was 1 report of Cerebral venous/Cerebral venous sinus thrombosis identified in the VAXZEVRIA group in US Study (D8110C00001), however, there was no new safety information received in the reporting period.

A review of the post-marketing data did not identify any index case or a new safety signal. There were no case reports with positive re-challenge (after the first and second dose of the vaccine). There are 573 and 89 cases for the cumulative and reporting period respectively. Cumulatively, there was a preponderance for female gender (61%) versus males (35%), and 68% cases were in age group 18-64 years. Twelve (12) fatal cases (92%) out of all 13 fatal cases (in all age groups) were reported in females in the reporting period. Cumulatively, 28 (60.8%) out of all 46 fatal cases were reported in females. There was no significant difference noted between the cumulative and reporting period in terms of the volume and distribution of cases.

A review of the published literature did not identify any new safety information on this topic in association with VAXZEVRIA.

The Observed versus Expected analysis was carried out using incidence rates from ACCESS: SIDIAP PCHOSP and Truven MarketScan (2019). SIDIAP PCHOSP is representative of the general population in terms of age, sex, and geographic distribution and that the rate was used by the EMA, and this would permit a comparison of the O/E analysis conducted by EMA, whereas Truven MarketScan was used for consistency with background rates for TTS generated using MarketScan. The results showed observed cases are more than expected in the general population globally. The age stratifications suggest that the O/E ratio is higher in younger age groups than in the older age groups and that the O/E ratio is higher in females than in males. However, it is important to note that O/E analyses are complementary to routine signal detection methods, and are not designed to determine a causal relationship; confounding factors were not considered in O/E (such as possible COVID-19 infections or other possible causes for CVST without thrombocytopenia).

CVST without thrombocytopenia is an important potential risk in the VAXZEVRIA Core Risk Management Plan and the topic will continue to be kept under close surveillance by AstraZeneca.

Conclusion

From the data identified during the reporting period and also taking into account the cumulative experience, AstraZeneca considers that there is currently insufficient evidence of a reasonable possibility of causal relationship between VAXZEVRIA and CVST without thrombocytopenia. CVST without thrombocytopenia is included in section 4.4 (section 4.4 Warnings and Precautions) of the CDS to inform prescribers that these events may require different treatment approaches than TTS. Healthcare professionals should consult applicable guidance. No changes to the CDS or product leaflets are warranted at this time.

AstraZeneca will continue to monitor safety information for CVST without thrombocytopenia as an important potential risk and take further actions as deemed appropriate.

16.3.1.2 Immune-mediated neurological conditions

Immune-mediated neurological conditions is considered as an important potential risk for VAXZEVRIA as per the AstraZeneca Core RMP.

During the period covered by this PBRER, two signals ('Hypoaesthesia and Paraesthesia' and 'Guillain-Barré syndrome' were closed. The signal of 'Hypoaesthesia and Paraesthesia' was closed and confirmed as a non-important identified risk and the CDS section 4.8 'Undesirable effects' was updated (please refer to Section 4 'Changes To Reference Safety Information' and Section 16.2.5 'Closed signals that are identified risks not categorised as important'). The signal of Guillain-Barré syndrome (GBS) was closed with update of the CDS section 4.4 'Special warnings and special precautions for use' (please refer to section 4 'Changes To Reference Safety Information' and section 16.2.2 'Closed signals categorised as important potential risks').

During the reporting interval of the PBRER, AstraZeneca had received health authority requests on 'Acute Disseminated Encephalomyelitis' which is discussed in section 15.2.12 Acute Disseminated Encephalomyelitis.

Reviews of specific topics relating to Immune-mediated neurological conditions/ Nervous system disorders, including immune-mediated neurological conditions with VAXZEVRIA, including Encephalitis, and Transverse myelitis (TM), as requested by PRAC for inclusion in the previous PBRER (DLP 28 December 2021) are continued in this PBRER.

During the period covered by this report (29 December 2021 – 28 June 2022), a total of 5641 cases from literature, non-interventional studies and spontaneous sources were reported within the concept of immune-mediated neurological disorders. Out of the 5641 cases, 1712 (30.3%) were medically confirmed (serious 788 (46.0%), non-serious 924 (54.0%)) and 3929 (69.7%) were consumer reports (serious 1314 (33.4%), non-serious 2615 (66.6%)). The 5641 cases had 6664 PTs. The most commonly reported PTs were Paraesthesia (2976), Hypoaesthesia (1982), Neuralgia (358), Guillain-Barre syndrome (318), Sensory disturbance (232), Neuropathy peripheral (93), Myelitis transverse (80), Sensory loss (79), Polyneuropathy (63), Optic

neuritis (49), Encephalitis (42), Acute disseminated encephalomyelitis (37), Myelitis (35), Multiple sclerosis (33), Chronic inflammatory demyelinating polyradiculoneuropathy (28), Multiple sclerosis relapse (24), Neuritis (19), Miller Fisher syndrome (18), Demyelination (18), Neuromyelitis optica spectrum disorder (15), Myelopathy (14), Peripheral sensory neuropathy (12), Myelin oligodendrocyte glycoprotein antibody-associated disease (12).

Cumulatively till 28 June 2022, a total of 36033 cases from literature, clinical studies, non-interventional studies and spontaneous sources were reported within the concept of immune-mediated neurological disorders. Out of the 36033 cases, 7625 (21.2%) were medically confirmed (3243 (42.5%) serious, 4382 (57.25%) non-serious) and 28408 were consumer reports (14073 (49.5%) serious, 14335 (50.5%) non-serious.

Literature review in the reporting period: Three relevant literature articles were identified (Atzenhoffer et al 2022, Keh et al 2022 and Netravathi et al 2022). Netravathi et al 2022 has been discussed in section 15.2.12 and in the sub section below 16.3.1.2.2.

Atzenhoffer et al 2022 conducted a study to assess the potential association of GBS with mRNA-based or adenovirus-vectored COVID-19 vaccines, performing a comparative analysis using data from VigiBase, the WHO international pharmacovigilance database. Case selection only involved mRNA-based SARS-CoV-2 vaccines or adenovirus-vectored SARS-CoV-2 vaccines, with exclusion criteria including (i) the time to onset between vaccination and the occurrence of GBS was missing, (ii) the time to onset was > 42 days after the most proximal dose, (iii) concomitant infections known to be associated with the occurrence of GBS were identified in the ICSR, and (iv) the report only mentioned "Intensive care unit weakness". Authors reported on 15 October 2021, 3466 cases of GBS associated with COVID-19 vaccine administration extracted from VigiBase, of which 967 (27.9%) were excluded. The most common causes of exclusion were an unknown time to onset, and time to onset over 42 days from last vaccination. Of the included cases, 1299 (52%) were male, 1185 (47.4%) were female, and 15 (0.6%) cases were unknown gender; 2192 (87.7%) patient reported age, with a median of 57 (45-66) years, 652 (29.7%) were older than 64 years, and 144 (5.6%) were younger than 26 years. The suspected vaccines were mRNA-based COVID-19 vaccines in 1342 (53.7%) cases and adenovirus-vectored COVID-19 vaccines in 1157 (46.3%). The subtype of acute polyneuropathy was GBS in 2445 (97.8%) patients and MFS in 54 (2.2%).

Authors state that the results support the moderate increased risk of GBS associated with adenovirus-vectored COVID-19 vaccines found by other investigators and suggest an absence of safety concern for the recipients of mRNA based COVID-19 vaccines.

AstraZeneca comment:

AstraZeneca agrees with the study limitations as mentioned, that studies based on spontaneous reports are subject to numerous uncertainties and misclassification of the events, as well

limited clinical data available from VigiBase, where several reports were classified as unevaluable and case ascertainment with respect to the BCC unfeasible, occasioning an important percentage of excluded cases for very limited quality data. A weakness with this type of analysis is that it is not adjusted for any confounders. The group receiving the AZD1222 vaccine were the oldest, which is expected since the study period included vaccines administrated up to August 15, 2021, several months after many countries restricted the use of AZD1222 to the older population. No information on comorbidities is available, so adjustment for health status is not possible.

Keh et al 2022 extracted GBS cases along with recorded diagnosis from the UK National Immunoglobin Database (NID) during the period 01 January 2021 to 31 October 2021. These numbers were compared to the historical GBS cases recorded in the NID from 2016 to 2020. GBS cases from NID (from 08 December 2021 to 08 July 2021) were linked to data from the National Immunisation Management System (NIMS) in England to identify exposure to a COVID-19 vaccine using the common NHS identifier.

The authors also conducted a prospective surveillance study to compare the demographic and phenotypic characteristics of GBS cases reported from 01 January 2021 to 07 November 2021, comparing GBS cases reported as having received COVID-19 vaccination and cases without vaccination.

The authors noted a spike of GBS cases above the 2016-2020 average occurred in March and April 2021. Using the linked NID/NIMS data (England), 198 GBS cases occurred within 6 weeks of the first dose of any COVID-19 vaccine (0.618 cases per 100,000 vaccinations in 6 weeks, all ages). Of the 198 GBS cases, 176 followed a first dose VAXZEVRIA vaccine (rate 0.868 per 100,000) and 21 followed a first dose Comirnaty vaccine (rate 0.183 per 100,000). Only one case was reported within 6 weeks of Spikevax (COVID-19 Vaccine Moderna) vaccination. Twenty-three GBS cases were reported within 6 weeks of any second vaccine dose (VAXZEVRIA vaccine/messenger RNA [mRNA] vaccine). Most of the 176 cases with first dose VAXZEVRIA vaccine were reported in male vaccinees (106 reports [60%] and in vaccinees aged 50-59 years (50 reports [28%]; estimated 6-week GBS case rate of 0.899/100,000) and 60-69 years (48 reports [27%]; estimated 6-week GBS case rate of 1.196 /100,000). The publication reported a peak of GBS cases was observed around 24 days following a first dose, with higher numbers of cases seen 2-4 weeks post vaccination than in other periods. As per the authors, the first doses of VAXZEVRIA vaccine accounted for the majority of this increase. Using case numbers from day 43-84 after first-dose vaccination as a comparison group (assuming this group represents a baseline random GBS rate), the authors concluded the excess risk in the first 42 days post-VAXZEVRIA vaccine was 0.576 GBS cases per 100,000 doses (95% CI 0.481-0.691). The absolute number of excess GBS cases was between 98-140 cases for first dose VAXZEVRIA vaccination from January-July 2021.

Secondly, the authors prospectively collected 121 UK GBS cases from the British Peripheral Nerve Society (BPNS) and the Association of British Neurologists (ABN) between 01 January and 07 November 2021. The median age of reported cases was 59 years (range 17 85), with 59% being male. A total of 106 patients (87.3%) had received COVID-19 vaccination prior to GBS onset, with 80 (66.1% of the total dataset) having received a first dose vaccination within 42 days of GBS onset. Based on the authors' analysis, 90% of GBS cases reported from January – April 2021 were within 6 weeks of vaccination, compared to only 35% of cases from May 2021 onwards. Vaccine manufacturer was identifiable in 102 of the 106 patients who received Covid-19 vaccine; 89 GBS reports were after VAXZEVRIA (87.3%) and 13 after Comirnaty (12.7%) administration.

Forty-two patients (34.7%) out of 121 cases of GBS were reported to have concurrent facial weakness. Facial weakness was bilateral in 37 of these patients. Only 7 patients (5.8%) were reported to have had pure bilateral facial paralysis with paraesthesia. Based on the data reported from a multicentre surveillance dataset, the authors concluded that no specific clinical features, including facial weakness, are associated with vaccination related GBS compared to non-vaccinated cases.

AstraZeneca comment:

The authors suggested that VAXZEVRIA's first dose is associated with an excess of GBS risk and that no specific clinical features, including facial weakness, are associated with vaccination related GBS compared to non-vaccinated cases.

AstraZeneca noted the following limitations: there was no information available on COVID-19 testing in the vaccinees included in the study. The incidence rates used in the publication included the year 2020, where GBS incidence was less in comparison to the previous years (Lunn et al 2021), possibly due to home isolation prior to vaccine availability. Including that year can, therefore, provide a suppressed pre-vaccine incidence rate for comparison. The authors report a spike of GBS cases in March and April 2021, where the main vaccine used in England was VAXZEVRIA, which could have contributed to more reported cases for VAXZEVRIA versus other vaccines. In addition, the observed clustering of cases around March-April 2021 coincides with a peak in the COVID-19 pandemic in England and increased viral circulation (Office for National Statistics 2022). Thus, if the spike would have been caused by VAXZEVRIA, the frequency of the reports would presumably have remained high as the vaccinations continued to be rolled out throughout 2021.

16.3.1.2.1 Encephalitis, including fatal

Review of Cases (Interval Period 29 December 2021 – 28 June 2022)

A search of the AstraZeneca global safety database was conducted for adverse event data (29 December 2021 to 28 June 2022) from all sources (clinical, spontaneous, solicited

reporting and literature) using the narrow MedDRA SMQ: Noninfective Encephalitis (excluding PT of Acute disseminated encephalomyelitis) and HLT: Encephalopathy with VAXZEVRIA.

The above search identified 93 case reports (64 were initial case reports and 29 were follow-up versions), in vaccinees who received VAXZEVRIA. Cumulatively till DLP of 28 June 2022, 343 cases pertaining to the searched term of encephalitis were received.

Out of the 93 cases received in the reporting period, 75 cases were spontaneously reported, and 18 cases were from literature.

Of the 93 cases, 90 (96.8%) cases were serious and 3 (3.2%) were non-serious. Fifty-eight (62.4%) cases were reported by healthcare professionals (medically confirmed) and 35 (37.6%) cases were not medically confirmed. In the 93 cases, 102 events were reported.

Out of the 93 reports, 19 (20.4%) were from the UK, 14 (15.1%) India, 13 (14.0%) Germany, 12 (12.9%) Brazil, 4 (4.3%) France, 3 (3.2%) cases each from Australia, Belgium, Poland, and Spain, 2 (2.2%) cases each from Austria, and Korea, Republic of, 1 (1.1%), case each from Indonesia, Iran, Italy, Mexico, Norway, Finland, Greece, Netherlands, Slovakia, Slovenia, Albania, Canada, Sweden, Thailand, and United States.

Table 175 Encephalitis case reports by Age and Gender stratification (Cumulative versus Interval period)

Age Group	Female		Male		Gender unknown		Total	
	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative	Interval	Cumulative
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
18-65 Years	38 (40.9%)	134 (39.1%)	28 (30.1%)	104 (30.3%)	0	0	66 (71%)	238 (69.4%)
>65 Years	8 (8.6%)	39 (11.4%)	8 (8.6%)	39 (11.4%)	0	0	16 (17.2%)	78 (22.7%)
Unknown	4 (4.3%)	12 (3.5%)	3 (3.2%)	9 (2.6%)	4 (4.3%)	6 (1.7%)	11 (11.8%)	27 (7.9%)

Mean and median age was 56 years and 52 years respectively for the interval period.

Table 176 Number and percentage (%) of the case reports of Encephalitis reported after respective doses of VAXZEVRIA cumulatively versus the Interval period.

No of Cases (%)	Interval	Cumulative
After Dose 1	61 (76.3%)	277 (87.4%)

Table 176 Number and percentage (%) of the case reports of Encephalitis reported after respective doses of VAXZEVRIA cumulatively versus the Interval period.

No of Cases (%)	Interval	Cumulative
After Dose 2	18 (22.5%)	39 (12.3%)
After both the Doses	0	0
After Dose 3	1 (1.3%)	1 (0.3%)
Dose unknown	13 (NA)	26 (NA)

Known Dose information used to calculate the percentage for the case reports.

Table 177 Time to onset for Encephalitis case reports (Cumulative versus Interval period)

Time to onset	Interval	Cumulative
	No. of cases (%)	No. of Cases (%)
0 to 1 days	9 (9.7%)	40 (11.7%)
2-42 days (Risk Window)	44 (47.3%)	173 (50.4%)
>42 days	12 (12.9%)	21 (6.1%)
Unknown	28 (30.1%)	109 (31.8%)

Time to onset (TTO) identified from VAXZEVRIA administration to the Encephalitis was ranged from 0-240 days and the median TTO for all the cases was 13 days.

The adverse event (PTs) reported included Encephalitis (42), Myelin oligodendrocyte glycoprotein antibody-associated disease (12), Encephalitis autoimmune (11), Encephalopathy (8), Encephalomyelitis (6), Noninfective encephalitis (6), Hypoxic-ischemic encephalopathy (3), Leukoencephalopathy (3), Autoimmune encephalopathy (2), Septic encephalopathy (2), Acute haemorrhagic leukoencephalitis (1), Encephalitis brain stem (1), Hypertensive encephalopathy (1), Posterior reversible encephalopathy syndrome (1), Immune-mediated encephalitis (1), Limbic encephalitis (1), and Opsoclonus myoclonus (1).

The distribution of adverse events outcome for Encephalitis case reports (cumulative versus reporting period) were presented in the Table 178 below.

Table 178 Adverse Event outcome for Encephalitis case reports (Cumulative versus Interval period)

Adverse Event Outcome	Interval	Cumulative
	No. of cases (%)	No. of Cases (%)
Fatal	7(6.9%)*	12 (3.3%)
Recovered	15 (14.7%)	64 (17.6%)
Recovering	14 (13.7%)	83 (22.9%)
Recovered with Sequelae	9 (8.8%)	18 (5.0%)
Not Recovered	22 (21.6%)	103 (28.4%)
Unknown	35 (34.3%)	82 (22.7%)

*7 fatal events in 6 cases (4 initial cases and 2 follow up cases).

All the cases during the interval period have been reviewed and analysed using Brighton Collaboration (BCC) classification summarized along with cumulative data in below sections.

Brighton Collaboration Criteria assessment of cases received during the reporting period (29 December 2021- 28 June 2022).

The Brighton collaboration criteria for diagnostic certainty (Law B 2021) was used for the review of the data available in the case reports during the interval period (29 December 2021-28 June 2022). One (1) out of 93 cases fulfilled BCC1 criteria, 6 fulfilled Level 2 criteria, 8 fulfilled Level 3 criteria, 57 considered in level 4 criteria and 21 cases did not fulfil BCC criteria for certainty (Level 5 criteria).

Brighton Collaboration Level 1

One (1) case out of the 93 case reports fulfilled Brighton collaboration level 1 criteria. The case is summarized in Table 179 below.

Table 179 Summary of cases fulfilling Brighton collaboration level 1 for encephalitis reported during the interval period (29 December 2021 - 28 June 2022).

No	Case ID/ Country/ Serious-YES/NO	Age (Years) /Gender (M/F)	Relevant Medical History/ concomitant medications	Time to Onset (days) /#Dose	Event Outcome	Additional Comment	WHO-UMC Causality Assessment
1	[redacted]/United Kingdom/YES	49/M	Bipolar Disorder/ Valproate Sodium	1/ #1st Dose	Death/ cause of death mentioned as Encephalitis	Although onset date of encephalitis is reported as one day after vaccination, it is also stated that diagnosis of encephalitis was made 3 weeks after vaccination. Hence causality is assessed as 'possible. However,the concomitant medication - valproate sodium is a confounder..	Possible with confounders

Brighton Collaboration Level 2

Six (6) out of the 93 cases fulfilled Brighton collaboration level 2. These cases are summarized in Table 180 below.

Table 180 Summary of cases fulfilling Brighton collaboration level 2 for encephalitis reported during the interval period (29 December 2021- 28 June 2022).

No	Case ID/ Country/ Serious- YES/NO	Age (Years) /Gender (M/F)	Relevant Medical History/ concomitant medications	Time to Onset (days) /#Dose	Event Outcome	Additional Comment	WHO-UMC Causality Assessment
1	[redacted] YES	49/F	Not Provided	10/ #1st Dose	Recovering	Questionable treatment with antiviral (Acyclovir); amnesia + decreased level of consciousness +confusion state +sensory loss+ fever. Limited information about medical history, concomitant medications, and diagnostic workup.	Possible with limited Information.
2	[redacted] / YES	Unknown / M	Not provided	13/ #2nd Dose	Recovering	No information about full clinical picture, medical history, concomitant medications, and diagnostic workup.	Possible with limited Information.
3	[redacted] / YES	64 / M	Not Provided	Unknown/ #1st Dose	Recovered	Fever, drowsiness and pleocytosis. No information on medical history, concomitant medications, family history, details of the clinical course.	Unassessable/unclassifiable.

Table 180 Summary of cases fulfilling Brighton collaboration level 2 for encephalitis reported during the interval period (29 December 2021- 28 June 2022).

No	Case ID/ Country/ Serious- YES/NO	Age (Years) /Gender (M/F)	Relevant Medical History/ concomitant medications	Time to Onset (days) /#Dose	Event Outcome	Additional Comment	WHO-UMC Causality Assessment
4	[redacted] / YES	20 / F	Not provided	Unknown/ #2nd Dose	Unknown	The specific date of onset of the symptoms and the event is not reported, however the timelines reported, as per case narrative are within the risk window. Limited information regarding patient's medical history, family history, concomitant medications, detailed clinical picture, and diagnostic workup.	Possible with limited information.
5	[redacted] YES	35 / F	Not Provided	about 3 to 4 weeks / #1st Dose	Recovered	Confusion state + mixed pleocytosis+ MRI findings. Although exact onset date of the event is unknown, about 3 to 4 weeks after vaccination, symptoms developed and diagnosis of cervical myelitis, meningoencephalitis and intracranial hypertension was made. Limited information about concomitant medications, history/screening for COVID infection.	Possible with limited Information.

Table 180 Summary of cases fulfilling Brighton collaboration level 2 for encephalitis reported during the interval period (29 December 2021- 28 June 2022).

No	Case ID/ Country/ Serious- YES/NO	Age (Years) /Gender (M/F)	Relevant Medical History/ concomitant medications	Time to Onset (days) /#Dose	Event Outcome	Additional Comment	WHO-UMC Causality Assessment
6	[redacted] YES	56/ M	Hypertension/ Not reported	2/ #1st Dose	Recovered	Limited information regarding patient's family history and concomitant medications.	Possible with limited Information.

MRI Magnetic resonance imaging; UK United Kingdom.

Brighton Collaboration Level 3

Eight (8) out of 93 cases fulfilled Brighton collaboration level 3. The cases are summarized below in Table 181.

Two (2) case reports concerned females and 6 were reported in male vaccinees. The age range was 36-65 years.

The risk factors/ confounding factors included prior encephalitis, seizures, herpes zoster and concomitant medications such as levetiracetam. In these 8 cases, the TTO range was between 0 to 62 days. The median TTO was 14 days. In most of the cases there was limited information to make a comprehensive causality assessment.

Table 181 Summary of Cases fulfilling Brighton collaboration level 3 for encephalitis reported during the interval period (29 December 2021- 28 June 2022).

No	Case ID/ Country/ Case Serious (YES/NO)	Age (Years)/Gender (M/F)	Relevant Medical History/ concomitant medications	Time to Onset (days) (#Dose)	Event Outcome	Additional Comment	WHO-UMC Causality Assessment
1	[redacted] / YES	38/F	Not Reported	0/ # 1st Dose	Not recovered	Outside the expected risk window (<1 day); multiple confounders: Multisystem inflammatory syndrome; organ systems disorder which are alternative causalities to the symptoms.	Unlikely.
2	[redacted] / YES	56/F	Not reported	7/ #1st Dose	Recovering	Limited information on histopathology, EEG, CT scan.	Possible with limited information.
3	[redacted] / NO	65/M	Not provided	10 #2nd Dose	Recovered	Behavioural changes, jerky movements, mild pleocytosis. Limited information about medical history, concomitant medications, clinical course and diagnostic workup.	Possible with limited information.

Table 181 Summary of Cases fulfilling Brighton collaboration level 3 for encephalitis reported during the interval period (29 December 2021- 28 June 2022).

No	Case ID/ Country/ Case Serious (YES/NO)	Age (Years)/Gender (M/F)	Relevant Medical History/ concomitant medications	Time to Onset (days) (#Dose)	Event Outcome	Additional Comment	WHO-UMC Causality Assessment
4	[redacted] / YES	36/M	Levetiracetam	13/ #1st Dose	unknown	Limited information about medical history, family history, diagnostic work up like lumbar puncture, CT/MRI, EEG. Confounder was the concomitant medication levetiracetam.	Possible with confounder.
5	[redacted] / YES	48/M	Encephalitis, Seizures/ anti-D immunoglobulin	62/ #1st Dose	Not recovered	TTO: outside the risk window. Confounder: past and current medical history of encephalitis.	Unlikely.
6	[redacted] / YES	63/ M	Herpes-Zoster Infection	17/ #1st Dose	Unknown	Confounder is ongoing herpes zoster. Limited information about detailed diagnostic work up including EEG and CSF analysis.	Possible with confounders.
7	[redacted] YES	51/M	Not Provided	21/ #Dose Unknown	Unknown	Limited information about medical history, family history, concomitant medications, diagnostic work up like lumbar puncture, CT/MRI, EEG.	Possible with Limited Information.

Table 181 Summary of Cases fulfilling Brighton collaboration level 3 for encephalitis reported during the interval period (29 December 2021- 28 June 2022).

No	Case ID/ Country/ Case Serious (YES/NO)	Age (Years)/Gender (M/F)	Relevant Medical History/ concomitant medications	Time to Onset (days) (#Dose)	Event Outcome	Additional Comment	WHO-UMC Causality Assessment
8	[redacted] / YES	63/M	Not provided	14/ #1st Dose	Not Recovered	Limited information about history or screening for covid infection, other infection screen to rule out viral/bacterial causes is missing.	Possible with Limited Information.

CSF Cerebrospinal Fluid, CT: computed tomography; EEG: Electroencephalography, F Female, M Male; MRI Magnetic resonance imaging, TTO Time to onset; UK United Kingdom

Brighton Collaboration Level 4

Based on the review, 57 out of 93 cases were classified as Brighton collaboration level 4. These cases did not fulfil criteria for a level 3, 2, or 1 certainty as there was insufficient information to confirm the diagnosis or medical assessment of the cases.

Brighton Collaboration Level 5

Based on the review, 21 out of 93 cases were classified as Brighton collaboration level 5 (ie, Encephalitis was excluded due to an alternative diagnosis).

Generally, there was too limited information in many case reports to make an informed assessment of causality or conclude on the presence of confounding factors.

Fatal cases

There were 6 case reports identified with fatal outcome reported during the interval period (29 December 2021- 28 June 2022). Summaries of these case reports with details are presented in below.

Table 182 Summary of cases with fatal outcome for Encephalitis (n = 6) reported during the interval period (29 December 2021- 28 June 2022).

No	Case ID/ Country/ Age/Gender/Medically confirmed (Y/N)/ Source	Brighton Collaboration classification	Relevant Medical History/ concomitant medications	Time between vaccination and death - days	Time to Onset (days) / # Dose	Other conditions associated to the fatal outcome/ Autopsy (Y/N)	Additional Comment/ WHO-UMC Causality Assessment
1	[redacted] United Kingdom/ YES/ 49/M/NO/ Spontaneous	BCC1	Bipolar Disorder/ Valproate Sodium	223	1 / # 1st Dose	Encephalitis / Yes	Although onset date of encephalitis is reported as one day after vaccination, it is also stated that diagnosis of encephalitis was made 3weeks after vaccination. Hence causality is assessed as 'possible with confounder' -confounder is the concomitant medication valproate sodium.
2	[redacted] Germany / YES/ 36/M/ YES/ Spontaneous	BCC3	Levetiracetam	17	13 / # 1st Dose	left parietal extensive intracerebral congestive hemorrhage/ Yes	Confounder was the concomitant drug levetiracetam. Limited information about medical history, family history, diagnostic work up like lumbar puncture, CT/MRI, EEG/ Possible with confounder.
3	[redacted] Brazil / Unknown / M/ Y/Spontaneous	BCC4		Unknown	37 / # 1st Dose	hypoxic encephalopathy / Not Mentioned	Limited information about medical history, family history, concomitant medications, diagnostic work up like lumbar puncture, CT/MRI, EEG/ Possible with limited Information

Table 182 Summary of cases with fatal outcome for Encephalitis (n = 6) reported during the interval period (29 December 2021- 28 June 2022).

No	Case ID/ Country/ Age/Gender/Medically confirmed (Y/N)/ Source	Brighton Collaboration classification	Relevant Medical History/ concomitant medications	Time between vaccination and death - days	Time to Onset (days) / # Dose	Other conditions associated to the fatal outcome/ Autopsy (Y/N)	Additional Comment/ WHO-UMC Causality Assessment
4	[redacted] India/ 58/F/ Y/ Spontaneous	BCC4	Not Provided	Unknown	Unknown / # Dose Unknown	Encephalopathy and thrombocytopenia/ Not mentioned	TTO unknown, missing medical history, concomitant meds, diagnostic workup/ Unassessable/ Unclassifiable
5	[redacted] India/ 23/F/ Y/ Spontaneous	BCC4	Not Provided	Unknown	Unknown / # Dose Unknown	Myelin oligodendrocyte glycoprotein antibody-associated disease/ Not Mentioned	TTO unknown, missing medical history, concomitant meds, diagnostic workup/ Unassessable/ Unclassifiable
6	[redacted] India/ 26/F/ Y/ Spontaneous	BCC4	Ibuprofen	34	34/ # 1st Dose	hypoxic-ischemic encephalopathy and anaphylactic shock/ Yes	Autopsy finding was that patient suffered hypoxic ischemic encephalopathy due to anaphylactic shock. Diclofenac injection could be considered as the possible confounder to the event. (as the symptoms of anaphylaxis started few hours after the administration of diclofenac injection in the patient.) There is also limited information diagnostic work up like lumbar puncture, CT/MRI, EEG in this case/ Possible with confounder

CSF Cerebrospinal Fluid, F Female; M Male; N No; TTO Time To Onset, CT: computed tomography; EEG: Electroencephalography, MRI Magnetic resonance imaging

Summary of Fatal case reports

Encephalitis is a serious neurological condition, which can be fatal. Encephalitis continues to cause 5.6 to 39.3% of deaths in affected patients. Case fatality rate is variable and dependent on causative factor (Wang H et al 2022).

Of the 6 case reports, the cause of death for 1 case ([redacted]) was reported as not related to encephalitis and it was reported as left parietal extensive intracerebral congestive haemorrhage. In the remaining cases the cause of death was encephalitis, hypoxic encephalopathy, encephalopathy, myelin oligodendrocyte glycoprotein antibody positive encephalomyelitis, and hypoxic ischemic encephalopathy in cases [redacted] and [redacted] respectively.

The median age in these fatal cases was 36 years. Out of the 6 case reports, the event onset in 2 cases were within risk window of 2-42 days, 1 was outside the risk window, and in the remaining 3 cases time to onset was unknown. One of the 6 case reports ([redacted]) was assessed as a BCC1 and causality was assessed as possibly related with confounder using WHO-UMC classification - this case report was from MHRA. It was reported that the patient experienced encephalitis on day 1. However, on further narrative review, it was stated that patient experienced dizziness on an unknown date after the first dose of AZ vaccine and the patient was hospitalized due to this. It was also reported that, 3 weeks after admission, patient was diagnosed with encephalitis. Therefore, TTO was conservatively presumed to be within the risk window and the causality assessed as 'possible with confounder' -confounder was the concomitant medication valproate sodium.

One (1) of the 6 cases was assessed as BCC3 ([redacted]) and the causality was assessed as 'possible with confounder' – the confounder was the concomitant medication levetiracetam. In this case, there was limited information about medical history, family history, diagnostic work up like lumbar puncture (LP), CT, MRI, and EEG.

The remaining 4 cases were assessed as BCC4 according to Brighton's collaboration criteria.

In conclusion, the review of these 6 case reports with fatal outcome did not identify definitive causal association between encephalitis and VAXZEVRIA.

Observed vs. Expected Analysis

The observed versus expected analysis for all cases of encephalitis reported cumulatively till DLP 28 June 2022 is presented with different risk windows (14 days, 30 days, and 42 days) in Table 183. This includes all reported cases irrespective of the Brighton collaboration criteria level. The risk window of 2-42 days was included from the Brighton case definition (Law B 2021). The background incidence rates used are from a meta-analysis of ACCESS rates

(Meningoencephalitis, 2010-2013 and 2017-2019) The outcome of observed versus expected analysis of all cases for encephalitis suggested that observed cases were less than expected. The observed versus expected analysis of cases for encephalitis showed that observed cases occurred significantly less frequently than expected for all age stratifications in EEA/UK, Brazil, and Australia. Most cases in all age groups from EEA/UK, Brazil and Australia showed insufficient information to make any causality assessment and only few cases met the Brighton Collaboration Criteria Level 1, 2 or 3.

O/E analysis showed that observed cases occurred significantly less than expected.

Conservatively, the exposure for global reports (448306152) is based on doses administered in 13 markets as explained in Appendix 8.

Table 183 Observed Versus Expected Analysis for all cases reporting encephalitis (Global reports) reported cumulatively till DLP 28 June 2022.

Adverse Events	Risk window (2-42 days)	IR	Exposure [a]	Observed number of cases	Expected number of cases[a]	O over E ratio (95% CI)	Conclusion
Overall Incidence Rate Encephalitis	14	9.1	448,306,152	129	1563.73	0.08 (0.07 - 0.1)	Observed significantly < expected
Overall Incidence Rate Encephalitis	30	9.1	448,306,152	160	3350.86	0.05 (0.04 - 0.06)	Observed significantly < expected
Overall Incidence Rate Encephalitis	42	9.1	448,306,152	171	4691.2	0.04 (0.03 - 0.04)	Observed significantly < expected
Overall Incidence Rate Encephalitis cases including unknown TTO	42	9.1	448,306,152	280	4691.2	0.06 (0.05 - 0.07)	Observed significantly < expected

Exposure until 28 June 2022; Incidence rate (IR) source: Meta-analysis of ACCESS rates (Meningoencephalitis, 2010-2013 and 2017-2019) CI Confidence Interval, E Expected, IR Incidence rate, O Observed

An observed versus expected analysis of cases stratified by age range and regions (EU/UK. Brazil and Australia) with different Risk windows are presented in Table 184.

Table 184 Observed Versus Expected Analysis for encephalitis cases stratified by age for EEA/UK, Brazil & Australia reported cumulatively till DLP 28 June 2022.

Age group	Risk window	IRa /100,000 PY	Exposure[b]	Observed number of cases	Expected number of cases[a]	O over E ratio (95% CI)	Conclusion
EEA UK, Brazil & Australia Encephalitis Age 18-49	14	7.48	100,987,434	47	289.54	0.16 (0.12 - 0.22)	Observed significantly < expected
EEA UK, Brazil & Australia Encephalitis Age 18-49	30	7.48	100,987,434	57	620.45	0.09 (0.07 - 0.12)	Observed significantly < expected
EEA UK, Brazil & Australia Encephalitis Age 18-49	42	7.48	100,987,434	59	868.63	0.07 (0.05 - 0.09)	Observed significantly < expected
EEA UK, Brazil & Australia Encephalitis Age 50-59	14	8.66	56,425,075	19	187.3	0.1 (0.06 - 0.16)	Observed significantly < expected
EEA UK, Brazil & Australia Encephalitis Age 50-59	30	8.66	56,425,075	26	401.36	0.06 (0.04 - 0.09)	Observed significantly < expected
EEA UK, Brazil & Australia Encephalitis Age 50-59	42	8.66	56,425,075	32	561.9	0.06 (0.04 - 0.08)	Observed significantly < expected
EEA UK, Brazil & Australia Encephalitis Age 60-69	14	9.87	57,182,485	31	216.34	0.14 (0.1 - 0.2)	Observed significantly < expected

Table 184 Observed Versus Expected Analysis for encephalitis cases stratified by age for EEA/UK, Brazil & Australia reported cumulatively till DLP 28 June 2022.

Age group	Risk window	IRa /100,000 PY	Exposure[b]	Observed number of cases	Expected number of cases[a]	O over E ratio (95% CI)	Conclusion
EEA UK, Brazil & Australia Encephalitis Age 60-69	30	9.87	57,182,485	41	463.58	0.09 (0.06 - 0.12)	Observed significantly < expected
EEA UK, Brazil & Australia Encephalitis Age 60-69	42	9.87	57,182,485	41	649.01	0.06 (0.05 - 0.09)	Observed significantly < expected
EEA UK, Brazil & Australia Encephalitis Age 70+	14	10.71	31,869,628	16	130.83	0.12 (0.07 - 0.2)	Observed significantly < expected
EEA UK, Brazil & Australia Encephalitis Age 70+	30	10.71	31,869,628	16	280.35	0.06 (0.03 - 0.09)	Observed significantly < expected
EEA UK, Brazil & Australia Encephalitis Age 70+	42	10.71	31,869,628	17	392.5	0.04 (0.03 - 0.07)	Observed significantly < expected

Source: Incidence rate (IR) source: Meta-analysis of ACCESS rates (Meningoencephalitis, 2010-2013 and 2017-2019)

Exposure until 28 June 2022 for EEA/UK, Brazil, and Australia

CI Confidence Interval; CPRD Clinical Practice Research Database; E Expected; EEA European Economic Area; IR: Incidence rate; O Observed; TTO Time to onset; UK United Kingdom CI Confidence Interval; CPRD Clinical Practice Research Database; E Expected; EEA European Economic Area; IR: Incidence rate; O Observed; TTO Time to onset; UK United Kingdom

An O/E analysis of cases meeting case definition according to Brighton Criteria (BC) for Level 1, 2 or 3, based on clinical course, examination such as brain histopathology, clinical features, and evaluations (Law B 2021) are presented in Table 185.

Table 185 Observed Versus Expected Analysis for encephalitis cases meeting the Brighton Criteria Level 1, 2 or 3 and stratified by age for EEA/UK regions reported cumulatively till DLP 28 June 2022.

Age group	Risk window	IRa /100,000 PY	Exposure[b]	Observed number of cases	Expected number of cases[a]	O over E ratio (95% CI)	Conclusion
EEA UK, Brazil & Australia; BCC 1-3; Age 18 -49	14	7.48	100,987,434	7	289.54	0.02 (0.01 - 0.05)	Observed significantly < expected
EEA UK, Brazil & Australia; BCC 1-3; Age 18 -49	30	7.48	100,987,434	11	620.45	0.02 (0.01 - 0.03)	Observed significantly < expected
EEA UK, Brazil & Australia; BCC 1-3; Age 18 -49	42	7.48	100,987,434	11	868.63	0.01 (0.01 - 0.02)	Observed significantly < expected
EEA UK, Brazil & Australia; BCC 1-3; Age 50-59	14	8.66	56,425,075	0	187.3	0 (0 - 0.02)	Observed significantly < expected
EEA UK, Brazil & Australia; BCC 1-3; Age 50-59	30	8.66	56,425,075	1	401.36	0 (0 - 0.01)	Observed significantly < expected
EEA UK, Brazil & Australia; BCC 1-3; Age 50-59	42	8.66	56,425,075	1	561.9	0 (0 - 0.01)	Observed significantly < expected
EEA UK, Brazil & Australia; BCC 1-3; Age 60-69	14	9.87	57,182,485	4	216.34	0.02 (0.01 - 0.05)	Observed significantly < expected
EEA UK, Brazil & Australia; BCC 1-3; Age 60-69	30	9.87	57,182,485	6	463.58	0.01 (0 - 0.03)	Observed significantly < expected

Table 185 Observed Versus Expected Analysis for encephalitis cases meeting the Brighton Criteria Level 1, 2 or 3 and stratified by age for EEA/UK regions reported cumulatively till DLP 28 June 2022.

Age group	Risk window	IRa /100,000 PY	Exposure[b]	Observed number of cases	Expected number of cases[a]	O over E ratio (95% CI)	Conclusion
EEA UK, Brazil & Australia; BCC 1-3; Age 60-69	42	9.87	57,182,485	6	649.01	0.01 (0 - 0.02)	Observed significantly < expected
EEA UK, Brazil & Australia; BCC 1-3; Age 70+	14	10.71	31,869,628	3	130.83	0.02 (0 - 0.07)	Observed significantly < expected
EEA UK, Brazil & Australia; BCC 1-3; Age 70+	30	10.71	31,869,628	3	280.35	0.01 (0 - 0.03)	Observed significantly < expected
EEA UK, Brazil & Australia; BCC 1-3; Age 70+	42	10.71	31,869,628	3	392.5	0.01 (0 - 0.02)	Observed significantly < expected

[a] Incidence rate (IR) source: Meta-analysis of ACCESS rates (Meningoencephalitis, 2010-2013 and 2017-2019)

[b] Exposure until 28 June 2022 for EEA/UK, Brazil, and Australia.

CI Confidence Interval, E Expected, EEA European Economic Area; IR Incidence rate, O Observed PY Person Years; TTO Time to onset; UK United Kingdom.

Literature review during the reporting period

Eight (8) relevant articles included 12 cases of encephalitis/ encephalopathy with VAXZEVRIA were identified which are included in the AstraZeneca safety database review above ([redacted]). These cases are reviewed and discussed as part of safety database review.

There were no other relevant articles identified in the reporting period concerning encephalitis and VAXZEVRIA.

Summary

Encephalitis is known to occur naturally at an overall annual incidence up to 10 cases per 100,000 persons (Willame et al 2021). Incidence is highly variable dependent upon age, demographics, season, causative agent, and presence of epidemic illness. The natural aetiology is multifactorial but includes infectious, toxic, neoplastic, autoimmune, and metabolic causes (Wang H et al 2022).

Of the 93 cases received during the reporting period, 65 (69.9%) of vaccinees were from the age group of 18-<65 (adult) and median age was found to be 52 years; there was a slight predominant stratification in female gender (53.8%). In 60 (64.5%) cases, the events were reported to have occurred after the first dose, 18 (19.4%) case reports after the second dose of vaccine, 1 case was reported with booster dose, and dose was not reported in 12 (5.93%) case reports.

Review of all cases during the interval period has revealed no clear pattern in clinical presentation or medical history. There is a wide range in time to onset (TTO) of cases from [0-240] days, with around half of the cases reporting a TTO with the 2–42 days risk window. The median TTO for all the cases was found to be 13 days. Forty-four (44) (47.3%) out of 93 cases were within the risk window of 2-42 days. 90 (96.8%) of 93 cases were serious. Case fatality rate is variable and dependent on causative factor (Wang H et al 2022). The review of 6 case reports with fatal outcome did not identify any substantial evidence of a causal association between encephalitis and VAXZEVRIA. No changes were identified for interval data considering both safety patterns and volumes.

Based on Brighton Collaboration criteria approach, out of the 93 cases, 1 case fulfilled level 1 criteria, 6 fulfilled level 2 criteria, 8 fulfilled level 3 criteria, 57 fulfilled level 4 criteria, and 21 cases fulfilled level 5 criteria. Four (4.3%) cases were evaluated with alternative causal factors noted and the remaining cases were evaluated with limited information to make any comprehensive causality assessment. The review of post authorization case reports did not find any evidence of a causal association between encephalitis and VAXZEVRIA.

The observed versus expected analysis of cumulative cases for encephalitis showed that observed cases occurred significantly less frequently than expected for all cases (343) and cases with BCC 1-3 (49), all age stratifications in EEA/UK, Brazil, and Australia, and risk windows. The contribution of

under-reporting cannot be estimated, but observed cases are significantly below expected and do not indicate a signal.

Overall, the clinical pattern of case presentation and numbers of reports are broadly consistent with what might be expected from the natural epidemiology of encephalitis, and there are no specific biological mechanism for development of encephalitis post vaccination with VAXZEVRIA.

Conclusion

From the data identified during the reporting period and taking into account the cumulative experience, there is currently insufficient evidence of a causal association between encephalitis and VAXZEVRIA.

VAXZEVRIA CDS Section 4.4 (Special warnings and special precautions for use) includes warnings on Neurological events: "Very rare events of demyelinating disorders, including Guillain-Barré syndrome (GBS), have been reported following vaccination with VAXZEVRIA". In addition, encephalitis (immune mediated neurological condition/ nervous system disorders, including immune-mediated neurological conditions.) is considered as an important potential risk in the Core and EU RMPs for VAXZEVRIA. No further updates to the VAXZEVRIA CDS or RMP are warranted at this time. As such, the topic will continue to be to be closely monitored as part of AstraZeneca's ongoing surveillance efforts for the important potential risk of nervous system disorders, including immune-mediated neurological conditions..

16.3.1.2.2 Transverse Myelitis

Review of Cases

Interval Period (29 December 2021 – 28 June 2022)

A search of the AstraZeneca safety database was conducted for the reporting period (29 December 2021 – 28 June 2022) using the following MedDRA (25.0) PTs: Myelitis transverse, Myelitis, and Acute necrotizing myelitis, and LLT: MOG-transverse myelitis.

The search identified 112 case reports in vaccinees who received VAXZEVRIA. Out of the 112 cases: 19 are literature reports; 2 are non- interventional / post-market reports; 91 are spontaneous reports (59 initial and 30 follow-up and % compared to cumulative).

Out of the 112 cases: 96 (85.7%) of the cases were serious and 47 (42.0%) were medically confirmed. Only 1 event of TM (in case [redacted]) was reported with fatal outcome in the reporting period of the PBRER.

Out of the 112 reports, 32 (28.6%) were from the United Kingdom (UK), 20 (17.9%) from Brazil, 12 (10.7%) from Germany, 11 (9.8%) from India, 8 (7.1%) from Australia, 5 (4.5%) from Spain, 4 (3.6%) each from France and Italy, 3 (2.7%) from the Netherlands, 2 (1.8%) each from the Republic

of Korea and Sweden, and 1 (0.9%) each from Argentina, Belgium, Ecuador, Guatamala, Iran, Portugal, Slovakia, Slovenia, and Taiwan.

There were 55 (49.1%) reports in female vaccinees, 54 (48.2%) were in male vaccinees, and the gender was not reported in 3 cases (2.7%). The age range was 20-82 years of age with a median age of 50 years. Seventy-four (74) (66.1%) vaccinees were in the age group of 18-64 years of age, 17 (15.2%) vaccinees were >65 years of age, and for 21 (18.8%) vaccinees the age was unknown.

The adverse events (PTs) reported included Myelitis transverse (80), Myelitis (35). An individual case report can have more than one of the above events reported.

Out of the 112 cases, 60 (53.6%) had the time to onset (TTO) within 42 days, and in 38 cases the TTO was unknown. The median TTO was 15 days (range 0-333 days). Out of the 112 cases, 35 (31.2%) reported the event occurring after the first dose, 22 (19.6%) after the second dose and 3 (2.7%) after a third/booster dose. All three cases had limited information or were confounded, and two had unknown TTOs. For 52 cases the dose was not specified.

Out of the 112 cases, 7 (6.3%) recovered, 19 (17.0%) were recovering, 6 (5.4%) recovered with sequelae, 46 (41.1%) had not recovered, and 2 (1.8%) had a fatal outcome (the event of interest pertaining to TM was reported with fatal outcome only in one case). In 32 (28.6%) cases the outcome was unknown.

Fatal events in the reporting period of the PBRER (29 December 2021 – 28 June 2022)

Out of the 112 reports received in the interval, one case was reported with a fatal outcome and is summarized below:

Case ID [redacted] was received from a pharmacist via regulatory authority in Australia (TGA), concerning a 72 year-old male vaccinee received Influenza vaccine (inact sag4v) and VAXZEVRIA (Dose 1) about 3 weeks apart. No medical history was reported. He experienced leg weakness (with difficulty in walking) two weeks after VAXZEVRIA which progressed to back pain, need for assistance to stand out of bed and then fevers with urinary retention. Neurological examination suggested lower limb reduction in sensation, weakness in ankles and hips but normal upper limb. The patient declined admission as advised initially, however had to be admitted to the ICU and intubated after two days (about one month post COVID-19 vaccination) due to delirium, hypoxia and aspiration pneumonia (on CT scan). It was reported that the clinical course and imaging findings felt to be in keeping with atypical GBS [acute axonal neuropathic (motor and sensory) GBS]. The event of Longitudinally extensive acute transverse myelitis was also reported. The patient was managed with anti-infective therapy, IvIg, methylprednisolone followed by plasma exchange. One failed attempt to extubate was reported. After an unspecified exact clinical course, it was reported that the patient developed side effect with IvIg (unspecified), no improvement with plasma exchange; he then

developed respiratory failure, cardiac arrest, and deceased two months post VAXZEVRIA vaccination.

AstraZeneca comment: The patient received a Flu vaccine and AZ vaccine about 3 weeks apart and subsequently developed neurological features of myelopathy - with encephalopathy. Termed atypical GBS and myelitis, although the features could be solely related to TM. The pattern of neurological symptoms is consistent with transverse myelitis, (longitudinally extensive TM as well as plexitis are noted in the narrative suggesting Imaging obtained of spinal cord), with an encephalopathy of hypoxic ischemic origin as noted upon hospital admission. Patient refused initial recommended admission which was based on lower extremity weakness and sensory change and urinary retention with upper extremity being normal. Upon admission approx. 2 days later there was a noted aspiration pneumonia and cognitive changes including delirium. There was insufficient information on exclusion of other causes of acute delirium. Insufficient response to IvIg, methylprednisolone and plasma exchange suggests possible non-immune etiology. Additionally, there was insufficient information on medical history, CNS investigations results (CSF), radiological investigations (although longitudinally extensive transverse myelitis was mentioned as well as plexitis), clinical and radiological course of transverse myelitis, autopsy and etiological work-up (in the context of fever, hypoxia). The BCC case classification for transverse myelitis was considered as BCC3 due to clinical observations and fever. There is insufficient information on imaging, carcinoma work up (plexitis),CSF investigation and autopsy. TTO of neurologic symptoms at a reasonable time-frame to both vaccinations (1 month to Influenza vaccine, 2 weeks to COVID-19 vaccine). BCC case classification for GBS was considered as BCC4, considering the lack of information in regard other clinical symptoms, electrophysiology test and CSF. The WHO-UMC causality assessed as Possible based on temporal association for TM.

Events with Recurrence/Rechallenge in the reporting period of the PBRER

There were no events with recurrence/rechallenge in the reporting period.

Review of cases as per BCC classification in the reporting period of the PBRER

The BCC (Law B 2021 [C]) was used for the review of the data available in the case reports. Based on this approach, out of the 112 cases: none of the cases fulfilled BCC Level 1 criteria; 13 cases fulfilled BCC Level 2 criteria; 11 cases fulfilled BCC Level 3 criteria; 66 cases fulfilled BCC Level 4 criteria; 22 (19.65) cases fulfilled BCC Level 5 criteria.

In addition to the BCC, the published Brighton Case Definition for Acute Myelitis (Law B 2021 [C]) was also referenced during the review of the cases for the assessment of evidence related to associated risk factors (eg, comorbidities, infections, vaccines and malignancies).

The cases fulfil BCC levels 1-5 based on the available information on clinical course, clinical examination, and diagnostic investigations

BCC Level 1 for Transverse myelitis: None

BCC Level 2 for Transverse myelitis

Thirteen (13) out of the 112 case reports fulfilled BCC level 2 criteria. They are presented in Table 108.

Out of these 13 cases, 4 were reported in females and 9 were reported in males and the age range was 27-68 years. The median age was 48 years.

Twelve (12) of the 13 cases had time to onset from vaccination within 42 days. In one case the time to onset was unknown. The median time to onset was 16 days.

Out of these 13 cases, 10 cases reported to have occurred after receiving the first dose, and the remaining 3 after a second dose. Out of the 13 cases fulfilling BCC Level 2, two as "Possible" (with alternate cause or confounders), nine as "Possible" (with limited information), and the remaining two cases as "Unlikely" as per WHO-UMC Causality assessment criteria.

Majority of the cases (10 out of 13 cases) presented predominantly with bowel/bladder dysfunction in addition to sensory and motor involvement of extremities. This also roughly correlated with involvement of multiple vertebral segments, (even conus involvement).

The CSF results presented a varied picture with respect to extent of pleocytosis (less than 100 cells/uL in 6 cases, more than 100 in 5 cases). Majority of cases had lymphocyte predominance (7 out of 9 cases reporting cell count differentials) versus polymorphic picture (2 out of 9 cases reporting cell count differentials).

Information on correlation of TM with IgG levels in serum and/or CSF was reported in 3 cases with concurrent increase in serum and CSF in 1 case ([redacted]), increase in CSF in 1 case ([redacted]), and no evidence of intrathecal IgG synthesis or normal IgG in 1 case ([redacted]). Information on oligoclonal bands in TM cases was reported in 4 cases (4 out of 13 cases; 3 negative and 1 positive).

Information on serum or CSF levels on anti-neuronal antibodies (eg: MOG-Ab, NMO-Ab, AQP4-Ab) was reported in 9 out of 13 cases. Out of these 9 cases, 3 cases had positive anti-neuronal antibodies [MOG-Ab positive in 2 cases ([redacted]) and NMO-Ab positive in 1 case([redacted])] while the remaining (6 out of 9 cases) had negative results. To summarize, either there was limited information or CSF picture including neuronal antibodies had a varied presentation to identify any possible singular immune etiopathogenetic role of VAXZEVRIA.

The event outcome was reported in few cases (5 out of 14 cases) with the majority reporting favourable outcome (n=4; recovered or recovering) and one case reported not recovered. The treatment administered to the patients comprised mainly pulse steroids with oral steroid tapering and plasmapheresis with addition of other immunosuppressants (mycophenolate mofetil, rituximab in 3 cases), IvIg (in 1 case), anti-virals (in 2 cases).

Table 186 Cases of Transverse Myelitis Fulfilling Brighton Collaboration criteria Level 2 (N = 13)

No	Case ID/ Country/ Serious-Y/N	Age (Years) /Gender (M/F)	Risk factors - Relevant comorbidities and concomitant medications	Dose # / Time to Onset (days)	Event / Outcome	WHO-UMC Causality Assessment
1	[redacted] /YES	41/M	Diabetes/Steroid use	1st dose/14	Myelitis transverse/Recovered	Possible; with limited information
	Comments: Presenting neurological features of left peripheral facial palsy followed later by paresthesia and weakness below T4. TTO is considered reasonable to VAXZEVRIA vaccine intake. No similar complaints on subsequent mRNA COVID-19 vaccine dose. MRI contrast enhanced of the spine revealed intramedullary enhancing lesion over the spinal cord. CSF: mild pleocytosis, and mild elevated protein levels. The tumor marker and autoimmune profiles, including the serum rheumatoid factor, serum complement C3 and C4, anti-Ro/La antibody, antinuclear antibody, and anti-ds-DNA antibody, were all in the normal range. However, aquaporin-4 antibodies were negative. There was remission and relapse of neurological symptoms (initially left peripheral facial nerve palsy and later LETM) on corticosteroid therapy may suggest either additional unknown new insult or dissemination in time and space. However, there was limited information on CSF oligoclonal bands and other laboratory data. Assessed as Possible based on temporal association.					
2	[redacted] /YES	27/F	none/Limited information	1st dose/21	Myelitis transverse/Not recovered	Possible; with limited information
	Comments Presenting neurological features of fever, low back pain, urinary retention, paresthesia of extremities and weakness of lower limbs. TTO considered reasonable to vaccine intake. MRI: LETM (cervical cord), multiple sparse focal lesions (thoracic cord). CSF: predominantly monomorphonuclear pleocytosis, increased proteins, negative oligoclonal bands. Elevated lgG levels in CSF and serum. There was however insufficient response to acyclovir, immunosuppressive or apheresis therapy. The authors reported as a limitation to this study that a complete autoantibody profile (broader autoantibody panel, including those targeting myelin oligodendrocyte glycoprotein, glial fibrillary acid protein and flotillin) and complete viral profile (syphilis and hepatitis), could not be done.					

Table 186 Cases of Transverse Myelitis Fulfilling Brighton Collaboration criteria Level 2 (N = 13)

No	Case ID/ Country/ Serious-Y/N	Age (Years) /Gender (M/F)	Risk factors - Relevant comorbidities and concomitant medications	Dose # / Time to Onset (days)	Event / Outcome	WHO-UMC Causality Assessment
	Assessed as Possible based on temporal association.					
3	[redacted] /YES	45/M	none/Limited information	1st dose/10	Myelitis transverse/Recovering	Possible; with limited information
	Comments: Presenting neurological features - thoracic back pain, urinary retention, altered sensation below T9 level and acute flaccid tetraparesis. MRI: LETM (C3 to T2 without gadolinium enhancement). TTO is considered reasonable to vaccine intake CSF: Pleocytosis (initially predominantly polymorphonuclear - granulocytes) later changed to mononuclear (100% lymphocytes), increased protein, degreased glucose, increased lactate, Oligoclonal bands – negative, Intrathecal Ig G synthesis – normal, Anti-neuronal autoantibodies* - negative Serum: SARS-CoV-2-IgG serum antibody - positive, SARS-COV-2 nucleocapsid antigen antibody – negative, AQP4-Ab: negative, MOG-Ab: negative CSF picture of predominant granulocytes at about 2 weeks after vaccination also suggest possibility of new insult (eg infectious etiology), a diagnosis of which could have been masked with broad-spectrum antibiotic use. Clinical, radiological and biochemical resolution to PS, antibiotics (Acyclovir, ceftriaxone and ampicillin), Plasmapheresis, Cyclophosphamide. Limited information on past and present medical history, family history, relevant lifestyle history, occupational history, and neoplasm. Assessed as Possible based on temporal association.					
4	[redacted] / NO	30/F	Not reported/Oligoclonal bands	1st dose/15	Myelitis transverse/Unknown	Possible (alt. cause)
	Comments Presenting neurological symptoms - Sensory (Paraesthesia's over both palms followed by development of girdle like sensation over waist and electric shock like sensation on flexion of neck). TTO is considered reasonable to vaccine intake MRI: brain – focal hyperintensity in corpus callosum; Spine - short segment hyperintensity in C3. Evoked potentials -normal CSF: mild pleocytosis; Oligoclonal bands positive					

Table 186 Cases of Transverse Myelitis Fulfilling Brighton Collaboration criteria Level 2 (N = 13)

No	Case ID/ Country/ Serious-Y/N	Age (Years) /Gender (M/F)	Risk factors - Relevant comorbidities and concomitant medications	Dose # / Time to Onset (days)	Event / Outcome	WHO-UMC Causality Assessment
	Serum: MOG-Ab negative, NMO Ab negative No medical history, concomitant medications, family history, relevant social history or work history. Assessed as Possible based on temporal association. There is possible early development of Multiple sclerosis based on the MRI findings and also the age and gender of the patient.					
5	[redacted] /NO	36/M	Not reported/Limited information	2nd dose/32	Myelitis transverse/Unknown	Possible; with limited information
	Comments Presenting neurological symptoms - Sensory (tingling and paraesthesias) at T4, Motor (weakness) below hip, autonomic (?) urinary disturbances TTO maybe within risk window, however no similar complaints after 1st dose. MRI: brain –hyperintensities along bilateral trigeminal nerves in pons MRI; MRI spine: LETM (obex till conus) CSF: pleocytosis (n=720, predominantly lymphocytes); Serum: MOG-Ab strongly positive, NMO Ab negative No medical history, concomitant medications, family history, relevant social history or work history. MRI findings do not correlate with exam findings-Normal cranial nerves, and MRI -hyperintensities along bilateral trigeminal nerves in pons. Assessed as Possible as temporal association cannot be excluded although any vaccine specific adaptive immune etiology is considered less likely considering the TTO to second dose.					
6	[redacted] /NO	31/M	Not reported/Limited information	1st dose/14	Myelitis transverse/Unknown	Possible; with limited information
	Comments Presenting neurological symptoms - Sensory (numbness whole body) below L1 (on clinical exam), Motor (weakness) lower limbs, autonomic (?) bladder disturbances TTO is considered reasonable to vaccine intake. MRI: LETM (long segment cervico-dorsal T2/FLAIR hyperintensity with subtle enhancement)					

Table 186 Cases of Transverse Myelitis Fulfilling Brighton Collaboration criteria Level 2 (N = 13)

No	Case ID/ Country/ Serious-Y/N	Age (Years) /Gender (M/F)	Risk factors - Relevant comorbidities and concomitant medications	Dose # / Time to Onset (days)	Event / Outcome	WHO-UMC Causality Assessment
	CSF: pleocytosis (n=370, predominantly lymphocytes), increased protein; MOG-Ab negative, NMO Ab negative Serum: MOG-Ab negative, NMO Ab negative No medical history, concomitant medications, family history, relevant social history or work history. Limited information regarding the patient's baseline health condition prior to vaccination. Assessed as Possible based on temporal association.					
7	[redacted] / NO	44/M	Not reported/Limited information	1st dose/7	Myelitis transverse/Unknown	Possible; with limited information
	Comments Presenting neurological symptoms - Double vision, Sensory/Cerebellar (imbalance in walking, hiccups), Motor (difficulty in walking), Autonomic (urinary retention) TTO is considered reasonable to vaccine intake. MRI: T2 hyperintensities in the cervical and dorsal cord and conus CSF: pleocytosis (n=130, predominantly lymphocytes),; MOG-Ab strongly positive Serum: MOG-Ab strongly positive No medical history, concomitant medications, family history, relevant social history or work history. Limited information regarding the patient's baseline health condition prior to vaccination. Assessed as Possible based on temporal association.					
8	[redacted] / YES	53/F	Paraneoplastic panel - positive/Paraneoplastic panel - positive	2nd dose/1	Myelitis transverse/Unknown	Possible (alt. cause)
	Comments Presenting neurological symptoms - Sensory (numbness, tingling. paraesthesias lower limbs) below level T4 on clinical exam, Autonomic? (urinary disturbances) TTO is considered reasonable to vaccine intake.					

Table 186 Cases of Transverse Myelitis Fulfilling Brighton Collaboration criteria Level 2 (N = 13)

No	Case ID/ Country/ Serious-Y/N	Age (Years) /Gender (M/F)	Risk factors - Relevant comorbidities and concomitant medications	Dose # / Time to Onset (days)	Event / Outcome	WHO-UMC Causality Assessment
	MRI: brain: T2/ FLAIR hyperintensity at bilateral subcortical, periventricular deep white matter, insula, cerebellar hemispheres, brainstem; MRI spine: short segment expansile T2 hyperintensities are noted at C5,6,7 & T6–7 CSF: pleocytosis (mild, predominantly lymphocytes); Paraneoplastic panel: Anti – recoverin 2+ Serum: MOG-Ab negative; NMO Ab negative No medical history, concomitant medications, family history, relevant social history or work history. Assessed as Possible based on temporal association, however paraneoplastic panel was positive which denotes an underlying condition and could also explain the events.					
9	[redacted] /NO	31/M	Not reported/Limited information	1st dose/42	Myelitis transverse/Unknown	Possible; with limited information
	Comments Presenting neurological symptoms - Sensory (history of progressive upper and lower limb tingling) level T4, Motor (difficulty in walking), Autonomic (urinary urgency, and constipation) TTO may be possibly considered within risk window of vaccine intake. MRI: brain: T2 Hyperintensities in cervicomedullary junction, right frontal subcortical region; MRI spine-LETM (cervical cord C2-C5), also in dorsal cord CSF: pleocytosis (n=32, all lymphocytes) Serum: MOG-Ab negative; NMO Ab negative Considering how high the MRI findings is, there may be a possibility of trauma. As reported, there was a history of (H/o) progressive upper and lower limb tingling, however there was limited information on chronology of origin and duration and underlying cause. Assessed as Possible based on temporal association					
10	[redacted] /NO	65/F	Not reported/Limited information	1st dose/42	Myelitis transverse/Unknown	Possible; with limited information

Table 186 Cases of Transverse Myelitis Fulfilling Brighton Collaboration criteria Level 2 (N = 13)

No	Case ID/ Country/ Serious-Y/N	Age (Years) /Gender (M/F)	Risk factors - Relevant comorbidities and concomitant medications	Dose # / Time to Onset (days)	Event / Outcome	WHO-UMC Causality Assessment
	Comments Presenting neurological symptoms – Blurred vision (Right eye), Sensory (numbness of hands), Motor (weakness of hands), history of urinary retention TTO may be possibly considered within risk window of vaccine intake. MRI: few hyperintensities in frontal subcortical white matter; MRI Spine: D2-D11 hyperintensity with patchy contrast enhancement and bright spotty areas CSF: pleocytosis (n=17). VEP: Right not recordable, Left normal Serum: MOG-Ab negative; NMO Ab strongly positive No medical history, concomitant medications, family history, relevant social history or work history and detailed etiological workup. Above pattern could possibly also be optic neuritis, neuromyelitis optica. As reported, there was a H/o urinary retention, however there was limited information on chronology of origin and duration and underlying cause. Assessed as Possible based on temporal association					
11	[redacted] YES	61/M	Spinal stenosis/Limited information	1st dose/7	Myelitis transverse/Recovering	Possible; with limited information
	Comments: Presenting neurological symptoms – Sensory (no sensation inside left thigh) loss of light touch and pin prick sensation below the T9 level on both sides on clinical exam, Motor (weakness of left lower limb), Autonomic (dysuria and defecation issues) TTO is considered reasonable to vaccine intake. MRI: T2-high-intensity spinal cord signal change at the T9-12 level and the focal heterogeneous signal of the left spinal cord at the T10-11 level CSF: mild protein increase, mild IgG elevation, Oligoclonal band negative Serum: MOG-Ab negative; NMO Ab negative Insufficient information on level of spinal stenosis and underlying disorder in the backdrop of spinal stenosis and hypertension (vascular pathology). Assessed as Possible based on temporal association					

Table 186 Cases of Transverse Myelitis Fulfilling Brighton Collaboration criteria Level 2 (N = 13)

No	Case ID/ Country/ Serious-Y/N	Age (Years) /Gender (M/F)	Risk factors - Relevant comorbidities and concomitant medications	Dose # / Time to Onset (days)	Event / Outcome	WHO-UMC Causality Assessment
12	[redacted] /YES	68/M	Spinal stenosis, Diabetes mellitus, dyslipidemia/	2nd dose/1	Myelitis/Unknown	Unlikely
	Comments: Presenting neurological symptoms – Sensory (both arms pain began) below level T4 on clinical exam, Motor (both legs motor weakness) TTO of one day is considered unreasonable. MRI: showed central canal stenosis with suspicious code signal intensity change in the C7-T1 level without diffuse hyperintensity representing myelitis Nerve conduction study (NCS) of extremities showed slow conduction velocity without conduction block, latency increase, and F-wave slowing. CSF: not reported Serum investigations: not reported There is insufficient information on etiological work up for infections, neoplasms, autoimmune conditions, endocrine disorders (in backdrop of diabetes, hyperlipidemia) and hypertension (possible vascular etiology) for a further comprehensive medical assessment.					
13	[redacted] /YES	31/M	Not reported/Anti-CMV IgG positive, Serum Varicella-Zoster IgG positive	1st dose/Unknown	Myelitis transverse/Recovering	Unlikely
	Comments: Presenting neurological symptoms – Motor (acute tetraparesis) and Autoimmune? (urinary retention) TTO of one day is considered unreasonable. MRI: LETM (cervical cord); Electromyography: asymmetric motor-sensory axonal polyneuropathy CSF: pleocytosis (n=30, predominantly lymphocytes Serum: Serum Varicella-Zoster IgG (UI/mL) - elevated; Anti-CMV IgM (AU/mL) - normal; Anti-CMV IgG (AU/mL) - elevated					

Table 186 Cases of Transverse Myelitis Fulfilling Brighton Collaboration criteria Level 2 (N = 13)

No	Case ID/ Country/ Serious-Y/N	Age (Years) /Gender (M/F)	Risk factors - Relevant comorbidities and concomitant medications	Dose # / Time to Onset (days)	Event / Outcome	WHO-UMC Causality Assessment
	TTO of onset of symptoms within 1 day of 1st dose of COVID-19 vaccination is considered unlikely based on temporal implausibility for an adaptive immune response and thereby extensive myelopathy. COVID-19 PCR was negative. However, the event can be better explained by concurrent Anti-CMV IgG and Serum Varicella-Zoster IgG (UI/mL) which are known to have a chronic latent phase.					

Ab Antibody, AQP4 Aquaporin 4, CMV Cytomegalovirus, CSF Cerebrospinal fluid, F Female, H/o History of, Ig Immunoglobulin, LETM Longitudinally Extensive Transverse Myelitis, M: Male, MOG Myelin Oligo-Dendrocyte, MRI Magnetic Resonance Imaging, NCS Nerve Conduction Study, NMO Neuromyelitis Optica, PCR Polymerase Chain Reaction, PS Pulse steroid, TM Transverse Myelitis, TTO Time To Onset, VEP Visual Evoked Potential.

BCC Level 3 for Transverse Myelitis

Nine (8.0%) out of the 112 case reports fulfilled BCC level 3 criteria. They are presented in Table 187.

Out of these nine cases, three were reported in females and six were reported in males and the age range was 20-72 years. The median age was 55 years. Out of these 9 cases, time to onset from vaccination was beyond 42 days in none of the cases and missing in two case. The median time to onset was 14 days.

In one of the case the event was reported to have occurred after receiving the second dose.

Out of the nine cases fulfilling BCC Level 3, six were assessed as Possible (with limited information), two were Possible (with alternate cause or confounders) and the remaining case was Unassessable/Unclassifiable as per WHO Causality assessment criteria.

The CSF results as available in 4 cases presented a varied picture with respect to extent of pleocytosis (normal count in 1 case, less than 100 cells/uL in 1 case, more than 100 in 2 cases with lymphocyte predominance). Information on serum or CSF levels on anti-neuronal antibodies (eg: MOG-Ab, NMO-Ab, AQP4-Ab) was reported in 4 out of 8 cases. Out of these 4 cases, 2 cases had positive anti-neuronal antibodies [MOG-Ab positive in 2 cases, and remaining (2 out of 4 cases) had negative results. Information on oligoclonal bands in TM cases was reported in one case only (positive). To summarize, either there was limited information or CSF picture including neuronal antibodies had a varied presentation to identify any singular etiopathogenetic possible role of VAXZEVRIA.

Table 187 Cases of Transverse Myelitis Fulfilling Brighton Collaboration criteria Level 3 (N = 9)

No	Case ID/ Country/ Serious- Y/N	Age (Years) /Gender (M/F)	Risk factors - Relevant Comorbidities/ concomitant medications	Dose # / Time to Onset (days)	Event / Outcome	WHO-UMC Causality Assessment	Additional Comment
1	[redacted] /YES	20/F	Not reported/Not reported	Unknown/3	Myelitis/Not recovered	Possible; with limited information	TTO is considered reasonable to vaccine intake. MRI: suggestive of lateral myelitis CSF: mild pleocytosis Limited information regarding MH,FH, childhood history of prior infections, event leading to the present patient condition. No detailed diagnostics and etiological workup were presented. Assessed as "Possible" based on temporal association.
2	[redacted] YES	55/M	Multiple sclerosis	1st dose/20	Myelitis transverse/ Not recovered	Possible; with limited information	Patient presented with progressive weakness of both limbs. TTO is considered reasonable to vaccine intake. MRI: LETM CSF: mild pleocytosis Serum: MOG-Ab positive Medical history included Multiple sclerosis (MS) which could be a possible confounder. There was insufficient information on clinical status of MS and complete etiological workup (infections, neoplasms).

Table 187 Cases of Transverse Myelitis Fulfilling Brighton Collaboration criteria Level 3 (N = 9)

No	Case ID/ Country/ Serious- Y/N	Age (Years) /Gender (M/F)	Risk factors - Relevant Comorbidities/ concomitant medications	Dose # / Time to Onset (days)	Event / Outcome	WHO-UMC Causality Assessment	Additional Comment
							Assessed as "Possible" based on temporal association.
3	[redacted] YES	Unk/M	Paraneoplastic syndrome	2nd dose/28	Myelitis transverse/ Not recovered	Possible (with confounders)	Patient presented with sensory (numb from the waist down), motor (leg weakness), Autonomic? (problems of bowel control, bowel dysfunction, bladder dysfunction) symptoms. TTO is considered reasonable to vaccine intake. MRI: LETM (unknown level) Assessed as "Possible" based on temporal association. However, a concomitant paraneoplastic condition was identified on CT scan (near adrenals) which could be confounder for the event.
4	[redacted] YES	59/M	Oligoclonal bands (increase in lesions despite intravenous methylprednisolone therapy and plasma exchange)	1st dose/14	Myelitis transverse/ Unknown	Possible; with limited information	Patient presented with sensory (ascending numbness of both feet with tingling paraesthesia) - sensory spinal cord syndrome below T10 with sensory ataxia, Motor (progressive gait disturbance), Autonomic (urinary retention and rectal dysfunction) symptoms. TTO is considered reasonable to vaccine intake.

Table 187 Cases of Transverse Myelitis Fulfilling Brighton Collaboration criteria Level 3 (N = 9)

No	Case ID/ Country/ Serious- Y/N	Age (Years) /Gender (M/F)	Risk factors - Relevant Comorbidities/ concomitant medications	Dose # / Time to Onset (days)	Event / Outcome	WHO-UMC Causality Assessment	Additional Comment
							MRI (spine): longitudinal myelopathy (cervical, thoracic and lumbar spinal cord (with conus involvement)); Visual evoked potentials - normal CSF: pleocytosis (n=110), Oligoclonal bands positive with a pattern IV Assessed as "Possible" based on temporal association. Ascending progression and oligoclonal bands not typical presentation. There was worsening of lesions despite intravenous methylprednisolone therapy and plasma exchange. However, we are still missing some baseline health condition of the patient and if there is any drug history.
5	[redacted] YES	Unk/F	Oligoclonal bands (no CSF pleiocytosis)	1st dose/10	Myelitis/Recovering	Possible; with limited information	Patient had tactile and pinprick sensation decreased from T4 dermatome, Motor (weakness and pain in the legs) symptoms. TTO is considered reasonable to vaccine intake. MRI of the brain and spinal cord showed no parenchymal hyperintensities, no gadolinium enhancement. Electromyography/Electroneurography of the upper

Table 187 Cases of Transverse Myelitis Fulfilling Brighton Collaboration criteria Level 3 (N = 9)

No	Case ID/ Country/ Serious- Y/N	Age (Years) /Gender (M/F)	Risk factors - Relevant Comorbidities/ concomitant medications	Dose # / Time to Onset (days)	Event / Outcome	WHO-UMC Causality Assessment	Additional Comment
							and lower limbs and motor/sensory evoked potentials were negative. CSF: pleocytosis (n=101, predominant lymphocytes), Oligoclonal bands positive with a pattern IV Insufficient information on etiological workup. Assessed as "Possible" based on temporal association.
6	[redacted] NO	50/F	Not reported	1st dose/28	Myelitis transverse/ Unknown	Possible (alt. cause)	Patient had bilateral feet paraesthesias, and lower limb weakness. TTO is considered reasonable to vaccine intake. MRI Spine: focal cervical syrinx (C7-T1), demyelination across C6 CSF: mild pleocytosis Serum: MOG-Ab: negative, NMO Ab: negative No medical history, no history of concomitant medications, no family history. Examination reveals bilateral finger extensor weakness, we have limited information regarding the patient's baseline health condition prior to vaccination. Limited information on

Table 187 Cases of Transverse Myelitis Fulfilling Brighton Collaboration criteria Level 3 (N = 9)

No	Case ID/ Country/ Serious- Y/N	Age (Years) /Gender (M/F)	Risk factors - Relevant Comorbidities/ concomitant medications	Dose # / Time to Onset (days)	Event / Outcome	WHO-UMC Causality Assessment	Additional Comment
							lifestyle style and work history. Assessed as "Possible" based on temporal association. However, looking at the MRI result of the spine is suggestion a possible hole in the spine which might indicate present of a pre-existing condition.
7	[redacted] YES	38/M	Tuberculosis	1st dose/Unknown	Myelitis transverse/ Unknown	Unassessable/ Unclassifiable (limited info)	Patient had sensory (decreased sensation in bilateral lower limbs, burning sensation in left thigh, needle prick sensation in bilateral thighs), Motor (bilateral lower limb weakness), autonomic? (dribbling of urination, constipation). However, TTO is unknown. MRI brain: multiple patchy areas (unknown location); spine: T2 hypersensitivity in spinal cord extending from cervicomedullary junction to conus medullaris CSF: not reported Serum: MOG-Ab: negative, NMO Ab: negative Baseline health information prior to vaccination was unknown. Patient had a past history

Table 187 Cases of Transverse Myelitis Fulfilling Brighton Collaboration criteria Level 3 (N = 9)

No	Case ID/ Country/ Serious- Y/N	Age (Years) /Gender (M/F)	Risk factors - Relevant Comorbidities/ concomitant medications	Dose # / Time to Onset (days)	Event / Outcome	WHO-UMC Causality Assessment	Additional Comment
							of TB. MRI reveals the susceptibility of hemorrhage. No past history of trauma was indicated. Detailed etiological and diagnostic workup was not done.
8	[redacted] YES	58/M	Not reported	2nd dose/5	Myelitis/Unknown	Possible; with limited information	Patient had unspecified sensory disturbance. TTO is considered reasonable to vaccine intake. MRI: Myelitis at Cervical cord C3, C4 CSF: Inflammatory picture (unspecified) Assessed as possible based on temporal association. Limited information on baseline health information prior to vaccination. Limited information on medical history, concomitant medications, family history, etiology and investigation workups
9	[redacted] YES	72/M	Not reported	1st dose/23	Myelitis transverse/ Died	Possible (limited info)	This case has been discussed in Section 6.3.2.2: Fatal events in the reporting period of the PBRER. Please refer to this Section for case details.

CSF: Cerebrospinal Fluid, F Female, GBS: Guillain Barre Syndrome, LETM: Lomgitudinally Extensive Transverse Myelitis, M Male, MRI: Magnetic resonance imaging, NOMSD: Neuromyelitis Optica spectrum disorder, PT Preferred Term, TM: Transverse Myelitis, TTO Time to onset, UMC Uppsala Monitoring Centre, WHO World Health Organization

BCC Level 4 for Transverse Myelitis

A total of 68 cases fulfilled BCC Level 4 criteria, these cases did not fulfil criteria for a level 3, 2, or 1 as there was insufficient information to confirm the diagnosis or medical assessment of the case. Limited information to make any causality assessment was noted in 58 of the cases, and alternative causal factors were noted in 10 of the cases.

BCC Level 5 for Transverse Myelitis

A case was categorised as Brighton Collaboration Level 5 for acute myelitis based on clinical history, examination, and laboratory investigation results to determine level of diagnostic certainty based on algorithm in Law B 2021 [C].

A total of 22 case reports fulfilled BCC level 5 criteria. Limited information to make any causality assessment was noted in 20 of the cases, and alternative causal factors were noted in 2 of the cases.

Case-level Review Summary

None of the cases of Transverse myelitis fulfilled BCC Level 1 criteria.

A total of 13 cases fulfilled BCC Level 2 criteria, and 2 of them assessed as "Possible" (with alternate cause or confounders), 9 as Possible (with limited information), and the remaining 2 cases as "Unlikely" as per WHO-UMC Causality assessment criteria. Cases assessed as "Possible" (with limited information), were classified solely based on the TTO parameter (reasonable TTO considered) as there was insufficient case information (such as on vaccinees' medical history, comorbidities, concomitant medications, etiological work-up, etc.) to rule out alternative explanations.

A total of 9 cases of transverse myelitis fulfilled BCC Level 3 criteria. Out of these 9 cases 2 cases were "Possible" (with alternate cause or confounders), 6 were "Possible" (with limited information), and the remaining case was "Unassessable/Unclassifiable" as per WHO Causality assessment criteria. Cases were assessed as "Possible" based solely on the TTO, however there was insufficient case information (such as on vaccinees' medical history, comorbidities, concomitant medications, etiological work-up etc.) for further evaluation.

A total of 68 cases fulfilled BCC Level 4 criteria and 22 cases fulfilled BCC Level 5 criteria.

Of the remaining cases, the event could also be explained by the vaccinees' diseases or other medications (Sarcoidosis, Devic's disease (Neuromyelitis Optica), Multiple sclerosis (necessitating treatment with fingolimod, CSF cell counts suggesting CSF infections, thrombosis milieu, pre-existing spinal stenosis suggesting pre-existing spinal pathologies, pre-existing immune and neuromuscular inflammatory milieu (as suggested by fibromyalgia, arthritis).

Cumulative Period (29 December 2020 – 28 June 2022)

A cumulative search of the AstraZeneca global patient safety was conducted through 28 June 2022 using the same search strategy described above. The search identified 354 case reports (with PTs Myelitis and Myelitis transverse) in vaccinees who received VAXZEVRIA.

Out of the 354 cases: 320 (90.4%) of the cases were serious and 142 (40.1%) were medically confirmed. Out of the 354 cases, 24 (6.8%) recovered, 69 (19.5%) were recovering, 10 (2.8%) recovered with sequelae, 192 (54.2%) had not recovered and 2 (0.5%) had a fatal outcome. In 56 (15.8%) cases the outcome was unknown.

There were 192 (54.2%) reports in female vaccinees, 153 (43.2%) were in male.

vaccinees, and the gender was not reported in 9 cases (2.5%). The age range was 16-88 years of age with a median age of 51 years. A total of 236 (66.7%) vaccinees were in the age group of 18-64 years of age, 60 (16.9%) vaccinees were >65 years of age, 1 (0.3%) vaccinee was <18 years of age, and for 57 (16.1%) vaccinees the age was unknown.

Out of the 354 cases, 206 had the time to onset (TTO) within 42 days, and in 112 cases the TTO was unknown. The median TTO was 12 days (range 0-333 days). One additional case from regulatory authority reported TTO as 387 days which may be considered as incorrect. Out of the 354 cases, 164 (46.3%) reported the event occurring after the first dose, 49 (13.8%) after the second dose, and 3 (0.8%) after a third/booster dose. In 138 (40.0%) cases the dose was not specified.

Observed Versus Expected Analysis (cumulative)

Please refer to Appendix 8 for the methodology of the O/E analyses and Appendix 9 for any additional sensitivity analysis.

The observed versus expected analysis was carried out for cases of transverse myelitis with VAXZEVRIA received cumulatively through 28 June 2022. There were 354 cases identified, out of which a total of 207 cases had the time to onset (TTO) within 42 days and in 111 cases, the TTO was unknown.

Willame et al 2021 [B] have as part of ADVANCE EUROPE given incidence rates for transverse myelitis, stratified by age. The rates are slightly lower than other rates found corresponding to a more conservative estimate for background rates. An appendix to the same article by Willame et al 2021 [B] has given incidence rates stratified by age and gender.

Global overall rates based on the rates from ADVANCED Europe are presented in Table 188 The observed numbers are presented both including and excluding cases with an unknown time to onset and stratified by cases fulfilling Brighton collaboration criteria levels 1-3 (BCC 1-3).

The risk window for myelitis as a product related reaction for inactivated or subunit vaccines is likely similar to ADEM, where the recommended risk window for individuals is 2-42 days (Law B 2021 [B]. A risk window of 42 days was used for this analysis, ie, cases that have the time to onset of 42 days or less from receiving the vaccine until the event occurred are counted in the observed numbers.

Conservatively, the exposure for global reports (448306152) is based on doses administered in 13 markets as explained in Appendix 8.

Table 188 Observed versus Expected Analysis for Transverse Myelitis Overall and for Brighton Collaboration cases

Age group/Gender	Risk window (days)	Back-ground rates	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
Overall	42	0.97	448306152	206	500.05	0.41 (0.36 - 0.47)	Observed significantly < expected
Overall +Unk TTO	42	0.97	448306152	318	500.05	0.64 (0.57 - 0.71)	Observed significantly < expected
Overall BCC 1-3	42	0.97	448306152	49	500.05	0.1 (0.07 - 0.13)	Observed significantly < expected
Overall +Unk TTO BCC 1-3	42	0.97	448306152	56	500.05	0.11 (0.08 - 0.15)	Observed significantly < expected

Exposure until 28 June 2022. All global reports are included in observed numbers. Exposure numbers are from United Kingdom, EEA, Australia, Canada, Philippines and Brazil. Exposure numbers from India are not included.

BCC, Brighton collaboration criteria; CI, Confidence Interval; TTO: Time to onset; Unk, Unknown

Observed versus expected analyses stratified by age in the UK, using rates from ADVANCED Europe (Willame et al 2021 [B]) are presented in Table 189. The observed numbers are presented both including and excluding cases with an unknown time to onset and stratified by cases fulfilling Brighton collaboration criteria levels 1-3 (BCC 1-3).

Table 189 Observed versus expected analysis, stratified by age, BCC and with and without cases with an unknown TTO in the UK

Age Group	Risk Window	Background rates	Exposure	Observed number of cases	Expected number of cases	O over E ratio	Background rates
15-24 years	42	0.64	996660	3	0.73	4.11 (0.85 - 12.01)	Observed > expected
25-44 years	42	1.36	9196134	25	14.38	1.74 (1.13 - 2.57)	Observed significantly > expected
45-64 years	42	1.23	24195841	31	34.22	0.91 (0.62 - 1.29)	Observed < expected
65 years +	42	0.76	14448845	18	12.63	1.43 (0.84 - 2.25)	Observed > expected
15-24 years including cases with an unknown TTO	42	0.64	996660	4	0.73	5.48 (1.49 - 14.03)	Observed significantly > expected
25-44 years Including cases with an Unknown TTO	42	1.36	9196134	35	14.38	2.43 (1.7 - 3.39)	Observed significantly > expected
45-46 Years Including cases with an Unknown TTO	42	1.23	24195841	53	34.22	1.55 (1.16 - 2.03)	Observed significantly > expected

Table 189 Observed versus expected analysis, stratified by age, BCC and with and without cases with an unknown TTO in the UK

Age Group	Risk Window	Background rates	Exposure	Observed number of cases	Expected number of cases	O over E ratio	Background rates
65 Years + Including cases with an Unknown TTO	42	0.76	14448845	26	12.63	2.06 (1.34 - 3.02)	Observed significantly > expected
15-24 years BCC 1-3	42	0.64	996660	0	0.73	0 (0 - 5.05)	Observed < expected
25-44 Years BCC 1-3	42	1.36	9196134	6	14.38	0.42 (0.15 - 0.91)	Observed significantly < expected
45-64 Years BCC 1-3	42	1.23	24195841	9	34.22	0.26 (0.12 - 0.5)	Observed significantly < expected
65 Years + BCC 1-3	42	0.76	14448845	1	12.63	0.08 (0 - 0.44)	Observed significantly < expected
15-24 years BCC 1-3 including cases with an unknown TTO	42	0.64	996660	0	0.73	0 (0 - 5.05)	Observed < expected
25-44 years BCC 1-3 including cases with an unknown TTO	42	1.36	9196134	8	14.38	0.56 (0.24 - 1.1)	Observed < expected
45-64 years BCC 1-3 including cases with an unknown TTO	42	1.23	24195841	10	34.22	0.29 (0.14 - 0.54)	Observed significantly < expected

Table 189 Observed versus expected analysis, stratified by age, BCC and with and without cases with an unknown TTO in the UK

Age Group	Risk Window	Background rates	Exposure	Observed number of cases	Expected number of cases	O over E ratio	Background rates
65 years + BCC 1-3 including cases with an unknown TTO	42	0.76	14448845	2	12.63	0.16 (0.02 - 0.57)	Observed significantly < expected

Exposure until 28 June 2022

BCC, Brighton Criteria; CI, Confidence Interval; TTO: Time to onset; Unk, Unknown

Observed versus expected analyses stratified by age and gender in the United Kingdom, using UK incidence rates from Willame et al 2021 [B], ie, UK The Health Improvement Network (UK_THIN), are presented in Table 190. The observed numbers are presented both including and excluding cases with an unknown time to onset.

Table 190 Observed versus expected analysis, stratified by age and gender in the UK in the context of the UK THIN background rates

Age group/Gender	Risk window	Background rates	Exposure	Observed number of cases	Expected number of cases	O over E ratio	Risk window
Female 15-24 years UK THIN	42	1.2	569765	1	0.79	1.27 (0.03 - 7.05)	Observed > expected
Female 25-44 years UK THIN	42	2.6	4910483	18	14.68	1.23 (0.73 - 1.94)	Observed > expected
Female 45-64 years UK THIN	42	1.9	11601973	15	25.35	0.59 (0.33 - 0.98)	Observed significantly < expected
Female 65 years+ UK THIN	42	0.8	7752759	10	7.13	1.4 (0.67 - 2.58)	Observed > expected
Female Overall UK THIN	42	1.6	24835162	52	45.69	1.14 (0.85 - 1.49)	Observed > expected

Table 190 Observed versus expected analysis, stratified by age and gender in the UK in the context of the UK THIN background rates

Age group/Gender	Risk window	Background rates	Exposure	Observed number of cases	Expected number of cases	O over E ratio	Risk window
Female 15-24 years UKTHIN + Unk TTO	42	1.2	569765	2	0.79	2.53 (0.31 - 9.15)	Observed > expected
Female 25-44 years UKTHIN + Unk TTO	42	2.6	4910483	26	14.68	1.77 (1.16 - 2.6)	Observed significantly > expected
Female 45-64 years UKTHIN + Unk TTO	42	1.9	11601973	25	25.35	0.99 (0.64 - 1.46)	Observed < expected
Female 65 years+ UKTHIN + Unk TTO	42	0.8	7752759	13	7.13	1.82 (0.97 - 3.12)	Observed > expected
Female Overall UKTHIN + Unk TTO	42	1.6	24835162	79	45.69	1.73 (1.37 - 2.15)	Observed significantly > expected
Male 15-24 years UK THIN	42	0.7	426659	2	0.34	5.88 (0.71 - 21.25)	Observed > expected
Male 25-44 years UK THIN	42	1.5	4284886	7	7.39	0.95 (0.38 - 1.95)	Observed < expected

Table 190 Observed versus expected analysis, stratified by age and gender in the UK in the context of the UK THIN background rates

Age group/Gender	Risk window	Background rates	Exposure	Observed number of cases	Expected number of cases	O over E ratio	Risk window
Male 45-64 years UK THIN	42	1.4	12593335	16	20.27	0.79 (0.45 - 1.28)	Observed < expected
Male 65 years + UK THIN	42	0.9	6695948	8	6.93	1.15 (0.5 - 2.27)	Observed > expected
Male Overall UK THIN	42	1.1	24000981	39	30.36	1.28 (0.91 - 1.76)	Observed > expected
Male 15-24 years UKTHIN +Unk TTO	42	0.7	426659	2	0.34	5.88 (0.71 - 21.25)	Observed > expected
Male 25-44 years UKTHIN +Unk TTO	42	1.5	4284886	8	7.39	1.08 (0.47 - 2.13)	Observed > expected
Male 45-64 years UKTHIN +Unk TTO	42	1.4	12593335	28	20.27	1.38 (0.92 - 2)	Observed > expected
Male 65 years + UKTHIN +Unk TTO	42	0.9	6695948	13	6.93	1.88 (1 - 3.21)	Observed > expected
Male Overall UKTHIN +Unk TTO	42	1.1	24000981	62	30.36	2.04 (1.57 - 2.62)	Observed significantly > expected

CI, Confidence Interval; E, Expected; O, Observed TTO: Time to onset; Unk, Unknown; UK, United Kingdom

An observed versus expected analysis, including cases fulfilling Brighton collaboration levels 1-3, stratified by age and gender in the UK are provided below, using background rates from UK THIN are presented in Table 191.

Table 191 Observed versus expected analysis, stratified by age and gender, BCC levels 1-3 in the UK in the context of the UK THIN background rates

Age group/Gender	Risk window	Background rates	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
Female 15-24 years UK THIN BCC 1-3	42	1.2	569765	0	0.79	0 (0 - 4.67)	Observed < expected
Female 25-44 years UK THIN BCC 1-3	42	2.6	4910483	6	14.68	0.41 (0.15 - 0.89)	Observed significantly < expected
Female 45-64 years UK THIN BCC 1-3	42	1.9	11601973	2	25.35	0.08 (0.01 - 0.28)	Observed significantly < expected
Female 65 years+ UK THIN BCC 1-3	42	0.8	7752759	0	7.13	0 (0 - 0.52)	Observed significantly < expected
Female Overall UK THIN BCC 1-3	42	1.6	24835162	8	45.69	0.18 (0.08 - 0.35)	Observed significantly < expected
Female 15-24 years UKTHIN +Unk TTO BCC 1-3	42	1.2	569765	0	0.79	0 (0 - 4.67)	Observed < expected
Female 25-44 years UKTHIN +Unk TTO BCC 1-3	42	2.6	4910483	8	14.68	0.54 (0.24 - 1.07)	Observed < expected
Female 45-64 years UKTHIN +Unk TTO BCC 1-3	42	1.9	11601973	3	25.35	0.12 (0.02 - 0.35)	Observed significantly < expected
Female 65 years + UKTHIN +Unk TTO BCC 1-3	42	0.8	7752759	1	7.13	0.14 (0 - 0.78)	Observed significantly < expected
Female Overall UKTHIN +Unk TTO BCC 1-3	42	1.6	24835162	12	45.69	0.26 (0.14 - 0.46)	Observed significantly < expected

Table 191 Observed versus expected analysis, stratified by age and gender, BCC levels 1-3 in the UK in the context of the UK THIN background rates

Age group/Gender	Risk window	Background rates	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
Male 15-24 years UK THIN BCC 1-3	42	0.7	426659	0	0.34	0 (0 - 10.85)	Observed < expected
Male 25-44 years UK THIN BCC 1-3	42	1.5	4284886	0	7.39	0 (0 - 0.5)	Observed significantly < expected
Male 45-64 years UK THIN BCC 1-3	42	1.4	12593335	7	20.27	0.35 (0.14 - 0.71)	Observed significantly < expected
Male 65 years + UK THIN BCC 1-3	42	0.9	6695948	1	6.93	0.14 (0 - 0.8)	Observed significantly < expected
Male Overall UK THIN BCC 1-3	42	1.1	24000981	8	30.36	0.26 (0.11 - 0.52)	Observed significantly < expected
Male 15-24 years UKTHIN +Unk TTO BCC 1-3	42	0.7	426659	0	0.34	0 (0 - 10.85)	Observed < expected
Male 25-44 years UKTHIN +Unk TTO BCC 1-3	42	1.5	4284886	0	7.39	0 (0 - 0.5)	Observed significantly < expected
Male 45-64 years UKTHIN +Unk TTO BCC 1-3	42	1.4	12593335	7	20.27	0.35 (0.14 - 0.71)	Observed significantly < expected
Male 65 years + UKTHIN +Unk TTO BCC 1-3	42	0.9	6695948	1	6.93	0.14 (0 - 0.8)	Observed significantly < expected

Table 191 Observed versus expected analysis, stratified by age and gender, BCC levels 1-3 in the UK in the context of the UK THIN background rates

Age group/Gender	Risk window	Background rates	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
Male Overall UKTHIN +Unk TTO BCC 1-3	42	1.1	24000981	9	30.36	0.3 (0.14 - 0.56)	Observed significantly < expected

BCC, Brighton collaboration criteria; CI, Confidence Interval; E Expected; O Observed; TTO, Time to Onset; UK United Kingdom; Unk, Unknown;

Observed versus expected analyses stratified by Dose number, age and gender, BCC in the United Kingdom, using UK incidence rates from Willame et al 2021 [B], ie, UK The Health Improvement Network (UK_THIN), are presented in Table 192.

Table 192 Observed versus expected analyses stratified by Dose number, age and gender, BCC in UK

Gender /Age group / Dose #	Risk window	Background rates	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
Male/ 15-24 years/ Dose 1	42	0.7	218242	0	0.18	0 (0 - 20.49)	Observed < expected
Male/ 25-44 years/ Dose 1	42	1.5	2183174	6	3.77	1.59 (0.58 - 3.46)	Observed > expected
Male/ 45- 64 years/ Dose 1	42	1.4	6356696	12	10.23	1.17 (0.61 - 2.05)	Observed > expected
Male/ 65 yrs +/ Dose 1	42	0.9	3370262	2	3.49	0.57 (0.07 - 2.07)	Observed < expected

Table 192 Observed versus expected analyses stratified by Dose number, age and gender, BCC in UK

Gender /Age group / Dose #	Risk window	Background rates	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
Male/ Overall/ Dose 1	42	1.1	12128462	26	15.34	1.69 (1.11 - 2.48)	Observed significantly > expected
Male/ 15-24 years/ Dose 1/ BCC 1-3	42	0.7	218242	0	0.18	0 (0 - 20.49)	Observed < expected
Male/ 25-44 years/ Dose 1/ BCC1-3	42	1.5	2183174	0	3.77	0 (0 - 0.98)	Observed significantly < expected
Male/ 45- 64 years/ Dose 1/ BCC 1-3	42	1.4	6356696	5	10.23	0.49 (0.16 - 1.14)	Observed < expected
Male/ 65 yrs +/ Dose 1/ BCC 1-3	42	0.9	3370262	0	3.49	0 (0 - 1.06)	Observed < expected
Male/ Overall/ Dose 1/ BCC-1-3	42	1.1	12128462	5	15.34	0.33 (0.11 - 0.76)	Observed significantly < expected
Male/ 15-24 years/ Dose 2	42	0.7	208057	0	0.17	0 (0 - 21.7)	Observed < expected

Table 192 Observed versus expected analyses stratified by Dose number, age and gender, BCC in UK

Gender /Age group / Dose #	Risk window	Background rates	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
Male/ 25-44 years/ Dose 2	42	1.5	2099173	0	3.62	0 (0 - 1.02)	Observed < expected
Male/ 45- 64 years/ Dose 2	42	1.4	6229817	3	10.03	0.3 (0.06 - 0.87)	Observed significantly < expected
Male/ 65 yrs +/ Dose 2	42	0.9	3316728	3	3.43	0.87 (0.18 - 2.56)	Observed < expected
Male/ Overall/ Dose 2	42	1.1	11853840	6	14.99	0.4 (0.15 - 0.87)	Observed significantly < expected
Male/ 15-24 years/ Dose 2/ BCC 1-3	42	0.7	208057	0	0.17	0 (0 - 21.7)	Observed < expected
Male/ 25-44 years/ Dose 2/ BCC 1-3	42	1.5	2099173	0	3.62	0 (0 - 1.02)	Observed < expected
Male/ 45- 64 years/ Dose 2/ BCC 1-3	42	1.4	6229817	1	10.03	0.1 (0 - 0.56)	Observed significantly < expected

Table 192 Observed versus expected analyses stratified by Dose number, age and gender, BCC in UK

Gender /Age group / Dose #	Risk window	Background rates	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
Male/ 65 yrs +/ Dose 2/ BCC 1-3	42	0.9	3316728	1	3.43	0.29 (0.01 - 1.62)	Observed < expected
Male/ Overall/ Dose 2/ BCC 1-3	42	1.1	11853840	2	14.99	0.13 (0.02 - 0.48)	Observed significantly < expected
Female/ 15-24 years/ Dose 1	42	1.2	290632	1	0.4	2.5 (0.06 - 13.93)	Observed > expected
Female/ 25-44 years/ Dose 1	42	2.6	2496917	12	7.47	1.61 (0.83 - 2.81)	Observed > expected
Female/ 45- 64 years/ Dose 1	42	1.9	5844968	9	12.77	0.7 (0.32 - 1.34)	Observed < expected
Female/ 65 yrs +/ Dose 1	42	0.8	3899933	6	3.59	1.67 (0.61 - 3.64)	Observed > expected
Female/ Overall/ Dose 1	42	1.6	12532563	32	23.06	1.39 (0.95 - 1.96)	Observed > expected
Female/ 15-24 years/ Dose 1/ BCC 1-3	42	1.2	290632	0	0.4	0 (0 - 9.22)	Observed < expected

Table 192 Observed versus expected analyses stratified by Dose number, age and gender, BCC in UK

Gender /Age group / Dose #	Risk window	Background rates	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
Female/ 25-44 years/ Dose 1/ BCC 1-3	42	2.6	2496917	3	7.47	0.4 (0.08 - 1.17)	Observed < expected
Female/ 45- 64 years/ Dose 1/ BCC 1-3	42	1.9	5844968	1	12.77	0.08 (0 - 0.44)	Observed significantly < expected
Female/ 65 years +/ Dose 1/ BCC 1-3	42	0.8	3899933	0	3.59	0 (0 - 1.03)	Observed < expected
Female/ Overall/ Dose 1/ BCC 1-3	42	1.6	12532563	4	23.06	0.17 (0.05 - 0.44)	Observed significantly < expected
Female/ 15-24 years/ Dose 2	42	1.2	278621	0	0.38	0 (0 - 9.71)	Observed < expected
Female/ 25-44 years/ Dose 2	42	2.6	2408701	3	7.2	0.42 (0.09 - 1.22)	Observed < expected
Female/ 45- 64 years/ Dose 2	42	1.9	5742260	3	12.55	0.24 (0.05 - 0.7)	Observed significantly < expected

Table 192 Observed versus expected analyses stratified by Dose number, age and gender, BCC in UK

Gender /Age group / Dose #	Risk window	Background rates	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
Female/ 65 years +/ Dose 2	42	0.8	3833359	0	3.53	0 (0 - 1.05)	Observed < expected
Female/ Overall/ Dose 2	42	1.6	12263010	7	22.56	0.31 (0.12 - 0.64)	Observed significantly < expected
Female/ 15-24 years/ Dose 2/ BCC 1-3	42	1.2	278621	0	0.38	0 (0 - 9.71)	Observed < expected
Female/ 25-44 years/ Dose 2 / BCC 1-3	42	2.6	2408701	1	7.2	0.14 (0 - 0.77)	Observed significantly < expected
Female/ 45- 64 years/ Dose 2 / BCC 1-3	42	1.9	5742260	0	12.55	0 (0 - 0.29)	Observed significantly < expected
Female/ 65 years +/ Dose 2 / BCC 1-3	42	0.8	3833359	0	3.53	0 (0 - 1.05)	Observed < expected

Table 192 Observed versus expected analyses stratified by Dose number, age and gender, BCC in UK

Gender /Age group / Dose #	Risk window	Background rates	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
Female/ Overall/ Dose 2 / BCC 1-3	42	1.6	12263010	1	22.56	0.04 (0 - 0.25)	Observed significantly < expected

BCC, Brighton collaboration criteria; CI, Confidence Interval; E Expected; O Observed TTO: Time to onset; UK United Kingdom; Unk, Unknown

Table 193 Observed versus expected analysis, stratified by Dose, age, BCC in the UK

Age Group/Dose	Risk window	Background rates	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
15-24 years/ Dose 1	42	0.64	508997	1	0.37	2.7 (0.07 - 15.06)	Observed > expected
25-44 years/ Dose 1	42	1.36	4680514	18	7.32	2.46 (1.46 - 3.89)	Observed significantly > expected
45- 64 years/ Dose 1	42	1.23	12201963	21	17.26	1.22 (0.75 - 1.86)	Observed > expected
65 Years + Dose 1	42	0.76	7270267	8	6.35	1.26 (0.54 - 2.48)	Observed > expected
Overall/ Dose 1	42	0.97	24732840	59	27.59	2.14 (1.63 - 2.76)	Observed significantly > expected
15-24 years/ Dose 1/ BCC 1-3	42	0.64	508997	0	0.37	0 (0 - 9.97)	Observed < expected

Table 193 Observed versus expected analysis, stratified by Dose, age, BCC in the UK

Age Group/Dose	Risk window	Background rates	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
25-44 years/ Dose 1/ BCC1-3	42	1.36	4680514	3	7.32	0.41 (0.08 - 1.2)	Observed < expected
45- 64 years/ Dose 1/ BCC 1-3	42	1.23	12201963	6	17.26	0.35 (0.13 - 0.76)	Observed significantly < expected
65 yrs +/ Dose 1/ BCC 1-3	42	0.76	7270267	0	6.35	0 (0 - 0.58)	Observed significantly < expected
Overall/ Dose 1/ BCC-1-3	42	0.97	24732840	9	27.59	0.33 (0.15 - 0.62)	Observed significantly < expected
15-24 years/ Dose 2	42	0.64	486791	0	0.36	0 (0 - 10.25)	Observed < expected
25-44 years/ Dose 2	42	1.36	4508213	3	7.05	0.43 (0.09 - 1.24)	Observed < expected
45- 64 years/ Dose 2	42	1.23	11972310	6	16.93	0.35 (0.13 - 0.77)	Observed significantly < expected
65 years +/ Dose 2	42	0.76	7150151	3	6.25	0.48 (0.1 - 1.4)	Observed < expected
Overall/ Dose 2	42	0.97	24149323	13	26.94	0.48 (0.26 - 0.83)	Observed significantly < expected
15-24 years/ Dose 2/ BCC 1-3	42	0.64	486791	0	0.36	0 (0 - 10.25)	Observed < expected

Table 193 Observed versus expected analysis, stratified by Dose, age, BCC in the UK

Age Group/Dose	Risk window	Background rates	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
25-44 years/ Dose 2/ BCC 1-3	42	1.36	4508213	0	0.36	0 (0 - 10.25)	Observed < expected
45- 64 years/ Dose 2/ BCC 1-3	42	1.23	11972310	1	7.05	0.14 (0 - 0.79)	Observed significantly < expected
65 years +/ Dose 2/ BCC 1-3	42	0.76	7150151	1	16.93	0.06 (0 - 0.33)	Observed significantly < expected
Overall/ Dose 2/ BCC 1-3	42	0.97	24149323	1	6.25	0.16 (0 - 0.89)	Observed significantly < expected

BCC, Brighton collaboration classification criteria; CI, Confidence Interval; E Expected; EEA, European Economic Area O Observed TTO: Time to onset; Unk, Unknown; UK, United Kingdom.

Observed vs expected analysis summary:

When the observed versus expected analysis is carried out overall for global reports for all ages and genders, the number of observed cases is significantly less than expected for all stratifications provided.

When stratified by age only in the UK using the ADVANCE EUROPE rates, observed cases are significantly more than expected for age groups 25-44 years regardless of whether cases with an unknown time to onset are included or not. For the age group 15-24 years, observed cases are more than expected, however the disproportionality was not significant when cases with unknown TTO are not included. For the age group 45-64 years observed cases are less than expected when cases with an unknown TTO are not included. For the older age group (65+) observed cases are more than expected when cases with an unknown TTO are not included. When the cases with an unknown TTO are included for all age groups, observed cases are more than expected with a significant disproportionality.

When only cases of transverse myelitis fulfilling BCC levels 1-3 are included, observed cases are significantly less than/less than expected for all stratifications.

The observed cases for females in the UK using the rate from UKTHIN are more than expected. When stratified by age and gender, observed cases for females were greater than expected in all the age groups except for 45-64 years, without the result being significant. In the 45-64 years group, observed cases were significantly less than expected. Observed cases were significantly more than expected for females overall when rate from UKTHIN and when cases with unknown TTO were included. For other stratifications, observed cases were either more or less than expected without the result being significant, the only exception being the 25-44 years group, where the observed was significantly more than expected.

When only cases fulfilling BCC levels 1-3 are included, observed cases are either less or significantly less than expected for all age stratifications (result is not significant for the youngest age group, 15-24 years, however, there are no observed cases with BCC 1-3 in that age group).

When stratified by age and gender, the observed cases for males are significantly more than expected for males overall when cases with an unknown TTO are included. For all age stratifications in males, the numbers are low, leading to the finding that the results for each age group are not significant. When the UKTHIN rates are used, the youngest age group (15-24 years) and the oldest age group (65+ years) have observed cases more than expected. When cases with unknown TTO were included, however, all age groups had observed higher than expected.

When males are stratified by BCC levels 1-3, observed cases were less/significantly less than expected in all age groups, regardless of whether unknown TTO was included.

Cases were also stratified by dose. For Dose 1 Overall, the observed cases were significantly less than expected. When Dose 1 cases in males were stratified using UK THIN background rates, the cases were either more or less than expected in all age stratifications. Overall the observed number of cases was significantly more than expected (26 cases to 15.34). Cases fulfilling BCC 1-3 criteria showed observed cases were significantly less than expected in males overall and the 25-44 years age group. For the other age groups observed cases were less than expected.

Cases in female patients after dose 1 stratified using the same UK THIN background rates did not have any significant findings except the BCC 1-3 cases where the observed cases were significantly less than expected (in females overall and ages 45-64 years age group).

When stratified by age only in the UK using the ADVANCE EUROPE rates, the observed cases were more than all age groups except the 25-44 years range where it was significantly more than expected for the first dose (18 observed, 7.32 expected). When stratified by cases fulfilling BCC 1-3, observed cases were significantly less than/less than expected.

For Dose 2, overall, the observed cases were significantly less than expected with and without unknown TTO cases and BCC 1-3. With the UK THIN background rates, observed cases were overall significantly less than expected in males and females after dose 2. This was also significantly less than observed for cases stratified by dose, age and BCC in the UK using ADVANCE EUROPE rates.

Review of Literature for the reporting period

The literature article by Netravathi et al 2022 presenting an observational comparative analysis study, case series (over a period from May 2021 to December 2021) of patients with different neurological manifestations of CNS demyelination presenting within 6 weeks of vaccination against SARS-CoV-2, was identified in the reporting period of this PBRER and its assessment did not find any safety finding with impact on benefit-risk profile of VAXZEVRIA. Please refer to section 15.2.12 'Acute Disseminated Encephalomyelitis' for the full literature review and assessment.

Overall Summary

The pathogenesis for TM is thought to be immune-mediated from infection, para-infectious processes, autoimmune disease, or paraneoplastic processes. The exact mechanism of TM following immunization is unknown.

There were 21 cases of TM (fulfilling at least BCC 3 criteria) received during the reporting period, of these, 18 were assessed to be classified as "Possible" according to WHO-UMC causality criteria (as either "Possible" with limited information/ "Possible" with confounders or alternate cause). Fourteen (14) of the 18 cases were classified as "Possible" with Limited Information based solely on the TTO parameter (reasonable TTO considered) as there was insufficient case information (such as vaccinees' medical history, comorbidities, concomitant medications, etiological work-up etc). For the remaining four cases the event could also be explained by the vaccinees' diseases or other medications.

In addition, an observed versus expected analysis of cumulative cases meeting Brighton collaboration criteria levels 1-3 showed that the observed number of TM cases fulfilling case definition are either less than or significantly less than the number of expected cases in all risk windows.

Conclusion

From the data identified during the reporting period and taking into account the cumulative experience, there is currently insufficient evidence of a causal association between Transverse Myelitis and VAXZEVRIA. As per Section 4.4 (Special warnings and special precautions for use) in the VAXZEVRIA CDS as below: Very rare events of demyelinating disorders have

been reported following vaccination with COVID-19_Vaccine AstraZeneca. A causal relationship has not been established._As with other vaccines, the benefits and potential risks of vaccinating individuals with VAXZEVRIA should be considered.

In conclusion, it is AstraZeneca's opinion that no changes to the VAXZEVRIA CDS, and RMP, are warranted based on the review of currently available information.

Surveillance of Transverse Myelitis will continue to be closely monitored as part of AstraZeneca's ongoing surveillance efforts for the important potential risk of Nervous system disorders, including immune-mediated neurological conditions.

Overall Conclusion for Immune Mediated Neurological Conditions:

During the period covered by this PBRER, the CDS section 4.8 'Undesirable effects' was updated with addition of paraesthesia and hypoaesthesia to the summary of post-authorisation data, with frequency "uncommon" and the CDS section 4.4 'Special warnings and special precautions for use' on Neurological events was updated to specifically reference very rare events of Guillain-Barré Syndrome, please refer to Section 4 and 16.2.2.

It is AstraZeneca's opinion that no further changes to the VAXZEVRIA CDS, RMPs, corresponding local labels or product leaflets are warranted based on the review of currently available information. Immune-mediated neurological conditions will continue to be closely monitored as part of AstraZeneca's ongoing surveillance efforts for the important potential risk of immune-mediated neurological conditions.

16.3.1.3 Vaccine-associated enhanced disease (VAED) / including vaccine-associated enhanced respiratory disease (VAERD)

Review of Cases

A cumulative search (29 December 2020 to 28 June 2022) and interval search (29 December 2021 to 28 June 2022) of the AstraZeneca Global Patient Safety Database was conducted for adverse event reports of Vaccine-associated enhanced disease (VAED) / Vaccine-associated enhanced respiratory disease (VAERD) in association with the use of VAXZEVRIA. The search was conducted using the following MedDRA (version 25.0) Preferred Terms: Acute lung injury; Acute respiratory failure; Autoimmune myositis; Breakthrough COVID-19; Coagulopathy; Coronavirus pneumonia; COVID-19 pneumonia; Cytokine abnormal; Cytokine release syndrome; Cytokine storm; Cytokine increased; Fibrinogen degradation products increased; Immune mediated lung disease; Immune-mediated myositis; The International Society on Thrombosis and Haemostasis (ISTH) score for disseminated intravascular coagulation; Mechanical ventilation; Multiple organ dysfunction syndrome; Organ failure; Pneumonia; Pneumonitis; Post-acute COVID-19 syndrome; Pulmonary haemorrhage; Respiratory failure; SARS-CoV-2 sepsis; Septic coagulopathy;

Septic cerebral embolism; Vaccine associated enhanced disease; Vaccine associated enhanced respiratory disease; Vaccine derived SARS-CoV-2 infection.

Interval Period (29 December 2021 – 28 June 2022)

During the interval period covered by this report, 555 events from 519 cases (278 initial and 241 follow-up) were retrieved under this AESI concept, which includes Pneumonia (196), COVID-19 pneumonia (135), Coagulopathy (66), Respiratory failure (48), Breakthrough COVID-19 (26), Acute respiratory failure (23), Multiple organ dysfunction syndrome (20), Pneumonitis (19), Organ failure (7), Cytokine storm (4), Autoimmune myositis (3), Pulmonary haemorrhage (3), Acute lung injury (1), Cytokine release syndrome (1), Immune-mediated myositis (1), Mechanical ventilation (1), Vaccine associated enhanced respiratory disease (1).

Among these 519 cases, the majority were from spontaneous sources (492, 94.8%), followed by non-interventional studies (14, 2.7%), literature (11, 2.1%), and AZ-sponsored clinical trials (2, 0.4%). Of these 519 cases, 321 cases (299 serious and 22 non-serious) were medically confirmed with the use of VAXZEVRIA. There were 210 (40.5%) case reports from elderly vaccinees, 274 (52.8%) from adult vaccinees, and age was unknown in 35 (6.7%) vaccinees. The outcome of potential VAED/VAERD events was fatal in 136 of the total 519 (26.2%) cases reported during the interval period.

Cumulative data through 28 June 2022

There have been 2139 case reports of potential VAED/VAERD which included 2238 events. These events include Pneumonia (911), COVID-19 pneumonia (380), Coagulopathy (376), Respiratory failure (188), Pneumonitis (104), Multiple organ dysfunction syndrome (93), Acute respiratory failure (75), Pulmonary haemorrhage (29), Breakthrough COVID-19 (26), Organ failure (15), Cytokine storm (12), Autoimmune myositis (5), Mechanical ventilation (5), Vaccine associated enhanced disease (5), Immune-mediated myositis (4), Acute lung injury (3), Cytokine release syndrome (3), Coronavirus pneumonia (1), Cytokine increased (1), SARS-CoV-2 sepsis (1), Vaccine associated enhanced respiratory disease (1).

Among these 2139 cases, the majority were from spontaneous sources (2077, 97.1%), followed by non-interventional studies (30, 1.4%), literature (28, 1.3%), and AZ-sponsored clinical trials (4, 0.2%). Of these 2139 cases, 1044 cases were reported from females and 1052 from males; and in the remaining 43 cases, gender was unknown. Among total cases, 997 (941 serious and 56 non-serious) were medically confirmed cases with the use of VAXZEVRIA. There were 839 (39.2%) case reports from elderly (≥65 years of age) vaccinees, 1133 (53%) from adult (18 - 64 years of age) vaccinees, 1 from a paediatric vaccinee, and age was unknown in 166 (7.8%) vaccinees. In 415 of the 2139 cases, the outcome of events was reported as fatal.

Literature

A search of the Embase and InsightMeme.com databases was undertaken covering the interval period to identify literature on VAED/VAERD with COVID-19 vaccines, including VAXZEVRIA.

A total of 75 (64 from Embase and 11 from InsightMeme) search results were obtained. Of these, none identified any new safety information or discussions of the mechanism of action relevant to the review of this topic.

Summary

On review of 519 cases of VAED/VAERD received during the reporting period, a majority (459 out of 519, 88.4%) of them were reported as serious, of which 299 cases were medically confirmed, and 136 out of 519 (26.2%) cases reported fatal outcomes. These cases had insufficient information on dose latency, medical history, concomitant medications, baseline medical condition prior to vaccination, clinical course, diagnostic and etiologic workup, and storage and transport conditions of the vaccine, which precluded a proper causal assessment. No hypothesized mechanism/pathways have been identified to date. No new safety information on this topic was identified through the review of the literature.

Conclusion

Based on evaluation of the available data during this reporting period and considering the cumulative experience, there is insufficient evidence of a reasonable possibility of a causal association between VAED/VAERD and VAXZEVRIA.

In conclusion, it is AstraZeneca's opinion that no changes to the VAXZEVRIA CDS or RMP are warranted based on the review of currently available information.

Since the concept of VAED/VAERD is an Important Potential Risk and an AESI with VAXZEVRIA, AstraZeneca recognizes the need for surveillance and will continue to closely monitor the reported events of VAED/VAERD.

More detailed information regarding this important potential risk is provided in Section 16.4.2.

16.3.2 New information on important identified risks

Important identified risks included in Section 16.1 and included in Table 194 below are kept under close surveillance by AstraZeneca.

Table 194 Important identified risks presented in Core RMP (Version 5; dated 09 December 2021

Section /Topic	Core RMP
Important identified risk	Thrombosis in combination with thrombocytopenia

16.3.2.1 Thrombosis in combination with thrombocytopenia / TTS

Review of Cases

A cumulative search of the AstraZeneca safety database was undertaken for AE reports under the HLT: Thrombocytopenia and SMQ: Hematopoietic Thrombocytopenia Narrow co-reported with events identified from the SMQ: Embolic and thrombotic events with VAXZEVRIA. This search criteria were also applied to retrieve case reports of Thrombosis with thrombocytopenia syndrome (TTS) following both first and second dose of VAXZEVRIA. Also, cases with a reported PT of Thrombosis with Thrombocytopenia Syndrome (TTS) or Vaccine-Induced Prothrombotic Immune Thrombocytopenia (VIPIT) or Vaccine-Induced Immune Thrombotic Thrombocytopenia (VITT) were included, as there is now corresponding PTs in MedDRA version 25.0. Also, cases of CVST from Section 16.3.2.1 with platelet count less than 150 × 109/ L were included. This covered the period up to 28 June 2022

The search resulted in a total of 2392 individual cases (cumulative up to 28 June 2022), and one case was considered as potential duplicate on further review. The below analysis was focused on 2391 unique reports. Of the 2391 cases, 2380 (99.5%) were serious and 11 were non serious, 1715 case reports were medically confirmed and 676 were consumer reports and 1715 case reports were from regulatory, 371 from spontaneous, 304 from literature sources, and 1 from Post-marketing/non-interventional study. There were 260 cases reported with thrombosis in combination with thrombocytopenia after Dose 2. There were 8 cases occurred after administration of a Dose 3/booster (either of VAXZEVRIA or an mRNA vaccine): 6 after a VAXZEVRIA booster, and 2 after an mRNA booster. The 2 cases after an mRNA booster are not further discussed here as they do not concern the use of VAXZEVRIA as a booster.

During the reporting interval (29 December 2021 to 28 June 2022), there were 447 cases (19% of the total cumulative cases) reported. Of the 447 case reports there were 255 initial reports (231 concerning Dose 1, 17 concerning Dose 2, and 7 cases concerning Dose 3). There were 192 follow-up reports [182 concerning Dose 1 and 10 concerning Dose 2]). Further analysis in this report is focused on the cumulative report.

Of these 2391 case reports, 1257 (53%) reports were reported in females, 1068 (45%) reports in males, and in 67 (3%) cases the gender was not reported.

1323 [55%] were reported from UK and the other cases (≥ 10) were from the following countries: Germany (275), Italy (127), Canada (76), France (63), Netherlands (60), Spain (60), India (52), Belgium (44), Austria (27), Sweden (25), Poland (22), Norway (22), Finland (18), Greece (14), Mexico (13), Czech Republic (11), Taiwan (11), Ireland (10).

Eight percent 8% (195) of the cases were reported for vaccinees aged 18-29 years; 10.5% (252) in vaccinees aged 30 to 39 years, 15.5% (373) in vaccinees aged 40 to 49 years; 18% (431) in vaccinees aged 50 to 59 years, 21% (509) in vaccinees aged 60 to 69 years, 12.7% (305) in vaccinees aged 70 to 79 years, 4.9% (119) in vaccinees aged ≥ 80 years, and in 8.6% (207) vaccinees age was unknown. The age range was 18 to 104 years with a median of 56 years.

Case level outcome was reported in 1957/2391 (82%) cases, of this 1957 cases the outcome was Recovering in 498 (21%) cases, Recovered in 269 (11%) cases, Recovered with sequelae in 44 (2%) cases, Not recovered in 732 (31%) cases, and Fatal in 414 (17%) cases. In 437 (18%) cases the outcome was unknown.

Seventeen percent 17% (414/2392) of the cases reported fatal outcome compared to the 17% (348/2059) fatal outcome reported in the previous PBRER (DLP: 28 December 2021) and October-November, August-September, July, June, May, April, and March SSRs with rates of 17% (332/1987), 17% (310/1809), 18% (267/1503), 18% (245/1375), 19% (210/1095), 22% (150/679) and 27% (49 out of 184), respectively. Fatality/survival rate cumulatively for each month up to 28 June 2022 is presented in Table 201 and Figure 8.

Time to onset (TTO) to TTS event was available in 1875 (78%) case reports and ranged from 0 day to 313 days; median time to onset (TTO) was 12 days. TTO for events within 14, 21, and 42 days by Dose 1, Dose 2, Dose 3 and fatal reports are presented in Table 195.

Table 195 Time to onset for thrombosis in combination with thrombocytopenia cases

	All cases N (%)	Dose 1 N (%)	Dose 2 N (%)	Dose 3 N (%)	Fatal reports N (%)
Time to onset available	1875(78)	1637(77)	232(89)	6(75)	307(74)
14 days	1193(64)	1064(65)	125(54)	4(67)	224(73)
21 days	1492(80)	1334(81)	153(66)	5(83)	268(87)
42 days	1749(93)	1546(94)	198(85)	6(100)	294(96)
Total number of cases	**2391**	**2123**	**260**	**8**	**414**

Percentage represents percent of total number of cases each dose and fatal report.

Of the 2391 case reports, the reported venous thrombotic sites included CVST (HLT: Cerebrovascular venous and sinus thrombosis) in 585 (24%) cases. Of the 2391 case reports, 120 (5.0%) had the co-reported events from the HLT: Coagulopathies (including 58 cases with DIC) and 850 (35%) case reports had co-reported bleeding event from the narrow SMQ: Haemorrhage terms (excel laboratory terms).

The most common (≥10) bleeding events included Cerebral haemorrhage (207), Haemorrhage (74), Haemorrhage intracranial (69), Subarachnoid haemorrhage (63), Disseminated intravascular coagulation (58), Contusion (55), Petechiae (51), Thrombotic thrombocytopenic purpura (45), Haemoptysis (26), Haematoma (24), Cerebral haematoma (22), Haemorrhagic stroke (17), Adrenal haemorrhage (16), Haemorrhagic transformation stroke (15), Rectal haemorrhage (14), Epistaxis (14), Haematuria (11), Haemorrhagic infarction (11), Ecchymosis (11), Haemorrhagic cerebral infarction (10).

A total of 367 case reports contained PTs from the SMQ: Embolic and thrombotic events, arterial; 1129 reports contained PTs from the SMQ: Embolic and thrombotic events, vessel type unspecified and mixed arterial and venous, and 1659 reports contained PTs from the SMQ: Embolic and thrombotic events, venous. Thrombosis events by site and age group and gender is presented in Appendix 18 Table 1 which includes all events irrespective of Dose 1, Dose 2 or Dose 3. One case may contain > 1 reported thrombosis event; hence the event count is more than the case count. There are 559 events in 367 case reports for SMQ: Embolic and thrombotic events, arterial. The most common (≥ 30) arterial Embolic and thrombotic events included, Peripheral artery thrombosis (58), Ischaemic stroke (54), Thrombotic thrombocytopenic purpura (49), Aortic thrombosis (41), Arterial thrombosis (35), Acute myocardial infarction (34), Carotid artery thrombosis (31). There are 1666 events in 1129 case reports for SMQ: Embolic and thrombotic events, vessel type unspecified and mixed arterial and venous. This included most common events (>30) Thrombosis (488), Thrombosis with thrombocytopenia syndrome (345), Cerebrovascular accident (102), Hemiparesis (93), Embolism (78), Cerebral infarction (69), Disseminated intravascular coagulation (64), Cerebral thrombosis (56), Heparin-induced thrombocytopenia (HIT) (47), Hemiplegia (34). There are 2784 events in 1659 case reports for SMQ: Embolic and thrombotic events, venous. This included most common events (>30) Pulmonary embolism (843), Deep vein thrombosis (506), Cerebral venous sinus thrombosis (463), Portal vein thrombosis (185), Cerebral venous thrombosis (128), Superior sagittal sinus thrombosis (78), Venous thrombosis (60), Mesenteric vein thrombosis (56), Jugular vein thrombosis (49), Splenic vein thrombosis (44), Hepatic vein thrombosis (39), Visceral venous thrombosis (38), Transverse sinus thrombosis (34), Superficial vein thrombosis (32). (Embolic and thrombotic events in thrombosis with thrombocytopenia case reports age group and gender provided in Appendix-18, Table 1)

Reporting Rate and Observed versus Expected Analysis

Reporting rate for thrombosis in combination with thrombocytopenia across all age groups based on the data from both UK and EEA by risk window of 21 days and 42 days is provided in Table 196 and Table 197, respectively. Reporting rate is also stratified by Dose 1 and Dose 2.

The overall TTS reporting rate from the UK was 10.87/million (532 identified reports with time to onset ≤ 21 days; estimated exposure 48.93 million administered doses) when compared to 5.6 (event rates per 1M Person Years (PY) per 21 days Truven Market Scan-2019, aligned with the Observational Health Data Science and Informatics (OHDSI) TTS algorithm) and 10.7 (event rates per 1M PY per 21days Truven Market Scan-2019).

The reporting rate for the cases where the MHRA case classification criteria was met (confirmed, probable, and possible) was 13.94/million administered doses.

The following reporting rate pertains to the risk window of 21 days, For UK, the reporting rate for Dose 1 and Dose 2 was 18.32 and 3.19/million doses administered doses respectively. For all administered doses and Dose 1, the reporting rate in the 18 to 39 and 40 to 49 age groups was higher when compared to background rate. For all administered doses the reporting rate in 50 to 64 age group was within the background rate. For Dose 1, the reporting rate in the 50 to 64 age group was higher than the background rate. For all administered doses the reporting rate in the 65+ age group was less compared to the background rate. Reporting rate for Dose 2 was less when compared to the background rate for overall and all age stratifications.

The following reporting rate pertains to the risk window of 42 days, For UK, the reporting rate for Dose 1 and Dose 2 was 21.72 and 3.98/million doses administered doses respectively. For all administered doses and Dose 1, the reporting rate in the 18 to 39 and 40 to 49 age groups was higher when compared to background rate.

The overall TTS reporting rate from the EEA was 12.43 /million (598 identified reports with time to onset ≤ 21 days; estimated exposure 48.11 million administered doses) when compared to 5.6 (event rates per 1M PY per 21 days Truven Market Scan-2019, aligned with the OHDSI TTS algorithm) and 10.7 (event rates per 1M PY per 21days Truven Market Scan-2019). The reporting rate for the cases where the MHRA case classification criteria was met (confirmed, probable and possible) was 6.59/million administered doses. Reporting rate for Dose 1 and Dose 2 was 12.25 and 0.35/million doses administered doses.

EEA Reporting rate in the 18 to 49 age group and the 50 to 59 years age group with all doses and Dose 1 was higher when compared to background rate; reporting rate for Dose 2 was less than the background rate for overall and all age stratifications.

The following reporting rate pertains to the risk window of 21 days, For EEA, the reporting rate for Dose 1 and Dose 2 was 22.79 and 1.01/million doses administered doses respectively.

For all administered doses and Dose 1, the reporting rate in the 18 to 49 age group was higher when compared to background rate. For all administered doses, the reporting rate in the 50 to 59 age group was within the background rate. For Dose 1, the reporting rate in the 50 to 59 age group was higher than the background rate.

The following reporting rate pertains to the risk window of 42 days. For EEA, the reporting rate for Dose 1 and Dose 2 was 25.41 and 1.44/million doses administered doses respectively. For all administered doses and Dose 1, the reporting rate in the 18 to 49 age group was higher when compared to background rate

The reporting rate for cases occurring within 42 days from UK and EEA are provided in Table 197. About 93% of the cases have occurred within 42 days after vaccination.

Table 196 Reporting rate for thrombosis in combination with thrombocytopenia by risk window of 21 days.

UK 21 Days RW								
Age Group	**Total Exposed**	**Cases within Risk Window of 21 days**	**Confirmed, probable and possible cases within Risk Window of 21 days**	**Reporting Rate (per million)**	**Reporting Rate (per million) for Confirmed, probable and possible cases**	**Background Rate (per million)[a]**	**Rate relative to Background (per million)**	**Rate relative to Background (per million) for Confirmed, probable and possible cases**
All Dose (UK)								
Age - 18-39 Yrs	5695728	93	84	16.33	14.75	2.1-3.2	14.23 to 13.13	12.65 to 11.55
Age - 40-49 Yrs	9705005	130	112	13.4	11.54	3.4-6.3	10 to 7.1	8.14 to 5.24
Age - 50-64 Yrs	18978058	170	152	8.96	8.01	7.3-14.9	1.66 to -5.94	0.71 to -6.89
Age - > 65 Yrs	14448845	106	90	7.34	6.23	23.4-44.4	-16.06 to -37.06	-17.17 to -38.17
Age Unknown	102827	33	28	320.93	272.3	-	-	-
Grand Total	**48930463**	**532**	**466**	**10.87**	**9.52**	**5.6-10.7**	**5.27 to 0.17**	**3.92 to -1.18**
Dose 1 (UK)								
Age - 18-39 Yrs	2905794	89	80	30.63	27.53	2.1-3.2	28.53 to 27.43	25.43 to 24.33
Age - 40-49 Yrs	4919521	123	107	25	21.75	3.4-6.3	21.6 to 18.7	18.35 to 15.45
Age - 50-64 Yrs	9560990	151	137	15.79	14.33	7.3-14.9	8.49 to 0.899	7.03 to -0.57
Age - > 65 Yrs	7270267	64	55	8.8	7.57	23.4-44.4	-14.6 to -35.6	-15.83 to -36.83
Age Unknown	70990	26	21	366.25	295.82	-	-	-

Table 196 Reporting rate for thrombosis in combination with thrombocytopenia by risk window of 21 days.

UK 21 Days RW								
Age Group	**Total Exposed**	**Cases within Risk Window of 21 days**	**Confirmed, probable and possible cases within Risk Window of 21 days**	**Reporting Rate (per million)**	**Reporting Rate (per million) for Confirmed, probable and possible cases**	**Background Rate (per million)[a]**	**Rate relative to Background (per million)**	**Rate relative to Background (per million) for Confirmed, probable and possible cases**
Grand Total	**24727562**	**453**	**400**	**18.32**	**16.18**	**5.6-10.7**	**12.72 to 7.62**	**10.58 to 5.48**
Dose 2 (UK)								
Age - 18-39 Yrs	2784710	4	4	1.44	1.44	2.1-3.2	-0.66 to -1.76	-0.66 to -1.76
Age - 40-49 Yrs	4778603	7	5	1.46	1.05	3.4-6.3	-1.94 to -4.84	-2.35 to -5.25
Age - 50-64 Yrs	9399336	18	14	1.92	1.49	7.3-14.9	-5.38 to -12.98	-5.81 to -13.41
Age - > 65 Yrs	7150151	41	35	5.73	4.9	23.4-44.4	-17.67 to -38.67	-18.5 to -39.5
Age Unknown	31787	7	7	220.22	220.22	-	-	-
Grand Total	**24144587**	**77**	**65**	**3.19**	**2.69**	**5.6-10.7**	**-2.41 to -7.51**	**-2.91 to -8.01**
All Dose (EEA)								
18-49	11775199	221	128	18.77	10.87	2.61-4.34	14.43 to 16.16	6.53 to 8.26
50-59	6494928	102	62	15.7	9.55	5.98-12.3	3.4 to 9.72	-2.75 to 3.57
60-69	20487444	184	95	8.98	4.64	11-22.5	-13.52 to -2.02	-17.86 to -6.36
70-79	8178431	63	21	7.7	2.57	22.3-45.2	-37.5 to -14.6	-42.63 to -19.73
80+	1167965	14	6	11.99	5.14	34.2-55.9	-43.91 to -22.21	-50.76 to -29.06
Age Unknown	7649	14	5	1830.3	653.68	-	-	-
Grand Total	**48111616**	**598**	**317**	**12.43**	**6.59**	**5.62-10.7**	**1.73 to 6.81**	**-4.11 to 0.97**

Table 196 Reporting rate for thrombosis in combination with thrombocytopenia by risk window of 21 days.

UK 21 Days RW								
Age Group	**Total Exposed**	**Cases within Risk Window of 21 days**	**Confirmed, probable and possible cases within Risk Window of 21 days**	**Reporting Rate (per million)**	**Reporting Rate (per million) for Confirmed, probable and possible cases**	**Background Rate (per million)[a]**	**Rate relative to Background (per million)**	**Rate relative to Background (per million) for Confirmed, probable and possible cases**
Dose 1 (EEA)								
18-49	6407149	216	125	33.71	19.51	2.61-4.34	29.37 to 31.1	15.17 to 16.9
50-59	3518861	100	62	28.42	17.62	5.98-12.3	16.12 to 22.44	5.32 to 11.64
60-69	10534615	174	92	16.52	8.73	11-22.5	-5.98 to 5.52	-13.77 to -2.27
70-79	4169066	57	19	13.67	4.56	22.3-45.2	-31.53 to -8.63	-40.64 to -17.74
80+	597525	14	6	23.43	10.04	34.2-55.9	-32.47 to -10.77	-45.86 to -24.16
Age Unknown	3914	14	5	3576.9	1277.47	-	-	-
Grand Total	**25231130**	**575**	**309**	**22.79**	**12.25**	**5.62-10.7**	**12.09 to 17.17**	**1.55 to 6.63**
Dose 2 (EEA)								
18-49	5363507	5	3	0.93	0.56	2.61-4.34	-3.41 to -1.68	-3.78 to -2.05
50-59	2973710	2	0	0.67	0	5.98-12.3	-11.63 to -5.31	-12.3 to -5.98
60-69	9949775	10	3	1.01	0.3	11-22.5	-21.49 to -9.99	-22.2 to -10.7
70-79	4007093	6	2	1.5	0.5	22.3-45.2	-43.7 to -20.8	-44.7 to -21.8
80+	569211	0	0	0	0	34.2-55.9	-55.9 to -34.2	-55.9 to -34.2
Age Unknown	3690	0	0	0	0	-	-	-
Grand Total	**22866986**	**23**	**8**	**1.01**	**0.35**	**5.62-10.7**	**-9.69 to -4.61**	**-10.35 to -5.27**

[a] Background event rates per 1M PY per 21 days from Truven Market Scan-2019

EEA European Economic Area; UK United Kingdom.

Table 197 Reporting rate for thrombosis in combination with thrombocytopenia by risk window of 42 days

UK 42 Days RW								
Age Group	**Total Exposed**	**Cases within Risk Window of 42 days**	**Confirmed, probable and possible cases within Risk Window of 42 days**	**Reporting Rate (per million)**	**Reporting Rate (per million) for Confirmed, probable and possible cases**	**Background Rate (per million)[a]**	**Rate relative to Background (per million)**	**Rate relative to Background (per million) for Confirmed, probable and possible cases**
All Dose (UK)								
Age - 18-39 Yrs	5695728	106	94	18.61	16.5	4.2-6.4	14.41 to 12.21	12.3 to 10.1
Age - 40-49 Yrs	9705005	145	124	14.94	12.78	6.8-12.6	8.14 to 2.34	5.98 to 0.18
Age - 50-64 Yrs	18978058	204	184	10.75	9.7	14.6-29.8	-3.85 to -19.05	-4.9 to -20.1
Age - > 65 Yrs	14448845	137	117	9.48	8.1	46.8-88.8	-37.32 to -79.32	-38.7 to -80.7
Age Unknown	102827	43	35	418.18	340.38	-	-	-
Grand Total	48930463	635	554	12.98	11.32	11.2-21.4	1.78 to -8.42	0.12 to -10.08
Dose 1 (UK)								
Age - 18-39 Yrs	2905794	100	89	34.41	30.63	4.2-6.4	30.21 to 28.01	26.43 to 24.23
Age - 40-49 Yrs	4919521	137	118	27.85	23.99	6.8-12.6	21.05 to 15.25	17.19 to 11.39
Age - 50-64 Yrs	9560990	181	165	18.93	17.26	14.6-29.8	4.33 to -10.87	2.66 to -12.54

Table 197 Reporting rate for thrombosis in combination with thrombocytopenia by risk window of 42 days

UK 42 Days RW								
Age Group	**Total Exposed**	**Cases within Risk Window of 42 days**	**Confirmed, probable and possible cases within Risk Window of 42 days**	**Reporting Rate (per million)**	**Reporting Rate (per million) for Confirmed, probable and possible cases**	**Background Rate (per million)[a]**	**Rate relative to Background (per million)**	**Rate relative to Background (per million) for Confirmed, probable and possible cases**
Age - > 65 Yrs	7270267	87	74	11.97	10.18	46.8-88.8	-34.83 to -76.83	-36.62 to -78.62
Age Unknown	70990	32	25	450.77	352.16	-	-	-
Grand Total	24727562	537	471	21.72	19.05	11.2-21.4	10.52 to 0.32	7.85 to -2.35
Dose 2 (UK)								
Age - 18-39 Yrs	2784710	6	94	2.15	33.76	4.2-6.4	-2.05 to -4.25	29.56 to 27.36
Age - 40-49 Yrs	4778603	8	124	1.67	25.95	6.8-12.6	-5.13 to -10.93	19.15 to 13.35
Age - 50-64 Yrs	9399336	22	183	2.34	19.47	14.6-29.8	-12.26 to -27.46	4.87 to -10.33
Age - > 65 Yrs	7150151	49	117	6.85	16.36	46.8-88.8	-39.95 to -81.95	-30.44 to -72.44
Age Unknown	31787	11	35	346.05	1101.08	-	-	-
Grand Total	24144587	96	553	3.98	22.9	11.2-21.4	-7.22 to -17.42	11.7 to 1.5
All Dose (EEA)								

Table 197 Reporting rate for thrombosis in combination with thrombocytopenia by risk window of 42 days

UK 42 Days RW								
Age Group	**Total Exposed**	**Cases within Risk Window of 42 days**	**Confirmed, probable and possible cases within Risk Window of 42 days**	**Reporting Rate (per million)**	**Reporting Rate (per million) for Confirmed, probable and possible cases**	**Background Rate (per million)[a]**	**Rate relative to Background (per million)**	**Rate relative to Background (per million) for Confirmed, probable and possible cases**
18-49	11775199	242	134	20.55	11.38	5.22-8.68	11.87 to 15.33	2.7 to 6.16
50-59	6494928	113	67	17.4	10.32	11.96-24.6	-7.2 to 5.44	-14.28 to -1.64
60-69	20487444	212	107	10.35	5.22	22-45	-34.65 to -11.65	-39.78 to -16.78
70-79	8178431	74	24	9.05	2.93	44.6-90.4	-81.35 to -35.55	-87.47 to -41.67
80+	1167965	18	9	15.41	7.71	68.4-111.8	-96.39 to -52.99	-104.09 to -60.69
Age Unknown	7649	15	5	1961.04	653.68	-	-	-
Grand Total	48111616	674	346	14.01	7.19	11.24-21.4	-7.39 to 2.77	-14.21 to -4.05
Dose 1 (EEA)								
18-49	6407149	236	131	36.83	20.45	5.22-8.68	28.15 to 31.61	11.77 to 15.23
50-59	3518861	111	67	31.54	19.04	11.96-24.6	6.94 to 19.58	-5.56 to 7.08
60-69	10534615	194	102	18.42	9.68	22-45	-26.58 to -3.58	-35.32 to -12.32
70-79	4169066	67	21	16.07	5.04	44.6-90.4	-74.33 to -28.53	-85.36 to -39.56

Table 197 Reporting rate for thrombosis in combination with thrombocytopenia by risk window of 42 days

UK 42 Days RW								
Age Group	**Total Exposed**	**Cases within Risk Window of 42 days**	**Confirmed, probable and possible cases within Risk Window of 42 days**	**Reporting Rate (per million)**	**Reporting Rate (per million) for Confirmed, probable and possible cases**	**Background Rate (per million)[a]**	**Rate relative to Background (per million)**	**Rate relative to Background (per million) for Confirmed, probable and possible cases**
80+	597525	18	9	30.12	15.06	68.4-111.8	-81.68 to -38.28	-96.74 to -53.34
Age Unknown	3914	15	5	3832.4	1277.47	0-0	-	-
Grand Total	25231130	641	335	25.41	13.28	11.24-21.4	4.01 to 14.17	-8.12 to 2.04
Dose 2 (EEA)								
18-49	5363507	6	3	1.12	0.56	5.22-8.68	-7.56 to -4.1	-8.12 to -4.66
50-59	2973710	2	0	0.67	0	11.96-24.6	-23.93 to -11.29	-24.6 to -11.96
60-69	9949775	18	5	1.81	0.5	22-45	-43.19 to -20.19	-44.5 to -21.5
70-79	4007093	7	3	1.75	0.75	44.6-90.4	-88.65 to -42.85	-89.65 to -43.85
80+	569211	0	0	0	0	68.4-111.8	-111.8 to -68.4	-111.8 to -68.4
Age Unknown	3690	0	0	0	0	-	-	-
Grand Total	22866986	33	11	1.44	0.48	11.24-21.4	-19.96 to -9.8	-20.92 to -10.76

[a] Background event rates per 1M PY per 42 days from Truven Market Scan-2019

EEA European Economic Area; UK United Kingdom.

Observed versus Expected Analysis

Please refer to Appendix 8 for the methodology of the O/E analyses and Appendix 9 for any additional sensitivity analysis.

Observed versus expected analyses for TTS (including CVST) and CVST with thrombocytopenia are presented in Appendix 18 tables 2, 3, 4 and 10. Background rates for TTS were derived from MarketScan (US claims) data, using OHDSI-aligned code lists and definitions for TTS. Algorithm 1 for TTS uses OHDSI-aligned TTS (TCP within -7/+7 days of thrombosis) whereas algorithm 2 for TTS uses OHDSI-aligned TTS (TCP within -1/+14 days of thrombosis), please also refer to further clarification in Section 15.2.10, response to Question 5.

The background rate (incidence rate) of TTS is 9.77/100,000 person years and 11.14/100,000 person years. The observed number of cases, for all risk windows of 14, 21, and 42 days (with unknown time to onset not included) is less than expected post vaccination by VAXZEVRIA.

The observed number of cases for risk windows of 14 days (with unknown time to onset included) post vaccination by VAXZEVRIA of TTS is greater than the expected with background rate 9.77/100,000 person years and lesser than the expected with background rate with 11.14/100,000 person years.

The observed number of cases for risk window of 21 days (with unknown time to onset included) post vaccination by VAXZEVRIA of TTS is less than the expected with both background rate 9.77/100,000 person years and background rate with 11.14/100,000 person years.

The observed number of cases for risk windows of 42 days (with unknown time to onset included) post vaccination by VAXZEVRIA of TTS is less than expected with both background rates.

For the EU, UK, Brazil, and Australia, the observed number of cases for ages 18 to 49 years, post vaccination by VAXZEVRIA of TTS are observed more than expected, for risk windows of 14 days, 21 days, and 42 days with the background rates and during the washout period the observed number of cases for ages 18 to 49 years are observed more than expected for the risk window of 14 days and 21 and less than expected for the risk window 42 days with the background rate.

The incidence Rate from Truven Market Scan (2019) aligned with the OHDSI TTS algorithm for the EU, the observed number of cases for female and male are significantly more than expected, for risk windows of 14 days, 21 days whereas observed number of cases for female

significantly more than expected and for observed number of cases male significantly less than expected in 42 days post vaccination by VAXZEVRIA of TTS with all background rates.

For the UK, in the risk window for 14 days and 21 days, post vaccination by VAXZEVRIA of TTS the observed number of cases for females age 18 to 49, 50 to 59, and 60 to 69 years are more than expected, whereas in age groups 70 to 79 and over 80 years are observed less than expected. Also, for risk window of 42 days post vaccination by VAXZEVRIA of TTS for females age 18 to 49, 50 to 59 years are more than expected, whereas age groups 60 to 69, 70 to 79 and over 80 years are observed less than expected.

For the EU, the observed number of cases for male ages 18 to 49 and 50 to 59 years are more than expected, whereas age group 60 to 69, 70 to 79, and over 80 years are observed less than expected, for risk window of 14 days, 21 days, and 42 days post vaccination by VAXZEVRIA of TTS with all background rates. (Observed versus Expected Analysis for TTS provided Appendix-18, Table 2, Table 3 and Table 4).

MHRA Case Definition

Anti-PF-4, D-Dimer, and platelet levels for Dose 1, Dose 2 and Fatal Reports

All 2391 case reports were reviewed to classify the cases based on the PTs and laboratory data, as per the Medicines and Healthcare products Regulatory Agency (MHRA) case definition for thrombosis in combination with thrombocytopenia (see Section 15.2.15, Figure 3.

Information in case reports was limited, with missing laboratory data on platelet count, D-dimer level, and PF-4 antibodies and also in many case reports there were incomplete entries (units, date of test, and type of test) for platelet levels, D-dimer, and PF-4.

Information on platelet count was available in 1642 (69%) of 2391 case reports; platelet count was $< 150 \times 10^9$/L in 1578 of the 1642 reports and in 64 case reports platelet count was $> 150 \times 10^9$/L. Among these 1578 vaccinees with reported platelet count $< 150 \times 10^9$/L, 662 (41%) had a platelet count of $< 50 \times 10^9$/L; 412 (26%) had a platelet count between 50 to $< 100 \times 10^9$/L; and 480 (30%) had a platelet count between 100 to 150×10^9/L.79, the platelet count was reported as $< 150 \times 10^9$/L, For the reaming 24 cases with platelet count less than 150, the value of platelet was unknown.

In the remaining 749 (31%) of the 2391 case reports, information on platelet, count was not available. In 386 of the 2391 case reports there was no venous/arterial thrombosis reported. Of the 2391 case reports, PF-4 antibodies were positive in 601 (25%) reports, negative in 495 (20%) reports, unknown or pending in 1295 (54%) case reports. D-dimer levels were reported in 974 (41%) of the 2391 case reports, however, in many reports the units were not

specified. In 218 (22%) D-dimer levels were < 4000 ng/mL and in 756 (78%) case reports D-dimer levels were > 4000 ng/mL. In 1471 (59%) case reports, D-dimer levels were not provided/reported.

Of the 2391 case reports reviewed, based on the above case classification criteria, there were 1561 (65%) cases which met the MHRA criteria of TTS (Confirmed, probable, or possible). The total number of confirmed cases was 342 (14%), probable cases - 381 (16%), possible cases – 838 (35%), unlikely - 1 (0.2%), and criteria were not met for 829 (34%) cases. Out of all cases (1561) which met the criteria, the confirmed cases (342) comprised 21% of the total cases.

In cases (1561) where the MHRA case classification criteria were met, 546 (35%) cases had confounding factors. Many of the cases had more than one confounding factor. The confounding factors were reported as follows:

- autoimmune disease (ITP, autoimmune thyroiditis, psoriasis, antiphospholipid syndrome (APLS), Crohn's disease, myasthenia gravis, inflammatory bowel disease, ulcerative colitis, ankylosing spondylitis, rheumatoid arthritis, guillain-barre syndrome, sarcoidosis, systemic lupus erythematous (SLE), autoimmune hepatitis (AIH), vasculitis, multiple sclerosis, hemolytic anaemia, polymyalgia rheumatica, thalassemia minor and connective tissue disorder);
- malignancies (breast cancer, prostate cancer, malignant melanoma, brain cancer, thyroid cancer, non-hodgkin's lymphoma, polycythemia vera, bladder cancer, pituitary tumour, lung cancer, metastatic cancer, tonsil cancer, ovarian cancer, pancreatic cancer, testicular cancer, carcinoma endometrium uterus, vulvar cancer, cervix carcinoma, renal cell carcinoma, chronic lymphocytic leukemia, glioblastoma, gliomas, leukemia, lymphoma, lymphoproliferative disease, metastatic neoplasm, myelodysplastic neoplasm, neoplasm, sarcoma);
- past history of heparin information on the dates of heparin administration was not available, obesity, past and current history of contraceptives, past history of thrombosis, hit, past history of frequent abortion, HIV infection, chronic hepatitis b, liver disease, covid-19 illness, cardiomyopathy resulting from fredrich's ataxia, chronic kidney disease, chronic glomerulonephritis, DRESS syndrome, liver transplant, past history of stroke, polycystic ovary syndrome, protein c deficiency, sickle cell disease, tcp chronic.
- concomitant medications; venaflaxine, and combination of citalopram and clopidogrel.

Out of 342 confirmed reports, there were 148 (43%) cases with confounding factors. The confounding factor associated were past history of heparin, malignancies (neoplasm, abdominal neoplasm, thyroid cancer, prostate cancer, vulvar cancer, metastatic cancer, skin cancer, pancreatic cancer, carcinoma endometrium uterus, non-Hodgkin's disease, breast cancer, malignant melanoma), obesity, contraceptives, ITP, autoimmune disease (sarcoidosis, Guillain-Barre syndrome, myasthenia gravis, ankylosing spondylitis, autoimmune thyroiditis, antiphospholipid syndrome, ulcerative colitis, rheumatoid arthritis, Crohn's disease), hit, past

history of thrombosis, chronic kidney disease. The dates of heparin administration were not reported in all cases.

Demographics (age, gender, and country) and clinical characteristics of thrombosis in combination of thrombocytopenia is provided in Table 198 and Table 199. Comparison of Platelet count, thrombosis event, PF-4 antibodies and D-dimer levels is provided in Appendix 18, Table 5, and Table 6.

TTS case reports by age/gender, Dose, Case Classification, and fatality are presented in Table 199.

Based on the MHRA case classification criteria, 65% (1561/2391) were categorised as confirmed/probable/possible (21% of the cases met confirmed criteria, 24% met probable criteria, 54% met possible criteria). The remaining 53% cases did not meet criteria and < 1% of the cases were classified as unlikely. There was no difference in the case categorisation criteria between Dose 1, Dose 2, and fatal case reports. For the cases that occurred after Dose 2, 71% were categorised as confirmed/probable/possible (5% of the cases met confirmed criteria, 18% met probable criteria, 47% met possible criteria) and 28% were categorised as criteria not met.

Table 198 MHRA case classification criteria of thrombosis in combination with thrombocytopenia case reports by age and country

Characteristic	Confirmed reports (n=342)	Probable Reports (n=381)	Possible Reports (n=838)	Unlikely Reports (n=1)	Criteria not met Reports (n=829)	All case reports (n=2391)
Median age in years (range)	47 (18-83)	55 (18-94)	59 (18-104)	65	58 (18-95)	56 (18-104)
Sex						
Female n (%)	197 (8.2)	203 (8.4)	431 (18)	0 (0)	426 (17)	1257 (52)
Male n (%)	144 (6.0)	172 (7.1)	401 (16)	1 (0.04)	350 (14.6)	1068 (44)
Unknown n (%)	1 (0.04)	6 (0.2)	6 (0.2)	0 (0)	53 (2.2)	66 (2.7)
Region						
EEA						
Austria	3 (0.13)	5 (0.21)	10 (0.42)	0 (0)	9 (0.38)	27 (1.13)
Belgium	11 (0.46)	3 (0.13)	13 (0.54)	0 (0)	17 (0.71)	44 (1.84)
Bulgaria	0 (0)	1 (0.04)	1 (0.04)	0 (0)	3 (0.13)	5 (0.21)
Croatia	1 (0.04)	1 (0.04)	1 (0.04)	0 (0)	0 (0)	3 (0.13)
Cyprus	0 (0)	2 (0.08)	1 (0.04)	0 (0)	1 (0.04)	4 (0.17)
Czech Republic	1 (0.04)	4 (0.17)	6 (0.25)	0 (0)	0 (0)	11 (0.46)

Table 198 MHRA case classification criteria of thrombosis in combination with thrombocytopenia case reports by age and country

Characteristic	Confirmed reports (n=342)	Probable Reports (n=381)	Possible Reports (n=838)	Unlikely Reports (n=1)	Criteria not met Reports (n=829)	All case reports (n=2391)
Denmark	1 (0.04)	0 (0)	0 (0)	0 (0)	3 (0.13)	4 (0.17)
Estonia	0 (0)	0 (0)	1 (0.04)	0 (0)	1 (0.04)	2 (0.08)
Finland	5 (0.21)	1 (0.04)	1 (0.04)	0 (0)	11 (0.46)	18 (0.75)
France	0 (0)	2 (0.08)	15 (0.63)	0 (0)	46 (1.92)	63 (2.63)
Germany	28 (1.17)	22 (0.92)	70 (2.93)	0 (0)	155 (6.48)	275 (11.5)
Greece	2 (0.08)	2 (0.08)	4 (0.17)	0 (0)	6 (0.25)	14 (0.59)
Hungary	0 (0)	1 (0.04)	2 (0.08)	0 (0)	2 (0.08)	5 (0.21)
Iceland	0 (0)	0 (0)	1 (0.04)	0 (0)	3 (0.13)	4 (0.17)
Ireland	3 (0.13)	1 (0.04)	6 (0.25)	0 (0)	0 (0)	10 (0.42)
Italy	12 (0.5)	21 (0.88)	26 (1.09)	0 (0)	68 (2.84)	127 (5.31)
Latvia	0 (0)	0 (0)	2 (0.08)	0 (0)	1 (0.04)	3 (0.13)
Lithuania	1 (0.04)	0 (0)	2 (0.08)	0 (0)	0 (0)	3 (0.13)
Luxembourg	2 (0.08)	0 (0)	2 (0.08)	0 (0)	0 (0)	4 (0.17)
Malta	0 (0)	0 (0)	1 (0.04)	0 (0)	2 (0.08)	3 (0.13)
Netherlands	7 (0.29)	11 (0.46)	31 (1.3)	0 (0)	11 (0.46)	60 (2.51)
Norway	10 (0.42)	2 (0.08)	2 (0.08)	0 (0)	8 (0.33)	22 (0.92)
Poland	0 (0)	3 (0.13)	8 (0.33)	0 (0)	11 (0.46)	22 (0.92)
Portugal	1 (0.04)	2 (0.08)	2 (0.08)	0 (0)	4 (0.17)	9 (0.38)
Slovakia	0 (0)	0 (0)	1 (0.04)	0 (0)	1 (0.04)	2 (0.08)
Slovenia	3 (0.13)	1 (0.04)	2 (0.08)	0 (0)	1 (0.04)	7 (0.29)
Spain	8 (0.33)	8 (0.33)	19 (0.79)	0 (0)	25 (1.05)	60 (2.51)
Sweden	0 (0)	0 (0)	3 (0.13)	0 (0)	22 (0.92)	25 (1.05)
UK						
United Kingdom	175 (0)	207 (0.91)	277 (1.08)	1 (0)	145 (0)	805 (0.75)
Rest of the world (ROW)						
Argentina	0 (0)	(0)	1 (0)	0 (0.04)	1 (0.08)	2 ()
Canada	17 (0.71)	3 (0.13)	14 (0)	0 (1.76)	42 (3.18)	76 ()
Chile	0 (0)	1 (0.04)	0 (0)	0 (0.17)	4 (0.21)	5 ()
Colombia	0 (0)	0 (0)	0 (0)	0 (0.04)	1 (0.04)	1 ()
Costa Rica	0 (0)	0 (0)	0 (0)	0 (0.04)	1 (0.04)	1 ()

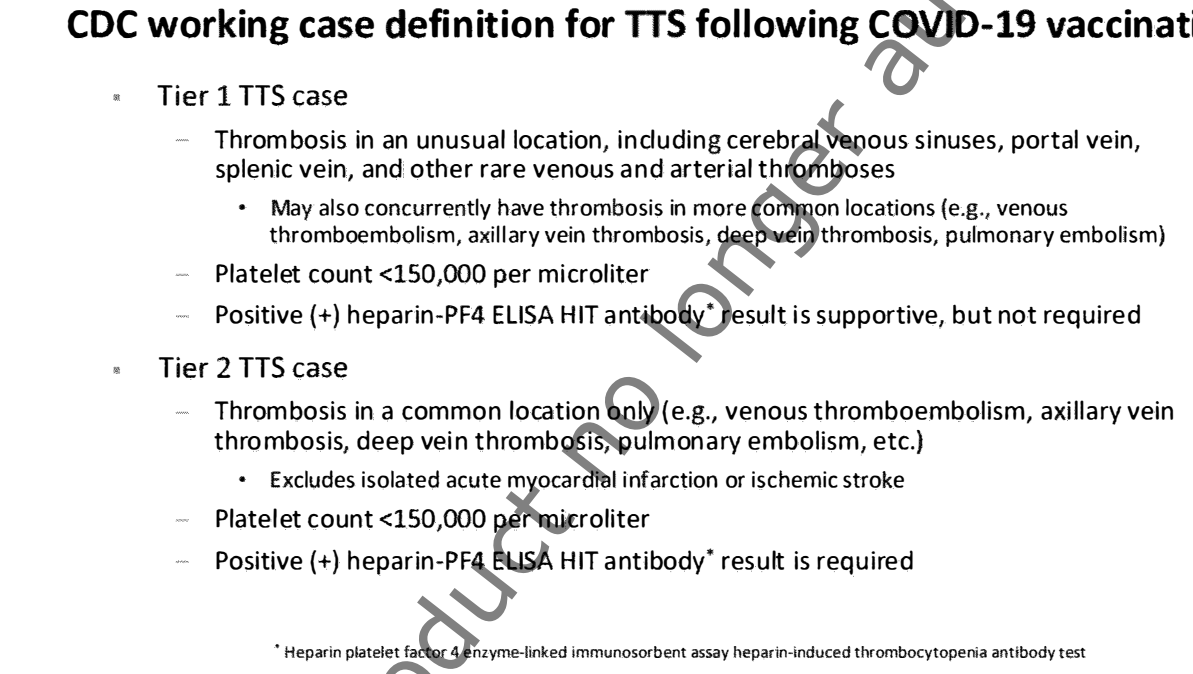
Table 198 MHRA case classification criteria of thrombosis in combination with thrombocytopenia case reports by age and country

Characteristic	Confirmed reports (n=342)	Probable Reports (n=381)	Possible Reports (n=838)	Unlikely Reports (n=1)	Criteria not met Reports (n=829)	All case reports (n=2391)
Ecuador	0 (0)	0 (0)	0 (0)	0 (0.04)	1 (0.04)	1 ()
Egypt	0 (0)	0 (0)	1 (0)	0 (0.08)	2 (0.13)	3 ()
India	3 (0.13)	4 (0.17)	19 (0)	0 (1.09)	26 (2.17)	52 ()
Iran	1 (0.04)	1 (0.04)	0 (0)	0 (0.08)	2 (0.17)	4 ()
Japan	1 (0.04)	1 (0.04)	0 (0)	0 (0)	0 (0.08)	2 ()
Jordan	0 (0)	0 (0)	0 (0)	0 (0.04)	1 (0.04)	1 ()
Korea, Republic of	3 (0.13)	0 (0)	0 (0)	0 (0.25)	6 (0.38)	9 ()
Kuwait	0 (0)	0 (0)	1 (0)	0 (0)	0 (0.04)	1 ()
Macedonia	0 (0)	2 (0.08)	0 (0)	0 (0.04)	1 (0.13)	3 ()
Malaysia	0 (0)	1 (0.04)	1 (0)	0 (0.17)	4 (0.25)	6 ()
Mexico	0 (0)	0 (0)	6 (0)	0 (0.29)	7 (0.54)	13 ()
New Zealand	0 (0)	0 (0)	0 (0)	0 (0.04)	1 (0.04)	1 ()
Northern Ireland	0 (0)	0 (0)	0 (0)	0 (0.08)	2 (0.08)	2 ()
Oman	1 (0.04)	1 (0.04)	0 (0)	0 (0)	0 (0.08)	2 ()
Philippines	0 (0)	0 (0)	0 (0)	0 (0.08)	2 (0.08)	2 ()
Saudi Arabia	0 (0)	2 (0.08)	4 (0)	0 (0.04)	1 (0.29)	7 ()
Sri Lanka	0 (0)	0 (0)	6 (0)	0 (0)	0 (0.25)	6 ()
Syria	0 (0)	0 (0)	1 (0)	0 (0)	0 (0.04)	1 ()
Taiwan	6 (0.25)	0 (0)	2 (0)	0 (0.13)	3 (0.46)	11 ()
Thailand	3 (0.13)	3 (0.13)	1 (0)	0 (0.08)	2 (0.38)	9 ()
Ukraine	0 (0)	0 (0)	0 (0)	0 (0.04)	1 (0.04)	1 ()
United States	0 (0)	0 (0)	0 (0)	0 (0.33)	8 (0.33)	8 ()
Uruguay	0 (0)	1 (0.04)	0 (0)	0 (0)	0 (0.04)	1 ()
Vietnam	0 (0)	0 (0)	0 (0)	0 (0.04)	1 (0.04)	1 ()
Seriousness						
Serious	342 (14.3)	381 (15.93)	832 (34.8)	1 (0)	823 (34.42)	2379 (99.5)
Non-serious	0 (0)	0 (0)	5 (0.21)	0 (0)	6 (0.25)	11 (0.46)
Medical confirmation						
Medically confirmed	308 (12.88)	322 (13.47)	601 (25.14)	1 (0)	483 (20.2)	1715 (71.73)
Consumer reports	34 (1.42)	59 (2.47)	237 (9.91)	0 (0)	346 (14.47)	676 (28.27)

CDC Case Definition:

All 2391 case reports were reviewed to classify the cases based on Centres for Disease Control and Prevention (CDC) case definition for thrombosis in combination with thrombocytopenia (Figure 8).

Figure 8 CDC working case definition for TTS following COVID-19 vaccination



Of the 2391 case reports, there were 699(29%) cases which met the CDC criteria of TTS (Tier 1 and 2), where 619 (26%) case reports met the Tier 1 TTS case criteria and 80 (3%) met Tier 2 TTS case criteria.

Table 199 Thrombosis with Thrombocytopenia Syndrome Case Reports by age/gender, Dose, Case Classification and fatality

All Dose																
	Confirmed (N (fatal cases)			Probable (N (fatal cases)			Possible (N (fatal cases)			Unlikely (N (fatal cases)			Criteria not met (N (fatal cases)			Grand Total (N (fatal cases)
Age category /Gender	F	M	U	F	M	U	F	M	U	F	M	U	F	M	U	
Age - 18-29 Yrs	21 (4)	16 (5)	0 (0)	18 (6)	11 (3)	1 (1)	34 (8)	25 (3)	0 (0)	0 (0)	0 (0)	0 (0)	44 (10)	25 (5)	0 (0)	195 (45)
Age - 30-39 Yrs	31 (10)	25 (7)	0 (0)	21 (6)	11 (3)	0 (0)	54 (10)	31 (6)	0 (0)	0 (0)	0 (0)	0 (0)	53 (10)	26 (5)	0 (0)	252 (57)
Age - 40-49 Yrs	56 (13)	34 (4)	1 (0)	47 (10)	25 (2)	0 (0)	46 (10)	53 (3)	0 (0)	0 (0)	0 (0)	0 (0)	72 (14)	38 (8)	1 (0)	373 (64)
Age - 50-59 Yrs	41 (8)	37 (7)	0 (0)	40 (11)	40 (4)	2 (0)	95 (15)	68 (9)	1 (1)	0 (0)	0 (0)	0 (0)	59 (15)	48 (10)	0 (0)	431 (80)
Age - 60-69 Yrs	22 (4)	27 (6)	0 (0)	35 (5)	44 (8)	1 (0)	109 (19)	86 (8)	0 (0)	0 (0)	1 (1)	0 (0)	87 (12)	96 (15)	1 (1)	509 (79)
Age - 70-79 Yrs	11 (2)	5 (3)	0 (0)	22 (2)	22 (3)	0 (0)	51 (10)	83 (3)	1 (0)	0 (0)	0 (0)	0 (0)	46 (5)	63 (7)	1 (0)	305 (35)
Age - 80+ Yrs	3 (1)	0 (0)	0 (0)	7 (2)	10 (2)	0 (0)	27 (3)	29 (2)	0 (0)	0 (0)	0 (0)	0 (0)	22 (2)	21 (5)	0 (0)	119 (17)
Age Unknown	12 (1)	0 (0)	0 (0)	13 (3)	9 (1)	2 (0)	15 (5)	26 (2)	4 (1)	0 (0)	0 (0)	0 (0)	43 (10)	33 (4)	50 (10)	207 (37)
Grand Total	197 (43)	144 (32)	1 (0)	203 (45)	172 (26)	6 (1)	431 (80)	401 (36)	6 (2)	0 (0)	1 (1)	0 (0)	426 (78)	350 (59)	53 (11)	2391 (414)
Dose 1																

Table 199 Thrombosis with Thrombocytopenia Syndrome Case Reports by age/gender, Dose, Case Classification and fatality

All Dose																
	Confirmed (N (fatal cases)			Probable (N (fatal cases)			Possible (N (fatal cases)			Unlikely (N (fatal cases)			Criteria not met (N (fatal cases)			Grand Total (N (fatal cases)
Age category /Gender	F	M	U	F	M	U	F	M	U	F	M	U	F	M	U	
Age - 18-29 Yrs	20 (4)	16 (5)	0 ()	17 (6)	10 (3)	1 (1)	31 (8)	23 (3)	0 (0)	0 (0)	0 (0)	0 (0)	43 (10)	23 (5)	0 (0)	184 (45)
Age - 30-39 Yrs	29 (10)	25 (7)	0 ()	21 (6)	11 (3)	0 (0)	52 (10)	30 (6)	0 (0)	0 (0)	0 (0)	0 (0)	51 (10)	26 (5)	0 (0)	245 (57)
Age - 40-49 Yrs	56 (13)	34 (4)	1 ()	45 (10)	23 (2)	0 (0)	42 (10)	46 (3)	0 (0)	0 (0)	0 (0)	0 (0)	67 (11)	34 (8)	1 (0)	349 (61)
Age - 50-59 Yrs	41 (8)	34 (7)	0 ()	38 (11)	37 (4)	2 (0)	91 (15)	56 (7)	1 (1)	0 (0)	0 (0)	0 (0)	54 (14)	43 (10)	0 (0)	397 (77)
Age - 60-69 Yrs	22 (4)	24 (6)	0 ()	32 (5)	34 (8)	1 (0)	92 (19)	71 (8)	0 (0)	0 (0)	1 (1)	0 (0)	80 (10)	79 (12)	1 (1)	437 (74)
Age - 70-79 Yrs	10 (2)	2 (1)	0 ()	18 (2)	12 ()	0 (0)	42 (7)	59 (2)	1 (0)	0 (0)	0 (0)	0 (0)	39 (5)	55 (6)	1 (0)	239 (25)
Age - 80+ Yrs	2 (1)	0 (0)	0 ()	4 (1)	7 (1)	0 (0)	17 (2)	21 (1)	0 (0)	0 (0)	0 (0)	0 (0)	16 (2)	19 (5)	0 (0)	86 (13)
Age Unknown	12 (1)	0 (0)	0 ()	9 (2)	7 (1)	2 (0)	15 (5)	18 (2)	3 (1)	0 (0)	0 (0)	0 (0)	42 (10)	29 (3)	49 (10)	186 (35)
Grand Total	192 (43)	135 (30)	1 ()	184 (43)	141 (22)	6 (1)	382 (76)	324 (32)	5 (2)	0 (0)	1 (1)	0 (0)	392 (72)	308 (54)	52 (11)	2123 (387)
Dose 2																

Table 199 Thrombosis with Thrombocytopenia Syndrome Case Reports by age/gender, Dose, Case Classification and fatality

All Dose																
	Confirmed (N (fatal cases)			Probable (N (fatal cases)			Possible (N (fatal cases)			Unlikely (N (fatal cases)			Criteria not met (N (fatal cases)			Grand Total (N (fatal cases)
Age category /Gender	F	M	U	F	M	U	F	M	U	F	M	U	F	M	U	
Age - 18-29 Yrs	1 (0)	0 (0)	0 (0)	1 (0)	0 (0)	0 (0)	3 (0)	1 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (0)	0 (0)	8 ()
Age - 30-39 Yrs	2 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (0)	1 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (0)	0 (0)	0 (0)	7 ()
Age - 40-49 Yrs	0 (0)	0 (0)	0 (0)	2 (0)	2 (0)	0 (0)	3 (0)	7 (0)	0 (0)	0 (0)	0 (0)	0 (0)	5 (3)	4 (0)	0 (0)	23 (3)
Age - 50-59 Yrs	0 (0)	3 (0)	0 (0)	2 (0)	2 (0)	0 (0)	4 (0)	12 (2)	0 (0)	0 (0)	0 (0)	0 (0)	5 (1)	5 (0)	0 (0)	33 (3)
Age - 60-69 Yrs	0 (0)	3 (0)	0 (0)	3 (0)	10 (0)	0 (0)	17 (0)	14 (0)	0 (0)	0 (0)	0 (0)	0 (0)	7 (2)	17 (3)	0 (0)	71 (5)
Age - 70-79 Yrs	1 (0)	3 (2)	0 (0)	4 (0)	10 (3)	0 (0)	9 (3)	24 (1)	0 (0)	0 (0)	0 (0)	0 (0)	6 (0)	8 (1)	0 (0)	65 (10)
Age - 80+ Yrs	1 (0)	0 (0)	0 (0)	3 (1)	3 (1)	0 (0)	10 (1)	8 (1)	0 (0)	0 (0)	0 (0)	0 (0)	6 (0)	2 (0)	0 (0)	33 (4)
Age Unknown	0 (0)	0 (0)	0 (0)	4 (1)	2 (0)	0 (0)	0 (0)	8 (0)	1 (0)	0 (0)	0 (0)	0 (0)	1 (0)	3 (0)	1 (0)	20 (1)
Grand Total	5 (0)	9 (2)	0 (0)	19 (2)	29 (4)	0 (0)	48 (4)	75 (4)	1 (0)	0 (0)	0 (0)	0 (0)	32 (6)	41 (4)	1 (0)	260 (26)
Dose 3																

Table 199 Thrombosis with Thrombocytopenia Syndrome Case Reports by age/gender, Dose, Case Classification and fatality

All Dose																
	Confirmed (N (fatal cases)			Probable (N (fatal cases)			Possible (N (fatal cases)			Unlikely (N (fatal cases)			Criteria not met (N (fatal cases)			Grand Total (N (fatal cases)
Age category /Gender	F	M	U	F	M	U	F	M	U	F	M	U	F	M	U	
Age - 18-29 Yrs	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	3 (3)
Age - 30-39 Yrs	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Age - 40-49 Yrs	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)
Age - 50-59 Yrs	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Age - 60-69 Yrs	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Age - 70-79 Yrs	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	1 (1)
Age - 80+ Yrs	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Age Unknown	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	1 (1)
Grand Total	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	6 (6)

Fatal cases

Seventeen percent (17%; 414/ 2391) of TTS cases reported fatal outcome. Age and gender stratification for fatal reports is presented in Table 200.

Table 200 Thrombosis with Thrombocytopenia Syndrome Case Reports by age/gender and fatality

Age group	Female N (fatal cases)	Male N (fatal cases)	Unknown Gender N (Fatal cases)	Grand Total
Age - 18-29 Yrs	117 (28)	77 (16)	1 (1)	195 (45)
Age - 30-39 Yrs	159 (36)	93 (21)	0(0)	252 (57)
Age - 40-49 Yrs	221 (47)	150 (17)	2 (0)	373 (64)
Age - 50-59 Yrs	235 (49)	193 (30)	3 (1)	431 (80)
Age - 60-69 Yrs	253 (40)	254 (38)	2 (1)	509 (79)
Age - 70-79 Yrs	130 (19)	173 (16)	2 (0)	305 (35)
Age - 80+ Yrs	59 (8)	60 (9)	0(0)	119 (17)
Age Unknown	83 (19)	68 (7)	56 (11)	207 (37)
Grand Total	1257 (246)	1068 (154)	66 (14)	2391 (414)

N Number, yrs Years.

TTO was available in 307/414 (74%) of the 414 fatal reports and ranged from 0 to 121 days with a median TTO of 11 days. Of the 414 fatal events, 388 fatal reports occurred after Dose 1, 26 fatal case reports occurred after Dose 2 and there were 01 fatal cases after Dose 3. TTO was available in 23 reports after Dose 2 with a range of 0 to 88 days and a median of 13 days.

The most frequently reported events of thrombosis in the fatal reports were: Cerebral venous sinus thrombosis (117), followed by (> 10) Thrombosis with thrombocytopenia syndrome (88), Pulmonary embolism (78), Thrombosis (65), Cerebral venous thrombosis (43), Portal vein thrombosis (34), Hemiparesis (33), Cerebral thrombosis (28), Disseminated intravascular coagulation (25), Cerebrovascular accident (25), Cerebral infarction (19), Deep vein thrombosis (18), Superior sagittal sinus thrombosis (17), Transverse sinus thrombosis (13), Ischaemic stroke (12), Peripheral artery thrombosis (11), Mesenteric vein thrombosis (11), Hemiplegia (11), Acute myocardial infarction (11).

The highest number of the fatal cases were due to HLT: Cerebrovascular and venous sinus thrombosis (173/414, 42%) and the Cerebral haemorrhage was the most common bleeding event associated with fatal event (112/414, 27%). In the previous PBRER (DLP 29 December 2021) he highest number of the fatal cases were due to HLT: Cerebrovascular

and venous sinus thrombosis and with similar percentage (150/349, 43%) and the Cerebral haemorrhage was also the most common bleeding event associated with fatal event.

For fatal cases, a total of 264/414 (64%) case reports reported venous sites of thrombosis, 262/414 (63%) case reported, PT from all 3 arterial, venous and vessel type and mixed arterial and in 81/414 (19%) case reported arterial site of thrombosis.

In 250 out of 414 fatal reports (64%), there was a co-reported bleeding event from the narrow SMQ: Haemorrhage terms (excl. laboratory terms). Most common (> 10) bleeding events included Cerebral haemorrhage (112), Haemorrhage intracranial (36), Subarachnoid haemorrhage (31), Disseminated intravascular coagulation (25), Haemorrhage (15), Contusion (12), Petechiae 11. Forty-seven (47) case reports had the co-reported events from the HLT: Coagulopathies, including 58 cases with DIC.

Fatality/survival rate over time

Fatality/survival rate over time was calculated based on the case onset date. The onset date was not reported in 564 of the 2391 case reports, and for 119 case reports with fatal outcome. In cases where the onset date was not reported, date initially received by AstraZeneca was used to calculate the reporting fatality/survival rate over time. Fatality/survival rate cumulatively for each month up to 28 June 2022 is presented in Table 201 and Figure 9.

The total number and percent of fatal reports since April 2021 are decreasing compared to January 2021-March 2021. There is an increased fatality rate in December 2021 (**7 reported fatal events out of 25 reports**) compared to the earlier months. However, vaccination in these 4 fatal cases occurred prior to December 2021, but were reported in December 2021 with unknown event onset dates, which could explain the reason for the increased fatality rate. Two (2) of the 7 reports ([redacted] and [redacted]) originated from India with the date of vaccination reported as 03 February 2021 and 07 June 2021, respectively. Event onset date and/or time to onset was not reported in either of these cases. The 3rd case ([redacted]) originated from Belgium and contained limited information with no reported vaccination dates, event onset dates, or time to event onset reported. The 4th case ([redacted]) originated from Brazil contained limited information with no reported vaccination dates, event dates, or information regarding time to event onset. This 4th case is a potential duplicate report of a previously reported case. The 5th case ([redacted]) originated from Germany and other 2 cases ([redacted] and [redacted]) from Iran and Italy respectively, contained limited information with no reported vaccination dates, event dates, there is an increased fatality rate in April 2021 (**9 reported fatal events out of 31 reports**) compared to the earlier months December 2021 and March 2021. Two of the 9 reports ([redacted] and [redacted]) originated from Brazil with the date of vaccination reported as 04 April 2022 and unknown, respectively. Two reports ([redacted] and [redacted]) originated from United Kingdom, two ([redacted] and [redacted]) originated from Netherlands and the

cases [redacted] and [redacted] originated from Taiwan, Poland and Norway respectively with the date of vaccination was unknown. The event onset date and/or time to onset was not reported in either of these cases.

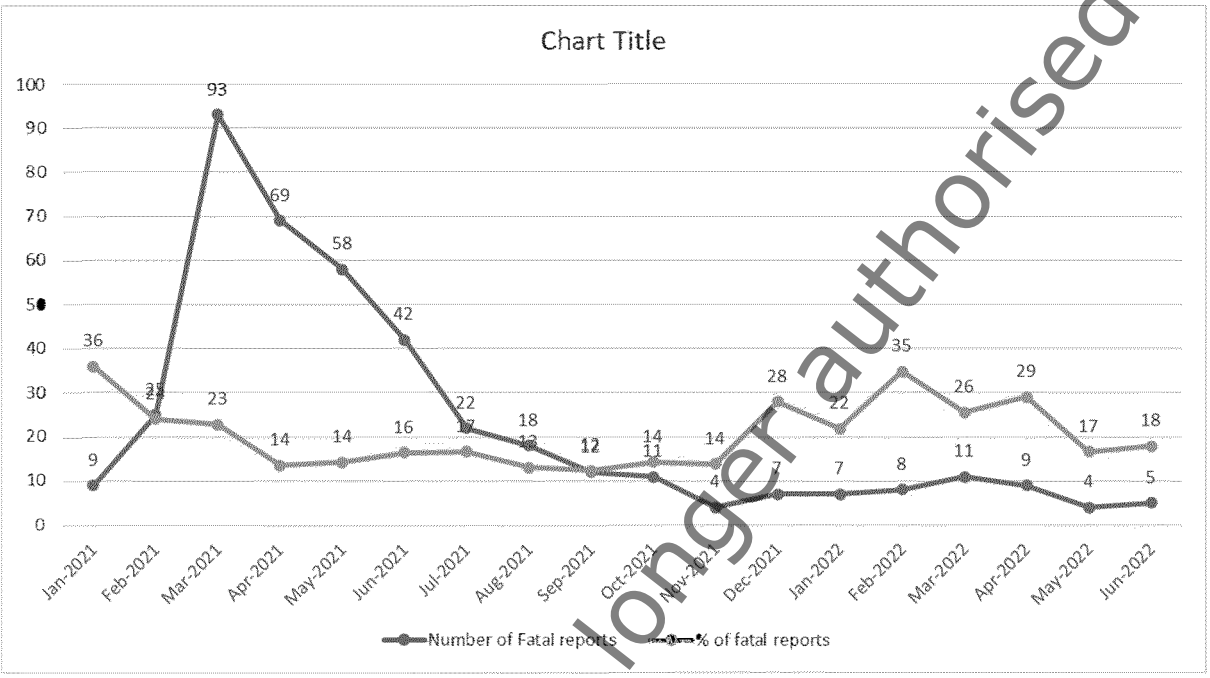
Number and percent of fatal reports since April 2021 has decreased compared to January-March 2021 which suggests the effectiveness of the diagnostic and treatment guidelines implemented (ASH 2021, EHP 2021and Thaler et al 2021) in March 2021.

Table 201 TTS fatality/survival rate over time

Case onset month [a]	Number of non-fatal reports	Number of Fatal reports	Grand Total	% of fatal reports
January 2021	16	9	25	36
February 2021	79	25	104	24.0
March 2021	316	93	409	22.7
April 2021	441	69	510	13.5
May 2021	351	58	409	14.2
June 2021	214	42	256	16.4
July-2021	110	22	132	16.7
August 2021	120	18	138	13.0
September 2021	85	12	97	12.4
October 2021	66	11	76	14.3
November 2021	25	4	29	13.8
December 2021	18	7	25	28.0
January 2022	25	7	32	21.9
February 2022	15	8	23	34.8
March 2022	32	11	43	25.6
April 2022	22	9	31	29.0
May 2022	20	4	24	16.7
June 2022	23	5	28	17.9
Grand Total	**1978**	**414**	**2391**	17.3

[a] In cases where case onset date was not available, date initially received by AstraZeneca was used to calculate the reporting fatality/survival rate over time. TTS Thrombosis with thrombocytopenia syndrome.

Figure 9 TTS fatality/survival rate over time



Fatality rate over time by age group/gender for all cases is presented in Appendix 18 Table 7 and fatality rate over time by age group/gender and doses (separately for all doses, Dose 1, and Dose 2) for confirmed/probable/possible cases is presented in Table 202.

Fatality rate in female vaccinees is higher (60%) compared to male (37%) for all cases and fatality rate in confirmed/probable/possible cases, is higher in female compared to male for all doses (60% vs 37%) and Dose 1 (60% vs 36%) but for Dose 2, fatality rate in female is less than male (46% vs 54%), the reason for this difference might be cases received with Dose 2 are very little and this would increase the percentage markedly.

For all cases, highest fatality rate in female vaccinees was 73% in 40 to 49 years and 61% in 50 to 59 years age group, whereas in male vaccinees the highest fatality rate was 48% in 60 to 69 years and 37% in 50 to 59 years age group. In confirmed/probable/possible cases, highest fatality rate in female vaccinees was 61% in 50 to 59 years, 78% in 40 to 49 years, 56% in 60 to 69 years age groups (all doses) and 64% in 50 to 59 years, 78% in 40 to 49 years, 56% in 60 to 69 years age groups (Dose 1) and 33% in 70 to 79 years age group (Dose 2), while in male vaccinees highest fatality rate in male vaccinees was 44% in 60 to 69 years and 36% in 50 to 59 years (all doses) and 44% in 60 to 69 years 33% in 50 to 59 years in age group (Dose 1) and 66% in 70 to 79 years age group (Dose 2). Fatality rate for some age groups/gender/months is increased compared to the previous period; however, reports received for these age groups/gender/months did not have onset dates of events and case received date was considered for analysis. This may be the reason for increased fatality rate,

also cases received for these months are very little and this would increase the percentages markedly.

TTS fatality/survival rate over time by age group/gender for all cases and Dose 1, Dose 2 for confirmed/probable and possible cases provided in Appendix-18, Table 7, Table 8, and Table 9.

Table 202 TTS fatality/survival rate over time by age group/gender and doses for confirmed/probable and possible cases

	FEMALE			MALE			UNKNOWN			Grand Total			
Case onset month/ Age group	**Number of non-fatal reports**	**Number of Fatal reports**	**% of fatal reports**	**Number of non-fatal reports**	**Number of Fatal reports**	**% of fatal reports**	**Number of non-fatal reports**	**Number of Fatal reports**	**% of fatal reports**	**Number of non-fatal reports**	**Number of Fatal reports**	**Total**	**% of fatal reports**
Age - 18-29 Yrs													
February 2021	3	1	25	1	1	50			0	4	2	6	33.3
March 2021	15	2	11.8	5	3	37.5			0	20	5	25	20
April 2021	11		0	14	2	12.5			0	25	2	27	7.4
May 2021	2		0	3	1	25			0	5	1	6	16.7
June 2021	6	3	33.3	3	2	40		1	100	9	6	15	40
July 2021	4	1	20	2		0			0	6	1	7	14.3
August 2021	5	3	37.5	2	1	33.3			0	7	4	11	36.4
September 2021	1	1	50	2	1	33.3			0	3	2	5	40
October 2021	2		0	1		0			0	3	0	3	0
November 2021	2		0			0			0	2	0	2	0
January 2022	1		0	2		0			0	3	0	3	0
February 2022			0	1		0			0	1	0	1	0

Table 202 TTS fatality/survival rate over time by age group/gender and doses for confirmed/probable and possible cases

	FEMALE			MALE			UNKNOWN			Grand Total			
Case onset month/ Age group	**Number of non-fatal reports**	**Number of Fatal reports**	**% of fatal reports**	**Number of non-fatal reports**	**Number of Fatal reports**	**% of fatal reports**	**Number of non-fatal reports**	**Number of Fatal reports**	**% of fatal reports**	**Number of non-fatal reports**	**Number of Fatal reports**	**Total**	**% of fatal reports**
March 2022	2	3	60	3		0			0	5	3	8	37.5
April 2022	1	1	50	1		0			0	2	1	3	33.3
May 2022		1	100	1		0			0	1	1	2	50
June 2022		2	100			0			0	0	2	2	100
Age - 30-39 Yrs													
January 2021	1	1	50	1	2	66.7			0	2	3	5	60
February 2021	5	2	28.6	1	1	50			0	6	3	9	33.3
March 2021	21	7	25	7	3	30			0	28	10	38	26.3
April 2021	19	3	13.6	6	5	45.5			0	25	8	33	24.2
May 2021	11	3	21.4	8	1	11.1			0	19	4	23	17.4
June 2021	3	3	50	4	1	20			0	7	4	11	36.4
July 2021	4	3	42.9	5	1	16.7			0	9	4	13	30.8
August 2021	4	1	20	3	1	25			0	7	2	9	22.2
September 2021	1	1	50	3		0			0	4	1	5	20
October 2021	1	1	50	1		0			0	2	1	3	33.3

Table 202 TTS fatality/survival rate over time by age group/gender and doses for confirmed/probable and possible cases

	FEMALE			MALE			UNKNOWN			Grand Total			
Case onset month/ Age group	**Number of non-fatal reports**	**Number of Fatal reports**	**% of fatal reports**	**Number of non-fatal reports**	**Number of Fatal reports**	**% of fatal reports**	**Number of non-fatal reports**	**Number of Fatal reports**	**% of fatal reports**	**Number of non-fatal reports**	**Number of Fatal reports**	**Total**	**% of fatal reports**
November 2021	2		0	2		0			0	4	0	4	0
December 2021	1		0	1	1	50			0	2	1	3	33.3
January-2022	1		0			0			0	1	0	1	0
February 2022	1		0	1		0			0	2	0	2	0
March 2022	2	1	33.3	5		0			0	7	1	8	12.5
May 2022	3		0	1		0			0	4	0	4	0
June 2022			0	2		0			0	2	0	2	0
Age - 40-49 Yrs													
February 2021	4	3	42.9	2		0			0	6	3	9	33.3
March 2021	21	13	38.2	12		0			0	33	13	46	28.3
April 2021	27	3	10	17	1	5.6			0	44	4	48	8.3
May 2021	30	6	16.7	36	3	7.7	1		0	67	9	76	11.8
June 2021	5	3	37.5	8		0			0	13	3	16	18.8
July 2021	4	1	20	3	1	25			0	7	2	9	22.2

Table 202 TTS fatality/survival rate over time by age group/gender and doses for confirmed/probable and possible cases

	FEMALE			MALE			UNKNOWN			Grand Total			
Case onset month/ Age group	**Number of non-fatal reports**	**Number of Fatal reports**	**% of fatal reports**	**Number of non-fatal reports**	**Number of Fatal reports**	**% of fatal reports**	**Number of non-fatal reports**	**Number of Fatal reports**	**% of fatal reports**	**Number of non-fatal reports**	**Number of Fatal reports**	**Total**	**% of fatal reports**
August 2021	2		0	4	1	20			0	6	1	7	14.3
September 2021	5	1	16.7	7		0			0	12	1	13	7.7
October 2021	5		0	3	1	25			0	8	1	9	11.1
November 2021	5	1	16.7	1		0			0	6	1	7	14.3
December 2021	1		0		1	100			0	1	1	2	50
January 2022	1	1	50	2		0			0	3	1	4	25
February 2022	1		0	2		0			0	3	0	3	0
March 2022	2	1	33.3	1		0			0	3	1	4	25
April 2022	2		0	1	1	50			0	3	1	4	25
May 2022	1		0	4		0			0	5	0	5	0
Age - 50-59 Yrs													
January 2021	2	1	33.3			0			0	2	1	3	33.3

Table 202 TTS fatality/survival rate over time by age group/gender and doses for confirmed/probable and possible cases

	FEMALE			MALE			UNKNOWN			Grand Total			
Case onset month/ Age group	Number of non-fatal reports	Number of Fatal reports	% of fatal reports	Number of non-fatal reports	Number of Fatal reports	% of fatal reports	Number of non-fatal reports	Number of Fatal reports	% of fatal reports	Number of non-fatal reports	Number of Fatal reports	Total	% of fatal reports
February 2021	6	1	14.3	4		0			0	10	1	11	9.1
March 2021	36	13	26.5	21	3	12.5			0	57	16	73	21.9
April 2021	36	3	7.7	40	6	13	2		0	78	9	87	10.3
May 2021	18		0	19	2	9.5		1	100	37	3	40	7.5
June 2021	13	4	23.5	14	2	12.5			0	27	6	33	18.2
July 2021	7	1	12.5	6	1	14.3			0	13	2	15	13.3
August 2021	4	3	42.9	7	1	12.5			0	11	4	15	26.7
September 2021	4	1	20	6		0			0	10	1	11	9.1
October 2021	3		0	1	2	66.7			0	4	2	6	33.3
November 2021	2	1	33.3	1		0			0	3	1	4	25
December 2021	2		0	1	1	50			0	3	1	4	25
January 2022	3	2	40		1	100			0	3	3	6	50
February 2022	1	1	50	1		0			0	2	1	3	33.3

Table 202 TTS fatality/survival rate over time by age group/gender and doses for confirmed/probable and possible cases

	FEMALE			MALE			UNKNOWN			Grand Total			
Case onset month/ Age group	**Number of non-fatal reports**	**Number of Fatal reports**	**% of fatal reports**	**Number of non-fatal reports**	**Number of Fatal reports**	**% of fatal reports**	**Number of non-fatal reports**	**Number of Fatal reports**	**% of fatal reports**	**Number of non-fatal reports**	**Number of Fatal reports**	**Total**	**% of fatal reports**
March 2022	1	2	66.7	3	1	25			0	4	3	7	42.9
April 2022	1	1	50	1		0			0	2	1	3	33.3
May 2022	1		0			0			0	1	0	1	0
June 2022	2		0			0			0	2	0	2	0
Age - 60-69 Yrs													
January 2021			0	2	2	50			0	2	2	4	50
February 2021	7	6	46.2	4	1	20			0	11	7	18	38.9
March 2021	27	6	18.2	22	3	12			0	49	9	58	15.5
April 2021	26	6	18.8	27	6	18.2	1		0	54	12	66	18.2
May 2021	31	8	20.5	30	6	16.7			0	61	14	75	18.7
June 2021	17		0	10	1	9.1			0	27	1	28	3.6
July 2021	5		0	6		0			0	11	0	11	0
August 2021	11		0	6		0			0	17	0	17	0
September 2021	2	1	33.3	11		0			0	13	1	14	7.1
October 2021	1		0	11	1	8.3			0	12	1	13	7.7

Table 202 TTS fatality/survival rate over time by age group/gender and doses for confirmed/probable and possible cases

	FEMALE			MALE			UNKNOWN			Grand Total			
Case onset month/ Age group	**Number of non-fatal reports**	**Number of Fatal reports**	**% of fatal reports**	**Number of non-fatal reports**	**Number of Fatal reports**	**% of fatal reports**	**Number of non-fatal reports**	**Number of Fatal reports**	**% of fatal reports**	**Number of non-fatal reports**	**Number of Fatal reports**	**Total**	**% of fatal reports**
December 2021	1		0	1		0			0	2	0	2	0
January 2022	3		0	1		0			0	4	0	4	0
February 2022			0		1	100			0	0	1	1	100
March 2022	2		0	2		0			0	4	0	4	0
April 2022	1	1	50	1	1	50			0	2	2	4	50
May 2022	2		0	1		0			0	3	0	3	0
June 2022	2		0			0			0	2	0	2	0
Age - 70-79 Yrs													
January 2021	2		0	2		0			0	4	0	4	0
February 2021	11	1	8.3	7	1	12.5			0	18	2	20	10
March 2021	5	1	16.7	6	1	14.3			0	11	2	13	15.4
April 2021	15	6	28.6	24	1	4	1		0	40	7	47	14.9
May 2021	9	1	10	16	3	15.8			0	25	4	29	13.8
June 2021	10	1	9.1	7	1	12.5			0	17	2	19	10.5

Table 202 TTS fatality/survival rate over time by age group/gender and doses for confirmed/probable and possible cases

	FEMALE			MALE			UNKNOWN			Grand Total			
Case onset month/ Age group	**Number of non-fatal reports**	**Number of Fatal reports**	**% of fatal reports**	**Number of non-fatal reports**	**Number of Fatal reports**	**% of fatal reports**	**Number of non-fatal reports**	**Number of Fatal reports**	**% of fatal reports**	**Number of non-fatal reports**	**Number of Fatal reports**	**Total**	**% of fatal reports**
July 2021	7	1	12.5	10	1	9.1			0	17	2	19	10.5
August 2021	4	1	20	10		0			0	14	1	15	6.7
September 2021	3		0	7	1	12.5			0	10	1	11	9.1
October 2021	2		0	7		0			0	9	0	9	0
November 2021			0	2		0			0	2	0	2	0
February 2022			0	1		0			0	1	0	1	0
March 2022	2	1	33.3			0			0	2	1	3	33.3
April 2022			0	1		0			0	1	0	1	0
May 2022			0	1		0			0	1	0	1	0
June 2022		1	100			0			0	0	1	1	100
Age - 80+ Yrs													
January 2021	1		0			0			0	1	0	1	0
February 2021	1	1	50		1	100			0	1	2	3	66.7

Table 202 TTS fatality/survival rate over time by age group/gender and doses for confirmed/probable and possible cases

	FEMALE			MALE			UNKNOWN			Grand Total			
Case onset month/ Age group	Number of non-fatal reports	Number of Fatal reports	% of fatal reports	Number of non-fatal reports	Number of Fatal reports	% of fatal reports	Number of non-fatal reports	Number of Fatal reports	% of fatal reports	Number of non-fatal reports	Number of Fatal reports	Total	% of fatal reports
March 2021	1	2	66.7	3	1	25			0	4	3	7	42.9
April 2021	8	2	20	8	1	11.1			0	16	3	19	15.8
May 2021	5	1	16.7	2		0			0	7	1	8	12.5
June 2021	1		0	6	1	14.3			0	7	1	8	12.5
July 2021	6		0	2		0			0	8	0	8	0
August 2021	3		0	6		0			0	9	0	9	0
September 2021	5		0	3		0			0	8	0	8	0
October 2021			0	3		0			0	3	0	3	0
November 2021			0	2		0			0	2	0	2	0
Age Unknown													
February 2021	2		0			0			0	2	0	2	0
March 2021	8	1	11.1	4	1	20	2		0	14	2	16	12.5
April 2021	7	2	22.2	6	1	14.3			0	13	3	16	18.8
May 2021	7	1	12.5	7	1	12.5	2		0	16	2	18	11.1
June 2021	3	1	25	7		0	1		0	11	1	12	8.3

Table 202 TTS fatality/survival rate over time by age group/gender and doses for confirmed/probable and possible cases

	FEMALE			MALE			UNKNOWN			Grand Total			
Case onset month/ Age group	**Number of non-fatal reports**	**Number of Fatal reports**	**% of fatal reports**	**Number of non-fatal reports**	**Number of Fatal reports**	**% of fatal reports**	**Number of non-fatal reports**	**Number of Fatal reports**	**% of fatal reports**	**Number of non-fatal reports**	**Number of Fatal reports**	**Total**	**% of fatal reports**
July 2021	1	2	66.7	2		0			0	3	2	5	40
August 2021	2		0	4		0			0	6	0	6	0
September 2021		1	100	1		0			0	1	1	2	50
October 2021	1		0			0			0	1	0	1	0
November 2021			0	1		0			0	1	0	1	0
February 2022		1	100			0			0	0	1	1	100
April 2022			0			0		1	100	0	1	1	100
Grand Total	**663**	**168**	**20.2**	**623**	**94**	**13.1**	**10**	**3**	**23.1**	**1296**	**265**	**1561**	**17**

TTS reports after Dose 2 of VAXZEVRIA

A search of the AstraZeneca global safety database was undertaken to retrieve adverse event reports of thrombosis in combination with thrombocytopenia reported following administration of the Dose 2 of the VAXZEVRIA. The search encompassed all cases retrieved up to 28 June 2022. The search criteria mentioned above was used to identify TTS cases post Dose 2. The cases of TTS following the Dose 2 were confirmed based on the dose number/information provided in the narrative, if the reports did not contain information on Dose 2, they were not included in the below analysis. The search identified 260 cumulative cases of TTS following the second dose of VAXZEVRIA. Time to onset was available in 260 of the 232 cases and ranged from 0 to 226 days with a median TTO of 14 days after 2nd dose. Time to onset by 14 days, 21 days, and 42 days is presented in Table 195.

The majority of the 260 case reports of TTS following second dose occurred in male vaccinees (154, 59%). Of the 260 case reports of TTS following second dose, 104 were female (40%), and gender was unknown in 2 report. The age range of vaccinees was from 22 to 95 years, age was not provided in 20 of the 260 reports. Median age was 65.5 years and 38 (14%) of the reports were in vaccinees > 50 years. Outcome in 88 cases were reported as Not recovered, 20 Recovered, 75 Recovering, 26 Fatal, 10 Recovered with sequalae and Unknown in 41 report.

These events included the following sites of thrombosis (≥ 5): Pulmonary embolism (122), Deep vein thrombosis (70), Thrombosis (37), Thrombosis with thrombocytopenia syndrome (19), Cerebrovascular accident (16), Cerebral venous sinus thrombosis (13), Embolism (10), Portal vein thrombosis (9), Superior sagittal sinus thrombosis (5), Peripheral artery thrombosis (5), Mesenteric vein thrombosis (5).

In 57 out of 260 reports (23%) with Dose 2, there was a co-reported bleeding event from the narrow SMQ: Haemorrhage terms (excl laboratory terms). The reported events (≥ 2) included: Thrombotic thrombocytopenic purpura (4), Haemorrhagic adrenal infarction (2), Haemorrhagic stroke (2). There were two case report with the co-reported events from the HLT: Coagulopathies following Dose 2 with the event Coagulopathy (1) and Antiphospholipid syndrome (1).

Using the estimated exposure of 104713978 administered 2nd vaccinations with VAXZEVRIA in UK, EEU, Canada, Iran, Korea, Republic of, Taiwan, Japan and Thailand the reporting rate of thrombotic events in combination with thrombocytopenia (with time to onset ≤ 21 days; 152 reports) following the second VAXZEVRIA was estimated to be 1.45 per million doses. Most of the vaccines who experienced TTS post Dose 2 were male (59%) and were older in age with a median age of 65 years. The rate of TTS following 2nd of VAXZEVRIA is less compared to the background rate for all age groups (see Table 196 and Table 197) of 5.62 (event rates per 1M PY per 21 days Truven Market Scan-2019, aligned

with the OHDSI TTS algorithm) and 10.75 (event rates per 1M PY per 21 days Truven Market Scan-2019, aligned with the OHDSI TTS algorithm [with updated OHDSI aligned codelists and washout periods]).

This rate of thrombotic events in combination with thrombocytopenia following 1st dose of VAXZEVRIA is below the estimated reporting rate of 12.58 per million doses for first dose of VAXZEVRIA (1319 identified reports with time to onset ≤ 21 days; estimated exposure 104768282 administered doses). TTS events following the second dose had a different demographic pattern as well, being older and more likely male compared to dose 1.

Summary and conclusion for TTS is presented below after discussion of CVST+ thrombocytopenia.

Reporting rate for Dose 1 and Dose 2 was 27.18 and 5.14/million doses administered doses respectively. For all administered doses and Dose 1, The observed number of cases are significantly more than expected, for risk windows of 14 days (with unknown time to onset included) post vaccination by VAXZEVRIA of TTS with both background rates.

TTS reports after Dose 3 of VAXZEVRIA

A search of the AstraZeneca global safety database was undertaken to retrieve adverse event reports of thrombosis in combination with thrombocytopenia reported following administration of the Dose 3 of the VAXZEVRIA. The search encompassed all cases retrieved up to 28 June 2022. The search criteria mentioned above was used to identify TTS cases post Dose 3. The cases of TTS following the Dose 3 were confirmed based on the dose number/information provided in the narrative. There were 8 cases occurred after administration of a Dose 3/booster (either of AZD1222 or an mRNA vaccine): 6 after an AZD1222 booster, and 2 after an mRNA booster. The 2 cases after an mRNA booster are not further discussed here as they do not concern the use of AZD1222 as a booster. Time to onset was available in 6 of the 8 cases and ranged from 1 to 60 days with a median TTO of 12 days after 3rd dose. Time to onset by 14 days, 21 days, and 42 days is presented in Table 195.

Of the 8 case reports of TTS following Dose 3/booster, 3 were female (40%), and 3 were male. The age range of vaccinees was from 21 to 74 years, age was not provided in 1 of the 8 reports. Median age was 28 years and 1 of the vaccinees was > 50 years. Outcome in 2 cases were reported as Not recovered, 3 Recovering, 1 Fatal report.

No confirmed cases of TTS following a heterologous AZD1222 booster have been identified. The rate of TTS following a homologous booster dose could not be estimated as the only potential homologous booster TTS case was in Mexico and exposure data are not available for Mexico.

Using the estimated exposure of 12833861administered Dose 3/booster vaccinations with VAXZEVRIA in Brazil the reporting rate of thrombotic events in combination with thrombocytopenia (with time to onset ≤ 21 days; 4 reports) following the Dose 3/booster VAXZEVRIA was estimated to be 0.31 per million doses. The rate of TTS following Dose 3/booster of VAXZEVRIA is less compared to the background rate for all age groups (see Table 196 and Table 197) of 5.62 (event rates per 1M PY per 21 days Truven Market Scan-2019, aligned with the OHDSI TTS algorithm) and 10.75 (event rates per 1M PY per 21 days Truven Market Scan-2019, aligned with the OHDSI TTS algorithm [with updated OHDSI aligned codelists and washout periods]).

No new or emerging concern regarding TTS has been identified with booster doses of AZD1222. Based on the review of available safety data, there is no indication suggesting that the safety profile of an AZD1222 booster after a primary series with another vaccine would be different with respect to TTS from that of a first vaccine dose of AZD1222.

Table 203 Post-Marketing Cases of Thrombosis with Thrombocytopenia Syndrome Related to AZD1222 and COVID-19 Vaccine Booster Use

Case ID Country	Events (PT)	Age/Sex	Primary / Booster vaccine	Time to onset	MHRA case classification	Comment
[redacted]	Cerebral venous sinus thrombosis; Immune thrombocytopenia; Cerebral venous thrombosis; Haemorrhage intracranial; Incorrect route of product administration; Seizure; Interchange of vaccine products	26/F	CoronaVac / AZD1222 (19 January 2022)	16 days	Criteria not met	This is a consumer report. Past drug therapy included COVID-19 vaccine (first 2 doses of the vaccine corresponded to the CoronaVac brand, without any problem) for prevention. On 19 January 2022, patient received Dose 3 of VAXZEVRIA. There is no radiological confirmation for thrombosis event.
[redacted]	Pulmonary embolism; Sepsis; Pulmonary sepsis; Lung neoplasm malignant; Thrombocytopenia; Pyrexia; Respiratory rate increased	74/F	AZD1222 / AZD1222	Same day	Criteria not met	No evidence of thrombocytopenia; considered to be a coding error and case was received from regulatory authority. Pulmonary embolism event was reported on same day of booster and in the context of pulmonary sepsis and malignant lung neoplasm. The patient outcome at the time of the report was not recovered.

Case ID Country	Events (PT)	Age/Sex	Primary / Booster vaccine	Time to onset	MHRA case classification	Comment
[redacted]	Paralysis; Thrombosis; Speech disorder; Coordination abnormal; Muscular weakness; Diplopia; Petechiae; Contusion; Pallor; Heavy menstrual bleeding; Vision blurred; Thrombocytopenia; Dizziness; Nausea; Expired product administered; Incorrect route of product administration; Fatigue; Headache; Decreased appetite; Pain in extremity	46/F	AZD1222 / AZD1222	5 days	Possible	This is a consumer report. VAXZEVRIA Dose 1: 09 June 2021 VAXZEVRIA Dose 2: 03 August 2021 VAXZEVRIA Dose 3: 06 September 2021 There are events of medication error (subcutaneous route administration and expired product administered). The lot ID for reported Dose 2 and Dose 3 are same; hence, it cannot be confirmed as booster dose. There is no radiological confirmation for thrombosis event (site of thrombosis not reported), and the patient was treated with prednisolone for thrombocytopenia. No information on D-dimer and anti-PF4.
[redacted]	Thrombosis; Platelet count decreased; Off label use	NA/M	Unknown/ Unidentified AstraZeneca Product	Unknown	Criteria not met	Report was based on a social media post. There is very little information in this case. Not clear if this was VAXZEVRIA, as VAXZEVRIA is not used in Italy for booster dose. The patient died from the event of thrombosis during December 2021.
[redacted]	Venous thrombois; Pulmonary embolism	28/M	COMIRNATY / AZD1222 (03 March 2022)	2 days	Possible	No details were provided regarding the primary vaccine except that the suspect product COVID-19 Pfizer COMIRNATY was removed. This case is considered as booster dose based on dosing date of VAXZEVRIA. Venous thrombosis occurred 2 days after the last dose and pulmonary embolism occurred, 14 days after last dose. Events were confirmed by CT angiography of chest and abdominal aorta on 18 March 2022. Normal D-dimer and negative PF4.

Case ID Country	Events (PT)	Age/Sex	Primary / Booster vaccine	Time to onset	MHRA case classification	Comment
[redacted]	Splenic infarction; Renal infarct; Thrombosis; Thrombosis with thrombocytopenia syndrome; Influenza; Haematuria; Dysuria; Back pain; Headache; Facial pain; Pyrexia; Abdominal pain lower	M/21	Pfizer vaccine Pfizer vaccine AstraZeneca Product	10 days	Probable	The vaccinee received First and second dose of Pfizer vaccine. There was no change in renal function or heptagram. No anaemia, no signs of haemolysis. There was no externalization of bleeding. No history of previous thrombosis

CT, computed tomography; MHRA, Medicines and Healthcare products Regulatory Agency; NA, not available; PT; preferred term

Literature

Articles were reviewed to understand the pathophysiology of TTS (Mechanism of action of TTS) in association with the VAXZEVRIA. Below is a brief discussion of the 4 relevant articles.

1. Cohen TS, Kelly EJ, Nylander S, Bansal H, Jepson BM, Bhuyan P, et al. Serum levels of anti-PF4 IgG after AZD1222 (ChAdOx1 nCoV-19) vaccination, Sci Rep. 2022;12(1):7961.
2. Pitk¨anen HH, Jouppila A, Helin T, Dulipati V, Kotimaa J, Meri S; COVID-19 adenovirus vaccine triggers antibodies against PF4 complexes to activate complement and platelets, Thromb Res.2021;208:129-37.
3. Buhr ND, Baumann T, Werlein C, Fingerhut L, Imker R, Meurer M, Götz F, Bronzlik P, P. Kühnel M, D. Jonigk4 D, Ernst J; Insights Into Immunothrombotic Mechanisms in Acute Stroke due to Vaccine-Induced Immune Thrombotic Thrombocytopenia, Front Immunol. 2022;13:879157.
4. Linda Schönborn, M.D. et.al; SARS-CoV-2 Infection in Patients with a History of VITT, N Engl J Med. 2022;387(1):88-90.

Cohen et al 2022 conducted a study to determine if vaccination with VAZXEVRIA (formerly AZD1222) induces an increase in levels of anti-PF4 IgG, we analyzed paired serum samples collected prior to and 15 days after vaccination with VAZXEVRIA or placebo from participants in a multicentre, randomized Phase 3 study (D8110C00001). For the purposes of this exploratory, post-hoc analysis, all participants (1777 participants who received VAZXEVRIA and 888 who received placebo) in the immunogenicity sub-study with available serum samples obtained on both day 1 and day 15 were included, and their paired serum samples were assessed for anti-PF4 IgG using a validated IgG-specific PF4-polyvinylsulfate enzyme-linked immunosorbent assay (Immucor). None of the 2665 participants experienced TTS following administration of vaccine or placebo. In the VAZXEVRIA and placebo groups, respectively, 98.0% and 97.7% of baseline serum samples were classified as being negative for anti-PF4 IgG, as were 97.5% and 97.6% of Day 15 serum samples. Optical density (OD) assay values were similar between the VAZXEVRIA and placebo group at both baseline (median OD: 0.100 and 0.101, respectively; P = 0.4416) and Day 15 (median OD: 0.105 and 0.099, respectively; P = 0.0567). Overall, 96.9% of paired samples in both groups (VAZXEVRIA: 1708/1762; placebo: 850/877) were classified as negative at baseline and also negative at Day 15. There was a minimal increase in OD values in the VAZXEVRIA arm from baseline to Day 15 (median OD: 0.100 to 0.105; P = 0.4); all were classified as moderate. None of these individuals in the VAZXEVRIA group increased to a high level of anti-PF4 IgG at Day 15 compared to 1 in the placebo group, while 10/35 (28.6%) and 6/20 (30.0%), respectively, decreased below the threshold for positivity. These data indicate that VAZXEVRIA does not induce a clinically relevant general increase in anti-PF4 IgG.

AstraZeneca comment: Data from publications and case reports have noted that individuals experiencing TTS after receiving VAXZEVRIA, had elevated levels of antibodies targeting platelet factor 4 (PF4). Data from this analysis demonstrates that AZD1222 did not result in an increased rate of detection of anti-PF4 IgG post-vaccination compared to placebo during the period of highest TTS risk (first 15 days after vaccination). The identification of specific markers associated with the development of TTS is challenging due to the extremely rare frequency of TTS.

Pitkanen et al 2021 conducted a study to assess antibodies in interaction with the activation of platelets and complement triggered by Vaccine-induced thrombotic thrombocytopenia (VITT). Antibodies against adenovirus type 2 hexon protein, ChAdOx1 adenoviral vector-specific IgG and PF4 were analyzed by enzyme immunoassays from VITT patients (n = 5). The EDTA plasma samples of the patients and controls were used to measure both terminal complement complexes (TCC) by ELISA and aggregation of healthy donor platelets. We studied the effects of human immunoglobulin (IVIG) and glycoprotein IIb/IIIa inhibitor (GPIIb/IIIa) on spontaneous and collagen-induced platelet aggregation supplemented with VITT plasma. VITT plasma had anti-PF4 antibodies and elevated TCC levels as a sign of complement activation. In isolated healthy donor platelets, VITT patient plasma caused marked, spontaneous aggregation of platelets, which was abolished by eptifibatide and high-dose therapeutic IVIG. Authors suggest that VITT is triggered by antibodies against adenovirus vector and PF4- polyanion complexes which strongly co-activate complement and platelets. The spontaneous platelet aggregation was suppressed by IVIG or eptifibatide, indicating that besides FcγRII, also GPIIb/IIIa receptor exerts platelet procoagulant role in VITT.

AstraZeneca comment: this study assessed antibodies against adenovirus vaccine and PF4-polyanion complexes in TTS/VITT, and provides new data on immunological stimulus that co-activates the complement system and triggers spontaneous aggregation of healthy platelets. This study does not address whether VAZXEVRIA causes a generalized increase in antibody levels post administration, also involvement of procoagulant microvesicles was not investigated, which have shown a potential role in VITT in other studies.

Bhur et al 2022 investigated blood and thrombus specimens of a female patient who suffered severe stroke due to VITT after vaccination with ChAdOx1 in comparison to 13 control stroke patients with similar clinical characteristics. Authors analyzed cerebral thrombi using histological examination, staining of complement factors, NET-markers, DNase and LL-37. NET markers were identified in thrombi of all patients. Interestingly, the thrombus of the VITT-patient exclusively revealed complement factors and high amounts of DNase and LL-37, serum of the VITT-patient inhibited reactive oxygen species-dependent NET-release by phorbol-myristate-acetate to a lesser degree compared to controls, indicating either less efficient NET-inhibition or enhanced NET-induction in the blood of the VITT-patient. The

authors suggest that not only an increased NETosis but also a disturbed endogenous degradation of NETs may be involved in thrombogenesis during VITT, contributing further to NETosis with a subsequent inflammatory response in the sense of a vicious cycle, and thus leading to an exaggerated pro-thrombotic state.

AstraZeneca comment: these findings are from a single subject with VITT and these are not compared with other cases of VITT. These findings need to be interpreted with caution and as potentially hypothesis generating.

Schönborn et al 2022 conducted a periodic evaluation of VITT antibody status (study registry, EUPAS45098) in a cohort of 69 patients with a history of VITT who had received an adenovirus vector Covid-19 vaccine. Of these patients, 24 did not receive any subsequent doses of a Covid-19 vaccine; the remaining 45 patients received subsequent doses of a messenger RNA (mRNA) vaccine (either the COMIRNATY [Pfizer–BioNTech] or the mRNA-1273 [Moderna] vaccine). Of these patients, 31 received a second dose and 14 received a third dose. Of the 69 patients, COVID-19 developed in 11 (16%), all of whom had mild symptoms. Covid-19 occurred more frequently in the patients who had received only the adenovirus vector vaccine than in those who had subsequently received one or two doses of an mRNA vaccine (7 of 24 patients [29%] vs. 4 of 45 patients [9%]; P = 0.04 by Fisher's exact test). In all the patients who had contracted COVID-19, a follow-up blood sample that was obtained after their recovery was available at a median of 2 weeks after the onset of infection. No major increases in PF4-antibody levels developed after recovery from COVID-19. In most of the patients, repeat optical density readings were lower than those in the last sample obtained before the onset of COVID, a finding that was consistent with the inherent natural decline in anti–PF4 antibodies. No patient had recurrent thrombocytopenia, new or recurrent thrombosis, or reversion to a positive platelet-activation assay.

AstraZeneca Comment: Authors noted that Covid-19 does not restimulate anti–PF4 antibodies in patients with a history of VITT. As described in section 4.3 of the CDS, VAZXEVRIA is contraindicated in vaccinees with major venous and/or arterial thrombosis in combination with thrombocytopenia following vaccination with any COVID-19 vaccine.

Published post DLP, Laffan et al 2022 presented a review of the clinical characteristics of all reports of TTS occurring after vaccination with VAXZEVRIA in the AstraZeneca Global Safety Database up to 28 December 2021. The authors conclude that the reporting rate of 'typical'/'possible' TTS post first-dose vaccination in this dataset is 7.5 per million vaccinated persons, with few cases were reported after subsequent doses, including booster doses. They found that peak reporting coincided with media-driven attention and that medical history differences versus a reference population indicate potentially unidentified risk factors. The publication also concluded that decreasing fatality rate correlates with increasing awareness and publication of diagnostic/treatment guidelines. The authors also present an algorithm to

classify potential TTS cases and state that comprehensive reporting could help further improve definition and management of this extremely rare syndrome. This article was co-authored by AstraZeneca and presents a review of ICSR case characteristics reported to AstraZeneca through to 28 December 21. This includes data and analysis already included in previous PBRERs/monthly summary reports, as well as in the cumulative review presented above in this PBRER, and therefore presents no new, additional evidence.

CVST with thrombocytopenia

Of the 2391 thrombosis with thrombocytopenia case reports reviewed cumulatively, the reported venous thrombotic sites included CVST (HLT: Cerebrovascular venous and sinus thrombosis) in 585 (25%) cases. Of these 585 cases, 64% were in females, 35% occurred in males, and in 1% gender was unknown.

In 173 of the 585 (29%) of the CVST with Thrombocytopenia cases were fatal. CVST with thrombocytopenia cases by age group/gender/dose and fatality are provided in Table 204.

Table 204 Cerebrovascular venous and sinus thrombosis with Thrombocytopenia Case Reports by age/gender

Age group	Female N (fatal)	Male N (fatal)	Unknown N (fatal)	Grand Total
Age - 18-29 Yrs	45 (11)	45 (11)	0 (0)	90 (22)
Age - 30-39 Yrs	67 (25)	33 (13)	0 (0)	100 (38)
Age - 40-49 Yrs	98 (29)	37 (7)	0 (0)	135 (36)
Age - 50-59 Yrs	67 (18)	42 (15)	0 (0)	109 (33)
Age - 60-69 Yrs	66 (16)	31 (10)	0 (0)	97 (26)
Age - 70-79 Yrs	14 (7)	4 (1)	0 (0)	18 (8)
Age - 80+ Yrs	2(0)	3(0)	0(0)	5(0)
Age Unknown	17(6)	10(2)	4(2)	31(10)
Grand Total	376(112)	205(59)	4(2)	585(173)
Dose 1				
Age - 18-29 Yrs	44(11)	44(11)	0(0)	88(22)
Age - 30-39 Yrs	67(25)	33(13)	0(0)	100(38)
Age - 40-49 Yrs	94(27)	31(7)	0(0)	125(34)
Age - 50-59 Yrs	65(18)	40(14)	0(0)	105(32)
Age - 60-69 Yrs	65(16)	28(10)	0(0)	93(26)
Age - 70-79 Yrs	14(7)	3()	0(0)	17(7)
Age - 80+ Yrs	1(0)	3(0)	0(0)	4(0)

Table 204 Cerebrovascular venous and sinus thrombosis with Thrombocytopenia Case Reports by age/gender

Age group	Female N (fatal)	Male N (fatal)	Unknown N (fatal)	Grand Total
Age Unknown	16(6)	9(2)	4(2)	29(10)
Grand Total	366(110)	191(57)	4(2)	561(169)
Dose 2				
Age - 18-29 Yrs	0(0)	1(0)	0(0)	1(0)
Age - 30-39 Yrs	0(0)	0(0)	0(0)	0(0)
Age - 40-49 Yrs	4(2)	6(0)	0(0)	10(2)
Age - 50-59 Yrs	2(0)	2(1)	0(0)	4(1)
Age - 60-69 Yrs	1(0)	3(1)	0(0)	4(1)
Age - 70-79 Yrs	0(0)	1(0)	0(0)	1(0)
Age - 80+ Yrs	1(0)	0(0)	0(0)	1(0)
Age Unknown	1(0)	1(0)	0(0)	2(0)
Grand Total	9(2)	14(2)	0(0)	23(4)

Reporting rates for CVST in combination with thrombocytopenia across age groups based on the data from the UK and EEA by risk window of 21 days and 42 days are provided in Table 205 and Table 206 respectively; reporting rate is also stratified by Dose 1 and Dose 2.

The reporting rate of CVST in combination with thrombocytopenia in the UK was higher across the age groups when compared to the background rate except for reports in vaccinees aged > 65 years (risk window 21 days) and > 50 years (risk window 42 days) with Dose 2.

The reporting rate of CVST in combination with thrombocytopenia in the EEA was higher when compared to the background rate in vaccinees aged < 70 years with all doses. In the EEA the reporting rate of CVST in combination with thrombocytopenia with Dose 2 was higher than the background rate for vaccinees aged < 49 years, however reporting rate in age group > 50 years was less compared to the background rate.

The observed versus expected analyses for TTS (including CVST) and CVST with thrombocytopenia are presented in Appendix 18 Tables 2,3,4 and Table 10. Background rates for TTS were derived from MarketScan (US claims) data, using OHDSI-aligned code lists and definitions for TTS.

Algorithm 2 for TTS uses updated OHDSI-aligned code lists and washout periods (previously patients with thrombosis in the 2 years prior to 2019 were excluded). The results of the observed versus expected analyses suggests that observed cases of CVST with thrombocytopenia are more than expected for all age stratifications.

Conservatively, the exposure for global reports (448306152) is based on doses administered in 13 markets as explained in Appendix 8.

Table 205 Reporting rate for CVST and thrombocytopenia (UK and EEA data) by risk window of 21 days

UK 21 Days RW								
Age Group	**Total Exposed**	**Cases within Risk Window of 21 days**	**Confirmed, probable and possible cases within Risk Window of 21 days**	**Reporting Rate (per million)**	**Reporting Rate (per million) for Confirmed, probable and possible cases**	**Background Rate (per million)[a]**	**Rate relative to Background (per million)**	**Rate relative to Background (per million) for Confirmed, probable and possible cases**
All Dose (UK)								
Age - 18-39 Yrs	5695728	43	50	7.55	8.78	0.1	7.45	8.68
Age - 40-49 Yrs	9705005	54	48	5.56	4.95	0.1	5.46	4.85
Age - 50-64 Yrs	18978058	52	7	2.74	0.37	0.2	2.54	0.17
Age - > 65 Yrs	14448845	7	6	0.48	0.42	0.2	0.28	0.22
Age Unknown	102827	8	40	77.8	389		77.8	389
Grand Total	**48930463**	**164**	**151**	**3.35**	**3.09**	**0.1**	**3.25**	**2.99**
Dose 1 (UK)								
Age - 18-39 Yrs	2905794	43	48	14.8	16.52	0.1	14.7	16.42
Age - 40-49 Yrs	4919521	51	46	10.37	9.35	0.1	10.27	9.25
Age - 50-64 Yrs	9560990	49	6	5.12	0.63	0.2	4.92	0.43
Age - > 65 Yrs	7270267	6	5	0.83	0.69	0.2	0.63	0.49
Age Unknown	70990	7	40	98.61	563.46		98.61	563.46
Grand Total	**24727562**	**156**	**145**	**6.31**	**5.86**	**0.1**	**6.21**	**5.76**
Dose 2 (UK)								
Age - 18-39 Yrs	2784710	0	0	0	0	0.1	-0.1	-0.1
Age - 40-49 Yrs	4778603	3	2	0.63	0.42	0.1	0.53	0.32
Age - 50-64 Yrs	9399336	3	2	0.32	0.21	0.2	0.12	0.01
Age - > 65 Yrs	7150151	1	1	0.14	0.14	0.2	-0.06	-0.06

Table 205 Reporting rate for CVST and thrombocytopenia (UK and EEA data) by risk window of 21 days

UK 21 Days RW								
Age Group	**Total Exposed**	**Cases within Risk Window of 21 days**	**Confirmed, probable and possible cases within Risk Window of 21 days**	**Reporting Rate (per million)**	**Reporting Rate (per million) for Confirmed, probable and possible cases**	**Background Rate (per million)[a]**	**Rate relative to Background (per million)**	**Rate relative to Background (per million) for Confirmed, probable and possible cases**
Age Unknown	31787	1	1	31.46	31.46		31.46	31.46
Grand Total	**24144587**	**8**	**6**	**0.33**	**0.25**	**0.1**	**0.23**	**0.15**
All Dose (EEA)								
18-49	11775199	104	64	8.83	5.44	0.07	8.76	5.37
50-59	6494928	24	17	3.7	2.62	0.16	3.54	2.46
60-69	20487444	45	27	2.2	1.32	0.4	1.8	0.92
70-79	8178431	5	2	0.61	0.24	0.47	0.14	-0.23
80+	1167965	1	0	0.86	0	0	0.86	0
Age Unknown	7649	2	2	261.47	261.47	-	-	-
Grand Total	**48111616**	**181**	**112**	**3.76**	**2.33**	**-**	**-**	**-**
Dose 1 (EEA)								
18-49	6407149	101	63	15.76	9.83	0.07	15.69	9.76
50-59	3518861	24	17	6.82	4.83	0.16	6.66	4.67
60-69	10534615	43	27	4.08	2.56	0.4	3.68	2.16
70-79	4169066	5	2	1.2	0.48	0.47	0.73	0.01
80+	597525	1	0	1.67	0	0	1.67	0
Age Unknown	3914	2	2	510.99	510.99	-	-	-
Grand Total	**25231130**	**176**	**111**	**6.98**	**4.4**	**-**	**-**	**-**
Dose 2 (EEA)								
18-49	5363507	3	1	0.56	0.19	0.07	0.49	0.12
50-59	2973710	0	0	0	0	0.16	-0.16	-0.16

Table 205 Reporting rate for CVST and thrombocytopenia (UK and EEA data) by risk window of 21 days

UK 21 Days RW								
Age Group	**Total Exposed**	**Cases within Risk Window of 21 days**	**Confirmed, probable and possible cases within Risk Window of 21 days**	**Reporting Rate (per million)**	**Reporting Rate (per million) for Confirmed, probable and possible cases**	**Background Rate (per million)[a]**	**Rate relative to Background (per million)**	**Rate relative to Background (per million) for Confirmed, probable and possible cases**
60-69	9949775	2	0	0.2	0	0.4	-0.2	-0.4
70-79	4007093	0	0	0	0	0.47	-0.47	-0.47
80+	569211	0	0	0	0	0	0	0
Age Unknown	3690	0	0	0	0	-	-	-
Grand Total	**22866986**	**5**	**1**	**0.22**	**0.04**	-	-	-

[a] Background event rates per 1M PY per 21 days from Truven Market Scan-2019.

CVST Cerebrovascular venous and sinus thrombosis, EEA European Economic Area, PY Person Years, UK United Kingdom, yrs Years.

Table 206 Reporting rate for CVST and thrombocytopenia (UK and EEA data) by risk window of 42 days

UK 42 Days RW								
Age Group	**Total Exposed**	**Cases within Risk Window of 42 days**	**Confirmed, probable and possible cases within Risk Window of 42 days**	**Reporting Rate (per million)**	**Reporting Rate (per million) for Confirmed, probable and possible cases**	**Background Rate (per million)[a]**	**Rate relative to Background (per million)**	**Rate relative to Background (per million) for Confirmed, probable and possible cases**
All Dose (UK)								
Age - 18-39 Yrs	5695728	44	55	7.73	9.66	0.2	7.53	9.46
Age - 40-49 Yrs	9705005	60	53	6.18	5.46	0.2	5.98	5.26
Age - 50-64 Yrs	18978058	57	9	3	0.47	0.4	2.6	0.07
Age - > 65 Yrs	14448845	10	8	0.69	0.55	0.4	0.29	0.15
Age Unknown	102827	10	41	97.25	398.73	-	-	-
Grand Total	**48930463**	**181**	**166**	**3.7**	**3.39**	**0.2**	**3.5**	**3.19**
Dose 1 (UK)								
Age - 18-39 Yrs	2905794	44	53	15.14	18.24	0.2	14.94	18.04
Age - 40-49 Yrs	4919521	57	51	11.59	10.37	0.2	11.39	10.17
Age - 50-64 Yrs	9560990	54	8	5.65	0.84	0.4	5.25	0.44
Age - > 65 Yrs	7270267	9	6	1.24	0.83	0.4	0.84	0.43
Age Unknown	70990	8	41	112.69	577.55	-	-	-
Grand Total	**24727562**	**172**	**159**	**6.96**	**6.43**	**0.2**	**6.76**	**6.23**
Dose 2 (UK)								
Age - 18-39 Yrs	2784710	0	0	0	0	0.2	-0.2	-0.2
Age - 40-49 Yrs	4778603	3	2	0.63	0.42	0.2	0.43	0.22
Age - 50-64 Yrs	9399336	3	2	0.32	0.21	0.4	-0.08	-0.19
Age - > 65 Yrs	7150151	1	1	0.14	0.14	0.4	-0.26	-0.26

Table 206 Reporting rate for CVST and thrombocytopenia (UK and EEA data) by risk window of 42 days

UK 42 Days RW								
Age Group	**Total Exposed**	**Cases within Risk Window of 42 days**	**Confirmed, probable and possible cases within Risk Window of 42 days**	**Reporting Rate (per million)**	**Reporting Rate (per million) for Confirmed, probable and possible cases**	**Background Rate (per million)[a]**	**Rate relative to Background (per million)**	**Rate relative to Background (per million) for Confirmed, probable and possible cases**
Age Unknown	31787	2	2	62.92	62.92	-	-	-
Grand Total	**24144587**	**9**	**7**	**0.37**	**0.29**	**0.2**	**0.17**	**0.09**
All Dose (EEA)								
18-49	11775199	110	64	9.34	5.44	0.14	9.2	5.3
50-59	6494928	27	17	4.16	2.62	0.32	3.84	2.3
60-69	20487444	48	29	2.34	1.42	0.8	1.54	0.62
70-79	8178431	6	2	0.73	0.24	0.94	-0.21	-0.7
80+	1167965	1	0	0.86	1.71	0	0.86	1.71
Age Unknown	7649	2	2	261.47	0.04	-	-	-
Grand Total	**48111616**	**194**	**114**	**4.03**	**2.37**	**-**	**-**	**-**
Dose 1 (EEA)								
18-49	6407149	107	63	16.7	9.83	0.14	16.56	9.69
50-59	3518861	27	17	7.67	4.83	0.32	7.35	4.51
60-69	10534615	46	29	4.37	2.75	0.8	3.57	1.95
70-79	4169066	6	2	1.44	0.48	0.94	0.5	-0.46
80+	597525	1	0	1.67	0	0	1.67	0
Age Unknown	3914	2	2	0	0	-	-	-
Grand Total	**25231130**	**189**	**113**	**7.49**	**4.48**	**-**	**-**	**-**
Dose 2 (EEA)								
18-49	5363507	3	1	0.56	0.19	0.14	0.42	0.05
50-59	2973710	0	0	0	0	0.32	-0.32	-0.32

Table 206 Reporting rate for CVST and thrombocytopenia (UK and EEA data) by risk window of 42 days

UK 42 Days RW								
Age Group	**Total Exposed**	**Cases within Risk Window of 42 days**	**Confirmed, probable and possible cases within Risk Window of 42 days**	**Reporting Rate (per million)**	**Reporting Rate (per million) for Confirmed, probable and possible cases**	**Background Rate (per million)[a]**	**Rate relative to Background (per million)**	**Rate relative to Background (per million) for Confirmed, probable and possible cases**
60-69	9949775	2	0	0.2	0	0.8	-0.6	-0.8
70-79	4007093	0	0	0	0	0.94	-0.94	-0.94
80+	569211	0	0	0	0	0	0	0
Age Unknown	3690	0	0	0	0	-	-	-
Grand Total	**22866986**	**5**	**1**	**0.22**	**0.04**	**-**	**-**	**-**

[a] Background event rates per 1M PY per 42 days from Truven Market Scan-2019.

CVST, Cerebrovascular venous and sinus thrombosis; EEA, European Economic Area; PY, Person Years; UK, United Kingdom, yrs Years.

Summary

The highest number of cases were reported from UK (55%) while receiving 49.02 million doses of the total worldwide doses.

The analysis of thrombosis in combination with thrombocytopenia following the second dose of VAXZEVRIA showed that the rate of events was extremely low and lower than after administration of the first dose. The majority of the vaccinees who experienced TTS events post Dose 2 were male (59% vs 42%) and were older (Median age was 65.5 years vs. 45 years) compared to first dose recipients. The median time to onset of second dose cases was 14 days compared to12 days for the cases with first dose.

Overall, the most common events were Cerebral venous sinus thrombosis, Deep vein thrombosis, Pulmonary embolism, and Thrombosis.

The time to onset was available for all doses in 78% (1875/2391) of cases; TTO was reported in 77% (1637/ 2123) for Dose 1 and 89% (232/ 260) for Dose 2. Overall, there were more fatal reports for TTO within 14 and 21 days. Seventy-three (73%) percent of the fatal reports occurred with 14 days compare to 64% for all cases and 87% of the fatal report occurred with 21 days compare to 80% for all cases.

The highest fatality rate for all dosage in female vaccinees was 28/117 (24%) in 18 to 29 years of age and male vaccinees was 21/93 (23%) in 30 to 39 years of age. The fatality rate in female vaccinees in Dose 1 found 28/111 (25%) in 18-29 years, whereas in male vaccinees it was 16/72 (22%) in 18 to 29 years of age and 21/92 (22%) in 30 to 39 years. The fatality rate in Dose 2 found in females was 2/27 (33%) in 60 to 69 years of age and in males 7/45 (15%) in 70 to 79 years age group.

No new or emerging concern regarding TTS post-booster has been identified with booster doses of VAXZEVRIA.

The highest number of fatal reports (28%) occurred due to HLT of Cerebrovascular venous and sinus thrombosis. Cerebral haemorrhage was the most common bleeding event associated with fatal event. The total number and percent of fatal reports since April 2021 are decreasing compared to January 2021 to March 2021. There is an increased fatality rate in December 2021; however, only 25 cases were reported in this month received which could explain the sharp increase in the percentages. There is an increased fatality rate in April 2021 (9 reported fatal events out of 31 reports) compared to the earlier months December 2021 and March 2021. Number and percent of fatal reports since April 2021 has decreased compared to January to March 2021 and percent of fatal reports decreased from May 2022 to June 2022.

The arterial events were reported highest in the age groups of 50 to 59 and 60 to 69 years. The distribution of events in male and female was roughly equal. The mixed or the combined arterial and venous events were equally distributed in age groups of 30 to 39,40 to 49,50 to 59 and 60 to 69 years, and the distribution of cases in female and male was roughly equal. The venous events were reported highest in the age groups of 40 to 49, 50 to 59, and 60 to 69 years; the occurrence in females was higher than in males.

The most common confounding factors in descending order of frequency in all 2391 cases were autoimmune conditions, malignancy, history of heparin, obesity, and concomitant use of contraceptives. The most common confounding factors in the confirmed reports were history of heparin use and malignancy. The dates of heparin administered were not reported in all cases.

Conclusion

Based on currently available data, no new safety information concerning TTS was identified. The current risk minimisation measures described in the product information are considered adequate.

From the data identified during the reporting period and also taking into account the cumulative experience, no updates to the VAXZEVRIA CDS or RMP are warranted at this time.

Thrombosis in combination with thrombocytopenia/TTS is contained in Section 4.4 (Special warnings and special precautions for use) and 4.8 in the VAXZEVRIA CDS. In addition, VAXZEVRIA is contraindicated (CDS Section 4.3) for use in any persons who have experienced thrombosis in combination with thrombocytopenia with any COVID-19 vaccine. Finally, thrombosis in combination with thrombocytopenia/ TTS is listed as an Important Identified Risk in the Core and EU RMPs for VAXZEVRIA. As such, the topic will continue to be kept under close safety surveillance by AstraZeneca and further actions will be taken as deemed appropriate.

More detailed information regarding this Important identified risk is provided in Section 16.4.1.1.

16.3.3 New information on other potential risks not categorised as important

The AESIs for VAXZEVRIA and associated PTs are listed in Appendix 7.

AESIs listed in Appendix 7 for VAXZEVRIA have been included for an O/E analyses for this PBRER and results are provided in Appendix 8 (O/E Analyses). Following an agreement with the MHRA, the frequency of the O/E analyses have been reduced from biweekly to 6-monthly aligned with PBRER.

The AESIs will continue to be kept under close surveillance by AstraZeneca.

16.3.4 New information on other identified risks not categorised as important

16.3.4.1 Reactogenicity

A cumulative search of the AstraZeneca Global Safety database through 28 June 2022 was conducted to identify serious, medically confirmed cases of reactogenicity with VAXZEVRIA (COVID-19 AstraZeneca Vaccine). The PTs used to define reactogenicity included: Headache, Nausea, Vomiting, Myalgia, Arthralgia, Injection site bruising, Injection site pain, Injection site pruritus, Injection site swelling, Injection site warmth, Injection site erythema, Fatigue, Malaise, Chills, Pyrexia, and Lymphadenopathy.

For the reporting period, a total of 79137 cases involving 218686 events of reactogenicity were identified from the Safety database. Of these 79137 cases, there were 2481 serious and medically confirmed initial cases of reactogenic events with VAXZEVRIA. Of the 2481 cases, 1549 (62.5%) occurred in females, 846 (34%) in males, and 86 (3.5%) were of unknown gender. The distribution of the reactogenic events in the reporting interval and cumulative is presented in Table 207.

Cumulatively, a total of 501840 cases of reactogenicity were identified from the global safety database. Of these 501840 cases, there were 13940 serious, medically confirmed cases of reactogenic events with VAXZEVRIA. Of the 13940 cases, 9663 (69%) occurred in females, 3998 (29%) in males, and 279 (2%) cases were of unknown gender. The distribution of the reactogenic events in the reporting interval and cumulative is presented in Table 207.

Table 207 Serious Medically confirmed reactogenicity events in the reporting interval and cumulative

Reactogenicity AEs (PT)	Reporting Interval count	Cumulative count
Pyrexia	1234	6655
Headache	1026	6498
Myalgia	591	2909
Fatigue	496	2734
Nausea	352	2456
Chills	344	2368
Malaise	313	1797
Arthralgia	270	1784
Vomiting	318	1777
Injection site pain	53	405
Lymphadenopathy	51	301
Injection site erythema	9	71

Table 207 Serious Medically confirmed reactogenicity events in the reporting interval and cumulative

Reactogenicity AEs (PT)	Reporting Interval count	Cumulative count
Injection site swelling	13	53
Injection site warmth	6	25
Injection site pruritus	0	11
Injection site bruising	1	4

AE Adverse event, Pt Preferred Term.

The commonly reported events of reactogenicity for both the interval period and cumulatively were pyrexia and headache, followed by myalgia, fatigue, nausea, and chills.

A review of the safety information identified during the reporting period, and also considering the cumulative experience, did not change the current understanding of this topic. Reactogenicity is considered appropriately described in the VAXZEVRIA CDS.

Conclusion

Data provided by the MAH, as well as found in literature, did not raise any new safety issue. The reactogenicity profile of VAXZEVRIA is considered as appropriately described in the product information at this stage.

16.3.4.2 Tinnitus

AstraZeneca received a signal in the preliminary assessment report from PRAC on VAXZEVRIA 2nd PBRER (28 June 2021 – 28 December 2021, to add tinnitus as ADRs to the EU label for VAXZEVRIA due to the number of reports identified with a temporal relationship (despite having risk/confounding factors). AstraZeneca further reviewed this topic, and this signal was internally validated on 20 May 2022.

A cumulative search of the AstraZeneca Global Patient Safety Database through 30 April 2022 was conducted for AE reports of Tinnitus in association with the use of VAXZEVRIA. The search term included PT Tinnitus. Please also refer to Section 15.2.1. for data until DLP for this report, according to request from PRAC.

In clinical studies, an imbalance between VAXZEVRIA and placebo is noted in the US study (D8110C00001), for tinnitus and VAXZEVRIA (28 [0.1%] versus 3 [<0.1%]); randomization ratio was 2:1). Out of the 28 events reporting Tinnitus in the AZD1222 arm, 10 reported having the event resolved within 7 days after event onset, 6 resolved after a longer time (8-78 days), 1 was resolving and 11 events had not yet resolved at the time of reporting.

An AZ Global Safety Database search retrieved 7442 cases reporting an AE of Tinnitus. A majority of the events were reported within 3 days (65%) and within 7 days (78%) after

vaccination (any dose). Of these, 12 reported a recurrence or worsening (interpreted as rechallenge), and of those, 9 cases reported a risk factor or a confounding factor. However, due to the recurrence and temporal relationship to both doses, causality with VAXZEVRIA cannot be excluded.

In regards the AE duration, 12.6% of 7442 cases reported outcomes of recovered or recovered with sequelae. Of those 84% of the cases recovered within 7 days and occurred within the reactogenicity period. Of note, 66.3% of the total number of cases report the event as "Not recovered", although, follow-up information is rarely provided. An O/E analysis showed that the observed events were significantly less than the expected events for all age, sex stratifications, and risk windows.

The medical/scientific literature review revealed one new case report with a temporal association with VAXZEVRIA, yet an alternative explanation for the event (glaucoma) was observed. With regard to mechanism of action for COVID-19 vaccines and tinnitus, the authors considered it undetermined and unconfirmed. Though, potential pathophysiological mechanisms discussed included molecular mimicry, autoimmune reaction, and anxiety-related reaction.

The quantitative signal searches from external databases (EVDAS and WHO VigiBase) for VAXZEVRIA -Tinnitus shows disproportionate reporting.

Conclusion

Based on the evaluation of currently available information from various sources, AstraZeneca considers that there is a reasonable possibility of a causal association between VAXZEVRIA and tinnitus. VAXZEVRIA CDS Section 4.8 (undesirable effects) is updated to include 'Tinnitus' during this reporting period (01 July 2022). A review of the safety information identified during the reporting period, and also taking into account the cumulative experience did not change the current understanding of this topic.

16.3.4.3 Hypoaesthesia and Paraesthesia

AstraZeneca received a signal from Therapeutic Goods Administration (TGA), Australia, to add hypoaesthesia and paraesthesia as ADRs to the local label for VAXZEVRIA as these were the most commonly reported adverse reactions reported to TGA for all COVID-19 vaccines, including VAXZEVRIA. AstraZeneca further reviewed this topic, and this signal was internally validated on 25 January 2022.

A search conducted in the AstraZeneca Clinical database for AE reports of Hypoaesthesia and Paraesthesia resulted in 15 (0.1%) case reports of hypoaesthesia in the AZD1222 group in comparison to 20 cases (0.1%) in the control group and 42 (0.3%) case reports of paraesthesia in the AZD1222 group in comparison to 51 cases (0.4%) in the control group from the Oxford

Pooled studies (COV001, COV002, COV003, and COV005). In the United States (US) study (D8110C00001) with a data cut-off date of 05 March 2021, there were 33 cases (0.2%) of hypoaesthesia in the AZD1222 group in comparison to 11 cases (0.1%) in the placebo group and 64 cases of paraesthesia (0.3%) in the AZD1222 group in comparison to 29 cases (0.3%) in the placebo group.

The medical/scientific literature review conducted to obtain information on literature articles about hypoaesthesia and paraesthesia identified 17 articles, which included 1 case report of hypoaesthesia and 20 case reports of paraesthesia after administration of VAXZEVRIA. Relevant underlying neurological disorders such as Guillain-Barre syndrome, acute disseminated encephalomyelitis, acute myelitis, polyradiculoneuropathy, lupus, and vaccine-induced immune thrombotic thrombocytopenia were associated with these cases. Hypoaesthesia and paraesthesia may be symptoms of these underlying disorders.

A cumulative search of the AstraZeneca Global Patient Safety Database through 12 December 2021 was conducted for AE reports of hypoaesthesia and paraesthesia in association with the use of VAXZEVRIA.

The search retrieved 10736 cases reporting an AE with a PT of hypoaesthesia, of which 2022 (18.8%) were medically confirmed reports of which 5322 (49.6%) reports were serious. Of the 10736 cases, hypoaesthesia was reported after Dose 1 in 6372 (59.4%) cases, after Dose 2 in 925 (8.6%) cases, after Dose 3 (booster dose) in 6 (< 0.1%) cases, after both Dose 1 and Dose 2 in 8 (< 0.1%) cases, and dose details were unknown in the remaining 3425 (31.9%) cases. Approximately 48% of the events had an outcome of recovered, recovered with sequelae, or were recovering. Of the 10736 cases of hypoaesthesia, there were 19 cases (9 medically confirmed and 10 consumer) with a fatal outcome. These cases with a fatal outcome had comorbidities or other co-reported events eg, cerebral infraction, acute myocardial infraction, brain stem haemorrhage, peripheral artery thrombosis, and pneumonia aspiration that led to a fatal outcome. These cases had limited information for further assessment. One case reported both hypoesthesia and paraesthesia.

Of the 10736 cases of hypoaesthesia,1019 (9.5%) reported hypoaesthesia as a solo event, of which 281 (27.6%) were medically confirmed reports and 243 (23.8%) were reported as serious. Of the 1019 cases, 281 were medically confirmed. Of the 281 medically confirmed cases, 255 had limited information which precluded a proper case assessment, and the remaining 26 included confounding medical history and/or confounding concomitant medications. Confounding medications included allopurinol, amitriptyline, amlodipine, atorvastatin, azithromycin, candesartan, clonazepam, digoxin, doxycycline, eplerenone, esomeprazole, estradiol, fluticasone, fluoxetine hydrochloride, itraconazole, lansoprazole, levocetirizine, pantoprazole, quetiapine, mirtazapine, montelukast, omeprazole, salbutamol, sertraline, telmisartan, venlafaxine, and zolpidem. Confounding medical history included

diabetes, osteoarthritis, smoking, transient ischemic attack, hypoaesthesia, and brainstem cavernoma.

A cumulative search of the AstraZeneca Global Patient Safety Database conducted for AE reports of paraesthesia retrieved 17721 cases reporting an AE with a PT of paraesthesia, of which 2785 (15.7%) were medically confirmed reports and 7642 (43.1%) reports were serious. Of the 17721 cases, paraesthesia was reported after Dose 1 in 10251 (57.8%) cases, after Dose 2 in 1607 (9.1%) cases, after Dose 3 (booster dose) in 9 (< 0.1%) cases, after both Dose 1 and Dose 2 in 7 (< 0.1%) cases, and dose details were unknown in the remaining 5847 (32.9%) cases. The TTO from the most recent dose ranged from the same day of vaccination in 5377 (30.3%) cases, 1 to 3 days in 4465 (25.2%) cases, 4 to 7 days in 1175 (6.6%) cases, 8 to 15 days in 883 (5.0%) cases, >15 days in 907 (5.1%) cases, and TTO was unknown or not reported in the remaining 4914 (27.7%) cases. Approximately 45% of the events had an outcome of recovered, recovered with sequelae, or were recovering. Of the 17721 cases of paraesthesia, there were 9 cases (4 medically confirmed and 5 consumer) with a fatal outcome. These cases with a fatal outcome had comorbidities or other co-reported events eg, cardia arrest, ischaemic stroke, and agonal death struggle that led to a fatal outcome. These cases had limited information for further assessment. One case reported both hypoesthesia and paraesthesia.

Of the 17721 cases of paraesthesia, 2030 (11.5%) reported paraesthesia as a solo event, of which 406 (20.0%) were medically confirmed reports and 393 (19.4%) were serious events. Of the 2030 cases, 406 were medically confirmed of which 355 had limited information which precluded a proper case assessment, and the remaining 51 cases included confounding medical history and/or confounding concomitant medications. Confounding medications included amiodarone, allopurinol, amitriptyline, amlodipine, atorvastatin, estradiol, and salbutamol. Confounding medical history included diabetes, carpal tunnel syndrome, anxiety, chronic kidney disease, influenza virus vaccine, smoking, hypothyroidism, transient ischemic attack, neuropathy, alcohol use disorder, Arnold-Chiari syndrome, stroke, multiple sclerosis, Raynaud's syndrome, and unspecified cerebrovascular disease.

The data from the clinical studies and literature was not indicative of a causal relationship. However, of the 6861 (63.9%) hypoaesthesia cases and 11324 (63.9%) paraesthesia cases that were reported with reactogenicity events, 2482 (36.2%) hypoaesthesia cases and 3719 (32.8%) paraesthesia cases, respectively, were reported on the same day of vaccination. The comparatively high number of reports with a plausible temporal relationship between the vaccination and the occurrence of the reported events, together with the lack of alternative explanations, was suggestive of a causal association between VAXZEVRIA (AZD1222) and the events of hypoaesthesia and paraesthesia appearing concurrently with other reactogenicity events.

During the period covered by this PBRER, the Core Data Sheet (CDS) for AZD1222 is amended with 'Hypoaesthesia' and 'Paraesthesia' in Section 4.8 (undesirable effects).

Conclusion:

Based on the evaluation of currently available information from all available sources, with particular focus on post-market data, AstraZeneca considers that there is a reasonable possibility of a causal association between VAXZEVRIA and hypoaesthesia and paraesthesia. Many of these events were co-reported with reactogenicity events. The information regarding hypoaesthesia and paraesthesia were added to the CDS and the company will continue to conduct routine pharmacovigilance activities on this safety topic. Hypoaesthesia and Paraesthesia are considered appropriately described in the VAXZEVRIA CDS (Section 4.8). A review of the safety information identified during the reporting period, and also taking into account the cumulative experience did not change the current understanding of this topic.

16.3.5 Update on missing information

No new information relevant to the previously recognised missing information, included in Section 16.1, has been identified during the reporting period. All safety concerns included in this category will continue to be considered missing information. Further information regarding missing information is provided in Section 16.4.3.

16.3.5.1 Use of AZD1222 in pregnant and breastfeeding women

16.3.5.1.1 Use of AZD1222 in pregnant women

Review of Cases

Reports of pregnancy were retrieved from the AstraZeneca Global Safety database using VAXZEVRIA and the AstraZeneca customized 'PSUR pregnancy' business objects report which includes the following search criteria:

The field Pregnant is marked as YES or Events code to one of the Medical Dictionary for Regulatory Activities (MedDRA) (Version 25.0) System Organ Classes (SOCs): Congenital, familial and genetic disorders, Pregnancy, puerperium and perinatal conditions or Events code to the MedDRA High-level Group Term: Foetal and neonatal investigations or Events code to one of the MedDRA High-level Terms: Induced abortion complications, Induced abortions or Events code to one of the MedDRA Preferred Terms (PTs): Aborted pregnancy, Amastia, Amnioscopy, Amnioscopy abnormal, Amnioscopy normal, Ectopic pregnancy termination, External cephalic version, Pregnancy of partner, Pregnancy test positive, Pregnancy test urine positive, Hyperplasia adrenal and Macroorchidism. Cases describing Pregnancy with adverse neonatal outcomes are included below.

Interval Review (29 December 2021 – 28 June 2022)

During the reporting period, 1527 case reports were retrieved using the above search strategy; however, 124 case reports were excluded since these cases were non-valid (duplicate cases or invalid cases). The remaining 1403 (969 initial and 434 follow-up reports) cases were considered for further analysis. Of the 1403 reports, 1096 reports included pregnancy/breastfeeding reports with other co-reported AEs and 307 reports were without other AEs.

Of the 1403 reports of exposure to VAXZEVRIA during or before pregnancy/breastfeeding, 13 were from interventional clinical trials, 417 were from post-marketing studies, and 973 were spontaneous. Of these 1403 reports, 502 were medically confirmed (174 serious and 328 non-serious).

Outcome of pregnancy cases are summarized below:

Of the total 1403 case reports, there were 131 cases of spontaneous abortion (SAB), 3 cases of abortion missed, 42 case reports with abnormal neonatal outcome, 4 case reports of stillbirth, 29 case reports of premature babies, 10 case reports of foetal death, 5 case reports of sudden infant death syndrome, 13 case reports with breech presentation, and 3 case reports of ectopic pregnancy. Pregnancy outcome was not available for the majority of cases.

Cumulative Review (through 28 June 2022)

Cumulatively through 28 June 2022, 5575 case reports were retrieved using the above search criteria; however, 207 case reports were excluded since these cases were non-valid (duplicate cases or invalid cases).

The remaining 5322 cases were considered for further analysis. Of the 5322 reports, 4698 reports included pregnancy/breastfeeding reports with other AEs and 624 reports were without AEs.

Of the 5322 reports of exposure to VAXZEVRIA during or before pregnancy/breastfeeding, 28 were from interventional clinical trials, 769 were from post-marketing studies, and 4525 were spontaneous. Of these 5322 reports, 1051 were medically confirmed (377 serious and 674 non-serious).

Spontaneous Abortion – Interval Review

A total of 131 pregnancy cases resulted in spontaneous abortion, of which 83% (109 out of 131) were reports from consumers and 17% (22 out of 131) of the reports were medically confirmed, with 71% of the reports being from the UK. Age was reported in 107 of the 131 case reports; median age was 34 years (range: from 19 to 43 years; 6 reports in women aged < 25 years, 61 reports in women aged 26 to 35 years, and 40 reports were in women aged > 36 years). There was one case of a 59-year-old female that was miscoded to include an event of

Abortion spontaneous. In 92 of the 131 reports, gestational week at the time spontaneous abortion was unknown; in the remaining 39 reports, 34 (87.2%) occurred in the 1st trimester, 5 (12.8%) were during the 2nd trimester, and none were during the 3rd trimester. In 124 of the 131 reports, gestational age at the time of exposure was unknown; in the remaining 7 reports, 6 (85.7%) were exposed in the 1st trimester, 1 (14.3%) was exposed during the 2nd trimester, and none were exposed during the 3rd trimester.

Spontaneous Abortion – Cumulative Review

A total of 386 pregnancy cases resulted in spontaneous abortion. A total of 83% (321 out of 386) were reports from consumers and 17% of the reports were medically confirmed, with 71% of the reports being from the UK. Age was reported in 334 of the 386 case reports; median age was 34 years (range: from 19 to 50 years; 28 reports in women aged < 25 years, 169 reports in women aged 26 to 35 years, and 137 reports were in women aged > 36 years). In 204 of the 386 reports, gestational week at the time spontaneous abortion was unknown; in the remaining 182 reports, 166 (91.2%) occurred in the 1st trimester, 14 (7.7%) were during the 2nd trimester, and 2 (1.1%) were during the 3rd trimester. In 326 of the 386 reports, gestational age at the time of exposure was unknown; in the remaining 60 reports, 52 (86.7%) were exposed in the 1st trimester, 8 (13.3%) were exposed during the 2nd trimester, and none were exposed during the 3rd trimester.

Observed Vs. Expected Analysis – Spontaneous abortion

The incidence rates for spontaneous abortions were calculated based on the reported rates by Hemminki and Forssas 1999 data on conceptions among women in England and Wales, 2018 from the UK Office of National Statistics (Conceptions in England and Wales 2018) to estimate the rates of spontaneous abortions per 100,000 women years.

Vaccine administration data based on the age and gender is only available from UK and the below analysis was based on case reports from UK. The observed versus expected analysis of spontaneous abortions with DLP 28 June 2022 showed that observed cases occurred significantly less frequently than expected for overall and for different age stratifications from UK. A summary of spontaneous abortion observed versus expected analysis is presented in Table 208.

Conservatively, the exposure for global reports (448306152) is based on doses administered in 13 markets as explained in Appendix 8.

Table 208 Spontaneous Abortion Observed Versus Expected Analysis (UK cases only)

Age group (years)	IR/100,000 PY	Risk Window	Exposure from UK	Observed Cases	Expected Cases	Ratio	Interpretation
18 to 24	1780.8	60	564993	3	1652.83	0 (0 - 0.01)	Observed significantly < expected
25 to 29	1437.5	60	656585	19	1550.49	0.01 (0.01 - 0.02)	Observed significantly < expected
30 to 34	1447	60	907770	37	2157.82	0.02 (0.01 - 0.02)	Observed significantly < expected
35 to 39	864.6	60	1120852	45	1591.96	0.03 (0.02 - 0.04)	Observed significantly < expected
40 to 44	223.3	60	2225276	25	816.29	0.03 (0.02 - 0.05)	Observed significantly < expected
18 to 24 plus Unk TTO	1780.8	60	564993	9	1652.83	0.01 (0 - 0.01)	Observed significantly < expected
25 to 29 plus Unk TTO	1437.5	60	656585	25	1550.49	0.02 (0.01 - 0.02)	Observed significantly < expected
30 to 34 plus Unk TTO	1447	60	907770	62	2157.82	0.03 (0.02 - 0.04)	Observed significantly < expected
35 to 39 60 plus Unk TTO	864.6	60	1120852	71	1591.96	0.04 (0.03 - 0.06)	Observed significantly < expected
40 to 44 60 plus Unk TTO	223.3	60	2225276	35	816.29	0.04 (0.03 - 0.06)	Observed significantly < expected
All ages	995.3	60	8004481	147	13087.51	0.01 (0.01 - 0.01)	Observed significantly < expected

Table 208 Spontaneous Abortion Observed Versus Expected Analysis (UK cases only)

Age group (years)	IR/100,000 PY	Risk Window	Exposure from UK	Observed Cases	Expected Cases	Ratio	Interpretation
All ages plus Unk TTO	995.3	60	8004481	246	13087.51	0.02 (0.02 - 0.02)	Observed significantly < expected

IR, Incidence Rate; PY, Person Years; TTO, Time to onset; UK, United Kingdom; Unk, Unknown.

For the observed versus expected analysis of Gestational diabetes, please see Appendix 8.

Conclusion

From the data identified during the reporting period, and also taking into account the cumulative experience, no causal relationship could be established between Abortion spontaneous and VAXZEVRIA. Pregnancy and Abortion spontaneous will continue to be kept under close surveillance by AstraZeneca.

Adverse Maternal Outcomes – Interval Review

Maternal outcomes that are part of the AE of special interest concept of "Pregnancy outcome – maternal" (as presented in the risk management plan) are shown in Table 209.

Table 209 Adverse Maternal Outcomes – Interval period

PT	Event count
Gestational diabetes	17
Pre-eclampsia	8
Placenta praevia	4
Eclampsia	3
Caesarean section	2
Premature labour	2
Uterine rupture	2
Amniotic cavity infection	1
Grand Total	39

PT Preferred Term.

Risk factor identified in these case are described under the cumulative summary.

Adverse Maternal outcomes – Cumulative Review

Maternal outcomes that are part of the AE of special interest concept of "Pregnancy outcome – maternal" (as presented in the risk management plan) are shown in Table 210.

Table 210 Adverse Maternal Outcomes – Cumulative period

PT	Event count
Gestational diabetes	30
Pre-eclampsia	16
Premature labour	8
Caesarean section	7
Placenta praevia	6
Eclampsia	5
Uterine rupture	3
Amniotic cavity infection	1
Grand Total	76

PT preferred Term.

The most common relevant risk factors reported in the cases included previous history of gestational diabetes, increased body mass index (BMI), hypertension, tobacco use, substance and alcohol use, multigravida, diabetes, history of spontaneous abortion and stillbirth, factor V Leiden mutation, previous "high risk pregnancy", history of kidney disease, Fabry's disease. No safety concern was identified from review of these reported PTs.

Conclusion

From the data identified during the reporting period, and also taking into account the cumulative experience, no causal relationship could be established between adverse maternal outcomes and VAXZEVRIA. Pregnancy and adverse maternal outcomes will continue to be kept under close surveillance by AstraZeneca.

Co-reported Adverse Events in the Pregnancy Cases - Interval Review

Of the 1403 pregnancy cases, 1096 cases had reported AEs in both mothers and infants. Most of the AEs reported in these cases were known reactogenicity events (Headache, Pyrexia, Fatigue, Chills, Myalgia, Nausea, Pain in extremity and Arthralgia). There were 82 cases with 218 AEs that occurred in the pediatric population, with the top 3 AEs being: Foetal exposure during pregnancy (50), Exposure via breast milk (22), and COVID-19 (10). There was no trend or signal observed from these AEs reported from the pregnancy cases.

Other co-reported Adverse Events in the Pregnancy Cases – Cumulative Review

Of the 5322 cases, 4698 cases had reported AEs. Most of the AEs reported in these cases were known reactogenicity events (Headache, Pyrexia, Fatigue, Chills, Myalgia, Nausea, Pain in extremity and Arthralgia). There are 280 cases with 503 AEs that occurred in the pediatric population, with the top 3 AEs being: Exposure via breast milk (170), Foetal exposure during pregnancy (63), and Maternal exposure during breast feeding (33). There was no trend or signal seen from these AEs reported from the pregnancy cases.

Abnormal Neonatal Outcomes – Cumulative and Interval Review

In order to appropriately assess all cases reported to the company with any congenital anomaly or adverse neonatal outcome, a search cumulatively and during the reporting period of this PBRER was done with the following MedDRA (version 25.0) PTs: " Congenital musculoskeletal disorder of limbs; Congenital musculoskeletal disorder of skull; Congenital musculoskeletal disorder of spine; Congenital female genital tract fistula; Oculo-digito-oesophageal-duodenal syndrome; Congenital musculoskeletal disorder of head and neck; Macrophthalmos; Congenital female reproductive tract disorder; Congenital musculoskeletal disorder; Congenital laryngeal malformation; Athelia; Congenital vocal cord paralysis; Congenital subglottic stenosis; Congenital vena cava stenosis; Aphallia; Congenital connective tissue disorder; Congenital musculoskeletal disorder of trunk; Congenital anisocoria; Congenital lip pits; Pleural malformation; Arhinencephaly; Acrocephalosyndactyly; Amniotic band syndrome; Anencephaly; Annular pancreas; Anomalous pulmonary venous connection; Anophthalmos; Anorectal malformation; Anotia; Aorticopulmonary septal defect; Arnold-Chiari malformation; Arteriovenous malformation; Atrial septal defect; Atrioventricular septal defect; Auditory neuropathy spectrum disorder; Brain malformation; Breast malformation; Cardiac septal defect; Cataract congenital; Cerebral arteriovenous malformation haemorrhagic; Cerebral cavernous malformation; Cerebrovascular arteriovenous malformation; Choanal atresia; Cleft lip; Cleft lip and palate; Cleft palate; Cloacal exstrophy; Coarctation of the aorta; Congenital absence of bile ducts; Congenital aortic valve stenosis; Congenital arterial malformation; Congenital cerebral haemangioma; Congenital coronary artery malformation; Congenital cystic kidney disease; Congenital diaphragmatic hernia; Congenital ectopic bladder; Congenital eye disorder; Congenital eyelid malformation; Congenital foot malformation; Congenital genital malformation; Congenital genital malformation female; Congenital genital malformation male; Congenital hand malformation; Congenital hearing disorder; Congenital heart valve disorder; Congenital heart valve incompetence; Congenital hydrocephalus; Congenital hydronephrosis; Congenital intestinal malformation; Congenital jaw malformation; Congenital joint malformation; Congenital large intestinal atresia; Congenital lymphoedema; Congenital megacolon; Congenital mitral valve incompetence; Congenital mitral valve stenosis; Congenital nose malformation; Congenital oesophageal stenosis; Congenital oral malformation; Congenital pulmonary artery anomaly; Congenital pulmonary valve atresia; Congenital rubella infection; Congenital rubella syndrome; Congenital skin disorder;

Congenital small intestinal atresia; Congenital syphilis; Congenital tricuspid valve atresia; Congenital vesicoureteric reflux; Conjoined twins; Constricted ear deformity; Craniorachischisis; Craniosynostosis; Cryptorchism; Cystic lymphangioma; Deaf mutism; Deafness congenital; Death neonatal; Developmental glaucoma; Developmental hip dysplasia; Double outlet right ventricle; Duodenal atresia; Dysmorphism; Ear malformation; Ebstein's anomaly; Encephalocele; Epispadias; Exomphalos; Fallot's tetralogy; Foetal alcohol syndrome; Foetal anticonvulsant syndrome; Foetal distress syndrome; Foetal growth restriction; Foetal malformation; Gastrointestinal arteriovenous malformation; Gastrointestinal malformation; Gastroschisis; Genitalia external ambiguous; Haemangioma congenital; Haemangioma of retina; Haemorrhagic arteriovenous malformation; Hepatic arteriovenous malformation; Heterotaxia; Holoprosencephaly; Hydrops foetalis; Hypoplastic left heart syndrome; Hypoplastic right heart syndrome; Hypospadias; Iniencephaly; Interruption of aortic arch; Intestinal atresia; Kidney malformation; Limb reduction defect; Lissencephaly; Low birth weight baby; Malformation biliary; Malformation venous; Microcephaly; Microencephaly; Microphthalmos; Microtia; Mitral valve atresia; Mitral valve hypoplasia; Multiple gastrointestinal atresias; Neural tube defect; Oesophageal atresia; Parachute mitral valve; Patent ductus arteriosus; Polydactyly; Porencephaly; Premature baby; Pulmonary aplasia; Pulmonary artery atresia; Pulmonary artery stenosis congenital; Pulmonary malformation; Pulmonary valve stenosis congenital; Pyloric stenosis; Rectal atresia; Renal aplasia; Renal arteriovenous malformation; Renal dysplasia; Renal failure neonatal; Renal hypoplasia; Respiratory tract malformation; Retinal arteriovenous malformation; Schizencephaly; Skeletal dysplasia; Skin malformation; Spina bifida; Spina bifida cystica; Spina bifida occulta; Spleen malformation; Stillbirth; Syndactyly; Talipes; Thyroid malformation; Tracheo-oesophageal fistula; Transposition of the great vessels; Truncus arteriosus persistent; Umbilical malformation; Univentricular heart; Urethral valves; Urinary tract malformation; VACTERL syndrome; Vascular malformation; Vein of Galen aneurysmal malformation; Venolymphatic malformation; Ventricular septal defect; Vallecular cyst; Foetal vascular malperfusion."

Cumulatively, 125 cases reporting any PTs (outlined above) from the concept of Pregnancy outcomes-Neonates were reported since launch until the DLP of this PBRER. Upon further review, 70 of these cases were acquired conditions and/or presented in elderly age or adults and not congenital malformations and hence not included for further review.

During the reporting period of this PBRER until 28 June 2022, 61 cases were reported among this concept of pregnancy outcomes - Neonates, upon further review 42 cases (containing 52 neonatal outcome events) were reported among neonatal age or were linked to a neonate or a pregnancy product, therefore included in this section. Among these, there were prematurity (14), foetal growth restriction (8), foetal distress syndrome (1), low birth weight baby (4), still birth (4), foetal vascular malperfusion (3), anencephaly (1), atrial septal defect (1), cleft lip (1), cleft palate (1), cleft lip and palate (1), Congenital cystic kidney disease, (1), Congenital

hydronephrosis (1), cryptorchism (1), Developmental hip dysplasia (1), Foetal malformation (2), Heterotaxia (1), hypospadias (1), Neural tube defect (1), Talipes (2), Transposition of great vessels (1), ventricular septal defect (1). Some cases of these section may be described in section regarding Use of VAXZEVRIA in pregnant women (Section 16.3.5.1.1). The cases reported during this interval are described below:

Review of the 42 cases with adverse neonatal outcomes received during the reporting period did not highlight any new significant safety concern. The majority of cases were either confounded or contained limited information to ascribe a causal relationship to VAXZEVRIA.

Case IDs for these 42 cases are:

[redacted]

AstraZeneca comment: Due to some confounders in maternal history (including but not limited to history of multiple miscarriages, eclampsia, tobacco, alcohol and recreational drug use) and limited information on complete demographics of vaccinee, baseline health condition before vaccination, relevant medical history, obstetric history, relevant family history, concurrent diseases, concomitant medications, details of the event, further circumstances surrounding the event, outcome of the event, further risk factors (such as chromosomal abnormalities, cerebral anoxia, severe maternal malnutrition and chronic conditions, smoking, alcohol and drugs exposure, maternal infections such as toxoplasmosis, cytomegalovirus, rubella, varicella and zika virus), genetic factors, other congenital abnormalities such as spina bifida, smoking during pregnancy, oligohydramnios) and detailed diagnostic and etiologic workup (physical examination, neurological, genetics testing, imaging studies such as Ultrasound and X-ray), the evaluation did not find evidence to suggest a causal relationship between all neonatal outcomes and VAXZEVRIA.

Conclusion

From the data identified during the reporting period, and also taking into account the cumulative experience, no causal relationship could be established between these events reported in neonates and VAXZEVRIA. Pregnancy and neonatal outcomes continue to be kept under close surveillance by AstraZeneca.

Literature Review - Pregnancy

Qiao et al 2021 presented the analysis an observational cross-sectional study using data from the Brazilian surveillance information system for adverse events (SI-EAPV) to characterize the safety of COVID-19 vaccines available (CoronaVac /Butantan, Pfizer/BioNTech, AstraZeneca and Janssen) in Brazilian pregnant and postpartum women after vaccination from April to August 2021. A total of 803563 doses were received, of which 65435 were the AstraZeneca vaccine. A total of 3,333 adverse events following COVID-19 immunization were reported for the study population in the SIEAPV. The incidence of AEs found was 309.4/100,000 doses (95% CI 297.23, 321.51). Of those, 473 were from women who received CoronaVac /Butantan, 788 Pfizer/BioNTech, 2,016 AstraZeneca and 56 Janssen vaccines. The most common maternal AE notified by pregnant and postpartum women included spontaneous abortion (2.37%) pregnancy bleeding (0.76%) and neonatal death (0.52%). Among the non-maternal AE, headache (18.54%), fever (13.79%), myalgia (10.30%) and pain (7.60%) were the most reported. The authors concluded that a similar pattern of AE as stated in other studies was found, with even better results for non-viral vector vaccines, corroborating to the recommendation of vaccination for these groups.

AstraZeneca comment: The study found that AEs were similar to those from the available literature for other studies that assessed safety of COVID-19 vaccines in different populations groups.

Summary

In summary, the cumulative and periodic review up until 28 June 2022 of all reports of exposure to VAXZEVRIA during pregnancy did not identify any new safety concerns for the mother or the babies. The reported adverse events are similar between the pregnant and non-pregnant populations.

The results of the O/E analyses for spontaneous abortion (UK reports) suggest that observed cases are less than would be expected in the unvaccinated pregnant women.

Conclusion

Based on these interval and cumulative reviews of the currently available data, it is AstraZeneca's opinion that no updates to product labelling or RMP are warranted. Use of VAXZEVRIA during pregnancy remains as Missing information for the product and is closely monitored.

16.3.5.1.2 Use of AZD1222 in Breastfeeding women

Breastfeeding cases were retrieved from the AstraZeneca customized 'PSUR pregnancy' business objects report by filtering for breastfeeding related PTs (Exposure via breast milk, Maternal exposure during breast feeding).

Interval Period (29 December 2021 – 28 June 2022)

During the interval period, there were 32 reports pertaining to infant exposure to VAXZEVRIA during breastfeeding. Overall, 3 cases were serious (of which 1 was medically confirmed). Within these 32 reports, (3 serious, 29 non-serious) reported 68 events in infants following breastfeeding. Of these 68 events, 9 were serious adverse events. Events occurring with a frequency of 2 or more in paediatric cases are shown in Table 211. No safety concern was identified.

Table 211 Adverse Events in Infants Following Breastfeeding (with a Frequency of ≥ 2 in Paediatric Cases)

Preferred Term	Non-serious	Serious	Total
Pyrexia	12	1	13
Diarrhoea	4	0	4
Chills	2	0	2
Influenza	2	0	2

There were no fatal cases reported within the infant lactation cases. Outcomes of these 32 cases were: Unknown (18), Recovered (7), Not recovered (5), and Recovering (2).

In the interval review of reports of VAXZEVRIA exposure during breastfeeding in the AstraZeneca Global Safety Database, there was limited information to suggest any reasonable association between exposure to VAXZEVRIA via breastfeeding and adverse outcomes in the neonates.

No safety relevant literature relating to VAXZEVRIA and breastfeeding was identified during the reporting period.

Cumulative Review (29 December 2020 – 28 June 2022)

Cumulatively through 28 June 2022, there were 247 reports pertaining to infant exposure to VAXZEVRIA during breastfeeding. Overall, 118 cases were serious (of which 10 were medically confirmed). Within these 247 reports, 247 cases (118 serious, 129 non-serious) reported 764 events in infants following breastfeeding. Of these 764 events, 327 were serious adverse events. No safety concern was identified.

The section 4.6 of the CDS for VAXZEVRIA includes the following text on breastfeeding:

Anti-SARS-CoV-2 S antibodies are excreted in breast milk of mothers vaccinated with VAXZEVRIA. In animal studies, lactational transfer of anti-SARS-CoV-2 S antibodies from maternal female mice to pups was observed. It is unknown whether the vaccine itself is excreted in human milk.

In animal studies no quantifiable levels of the vaccine were detected in the mammary gland in female mice.

Available non-clinical, clinical and post-marketing data do not suggest a risk to breastfed newborns/infants.

Conclusion

From the data identified during the reporting period, and also taking into account the cumulative experience, there is no new safety information or a safety concern identified with the exposure to VAXZEVRIA during pregnancy or breast feeding. Use of VAXZEVRIA in pregnant and breastfeeding women / Use during pregnancy and while breastfeeding will continue to be considered missing information for VAXZEVRIA.

Use of VAXZEVRIA in pregnant and breastfeeding women / Use during pregnancy and while breastfeeding will be primarily investigated in the ongoing non-interventional pregnancy registry study (D8110C00003) of women exposed to VAXZEVRIA immediately before or during pregnancy as part of the C-VIPER Registry Consortium. Refer to Appendix 4 for additional details.

More detailed information is provided in Section 16.4.3.1.

16.3.5.2 Use of AZD1222 in subjects with severe immunodeficiency

Vaccines may be less effective in severely immunocompromised individuals, as the vaccinees weakened immune system may not mount a sufficient response. Additionally, immunocompromised individuals may also be at a greater risk of morbidity and mortality from vaccine-preventable disease, and consequently this population has been identified as a priority group for initial vaccination in several jurisdictions. Although there is no evidence that the safety profile of VAXZEVRIA in this population will be different than that of the general population, given the paucity of data, the possibility cannot be excluded.

Review of Cases

A cumulative and interval search of the AstraZeneca Global Safety Database was undertaken for AE reports received for VAXZEVRIA in subjects with medical history of severe immunodeficiency and in immunocompromised patients, using MedDRA High Level Term: Immune and associated conditions NEC.

Interval Period (29 December 2021– 28 June 2022)

For the period covered by this report, a total of 936 cases were identified from all sources using the above-mentioned search strategy, including 80.98% spontaneous cases, 17.2% non-interventional/ post-marketing cases and 1.82% literature cases.

Of the 936 cases, 72.82% were reported in females and 25% were in males. Gender was not reported in the remaining 2.18% of cases. Age ranged from 0 to <18 years in <1% (2 cases), 18 years to <65 years in 67.63% (633 cases) and 65+ years in 24.79% (232 cases). Age was not reported in the remaining 7.37% (69) cases. The majority of reports 777 (83.01%) were not medically confirmed with the remaining 159 (16.99%) being consumer reports.

Of these 936 cases, 423 (45.19%) were considered serious, and the reported seriousness criteria were medially important (319), disability (102), hospitalization (111), life threatening (48) and/or death (22). Cases may have met more than one criterion for seriousness. The remaining 513 (54.81%) reports were non-serious.

Of these 936 cases, 156 reported Covid-19 and 83 were considered serious and 2 were medically confirmed.

The top 20 reported PTs were Headache (342), Fatigue (338), COVID-19 (314), Chills (284), Dizziness (276), Pyrexia (231), Pain in extremity (193), Dyspnoea (146), Arthralgia (134), Chest pain (129), Myalgia (118), Pain (114), Paraesthesia (102), Migraine (88), Nausea (87), Psoriasis (82), Injection site pain (74), Syncope (69), Malaise (68) and Contusion (64).

Information on time to AE onset from vaccination with VAXZEVRIA was available for 792 events (68%) of the 936 cases, of which 433 events (38.45%) occurred within one day of vaccination, 126 events (11.2%) occurred between 2- 15 days post-vaccination, 174 events (15.45%) occurred between 16-200 days postvaccination, 59 events (5.23%) occurred >200 days after vaccination and for the remaining 334 events (29.67%) the time from vaccination to AE onset was unknown.

Outcome was reported for 841 cases (89.85%) of the total 936 cases, with 295 (31.51%) reported as Recovered, 120 (12.82%) as Recovering, 379 (40.5%) Not recovered, 25 events (2.67%) as Recovered with sequelae and unknown for 95 (10.15%) of reports. The outcome was fatal in 38 (<1%) of the total case count.

There were 22 deaths (2.4%) out of 936 cases reported during this period. Age of the 22 vaccinees with a fatal outcome ranged from 18 to 86 years with a median of 66 years. The reported PTs with a fatal outcome in the 38 cases in order of frequency (>6) were Thrombosis with thrombocytopenia syndrome (16), Cyanosis (16), Dyspnoea (14), Acute respiratory distress syndrome (12), Gangrene (12), Vasculitis (12), Psoriasis (10), Psoriatic arthropathy (12), Cerebrovascular accident (8), Decreased appetite (8), Intestinal ischaemia (8), Mesenteric artery stenosis (8), Myeloproliferative neoplasm (8), Renal ischaemia (8), Skin ulcer (8) and Uterine haemorrhage (8).

There were 5 cases were a fatal event occurred after 1st and 3 cases after 2nd dose of VAXZEVRIA. In 8 cases dose 1 and dose 2 were reported. In 1 case booster dose was reported. The dose was unknown in 5 cases.

Cumulative period (29 December 2020 – 28 June 2022)

The search of the AstraZeneca Global Safety database identified a cumulative total of 14928 cases from all sources, reported in subjects with severe immunodeficiency and in immunocompromised patients in association with VAXZEVRIA including 92.2% spontaneous cases, 7.5% non-interventional/post-marketing cases and 0.3% literature.

Of the 14928 cases, 72.83% were reported in females, 24.46% were in males and gender was not reported in the remaining 2.71% of cases. Age ranged from 0 to 18 years in 45 cases (0.3%), between 18 years to <65 years in 11477 (76.9%) of the reports, 65+ Years in 2325 (15.57%), and 65 were reported in adult, elderly and infants (0.43%) age was not specified. Age was not reported in the remaining 6.8% (1016) of cases.

The majority of reports (88.46%) were not medically confirmed with the remaining 11.54% being consumer reports.

Of these 14928 cases, 9875 (66.15%) were considered serious and the reported seriousness criteria were medially important (8463), disability (1507), hospitalization (1109), life threatening (382) and in death (120). Cases may have met more than one criterion for seriousness. The remaining 5053 (33.85%) reports were non-serious.

Of these 14928 cases, 249 reported Covid-19 and 177 were considered serious and 24 medically confirmed.

The top 20 reported PTs were Headache (6089), Pyrexia (4652), Fatigue (4531), Chills (3214), Nausea (2395), Myalgia (2326), Arthralgia (2140), Pain in extremity (1895), Dizziness (1738), Malaise (1368), Pain (1350), Influenza like illness (862), Diarrhoea (851), Vomiting (848), Dyspnoea (842), Pruritus (731), Hyperhidrosis (653), Rash (649), Migraine (647) and Tremor (644).

Information on time to AE onset from vaccination was available for 13342 events of the 16345 events, with most 9361(50.48%) occurred within one day of vaccination, 2480 (15.17%) occurred within 2-15 days post-vaccination, 2480 events (8.08%) occurred between 16-200 days post-vaccination, 180 events (1.10%) occurred >200 days after vaccination and for 3003 (18.37%) reports time from vaccination to AE onset was unknown.

Outcome was available for 96.43% of the 14928 cases, with 3433 (22.99%) reported as Recovered, 2973 (19.91%) as Recovering, 7565 (50.7%) Not recovered, 303 (2.03%) as

Recovered with sequelae and unknown in 534 (3.57%) of reports. The outcome was fatal in 120 (0.8%) of the total case count.

Cumulatively there were 120 deaths out of 14928 case reports. Age of the 88 vaccinees with a fatal outcome ranged from 18 to 96 with a median of 66 years. The reported PTs with a fatal outcome in the 88 cases in order of frequency (>7) Death (26), Headache (23), Dyspnoea (20), Immune thrombocytopenia (16), Thrombocytopenia (16), Cardiac arrest (15), Malaise (14), Cerebrovascular accident (12), Circulatory collapse (12), COVID-19 (11), Myocardial infarction (11), Cerebral venous sinus thrombosis (10), Photophobia (10), Pneumonia (10), Cerebral haemorrhage (9), Hemiplegia (9), Seizure (9), Vomiting (9), Aphasia (8), Fatigue (8), Multiple organ dysfunction syndrome (8), Pulmonary embolism (8), Thrombosis (8).There were 53 cases were a fatal event occurred after 1st and in 14 cases – after 2nd dose. In 13 cases both doses were reported. In 1 case booster dose was reported. The dose was unknown in the 38 cases.

Review of Cases from Literature: 44 cases were received from the literature. For VAXZEVRIA in subjects with severe immunodeficiency and in immunocompromised patients. Of these 44 cases (31 medically confirmed and 13 non-medically confirmed), 33 were serious and 111 were non-serious. Of these 44 cases, 21 were reported in female 21 were reported in male and not reported in 2 cases. The reported PTs in order of frequency (>6) Interchange of vaccine products (12), Off label use (12), Immune thrombocytopenia (11), Vaccination failure (8) and Psoriasis (7)

Review of Literature

A search of Embase and InsightMeme was conducted to identify literature articles on "Immune and associated conditions" disease' following the use of VAXZEVRIA. The search identified 15 articles, out of which 5 literature articles were found to be relevant to the topic and have been discussed here in detail.

Benning et. al 2022 studied antibody response post vaccination in impaired kidney transplant recipients. They concluded that seroconverted kidney transplant recipients show impaired neutralization against emerging variants of concern after standard two-dose vaccination. After first vaccination with an mRNA or VAXZEVRIA, anti-S1 IgG antibodies were significantly lower in kidney transplant recipients. This is the first study to provide an in-depth characterization of humoral responses to different variants of concern in kidney transplant recipients. Anti-S1 IgG antibodies were significantly lower in kidney transplant recipients after homologous mRNA/mRNA and VAXZEVRIA/ VAXZEVRIA or heterologous VAXZEVRIA/mRNA standard two dose vaccination. Seroconversion rates were reduced after second vaccination in kidney transplant recipients, and neutralizing antibody levels were significantly lower compared with levels in healthy controls. After first vaccination with an mRNA or VAXZEVRIA anti-S1 IgG antibodies were significantly lower in kidney transplant

recipients with median indices of 0.1 (IQR,0–0.3) and 0.1 (IQR, 0–0.3) compared with 9 (IQR, 6–17; P,0.001) and 2 (IQR, 1–3; P,0.001), respectively, in the full healthy control cohort. First vaccination with VAXZEVRIA led to neutralizing antibody activity that did not differ between groups with a median of 21% (IQR, 0%–26%) in kidney transplant recipients compared with 16% (IQR, 5%–39%) in healthy controls. In both kidney transplant recipients and matched healthy controls, the neutralization activity against the variants of concern B.1.351 and B.1.617.2 was significantly lower compared with activity against B.1.1.7(for all P,0.001).

AZ comment: The author concluded that additional vaccinations appear to be required in kidney transplant recipients to maintain high levels of neutralizing antibodies for the variants with partial escape from neutralizing antibodies become more prevalent. AstraZeneca is monitoring the safety profile of VAXZEVRIA in immunocompromised individuals.

Callagen et al. 2022 studied real-world, risk-adjusted vaccine effectiveness (VE) in solid organ transplant (SOT) recipients following 2 widely used SARS-CoV-2 vaccines in the United Kingdom. Incidence of testing positive for SARS-CoV-2 RNA and risk of death within 28 days following a positive test for SARS-CoV-2. Furthermore, VE was compared between the 2 most widely used vaccines in the United Kingdom, Pfizer-BioNTech (COMIRNATY) and VAXZEVRIA. Of the 4147 SOT recipients with laboratory-confirmed SARS-CoV-2 infection, 407 (9.8%) died within 28 days. Differences in effectiveness between vaccine types were also investigated with unadjusted and risk-adjusted analyses. Kaplan-Meier survival curves suggested that rates of death within 28 days following SARS-CoV-2 infection were lower after vaccination with 2 doses of VAXZEVRIA versus those receiving COMIRNATY. Recipients who had been vaccinated with 2 doses of the VAXZEVRIA vaccine had a hazard ratio (95% CI) for death of 0.69 (0.52-0.92), indicating a 31% reduction in risk of death compared with unvaccinated recipients.

In Israel, a 2-dose program in the general population, with a 3-wk gap between doses using the COMIRNATY vaccine, was associated with 95% and 96% reduction in risk of infection and death, respectively, during an Alpha variant–dominant period. In the United Kingdom, a 2-dose program with a 12-week gap between doses, predominantly with VAXZEVRIA or COMIRNATY vaccines, was reported as showing 79% reduction in risk of infection during the Alpha-dominant and 67% risk reduction during the Delta variant–dominant periods,28 with the extended dosing schedule associated with superior VE.

AZ comment: The author concluded that vaccination reduce risk of death from COVID-19 compared with unvaccinated SOT recipients, though the level of vaccine enabled protection in SOT recipients is markedly less than that observed in the general population.

Neagoie et at 2021 conducted a prospective evaluation of safety and the development of protective response against SARS-CoV-2 vaccines in allogeneic transplanted patients. The

anti-SARS-CoV-2 Spike protein antibodies were measured in blood samples to assess the humoral response. In case of no response with undetectable anti-Spike antibodies 2 week after the second dose of vaccine, measurements repeated at regular intervals until week + 6-8 after the completion of vaccination (77% 7%) received COMIRNATY and 8% VAXZEVRIA). Patients with no measurable antibodies 8 weeks after completion of the vaccination were considered as no responders. Overall, the two vaccine doses were well tolerated, with only 5% of patients developing are activation of GvHD. No relevant grade 3 or 4 organ toxicities were observed Overall, 66% of patients in cohort showed a humoral response. The incidence of positive serology was lower in patients who underwent the vaccination within the first 18 months after allo-SCT (29% vs 83% for patients >18 months after allo-SCT, p< 0).

AZ comment: The author suggested that a humoral response can be achieved, especially for those patients who are in the long-term follow-up, underwent immune reconstitution and are free from immunosuppression. More studies are required to assess the immune response in immunocompromised state. AstraZeneca is monitoring the safety profile of VAXZEVRIA in immunocompromised individuals.

Benedict Osei-Boadu et al 2022 performed an audit on 352 patients from routine clinics which included diagnosis, type of vaccine, number of doses, side effects of the vaccines and flare up of arthritis or underlying autoimmune condition, to check the uptake and side effects of the COMIRNATY and VAXZEVRIA. 146 patients experienced mild side effects based on CTAE v5.0 criteria. Only 3 patients (2.1%) had severe side effects Grade 3 or above, this included Pulmonary embolism, Stroke, and symptomatic pleural effusion. 15(10%) reported Arthritis flare. Most common side effects were Headache 50(34%), Fatigue 32(22%, Myalgia 32(22%), Fever 30(21%), Chills 30(21%), Injection site pain 28(19%), Rhinorrhoea 11(7.5%), Lethargy 11(7.5%) and maculopapular rash 5(3.4%). The audit suggested that both VAXZEVRIA and COMIRNATY are safe for use in immune-deficient patients.

AZ comment: The result suggested that both the VAXZEVRIA and COMIRNATY are safe for use in immune-deficient patients. The adverse events are in line with that observed for VAXZEVRIA in AstraZeneca Safety database. More studies focusing on different vaccines, non-humoral immune responses, and risk-benefit analyses are warranted.

Whitaker et al 2022, conducted a cohort study to estimate vaccine antibody response and vaccine effectiveness against medically attended COVID-19 amongst individuals in clinical risk groups using cohort and test-negative case control designs. Reduced vaccine effectiveness against clinical disease was noted in the immunosuppressed group; after a second dose, effectiveness was moderate (Pfizer: 59.6%, 95%CI 18.0–80.1%; VAXZEVRIA 60.0%, 95%CI -63.6–90.2%).

AZ comment: The authors concluded that reduced antibody response and vaccine effectiveness were seen after 1 dose of vaccine amongst a broad immunosuppressed group,

and after second dose vaccine effectiveness was moderate. More studies are needed to understand vaccine effectiveness against severe disease amongst immunosuppressed groups, including the added value of 3rd and 4th doses.

Summary

Of the 14928 cases cumulatively and 936 for the reporting period, of subjects with severe immunodeficiency and in immunocompromised patient's reported globally and included in AstraZeneca's post-marketing database. Cases were assessed by age, sex, type of event, and outcome.

Cumulatively 120 cases had a fatal outcome, (22 were reported in interval period) and 1109 were hospitalised. There were 249 COVID-19 reports cumulatively, however many did not have sufficient information for complete assessment.

The review and analysis of the available literature did not highlight any particular safety concerns with VAXZEVRIA when used in immunocompromised patients. There were no articles identified with a specific reference to any new safety concerns associated with VAXZEVRIA.

The authors concluded that vaccination reduce risk of death from COVID-19 compared with unvaccinated SOT recipients, though the level of vaccine enabled protection in SOT recipients is markedly less than that observed in the general population.

No usual trends or clusters were identified.

In summary, the review of available data from spontaneous reports regarding subjects with severe immunodeficiency and in immunocompromised patient's did not identify an index case or other evidence of a new or emerging signal.

Conclusion

This cumulative and periodic review of the Use of VAXZEVRIA in subjects with severe immunodeficiency/Use in immunocompromised patients did not indicate any new safety concerns. Overall, the review of the currently available data did not reveal any new safety information in immune-compromised individuals that has not been identified in the overall population.

Use of VAXZEVRIA in subjects with severe immunodeficiency/Use in immunocompromised patients will be investigated primarily in the ongoing non-interventional post-marketing observational study using existing secondary health data sources (D8110R00002 [US] and D8111R00006 [EU/UK]) study of subgroups exposed to AZD1222. Refer to Appendix 4 for additional details.

AstraZeneca will continue to monitor safety information in vaccinees with severe immunodeficiency and in immunocompromised patients as part of the routine safety surveillance activities for VAXZEVRIA and take further actions as deemed appropriate.

Additional information regarding the Use of VAXZEVRIA in immuno-compromised individuals is provided in Section 16.4.3.2.

16.3.5.3 Use of AZD1222 in subjects with severe and/or uncontrolled underlying disease/ Use in frail patients with co-morbidities (eg, chronic obstructive pulmonary disease [COPD], diabetes, chronic neurological disease, cardiovascular disorder)

Subjects with severe and/or uncontrolled underlying diseases are potentially at risk of developing a more severe manifestation of COVID-19 and, as a consequence, have been included as a priority group for initial vaccination in several jurisdictions. Although there is no evidence that the safety profile of VAXZEVRIA in this population will be different to that of the general population, given the paucity of data, the possibility cannot be excluded.

Indicators of frailty used in the review of cases were defined in the protocol for the VAXZEVRIA PASS: A post-authorisation/post-marketing observational study to evaluate the association between exposure to VAXZEVRIA and safety concerns using existing secondary health data sources. This protocol was approved by EMA on 27 January 2022, As no follow-up questionnaires are sent for this missing information concept, no scale of frailty was used for the assessment of the spontaneous cases. Rather, a case narrative text search of VAXZEVRIA reports in the AstraZeneca global safety database using the parameters for each indicator of frailty in Table 212 was used to identify cases for review in the sub-sections below:

Table 212 Indicators of Frailty

Frailty Indicator	Search Parameter
Frailty	"Frailty" "Bedridden"
Dispensing of or reimbursement for durable medical equipment (eg, wheelchairs, home oxygen)	"oxygen" "O2" "scooter" "walker" "wheelchair" "wheel-chair"
Residence in long-term facility or nursing home	"long term" "nursing home" "skilled care" "skilled-care"

Table 212 Indicators of Frailty

Frailty Indicator	Search Parameter
Hip fracture	"hip fracture" "fractured hip" "broken hip" "hip broken"
Palliative care	"palliative" "hospice" "palliate"
Metastatic cancer	"metastatic" "metastasis" "metastases" "metastasise" "cancer spreading" "cancer spread"
Cachexia	"cachexia" "wasting" "waste"
Dementia	"dementia" "Alzheimer" "memory" "cognitive" "cognition"
Pressure ulcers	"ulcer"
Bladder incontinence	"bladder" "urine" "leak"

Search Strategy

A cumulative and periodic search of the AstraZeneca Global Safety Database through 28 June 2022 was undertaken to review AEs reported after vaccination with VAXZEVRIA in individuals identified as having severe and/or uncontrolled underlying disease or were identified as frail. All the categories are described below:

16.3.5.3.1 Frailty

Reporting Period (29 December 2021 – 28 June 2022)

The search identified 128 spontaneous case reports in frail vaccinees who received VAXZEVRIA.

Of the 128 cases, 94 (73.4%) were reported in females, 27 (21.1%) in males and gender was not reported in the remaining 7 (5.5%) case. Age ranged from 0 to <18 Years in 0.8% of the reports, 18 years to <65 years in 55.5%; 65+ years in 28.9% and age was not reported in the remaining 14.8% of cases. The 88.3%of reports were from consumers with the remaining 11.7% being medically confirmed.

Of these 128 cases, 43 (33.6%) were serious, reported seriousness criteria were medically important (29), disability (12), hospitalization (13), life threatening (6), and death (10). Cases may have met more than one criteria for seriousness.

The remaining 88 (66.4%) reports were non serious.

The top 20 reported PTs in these cases were Bedridden (155), Headache (83), Fatigue (82), Pyrexia (81), Chills (53), Myalgia (48), Pain (48), Malaise (44), Arthralgia (39), Asthenia (39), Nausea (36), Dyspnoea (30), Dizziness (28), Pain in extremity (28), Hyperhidrosis (19), Vomiting (19), Back pain (18), Decreased appetite (17), Influenza (17) and Cough (16).

Outcome was available for 67.8% (135 events) of the 128 cases, with 30.2% reported as Recovered, 14.1% as Recovering, 17.1% Not recovered, 1.5% as Recovered with sequelae and unknown in 32.2% of reports. The outcome was fatal in 10 (5.0%) of the total case count.

Of the 128 reports, there were 10 (7.8%) cases with fatal outcome reported during this period. Age of the 10 vaccinees who died ranged from 0 to 95 years with a median of 61 years. The reported PTs in the 10 cases with a fatal outcome in order of frequency (>2) were as follows: Bedridden (3), Pyrexia (3), Vomiting (3). There were 4 cases were a fatal outcome occurred after 1st dose of vaccine and 1 case – after 2nd dose and in 5 cases dose was unknown. The cause of death disease PTs in these 10 cases were: Death (2), Respiratory distress (2), Vomiting (2), Adverse event following immunisation (1),Asthenia (1), Bedridden (1), Biliary sepsis (1), Brain injury (1), Cerebral haemorrhage (1), Cerebrovascular accident (1), Dementia Alzheimer's type (1), Dysphemia (1), Elderly (1), Haemorrhage intracranial (1), Headache (1), Intracranial pressure increased (1), Nausea (1), Peripheral ischaemia (1), Pneumonia (1), Pyrexia (1), Respiratory tract infection (1),Seizure (1) and Thrombosis (1).

Cumulative Review (29 December 2020 – 28 June 2022)

The search of the AstraZeneca global safety database identified a cumulative total of 768 cases (98.4% spontaneous cases, 1.6% non-interventional/post-marketing cases) for the topic use of VAXZEVRIA in individuals identified in the Global Safety Database through a Standard Search Query for the report title Indicators of frailty_frail.

Of the 768 cases, 597 (77.7%) were reported in females, 140 (18.2%) - in males and gender was not reported in the remaining 31 (4.0%) of cases. Age ranged from 0 to <18 Years in

0.1%, 18 years to <65 years in 56.6% of the reports; 65+ years in 28.9%, in adult and elderly 1.3% and age was not reported in the remaining 13% of cases. The majority of reports (79.6%) were medically confirmed with the remaining 20.4% being consumer reports.

Of these 768 cases, 422 (54.9%) were serious reported seriousness criteria were medically important (294), disability (109), hospitalization (65), life threatening (26), and death (88). Cases may have met more than one criteria for seriousness. The remaining 346 (45.1%) reports were non serious.

The top 20 reported PTs were Bedridden (655), Headache (400), Pyrexia (382), Fatigue (314), Chills (253), Nausea (235),Pain (186), Myalgia (184), Malaise (177), Asthenia (168), Dizziness (166), Arthralgia (151), Pain in extremity (123), Vomiting (104), Dyspnoea (96), Decreased appetite (92), Hyperhidrosis (75), Diarrhoea (64), Influenza like illness (61) and Back pain (53).

Outcome was reported for 75.1% (1001 events) of the 768 cases, with 30.2% reported as Recovered, 16.4% as Recovering, 19.0% Not recovered, 2.9% as Recovered with sequelae and unknown in 24.9% of reports. The outcome was reported as fatal for 88 (6.6%) cases, of which 10 cases with fatal outcome were reported during the interval period, as described above.

16.3.5.3.2 Hip Fracture

Search Strategy

A cumulative and periodic search of the global safety database was conducted to review AEs reported from all sources (clinical, spontaneous, solicited reporting and literature) after vaccination with VAXZEVRIA in individuals identified through a Standard Search Query for the report title Hip fracture.

Reporting Period (29 December 2021 – 28 June 2022)

The search identified 3 case reports in frail vaccinees with hip fracture who received VAXZEVRIA and all cases were spontaneously reported. Of the 3 cases, 66.7% (2) of were reported in females and 33.3% (1) were in males. Age ranged from 18 years to <65 years in 33.3% of the reports and 65+ years in 66.7%. All 3 reports were not medically confirmed.

All of these 3 cases were serious, reported seriousness criteria were medically important.

The reported PTs were Erythema (7), Fall (7), Hip fracture (7), Peripheral swelling (7), Pain in extremity (5), Cardiovascular disorder (4), Herpes zoster (4), Inappropriate schedule of product administration (4), Product dose omission issue (4), Anion gap decreased (3), Arthralgia (3), Asthenia (3), Back injury (3), Back pain (3), Bedridden (3), Blood creatine

phosphokinase increased (3), Blood potassium increased (3), Blood pressure systolic increased (3),Blood sodium decreased (3) and Bronchopleural fistula (3).

Outcome was reported in 66.7% of the cases, with 33.3% (1) reported as not Recovered, 33.7% (1) as Recovered With Sequelae.

The outcome was unknown in remaining 50 % of reports. There were no fatal cases reported in individuals with hip fracture during the interval.

Cumulative Review (29 December 2020 – 28 June 2022)

The search of the AstraZeneca Global Safety Database identified a cumulative total of 26 spontaneous cases for the topic use of VAXZEVRIA in individuals with hip fracture.

Of the 26 cases, 76.9% (20 cases) were reported in females and 23.1% (6 cases) were in males. Age ranged from 18 years to <65 years in 34.6% of the reports, 65+years in 65.4%.

The majority of reports (76.9%) were from consumers with the remaining 23.1% being medically confirmed.

Of these 26 cases, 19 (73.1%) were serious, reported seriousness criteria were medically important (14), disability (5), hospitalization (9), life threatening (2), and death (3). Cases may have met more than one criteria for seriousness.

The remaining 7 (26.9%) reports were non serious.

The top 20 reported PTs were Headache (9),Fall (8), Peripheral swelling (8), Erythema (7), Hip fracture (7), Pain in extremity (7), Arthralgia (6), Pyrexia (6), Dyspnoea (5), Fatigue (5), Myalgia (5), Asthenia (4), Cardiovascular disorder (4), Chills (4), Deep vein thrombosis (4), Dizziness (4), Feeling hot (4), Herpes zoster (4), Inappropriate schedule of product administration (4), and Pain (4).

Outcome was available for 73.7% of the 26 cases, with 28.9% reported as Recovered, 7.9% as Recovering, 2.6% Recovered With Sequelae, 26.3% Not recovered and unknown in 26.3% of cases. There were 3 fatal cases reported cumulatively in individuals with hip fracture.

16.3.5.3.3 Cachexia

Search Strategy

A cumulative and periodic search of the AstraZeneca Global Safety Database was conducted to review AEs reported from all sources (clinical, spontaneous, solicited reporting and literature) after vaccination with VAXZEVRIA in individuals identified through a Standard Search Query for the report title Cachexia.

Reporting Period (29 December 2021 – 28 June 2022)

The search identified 30 spontaneous case reports in cachexic individuals who received VAXZEVRIA.

Out of 30 cases, 36.7% (11) were reported in females, 18% (60) in males and gender was not reported in the remaining 3.3% (1) of cases. Age ranged from 18 years to <65 years in 63.3% (19 cases); 65+ years in 20.0% (6cases) and age was not reported in the remaining 13.3% (4 cases). Majority of reports 70% (21 cases) were from consumers, with the remaining 30% (9 cases) being medically confirmed.

Of these 30 cases, 26 (86.7%) were serious, reported seriousness criteria were medically important (17), disability (6), hospitalization (9), life threatening (3), and death (4). Cases may have met more than one criteria for seriousness. The remaining 4 (13.3%) reports were non serious.

Outcome was available for 74.0% (37 events) of the cases, with 12.0% reported as Recovered, 16.0% as Recovering, 4.0% Recovered with Sequelae,34.0% Not recovered and unknown in 26.0%. Outcome was reported as fatal in 8.0% (4) cases.

The top 20 reported PTs Pain (21), Muscle atrophy (18), Myalgia (18), Pain in extremity (18), Arthralgia (17), Dyspnoea (14), Headache, (13), Muscular weakness (13), Back pain (12), Muscle spasms (10), Peripheral swelling (10), Dizziness (9), Malaise (8), Asthenia (6), Chest pain (6), Depressed mood (6), Joint swelling (6), Erythema (5), Fatigue (5) and Feeling hot (5).

Of the 30 reports, there were 4 cases with fatal outcome reported during this period. The cause of death disease PTs reported in these 4 cases are Bronchitis chronic (1), Death (1), Haemophagocytic lymphohistiocytosis, (1), Hypertension (1), Left ventricular failure (1), Lung cancer metastatic (1), Myocardial infarction (1), Poisoning, (1), Pulmonary oedema (1) and Sepsis (1). Age of the vaccinees with a fatal outcome ranged from 48 to 78 years with a median of 69 years. The reported PTs in the 4 cases with a fatal outcome in order of frequency (>1) were as follows: Malaise (4), Dyspnoea (3), Asthenia (2), Cough (2), Decreased appetite (2), Fatigue (2), Pyrexia (2) and White blood cell count decreased (2). There was 1 case were a fatal outcome occurred after 1st dose of vaccine, in 1 case after second dose of vaccine and in 2 cases dose was unknown.

Cumulative Review (29 December 2020 – 28 June 2022)

The search of the AstraZeneca Global Safety Database identified a cumulative total of 198 cases (all spontaneous cases) in individuals identified through a Standard Search Query for the report title Cachexia.

Of the 198 cases, 56.6% (112 cases) were reported in females, 40.9% (81 cases) in males and gender was not reported in the remaining 2.5% (5) of cases. Age ranged from 18 years to <65 years in 72.2% (143) of the reports; 65+ years in 18.7% (37); 0.5% (1 case) was reported in adult population. Age was not reported in the remaining 8.6% (17) of cases. The majority of reports 78.8% (156) were from consumers, with the remaining 21.2% (42) cases being medically confirmed.

Of these 198 cases, 148 (74.7%) were serious, reported seriousness criteria were medially important (84), disability (33), hospitalization (52), life threatening (14), and death (10). Cases may have met more than one criteria for seriousness. The remaining 50 (25.3%) reports were non serious.

The top 20 reported PTs were: Headache (74), Fatigue (56), Pyrexia (46), Myalgia (45), Pain in extremity (43), Muscular weakness (41), Pain (40), Paraesthesia (40), Dizziness (39), Muscle atrophy (39), Arthralgia (34), Chills (29), Malaise (28), Hypoaesthesia (26), Asthenia (24), Dyspnoea (24), Back pain (21), Influenza like illness (21), Nausea (21) and Diarrhoea (16).

Outcome was available for 76.1% of the 198 cases, with 23.6% reported as Recovered, 14.2% as Recovering, 31.8% Not recovered, 3.3% as Recovered with sequelae and unknown for 23.9% of reports. Outcome was reported as fatal for 10 (3%) cases, of which 4 were reported during the interval period, as described in the previous section.

Of these 198 cases, 10 cases were reported as fatal (4 reported in interval period). The PTs reported in these cases were: Death, (4), Cardiac failure acute (1), Condition aggravated (1), Dyspnoea (1), Haemophagocytic lymphohistiocytosis, (1), Left ventricular failure (1), Lung cancer metastatic (1), Myocardial infarction (1), Oropharyngeal pain (1), Pulmonary embolism (1), Pulmonary oedema (1), Respiratory failure (1), Sepsis (1), Sudden death (1) and Tachycardia (1).

16.3.5.3.4 Bladder Incontinence

Search Strategy

A cumulative and periodic search of the AstraZeneca Global Safety Database was conducted to review AEs reported from all sources (clinical, spontaneous, solicited and literature) after vaccination with VAXZEVRIA in individuals identified through a Standard Search Query for the report title Bladder incontinence.

Reporting Period (29 December 2021 – 28 June 2022)

The search identified a total of 638 case reports in individuals with underlying bladder incontinence who received VAXZEVRIA (86.4% spontaneous cases, 10.5% literature, 2.7%

non-interventional/post-marketing, and 0.2% each from the study ChAdOx1 nCoV-19_ZA_phI/II, D8110C00001 and D8111C00013.

Of the 638 cases, 65.8% (420) were reported in females, 32.6% (208) in males and gender was not reported in the remaining 1.6% (10) of cases. Age ranged from, 18 to <65 years in 65.2% (416), 65+ years in 25.1% (160) cases; in 0.7% (4) cases reported adult and elderly and age was not reported in the remaining 9.1% (58 cases). The majority of cases 65.5% (418) were consumer reports with the remaining 34.5% (220) cases being medically confirmed.

Of these 638 cases, 432 (67.7%) were serious, reported seriousness criteria were medically important (289), disability (69), hospitalization (200), life threatening (52), and death (33). Cases may have met more than one criteria for seriousness. The remaining 206 (32.3%) reports were non serious.

The top 20 reported PTs in the remaining cases were Headache (288), Fatigue (249), Pyrexia (213), Pain in extremity (145), Nausea (134), Chills (126), Malaise (126), Dizziness (121), Myalgia (121), Arthralgia (105), Pain (98), Asthenia (92), Dyspnoea (91), Paraesthesia (83), Chest pain (74), Vomiting (73), Abdominal pain (70), Muscle spasms (68) Hypoaesthesia (67), and Back pain (62)

Outcome was reported for 76.4% of the 638 cases, with 27.6% reported as Recovered, 16.9% as Recovering, 24.9% Not recovered, 3.8% as Recovered with sequelae and unknown in 23.6% of reports. The outcome was reported as fatal in 33 (3.2%) of the total case count.

Of the 638 reports, there were 33 cases with fatal outcome reported during this period. Age of the 33 vaccinees with a fatal outcome ranged from 23 to 87 years with a median of 51 years. The reported PTs in the 33 cases with a fatal outcome in order of frequency (>3) were as follows: Dyspnoea (7), Pulmonary embolism (7), Pyrexia (7), Fatigue (5), Multiple organ dysfunction syndrome (5), Renal failure (5), Amnesia (4), Capillary leak syndrome (CLS) (4), Cardiac arrest (4), Cough (4), Death (4), Malaise (4), Thrombocytopenia (4) and Thrombosis (4).There were 12 cases where a fatal event occurred after 1st dose of vaccine and 4 cases – after 2nd dose. In 6 cases both dose were reported. The dose was missing in 11 cases.

Cumulative Review (29 December 2020 – 28 June 2022)

The search of the AstraZeneca Global Safety Database identified a cumulative total of 4584 cases (95.4% spontaneous cases, 2.3% non-interventional/post-mark pet, 2.1% from literature and 2 cases each from the study ChAdOx1 nCoV-19_ZA_phI/II and D8110C00001, 1 case from COV002, D8111C00013and ICMR/SII-AZD-COVID-19/2020) in individuals with underlying bladder incontinence.

Of the 4584 cases, 67.6% (3097) were reported in females, 30.2% (1385) in males and gender was not reported in the remaining 2.2% (100) of cases. Age ranged from 0 to <18 years in 0.1% (3) of the reports; 18 to <65 years in 65.7% (3011) cases, 65+ years in 25.6% (1172) and age was not reported in the remaining 7.9% (361) of cases. The age group of adolescent, adult and elderly and foetus (age was not specified) was reported for 0.8% (37) cases. The majority of reports (82.2%) were from consumers with the remaining 17.8% being medically confirmed.

Of these 4584 cases, 3293 (71.8%) were serious, reported seriousness criteria were medically important (2588), disability (506), hospitalization (900), life threatening (242), and death (149). Cases may have met more than one criteria for seriousness. The remaining 1291 (28.2%) reports were non serious.

The top 20 reported PTs were Headache (1650), Pyrexia (1354), Fatigue (1307), Chills (862), Nausea (798), Pain in extremity (648), Arthralgia(627), Dizziness (615), Myalgia (606), Malaise (552), Pain (523), Dyspnoea (391), Vomiting (365), Paraesthesia (348), Asthenia (337), Diarrhoea (328), Abdominal pain (322), Back pain (301), Hypoaesthesia (270) and Chromaturia (261).

Outcome was reported for 78.1% of the 4584 cases, with 26.4% reported as Recovered, 20.7% as Recovering, 26.2% Not recovered, 3% as Recovered with sequelae and unknown in 21.9% of reports. Outcome was reported as fatal in 149 (1.8%) of the total case count, of which 33 cases with fatal outcome were reported during the interval period, as described in the previous section.

16.3.5.3.5 Dementia

Search Strategy

A cumulative and periodic search of the AstraZeneca Global Safety Database was conducted to review AEs reported from all sources (clinical, spontaneous, solicited and literature) after vaccination with VAXZEVRIA in individuals identified through a Standard Search Query for the report title AZD1222_Dementia.

Reporting Period (29 December 2021 – 28 June 2022)

The search identified a total of 562 case reports (95% spontaneous, 3.0% literature and 1.8% noninterventional/ post-market) in individuals with underlying dementia who received VAXZEVRIA. Of the 562 cases, 66.9% (376) were reported in females, 30.6% (172) in males and gender was not reported in the remaining 2.5% (14) of cases. Age ranged from 0 to <18 Years in 0.2% (1), 18 to <65 years in 67.1% (371); 65+ years in 23.5% (132) and age was not reported in the remaining 9.6% (54) of cases.The age group of adult and elderly (age was not specified) was reported for 0.7% (4 cases).

The majority of reports 429 (76.3%) were from consumers, with the remaining 23.7% (133) cases being medically confirmed.

Of these 562 cases, 379 (67.4%) were serious, reported seriousness criteria were medically important (254), disability (111), hospitalization (145), life threatening (42), and death (28). Cases may have met more than one criteria for seriousness. The remaining 183 (32.6%) reports were non serious.

The top 20 reported PTs in the remaining cases were Headache (121), Memory impairment (113), Fatigue (104), Pyrexia (74), Amnesia (68), Dizziness (59), Chills (50), Disturbance in attention (49), Myalgia (42), Nausea (38), Arthralgia (34), Cognitive disorder (34), Malaise (30), Asthenia (25), Dyspnoea (22), Pain in extremity (20), Pain (18), Injection site pain (16), Visual impairment (15) and Diarrhoea (14).

Outcome was available for 78.1% (733 events) of the 951 cases, with 20.0% reported as Recovered, 18.1% as Recovering, 31.0% Not recovered, 6.0% as Recovered with sequelae and was unknown in 21.9% of reports. Outcome was reported as fatal in 28 (3.0%) of the total case count.

Of the 562 reports, there were 28 cases with fatal outcome reported during this period. Age of the 28 vaccinees with a fatal outcome ranged from 42 to 94 years with a median of 51 years.

The reported PTs in the 28 cases with a fatal outcome in order of frequency (>3) were: Cerebrovascular accident (8), Amnesia (7), Headache (7), Confusional state (6), Death (6), Cerebral haemorrhage (5), Dementia (5), Mobility decreased (5), Pneumonia (5), Pyrexia (5), Condition aggravated (4), Decreased appetite (4), Intracranial aneurysm (4), Memory impairment (4) and Pneumonia aspiration (4). There were 11 cases were a fatal outcome occurred after 1st dose of vaccine and 3 cases – after 2nd dose. In 8 cases both doses were administered. In 1 case first and third dose (booster) was reported There was limited information in 4 cases.

Cumulative Review (29 December 2020 – 28 June 2022)

The search of the AstraZeneca Global Safety Database identified a cumulative total of 2802 cases (97.5% spontaneous, 1.6% non-interventional/post-marketing, 0.8% from literature and 0.1% (2) from the study D8110C00001 and 0.0% (1 case) ICMR/SII-AZD-COVID-19/2020) in individuals with dementia who received VAXZEVRIA.

Of the 2802 cases, 65.5% (1835) were reported in females, 32.2% (901) in males and gender was not reported for the remaining 2.4% (66) of cases. Age ranged from 0 to <18 years in 0.1% (3) of the reports; 18 to <65 years in 54.6% (1530), 65+ years in 35.4% (993) and age was not reported in the remaining 8.8% (246) of cases. The age group of adult and elderly

(age was not specified) was reported for 30 (1.1%) cases. The majority of reports 2177 (77.7%) were from consumers with the remaining 625 cases (22.3%) being medically confirmed.

Of these 2802 cases, 2088 (74.5%) were serious, reported seriousness criteria were medically important (1440), disability (549), hospitalization (634), life threatening (214), and death (183). Cases may have met more than one criteria for seriousness. The remaining 714 (25.5%) reports were non serious.

The top 20 reported PTs were Headache (1120), Fatigue (1105), Memory impairment (869), Amnesia (839), Pyrexia (637), Dizziness (636), Cognitive disorder (459), Confusional state (439), Myalgia (429), Arthralgia (413), Nausea (405), Chills (387), Disturbance in attention (361), Malaise (328), Dyspnoea (307), Pain in extremity (296), Asthenia (290), Pain (258), Paraesthesia (250) and Feeling abnormal (214).

Outcome was reported for 79.8% of the 3921 cases, with 21.6% as Recovered, 19.2% as Recovering, 30.3% Not recovered, 4.9% as Recovered with sequelae and unknown in 20.2% of reports. Outcome was reported as fatal in 183 (3.7%) of the total case count, of which 28 cases with fatal outcome were identified during the reporting period, as described in the previous section.

16.3.5.3.6 Long term Frailty

Search Strategy

A cumulative and periodic search of the AstraZeneca Global Safety Database was conducted to review AEs reported from all sources (clinical, spontaneous, solicited and literature) after vaccination with VAXZEVRIA in individuals identified through a Standard Search Query for the report title Indicators of frailty long term.

Reporting Period (29 December 2021 – 28 June 2022)

The search identified a total of 139 case reports in individuals with long term frailty who received VAXZEVRIA (74.1% spontaneous cases,16.5% noninterventional/ post-marketing and 9.4% literature).

Of the 139 cases, 57.6% (80) were reported in females, 40.3% (56 cases) in males and gender was not reported in the remaining 2.2% (3) of cases. Age ranged from 18 to <65 years in 74.1% (103) cases; 65+ years in 22.3% (31) cases and age was not reported in the remaining 3.6% (5) of cases. The majority of reports 86 (61.9%) were from consumers with the remaining 53cases (38.1%) being medically confirmed.

Of these 139 cases, 100 (71.9%) were serious, reported seriousness criteria were medically important (65), disability (29), hospitalization (45), life threatening (16), and death (8). Cases

may have met more than one criteria for seriousness. The remaining 39 (28.1%) reports were non serious.

The top 20 reported PTs in the remaining case reports were Fatigue (65), COVID-19 (52), Headache (50), Pain in extremity (37), Pyrexia (35), Dyspnoea (27), Chills (22), Dizziness (22), Palpitations (19), Asthenia (18), Myalgia (18), Pulmonary embolism (17), Arthralgia (16), Hypoaesthesia (15), Nausea (15), Pain (15), Malaise (14), Disturbance in attention (13), Chest pain (11) and Tachycardia (11)

Outcome was reported for 74.3% (182 events) of the 139 cases, with 22.4% reported as Recovered, 16.3% as Recovering, 24.9% Not recovered, 7.3% as Recovered with sequelae and unknown in 25.7% of reports. Outcome was reported as fatal for 8 (3.3%) of the total case count.

Of the 139 reports, there were 8 cases with fatal outcome reported during this period. Age of the 8 vaccinees who died ranged from 54 to 88 years with a median of 50 years. The reported PTs in the 8 cases with a fatal outcome in order of frequency (>3): Adrenal haemorrhage (6), Brain oedema (6), Cerebral haemorrhage (6), Cerebral venous sinus thrombosis (6), Disseminated intravascular coagulation (6), Epilepsy (6), Haemorrhage intracranial (6), Haemorrhagic cerebral infarction (6), Thrombosis with thrombocytopenia syndrome (6), COVID-19 pneumonia (4) and

Vaccination failure (4). There was 1 case were a fatal event occurred after 1st dose of vaccine. In 1 case with 2nd dose was reported. In 1 case all 3 doses were reported. In 1 case 2nd and booster dose was reported. In 1 case only booster dose was reported. There was limited information in 3 cases.

Cumulative Review (29 December 2020 – 28 June 2022)

The search of the AstraZeneca global safety database identified a cumulative total of 789 cases (98.07% spontaneous, 1.03% non-interventional/post-marketing, 0.74% literature and 0.14% from study COV002) in individuals with long term frailty.

Of the 789 cases, 62.2% (491) were reported in females, 35.4% (279 cases) in males and gender was not reported in the remaining 2.4% (19) of cases. Age ranged from 0 to <18 years in 0.1% (1 case); 18 to <65 years in 68.4% (523) cases; 65+ years in 24.1% (190) cases and age was not reported in the remaining 8.5% (67) of cases. The age group of adult and elderly (age not specified) was reported for 1.0% cases. The majority of reports 651 (82.5%) were from consumers with the remaining 138 cases (17.5%) being medically confirmed.

Of these 789 cases, 704 (89.2%) were serious, reported seriousness criteria were medically important (513), disability (160), hospitalization (221), life threatening (82), and death (59).

Cases may have met more than one criteria for seriousness. The remaining 85 (10.8%) reports were non serious.

The top 20 reported PTs were Fatigue (271), Headache (271), Pyrexia (171), Pain in extremity (137), Dizziness (117), Chills (116), Paraesthesia (111), Nausea (105), Arthralgia (103), Dyspnoea (103), Malaise (93), Myalgia (91), Pain (90), Hypoaesthesia (88), COVID-19 (62), Pulmonary embolism (61), Chest pain (60), Palpitations (59),Asthenia (56) and Influenza like illness (55).

Outcome was reported for 76.8% (1148 events) of the 789 cases, with 21.0% reported as Recovered, 19.5% as Recovering, 27.4% Not recovered, 5.0% as Recovered with sequelae and unknown in 23.2% of reports. Outcome was reported as fatal for 59 (3.9%) of the total case count. of which 8 cases with fatal outcome were identified during the reporting previous, as described in the previous section.

16.3.5.3.7 Metastatic Cancer

Search Strategy

A cumulative and periodic search of the AstraZeneca Global Safety Database was conducted to review AEs reported from all sources (clinical, spontaneous, solicited reporting and literature) after vaccination with VAXZEVRIA in individuals identified through a Standard Search Query for the report title report title metastatic cancer.

Reporting Period (29 December 2021 – 28 June 2022)

The search identified a total of 52 case reports in vaccinees with metastatic cancer who received VAXZEVRIA (90.4% spontaneous, and 9.6% literature).

Of the 52 cases, 55.8% (29) were reported in females, 44.2% (23) in males. Age ranged from 18 to <65 years in 48.1% (25) cases; 65+ years in 50.0% (26) reports and age was not reported in the remaining 1.9% (1) of cases.

The majority of reports 28 (53.8%) were from consumers with the remaining 24 cases (46.2%) being medically confirmed.

Of these 52 cases, 42 (80.8%) were serious, reported seriousness criteria were medically important (24), disability (2), hospitalization (19), life threatening (6), and death (14). Cases may have met more than one criteria for seriousness. The remaining 10 (19.2%) reports were non serious.

The top 20 reported PTs in the r were Pyrexia (19), Fatigue (17), Asthenia (13), Dyspnoea (11), Lymphadenopathy (10), Pain (10), Headache (8), Interchange of vaccine products (8), Off label use (8), Arthralgia (7), Cough (7), Decreased appetite (7), Malaise (6), Tachycardia

(6), Vaccination failure, (6), Breast pain (5), COVID-19 pneumonia (5), General physical health deterioration (5). Palpitations (5) and Abdominal mass (4).

Outcome was available for 67.1 % (47 events) of the 52 cases, with 20.0% reported as Recovered, 5.7% as Recovering, 18.6% Not recovered and 2.9% as Recovered with sequelae. Outcome was unknown in 32.9% of reports and was reported as fatal in 14 (20.0%)of the total case count.

Of the 52 reports, there were 14 (26.9%) cases with fatal outcome reported during this period. Age of the 24 vaccinees who died ranged from 56 to 78 years with a median of 65 years. The reported PTs in the 24 cases with a fatal outcome in order of frequency (>3) were: Dyspnoea (6), COVID-19 pneumonia (5), Asthenia (4), Cough (4), Haemoptysis (4), Pneumonia (4) and Vaccination failure (4).There were 4 cases were a fatal event occurred after 1st dose of vaccine and 2 cases– after 2nd dose. In 2 cases both doses were reported. In 1 case all 3 doses were reported. There was limited information in 5 cases.

Cumulative Review (29 December 2020 – 28 June 2022)

The search of the AstraZeneca Global Safety Database identified a cumulative total of 407 cases (96.8% spontaneous, 1.2% non-interventional/post-marketing and 2.0% literature) in individuals with metastatic cancer who received VAXZEVRIA.

Of the 407 cases, 56.5% (230 cases) were reported in females, 42.0% (171 cases) in males and gender was not reported in the remaining 1.5% (6) cases. Age ranged from 0 to <18 years in0.2% (1 case); 18 years to <65 years in 49.1% (200) of the reports and 65+ years in 44.2% (180) cases. The age group of adult and elderly (age not specified) was reported in 1.0% and age was not reported in the remaining 5.4% (22) of cases. The majority of reports 252 (61.9%) were from consumers with the remaining 155 cases (38.1%) being medically confirmed.

Of these 407 cases, 349 (85.7%) were serious, reported seriousness criteria were medically important (234), disability (39), hospitalization (130), life threatening (47), death (56). Cases may have met more than one criteria for seriousness. The remaining 58 (14.3%) reports were non serious.

The top 20 reported PTs were Headache (98), Pyrexia (91), Fatigue (81), Pulmonary embolism (54), Dyspnoea (49), Chills (47), Thrombocytopenia (45), Nausea (39), Arthralgia (32), Pain (32), Asthenia (30), Malaise (29), Myalgia (29), Deep vein thrombosis (25), Diarrhoea (25), Dizziness (24), Thrombosis (24), Tremor (24), Pain in extremity (23) and Chest pain (20)..

Outcome was available for 73.4% (477 events), with 19.7% (128 events) reported as Recovered, 20.6% (134 events) as Recovering, 21.2% (138 events) Not recovered, 3.2% (21

events) as Recovered with sequelae and unknown in 26.6% (173 events). The outcome was reported as fatal in 56 (8.6%) of the total case count, of which 14 cases with fatal outcome were identified during the reporting period, as described in the previous section.

16.3.5.3.8 Supplemental Oxygen Use

Search Strategy

A cumulative and periodic search of the AstraZeneca Global Safety Database was conducted to review AEs reported from all sources (clinical, spontaneous, solicited reporting and literature) after vaccination with VAXZEVRIA in individuals identified through a Standard Search Query for the report title report title Indicators of frailty_oxygen.

Reporting Period (29 December 2021 – 28 June 2022)

The search identified a total of 577 case reports in individuals who received VAXZEVRIA (90.1% spontaneous, 0.5% non-interventional/post-marketing, 8.0% literature, 1.2% from the study D8110C00001 and 0.2% from D8111C00013) identified through a Standard Search Query for the report title Indicators of frailty_oxygen.

Of the 577 cases, 58.6% (338) were reported in females, 38.6% (223) in males and gender was not reported in the remaining 2.8% (16 cases). Age ranged from 0 to <18 years in 0.5% (3) cases; 18 to <65 years in 61% (352); 65+ years in 17.9% (103) and age was not reported in the remaining 20.3% (117) cases. The age group of neonate (age not specified) was reported in 0.3% of cases. The majority of reports (66.7%) were medically confirmed with the remaining 33.3% being consumer reports.

Of these 577 cases, 393 (68.1%) were serious, reported seriousness criteria were medically important (193), disability (54), hospitalization (233), life threatening (62), and death (75). Cases may have met more than one criteria for seriousness. The remaining 184 (31.9%) reports were non serious.

The top 20 reported PTs in the remaining cases were Headache (180), Pyrexia (180), Oxygen saturation decreased (166), Dyspnoea (159), Fatigue (118), Cough (99), Myalgia (84), Dizziness (81), Pain (75), Asthenia (74), Malaise (71), Arthralgia (68), Chills (66), Pain in extremity (65), Nausea (60),Diarrhoea (53), COVID-19 (47), Syncope (42), Oropharyngeal pain (41), Peripheral swelling (37).

Outcome was available for 67.1% of the 577 cases, with 25.9% reported as Recovered, 14.4% as Recovering, 13.8% Not recovered, 2.3% as Recovered with sequelae and unknown in 33.9% of reports. The outcome was reported as fatal in 75 (9.7%) of the total case count.

Out of 577 reports, there were 75 cases with fatal outcome reported during this period. Age of the 75 vaccinees who died ranged from 20 to 90 years with a median of 58 years. The reported

PTs in the 75 cases with a fatal outcome in order of frequency (>6) were: Dyspnoea (29), Oxygen saturation decreased (27), Pyrexia (19), Death (17), Cough (13), Cardiac arrest (10), Malaise (10), Confusional state (9), Headache (9), Productive cough (9), Fatigue (8), Seizure (8), Vomiting (8), Asthenia (7), COVID-19 (7) and Myalgia (7). There were 20 cases were a fatal outcome occurred after 1st dose of vaccine and 2 cases – after 2nd dose. In 15 cases both doses were reported. In 2 cases 1st and 2nd dose was reported. There was limited information in 35 cases.

Cumulative Review (29 December 2020 – 28 June 2022)

The search of the AstraZeneca Global Safety Database identified a cumulative total of 2987 cases (96.5% spontaneous, 0.5% non-interventional/post-marketing,2.5% literature and 0.3% from D8110C00001, 0.1% from D8111C00013 and 1 case from ICMR/SII-AZD-COVID-19/2020) in individuals identified through a Standard Search Query for the report title Indicators of frailty_oxygen.

Of the 2987 cases, 59.3% (1772) were reported in females, 38.5% (1149) in males and gender was not reported in the remaining 2.2% (66) of cases. Age ranged from 0 to <18 years in 0.3% (9) cases; 18 years to <65 years in 61.6% (1840) of the reports and 65+ years in 23.8% (711).

The age group of neonate, adult and elderly (age not specified) was reported in 0.6% (17) and age was not available for the remaining 13.7% (410) of cases. The majority of cases 1623 (54.3%) were consumers reports with the remaining 45.7% (1364) of cases being medically confirmed.

Of these 2987 cases, 2198 (73.6%) were serious, reported seriousness criteria were medically important (1378), disability (265), hospitalization (1000), life threatening (320), and death (251). Cases may have met more than one criteria for seriousness. The remaining 789 (26.4%) cases were non serious.

The top 20 reported PTs were Pyrexia (1081), headache (883), Dyspnoea (880), Oxygen saturation decreased (675), Fatigue (613), Chills (420), Myalgia (418), Dizziness (407), Nausea (366), Cough (328), Malaise (292), Pulmonary embolism (287), Asthenia (279), Pain (274), Arthralgia (260), Pain in extremity (238), Chest pain (229), Vomiting (210), COVID-19 (185) and Diarrhoea (182).

Outcome was reported in 71.9% (3468 events) of the 2987 cases, with 27.1% (1308) reported as Recovered, 19.8% (956) as Recovering, 17.1% (826) Not recovered, 2.6% (127) as Recovered with sequelae and unknown in 28.1% (1356) of reports. Outcome was reported as fatal in 251 (5.2%) of the total case count, of which 75 cases with fatal outcome were identified during the reporting period, as described in previous section.

16.3.5.3.9 Palliative Care

Search Strategy

A cumulative and periodic search of the AstraZeneca Global Safety Database was conducted to review AEs reported from all sources (clinical, spontaneous, solicited reporting and literature) after vaccination with VAXZEVRIA in individuals identified through a Standard Search Query for the report title Palliative.

Reporting Period (29 December 2021 – 28 June 2022)

The search identified a total of 9 case reports in individuals who received VAXZEVRIA (77.8% spontaneous, 22.2 % literature) identified through a Standard Search Query for the report title Palliative.

Of the 9 cases, 55.6% (5) were reported in females and 44.4% (4) were in males. Age ranged from 18 to <65 years in 33.3% (3) and reports; 65+ years in 66.7% (6). The majority of reports 6 (66.7%) were medically confirmed with the remaining 3 (33.3%) being consumer reports.

All of these 9 cases, were serious, reported seriousness criteria were medically important (2), hospitalization (8), life threatening (1), and death (8). Cases may have met more than one criteria for seriousness.

The top 20 reported PTs were Haemophagocytic lymphohistiocytosis (4), Cerebrovascular accident (3), Dyspnoea, (3), Haemorrhage intracranial (3), Pyrexia (3), Renal failure (3), Thunderclap headache (3), Vomiting (3), Breast cancer metastatic (2), Cognitive disorder (2), Pericarditis (2), Pneumonia (2), Acute disseminated encephalomyelitis (1), Agitation (1), Arterial occlusive disease (1),) Asymptomatic COVID-19 (1), Cerebral venous sinus thrombosis (1), Contusion (1), Death (1) and Erythema, (1).

Outcome was reported for 61.0% (25 events) of the 9 cases, with 4.9% (2 events) Not recovered, 4.9 Recovered With Sequelae and unknown for 39.0% (16 events). Outcome was reported as fatal for 8 (51.2%) of the total case count.

Out of 9 reports, there were 8 cases with fatal outcome reported during this period. Age of the 8 vaccinees who died ranged from 48 to 88 years with a median of 79 years. The reported PTs in the 17 cases with fatal outcome in order of frequency (>2) were: Haemophagocytic lymphohistiocytosis (4), Cerebrovascular accident (3), Haemorrhage intracranial (3), Pyrexia (3), Renal failure (3), Thunderclap headache (3) and Vomiting (3). There were 3 cases were a fatal outcome occurred after both dose of vaccine. In 1 case all 3 doses were reported. There was limited information in 4 cases.

Cumulative Review (29 December 2020 – 28 June 2022)

The search of the AstraZeneca Global Safety Database identified a cumulative total of 105 cases (95.2% spontaneous s, Non-interventional / Post-marketing1.0%, and literature 3.8%) in individuals identified through Standard Search Query for the report title Palliative.

Of the 105 cases, 46.7% (49) were reported in females and 53.3% (56) were in males. Age ranged from 18 years to <65 years in 22.9% (24) cases; 65+ years in 72.4% (76) and age was not reported for the remaining 4.8% (5) cases. The majority of cases 61 (58.1%) were medically confirmed with the remaining 44 (41.9%) being consumer reports.

Of these 105 cases, 102 (97.1%) were serious, reported seriousness criteria were medically important (58), disability (17), hospitalization (47), life threatening (9), death (30). Cases may have met more than one criteria for seriousness.

The remaining 3 (2.9%) cases were non serious.. The top 20 reported PTs were Cerebrovascular accident (17), Death (13), Malaise (13), Dyspnoea (12), Headache (11), Vomiting (10), Pyrexia (9), Fatigue (8), Pneumonia (8), Syncope (8), Thrombocytopenia (8), Confusional state (7), Cerebral haemorrhage (6), Facial paralysis (6), Myalgia (6), Nausea (6), Pulmonary embolism (6), Renal failure (6), Chills (5) and Erythema (5).

Outcome was reported for 71.6% (126 events) of the 105 cases, with 10.2% reported as Recovered, 4.5% as Recovering, 22.2% Not recovered, 1.7% as Recovered with sequelae and unknown in 28.4% of reports. Outcome was reported as fatal in 58 (33%) of the total case count, of which 8 cases with fatal outcome where identified during the reporting period, as described in the previous section.

16.3.5.3.10 Pressure Ulcers

Search Strategy

A cumulative and periodic search of the AstraZeneca Global Safety Database was conducted to review AEs reported from all sources (clinical, spontaneous, solicited reporting and literature) after vaccination with VAXZEVRIA in individuals identified through a Standard Search Query for the report title _Pressure ulcers.

Reporting Period (29 December 2021 – 28 June 2022)

The search identified a total of 408 case reports (91.4% spontaneous, 4.9% noninterventional/ post-marketing and 3.7% literature) in individuals with underlying pressure ulcers who received VAXZEVRIA.

Of the 408 cases, 68.9% (281) were reported in females, 30.4% (124) in males and gender was unknown in 0.7% (3) of cases. Age ranged from 0 to <18 years in 1% (4); 18 to <65 years in 69.6% (284); 65+ years in 18.9% (77). Age was not reported for the remaining 10.0% (41) of cases. The age group of adult and elderly (age not specified) was reported for 0.5% cases. The

majority of reports 269 (65.9%) were from consumers with the remaining 221 (22%) cases being medically confirmed.

Of these 408 cases, 168 (41.2%) were serious, reported seriousness criteria were as medically important (124), disability (20), hospitalization (63), life threatening (14), and death (11). Cases may have met more than one criteria for seriousness. The remaining 240 (58.8%) cases were non serious.

The top 20 reported PTs were Psoriasis (6),Malaise (5), Thrombosis with thrombocytopenia syndrome (5), Acute respiratory distress syndrome (4), Anaemia (4), Angiopathy (4), Arterial stenosis (4), Arteriosclerosis (4), Circulatory collapse (4), C-reactive protein increased (4),Cyanosis (4), Fibrosis (4), Gangrene (4), Intestinal ischaemia (4), Mesenteric artery stenosis (4), Multiple organ dysfunction syndrome (4),Myeloproliferative neoplasm (4), Nephrosclerosis (4), Peripheral artery thrombosis (4) and Peripheral ischaemia(4).

Outcome was available for 81.3% (478) of the 408 cases, with 30.8% (181) reported as Recovered, 19.4% (114) as Recovering, 27.7% (163) Not recovered and unknown in 18.7% (110) of reports. Outcome was reported as fatal in 11 (1.9%) of the total case count.

Out of 408 cases, there were 11 reports with fatal outcome reported during this period. Age of the 22 vaccinees who died ranged from 46 to 88 years with a median of 55 years. The reported PTs in the 11 cases with a fatal outcome in order of frequency (>3) were: Psoriasis (6), Malaise (5), Thrombosis with thrombocytopenia syndrome (5), Acute respiratory distress syndrome (4), Anaemia (4), Angiopathy (4), Arterial stenosis (4), Arteriosclerosis (4), Circulatory collapse (4), C-reactive protein increased (4), Cyanosis (4), Fibrosis (4), Gangrene (4), Intestinal ischaemia (4), Mesenteric artery stenosis (4), Multiple organ dysfunction syndrome (4), Myeloproliferative neoplasm (4), Nephrosclerosis (4), Peripheral artery thrombosis (4), Peripheral ischaemia (4), Psoriatic arthropathy (4), Pulse pressure decreased (4), Rash (4), Renal ischaemia (4), Respiratory failure (4), Sepsis (4),Skin ulcer (4), Uterine haemorrhage (4), Vasculitis (4) and Weight decreased (4). There were 4 cases were a fatal outcome occurred after 1st dose of vaccine and 1 case after 2nd dose. In 4 cases both doses were reported. There was limited information in 2 cases.

Cumulative Review (29 December 2020 – 28 June 2022)

The search of the AstraZeneca Global Safety Database identified a cumulative total of 3966 cases (96.6% spontaneous, 2.7% non-interventional/post-marketing, 0.6% literature and 1 case each from the study D8110C00001 and ICMR/SII-AZD-COVID-19/2020) in individuals with pressure ulcers.

Of the 3966 cases, 70.6% (2800) were reported in females, 27.1% (1073) in males and gender was not reported in the remaining 2.3% (93) of cases. Age ranged from 0 to <18 years in

0.3%(10); 18 years to <65 years in 73.8% (2926) of the reports and 65+ years in 17.7% (703) cases. The age group of adult and elderly (age not specified) was reported for 0.6% cases. Age was not reported in the remaining 7.6% (302) of cases. The majority of reports 3240 (81.7%) were from consumers with the remaining 726 (18.3%) cases being medically confirmed.

Of these 3966 cases, 2287 (57.7%) were serious, reported seriousness criteria were medically important (1869), disability (315), hospitalization (364), life threatening (91), and death (57). Cases may have met more than one criteria for seriousness. The remaining 1679 (42.3%) cases were non serious.

Outcome was available for 82.6% (5656) of the 3966 cases, with 27.3% reported as Recovered, 22.1% as Recovering, 29.9% Not recovered, 2.5% as Recovered with sequelae. And unknown in 17.3% (1183) of reports. Outcome was reported as fatal in 57 (0.8%) of the total case count, out of which 11 cases with fatal outcome were identified during the reporting period, as described in the previous section.

The top 20 reported PTs were Headache (1466), Pyrexia (1174), Fatigue (1098), Mouth ulceration (1037), Chills (753), Myalgia (590), Nausea (589), Arthralgia (526), Pain in extremity (453), Dizziness (448), Malaise (386), Aphthous ulcer (384), Pain (300), Diarrhoea (273), Colitis ulcerative (212), Oropharyngeal pain (210), Vomiting (207), Pruritus (198), Paraesthesia (184) and Influenza like illness (183).

Conclusion

This review of the cumulative and periodic data in individuals with frailty, severe and/or uncontrolled underlying disease and comorbidities did not revile any new safety concern. There was no increase in events seriousness (for all discussed topics) or severity. In the subjects with supplemental oxygen use there was 2 fold increase in the number of the fatal cases reported in (5.3%) (9.7%) the current interval period (77 vs. 35 respectively) as compared to the previous PBRER. This was due to increased severity of underlying acute or chronic hypoxemia causing detrimental decrease in oxygen saturation in patients with uncontrolled pulmonary infection, COPD, bronchitis, congestive heart failure, and Covid-19.

Out of the 77 fatal cases reported during the reporting interval, 35 were follow-up reports. Of note, out of the 42 new reports received by AstraZeneca during the reporting interval, 31 cases had the onset date at an earlier point during 2021 before the start of the reporting interval, however, were not reported to AstraZeneca until later. Therefore, this increase could possibly be explained by reporting backlog for some markets.

In summary, no abnormal trends or significant new safety concerns were identified in the interval period with respect to the cumulative data. Majority of the adverse events reported in patients with frailty and/or uncontrolled underlying disease were either related or heavily

confounded by patients' medical history and underlying disorders or were consistent with the known safety profile of the vaccine.

This cumulative and periodic review of currently available data from the use of VAXZEVRIA in subjects with frailty, severe and/or uncontrolled underlying diseases and comorbidities did not identify any new safety concerns.

This topic will continue to be considered missing information and will be kept under close surveillance by AstraZeneca.

Use of VAXZEVRIA in subjects with severe or uncontrolled underlying disease/Use in frail patients will be investigated primarily in the ongoing non-interventional post-marketing observational study using existing secondary health data sources (D811110R00002 [US] and D8111R00006 [EU/UK]) study of subgroups exposed to VAXZEVRIA. Refer to Appendix 4 for additional details.

More detailed information is provided in Section 16.4.3.3.

16.3.5.4 Use of AZD1222 with other vaccines

The safety, immunogenicity, and efficacy of VAXZEVRIA when co-administered with other vaccines has not been evaluated in clinical trials. Therefore, while there is currently no evidence to suggest the safety profile of the subjects receiving VAXZEVRIA when co-administered with other vaccines would be impacted, given the paucity of data, the possibility cannot be excluded.

A cumulative search of the AstraZeneca Global Safety Database through 28 June 2022 was undertaken to review AEs reported after vaccination with VAXZEVRIA with other non-COVID-19 vaccines, including seasonal influenza vaccine, herpes vaccine, varicella vaccine, and pneumococcal pneumonia vaccine. Reports were identified in the Global Safety Database through a search of the concomitant medications for: seasonal Influenza vaccine, Herpes vaccines, Pneumococcal vaccine and Varicella vaccine.

16.3.5.4.1 Influenza Vaccine

Assessment for cases received with Influenza Vaccine (reporting interval):

This search identified a total of 1297 cases (86.6% spontaneous cases, 13.7% non-interventional/post-marketing cases, 0.1% Clinical trial, and 0.2% literature) for the topic use of VAXZEVRIA with seasonal influenza vaccine.

Of the 1297 cases, 65.9% (855) were reported in females, 33.1% (429) in males, and gender was not reported in the remaining 1.0% (13) of cases. The age ranged from 18 years to <65 years in 48.1% (624) of the reports, 65+ years in 45.9% (595), and 0.1% (1) in less than 18

years of age. In 5.9% (77) cases the age was reported as unknown. Of the 1297 reports, 12.3% (159) were medically confirmed, with the remaining 87.7% (1138) being consumer reports.

Of the 1297 reports, 35.6% (462) were serious and reported seriousness criteria were medically important (340), disability (22), hospitalization (62), life threatening (18), and the death (20). Cases may have met more than one criteria for seriousness. The remaining 64.4% (835) cases were non-serious.

A total of 4288 AEs were reported within the 1297 reports. The top 20 reported PTs were Headache (420), Fatigue (385), Pain in extremity (233), Pyrexia (217), Myalgia (185), Chills (176), Arthralgia (140), Nausea (109), COVID-19 (103), Injection site pain (93), Dizziness (84), Malaise (80), Pain (74), Influenza like illness (62) Limb discomfort (43), Influenza (38), Diarrhoea (36), Lymphadenopathy (32), Paraesthesia (28), and Musculoskeletal stiffness (28).

The time to onset from vaccination to the event was available for 68.6% of AEs of which 15.3% of events occurred within day 0 of vaccination, 14.1% occurred on day 1 post vaccination, 6.8% events occurred within days 2-15 post-vaccination, 19.3% events occurred between 16-200 days post-vaccination, 13.1% events occurred > 200 days post-vaccination, and for 31.4% events the time from vaccination to AE onset was not reported.

Outcomes for AEs were reported as 52.6% (2255) recovered, 14.3% (615) as recovering, 1.0% (44) as recovered with sequelae, 18.6% (798) not recovered, 1.4% (58) as fatal and 12.1% (518) as unknown. There were 20 fatal cases (reporting 58 events) in the reporting interval. Age was reported in 14 out of 20 cases with a median age of 62 years; range 20 to 97 years. Time to onset was reported for 35 of 58 fatal events with a median of 7 days; range 0 to 322 days. Cause of death PTs included: Cardiac arrest (3), Death (3), Cluster headache (2), Pulmonary embolism (2), Myocardial infarction (2), Cerebral haemorrhage (2), Pyrexia (2), Chest pain (2), Sudden death (2) and 1 each for Pneumonia, Ischaemic stroke, Feeling cold, Cardio-respiratory arrest, Myelitis transverse, Cardiovascular disorder, Cardiac failure acute, Cerebellar haemorrhage, Guillain-Barre syndrome, Cerebral artery thrombosis, Malaise, Atrial fibrillation, Arteriosclerosis coronary artery, Cerebral infarction, Cardiac death, Cerebral thrombosis, Fatigue, Basal ganglia stroke, Fibrin D dimer increased, Brain death, Immunology test, Coma, Jugular vein thrombosis, COVID-19, Mesenteric vein thrombosis, Respiratory failure, Myocardial fibrosis, Asthenia, Pericarditis, Thrombosis, Portal vein thrombosis, Visceral venous thrombosis, Cardiac failure, Dyspnoea at rest, Eczema, Thrombocytopenia, Deep vein thrombosis, Vena cava thrombosis, Dizziness, Abdominal pain, and Dyspnoea.

Assessment for cases received with Influenza Vaccine (cumulative search):

This search identified a total of 13185 cases (90.3% spontaneous cases, 9.6% non-interventional/post-marketing cases, 0.02% Clinical trial, and 0.07% literature) for the topic use of VAXZEVRIA with seasonal influenza vaccine.

Of the 13185 cases, 73.6% (9699) were reported in females, 24.0% (3167) in males, and gender was not reported in the remaining 2.4% (319) of cases. The age ranged from 18 years to <65 years in 66.8% (8802) of the reports, 65+ years in 27.3% (3599), and 0.3% (45) in less than 18 years of age. In 5.6% (739) cases the age was reported as unknown. Of the 13185 reports, 8.4% (1103) were medically confirmed, with remaining 91.6% (12082) being consumer reports.

Of the 13185 reports, 63.0% (8300) were serious and reported seriousness criteria were medically important (7127), disability (630), hospitalization (340), life threatening (135), and death (68); 20 of 68 fatal cases occurred in the reporting period. Cases may have met more than one criteria for seriousness. The remaining 37.0% (4885) cases were non-serious.

A total of 56430 AEs were reported within the 13185 cases received.

The top 20 reported PTs were Headache (6127), Pyrexia (4303), Fatigue (4190), Chills (3708), Nausea (2540), Myalgia (2241), Arthralgia (1756), Pain in extremity (1622), Dizziness (1430), Pain (1036), Malaise (1019), Influenza like illness (782), Tremor (769), Vomiting (712), Diarrhoea (609), Hyperhidrosis (581), Paraesthesia (509), Decreased appetite (498), Injection site pain (485), and Influenza (480).

The time to onset from vaccination to the event was available for 71.7% events of which 30.8% occurred the same day as vaccination, 23.6% occurred on day 1 post-vaccination, 8.9%% events occurred within days 2-15 post-vaccination, 5.5% events occurred between 16-200 days post-vaccination, 2.9% events occurred > 200 days post-vaccination, and for 28.3% events the time from vaccination to AE onset was not reported.

Outcomes for AEs were reported as 42.1% (23757) recovered, 20.4% (11512) as recovering, 1.2% (677) as recovered with sequelae, 21.8% (12302) not recovered, 0.3% (169) as fatal, and 14.2% (8013) as unknown.

16.3.5.4.2 Herpes Vaccine

Assessment for cases received with Herpes vaccine (Reporting Interval):

This search identified 2 spontaneous cases involving use of VAXZEVRIA with Herpes vaccine.

[redacted] A 75-year-old female with a medical history including pleural effusion, asthma, obesity, gallstones, and seronegative arthritis. She received the Pneumococcal vaccine on 02-Oct-2002, herpes simplex vaccine on 29-OCT-2020, dose 1 of unknown COVID-19 vaccine on an unknown date, dose 2 of VAXZEVRIA on 21-APR-2021, and dose 3 of Covid-19 mRNA Vaccine Biontech on 06-NOV-2021. On 07-Nov-2021, she experienced events of COVID-19 and Feeling hot. On 19-Nov-2021, she experienced Abdominal pain. On an

unknown dates, she experienced Thrombosis, Pulmonary embolism, and Chills. On 20-Nov-2021, she died from the events of Thrombosis, Pulmonary embolism, COVID-19, Chills, Feeling hot, and Abdominal pain. An autopsy was performed. The cause of death was pulmonary embolism (confirmed at autopsy), deep vein thrombosis (confirmed at autopsy) and covid-19 (confirmed at autopsy). No additional information was reported.

AZ Comment: Fatal events of Thrombosis, Pulmonary embolism, COVID-19, Chills, Feeling hot and Abdominal pain are not listed in the company core data sheet of AZD1222. Cause of death is reported as Pulmonary embolism, Deep Vein Thrombosis and COVID-19. Current pandemic situation of COVID-19 and vaccinee's obesity status could be considered as a contributory risk factor for COVID-19 while the age of the patient could be considered as contributory to the fatality of Thrombosis, Pulmonary embolism and COVID-19. The surgical history and the medical history of obesity could be considered as confounding factors for Pulmonary Embolism and Thrombosis. Due to limited information on the baseline health characteristics of the patient before vaccination, circumstances leading to the events, family history of the patient, possible risk factors, and clinical course of COVID-19, the evaluation did not find evidence to suggest a causal relationship between the events and VAXZEVRIA.

[redacted] A 35-year-old male who received VAXZEVRIA on 02-JUN-2021 and herpes zoster vaccine on an unknown date. On 02-JUN-2021, he experienced Chills and Headache. On 03-JUN-2021, he experienced Herpes zoster. He recovered from the events of Chills on 03-JUN-2021 and Headache on 07-JUN-2021. At the time of reporting, the event of Herpes zoster was ongoing. All events were considered non-serious.

AZ Comment: A consumer report with non-serious events of Herpes zoster, Chills, and Headache. Limited information precludes causal assessment.

Assessment for cases received with Herpes vaccine (Cumulative search):

Cumulatively, this search has identified a total 3 cases, including the two cases from the reporting interval. The additional case has been described in the previous PBRER.

16.3.5.4.3 Pneumococcal Vaccine

Assessment for cases received with Pneumococcal vaccine (Reporting interval):

This search identified a total of 110 cases (99.1% spontaneous cases and 0.9% non-interventional/post-marketing cases) for the topic use of VAXZEVRIA with Pneumococcal vaccine.

Of the 110 cases, 80.0% (88) were reported in females, 18.2% (20) in males, and 1.8% (2) of unknown gender. The age ranged from 18 years to <65 years in 32.7% (36) of the reports and 65+ years in 24.5% (27). In 42.7% (47) cases the age was not reported. Of the 110 reports,

75.5% (83) cases were medically confirmed with remaining 24.5% (27) being consumer reports.

Of the 110 reports, 9.1% (10) were serious and reported seriousness criteria were medically important (3), disability (1), hospitalization (1), life threatening (1), and death (4). Cases may have met more than one criteria for seriousness. The remaining 90.9% (100) cases were non-serious.

A total of 305 AEs were reported within the 110 reports.

The top 20 reported PTs were Oedema (33), Pyrexia (22), Headache (21), Fatigue (13), Pain (11), Pain in extremity (11), Application site pain (10), Myalgia (10), Erythema (9), Feeling hot(9), Flushing (9), Dizziness (8), Chills (7), Hyperaemia (7), Arthralgia (5), Application site warmth (4), Oedema peripheral (4), Abdominal pain (3), Chest pain (3), and Hypertension (3).

The time to onset from vaccination to the event was available for 84.9% of AEs, of which 17.2% occurred within day 0 of vaccination, 9.1% occurred on day 1 post vaccination, 5.5% events occurred within days 2-15 post-vaccination, 28.4% events occurred between 16-200 days post-vaccination, 23.9% events occurred > 200 days post-vaccination. For 15.9% events, the time to onset post vaccination was not reported.

Outcomes for AEs were reported as recovered for 118 (38.7%, recovering for 35 (11.5%), recovering with sequelae for 4 (1.3%), not recovered for 36 (11.8%), fatal for 9 (3.0%), and unknown for 103 (33.8%).

Of the 4 fatal cases, two have been identified as duplicates of each other and the consolidated case is detailed below in the Varicella vaccine (Reporting interval) section. Of the remaining 2 fatal cases, one ([redacted] involved a 73-year-old male with a history of autoimmune disorder, hepatitis C, and overweight. He received VAXZEVRIA on an unknown date. It was not reported when he received the Pneumococcal vaccine. During Aug-2021, he experienced Subdural haematoma. On 31-Aug-2021, he experienced Thrombocytopenia. On an unknown dates, he experienced Syncope, Fall, Contusion, Haemorrhage, Loss of consciousness, and Platelet count decreased. He died from the event of Thrombocytopenia on 31-Aug-2021. An autopsy was not performed. The cause of death was Thrombocytopenia.

AZ Comment: The events could be in association with each other and with reported event of Platelet count decreased. Vaccinee's advanced age, medical history of possible Diabetes mellitus and Autoimmune disorder could be considered as confounding factors to the events. Due to limited information on baseline health condition before vaccination, relevant medical history (diabetes mellitus control and therapy compliance, clarification on autoimmune disorder), date of vaccination, concurrent conditions (infections, hypoglycaemia, ketoacidosis, dehydration), further details on concomitant medications, details and circumstances

surrounding the events, possible risk factors (trauma, blood clotting disorders, vitamin c or k deficiency, blood thinners, alcohol or drug abuse), and detailed diagnostic and etiologic workup (complete blood analysis including coagulation profile, platelet count complete report, infection profile, relevant imaging studies, medical notes from health care provider), autopsy report with confirmed diagnosis, the evaluation did not find evidence to suggest a causal relationship between the events and VAXZEVRIA.

The remaining fatal case ( ) is detailed above in the Herpes vaccine (Reporting Interval) section.

Assessment for cases received with Pneumococcal vaccine (Cumulative search):

This search identified a total of 387 cases (93.0% spontaneous cases, 6.7% non-interventional/post-marketing cases, and 0.3% literature cases) for the topic use of VAXZEVRIA with Pneumococcal vaccine.

Of the 387 cases, 73.4% (284) were reported in females, 24.5% (95) in males, and gender was not reported in the remaining 2.1% (8) of cases. The age ranged from 18 years to <65 years in 43.7% (169) of the reports, 65+ years in 39.5% (153), and 0.5% (2) in less than 18 years of age. In 16.3% (63) cases the age was not reported. Of the 387 reports, 33.6% (130) cases were medically confirmed with remaining 66.4% (257) being consumer reports.

Of the 387 reports, 49.9% (193) were serious and reported seriousness criteria were medically important (153), disability (16), hospitalization (14), life threatening (6), and death (4). Cases may have met more than one criteria for seriousness. The remaining 51.1% (194) cases were non-serious.

A total of 1592 AEs were reported within the 387 reports.

The top 20 reported PTs were Headache (130), Pyrexia (91), Fatigue (91), Chills (76), Myalgia (60), Nausea (54), Pain in extremity (48), Arthralgia (39), Dizziness (41), Oedema (34), Pain (33), Malaise (27), Tremor (19), Erythema (17), Feeling hot (17), Influenza like illness (17), Asthenia (15), Feeling cold (15), Pruritus (13), and Vomiting (13).

The time to onset from vaccination to the event was available for 71.9% of AEs, of which 27.4% occurred within day 0 of vaccination, 14.9% occurred on day 1 post vaccination, 6.7% events occurred within days 2-15 post-vaccination, 13.8% events occurred between 16-200 days post-vaccination, 8.9% events occurred > 200 days post-vaccination. For 28.1% events, the time to AE onset post vaccination was not reported.

Outcomes for AEs were reported as recovered 662 (41.6%), recovering for 243 (15.3%), 1recovering with sequelae for 20 (1.3%), not recovered for 330 (20.7%), died for 9 (0.6%), and unknown for 328 (20.6%).

16.3.5.4.4 Varicella Vaccine

Assessment for cases received with Varicella vaccine (Reporting interval):

This search identified a total of 17 cases (100% spontaneous cases) for the topic use of VAXZEVRIA with Varicella vaccine.

Of the 17 cases, 52.9% (9) were reported in females, 29.4% (5) in males, and 17.6% (5) in unknown gender. The age ranged from 18 years to <65 years in 23.5% (4) of the reports, 65+ years in 70.6% (12), and 5.9% (1) of unknown age. Of the 17 reports, 17.6% (3) cases were medically confirmed with remaining 82.4% (14) being consumer reports.

Of the 17 reports, 41.2% (7) were serious and reported seriousness criteria were medically important (3), hospitalization (1), life threatening (1), and death (2). Cases may have met more than one criteria for seriousness. The remaining 58.8% (10) cases were non-serious.

A total of 45 AEs were reported within the 17 reports.

The top 20 reported PTs were Headache (5), Herpes zoster (3), Musculoskeletal stiffness (3), Pyrexia (2), Chills (2), Fatigue (2), Guillain-Barre syndrome (2), Hypertension (2), Vaccination failure (2), and 1 each for Asthenia, Cough, Dizziness postural, Facial paralysis, Feeling hot, Flushing, Influenza like illness, Injection site pain, Mesothelioma, Myalgia, and Nasal congestion.

The time to onset from vaccination to the was available for 57.8% of AEs, of which 9.6% occurred within day 0 of vaccination, 13.3% occurred on day 1 post vaccination, 1.2% events occurred within days 2-15 post-vaccination, 18.1% events occurred between 16-200 days post-vaccination and 15.7% events occurred >200 days post-vaccination. For 42.2% events, the time to onset post vaccination was not reported.

Outcomes for AEs were reported as recovered for 13 (28.9%), recovering for 4 (8.9%), not recovered for 6 (13.3%), died for 2 (4.4%), and unknown for 20 (44.4%).

The fatal cases have been identified as duplicates of each other. The fatal case ([redacted]) during the reporting period involved a 71-year-old vaccinee of unknown gender who received the first dose of VAXZEVRIA on 09-Feb-2021 and the second dose on 26-Apr-2021. The vaccinee received the Pneumococcal Polysaccharide Vaccine and Zostavax (varicella zoster vaccine live) on 11-Jun-2021. On 20-Oct-2021, the vaccinee experienced Guillain-Barre syndrome, and, on an unknown date, Hypertension and Pneumonia aspiration). On 20-Oct-2021, the patient died from the event of Guillain-Barre syndrome. The outcome of the event of Hypertension was unknown. It was not known whether an autopsy was performed. The cause of death was aspiration pneumonia and Guillain-Barre syndrome.

AZ Comment: Age of vaccinee could be considered a risk factor for fatal outcome. Guillain-Barre syndrome can be a confounding factor to the events of Pneumonia aspiration and Hypertension. Due to limited information on date of vaccination, onset date of events, risk factors (viral infection, surgery, trauma), circumstances surrounding the events, concurrent conditions, concomitant medications, therapeutic measures taken with respect to the events, relevant medical history, detailed etiological and diagnostic work-up (complete blood analysis, physical examination, neurological workup, radiological investigations including imaging studies, autopsy report with confirmed final diagnosis) the evaluation did not find evidence to suggest a causal relationship between the events and VAXZEVRIA.

Assessment for cases received with Varicella vaccine (Cumulative search):

This search identified a total of 60 cases (93.3% spontaneous cases, and 6.7% non-interventional/post-marketing cases) for the topic use of VAXZEVRIA with Varicella vaccine.

Of the 60 cases, 58.3% (35) were reported in females, 33.3% (20) in males, and gender was not reported in the remaining 8.3% (5) of cases. The age ranged from 18 years to < 65 years in 23.3% (14) of the reports, and 65+ years in 71.7% (43). In 5.0% (3) cases the age was not reported. Of the 60 reports, 23.3% (14) were medically confirmed with remaining 76.7% (46) being consumer reports.

Of the 60 reports, 50.0% (30) were serious and reported seriousness criteria were medically important (22), disability (1), hospitalization (3), life threatening (2), and death (2). Cases may have met more than one criteria for seriousness. The remaining 50.0% (30) cases were non-serious.

A total of 206 AEs were reported within the 60 reports.

The top 20 reported PTs were Pyrexia (13), Headache (13), Herpes zoster (10), Chills (9), Fatigue (9), Nausea (7), Pain in extremity (6), Vaccination failure (6), Arthralgia (4), Myalgia (4), Pain (4), Rash (4), Asthenia (3), Blister (3), Influenza like illness (3), Musculoskeletal stiffness (3), Pruritus (3), Urticaria (2), Abdominal pain upper (2), and Deep vein thrombosis (2).

Time to onset from vaccination to the event was available for 59.9% of AEs, of which 14.9% of events occurred within day 0 of vaccination, 12.8% occurred on day 1 post vaccination, 5.5% events occurred within days 2-15 post-vaccination, 16.6% events occurred between 16-200 days post-vaccination, and 10.0% events occurred > 200 days post-vaccination. For 29.3% events, the time to onset post vaccination was not reported.

Outcomes for AEs were reported as recovered for 62 (30.1%), recovering for 39 (18.9%), recovered with sequelae for 5 (2.4%), not recovered for 39 (18.9%), died for 2 (1.0%), and unknown for 59 (28.6%).

Discussion

The most common adverse events reported of VAXZEVRIA when co-administered with other vaccines were similar to VAXZEVRIA when given alone. In most cases, there was limited information. There were no additional reports received regarding Use of VAXZEVRIA with other vaccines.

Conclusion

This cumulative and periodic review of the Use of VAXZEVRIA with other vaccines did not indicate any new safety concerns.

Use of VAXZEVRIA with other vaccines will continue to be considered missing information for VAXZEVRIA. Use of VAXZEVRIA with other vaccines will be investigated primarily in the ongoing non-interventional post-marketing observational study using existing secondary health data sources (D811110R00002 [US] and D8111R00006 [EU/UK]) study of subgroups exposed to VAXZEVRIA. Refer to Appendix 4 for additional details.

16.4 Characterisation of risks

At the end of the reporting period, the VAXZEVRIA safety specification (presented in the global AstraZeneca Core Risk Management Plan, Version no. 7.0, dated 22 February 2022) included the following important identified and important potential risks, and missing information (see Table 213). Characterisations of the safety concerns are presented in Sections 16.4.1, 16.4.2 and 16.4.3 respectively.

Table 213 Summary of safety concerns – AstraZeneca Core Risk Management Plan for VAXZEVRIA (Version no. 7.0, dated 22 February 2022)

Risk Category	Safety concern
Important identified risks	Thrombosis in combination with thrombocytopenia
Important potential risks	Immune-mediated neurological conditions
	Vaccine-associated enhanced disease (VAED)
	Cerebrovascular venous sinus thrombosis without thrombocytopenia
Missing information	Use of VAXZEVRIA in pregnant and breastfeeding women
	Use of VAXZEVRIA in subjects with severe immunodeficiency
	Use in subjects with severe and/or uncontrolled underlying disease
	Use of VAXZEVRIA with other vaccines

In the following sections, detailed information is given on the important identified and potential risks, and missing information included in Table 213 above.

16.4.1 Important identified risks

The following safety concern is considered as important identified risk:

- Thrombosis in combination with thrombocytopenia (Section 16.4.1.1).

16.4.1.1 Thrombosis in combination with thrombocytopenia

Table 214 Important identified risk - Thrombosis in combination with thrombocytopenia

Characterisation	Summary
Frequency	There were no reports of thrombosis concurrent with thrombocytopenia in the VAXZEVRIA clinical development programme. Very rare events of serious thrombosis concurrent with thrombocytopenia (including fatal events), have been observed following vaccination with VAXZEVRIA during post-authorisation use. The majority of the events occurred within the first 21 days following vaccination and some events had a fatal outcome. The reporting rates after the second dose are lower compared to after the first dose.
Potential mechanism	The exact mechanism of thrombosis concurrent with thrombocytopenia following immunisation with VAXZEVRIA is unknown. Several hypothetical biologic mechanisms have been proposed to explain the pathophysiology of thromboembolic events with thrombocytopenia following vaccination (Greinacher et al 2021 (NEJM)). Among them a study by Baker et al 2021, proposes an interaction between the ChAdOx1 vaccine vector used in VAXZEVRIA and PF4; however, it is unknown if the adenoviral ChAdOx1 interaction with PF4 is actually platelet activating or thrombogenic (causal of blood clots). Greinacher et al 2021 (NEJM) suggested that ChAdOx1 itself or proteins contained within the vaccine can bind to PF4 to form immune complexes which may drive a B-cell response causing high-titer anti-PF4 antibodies resulting in TTS. However, none of these hypotheses have been confirmed.
Risk groups or risk factors	There are no known risk factors for the development of thrombosis with thrombocytopenia following vaccination.

Table 214 Important identified risk - Thrombosis in combination with thrombocytopenia

Characterisation	Summary
Preventability	Prevention of thrombosis concurrent with thrombocytopenia in the context of COVID-19 vaccination is currently unknown. As described in Section 4.4 of the CDS, HCPs should be alert to the signs and symptoms of thromboembolism and thrombocytopenia, as well as coagulopathies. Vaccinated individuals should be instructed to seek immediate medical attention if they develop symptoms such as a severe or persistent headaches, blurred vision, confusion, seizures, shortness of breath, chest pain, leg swelling, leg pain, persistent abdominal pain, or unusual skin bruising and/or petechia a few days after vaccination.
Impact on the risk-benefit balance of the product	Thrombosis with thrombocytopenia is a potentially life-threatening event if not recognised or managed appropriately, may result in persistent or significant disability or incapacity. Thrombosis with thrombocytopenia requires immediate medical intervention.
Public health impact	The public health benefit of vaccination is considered to outweigh the very rare occurrence of these events.

16.4.2 Important potential risks

The following 3 safety concerns are considered as important potential risks:

- Immune-mediated neurological conditions (Section 16.4.2.1).
- Vaccine-associated enhanced disease (VAED) (Section 16.4.2.2).
- Cerebrovascular venous sinus thrombosis (CVST) without thrombocytopenia (Section 16.4.2.3).

16.4.2.1 Immune-mediated neurological conditions

Table 215 Important potential risk – Immune-mediated neurological conditions

Characterisation	Summary
Frequency	Overall, in clinical studies there were no clinically meaningful imbalances in the incidence of neurological AESIs. In the US study, neurologic or neuroinflammatory AESIs were reported in 0.6% (121/21,587 participants) in the VAXZEVRIA (formerly AZD1222) group and 0.4% (48/10,792 participants) in the placebo group. In the pooled Oxford studies as of 07 December 2020, neurologic or neuroinflammatory AESIs were reported in 0.7% (81/12,282 participants) in the VAXZEVRIA (formerly AZD1222) group and 0.8% (90/11,963 participants) in the control group. Furthermore, in the pooled Oxford studies no clinically meaningful imbalance was noted in the incidence of AESIs of neuroinflammatory disorders, which were reported in 7 participants (0.1%) in the VAXZEVRIA (formerly AZD1222) group and 4 participants (< 0.1%) in the control group in the pooled safety dataset (any dose group). Of these, the most frequently reported events were nonserious AEs of facial paralysis occurred in 4 participants in the VAXZEVRIA (formerly AZD1222) group and 3 participants in the control group. In the US study, there were 5 nonserious AEs of facial paralysis, all in the VAXZEVRIA (formerly AZD1222) group. In the US study, there was 1 SAE of a demyelinating event: a participant in the VAXZEVRIA (formerly AZD1222) group had an AE initially reported as Guillain-Barre syndrome, which was subsequently diagnosed as an SAE of Chronic inflammatory demyelinating polyradiculoneuropathy. In the pooled Oxford studies, there were 3 SAEs of demyelinating events: 2 cases in the VAXZEVRIA (formerly AZD1222) group (1 case of transverse myelitis, and 1 case of multiple sclerosis in a participant with pre-existing, but previously unrecognised, multiple sclerosis), and 1 case of myelitis in the control group.
Potential mechanism	Several hypothetical biologic mechanisms have been proposed to explain the pathophysiology of neurologic adverse reactions following immunisation; most involve the concept of autoimmunity and the possibility that the vaccine's immunostimulatory effect results in an aberrant immunologic response (Stratton et al 1994).
Risk groups or risk factors	There are no known risk factors for the development of immune-mediated neurological conditions following vaccination.
Preventability	Prevention of immune-mediated neurological conditions in the context of SARS-COV-2 vaccination is unknown.

Table 215 Important potential risk – Immune-mediated neurological conditions

Characterisation	Summary
Impact on the risk-benefit balance of the product	Severe immune-mediated neurological conditions, if not recognised or managed appropriately, may result in persistent or significant disability or incapacity.
Public health impact	Immune-mediated neurological disorders are very rare, and as such the public health benefit of vaccination is considered to outweigh the very rare potential occurrences of such events.

AE Adverse Event; AESI Adverse Events of Special Interest; SARS-COV-2 Severe Acute Respiratory Coronavirus 2.

16.4.2.2 Vaccine-associated enhanced disease (VAED)

Table 216 Important potential risk – Vaccine-associated enhanced disease (VAED)

Characterisation	Summary
Frequency	In the VAXZEVRIA clinical programme, there was no evidence of an association between VAXZEVRIA and VAED; proportionally more AESIs based on study specific lists of terms related to COVID-19[1] occurred in the control group than among VAXZEVRIA (formerly AZD1222) recipients. In the US study, COVID-related AESIs were reported in 1.7% (374/21,587 participants) in the VAXZEVRIA (formerly AZD1222) group and 3.4% (362/10,792 participants) in the placebo group. In the pooled Oxford studies as of 07 December 2020, COVID-related AESIs were reported in 0.1% (15/12,282 participants) in the VAXZEVRIA (formerly AZD1222) group and 0.3% (36/11,963 participants) in the control group. There have been no confirmed post-marketing reports of VAED.
Potential mechanism	The pathogenesis of VAED in the context of SARS-CoV-2 is unclear, and there are no consistent mechanisms or immune markers of disease enhancement from nonclinical studies (Haynes et al 2020).
Risk groups or risk factors	There are no known risk factors identified for VAED.
Preventability	Prevention of VAED in the context of SARS-COV-2 is currently unknown.

[1] Based on the selected terms: Acute lung injury, Acute respiratory distress syndrome, Pneumonitis, Coronavirus infection, COVID-19, COVID-19 pneumonia, Multisystem inflammatory syndrome in children, SARS-CoV-2 sepsis, Suspected COVID-19.

Table 216 Important potential risk – Vaccine-associated enhanced disease (VAED)

Characterisation	Summary
Impact on the risk-benefit balance of the product	Vaccine-associated enhanced disease may present as severe disease or modified/unusual clinical manifestations of a known disease presentation and may involve one or multiple organ systems. Subjects with VAED may experience rapid clinical deterioration and will likely require non-invasive or invasive mechanical ventilation; and patients diagnosed with ARDS have poorer prognosis and potentially higher mortality rate.
Public health impact	As this safety concern is currently theoretical in relation to VAXZEVRIA administration, there is no public health impact noted at this time.

AESI Adverse Events of Special Interest; COVID-19 Coronavirus Disease of 2019; SARS-COV-2 Severe Acute Respiratory Coronavirus 2; VAED Vaccine-associated enhanced disease.

16.4.2.3 Cerebrovascular venous sinus thrombosis (CVST) without thrombocytopenia

Table 217 Important potential risk – Cerebrovascular venous sinus thrombosis (CVST)

Characterisation	Summary
Frequency	There were no reports of CVST identified in the VAXZEVRIA (formerly AZD1222) group in the US study (D8110C00001 [DCO: 15 March 2021] and D8111C00002 [DCO: 10 January 2021]), and in the pooled Oxford studies (COV001, COV002, COV003 and COV005; DCO: 07 December 2020). In the post-marketing setting, CVST without thrombocytopenia have been reported very rarely following vaccination with VAXZEVRIA.
Potential mechanism	The exact mechanism of CVST without thrombocytopenia following administration with VAXZEVRIA is unknown.
Risk groups or risk factors	There are no known risk factors for the development of CVST without thrombocytopenia following vaccination.
Preventability	Prevention of CVST without thrombocytopenia in the context of COVID-19 vaccination is currently unknown. The events of CVST without thrombocytopenia can be fatal and may require different treatment approaches than thrombosis in combination with thrombocytopenia.
Impact on the risk-benefit balance of the product	CVST without thrombocytopenia is a potentially life-threatening event, and if not recognised or managed appropriately, may result in persistent or significant disability or incapacity, and hence requires immediate medical intervention.

Table 217 Important potential risk – Cerebrovascular venous sinus thrombosis (CVST)

Characterisation	Summary
Public health impact	The public health benefits of vaccination are considered to outweigh the very rare occurrence of these events.

COVID-19 Coronavirus Disease of 2019; CVST- Cerebral Venous Sinus Thrombosis.

16.4.3 Missing information

The following 4 safety concerns are considered as missing information:

- Use of VAXZEVRIA in pregnant and breastfeeding women (Section 16.4.3.1)
- Use of VAXZEVRIA in subjects with severe immunodeficiency (Section 16.4.3.2)
- Use of VAXZEVRIA in subjects with severe and/or uncontrolled underlying disease (Section 16.4.3.3)
- Use of VAXZEVRIA with other vaccines (Section 16.4.3.4)

16.4.3.1 Use of VAXZEVRIA in pregnant and breastfeeding women

Evidence source

As per the VAXZEVRIA CDS Section 4.6, data from more than 400 case reports of pregnant women or women who became pregnant after receiving VAXZEVRIA do not suggest unusual patterns of pregnancy complications or foetal/neonatal outcomes. No increased risk of maternal thrombosis in combination with thrombocytopenia has been observed. Preliminary non-clinical safety studies have not indicated any concern to date, and available non-clinical, clinical and post-marketing data do not suggest a risk to breastfed newborns/infants. As VAXZEVRIA is intended for use in mass vaccination campaigns in a large proportion of the global population, the collection of pregnancy and infant outcomes data with the aim of further characterising the safety profile in this population, is still considered necessary.

Population in need of further characterisation

Although there are data in the post-marketing setting in pregnant and breastfeeding women, use of VAXZEVRIA in pregnant and breastfeeding women will continue to be investigated in the ongoing PASS (EAS, a post-marketing observational study using existing secondary health data sources, and a pregnancy registry).

16.4.3.2 Use of VAXZEVRIA in subjects with severe immunodeficiency

Evidence source

Vaccines may be less effective in severely immunocompromised subjects, as the vaccinees weakened immune system may not mount a sufficient response; however, immunocompromised individuals may also be at greater risk of morbidity and mortality from

vaccine-preventable disease, and consequently this population have been identified as a priority group for initial vaccination in several jurisdictions following vaccine availability.

Although there is no evidence that the safety profile of this population receiving VAXZEVRIA will be different to that of the general population, given the paucity of data, the possibility cannot be excluded.

Population in need of further characterisation

Use of VAXZEVRIA in subjects with severe immunodeficiency will continue to be investigated in the planned PASS (EAS and a post-marketing observational study using existing secondary health data sources, a post-marketing safety study in patients receiving immunosuppressant medication or with primary immunodeficiency, and an interventional study in immunocompromised subjects) and in ongoing clinical study COV005).

16.4.3.3 Use of VAXZEVRIA in subjects with severe and/or uncontrolled underlying disease

Evidence source

Subjects with severe and/or uncontrolled underlying disease are potentially at risk of developing a more severe manifestation of COVID-19, and as a consequence have been included as a priority group for initial vaccination in several jurisdictions following vaccine availability. Although there is no evidence that the safety profile of this population receiving VAXZEVRIA will be different to that of the general population, given the paucity of data, the possibility cannot be excluded.

Population in need of further characterisation

Use of VAXZEVRIA in patients with severe and/or uncontrolled disease will continue to be investigated in the planned PASS (EAS and a post-marketing observational study using existing secondary health data sources).

16.4.3.4 Use of VAXZEVRIA with other vaccines

Evidence source

There is currently limited information regarding the safety, immunogenicity, and efficacy of VAXZEVRIA when co-administered with other vaccines (eg, concurrently with seasonal illness vaccines). While there is currently no evidence to suggest the safety profile or efficacy of VAXZEVRIA when co-administered with other vaccines would be impacted, given the paucity of data, the possibility of an interaction causing an altered safety profile or reduced efficacy of either VAXZEVRIA or the co-administered vaccine cannot be excluded.

Population in need of further characterisation

The co-administration of VAXZEVRIA with other vaccines (either together, or 30 days before or after administration) will continue to be investigated in the planned PASS (a post-marketing observational study using existing secondary health data sources).

16.5 Effectiveness of risk minimisation

No information on the effectiveness of risk minimisation activities relevant to the benefit-risk assessment became available during the reporting period.

17 BENEFIT EVALUATION

17.1 Important baseline efficacy/effectiveness information

At the beginning of the reporting period, VAXZEVRIA was authorised for "active immunisation of individuals > 18 years old for the prevention of COVID-19".

A summary of the information supporting the efficacy and effectiveness of VAXZEVRIA in this approved indication is provided in the sub-section below.

17.1.1 Active immunisation of individuals ≥18 years old for the prevention of COVID-19

The efficacy and immunogenicity of a two-dose regimen of VAXZEVRIA is being investigated in 11 ongoing clinical trials (as presented in Section 7), with initial VE against symptomatic disease being demonstrated from a pooled analysis across four trials (COV001, COV002, COV003, COV005) as well as a Phase III study in the USA, Peru and Chile (D8110C00001). The vaccine has also shown to be highly immunogenic after a single dose, with increase in seroconversion after a second dose. Moreover, adults (including those over the age of 65 years) with pre-existing comorbidity showed similar VE and immune responses when compared to the general population.

Therefore, VAXZEVRIA is able to elicit a strong immune response capable of preventing serious symptomatic infections with SARS-COV-2, the causative agent of COVID-19, a life-threatening disease, particularly in older age groups. VAXZEVRIA has been shown to be efficacious in preventing severe disease, avoiding hospitalization and death.

Emerging data suggest that waning protection in the months following a 2-dose primary series is contributing to the incidence of breakthrough infection.

Data supporting an AZD1222 booster dose option are supported by analysis of the University of Oxford-sponsored COV001 study as reported by Flaxman et al 2021. In participants previously vaccinated with a 2-dose course of AZD1222, data reported by Flaxman et al 2021 indicate that a third dose booster of AZD1222 administered 28 or more weeks after a second dose induces high levels of antibodies and boosts T-cell responses. Data from the COV-BOOST trial (Munro et al 2021) indicate that booster doses of COVID-19 vaccines are generally well tolerated and provide a substantial increase in vaccine-induced immune responses. The authors concluded that all vaccines studied boosted antibody and neutralising responses after an initial course of AZD1222/AZD1222, with no safety concerns, and that the

substantial differences in humoral and cellular responses in combination with vaccine availability will influence policy choices for booster vaccination. In addition, heterologous boosting with AZD1222 on top of an initial course of an mRNA vaccine COMIRNATY) showed similar results as after an initial course of AZD1222/AZD1222 followed by a booster, with no safety concerns.

On 26 November 2021, the WHO designated the Omicron variant (B.1.1.529) a variant of concern (Tracking SARS-CoV-2 variants). Researchers at the University of Oxford have issued a preprint regarding the neutralisation of Omicron by large panel of sera, including from convalescent patients and from vaccinees receiving 2 or 3 doses of VAXZEVRIA or COMIRNATY vaccine (Dejnirattisai et al 2021).

AstraZeneca has also collaborated with the University of Oxford researchers who conducted these assessments and with the UKHSA (formerly called Public Health England) to analyse sera from participants in ongoing AstraZeneca-sponsored study D7220C00001 who had received 3 doses of AZD1222.

Collectively, these preliminary live virus neutralisation data suggest that 2-dose primary series immunisation with AZD1222 will likely provide limited protection against infection with the Omicron variant. These data also suggest that adding a third booster dose of AZD1222 will likely provide increased protection against infection with the Omicron variant, though still less protection than as against the original Wuhan-Hu-1 strain or other variants of concern.

17.2 Newly Identified Information on efficacy/ effectiveness

During the reporting period of this PBRER, key data and relevant information became available on: i)AstraZeneca sponsored studies D8110C00001 and D8111C00002 ii) Homologous and Heterologous Third dose booster; iii) Vaccine effectiveness against dominant SARS-COV-2 variant of concern omicron and iv) R-pharm multicentric study assessing the safety and immunogenicity of interchangeability of two different adenovirus vector vaccines (rAd26 and VAXZEVRIA). A summary of new information supporting the efficacy and effectiveness of VAXZEVRIA against COVID-19 is provided below.

17.2.1 AstraZeneca sponsored study

New information on the efficacy of VAXZEVRIA for the approved indication of the prevention of COVID-19 in adults became available from a 6-months follow up data obtained from study D8110C00001.

Since the last PBRER, data analysis from a third database lock (DCO3) occurring in September 2021 became available for the ongoing study D8110C00001. These data included a 6-month data follow up after cut-off on 30 July 2021. The majority of participants (90.3% in the AZD122 group and 89.8% in the placebo group) had been unblinded at the time of the

data cut-off date of 30 July 2021 and the median follow-up time post second dose for the full data set (FVS) over the double-blind period was 78.0 days for the AZD1222 group and 71.0 days for the placebo group.

Participants were allowed to request unblinding and receive non study COVID-19 vaccines as these became available to them. For the primary efficacy endpoint in the double-blind period (141 and 184 events; incidence rates: 39.2 and 118.8 per 1,000-person-years, median follow-up from second dose 78 (AZD1222) and 71 days (placebo)), vaccine efficacy was 67.0% ($P < 0.001$). In the period to non-study COVID-19 vaccination, incidence of events remained consistently low and stable through 6 months in the AZD1222 group; for the primary efficacy endpoint (328 and 219 events; incidence rates: 36.4, 108.4, median follow-up 201 and 82 days) and severe/critical disease (5 and 13 events; incidence rates: 0.6, 6.4), respective vaccine efficacy estimates were 65.1% and 92.1%. AZD1222 elicited humoral immune responses over time, with waning observed at day 180 and demonstrated durable protection.

17.2.2 D8111C00002

During the reporting period one trial was completed (Study D8111C00002), which assessed the safety and immunogenicity of VAXZEVRIA in 256 participants in Japan across all age groups. In the AZD1222 group, antibody titers for the S and RBD antigens and for the nAb (pseudoneutralization) to SARS-CoV-2 increased substantially after the first dose of study intervention, increasing further after the second dose. After one year of follow up, it was observed that humoral responses against SARS-CoV-2 waned over time from previously reported peak responses post-second dose. At Day 365, anti-SARS-CoV-2 spike-binding and receptor-binding domain mean antibody titers remained above Day 15 levels across all ages. Neutralizing antibody titers declined and were below detection levels in many participants by Day 365.

17.2.3 Homologous and Heterologous Third dose booster

During the reporting period, further evidence of immunogenicity of AZD1222 evaluating a homologous and/or heterologous third-dose booster of AZD1222 were identified in AstraZeneca-sponsored study D7220C00001 (Clinical Study Report (CSR) provided in Appendix B), COV-BOOST (Xinxue Liu et al. 2022), RHH-001 study (Clemens et al 2022), and two other observational type studies (Jara et al 2022, Muñoz-Valle et al 2022). A summary of these studies is provided below, with conclusions on how they support use of a heterologous booster dose of AZD1222 after a primary course of other authorised COVID-19 vaccines.

D7220C00001 evaluated AZD1222 as a homologous booster and as a heterologous booster after a primary 2-dose series of an mRNA vaccine. The humoral immune response to a booster dose of AZD1222 in participants previously vaccinated with either AZD1222 or an mRNA vaccine was non-inferior to the response elicited by primary vaccination with

AZD1222 (AZD1222 cohort GMT ratio: 1.03 [95% CI: 0.92 to 1.15]; mRNA cohort GMT ratio: 3.08 [95% CI: 2.78 to 3.41]).

Xinxue Liu et al. 2022 evaluated the persistence of immunogenicity after seven COVID-19 vaccines given as third dose boosters following two doses of VAXZEVRIA or COMIRNATY in the UK over the course of 3 months.

The authors reported that 84 days after a third dose of COVID-19 vaccine there were substantial differences in the decay rates of humoral response across the vaccines. Whilst ChAd and Ad26 arms had significantly lower anti-spike IgG than BNT at D28 with adjusted GMR of 0.62 (95%CI: 0.51, 0.76) and 0.72 (95%CI: 0.61, 0.85), this was no longer the case at D84 with adjusted GMR increasing to 0.95 (95%CI: 0.78, 1.15) and 1.20 (95%CI: 1.01,1.43), respectively.

One of the conclusions reached was that the anti-spike IgG in adenoviral vector vaccine arms (ChAd and Ad26) after the BNT/BNT prime showed the most persistent schedules up to D84. The immunogenicity at D84 post boost for ChAd and Ad26 was similar to, or higher than, the three dose BNT schedule (BNT/BNT/BNT), especially in older people.

RHH-001 (Clemens et al 2022), evaluated AZD1222 as a heterologous booster after a 2-dose primary series of the inactivated whole-virion adjuvanted vaccine CoronaVac. This study also evaluated COMIRNATY and JCOVDEN compared to a third dose homologous booster of CoronaVac. After 28 days, all heterologous boosting elicited a significantly superior response ($p<0.0001$) in anti-Spike IgG concentration and pseudoneutralising titres compared to homologous boosting with CoronaVac. The AZD1222 boost elicited a 90- fold rise in the anti-spike IgG from baseline versus a 12.4 -fold rise in the homologous booster dosing. All heterologous booster regimens induced high concentrations of pseudovirus nAbs. At Day 28, all groups except for the homologous boost in the older adults reached 100% seropositivity: geometric mean ratios (heterologous vs homologous) were 8.7 (95% CI: 5.9 to 12.9) for JCOVDEN, 21.5 (95% CI: 14.5 to 31.9) for COMIRNATY, and 10.6 (95% CI: 7.2 to 15.6) for AZD1222. Live virus nAbs were also boosted against the Delta (B.1.617.2) and Omicron variants (B.1.1.529). These data provide supportive evidence of AZD1222's immunogenicity and safety profile when used as a heterologous booster.

Jara et al 2022 also evaluated the vaccine effectiveness of AZD1222 as a heterologous booster after a 2-dose primary series of CoronaVac. This study was a large prospective national cohort sample following campaign immunization with CoronaVac in Chile, and assessed the effectiveness of a third dose of either CoronaVac, COMIRNATY or AZD1222. Heterologous boosting with AZD1222, following a two-dose CoronaVac primary vaccination series, yielded vaccine effectiveness of 97·7% (95% CI: 97·3-98·0) against COVID-19-related hospitalisation, 98·9% (95% CI: 98·5%-99·2%) against ICU admission, and 98·1% (95% CI:

97·3–98·6) against death. These data provide further supportive evidence on the high level of protection conferred by AZD1222 when used as a heterologous booster.

Muñoz-Valle et al 2022 evaluated AZD1222 as a heterologous booster after primary immunisation with the adenoviral vector vaccine Convidecia (CanSino Biologics Inc, China). This descriptive study involved 62 participants from a prior study of Convidecia who had received a heterologous booster with AZD1222, JCOVDEN, COMIRNATY, or mRNA-127 at 4.5 to 5 months after single-dose primary vaccination with Convidecia. A control group of 62 unboosted individuals was matched with the boosted group for age, gender, treatment, COVID-19 history, and baseline antibody levels 21 days after primary vaccination. At baseline, the median percentage of neutralizing antibodies was similar in booster and control groups (78.16% vs. 78.65%, $p > 0.05$), but at 6 months post-booster was significantly higher in the boosted group versus controls (96.41% vs. 89.33%, $p = 0.0004$), with no differences between vaccines. There were also no differences in adverse events between booster vaccines. The authors concluded that a heterologous regimen of 1 dose of Convidecia followed by a booster dose of a different vaccine is safe and results in a robust humoral immune response. These data support the use of AZD1222 as a heterologous booster after a primary series of an adenovirus vector vaccine.

17.2.4 Vaccine effectiveness against dominant SARS-COV-2 variant of concern - Omicron

A recent test-negative case-control study examined the VE against symptomatic disease caused by the Delta and Omicron variants (Andrews et al 2022). The study included a representative sample of the general population in England who had PCR tests performed when prevalence of Omicron had surpassed that of Delta variant in the UK. The data set included 886774 persons with symptomatic disease who were infected with the Omicron variant, 204154 persons infected with the Delta variant, and 1572621 test-negative controls. Protection against severe COVID-19 or hospitalisations due to COVID-19 was not assessed in this study. No effect against the Omicron variant was observed from 20 weeks after a primary vaccination with AZD1222, but the VE of a booster dose was 55.6% at 2 to 4 weeks and 46.7% at 5 to 9 weeks following booster administration. This decrease in VE was also noted with a third homologous dose of COMIRNATY, with VE decreasing from 67.2% at 2 to 4 weeks to 45.7% after 10 or more weeks, and mRNA-1273, for which VE declined from 73.9% after 2 to 4 weeks to 64.4% after 5 to 9 weeks.

In another real-world evidence study conducted by the United Kingdom Health Security Agency (Kirsebom et al 2022), a test-negative case control design was used to estimate the VE of an AZD1222 or COMIRNATY booster following a primary series of AZD1222 against symptomatic disease and hospitalisation after infection with the SARS-CoV-2 Omicron variant in England. Protection against symptomatic disease in those aged 65 years and older peaked at 66.1% and 68.5% among those who received AZD1222 and COMIRNATY

boosters, respectively, and waned to 44.5% and 54.1% after 5 to 9 weeks. VE against hospitalisation after infection with the SARS-CoV-2 Omicron variant peaked at 82.3% after an AZD1222 booster and 90.9% after a COMIRNATY booster. The authors noted differences between the population receiving AZD1222 and the population receiving COMIRNATY, with those receiving 3 doses of AZD1222 more likely to be in risk groups; this was also true for Andrews et al 2022. While AZD1222-induced nAb concentrations were lower against the Omicron variant than for other variants, no correlates of protection have been established, and clinical effectiveness of an AZD1222 booster has been observed in real-world studies against COVID-19 due to the Omicron variant.

Additional real world studies have demonstrated high vaccine effectiveness (VE) against the Omicron variant in a variety of settings and populations, particularly with regard to prevention of severe disease and are summarized below.

- Effectiveness of a 2-dose primary series of AZD1222 remains high (61-71% VE) against hospitalisation due to Omicron variant in individuals 65+ years of age in England who completed their primary series >175 days previously (Kirsebom et al 2022, Stowe et al 2022).
- At 7+ days after a 3rd dose AZD1222 booster on top of an AZD1222 primary series, effectiveness against hospitalisation due to the Omicron variant is 82% (95% CI 64-91%). (Kirsebom et al 2022).
- Against symptomatic Omicron infection in Thailand, AZD1222 given as a 1st booster was shown to have 26% VE (95% CI 8-40), whilst AZD1222 as a 2nd booster offered significantly higher protection, with 71% VE (85% CI 59-79; Chariyalertsak et al 2022)
- Effectiveness of hybrid immunity (infection plus vaccination) against infection for AZD1222 vaccine as 1st booster peaked at 72.1% (95% CI: 71.4-72.8%) during a period when Omicron was dominant in Brazil. Protection against severe illness (hospitalization or death) provided by a 1st booster dose of AZD1222 peaked at 98.1% (95% CI: 97.7-98.5%) during an Omicron predominant period (Cerqueira-Silva et al 2022).
- In a prison population in Zambia that included over 10.5% of individuals who were living with HIV, effectiveness of an AZD1222 primary series against infection with Omicron was 89.4% (95% CI: 59.5-97.8%), whilst effectiveness against symptomatic infection with Omicron was 85.1% (95% CI: 19.5-98.0%; Simwanza et al 2022).

17.2.5 R-pharma sponsored study NCT04684446, r-pharm code: CV03872097

A Phase I/II Single-Blinded Randomised Safety and Immunogenicity Study in Adults of VAXZEVRIA and rAd26-S Administered as Heterologous Prime Boost Regimen for the Prevention of COVID-19".

This is an ongoing international, multicentre, single-blinded, randomised, phase I/II, study assessing the immunogenicity and safety of AZD1222 and rAd26-S administered as heterologous prime boost in alternating order in 2 study groups (ie, group A received

one intramuscular (IM) injection of 5 × 1010 viral particles (vp) (nominal) of AZD1222 on Day 1 followed by rAd26-S 1 × 1011 vp (nominal) on Day 29 and group B received one IM injection of rAd26-S 1 × 1011 vp (nominal) on Day 1 followed by AZD1222 5 × 1010 vp (nominal) on Day 29.

Preliminary safety data became available during the reporting period and are provided below. Final analyses have not been completed and will be provided at the next PBRER. Immunogenicity data are not available.

Overall, AZD1222 and rAd26-S components have demonstrated an acceptable safety profile with no new safety concerns from combination use of vaccines (administered in either order) in healthy adults without known past laboratory-confirmed SARS-CoV-2 infection, positive SARS-CoV-2 RT-PCR test at screening, or seropositivity to SARS-CoV-2 at screening.

Reactogenicity, as evaluated by the incidence of solicited AEs for 7 days post each dose, appeared to be greater in the sequence AZD1222/rAd26-S compared with the sequence rAd26-S/AZD1222, particularly with respect to the incidence of Grade 3 (severe) solicited local and systemic AEs observed during the first few days after injection. Overall, the reactogenicity findings were consistent with the known and well-established safety profile of AZD1222.

17.3 Characterisation of benefits

The benefits of VAXZEVRIA (AZD1222) remain essentially the same as those presented in the previous PBRER. During the reporting period, VAXZEVRIA received EMA approval to be administered intramuscularly (0.5ml) to individuals who completed the primary vaccination course with VAXZEVRIA or an approved mRNA COVID-19 vaccine and a minimum of 3 months have elapsed from the completion of the primary vaccination.

The benefits of the vaccine have been demonstrated through controlled clinical studies conducted by AstraZeneca and the University of Oxford, as well as data from real world effectiveness studies. Analysis of efficacy across multiple clinical trials demonstrates that AZD1222 is effective against SARS-CoV-2 RT-PCR-positive symptomatic illness and prevents the development of severe/critical cases of COVID-19, including COVID-19 hospitalizations and deaths, confirming important advantages not only for the health of vaccine recipients, but also for the potential to reduce use of healthcare resources.

Availability of the D8110C00001 DCO3 (30 July 2021) analysis support maintenance of efficacy for at least 6-months (VE= 66.98% and a lower bound of the 95% CI of 58.87%.). Moreover, a closely similar level of efficacy is obtained across age groups. Furthermore, VAXZEVRIA elicited a strong humoral immune response in this study. Analysis of efficacy against variants demonstrated additional benefit, with an overall VE in sequenced variants similar to the VE of the primary analysis in study D8110C00001.

The RWE study data that became available during the reporting period provides evidence that the benefits of VAXZEVRIA extend to protection against the widely circulating omicron variant, both in the primary vaccination course and in the booster setting, particularly against progression to severe disease, hospitalization or death. These results are concordant with live virus neutralization data from exploratory analysis, conducted separately, which suggest that 2-dose primary series immunization with VAXZEVRIA will likely provide protection against infection with the Variants of Concern, including Omicron, and clinically meaningful protection against hospitalization and severe disease would be maintained. Moreover, it is anticipated that VAXZEVRIA -induced T cell responses likely will be less affected than antibody responses. Moreover, these latest RWE data are in line with the results previously reported by Flaxman et al 2021and Munro et al 2021 whereby an VAXZEVRIA booster in participants previously vaccinated with a primary series of VAXZEVRIA or mRNA vaccine, elicits strong humoral immune responses against a range of Variants of Concern.

Thus, the benefits of VAXZEVRIA 2-dose primary vaccinations are demonstrated by the efficacy and immunogenicity data in AstraZeneca-sponsored studies, University of Oxford-sponsored studies and from RWE studies, for both the primary vaccination and for the booster settings.

18 INTEGRATED BENEFIT-RISK ANALYSIS FOR APPROVED INDICATIONS

The analysis of the benefit-risk balance incorporates an evaluation of the safety and efficacy/effectiveness information that became available during the reporting period, in the context of what was known previously. This evaluation involves the following:

- Critically examining information that has emerged during the reporting period to determine whether it has generated new signals, led to the identification of new potential or identified risks, or contributed to knowledge of previously identified risks.
- Critically summarising relevant new safety and efficacy/effectiveness information that could have an impact on the benefit-risk balance.
- Conducting an integrated benefit-risk analysis for all approved indication(s) based on the cumulative information available since the DIBD (where the DIBD is unknown or AstraZeneca does not have access to data from the clinical development period, the earliest possible applicable date is used as the starting point for inclusion and evaluation of the cumulative information).
- Summarising any risk minimisation actions that may have been taken or implemented during the reporting period, as well as risk minimisation actions that are planned to be implemented.
- Outlining plans for signal or risk evaluations, including timelines and/or proposals for additional pharmacovigilance activities.

18.1 Benefit-risk context - medical need and important alternatives

A description of the medical need for VAXZEVRIA and important alternatives available is provided for each of the approved indications below.

18.1.1 Active immunisation of individuals ≥18 years old for the prevention of COVID-19

- **Medical need for the product**

Soon after the 2019 report of the then unknown pneumonia occurring in clusters of patients in Hubei province of Wuhan, China [http://wjw.wuhan.gov.cn/front/web/ show Detail/2019123108989], the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was identified as the causative agent of COVID-19 in January 2020 (Na Zhu 2020). Following the WHO declaration of the COVID-19 pandemic on 11 March 2020, COVID-19 has been reported in 223 Countries, devastating lives and causing economic chaos across the Globe.

As of 12 July 2022, WHO reported that worldwide, over 550 million cases of COVID-19 had been confirmed and over 6 million people had lost their lives to COVID-19 (WHO Coronavirus (COVID-19) Dashboard). Airfinity estimated the impact of VAXZEVRIA on lives saved to be 6.3 million based on data from Watson & Barnsley et al 2022.

There is a medical need to also maintain and/or increase protection in vaccinated individuals in the face of waning immunity and emerging variants of SARS-CoV-2. For many infectious diseases, multiple or additional 'booster' doses beyond those prescribed by the original vaccination protocol are a standard part of the vaccination schedule. For example, booster vaccines are given for tetanus, diphtheria, and polio (NHS 2021). Boosters can help to elevate the level of antibodies and memory immune cells, and in some instances, strengthen their potency (Callaway 2021).

As recommendations and regulatory authorizations for booster dosing with COVID-19 vaccines continue to expand, the authorization of AZD1222 for booster vaccination will help address the demand for COVID-19 vaccine doses, when a substantial number of people, particularly in low and low-to-middle income countries, have not received or completed a primary vaccination series (Ritchie et al 2020).

Later in the COVID-19 pandemic, viral mutations led to the emergence of more efficiently transmissible versions of SARS-COV-2, actively monitored by WHO and categorized as variants of interest or variants of concern, depending on their epidemiological characteristics and pathogenesis. During previous reporting (June to December 2021), AstraZeneca reported on WHO-labelled variants of concerns, ie, Alpha (B.1.1.7); Beta (B.1.351); Gamma (P.1) and Delta (B.1.617.2). The epidemiological landscaped has now changed and more recently, further mutations in SARS-COV-2 led to the identification of more (Nyberg et al 2022)

rapidly transmissible Omicron variants of concern, now dominating transmission within communities worldwide (ie, Omicron BA.1, BA.2, BA.3, BA.4 and BA.5) CDC 2022.

It has been noticed that hybrid immunity conferred by a mix of natural infection and immunization is not as effective against Omicron variants in comparison with the earlier strains of SARS-COV-2. Once infected with SARS-COV-2, the majority of individuals may remain asymptomatic or will experience light to mild symptoms. When severely affected, patients may need hospitalization to primarily treat pneumonia and acute respiratory distress syndrome. Systemic failure of multiple organs may ensue, leading to death. Certain comorbidities and older age are known to increase the risk for severe COVID-19 and death (Coopersmith et al 2021). Recently included in the therapeutic arsenal to treat COVID-19 are: antiviral medications (eg, molnupiravir, ritonavir in combination with nirmatrelvir, remdesivir), anti-SARS-CoV-2 monoclonal antibodies (eg, Evusheld (Tixagevimab and cilgavimab), sotrovimab), anti-inflammatory drugs (eg, dexamethasone), and immunomodulators agents (eg, baricitinib, tocilizumab). Although the contribution of the available therapeutic armamentarium towards the treatment of Covid-19 or prophylaxis from infection is significant and growing as new therapeutics are being developed, vaccines to prevent severe COVID-19 and death remain the primary agents of choice to control the COVID-19 pandemic.

- **Important alternatives available**

Following the WHO declaration of the COVID-19 pandemic on 11 March 20, accelerated vaccine development began worldwide to prevent infection with the causative agent, SARS-COV-2. Until the end of the reporting period (28 June 2022), 344 Covid-19 vaccine candidates had either been developed or were in development. (London School of Hygiene & Tropical Medicine).

Currently, five main technologies are included in approved worldwide: messenger RNA [mRNA], viral-vectored, inactivated whole virus, protein subunit, and plasmid DNA approaches (Nohynek and Wilder 2022). VAXZEVRIA is among vaccines that do not need added adjuvant to enhance immune response, unlike some whole-virus and protein subunit vaccines.

Apart from VAXZEVRIA, there are 5 other vaccines are currently approved in the EU/EEA and UK: Comirnaty (Pfizer), Spikevax (Moderna), Nuvaxovid (Novavax), JCOVDEN (Janssen), and VLA2001 (Valneva).

18.2 Benefit-risk analysis evaluation

18.2.1 Active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 18 years of age and older

An evaluation of the benefit-risk profile for the use of VAXZEVRIA in the authorised indications cited in Section 17.1 (Important baseline efficacy/effectiveness information) is provided below.

18.2.1.1 Context of use of the medicinal product

The COVID-19 epidemic has caused major disruption to healthcare systems with significant socioeconomic impacts. Containment measures have failed to stop the spread of the virus, which has resulted in pandemic levels. World-wide efforts to develop effective vaccines against SARS-CoV-2 are ongoing. Given the extent and continued rapid pace of infection, severity of the pandemic's medical and socioeconomic impact, and the supply challenges associated with a global vaccination program, multiple vaccines are needed. VAXZEVRIA was developed to address this public health need.

VAXZEVRIA primary vaccination course consists of two separate doses of 0.5 ml each. The second dose should be administered between 4 and 12 weeks after the first dose. It is recommended that individuals who receive a first dose of VAXZEVRIA complete the vaccination course with VAXZEVRIA.

Emerging data suggest that waning protection in the months following a 2-dose primary series is contributing to the incidence of breakthrough infection. Several studies have demonstrated that a third dose of homologous / heterologous booster vaccinations have been safe and were able to elicit a humoral immune response regardless of the combination of primary series and booster doses.

During the reporting period, the CDS was updated to indicate that VAXZEVRIA may be given as a booster dose (third dose) of 0.5 ml to individuals who completed the primary vaccination course with VAXZEVRIA or another authorised COVID-19 vaccine. The third dose should be administered at least 3 months after completing the primary vaccination course.

There have been no new data or information received during the reporting period that impacts the previously established efficacy and effectiveness of VAXZEVRIA in the approved indication of prevention of COVID-19 in adults 18 years of age and older.

Additionally, analysis of efficacy at the 6-month data cut-off, demonstrated that vaccine efficacy of VAXZEVRIA was maintained up to 6 months post first dose. The results of the 6-month humoral immunogenicity are still under analysis. Analysis of efficacy against variants demonstrated additional benefit, with an overall VE in sequenced variants similar to

the VE of the primary analysis in study D8110C00001. Preliminary live virus neutralization data from exploratory analysis conducted separately suggest that a 2-dose primary series immunization with VAXZEVRIA will likely provide protection against infection with the current variant of concern, Omicron, and clinically meaningful protection against hospitalization and severe disease would be maintained. Moreover, it is anticipated that VAXZEVRIA induced T cell responses likely will be less affected than antibody responses.

Analysis of efficacy against variants demonstrated additional benefit, with an overall VE in sequenced variants similar to the VE of the primary analysis in study D8110C00001. Preliminary live virus neutralization data from exploratory analysis conducted separately suggest that a 2-dose primary series immunization with VAXZEVRIA will likely provide protection against infection with the current variant of concern, Omicron, and clinically meaningful protection against hospitalization and severe disease would be maintained. Moreover, it is anticipated that VAXZEVRIA induced T cell responses likely will be less affected than antibody responses.

Analysis of efficacy against variants demonstrated additional benefit, with an overall VE in sequenced variants similar to the VE of the primary analysis in study D8110C00001. Preliminary live virus neutralization data from exploratory analysis conducted separately suggest that a 2-dose primary series immunization with VAXZEVRIA will likely provide protection against infection with the current variant of concern, Omicron, and clinically meaningful protection against hospitalization and severe disease would be maintained. Moreover, it is anticipated that VAXZEVRIA induced T cell responses likely will be less affected than antibody responses.

With the COVID-19 pandemic causing a global health crisis with severe illness, hospitalisations, and death in many individuals, in addition to major disruption to healthcare systems, it is clear that multiple vaccines with a positive benefit-risk are needed. With its proven effect in preventing COVID-19 and related hospitalisations, including protection against current variants, VAXZEVRIA is considered appropriate to address this urgent unmet medical need. Moreover, the easy storage and handling of the VAXZEVRIA formulation is considered to be an important additional benefit that enables wide access to the vaccine.

Real World Evidence data obtained later in the COVID-19 pandemic, demonstrated that, as with other vaccines approved to prevent COVID-19, VAXZEVRIA is able to elicit humoral immune response following primary series immunization with any approved COVID-19 vaccine.

In conclusion, the overall benefits of VAXZEVRIA in the prevention of COVID-19 with robust efficacy overall, in a wide array of subgroups, including adults ≥ 65 years of age and persons with at least one comorbidity at enrolment, and in the prevention of severe/critical COVID-19 illness and COVID-19 related emergency department (ED) visits and deaths

continue to outweigh risks from adverse events, including the very rare risk of thrombosis in combination with thrombocytopenia identified through post-marketing safety reports.

18.2.1.2 Considerations relating to key benefit(s)

During the reporting period, the benefit-risk profile of VAXZEVRIA has been shown to be consistently favourable across the clinical development programme and in published real-world evidence studies. The benefit-risk profile is favourable for the proposed indication in adults age 18 years and older, including adults age 65 years and above, as well as those with comorbidities.

As described in section 17, the durability of protection against COVID-19 was demonstrated after 6 months of follow-up data obtained from study DC8110C00001, and real world evidence data confirmed VAXZEVRIA continues to protect vaccinated individuals against severe disease and death.

Several studies have demonstrated that a third dose of VAXZEVRIA given as a homologous or a heterologous booster vaccination have been safe and were able to elicit humoral immune response regardless of the combination of primary series and booster doses.

18.2.1.3 Considerations relating to risk

The important identified and potential risks associated with VAXZEVRIA are characterised in detail in Section 16.4.

Considerations regarding the key important identified and potential risks are summarised below:

- **Thrombosis in combination with thrombocytopenia**: A very rare and serious combination of thrombosis and thrombocytopenia, including thrombosis with thrombocytopenia syndrome (TTS), in some cases accompanied by bleeding, has been observed following vaccination with VAXZEVRIA during post-authorisation use. The majority of the events occurred within the first 21 days following vaccination and some events had a fatal outcome. The reporting rates after the second dose are lower compared to the first dose. No new or emerging concern regarding TTS has been identified with booster doses of AZD1222. Based on the available data, thrombosis in combination with thrombocytopenia is considered a very rare adverse reaction of VAXZEVRIA. The CDS reflects AstraZeneca's position on this risk.
- **Immune-mediated neurological conditions:** There is a theoretical concern that vaccination could be associated with immune-mediated neurological conditions. Very rare events of demyelinating disorders were reported in the VAXZEVRIA clinical development programme and in the post-marketing use, however, there is no evidence suggesting a causal relationship between VAXZEVRIA and demyelinating disorders. Severe neurological conditions may result in persistent or significant disability or

incapacity and require early detection, careful monitoring, and timely medical intervention. CDS reflects AstraZeneca's position on this risk.

- **CVST without thrombocytopenia:** Events of cerebrovascular venous and sinus thrombosis (CVST) without thrombocytopenia have been reported very rarely in the post-authorisation setting following vaccination with VAXZEVRIA. The exact mechanism of CVST without thrombocytopenia following administration with VAXZEVRIA is unknown. There are no known risk factors for the development of CVST without thrombocytopenia following vaccination. Events of CVST without thrombocytopenia may require different treatment approaches than thrombosis in combination with thrombocytopenia (eg, use of heparin or warfarin). Based on the available data, a causal association has not been established between VAXZEVRIA and CVST without thrombocytopenia. However, such events are considered an important potential risk and CDS reflects AstraZeneca's position on this risk.
- **Vaccine-associated enhanced disease (VAED) / Vaccine-associated enhanced respiratory disease (VAERD):** This safety concern is currently theoretical in relation to VAXZEVRIA administration, and based on the available data, a causal association has not been established between VAXZEVRIA and VAED / VAERD. Therefore, there is no public health impact noted at this time.

The significance of the information that became available during the reporting period has been evaluated in the context of what was known previously. An integrated evaluation of the key benefits and risks continue to suggest an overall positive benefit-risk profile for the use of VAXZEVRIA. The data gathered during the reporting period of this PBRER did not provide any additional evidence which would alter the efficacy or safety evaluation of VAXZEVRIA.

18.2.1.4 Strengths, weaknesses, and uncertainties of the evidence

The efficacy results have been confirmed in study D8110C00001 conducted in the US, Chile and Peru and from the pooled analysis of 4 Oxford University Sponsored studies (COV 001, COV002, COV003 & COV005 studies) all of which are randomised, controlled trials.

AZD1222 confers a strong immunogenicity response when administered as a booster both in the homologous or heterologous primary series settings and considered safe for use. During the reporting period, this is reflected with a positive CHMP opinion received for use of VAXZEVRIA as a third dose booster in individuals who completed their primary vaccination course with VAXZEVRIA or an approved mRNA COVID 19 vaccine as indicated in the EU SmPC.

Additional real world studies have demonstrated high vaccine effectiveness (VE) against the Omicron variant in a variety of settings and populations, particularly with regard to prevention of severe disease, please refer to section 9.1.

Populations in need of further characterisation include use of VAXZEVRIA in pregnant and breastfeeding women, in subjects with severe immunodeficiency, in patients with severe and/or uncontrolled disease, and co-administration / interaction of VAXZEVRIA with other vaccines. However, these patient populations will continue to be investigated in ongoing PASS activities.

18.2.1.5 Methodology and reasoning used to develop the benefit-risk evaluation

A qualitative assessment of the benefit-risk balance for the use of VAXZEVRIA for active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals >18 years of age has been performed.

Conclusions on efficacy from the VAXZEVRIA (AZD1222) clinical development programme, in particular from pooled analysis of Studies COV001, COV002, COV003, COV005 and the preliminary analysis of the US study (D8110C00001), provide evidence of the key benefits associated with the use of VAXZEVRIA in the approved indication. Key benefits are those that are considered to have a substantial positive impact on the benefit-risk balance.

AstraZeneca's pharmacovigilance system provides the framework for the identification of any risks associated with the use of VAXZEVRIA in the approved indication. All information that has emerged during the reporting period has been reviewed and evaluated by AstraZeneca, irrespective of reporting source, seriousness, or causality. This has included an analysis of clinical trials, literature studies, safety topics that are kept under close surveillance, as well as an assessment of any new safety issues.

The significance of the information that became available during the reporting period has been evaluated in the context of what was known previously. An integrated evaluation of the key benefits and risks give an overall positive benefit-risk profile for the use of VAXZEVRIA. The data gathered during the reporting period of this PBRER did not provide any additional evidence which would alter the efficacy or safety evaluation of VAXZEVRIA.

19 CONCLUSIONS AND ACTIONS

VAXZEVRIA is used for active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals >18 years of age, as described in the previous sections.

There has been no new efficacy related information received during the reporting period that impacts previously established efficacy and effectiveness of VAXZEVRIA in the approved indication. VAXZEVRIA confers a strong immunogenicity response when administered as a booster both in the homologous or heterologous primary series settings and considered safe for use. During the reporting period VAXZEVRIA was approved in EU as a third dose booster in individuals who completed their primary vaccination course with VAXZEVRIA or

an approved mRNA COVID 19 vaccine. The RWE study data that became available during the reporting period provides evidence that the benefits of VAXZEVRIA extend to protection against the widely circulating omicron variant, both in the primary vaccination course and in the booster setting, particularly against progression to severe disease, hospitalization or death.

There were no new significant safety findings from any of the AstraZeneca-sponsored or Oxford-sponsored clinical trials with VAXZEVRIA (AZD1222) during the reporting period. AstraZeneca is not aware of any safety signals arising for VAXZEVRIA from any other studies conducted by AstraZeneca partner companies.

During the reporting period, CDS Section 4.6 was updated to reflect the most current non-clinical, clinical and post-authorization data regarding the use of VAXZEVRIA during pregnancy and while breastfeeding. The use of the vaccine should be considered during pregnancy when the benefits outweigh the risks. CDS Section 4.2 (Posology and method of administration) was also updated with the recommendation for use of a booster dose (third dose) in individuals who completed the primary vaccination course with VAXZEVRIA or another authorised COVID-19 vaccine. In addition, AstraZeneca validated the signals of hypoaesthesia/paraesthesia, GBS and Tinnitus. During the reporting period, the signal of hypoaesthesia/paraesthesia was confirmed, and the CDS Section 4.8 (Undesirable effects) was updated with the addition of paraesthesia and hypoaesthesia as uncommon adverse drug reactions. Although the signal GBS was refuted, CDS Section 4.4 (Special warnings and special precautions for use) the existing warning on neurological events was amended to include a specific reference to GBS. The signal Tinnitus was confirmed post DLP, and Section 4.8 of the CDS was updated with the addition of Tinnitus with a frequency of uncommon.

After the DLP, the signal cutaneous vasculitis was validated and subsequently confirmed. VAXZEVRIA CDS is currently in the progress to be updated to include cutaneous vasculitis as ADR in Section 4.8. The updated CDS will be internally approved before the due date of this PBRER. AstraZeneca is further reviewing the signal of immune thrombocytopenia as part of internal signal evaluation processes and will provide the conclusions and any recommended actions within the next PBRER.

The benefit of vaccination VAXZEVRIA has been weighed against the safety experience in the clinical programmes as well from post-authorization use. The data received during this reporting period, combined with analyses of the cumulative efficacy and safety data available, does not indicate a change in the positive benefit-risk profile of VAXZEVRIA. It is AstraZeneca's opinion that the information in the current document and the CDS accurately reflects the known benefit-risk profile for VAXZEVRIA.

20 APPENDICES TO THE PBRER

A full list of Appendices and Regional Appendices is provided in the List of Appendices presented in the Table of Contents.

Where submitted, Regional Appendices R1 to R8 provide information meeting local requirements.

21 REFERENCES

Abousy et al 2021
Abousy M, Bohm K, Prescott C, Bonsack JM, Rowhani-Farid A, Eghrari AO. Bilateral EK Rejection After COVID-19 Vaccine. Eye & contact lens. 2021 1;47(11):625-8.

Abramson et al 2021
Abramson M, Yu SM, Campbell KN, Chung M, Salem F. IgA nephropathy after SARS-CoV-2 vaccination. Kidney Medicine. 2021 Sep 1;3(5):860-3.

Acharya et al 2021
Acharya PC, Acharya C, Medaura JA. IgA nephropathy post COVID-19 vaccination. Journal of the American Society of Nephrology. 2021:88-9.

ACS 2020
American Community Survey DP05 Demographics and Housing Estimates. 2020. Available from: https://data.census.gov/cedsci/table?y=2020&d=ACS%205-Year%20Estimates%20Data%20Profiles&tid=ACSDP5Y2020.DP05.

Adelmeyer et al 2022
Adelmeyer J, Goebel JN, Kauka A, Kann PH. Two Case Reports of Subacute Thyroiditis after Receiving Vaccine for COVID-19. Case Reports in Endocrinology. 2022 Apr 14;2022.

Agrawal et al 2021
Agrawal U, Katikireddi SV, McCowan C, Mulholland RH, Azcoaga-Lorenzo A, Amele S et al. COVID-19 hospital admissions and deaths after COMIRNATY and ChAdOx1 nCoV-19 vaccinations in 2· 57 million people in Scotland (EAVE II): a prospective cohort study. The Lancet Respiratory Medicine. 2021;9(12):1439-49.

Ahmed et al 2021
Ahmed SH, Waseem S, Shaikh TG. SARS-CoV-2 vaccine-associated-tinnitus: A review. Ann Med Surg (Lond). 2022;75:103293. doi:10.1016/j.amsu.2022.103293

Ahmed S K et al 2022
Ahmed SK, Mohamed MG, Essa RA, Rashad EA, Ibrahim PK, Khdir AA, Wsu ZH. Global reports of myocarditis following COVID-19 vaccination: A systematic review and meta-analysis. Diabetes & Metabolic Syndrome: Clinical Research & Reviews. 2022:102513.

Ai et al 2021
Ai S, Awford A, Roncolato F. Hemophagocytic lymphohistiocytosis following ChAdOx1 nCov-19 vaccination. J Med Virol. 2021;10. 1002/jmv.27279. doi: 10.1002/jmv.27279.

Akyea et al 2021
Akyea R, Vinogradova Y, Quereshi N, Patel R, Kontopantelis E, Ntaios G et al Sex, Age, and Socioeconomic Differences in Nonfatal Stroke Incidence and Subsequent Major Adverse Outcomes. Stroke. 2021;52:396–405.

Aladdin et al 2021
Aladdin Y, Algahtani H, Shirah B. Vaccine-Induced Immune Thrombotic Thrombocytopenia with Disseminated Intravascular Coagulation and Death following the ChAdOx1 nCoV-19 Vaccine. J Stroke Cerebrovasc Dis. 2021;30(9):105938.

Al-Ali D et al 2021
Al-Ali D, Elshafeey A, Mushannen M, Kawas H, Shafiq A, Mhaimeed N, et al. Cardiovascular and haematological events post COVID-19 vaccination: A systematic review. Journal of cellular and molecular medicine. 2022;26(3):636-53.

Alami A et al 2022
Alami A, Krewski D, Mattison D, Wilson K, Gravel CA, Villeneuve PJ, et al. Risk of Myocarditis and Pericarditis among Young Adults following mRNA COVID-19 Vaccinations. Vaccines. 2022;10(5):722.

Alcas O et al 2021
Alcas O, Mamani D. Hipoacusia súbita luego de vacunación contra la COVID-19. Revista Peruana de Medicina Experimental y Salud Pública. 2022 Apr 1; 38:664-5.

Alkis et al. 2022
Alkis N, Baysal M. Subacute thyroiditis after SARS-CoV-2 BNT162b2 vaccine in a multiple myeloma patient. SAGE open medical case reports. 2022;10:2050313X221091392.

Alshararni 2021
Alshararni A. International Journal of Research in Pharmaceutical Sciences. 2021;12(3):2083-7. Available from: https://www.embase.com/search/results?subaction=viewrecord&id=L2013006728&from=export.

American Society of Hematology 2021
American Society of Hematology. COVID-19 resources. Thrombosis with Thrombocytopenia Syndrome (also termed Vaccine-induced Thrombotic Thrombocytopenia). Available at: https://www.hematology.org/COVID-19/vaccine-induced-immune-thrombotic-thrombocytopenia. Accessed 19 November 2021.

Amit et al 1986
Amit R, Shapira Y, Blank A. (1986). Acute, severe, central and peripheral nervous system combined demyelination. Pediatr Neurol 2: 47–50.

Ancau et al 2022
Ancau M, Liesche-Starnecker F, Niederschweiberer J, Krieg SM, Zimmer C, Lingg C, et al. Case series: Acute Hemorrhagic Encephalomyelitis After SARS-CoV-2 Vaccination. Front Neurol. 2021;12:820049.

Andrews et al 2022
Andrews N, Stowe J, Ramsay MEB, Miller E, et al. Risk of venous thrombotic events and thrombocytopenia in sequential time periods after ChAdOx1 andBNT162b2COVID-19 vaccines: A national cohort study in England. The Lancet Regional Health- Europe 2022;13: 100260 Published online xxx https://doi.org/10.1016/j. lanepe.2021.100260

Andrews et al 2022a
Andrews N, Tessier E, Stowe J, Gower C, Kirsebom F, Simmons R, et al. Duration of Protection against Mild and Severe Disease of Covid-19 Vaccines. N Engl J Med 2022; 386:340-350DOI: 10.1056/NEJMoa2115481

Andrews et al 2022b
Andrews N, Stowe J, Kirsebom F, Toffa S, Rickeard T, Gallagher E et al. Covid-19 Vaccine Effectiveness against the Omicron (B.1.1.529) Variant. N Engl J Med 2022; DOI: 10.1056/NEJMoa2119451 386:1532-46.

Andrzejczak-Grządko et al 2021
Andrzejczak-Grządko S, Czudy Z, Donderska M. Side effects after COVID-19 vaccinations among residents of Poland. Eur Rev Med Pharmacol Sci. 2021;25(12):4418-21.

Aneja et al 2021
Aneja R. Idiopathic systemic capillary leak syndrome. UpToDate. 2021; https://www.uptodate.com/contents/idiopathic-systemic-capillary-leak-syndrome.

Ang et al 2004
Ang CW, Jacobs BC, Laman JD. The Guillain-Barré syndrome: a true case of molecular mimicry. Trends Immunol. 2004;25(2):61-6.

Anlar et al 2003
Anlar B, Basaran C, Kose G, Guven A, Haspolat S, Yakut A, et al. Acute disseminated encephalomyelitis in children: outcome and prognosis. Neuropediatrics. 2003;34:194-9.

Apak et al 1999
Apak RA, Kose G, Anlar B. Acute disseminated encephalomyelitis in childhood: report of 10 cases. J Child Neurol. 1999;14: 198–201.

Ardalan M et al 2022
Ardalan M, Moslemi H, Shafiei, S, Tabrizi R, Moselmi M, et al. Herpes-like skin lesion after AstraZeneca vaccination for COVID-19: A case report. Clinical Case Reports, 2021:9(10).

Arkema and Cozier 2018
Arkema EV, Cozier YC. Epidemiology of sarcoidosis: current findings and future directions. Ther Adv Chronic Dis. 2018;9(11):227-240. doi: 10.1177/2040622318790197.

Arkemer et al 2020
Sarcoidosis epidemiology: recent estimates of incidence, prevalence and risk factors. Curr Opin Pulm Med. 2020 September ; 26(5): 527–534. doi:10.1097/MCP.0000000000000715

ASH 2021
American Society of Hematology. Thrombosis with Thrombocytopenia Syndrome (also termed Vaccine-induced Thrombotic Thrombocytopenia). Version 1.4; last updated April 29, 2021. Available at: https://www.hematology.org/COVID-19/vaccine-induced-immunethrombotic- thrombocytopenia.

Ashod Kherlopian and Gayle Fischer 2022
Ashod Kherlopian; Gayle Fischer. Herpes simplex virus (HSV) reactivation leading to mucocutaneous infection after COVID-19 Vaccination: A Case Series. Australasian Journal of Dermatology, 2022:63(1), 91-2.

Attwell et al 2021
Attwell L, Zaw T, McCormick J, Marks J, McCarthy H. Haemophagocytic lymphohistiocytosis after ChAdOx1 nCoV-19 vaccination. J Clin Pathol. 2021 22; jclinpath-2021-207760. doi: 10.1136/jclinpath-2021-207760.

Atzenhoffer et al 2022
Atzenhoffer M, Auffret M, Pegat A, Masmoudi K, Khouri C, Bertin B, Vial T. Guillain–Barré Syndrome Associated with COVID-19 Vaccines: A Perspective From Spontaneous Report Data. Clinical Drug Investigation. 2022:1-2.

Avallone et al 2022
Avallone G, Quaglino P, Cavallo F, Roccuzzo G, Ribero S, Zalaudek I, et.al. SARS-CoV-2 vaccine-related cutaneous manifestations: a systematic review. Int J Dermatol.

2022;9:10.1111/ijd.16063. doi: 10.1111/ijd.16063. Epub ahead of print. PMID: 35141881; PMCID: PMC9111829.

Avci and Abasiyanik 2021
Avci and Abasiyanik. Autoimmune hepatitis after SARS-CoV-2 vaccine: New-onset or flare-up? J Autoimmun.2021;125:102745. https://doi.org/10.1016/j.jaut.2021.102745.

Azdaki et al 2021
Azdaki N, Farzad M. Long QT interval and syncope after a single dose of COVID-19 vaccination: a case report. Pan Afr Med J. 2021 30;40:67.

Baek et al 2022
Baek DW, Hwang S, Kim J, Lee JM, Cho HJ, Moon JH et al. Patients presenting high fever with lymphadenopathy after COVID-19 vaccination were diagnosed with hemophagocytic lymphohistiocytosis. Infect Dis (Lond). 2022;54(4):303-7.

Baena-García et al 2022
Baena-García L, Aparicio VA, Molina-López A, Aranda P, Cámara-Roca L et al. Premenstrual and menstrual changes reported after COVID-19 vaccination: The EVA project. Women's Health. 2022.

Baker et al 2021
Baker AT, Boyd RJ, Sarkar D, Teijeira-Crespo A, Chan CK, Bates E et al. ChAdOx1 interacts with CAR and PF4 with implications for thrombosis with thrombocytopenia syndrome. Sci Adv. 2021;7(49):eabl8213

Bangash et al 2021
Bangash B, Pitcher J, Makki I. Multisystem inflammatory syndrome in children and adolescents (mis-c) in a young adult with recent vaccination. Chest. 2021 1;160(4):a660.

Banks et al 2021
Banks D, H Hansra. Annual Meeting Assembly and Technical Exhibition of the American Academy of Physical Medicine and Rehabilitation (AAPMR). 2021;384.

Barda et al 2021
Barda N, Dagan N, Ben-Shlomo Y. Safety of the BNT162b2 mRNA Covid-19 Vaccine in a Nationwide Setting. *N Engl J Med*. 2021;385(12):1078-1090. doi:10.1056/NEJMoa2110475

Baxter et al 2013
Baxter R, Bakshi N, Fireman B, Lewis E, Ray P, Vellozzi C. Lack of association of Guillain-Barré syndrome with vaccinations. Clin. Infect. Dis. 2013;57:197–204. doi: 10.1093/cid/cit222.

Baxter et al 2016
Baxter R, Lewis E, Goddard K, Fireman B, Bakshi N, DeStefano F, et al. Acute demyelinating events following vaccines: a case-centered analysis. Clin Infect Dis. 2016;63(11):1456-62.

Behan et al 1972
Behan PO, Behan WM, Feldman RG, Kies MW. Cellmediated hypersensitivity to neural antigens. Occurrence in human patients and nonhuman primates with neurological diseases. Arch Neurol. 1972;27:145-52.

Behan et al 1973
Behan PO, Kies MW, Lisak RP, Sheremata W, Lamarche JB. Immunologic mechanisms in experimental encephalomyelitis in nonhuman primates. Arch Neurol. 1973;29:4-9.

Benedict Osei-Boadu et al 2022
Benedict Osei-Boadu, Gurdas Singh-Rathore, Sunitha Achandil, Gouri M Koduri, P072 Audit on the uptake of COVID-19 vaccination in biologic patients with autoimmune conditions, Rheumatology, Volume 61, Issue Supplement_1, May 2022, keac133.071.

Bennetto and Scolding 2004
Bennetto L, Scolding N. Inflammatory/post-infectious encephalomyelitis. J Neurol Neurosurg Psychiatry. 2004;75(Suppl 1):i22-i28.

Benning et. al 2022
Benning L, Morath C, Bartenschlager M, Nusshag C, Kälble F, Buylaert M, Schaier M, Beimler J, Klein K, Grenz J, Reichel P. Neutralization of SARS-CoV-2 variants of concern in kidney transplant recipients after standard COVID-19 vaccination. Clinical Journal of the American Society of Nephrology. 2022 Jan 1;17(1):98-106.

Berg et al 1995
Berg VLH, Mollee J, Wokke JH and Logtenberg T. Increased frequencies of HPRT mutant T lymphocytes in patients with Guillain-Barré syndrome and chronic inflammatory demyelinating polyneuropathy: further evidence for a role of T cells in the etiopathogenesis of peripheral demyelinating diseases. J. Neuroimmunol. 1995;58, 37–42.

Berg et al 2014
van den Berg B, Walgaard C, Drenthen J, et al. Guillain-Barré syndrome: pathogenesis, diagnosis, treatment and prognosis. Nat Rev Neurol 2014;10:469–82. 10.1038/nrneurol.2014.121.

Berild et al, 2022
Berild et al. Analysis of Thromboembolic and Thrombocytopenic Events After the AZD1222, BNT162b2, and MRNA-1273 COVID-19 Vaccines in 3 Nordic Countries. JAMA Network Open. 2022;5(6):e2217375. doi:10.1001/jamanetworkopen.2022.17375

Bernal et al 2021
Bernal JL, Andrews N, Gower C, Stowe J, Robertson C, Tessier E, et al. Effectiveness of the Pfizer-BioNTech and Oxford-AstraZeneca vaccines on covid-19 related symptoms, hospital admissions, and mortality in older adults in England: test negative case-control study. BMJ. 2021; 13;373:n1088. doi: 10.1136/bmj.n1088.

Bews H et al 2022
COVID-19 Vaccination-Induced Myopericarditis: An Imager's Perspective. CJC Open. 2022 May;4(5):497-500. doi: 10.1016/j.cjco.2022.01.007. Epub 2022 Jan 29. PMID: 35128370; PMCID: PMC8800170.

Bhavsar et al 2016
Bhavsar KV, Lin S, Rahimy E, Joseph A, Freund KB, Sarraf D et al. Acute macular neuroretinopathy: A comprehensive review of the literature. Surv Ophthalmol. 2016;61(5):538-65.

Bhur et al 2022
Buhr ND, Baumann T, Werlein C, Fingerhut L, Imker R, Meurer M, Götz F, Bronzlik P, P. Kühnel M, D. Jonigk4 D, Ernst J; Insights Into Immunothrombotic Mechanisms in Acute Stroke due to Vaccine-Induced Immune Thrombotic Thrombocytopenia, Front Immunol. 2022;13:879157.

Bhuyan et al 2021
Bhuyan P, Medin J, da Silva HG, Yadavalli M, Shankar NK, Mullerova H, et al. Very rare thrombosis with thrombocytopenia after second AZD1222 dose: a global safety database analysis. Lancet. 2021 Aug 14;398(10300):577-578.

Biradar et al 2022
Biradar V, Konnur A, Gang S, Hegde U, Rajapurkar M, Patel H et al. Adult-onset nephrotic syndrome following coronavirus disease vaccination. Clinical Kidney Journal. 2022;15(1):168-70.

Bøhler et al 2021
Bøhler AD, Strøm ME, Sandvig KU, Moe MC, Jørstad ØK. Acute macular neuroretinopathy following COVID-19 vaccination. Eye (Lond). 2021 Jun 22:1–2.

Bollano E et al 2022
Somatostatin receptor positron emission tomography/computed tomography in myocarditis following mRNA COVID-19 vaccination, European Heart Journal - Case Reports, Volume 6, Issue 4, April 2022, ytac117, https://doi.org/10.1093/ehjcr/ytac117

Bolletta et al 2021
Bolletta, E., D. Iannetta, V. Mastrofilippo, L. De Simone, F. Gozzi, S. Croci, M. Bonacini, L. Belloni, A. Zerbini, C. Adani, L. Fontana, C. Salvarani,L. Cimino Uveitis and other ocular complications following covid-19 vaccination Journal of Clinical Medicine 2021 10(24).

Bomback et al 2021
Bomback AS, Kudose S, D'Agati VD. De novo and relapsing glomerular diseases after COVID-19 vaccination: what do we know so far? Am J Kidney Dis. 2021 Oct;78(4):477–80.

Bonifacio et al 2021
Bonifacio GB, Patel D, Sarah C, Purcaru E, Couzins M, Domjan J et al. Bilateral facial weakness with paraesthesia variant of Guillain-Barré syndrome following VAXZEVRIA COVID- 19 vaccine. Journal of Neurology, Neurosurgery and Psychiatry 2021.

Book et al 2021
Book BAJ, Schmidt B, Foerster AMH. Bilateral Acute Macular Neuroretinopathy After Vaccination Against SARS-CoV-2. JAMA Ophthalmol. 2021;139(7):e212471.

Bordon 2021
Bordon Y. Immune readouts from the Oxford COVID-19 vaccine. Nat Rev Immunol 2021; 21: 70–1.

Bostan et al. 2022
Bostan H, Unsal IO, Kizilgul M, Gul U, Sencar ME, Ucan B, Cakal E. Two cases of subacute thyroiditis after different types of SARS-CoV-2 vaccination. Archives of Endocrinology and Metabolism. 2022 Jan 17;66:97-103.

Botton et al 2022
Botton et al. (translation from French) Assessment of the risk of myocardial infarction, stroke and pulmonary embolism following the various COVID-19 vaccines in adults under 75 years of age in France. Epi-Phare. https://assurance-maladie.ameli.fr/etudes-et-donnees/2022-vaccins-covid-19-avc-infarctus-embolie-pulmonaire.

Bourguignon et al 2021
Bourguignon A, Arnold DM, Warkentin TE, Smith JW, Pannu T, Shrum JM et al. Adjunct Immune Globulin for Vaccine-Induced Immune Thrombotic Thrombocytopenia. N Engl J Med. 2021;385(8):720-8.

Bricoli S et al 2021
Myocarditis after COVID-19 vaccination—a case series, *European Heart Journal Supplements*, Volume 23, Issue Supplement_G, December 2021, suab135.008, https://doi.org/10.1093/eurheartj/suab135.008

Brighton Collaboration-GBS 2021
Law B. Brighton Collaboration. Safety Platform for Emergency Vaccines. SO2-D2.5.2.1 – AESI Case Definition Companion. Guide for 1st Tier AESI. Guillain Barré and Miller Fisher Syndromes. V1.0 09 February 2021. Available from: https://brightoncollaboration.us/wp-content/uploads/2021/03/SPEAC_D2.5.2.1-GBS-Case-Definition-Companion-Guide_V1.0_format12062-1.pdf.

Brighton Collaboration–TCP/ITP 2021
Law B. Brighton Collaboration. Safety Platform for Emergency Vaccines. SO2-D2.5.2.1 – AESI Case Definition Companion. Guide for 1st Tier AESI. Thrombocytopenia. V1.0 08 February 2021. Available from: https://brightoncollaboration.us/wp-content/uploads/2021/03/SPEAC_D2.5.2.1-Thrombocytopenia-Case-Definition-Companion-Guide_V1.0_format12065-1.pdf

Brighton Collaboration–TM 2020
Law, B. Brighton Collaboration. Safety Platform for Emergency Vaccines: SO2- D2.5.2.1 - AESI Case Definition Companion: Guide for 1st Tier AESI: Acute Myelitis. V 2.0 5 November 2020. Available from: https://brightoncollaboration.us/wp-content/uploads/2020/11/SPEAC_D2.5.2.1_AESI-Case-Definition-Companion-Guide.pdf

Bril et al 2021
Bril F, Al Diffalha S, Dean M, Fettig DM. Autoimmune hepatitis developing after coronavirus disease 2019 (COVID-19) vaccine: Causality or casualty [letter]? J Hepatol. 2021;75(1):222-4. https://doi.org/10.1016/j.jhep.2021.04.003.

Burillo et al 2021
Burillo C, Martinez L, Arguedas G, Pueyo M. Amyotrophic neuralgia secondary to Vaxzevri (AstraZeneca) COVID-19 vaccine. Neurologia (Engl Ed). 2021;36(7):571-2.

Burlando et al 2021
Burlando M, Herzum A, Micalizzi C, Cozzani E, Parodi A. Cutaneous reactions to COVID-19 vaccine at the dermatology primary care. Immun Inflamm Dis. 2022;10(2):265-71.

Burn et al 2021a
Burn et al. Thrombosis and thrombocytopenia after vaccination against and infection with SARS-CoV-2: a population-based cohort analysis. medRxiv 2021.07.29.21261348; doi: https://doi.org/10.1101/2021.07.29.21261348

Burn et al 2021b
Burn et al. (b) Thromboembolic events and thrombosis with thrombocytopenia after COVID-19 infection and vaccination in Catalonia, Spain.
https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3886421

Burn et al.2022
Burn E, Li X, Kostka K, et al. Background rates of five thrombosis with thrombocytopenia syndromes of special interest for COVID-19 vaccine safety surveillance: Incidence between 2017 and 2019 and patient profiles from 38.6 million people in six European countries. Pharmacoepidemiol Drug Saf 2022;31(5):495-510. doi: 10.1002/pds.5419 [published Online First: 2022/02/23]

Burns et al 1992
Burns J, Littlefield K, Gill J, Trotter JL. Bacterial toxin superantigens activate human T lymphocytes reactive with myelin autoantigens. Ann Neurol. 1992;32:352-357.

Burrows et al 2021
Burrows A, Bartholomew T, Rudd J, Walker D. Sequential contralateral facial nerve palsies following COVID-19 vaccination first and second doses. *BMJ Case Rep*. 2021;14(7):e243829. Published 2021 Jul 19. doi:10.1136/bcr-2021-243829.

Callagen et al. 2022
Callaghan CJ, Mumford L, Curtis RM, Williams SV, Whitaker H, Andrews N, Bernal JL, Ushiro-Lumb I, Pettigrew GJ, Thorburn D, Forsythe JL. Real-world effectiveness of the Pfizer-BioNTech BNT162b2 and Oxford-AstraZeneca ChAdOx1-S vaccines against SARS-CoV-2 in solid organ and islet transplant recipients. Transplantation. 2022 Mar;106(3):436.

Callaway 2021
Callaway E. COVID vaccine boosters: the most important questions. Nature. 2021;596(7871):178-80. Available at: https://doi.org/10.1038/d41586-021-02158-6 https://doi.org/10.1038/d41586-021-02158-6. Accessed 19 November 2021.

Camera et al 2021
Camera V, O'Riordan J, Leite M, Palace J. Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS). 2021;P894.

Capezzone M et al 2022
Capezzone M, Tosti-Balducci M, Morabito EM, Caldarelli GP, Sagnella A, Cantara S, Alessandri M, Castagna MG. Silent thyroiditis following vaccination against COVID-19: report of two cases. Journal of Endocrinological Investigation. 2022 May;45(5):1079-83.

Caporale et al 2006
Caporale CM, Papola F, Fioroni MA, Aureli A, Giovannini A, Notturno F, Adorno D, Caporale V, Uncini A. Susceptibility to Guillain-Barré syndrome is associated to polymorphisms of CD1 genes. J Neuroimmunol. 2006 Aug;177(1-2):112-8. doi: 10.1016/j.jneuroim.2006.05.018. Epub 2006 Jul 3. PMID: 16820217.

Cari et al 2021
Cari L, Alhosseini MN, Fiore P, Pierno S, Pacor S, Bergamo A et al. Cardiovascular, neurological, and pulmonary events following vaccination with the BNT162b2, ChAdOx1 nCoV-19, and Ad26. COV2. S vaccines: An analysis of European data. Journal of autoimmunity. 2021 1;125:102742.

Carol Liu et al 2020
Carol Liu YC, Ibekwe T, Kelso JM, Klein NP, Shehu N, Steuerwald W et al. Sensorineural hearing loss (SNHL) as an adverse event following immunization (AEFI): Case definition & guidelines for data collection, analysis, and presentation of immunization safety data. Vaccine. 2020;38(30):4717-31.

Carol Liu et al. 2020
Liu YC, Ibekwe T, Kelso JM, Klein NP, Shehu N, Steuerwald W, Aneja S, Dudley MZ, Garry R, Munoz FM, Brighton Collaboration SNHL Working Group. Sensorineural hearing loss (SNHL) as an adverse event following immunization (AEFI): Case definition & guidelines for data collection, analysis, and presentation of immunization safety data. Vaccine. 2020 Jun 19;38(30):4717-31.

Carr et al 2021
Carr EJ, Kronbichler A, Graham-Brown M, Abra G, Argyropoulos C, Harper L. Review of early immune response to SARS-CoV-2 vaccination among patients with CKD. Kidney international reports. 2021 Sep 1;6(9):2292-304.

Casucci and Acanfora 2021
Casucci G, Acanfora D. DIC-Like Syndrome Following Administration of ChAdOx1 nCov-19 Vaccination. Viruses. 2021;13(6):1046.

Català et al 2022
Català A, Muñoz-Santos C. Cutaneous reactions after SARS-CoV-2 vaccination: a cross-sectional Spanish nationwide study of 405 cases. Br J Dermatol. 2022;186(1):142-52.

Cau R et al 2022
Role of imaging in rare COVID-19 vaccine multiorgan complications. Insights Imaging. 2022 Mar 14;13(1):44. doi: 10.1186/s13244-022-01176-w. PMID: 35286509; PMCID: PMC8919150.

CDC 2019
CDC (Centers for Disease Control and Prevention).Guillain-Barre Syndrome and Vaccines 2019. Available at: https://www.cdc.gov/vaccinesafety/concerns/guillain-barresyndrome.Html.

CDC 2021
Centers for Disease Control and Prevention (CDC) 2021. CDC Case Definition of TTS 2021. Available from: https://brightoncollaboration.us/wp-content/uploads/2021/05/TTS-Interim-Case-Definitionv10.16.3-May-23-2021.pdf.

CDC 2021 [A]
National Center for Immunization and Respiratory Diseases (U.S.). Division of Viral Diseases. Centers for Disease Control and Prevention. Interim clinical guidance for management of patients with confirmed coronavirus disease (COVID-19). Accessed on 25 Jan 2021 from https://stacks.cdc.gov/view/cdc/89980.

CDC 2021 [B]
Genital Herpes Fact Sheet from CDC. What is Herpes? How common is Herpes? How do people get Herpes? And more. Available at: https://www.cdc.gov/STD/Herpes/STDFact-Herpes-detailed.htm. Assessed on 13 October 2021

CDC 2021 [C]
Chickenpox, varicella, clinical overview of varicella. Available at: https://www.cdc.gov/chickenpox/hcp/index.html. Assessed on 30 November 2021

CDC 2021 [D]
The Possibility of COVID-19 after Vaccination: Breakthrough Infections. Available at: https://www.cdc.gov/coronavirus/2019-ncov/vaccines/effectiveness/why-measure-effectiveness/breakthrough-cases.html. Assessed on 17 December 2021.

CDC 2022
Centers for Disease Control and Prevention. Rates of COVID-19 Cases or Deaths by Age Group and Vaccination Status Public Use Data, COVID-19 Response. April 15, 2022. Available from: https://data.cdc.gov/Public-Health-Surveillance/Rates-of-COVID-19-Cases-or-Deaths-by-Age-Group-and/3rge-nu2a

Cerne D et al
Recrudescence Of Myocarditis After COVID-19 Vaccine In Patient With Previous Myocarditis And Parainfectious Guillain-Barré Syndrome Related To Influenza A H1N1. 12th Annual Meeting of the Italian Association for the Study of the Peripheral Nervous System (ASNP)

Cerqueira-Silva et al 2022
Cerqueira-Silva T, Katikireddi, S.V, de Araujo Oliveira, V. et al. Vaccine effectiveness of heterologous CoronaVac plus BNT162b2 in Brazil. Nat Med. 2022:28, 838–43.

Chadban & Atkins 2005
Chadban SJ & Atkins RC. Glomerulonephritis. The Lancet. 2005 May;365(9473):1797-1806.

Chailimpamontree et al, 2009
Chailimpamontree W, Dmitrienko S, Li G, Balshaw R, Magil A et al. Probability, predictors, and prognosis of posttransplantation glomerulonephritis. Journal of the American Society of Nephrology. 2009 Apr 1;20(4):843-51.

Chan et al 2022
Chan AT, Tang SC. De novo and relapsing glomerulonephritis after COVID-19 vaccination: how much do we know?. Nephrology. 2022 Jan;27(1):5-6.

Chariyalertsak et al 2022
Chariyalertsak S, Intawong K, ChalomK., et al. Effectiveness of heterologous 3rd and 4th dose COVID-19 vaccine schedules for SARS-CoV-2 infection during delta and omicron predominance in Thailand., 28 June 2022, PREPRINT (Version 1) available at Research Square [https://doi.org/10.21203/rs.3.rs-1792139/v1]

Chavez L O et al 2016
Beyond muscle destruction: a systematic review of rhabdomyolysis for clinical practice. Crit Care 20, 135 (2016). https://doi.org/10.1186/s13054-016-1314-5

Chellapandian SB et al 2022
Myocarditis following COVID-19 mRNA (mRNA-1273) vaccination. Clin Case Rep. 2022 Apr 18;10(4):e05741. doi: 10.1002/ccr3.5741. PMID: 35449778; PMCID: PMC9014704.

Chen et al 2020
Chen L, Li X, Chen M, Feng Y, Xiong C. The ACE2 expression in human heart indicates new potential mechanism of heart injury among patients infected with SARS-CoV-2. Cardiovascular Research. 2020; 116(6): 1097–100.

Chen et al 2021
Chen X, Chen Z, Azman AS, Sun R, Lu W, Zheng N et al. Neutralizing antibodies against SARS-CoV-2 variants induced by natural infection or vaccination: a systematic review and pooled meta-analysis. Clin Infect Dis. 2021:ciab646.

Chen et al, 2022
Chen et al. Safety of Global SARS-CoV-2 Vaccines, a Meta-Analysis. Vaccines 2022, 10, 596. https://doi.org/10.3390/vaccines10040596

Chin SE et al 2022
Cardiac Complications Associated with COVID-19, MIS-C, and mRNA COVID-19 Vaccination. Pediatr Cardiol. 2022 Mar;43(3):483-488. doi: 10.1007/s00246-022-02851-x. Epub 2022 Mar 8. PMID: 35258639; PMCID: PMC8902276.

Choi et al 2021
Choi W. Comprehensive Understanding and Field Application of COVID-19 Vaccine. Korean J Med. 2021;96(3):155-9. DOI: 10.3904/KJM.2021.96.3.155.

Chong et al 2021
Chong b, Leung H, Perdomo J, Ahmadi Z, Rashid F, Enjeti A, et al. NETosis and thrombosis in vaccine-induced immune thrombotic thrombocytopenia (preprint). Nature portfolio. Version 1, 30 Sept 2022. https://doi.org/10.21203/rs.3.rs-753825/v1

Chou OHI et al 2022
Comparisons of the risk of myopericarditis between COVID-19 patients and individuals receiving COVID-19 vaccines: a population-based study. Clin Res Cardiol. 2022 Mar 25:1–6. doi: 10.1007/s00392-022-02007-0. Epub ahead of print. PMID: 35333945; PMCID: PMC8951670.

Chouchana L et al 2021
Features of Inflammatory Heart Reactions Following mRNA COVID-19 Vaccination at a Global Level. Clin Pharmacol Ther. 2022 Mar;111(3):605-613. doi: 10.1002/cpt.2499. Epub 2021 Dec 27. PMID: 34860360; PMCID: PMC9015432.

Christensen et al 2021
Christensen SK, Ballegaard M, Boesen MS. [Guillian Barré syndromeafter mRNA-1273 vaccination against COVID-19]. Ugeskr Laeger. 2021;183(35):V05210455. Danish. PMID: 34477091.

Christl J et al 2021
Christl J. Vulvar aphthous ulcer in an adolescent with COVID-19. J Pediatr Adolesc Gynecol 2021; 34:418–20.

Christophe A et al 2021
A case series of acute myocarditis associated with SARS-CoV-2 mRNA vaccination. DOI: https://doi.org/10.4414/cvm.2021.w10103 Cardiovasc Med. 2021;24:w10103

Ciaponi et al 2021
Ciaponi A, Bardach A, Mazzoni A, Alconda T, Anderson S, Argento F et al. Safety of components and platforms of COVID-19 vaccines considered for use in pregnancy: A rapid review. Vaccine. 2021; 39 (40): 5891-5908.

Ciorba et al 2018
Ciorba A, Corazzi V, Bianchini C, Aimoni C, Pelucchi S, Skarzynski,et al. Autoimmune inner ear disease (AIED): A diagnostic challenge. Int J Immunopathol Pharmacol. 2018;32:2058738418808680. doi: 10.1177/2058738418808680.

Clark et al 2021
Clark RT, Johnson L, Billotti J, Foulds G, Ketels T, Heard K et al. Early outcomes of bivalirudin therapy for thrombotic thrombocytopenia and cerebral venous sinus thrombosis after Ad26. COV2. S vaccination. Annals of Emergency Medicine. 2021 1;78(4):511-4.

Clayton-Chubb et al 2021
Clayton-Chubb D, Schneider D, Freeman E, Kemp W, Roberts S. Autoimmune hepatitis developing after the ChAdOx1 nCoV-19 (Oxford-AstraZeneca) vaccine. J Hepatol. 2021;75(5):1249-50.

Clemens et al 2022
Clemens SA, Weckx L, Clemens R, Almeida Mendes AV, Ramos Souza A, Silveira MBV et al. Heterologous versus homologous COVID-19 booster vaccination in previous recipients of two doses of CoronaVac COVID-19 vaccine in Brazil (RHH-001): a phase 4, non-inferiority, single blind, randomised study. Lancet. 2022;399(10324):521-529.

Cohen 2022
Cohen, T.S., Kelly, E.J., Nylander, S. et al. Serum levels of anti-PF4 IgG after AZD1222 (ChAdOx1 nCoV-19) vaccination. Sci Rep 12, 7961 (2022). https://doi.org/10.1038/s41598-022-11623-9

Cohen et al 2022
Cohen TS, Kelly EJ, Nylander S, Bansal H, Jepson BM, Bhuyan P, Sobieszczyk ME, Falsey AR. Serum levels of anti-PF4 IgG after AZD1222 (ChAdOx1 nCoV-19) vaccination. Scientific reports. 2022 May 13;12(1):1-5.

Cohn et al 2021
Cohn BA, Cirillo PM, Murphy CC, Krigbaum NY, Wallace AW. Breakthrough SARS-CoV-2 infections in 620,000 U.S. Veterans, February 1, 2021 to August 13, 2021. Preprint posted 14 October 2021. Available from: https://doi.org/10.1101/2021.10.13.21264966. Accessed 19 November 2021.

Cole et al 2019
Cole J, Evans E, Mwangi M, Mar S. Acute disseminated encephalomyelitis in children: an updated review based on current diagnostic criteria. Pediatr Neurol. 2019;100:26-34.

Conceptions in England and Wales 2018
Conceptions in England and Wales Dataset. Available from https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/conceptionandfertilityrates/datasets/conceptionstatisticsenglandandwalesreferencetables.

Coopersmith et al 2021
Coopersmith CM, Antonelli M, Bauer SR, Deutschman CS, Evans LE, Ferrer R, Hellman J, Jog S, Kesecioglu J, Kissoon N, Martin-Loeches I, Nunnally ME, Prescott HC, Rhodes A,

Talmor D, Tissieres P, De Backer D. The Surviving Sepsis Campaign: Research Priorities for Coronavirus Disease 2019 in Critical Illness. Crit Care Med. 2021;49(4):598-622.

Corrao et al, 2022
Corrao et al. Balancing Benefits and Harms of COVID-19 Vaccines: Lessons from the Ongoing Mass Vaccination Campaign in Lombardy, Italy. Vaccines 2022, 10, 623. https://doi.org/10.3390/vaccines10040623

Cory et al 2021
Cory P, Lawrence H, Abdulrahim H, Mahmood-Rao H, Hussein A, Gane J. Lessons of the month 3: Haemophagocytic lymphohistiocytosis following COVID-19 vaccination (ChAdOx1 nCoV-19). Clin Med (Lond). 2021;21(6):e677-e679.

Couser 1999
Couser WG. Glomerulonephritis. The Lancet. 1999 May;353(9163):1509-1515.

COVID-NET 2022
COVID-NET. Laboratory-Confirmed COVID-19-Associated Hospitalizations. Available from: (https://gis.cdc.gov/grasp/COVIDNet/COVID19_3.html). Note: covers approximately 10% of the US population.

Croft 1969
Croft PB. Para-infectious and post-vaccinal encephalomyelitis. Postgrad Med J. 1969;45:392400.

Dale et al 2000
Dale RC, de Sousa C, Chong WK, Cox TC, Harding B, Neville BG. Acute disseminated encephalomyelitis, multiphasic disseminated encephalomyelitis and multiple sclerosis in children. Brain. 2000;123:2407-22.

Danesh et al 2021
Danesh L, Ali A, Aslam I, Mensah-Djan A. The effects of SARS-CoV-2 on menstruation. Reprod Biomed Online. 2021;43(4):769. doi: 10.1016/j.rbmo.2021.08.014. Epub 2021 Aug 20. PMID: 34489182; PMCID: PMC8378059.

De Marco F et al 2018
De Marco F, De Cesare DP, Di Folco F, Massoni F, Tomei G, Di Luca NM, Sacco C, Tomei F, Serafino R. Post vaccinal temporary sensorineural hearing loss. International Journal of Environmental Research and Public Health. 2018 Aug;15(8):1780.

Dejnirattisai et al 2021
Dejnirattisai W, Hou J, Zhou D, Zahradnik J, Supasa P, Liu C et al. Omicron-B.1.1.529 leads to widespread escape from neutralizing antibody responses. bioRxiv 2021 [Preprint]; Posted 22 December 2021. Available online at: https://doi.org/10.1101/2021.12.03.471045.

Di Mauro et al 2022
Di Mauro P, La Mantia I, Cocuzza S, Sciancalepore PI, Rasà D, Maniaci A, Ferlito S, Tundo I, Anzivino R. Acute Vertigo After COVID-19 Vaccination: Case Series and Literature Review. Front Med (Lausanne). 2022 Jan 6;8:790931. doi: 10.3389/fmed.2021.790931. PMID: 35071270; PMCID: PMC8770332.

Di Pede et al 2021
Di Pede F, A Covolo, E Della Sala, G Gadaleta, C Gojani, M Laudadio et al. Calvo Journal of the Neurological Sciences 2021:429.

Dias et al 2021
Dias L, Soares-dos-Reis R, Meira J, Ferrão D, Soares PR, Pastor A et al. Cerebral Venous Thrombosis after BNT162b2 mRNA SARS-CoV-2 vaccine. Journal of Stroke and Cerebrovascular Diseases. 2021 25:105906.

Diebold et al 2022
Diebold M, Locher E, Boide P, Enzler-Tschudy A, Faivre A, Fischer I, et al. Incidence of Glomerulonephritis after SARS-CoV-2 mRNA Vaccination.
https://doi.org/10.1101/2022.05.18.22275112

Druey et al 2017
Druey KM, Parikh SM. Idiopathic systemic capillary leak syndrome (Clarkson disease). J Allergy Clin Immunol. 2017; 140(3):663-70.

Drüke et al 2021
Drüke D, Pleyer U, Hoerauf H, Feltgen N, Bemme S. Acute macular neuroretinopathy (AMN) following COVID-19 vaccination. Am J Ophthalmol Case Rep. 2021 Dec;24:101207.

Dudley et al 2020
Dudley MZ, Halsey NA, Omer SB, Orenstein WA, O'Leary ST, Limaye RJ, et al. The state of vaccine safety science: systematic reviews of the evidence. Lancet Infect Dis. 2020;20(5):e80-e89.

Dursun AD et al 2022
The Evaluation of Oxidative Stress in the Young Adults with COVID-19 mRNA Vaccines Induced Acute Pericarditis- Myopericarditis. Int J Gen Med. 2022 Jan 6;15:161-167. doi: 10.2147/IJGM.S347977. PMID: 35023954; PMCID: PMC8747758.

Dutta et al 2021
Dutta A, Ghosh R, Bhattacharya D, Bhat S, Ray A, Pandit A et al. Anti-PF4 antibody negative cerebral venous sinus thrombosis without thrombocytopenia following immunization with COVID-19 vaccine in an elderly non-comorbid Indian male, managed with conventional heparin warfarin based anticoagulation. Diabetes Metab Syndr, (2021) 15 (4): 102184.

ECDC 2021
https://www.ecdc.europa.eu/en/publications-data/data-daily-new-cases-covid-19-eueea-country

Efthimiou et al 2021
Efthimiou P, Kontzias A, Hur P, Rodha K, Ramakrishna GS, Nakasato P. Adult-onset Still's disease in focus: Clinical manifestations, diagnosis, treatment, and unmet needs in the era of targeted therapies. InSeminars in Arthritis and Rheumatism 2021;51(40):858-74).

EHP 2021
Guidance from the Expert Haematology Panel (EHP) on COVID-19 Vaccine-induced Immune Thrombocytopenia and Thrombosis (VITT). Updated Guidance on Management. May 28.

El Haddad et al 2022
El Haddad H, El Meligui A, Salam R, El Din HM, Rabie A, Amin S, Youssry M, Tarek N. Sub acute thyroiditis following COVID infection or vaccine. InEndocrine Abstracts 2022; 7:81. Bioscientifica.

Elarbed et al 2021
Elarbed A, Fackrell K, Baguley DM, Hoare DJ. Tinnitus and stress in adults: a scoping review. Int J Audiol. 2021;60(3):171-82. doi: 10.1080/14992027.2020.1827306.

EMA 2022
European Medicines Agency. EMA workshop on thrombosis with thrombocytopenia syndrome. Virtual workshop, 27 June 2022. Available on: https://www.ema.europa.eu/en/events/ema-workshop-thrombosis-thrombocytopenia-syndrome

Erdem et al 2021
Erdem NS, Demirci S, ÖZel T, Mamadova K, Karaali K, ÇElik HT et al. Acute transverse myelitis after inactivated covid-19 vaccine. Ideggyogyaszati Szemle. 2021;74(7-8):273-6. Available from: https://www.embase.com/search/results?subaction=viewrecord&id=L2014491663&from=export

Ersoy 2021
Ersoy, A. 7th International Congress on Medical and Health Sciences Researche (UTSAK) – Bandirma Onyedi Eylul University. 2021;79. Available at: https://avesis.ebyu.edu.tr/yayin/8dfcfc3fd404-4b69-85d8-6f0327cd75de/three-myelitis-cases-following-covid-19-vaccination.

Escolà et al 2022
Escolà JK, Deuschl C, Junker A, Dusse F, Pul R, Kleinschnitz C, et al. MOG antibody–associated encephalomyelitis mimicking bacterial meningomyelitis following ChAdOx1 nCoV-19 vaccination: a case report. Therapeutic Advances in Neurological Disorders. 2022;15:1-6. doi:10.1177/17562864211070684.

Fahmy et al 2021
Fahmy E, Yeap B, Baharuddin M, Abdelhafez M, Than W, Soe M et al. Obstetric challenges during COVID-19 pandemic: A narrative review. Annals of Medicine and Surgery. 2021 ; 71 (102995).

Falkenhain-López D 2020
Falkenhain-López D: COVID-19-related acute genital ulcers. J Eur Acad Dermatol Venereol 2020; 34:e655–6.

Falsey et al 2021
Falsey AR, Sobieszczyk ME, Hirsch I, Sproule S, Robb M et al. Efficacy of AZD1222 (ChAdOx1 nCoV-19) Covid-19 Vaccine. N Engl J Med. 2021; 385: 2348-60. DOI: 10.1056/NEJMoa2105290

Fardet et al 2014
Fardet L, Galicier L, Lambotte O, Marzac C, Aumont C, Chahwan D et al. Development and validation of the HScore, a score for the diagnosis of reactive hemophagocytic syndrome. Arthritis Rheumatol. 2014, 66, 2613–20.

Farooq et al 2021
Farooq H, Rehman MA, Asmar A, Asif S, Mushtaq A, Qureshi MA. The pathogenesis of COVID-19-induced IgA nephropathy and IgA vasculitis: A systematic review. Journal of Taibah University Medical Sciences. 2021 Sep 28.

Fatima M et al 2022
Development of myocarditis and pericarditis after COVID-19 vaccination in adult population: A systematic review. Ann Med Surg (Lond). 2022;76:103486. doi: 10.1016/j.amsu.2022.103486. Epub 2022 Mar 11. PMID: 35291413; PMCID: PMC8912977.

Fatourechi et al 2003
Fatourechi V, Aniszewski JP, Fatourechi GZ, Atkinson EJ, Jacobsen SJ. Clinical features and outcome of subacute thyroiditis in an incidence cohort: Olmsted County, Minnesota, study. J Clin Endocrinol Metab. 2003 May;88(5):2100-5. doi: 10.1210/jc.2002-021799. PMID: 12727961. Accessed at: https://academic.oup.com/jcem/article/88/5/2100/2845301

Felten et al 2021
Felten R, Dubois M, Ugarte-Gil M, Fuentes-Silva Y, Piga M, Arnaud L. Tolerance of COVID-19 vaccination in patients with systemic lupus erythematosus: the international VACOLUP study. The Lancet Rheumatology. 3(9), 2021, Pages e613-e615.

Fix et al 2021
Fix O, Blumberg E, Mi-Chang K, Chu J, Chung R, Goacher E et al. American Association for the Study of Liver Diseases Expert Panel Consensus Statement: Vaccines to Prevent Coronavirus Disease 2019 Infection in Patients With Liver Disease. Hepatology. 2021;74(2):1049-64.

Flaxman et al 2021
Flaxman A, Marchevsky NG, Jenkin D, Aboagye J, Aley PK, Angus B, et al. Reactogenicity and immunogenicity after a late second dose or a third dose of ChAdOx1 nCoV-19 in the UK: a substudy of two randomised controlled trials (COV001 and COV002). Lancet. 2021;398(10304):981-90. doi: 10.1016/S0140-6736(21)01699-8.

Formeister et al 2022
Formeister EJ, Wu MJ, Chari DA, Meek R, Rauch SD, Remenschneider AK, Quesnel AM, De Venecia R, Lee DJ, Chien W, Stewart CM. Assessment of sudden sensorineural hearing loss after COVID-19 vaccination. JAMA Otolaryngology–Head & Neck Surgery. 2022 Apr 1;148(4):307-15.

Friedman et al 2021
Friedman M, Curtis J, Winthrop K. Impact of disease-modifying antirheumatic drugs on vaccine immunogenicity in patients with inflammatory rheumatic and musculoskeletal diseases. Ann Rheum Dis. 2021;80(10):1255-65.

Fujinami and Oldstone 1985
Fujinami RS, Oldstone MB. Amino acid homology between the encephalitogenic site of myelin basic protein and virus: mechanism for autoimmunity. Science. 1985;230:1043-45.

Fujinami et al 2006
Fujinami RS, von Herrath MG, Christen U, Whitton JL. Molecular mimicry, bystander activation, or viral persistence: infections and autoimmune disease. Clinical microbiology reviews. 2006;19(1):80-94.

Fujita et al, 2022
Fujita Y, Yoshida K, Ichikawa D, Shibagaki Y, Yazawa M. Abrupt worsening of occult IgA nephropathy after the first dose of SARS-CoV-2 vaccination. CEN case reports. 2022 Jan 6:1-7.

Gallo Marin B.et al 2021
Gallo Marin B, Aghagoli G, Lavine K. Predictors of COVID-19 severity: A literature review. Rev Med Virol. 2021;31(1):1-10.

Galvan-Casas et al 2021
Galvan-Casas C, Catala A, Munoz-Santos C. Vacunas frente a SARS-CoV-2 y pielSARS-CoV-2 Vaccines and the Skin. Actas Dermo-Sifiliográficas; 2021 112 (9): 828-36.

Gambichler et al 2022
Gambichler T, Boms S, Susok L, Dickel H, Finis C, Abu Rached N. Cutaneous findings following COVID-19 vaccination: review of world literature and own experience. J Eur Acad Dermatol Venereol. 2022;36(2):172-180.

Gao et al 2021
Gao JJ, Tseng HP, Lin CL, Shiu JS, Lee MH, Liu CH. Vaccines. 2021;9(9). Available from https://www.embase.com/search/results?subaction=viewrecord&id=L2013791478&from=export.

Garg 2003
Garg RK. Acute disseminated encephalomyelitis. Postgrad Med J. 2003;79:11-7.

Garg and Paliwal 2021
Garg RK, Paliwal VK. Spectrum of neurological complications following COVID-19 vaccination. Neurol Sci. 2022;43(1):3-40. doi:10.1007/s10072-021-05662-9.

Garg et al 2022
Garg A, Batra PK, Gupta P. Post COVID-19 vaccination acute disseminated encephalomyelitis: a case report. Curr Med Imaging. 2022:1-5. doi: 10.2174/1573405618666220509205457.

Garrido et al 2021
Garrido I, Lopes S, Simões MS, Liberal R, Lopes J, Carneiro F, Macedo G. Autoimmune hepatitis after COVID-19 vaccine–more than a coincidence. Journal of autoimmunity. 2021 1;125:102741.

GBD 2021
Global, regional, and national burden of stroke and its risk factors, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. The Lancet Neurol. 2021 20(10):795-820. doi: 10.1016/S1474-4422(21)00252-0. Epub.

Ghielmetti et al 2021
Ghielmetti M, Schaufelberger HD, Mieli-Vergani G, Cerny A, Dayer E, Vergani D, Beretta-Piccoli BT. Acute autoimmune-like hepatitis with atypical anti-mitochondrial antibody after

mRNA COVID-19 vaccination: A novel clinical entity?. Journal of Autoimmunity. 2021 1;123:102706.

Ghoshouni H et al 2022
Unraveling the Mystery of COVID-19 Postvaccination Myocarditis: A Systematic Review of Current Cases. Int J Clin Pract. 2022 Jan 31;2022:2438913. doi: 10.1155/2022/2438913. PMID: 35685560; PMCID: PMC9159134

Gianfredi et al 2021
Gianfredi V, Minerva M, Casu G, Capraro M, Chieca G, Gaetti G et al. Immediate adverse events following COVID-19 immunization. A cross-sectional study of 314,664 Italian subjects. Acta Biomed. 2021 19;92(S6):e2021487.

Giannotta et al 2021
Giannotta J, Fattizzo B, Girmenia C, Lelo C, Metafuni E, Visentin A et al. Sars-Cov-2 Vaccination in Patients with Paroxysmal Nocturnal Hemoglobinuria: An Italian Multicenter Survey. Blood (2021) 138 (1): 2180.

Gibbons 1956
Gibbons JL, Miller HG, Stanton JB. Para-infectious encephalomyelitis and related syndromes; a critical review of the neurological complications of certain specific fevers. Q J Med. 1956;25:427-505.

Girbardt et al 2021
Girbardt C, Busch C, Al-Sheikh M, Gunzinger JM, Invernizzi A, Xhepa A et al. Retinal Vascular Events after mRNA and Adenoviral-Vectored COVID-19 Vaccines-A Case Series. Vaccines (Basel). 2021;9(11):1349.

GISAID 2022
CoVariants: Overview of Variants in Countries: United States. 2022. Available from: https://covariants.org/per-country?region=United+States

Gluckman T J et al 2022
2022 ACC Expert Consensus Decision Pathway on Cardiovascular Sequelae of COVID-19 in Adults: Myocarditis and Other Myocardial Involvement, Post-Acute Sequelae of SARS-CoV-2 Infection, and Return to Play: A Report of the American College of Cardiology Solution Set Oversight Committee. J Am Coll Cardiol. 2022 May 3;79(17):1717-1756. doi: 10.1016/j.jacc.2022.02.003. Epub 2022 Mar 16. PMID: 35307156; PMCID: PMC8926109.

Go et al 2021
Go AS, Tan TC, Chertow GM, Ordonez JD, Fan D, Law D et al. Primary Nephrotic Syndrome and Risks of ESKD, Cardiovascular Events, and Death: The Kaiser Permanente

Nephrotic Syndrome Study. J Am Soc Nephrol. 2021 Sep;32(9):2303-2314. doi: 10.1681/ASN.2020111583. Epub 2021 Jun 18. PMID: 34362836; PMCID: PMC8729848.

Gold et al 2020
Gold MS, MacDonald NE, McMurtry CM, Balakrishnan MR, Heininger U, Menning L, et al. Immunization stress-related response - Redefining immunization anxiety-related reaction as an adverse event following immunization. Vaccine. 2020 Mar 23;38(14):3015-3020. doi: 10.1016/j.vaccine.2020.02.046.

Goldberg et al 2021
Goldberg Y, Mandel M, Bar-On YM, Bodenheimer O, Freedman L, Haas EJ et al. Waning Immunity after the BNT162b2 Vaccine in Israel. N Engl J Med. 2021;385(24):e85.

Gomez Martín A M et al 2022
Acute myopericarditis after administration of mRNA vaccines against the SARS-CoV-2 virus. Med Clin (Barc). 2022 Jun 24;158(12):e11-e12. English, Spanish. doi: 10.1016/j.medcli.2021.10.008. Epub 2021 Nov 13. PMID: 34895751; PMCID: PMC8590496.

González-Romero et al 2021
González-Romero N, Morillo V, Sánchez VI, García GM. Úlceras De Lipschütz Tras La Vacuna Frente A La Covid-19 De Astrazeneca [Lipschütz Ulcers After the AstraZeneca COVID-19 Vaccine]. Actas Dermosifiliogr (Engl Ed). 2021 2.

Goss et al 2021
Goss, AL, Samudralwar RD, Das RR, Nath A. Annals of Neurology. 2021;89(5): 856-7.

Granerod et al 2013
Granerod J, Cousens S, Davies NW, Crowcroft NS, Thomas SL. New estimates of incidence of encephalitis in England. Emerg Infect Dis. 2013;19(9):1455–62.

Grant et al 2008
Grant C, Oh U, Yao K, Yamano Y, Jacobson S. Dysregulation of TGF-beta signaling and regulatory and effector T-cell function in virus-induced neuroinflammatory disease. Blood. 2008;111:5601-09.

Grasselli et al 2020
Grasselli G, Greco M, Zanella A, Albano G, Antonelli M, Bellani G, et al. Risk Factors Associated With Mortality Among Patients With COVID-19 in Intensive Care Units in Lombardy, Italy. JAMA Intern Med. 2020;180(10):1345-55.

Greene et al 2013
Greene SK, Rett MD, Vellozzi C, Li L, Kulldorff M, Marcy SM et al. Guillain-Barré Syndrome, Influenza Vaccination, and Antecedent Respiratory and Gastrointestinal

Infections: A Case-Centered Analysis in the Vaccine Safety Datalink, 2009-2011. PLoS One. 2013;8(6):e67185.

Greinacher et al 2021
Greinacher A, Thiele T, Warkentin TE, Weisser K, Kyrle PA, Eichinger S. Thrombotic Thrombocytopenia after ChAdOx1 nCov-19 Vaccination. N Eng J Med. Published online on 09 April 2021. DOI: 10.1056/NEJMoa2104840

Greinacher et al 2021 (Blood)
Greinacher A, Selleng K, Palankar R, Wesche J, Handtke S, Wolff M.et al. Insights in ChAdOx1 nCoV-19 vaccine-induced immune thrombotic thrombocytopenia. Blood. 2021;138(22):2256-68.

Greinacher et al 2021 (NEJM)
Greinacher A, Thiele T, Warkentin TE, Weisser K, Kyrle PA, Eichinger S (2021). Thrombotic Thrombocytopenia after ChAdOx1 nCov-19 Vaccination. The new england journal of medicine (NEJM), 384 (22): 2092-101. DOI: 10.1056/NEJMoa2104840

Guan et al 2020
Guan W, Liang W, Zhao Y, Liang H, Chen Z, Li Y, et al. Comorbidity and its impact on 1590 patients with COVID-19 in China: a nationwide analysis. Eur Respir J 2020;55:1-14.

Guillain-Barré syndrome, 2021
Sweden, accessed 26 January 2022, last updated 12 Apr. 2021 https://nhi.no/sykdommer/hjernenervesystem/infeksjoner/guillain-barre-syndrom/.

Guo et al 2021
Guo Q, Wu S, Xu C, Wang J, Chen J. Global Disease Burden From Acute Glomerulonephritis 1990–2019. Kidney International Reports. 2021 Aug;6(8):2212.

Gupte et al 2003
Gupte G, Stonehouse M, Wassmer E et al. (2003). Acute disseminated encephalomyelitis: a review of 18 cases in childhood. J Paediatr Child Health 39: 336–42.

Hamed 2019
Hamed SA. Neurologic conditions and disorders of uremic syndrome of chronic kidney disease: presentations, causes, and treatment strategies. Expert Rev Clin Pharmacol. 2019;12(1):61-90.

Hamza and Beers, 2021
Hamza M, Beers KH. Iga nephropathy flare following COVID-19 vaccination. Journal of the American Society of Nephrology. 2021:90.

Han et al 2021
Han B, Song Y, Li C, Yang W, Ma Q, Jiang Z et al. Safety, tolerability, and immunogenicity of an inactivated SARS-CoV-2 vaccine (CoronaVac) in healthy children and adolescents: a double-blind, randomised, controlled, phase 1/2 clinical trial. *Lancet Infect Dis.* 2021 21(12):1645-53.

Hanna et al, 2021
Hanna C, Hernandez LP, Bu L, Kizilbash S, Najera L, Rheault MN, Czyzyk J, Kouri AM. IgA nephropathy presenting as macroscopic hematuria in 2 pediatric patients after receiving the Pfizer COVID-19 vaccine. Kidney international. 2021 Sep 1;100(3):705-6.

Hartfield et al 1999
Hartfield DS, Loewy JA, Yager JY. Transient thalamic changes on MRI in a child with hypernatremia. Pediatr Neurol. 1999;20:60-2.

Hartung and Grossman 2001
Hartung HP, Grossman RI (2001). ADEM: distinct disease or part of the MS spectrum? Neurology 56: 1257–60.

Hartung et al 1990
Hartung, H.P., Hughes, R.A.C., Taylor, W.A., Heininger, K., Rein-ers, K. and Toyka, K.V. (1990) T cell activation in Guillain-Barr6 syndrome and in MS: elevated serum levels of soluble IL-2 receptors. Neurology 40, 215-8.

Hartung et al 1991
Hartung, H.P., Reiners, K., Schmidt, B., Stoll, G. and Toyka, K.V. (1991) Serum interleukine-2 concentrations in Guillain-Barr6 syn- drome and chronic idiopathic demyelinating polyradiculoneuropathy: comparison with other neurological diseases of presumed immunopathogenesis. Ann. Neurol. 30, 48-53.

Hassanzadeh S et al 2022
Myocarditis following AstraZeneca (an adenovirus vector vaccine) COVID-19 vaccination: A case report. Clin Case Rep. 2022 Apr 15;10(4):e05744. doi: 10.1002/ccr3.5744. PMID: 35441011; PMCID: PMC9011044

Haynes et al 2020
Haynes BF, Corey L, Fernandes P, Gilbert PB, Hotez PJ, Rao S, et al. Prospects for a safe COVID-19 vaccine. Sci Transl Med. 2020;12(568):eabe0948. Epub 2020.

Helseinformatikk 2020
Helseinformatikk N. Transverse Myelitt 2020. Available from: https://nhi.no/sykdommer/hjernenervesystem/ryggmargssykdommer/transvers-myelitt/

Hemachudha et al 1987 [A]
Hemachudha T, Griffin DE, Giffels JJ, Johnson RT, Moser AB, Phanuphak P. Myelin basic protein as an encephalitogen in encephalomyelitis and polyneuritis following rabies vaccination. N Engl J Med. 1987;316:369-374.

Hemachudha et al 1987 [B]
Hemachudha T, Phanuphak P, Johnson RT, Griffin DE, Ratanavongsiri J, Siriprasomsup W. Neurologic complications of Semple-type rabies vaccine: Clinical and immunologic studies. Neurology. 1987;37(4):550.

Hemminki and Forssas 1999
Hemminki E, Forssas E. Epidemiology of miscarriage and its relation to other reproductive events in Finland. Am J Obstet Gynecol. 1999;181(2):396-401.

Hibbs et al 2015
Hibbs B, Moro PL, Lewis P, Miller ER, Shimabukuro TT. Vaccination errors reported to the Vaccine Adverse Event Reporting System, (VAERS) United States, 2000–2013. Vaccine. 2015;33:3171–8.

Higgins et al 2021
Higgins R, Hamilton H, Weisman M, Reveille J, Ogle K, Shafer C et al. Most Patients with Spondylitis Accept COVID-19 Vaccination and Few Experience Disease Exacerbation After Immunization [abstract]. Arthritis Rheumatol. 2021; 73 (suppl 10).

Hillson et al 2021
Hillson K, Clemens S, Madhi S, Voysey M, Pollard A, Minassian A et al. Fertility rates and birth outcomes after ChAdOx1 nCoV-19 (AZD1222) vaccination. The Lancet. 2021. 398(10312), 2021, 1683-4.

Hippisley-Cox et al 2021
Hippisley-Cox et al. Risk of thrombocytopenia and thromboembolism after covid-19 vaccination and SARS-CoV-2 positive testing: self-controlled case series study. BMJ 2021;374:n1931 http://dx.doi.org/10.1136/bmj.n1931

Hjortdal et al 2013
Hjortdal J, Pedersen IB, Bak-Nielsen S, Ivarsen A. Graft rejection and graft failure after penetrating keratoplasty or posterior lamellar keratoplasty for fuchs endothelial dystrophy. Cornea. 2013 1;32(5):e60-3.

Honda et al 2016
Honda K., Littman D.R. The microbiota in adaptive immune homeostasis and disease. Nature. 2016;535:75–84. doi: 10.1038/nature18848.

Hou et al 2021
Hou YC, Lu KC, Kuo KL. The Efficacy of COVID-19 Vaccines in Chronic Kidney Disease and Kidney Transplantation Patients: A Narrative Review. Vaccines. 2021;9:885. https://doi.org/10.3390/vaccines9080885.

Hoyer et al 2021
Hoyer B, Lorenz H, Pfeil A, Richter J, Regierer A, Schmeiser T et al. Safety of COVID-19 Vaccines After First Vaccination in Patients with Rheumatic Diseases in a Patient Reported Survey. Arthritis Rheumatol. 2021; 73 (suppl 10).

Hozumi et al 1999
Hozumi N, Yuki K, Yamazaki K, Hirati. Facial diplegia with paraesthesias: facial nerve enhancement in three dimensional MRI. J Neurol Neurosurg Psychiatry 1999;66:688–97.

Hull and Goldsmith, 2008
Hull RP, Goldsmith DJ: Nephrotic syndrome in adults. BMJ. 2008;336: 1185–9.

Hung et al 2022
Hung YP. Sun KS. A case of myopericarditis with pleuritis following AstraZeneca Covid-19 vaccination. QJM. 2022 9;114(12):879-81.

Huynh et al 2021
Huynh A, Kelton JG, Arnold DM, Daka M, Nazy I. Antibody epitopes in vaccine-induced immune thrombotic thrombocytopaenia. Nature. 2021 Aug;596(7873):565-9. doi: 10.1038/s41586-021-03744-4. Epub 2021 Jul 7. PMID: 34233346.

Hviid et al, 2022
Hviid et al. Association of AZD1222 and BNT162b2 COVID-19 Vaccination With Thromboembolic and Thrombocytopenic Events in Frontline Personnel. A Retrospective Cohort Study. Ann Intern Med. doi:10.7326/M21-2452

Hynson et al 2001
Hynson JL, Kornberg AJ, Coleman LT, Shield L, Harvey AS, Kean MJ. Clinical and neuroradiologic features of acute disseminated encephalomyelitis in children. Neurology. 2001;56:1308-12.

Iba and Levy 2022
Iba T, Levy JH. Thrombosis and thrombocytopenia in COVID-19 and after COVID-19 vaccination. Trends in Cardiovascular Medicine. 2022.

Iescheck et al
Iescheck, K., L. Filla, L. Rio, L. Petroli, G. Favero,P. Bonilha 29th Brazilian Congress on Neurology - Brazilian Academy of Neurology (ABN): PO 102108.

IHME 2022
University of Washington School of Medicine, Institute for Health Metrics and Evaluation. COVID-19 Vaccine Efficacy Summary. 18 February 2022. Available from: https://www.healthdata.org/covid/covid-19-vaccine-efficacy-summary

Ilonze OJ et al 2022
Myocarditis following COVID-19 vaccination in adolescents and adults: a cumulative experience of 2021. Heart Fail Rev. 2022 Apr 22:1–11. doi: 10.1007/s10741-022-10243-9. Epub ahead of print. PMID: 35449353; PMCID: PMC9023259.

Introna et al 2021
Introna A., Caputo F, Santoro C, Guerra T, Ucci M, Mezzapesa DM et al. Guillain- Barré syndrome after AstraZeneca COVID-19-vaccination: A causal or casual association. Clin Neurol Neurosurg 2021 208: 106887.

Ioannidis et al 2021
Ioannidis J.P.A. COVID-19 vaccination in children and university students. *Eur J Clin Invest.* 2021;51:e13678.

Ismail and Salama 2022
Ismail II, Salama S. A systematic review of cases of CNS demyelination following COVID-19 vaccination. Journal of Neuroimmunology. 2022;15;362:577765.

Iwanaga et al 2022
Iwanaga J, Fukuoka H, Fukuoka N, Yutori H, Ibaragi S, Tubbs RS et al. A narrative review and clinical anatomy of herpes zoster infection following COVID-19 vaccination. Clin Anat. 2022;35(1):45-51. doi:10.1002/ca.23790.

Izzedine et al 2021
Izzedine H, Bonilla M, Jhaveri KD. Nephrotic syndrome and vasculitis following SARS-CoV-2 vaccine: true association or circumstantial? Nephrol Dial Transplant. 2021 Aug;36(9):1565–9.

James C et al 2020
James C, Harfouche M, Welton NJ, Turner KM, Abu-Raddad LJ, Gottlieb SL et al. Herpes simplex virus: global infection prevalence and incidence estimates, 2016. Bull World Health Organ. 2020 May 1;98(5):315-29.

James et al 2021
James J, Jose J, Gafoor AV, Smita B, Balaram N. Guillain-Barré syndrome following ChAdOx1 nCoV-19 COVID-19 vaccination: A case series. Neurology and Clinical Neuroscience 2021 9(5): 402-405.

Jamie S Y et al 2021
A review of COVID-19 vaccination and the reported cardiac manifestations. Singapore Med J 2021, 1–21 https://doi.org/10.11622/smedj.2021210

Jamme et al 2021
Jamme M, Elalamy I, d'Izarny Gargas T, Pettenati C, Desire E, Tissot A et al. Transplantation Outcome in Recipients Engrafted With Organs Recovered From the First French Deceased Donor With a SARS-COV-2 Vaccine-induced Thrombotic Thrombocytopenia. Transplantation. 2021;105(8):e84-e86.

Jara et al 2022
Jara A, Undurraga EA, Zubizarreta JR, González C, Pizarro A, Acevedo J, et.al. Effectiveness of homologous and heterologous booster doses for an inactivated SARS-CoV-2 vaccine: a large-scale prospective cohort study. Lancet Glob Health. 2022 Jun;10(6):e798-e806. doi: 10.1016/S2214-109X(22)00112-7. Epub 2022 Apr 23. PMID: 35472300; PMCID: PMC9034854.

Javed and Khan 2014
Javed A, Khan O. Acute disseminated encephalomyelitis. Handbook of clinical neurology. 2014 Jan 1;123:705-17.

Jeon et al 2021
Jeon YH, Lim DH, Choi SW, Choi SJ. A flare of Still's disease following COVID-19 vaccination in a 34-year-old patient. Rheumatol Int. 2021:1–6. doi: 10.1007/s00296-021-05052-6.

Jeong J et al 2021
Jeong J, Choi HS. Sudden sensorineural hearing loss after COVID-19 vaccination. International Journal of Infectious Diseases. 2021 Dec 1; 113:341-3.

Johnson et al 2015
Johnson RW, Alvarez-Pasquin MJ, Bijl M, Franco E, Gaillat J, Clara JG et al. Herpes zoster epidemiology, management, and disease and economic burden in Europe: a multidisciplinary perspective. Ther Adv Vaccines. 2015 Jul;3(4):109-20.

Jorens et al 2000
Jorens PG, VanderBorght A, Ceulemans B, Van Bever HP, Bossaert LL, Ieven M, et al. Encephalomyelitis-associated antimyelin autoreactivity induced by streptococcal exotoxins. Neurology. 2000;54:1433-41.

Joubert et al 2021
Joubert E, Kekeh AC, Amin C. COVID-19 and novel mRNA vaccines in pregnancy: an updated literature review. BJOG. 2021; 129 (1): 21-8.

Kadkhoda K 2021
Post RNA-based COVID vaccines myocarditis: Proposed mechanisms. Vaccine. 2022 Jan 24;40(3):406-407. doi: 10.1016/j.vaccine.2021.11.093. Epub 2021 Dec 9. PMID: 34895937; PMCID: PMC8658401.

Kampmann et al 2021
Kampmann B, Okomo U. COVID-19 vaccines for children in LMICs: another equity issue. *LANCET*. 2021; 398(10302): 731-2.

Kanabar et al
Kanabar, G.,P. Wilkinson. BMJ case reports 2021 14(10).

Kanamori 2021
Kanamori H. POS-901 Gross hematuria after COVID-19 vaccination led to the diagnosis of IgA nephropathy. Kidney International Reports. 2022 Feb;7(2):391.

Kanamori 2022
Kanamori H. POS-901 Gross hematuria after COVID-19 vaccination led to the diagnosis of IgA nephropathy. Kidney International Reports. 2022 Feb;7(2):391.

Kanduc and Shoenfeld 2020
Kanduc D, Shoenfeld Y. Molecular mimicry between SARS-CoV-2 spike glycoprotein and mammalian proteomes: implications for the vaccine. Immunol Res. 2020;68(5):310-3. doi: 10.1007/s12026-020-09152-6.

Kang DH et al 2022
Fulminant Giant Cell Myocarditis following Heterologous Vaccination of ChAdOx1 nCoV-19 and Pfizer-BioNTech COVID-19. Medicina (Kaunas). 2022 Mar 20;58(3):449. doi: 10.3390/medicina58030449. PMID: 35334625; PMCID: PMC8950462.

Kaul R et al 2021
Myocarditis following COVID-19 vaccination. Int J Cardiol Heart Vasc. 2021 Oct;36:100872. doi: 10.1016/j.ijcha.2021.100872. Epub 2021 Sep 20. PMID: 34568540; PMCID: PMC8450283.

Kawano H et al 2022
Fulminant Myocarditis 24 Days after Coronavirus Disease Messenger Ribonucleic Acid Vaccination: A Case Report. Intern Med. 2022 May 31. doi: 10.2169/internalmedicine.9800-22. Epub ahead of print. PMID: 35650138.

Kazi and Hashmi 2022
Kazi AM, Hashmi MF. Glomerulonephritis. [Updated 2022 Feb 16]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK560644/

KDIGO 2012
Kidney Disease: Improving Global Outcomes (KDIGO) Glomerulonephritis Work Group. KDIGO Clinical Practice Guideline for Glomerulonephritis.Kidney Inter Suppl, 2 (2012), pp. 139-274.

Keane 1994
James R. Keane. Bilateral seventh nerve palsy Analysis of 43 cases and review of the literatureNeurology 1994, 44 (7) 1198; DOI: 10.1212/WNL.44.7.1198

Keh et al 2022
Keh RYS, Scanlon S, Datta-Nemdharry P, Donegan K, Cavanagh S, Foster M et al. COVID-19 vaccination and Guillain-Barré syndrome: analyses using the National Immunoglobulin Database. Brain. 2022:awac067.

Khan and Brassill 2021.
Khan F and Brassill MJ. Subacute thyroiditis post-Pfizer-BioNTech mRNA vaccination for COVID-19. Endocrinol Diabetes Metab Case Rep. 2021 Dec 1;2021:21-0142. doi: 10.1530/EDM-21-0142. Epub ahead of print. PMID: 34907904; PMCID: PMC8686178.

Khan et al 2022
Khan SM, Shilen A, Heslin KM, Ishimwe P, Allen AM, et al. SARS-CoV-2 infection and subsequent changes in the menstrual cycle among participants in the Arizona CoVHORT study. Am J Obstet Gynecol. 2022;226(2):270-3.

Kiblboeck D et al 2022
Myocarditis following mRNA COVID-19 vaccination: call for endomyocardial biopsy. ESC Heart Fail. 2022 Jun;9(3):1996-2002. doi: 10.1002/ehf2.13791. Epub 2022 Feb 23. PMID: 35194974; PMCID: PMC9065833.

Kim et al 2021
Dong Kim, H., K. Eun Hwang, C. Young Moon, J. Woo Lee,I. Cho. Multiple Retinal Hemorrhages with Retinal Vein Thrombosis after a COVID-19 Vaccination: A Case Report. 14th Congress of the Asia-Pacific Vitreo-Retina Society (APVRS) - VIRTUAL: 201235.

Kirsebom et al 2022
Kirsebom, F. et al. (2022) "Effectiveness of ChAdOx1-S COVID-19 Booster Vaccination against the Omicron and Delta variants in England". medRxiv. doi: https://doi.org/10.1101/2022.04.29.22274483
https://www.medrxiv.org/content/10.1101/2022.04.29.22274483v1

Kiryluk et al, 2012;
Kiryluk K, Li Y, Sanna-Cherchi S, Rohanizadegan M, Suzuki H et al. Geographic differences in genetic susceptibility to IgA nephropathy: GWAS replication study and geospatial risk analysis. PLoS genetics. 2012 Jun 21;8(6):e1002765.

Kiryluk et al, 2014
Kiryluk K, Li Y, Scolari F, Sanna-Cherchi S, Choi M et al. Discovery of new risk loci for IgA nephropathy implicates genes involved in immunity against intestinal pathogens. Nature genetics. 2014 Nov;46(11):1187-96.

Kitamura et al 1998
Kitamura H, Nakano T, Kakihara M, Nishino M, Isshiki K, Kawano K et al. A case of Guillain-Barré syndrome developed minimal change nephrotic syndrome simultaneously. Am J Nephrol. 1998;18(2):151-4.

Kittichokechai P et al
P-109 Dynamic change of an electrocardiogram in myocarditis following m-RNA COVID-19 vaccination. 55th Annual Meeting of the Association for European Paediatric and Congenital Cardiology (AEPC)

Klamer TA et al 2022
The benefit of vaccination against COVID-19 outweighs the potential risk of myocarditis and pericarditis. Neth Heart J. 2022 Apr;30(4):190-197. doi: 10.1007/s12471-022-01677-9. Epub 2022 Mar 9. PMID: 35266090; PMCID: PMC8906525.

Klomjit et al 2021
Klomjit N, Zoghby Z, Fervenza FC, Zand L. New diagnosis of glomerulonephritis and relapse of prior glomerulonephritis post mRNA COVID-19 vaccination. Journal of the American Society of Nephrology. 2021:90.

Kodner 2016
Kodner C: Diagnosis and management of nephrotic syndrome in adults. Am Fam Physician 93: 479–485, 2016.

Kompaniyets et al 2021
Kompaniyets L, Pennington AF, Goodman AB, Rosenblum HG, Belay B, Ko JY et al. Underlying Medical Conditions and Severe Illness Among 540,667 Adults Hospitalized With COVID-19, March 2020–March 2021. Prev Chronic Dis 2021;18:210123.

Ku et al 2021
Ku CR, Jung KY, Ahn CH, Moon JS, Lee JH, Kim EH et al. Committee of Clinical Practice Guideline of the Korean Endocrine Society. COVID-19 Vaccination for Endocrine Patients: A Position Statement from the Korean Endocrine Society. Endocrinol Metab (Seoul). 2021;36(4):757-65.

Kudose et al, 2021
Kudose S, Friedmann P, Albajrami O, D'Agati VD. Histologic correlates of gross hematuria following Moderna COVID-19 vaccine in patients with IgA nephropathy. Kidney International. 2021 Aug 1;100(2):468-9.

Kumar et al 2022
Kumar A, Sabharwal P, Gupta P, Singh VK, Rao BK. A fatal case of acute disseminated encephalomyelitis: a diagnosis to ponder in pandemic. Indian J Crit Care Med. 2022;26(4):518-520. doi: 10.5005/jp-journals-10071-24185.

Kwak et al 2019
Kwak Y, Kim Y, Baek KA. Prevalence of irregular menstruation according to socioeconomic status: A population-based nationwide cross-sectional study. PLoS One. 2019 Mar 19;14(3):e0214071.

Laffan et al 2022
Laffan MA, Rees S, Yadavalli M, Ferstenberg LB, Shankar NK, Medin J, et al. Thrombosis with thrombocytopenia after AZD1222 (ChAdOx1 nCov-19) vaccination: Case characteristics and associations. Vaccine. 2022.

Laganà et al 2022
Laganà AS, Veronesi G, Ghezzi F, Ferrario MM, Cromi A, Bizzarri M et al. Evaluation of menstrual irregularities after COVID-19 vaccination: Results of the MECOVAC survey. Open Medicine (Poland). 2022 17(1):475-84.

Lai et al, 2016
Lai KN, Tang SC, Schena FP, Novak J, Tomino Y, Fogo AB, et al. IgA nephropathy. Nature reviews Disease primers. 2016 Feb 11;2(1):1-20.

Lane S et al 2021
Systematic review of spontaneous reports of myocarditis and pericarditis in transplant recipients and immunocompromised patients following COVID-19 mRNA vaccination. medRxiv 2021.12.20.21268102; doi: https://doi.org/10.1101/2021.12.20.21268102

Laporte et al 2021
Laporte et al. Vaccines against Covid-19, venous thromboembolism, and thrombocytopenia. A population-based retrospective cohort study. medRxiv 2021.07.23.21261036; doi: https://doi.org/10.1101/2021.07.23.21261036

Laporte et al 2021
Laporte et al. Vaccines against Covid-19, venous thromboembolism, and thrombocytopenia. A population-based retrospective cohort study. medRxiv 2021.07.23.21261036; doi: https://doi.org/10.1101/2021.07.23.21261036

Larsen et al 2021
Larsen SE., Nilsson CA, Justesen SU, Voss A, Johansen SI. Annual Meeting of the American College of Rheumatology (ACR) held jointly with the 2021 Annual Meeting of the Association of Rheumatology Professionals (ARP). 2021:0876

Law B 2021
Law B. Safety Platform for Emergency vaccines. SO2- D2.5.2.1 - AESI Case Definition Companion. Guide for 1st Tier AESI. Acute Encephalitis. Accessed on 29 June 2022. Available from: https://brightoncollaboration.us/wp-content/uploads/2021/03/SPEAC_D2.5.2.1_Encephalitis-Case-Definition-Companion-Guide_V1.0_format12064-1.pdf.

Law B 2021 [A]
Law B. Safety Platform for Emergency vaccines. SO2- D2.5.2.1 - AESI Case Definition Companion. Guide for 1st Tier AESI. Guillain Barré and Miller Fisher Syndromes. Accessed on 05 December 2021. Available from: https://brightoncollaboration.us/wpcontent/uploads/2021/03/SPEAC_D2.5.2.1-GBS-Case-Definition-Companion-Guide_V1.0_format12062-1.pdf.

Law B 2021 [B]
Law B. Safety Platform for Emergency vaccines. SO2- D2.5.2.1 - AESI Case Definition Companion. Guide for 1st Tier AESI. Acute Disseminated Encephalomyelitis. 2021; Available from: https://brightoncollaboration.us/wp-content/uploads/2021/03/SPEAC_D2.5.2.1_ADEM-Case-Definition-Companion-Guide_V1.0_format12063-1.pdf.

Law B 2021 [C]
Law B. Safety Platform for Emergency vaccines. SO2- D2.5.2.1 - AESI Case Definition Companion. Guide for 1st Tier AESI. Acute Myelitis. 2021; Available from: https://brightoncollaboration.us/wp-content/uploads/2021/03/SPEAC_D2.5.2.1_Myelitis-Case-Definition-Companion-Guide_V3.0_13Feb2021_format12066-1.pdf.

Lazaro et al 2021
Lazaro L, Pera Cosio J, Luis B, Tamagnini F, Paguay Mejía D, Fernandez N, et al. Alonso. Multiple Sclerosis Journal. 2021;27(2):145.

Lazaros G et al 2021
The Novel Platform of mRNA COVID-19 Vaccines and Myocarditis: Clues into the Potential Underlying Mechanism. Vaccine. 2021 Aug 16;39(35):4925-4927. doi: 10.1016/j.vaccine.2021.07.016. Epub 2021 Jul 13. PMID: 34312010; PMCID: PMC8275472.

Leake et al 2004
Leake JA, Albani S, Kao AS, Senac MO, Billman GF, Nespeca MP, et al. Acute disseminated encephalomyelitis in childhood: epidemiologic, clinical and laboratory features. Pediatr Infect Dis J. 2004;23:756-64.

Lechasa-Muniz et al 2021
Lechasa-Muniz C, Paz-Zuleta M, Mendez-Legazo J, Irure-Ventura J, Gonzalez R et al. Induction of SARS-CoV-2-Specific IgG and IgA in Serum and Milk with Different SARS-CoV-2 Vaccines in Breastfeeding Women: A Cross-Sectional Study in Northern Spain. MDPI. nt. J. Environ. Res. Public Health. 2021, 18, 8831.

Leclerc et al 2021
Leclerc S, Royal V, Lamarche C, Laurin LP. Minimal change disease with severe acute kidney injury following the Oxford-AstraZeneca COVID-19 vaccine: a case report. American Journal of Kidney Diseases. 2021 Oct 1;78(4):607-10.

Lee CH et al 2022
FDG PET/MRI of Acute Myocarditis After mRNA COVID-19 Vaccination. Clin Nucl Med. 2022 May 1;47(5):e421-e422. doi: 10.1097/RLU.0000000000004123. PMID: 35234199; PMCID: PMC8983619.

Lee et al 2022
Lee S, Hor JY, Koh KL, Chia YK. Central Nervous System Demyelination Following COVID-19 mRNA-Based Vaccination: Two Case Reports and Literature Review. J Cent Nerv Syst Dis. 2022;11;14:11795735221102747.

Leik et al 2021
Leik N, Ahmedy F, Mac Guard R, Baharuddin M. COVID-19 vaccine and its consequences in pregnancy: Brief review. Annals of Medicine and Surgery. 2021 (72).

Levin et al 2021
Levin EG, Lustig Y, Cohen C, Fluss R, Indenbaum V, Amit S, et al. Waning immune humoral response to BNT162b2 Covid-19 vaccine over 6 months. N Engl J Med. 2021;NEJMoa2114583. Epub 2021 Oct 6. Accessed 19 November 2021.

Li et al 2022
Li S-Y, Chen H-H, Liu P-Y, et al. Case report of acute encephalitis following the AstraZeneca COVID-19 vaccine. Int J Rheum Dis. 2022;00:1-7. doi: 10.1111/1756-185X.14372.

Li et al. 2022
Grace Li, Federica Cappuccini, Natalie G Marchevsky, Parvinder K Aley, Robert Aley, Rachel Anslow et al. Safety and immunogenicity of the ChAdOx1 nCoV-19 (AZD1222) vaccine in children aged 6-17 years: a preliminary report of COV006, a phase 2 single-blind, randomised, controlled trial. Lancet. 2022 Jun 11;399(10342):2212-2225. doi: 10.1016/S0140-6736(22)00770-X.

Li G et al 2021
Li G, Finn A, Pollard AJ. Should we be vaccinating children against COVID-19 in high-income countries? *Expert Rev Vaccines*. 2021; 20:1043–6.

Li NL et al 2021
Li NL, Coates PT, Rovin BH. COVID-19 vaccination followed by activation of glomerular diseases: does association equal causation?. Kidney International. 2021 Nov 1;100(5):959-65.

Li S et al 2021
Li S, Jia X, Yu F, Wang Q, Zhang T, Yuan J. Herpetic keratitis preceded by COVID-19 vaccination. Vaccines. 2021;9(12):1394.

Lin RJ et al 2012
Lin RJ, Krall R, Westerberg BD, Chadha NK, Chau JK. Systematic review and meta-analysis of the risk factors for sudden sensorineural hearing loss in adults. The Laryngoscope. 2012 Mar;122(3):624-35.

Ling et al 2021
Ling L, S. M. Bagshaw P. M. Villeneuve. CMAJ 2021;193(46): E1766-E1769.

Ling RR et al 2022
Myopericarditis following COVID-19 vaccination and non-COVID-19 vaccination: a systematic review and meta-analysis. Lancet Respir Med. 2022 Apr 11;10(7):679–88. doi: 10.1016/S2213-2600(22)00059-5. Epub ahead of print. Erratum in: Lancet Respir Med. 2022;: PMID: 35421376; PMCID: PMC9000914.

Liu et al 2018
Liu JC, Nesper PL, Fawzi AA, Gill MK. Acute macular neuroretinopathy associated with influenza vaccination with decreased flow at the deep capillary plexus on OCT angiography. Am J Ophthalmol Case Rep. 2018;10:96-100.

Liu et al 2020
Liu CY, Ibekwe T, Kelso JM, Klein NP, Shehu N, Steuerwald W, et al. Sensorineural hearing loss (SNHL) as an adverse event following immunization (AEFI): Case definition & guidelines for data collection, analysis, and presentation of immunization safety data. Vaccine. 2020;38(30):4717-31. doi: 10.1016/j.vaccine.2020.05.019. Epub 2020 May 15. https://doi.org/10.1016/j.vaccine.2020.05.019.

Lo and Chan 2021
Lo WK, Chan KW. Gross haematuria after mRNA COVID-19 vaccination in two patients with histological and clinical diagnosis of IgA nephropathy. Nephrology (Carlton, Vic.). 2021 Nov 11.

London School of Hygiene and Tropical Medicine
London School of Hygiene and Tropical Medicine. COVID-19 vaccine tracker (https://vac-lshtm.shinyapps.io/ncov_vaccine _landscape/)

Londoño et al 2021
Londoño MC, Gratacós-Ginès J, Sáez-Peñataro J. Another case of autoimmune hepatitis after SARS-CoV-2 vaccination. Still casualty?. Journal of Hepatology. 2021 12.

Loo et al 2022
Loo LK, Salim O, Liang D, Goel A, Sumangala S, Gowda A et al. Acute-onset polyradiculoneuropathy after SARS-CoV2 vaccine in the West and North Midlands, United Kingdom. Muscle Nerve. 2022;65(2):233-7.

Lourdes et al 2014
Lourdes Álvarez-Arellano, Carmen Maldonado-Bernal; Helicobacter pylori and neurological diseases: Married by the laws of inflammation. World J Gastrointest Pathophysiol 2014; 5(4): 400-4).

Ludwig et al 2021
Ludwig H, Sonneveld P, Facon T, San-Miguel J, Avet-Loiseau H, Mohty M et al. COVID-19 vaccination in patients with multiple myeloma: a consensus of the European Myeloma Network. The Lancet Haematology. 2021;8(12):e934-46.

LV et al 2021
LV M., Luo X, Shen Q, Lei R, Liu X, Liu E et al. Safety, Immunogenicity, and Efficacy of COVID-19 Vaccines in Children and Adolescents: A Systematic Review. Vaccines (Basel). 2021;9(10):1102.

Mac Grory et al 2021
Mac Grory B, Schrag M, Biousse V, Furie KL, Gerhard-Herman M, Lavin PJ et al. American Heart Association Stroke Council; Council on Arteriosclerosis, Thrombosis and Vascular Biology; Council on Hypertension; and Council on Peripheral Vascular Disease. Stroke. 2021;52(6):e282-e294.

Machaczka et al 2011
Machaczka M, Vaktnäs J, Klimkowska M, Hägglund H. Malignancy-associated hemophagocytic lymphohistiocytosis in adults: a retrospective population-based analysis from a single center. Leuk Lymphoma. 2011 Apr;52(4):613-9.

Mack et al 2020
Mack CL, Adams D, Assis DN, Kerkar N, Manns MP, Mayo MJ et al. Diagnosis and management of autoimmune hepatitis in adults and children: 2019 practice guidance and guidelines from the American Association for the study of liver diseases. Hepatology. 2020;72(2):671-722.

Maguire et al 2021
Maguire D, McLaren DS, Rasool I, Shah PM, Lynch J, Murray RD. ChAdOx1 SARS-CoV-2 vaccination: A putative precipitant of adrenal crises. Clin Endocrinol (Oxf). 2021:10.1111/cen.14566. doi: 10.1111/cen.14566.

Male et al 2021
Male V. Menstrual changes after COVID-19 vaccination. BMJ. 2021 Sep 15;374:n2211.

Malhotra et al 2021
Malhotra HS, Gupta P, Prabhu V, Garg RK, Dandu H, Agarwal V et al. COVID-19 vaccination-associated myelitis. QJM 2021;114(8):591-3.

Mambretti et al 2021
Mambretti M, Huemer J, Torregrossa G, Ullrich M, Findl O, Casalino G. Acute Macular Neuroretinopathy following Coronavirus Disease 2019 Vaccination. Ocul Immunol Inflamm. 2021;29(4):730-3.

Manzano et al 2021
Manzano GS, McEntire CRS, Martinez-Lage M, Mateen FJ, Hutto SK. Acute Disseminated Encephalomyelitis and Acute Hemorrhagic Leukoencephalitis Following COVID-19: Systematic Review and Meta-synthesis. Neurol Neuroimmunol Neuroinflamm. 2021;8(6):e1080. doi: 10.1212/NXI.0000000000001080. PMID: 34452974; PMCID: PMC8404207.

Maragakis et al 2021
Maragakis L and Kelen G. Breakthrough Infections: Coronavirus After Vaccination. Available at: https://www.hopkinsmedicine.org/health/conditions-and-diseases/coronavirus/breakthrough-infections-coronavirus-after-vaccination. Assessed on 23 November 2021.

Maramattom et al 2022
Maramattom BV, Lotlikar RS, Sukumaran S. Central nervous system adverse events after ChAdOx1 vaccination. Neurol Sci. 2022;43:3503–7. doi.org/10.1007/s10072-022-06000-3.

Maria et al 2021
Maria Simone, Anna; Monti, Giulia; Amidei, Stefano; Costa, Manuela; Vaghi, Luca; Devetak, Massimiliano; De Pasqua, Silvia; Fileccia, Enrico; Santangelo Acute Disseminated Encephalomyelitis associated with Anti-myelin oligodendrocyte glycoprotein (MOG-IGG) antibody in a patient with recent vaccination against SARS-COV-2, Mario25th Biennial World Congress of Neurology (WCN) - World Federation of Neurology (WFN)

Markus et al 1997
Markus R, Brew BJ, Turner J et al. (1997). Successful outcome with aggressive treatment of acute haemorrhagic leukoencephalitis. J Neurol Neurosurg Psychiatry 63: 551.

Marlene et al 2021
Marlene P, K. Mese, J. T. Kowallick, A. Schuster, D. Tampe,B. Cytomegalovirus Reactivation and Pericarditis Following ChAdOx1 nCoV-19 Vaccination Against SARS-CoV-2. Frontiers in Immunology 2021 12.

Marsukjai A et al 2022
Concomitant myocarditis and painless thyroiditis after AstraZeneca coronavirus disease 2019 vaccination: a case report. J Med Case Rep. 2022 May 17;16(1):212. doi: 10.1186/s13256-022-03438-z. PMID: 35581666; PMCID: PMC9112634.

Marsukjai et al. 2022
Marsukjai A, Theerasuwipakorn N, Tumkosit M, Chattranukulchai P, Srichomkwun P, Prechawat S. Concomitant myocarditis and painless thyroiditis after AstraZeneca coronavirus disease 2019 vaccination: a case report. Journal of Medical Case Reports. 2022 Dec;16(1):1-4.

Matsuzaki et al, 2021
Matsuzaki K, Aoki R, Nihei Y, Suzuki H, Kihara M, Yokoo T, Kashihara N, Narita I, Suzuki Y. Gross hematuria after SARS-CoV-2 vaccination: questionnaire survey in Japan. Clinical and experimental nephrology. 2021 Nov 13:1-7.

McGrogan 2011
McGrogan A, Franssen CF, de Vries CS. The incidence of primary glomerulonephritis worldwide: a systematic review of the literature. Nephrology Dialysis Transplantation. 2011 Feb 1;26(2):414-30.

McGrogan et al 2008
McGrogan A, Seaman HE, Wright JW, de Vries CS. The incidence of autoimmune thyroid disease: a systematic review of the literature. Clin Endocrinol (Oxf). 2008;69(5):687-96. doi: 10.1111/j.1365-2265.2008.03338.x. Epub 2008.

McKean et al 2021
McKean N, Chircop C. Guillain-Barré syndrome after COVID-19 vaccination. BMJ Case Rep. 2021;14(7):e244125. Published 2021 Jul 30. doi:10.1136/bcr-2021-244125.

McKenna MC et al 2019
Spectrum of rhabdomyolysis in an acute hospital. Ir J Med Sci. 2019 Nov;188(4):1423-1426. doi: 10.1007/s11845-019-01968-y. Epub 2019 Jan 24.

McLaurin-Jiang et al 2021
McLaurin-Jiang S, Christine D. Garner, Kaytlin Krutsch, and Thomas W. Hale.Breastfeeding Medicine. 2021.16 (9) 702-709.http://doi.org/10.1089/bfm.2021.0079

McNeil et al 2018
McNeil MM, DeStefano F. Vaccine-associated hypersensitivity. J Allergy Clin Immunol. 2018;141(2):463-472.

McQuarrie et al 2014.
McQuarrie EP, Mackinnon B, McNeice V, Fox J, Geddes CC. The incidence of biopsy-proven IgA nephropathy is associated with multiple socioeconomic deprivation. Kidney International. 2014 Jan 1;85(1):198-203. PMID24025641.

McShane et al 2021
McShane C, Kiat C, Rigby J, Crosbie Ó. The mRNA COVID-19 vaccine–A rare trigger of autoimmune hepatitis?. Journal of Hepatology. 2021;75(5):1252-4.

Medina et al 2022
Medina CM, Ramirez Gómez M. Tinnitus, Sudden Sensorineural Hearing Loss, and Vestibular Neuritis As Complications of the Astra Zeneca COVID-19 Vaccine. Cureus. 2022 Jan 3;14(1):e20906. doi: 10.7759/cureus.20906. PMID: 35145810; PMCID: PMC8810281.

Mehraeen et al 2021
Mehraeen E, Seyed Alinaghi S, Amirali K. Can children of the Sputnik V vaccine recipients become symptomatic? *Hum. Vaccines Immunother*. 2021 17:10, 35003501.

Mehta et al 2021
Mehta PR, Mangion SA, Benger M, Stanton BR, Czuprynska J, Arya R et al. Cerebral venous sinus thrombosis and thrombocytopenia after COVID-19 vaccination–A report of two UK cases. Brain, behavior, and immunity. 2021 20.

Menge et al 2005
Menge T, Hemmer B, Nessler S, Wiendl H, Neuhaus O, Hartung H-P, et al. Acute disseminated encephalomyelitis: an update. Arch Neurol. 2005 ;62:1673-80.

Menge et al 2007
Menge T, Kieseier BC, Nessler S, Hemmer B, HartungH-B, Stüve O. Acute disseminated encephalomyelitis: an acute hit against the brain. Curr Opin Neurol. 2007;20:247-54.

Mengesha B et al 2022
Severe Acute Myocarditis after the Third (Booster) Dose of mRNA COVID-19 Vaccination. Vaccines (Basel). 2022 Apr 8;10(4):575. doi: 10.3390/vaccines10040575. PMID: 35455324; PMCID: PMC9024648.

Merkler et al 2006
Merkler D, Horvath E, Bruck W, Zinkernagel RM, del la Torre JC, Pinschewer DD. "Viral deja vu" elicits organ-specific immune disease independent of reactivity to self. J Clin Invest. 2006;116:1254-63.

Michel et al 2021
Michel T, Stolowy N, Gascon P, Dupessey F, Comet A, Attia R. Acute Macular Neuroretinopathy After COVID-19 Vaccine. Research Square. https://doi.org/10.21203/rs.3.rs-632137/v1

Milano et al 2021
Milano G, Gal J, Creisson A, Chamorey E. Myocarditis and COVID-19 mRNA vaccines: a mechanistic hypothesis involving dsRNA. Future Virol. 2021;10.2217/fvl-2021-0280.

Min et al 2021
Min GY, Ju W, Ha YE, Ban JJ, Lee SA, Sung JJ et al. Sensory Guillain-Barre syndrome following the ChAdOx1 nCov-19 vaccine: Report of two cases and review of literature. Journal of Neuroimmunology 2021 359.

Mohta et al 2021
Mohta A, Arora A, Srinivasa R, Mehta RD. Recurrent herpes zoster after COVID-19 vaccination in patients with chronic urticaria being treated with cyclosporine-A report of 3 cases. *J Cosmet Dermatol*. 2021;20(11):3384-3386. doi:10.1111/jocd.14437.

Moosmann J et al 2022
COVID Vaccine-Associated Myocarditis in Adolescent Siblings: Does It Run in the Family? Vaccines (Basel). 2022 Apr 14;10(4):611. doi: 10.3390/vaccines10040611. PMID: 35455360; PMCID: PMC9028976.

Moslemi, Mohammadreza, et al 2022
Moslemi, M., Ardalan, M., Haramshahi, M., Mirzaei, H., Sani, S.K., Dastgir, R. and Dastgir, N., 2022. Herpes simplex encephalitis following ChAdOx1 nCoV-19 vaccination: a case report and review of the literature. *BMC Infectious Diseases*, *22*(1), pp.1-4.

Muhaidat et al 2022
Muhaidat N, Alshrouf MA, Al-Nazer MW, Azzam MI, Karam AM Al-Ani A. Menstrual Symptoms After COVID-19 Vaccine: A Cross-Sectional Investigation in the MENA Region. International Journal of Women's Health. 2022 14:395-404.

Mullerova et al
Müllerová H, Medin J, Arnold M, Gomes da Silva H, Kumar S, Nord M, et al. Background rate estimations for thrombosis with thrombocytopenia: challenges in evaluating rare safety signals following vaccination in real time during a pandemic. Submitted BMJ Open

Mumoli et al 2021
Mumoli L, Vescio V, Pirritano D, Russo E, Bosco D. ADEM anti-MOG antibody-positive after SARS-CoV2 vaccination. Neurol Sci. 2022;43:763–766. doi.org/10.1007/s10072-021-05761-7.

Mungmunpuntipantip and Wiwanitkit 2022
Mungmunpuntipantip R and Wiwanitkit V. Thyrotoxicosis after COVID-19 vaccination. Endocrine. 2022 Jan;75(1):22. doi: 10.1007/s12020-021-02922-8. Epub 2021 Oct 29. PMID: 34714513; PMCID: PMC8554509.

Muñoz-Valle et al 2022
Muñoz-Valle JF, Sánchez-Zuno GA, Matuz-Flores MG, Hernández-Ramírez CO, Díaz-Pérez SA, Baños-Hernández CJ, et.alficacy and Safety of Heterologous Booster Vaccination after Ad5-nCoV (CanSino Biologics) Vaccine: A Preliminary Descriptive Study. Vaccines (Basel). 2022;10(3):400. doi: 10.3390/vaccines10030400. PMID: 35335032; PMCID: PMC8954152.

Munro et al 2021
Munro APS, Janani L, Cornelius V, Aley PK, Babbage G, Baxter D et al. Safety and immunogenicity of seven COVID-19 vaccines as a third dose (booster) following two doses of ChAdOx1 nCov-19 or BNT162b2 in the UK (COV-BOOST): a blinded, multicentre, randomised, controlled, phase 2 trial. Lancet. Published online 2 December 2021. Available from: https://doi.org/10.1016/S0140-6736(21)02717-3. Accessed 8 December 2021.

Murakami Y et al 2021
Myocarditis Following a COVID-19 Messenger RNA Vaccination: A Japanese Case Series. Intern Med. 2022 Feb 15;61(4):501-505. doi: 10.2169/internalmedicine.8731-21. Epub 2021 Nov 27. PMID: 34840235; PMCID: PMC8907764.

Murthy et al 2002
Murthy SN, Faden HS, Cohen ME, Bakshi R. Acute disseminated encephalomyelitis in children. Pediatrics. 2002;110:e21.

Muruve 2004
Muruve D. The innate immune response to adenovirus vectors. Hum Gene Ther. 2004 Dec;15(12):1157-66.

Musumeci et al 2021
Musumeci M, Caruso G, Trecarichi A, Micali G. Safety of SARS-CoV-2 vaccines in psoriatic patients treated with biologics: A real life experience. Dermatologic Therapy. 2021.

Myocarditis/Pericarditis Case Definition 2021
Myocarditis/Pericarditis Case Definition, November 2021, https://brightoncollaboration.us/myocarditis-case-definition-update/

Na Zhu 2020
Na Zhu. A Novel Coronavirus from Patients with Pneumonia in China, 2019. N engl j med 382;8 nejm.org. 2020.

Nagaratnam et al 2022
Nagaratnam SA, Ferdi AC, Leaney J, Lee RLK, Hwang YT, Heard R. Acute disseminated encephalomyelitis with bilateral optic neuritis following ChAdOx1 COVID-19 vaccination. BMC Neurol. 2022;22, 54. doi.org/10.1186/s12883-022-02575-8.

Nakanishi Y et al 2022
Constrictive pericarditis after SARS-CoV-2 vaccination: A case report. Int J Infect Dis. 2022 Mar;116:238-240. doi: 10.1016/j.ijid.2022.01.027. Epub 2022 Jan 19. PMID: 35063679; PMCID: PMC8767927.

Nance JR et al 2015
Diagnostic evaluation of rhabdomyolysis. Muscle Nerve. 2015 Jun;51(6):793-810. doi: 10.1002/mus.24606. Epub 2015 Mar 14. PMID: 25678154; PMCID: PMC4437836.

Nazir et al 2022
Nazir M, Asghar S, Rathore MA, Shahzad A, Shahid A et al. Menstrual abnormalities after COVID-19 vaccines: A systematic review. Vacunas. 2022.

Neagoie et at 2021
Neagoie A, Sommer C, Gantner A, Wais V, Schnell J, Simon H, Viardot A, Döhner H, Bunjes D, Sala E. COVID-19 Vaccination after Allogeneic Stem Cell Transplantation: Real Word Data on Safety and Efficacy. a Single Center Experience. Blood. 2021 Nov 23;138:4868. doi: 10.1182/blood-2021-151061. Epub 2021 Dec 24. PMCID: PMC8701595.

Negrea and Rovin 2021
Negrea L, Rovin BH. Gross hematuria following vaccination for severe acute respiratory syndrome coronavirus 2 in 2 patients with IgA nephropathy. Kidney international. 2021 Jun 1;99(6):1487.

Nelson K.E. 2012
Nelson KE. Invited commentary: Influenza vaccine and Guillain-Barre syndrome--is there a risk? Am J Epidemiol 2012;175:1129–32. 10.1093/aje/kws194

Netravathi et al 2022
Netravathi M, Dhamija K, Gupta M, et al. COVID-19 vaccine associated demyelination & its association with MOG antibody. Mult Scler Relat Disord. 2022 Apr;60:103739. doi: 10.1016/j.msard.2022.103739. Epub 2022 Mar 13. PMID: 35306244; PMCID: PMC8917969.

Neurath et al 2021
Neurath MF. COVID-19: biologic and immunosuppressive therapy in gastroenterology and hepatology. Nat Rev Gastroenterol Hepatol. 2021;18:705–15.

Neves et al 2022
Neves PD, Caires RA, Guimarães MP, Costalonga EC, Cavalcante LB, Costa E Silva VT, et al. Collapsing glomerulopathy following SARS-CoV-2 adenovirus-vector–based vaccine: report of 2 cases. Kidney International. 2022 Mar 1;101(3):637-9.

NHS 2021
NHS 2021National Health Service. 3-in-1 teenage booster overview. [Cited October 2021]. Available from: https://www.nhs.uk/conditions/vaccinations/3-in-1-teenage-booster/. Accessed 19 November 2021.

Nihei 2022
Nihei Y, Kishi M, Suzuki H, Koizumi A, Yoshida M, Hamaguchi S, Iwasaki M, Fukuda H, Takahara H, Kihara M, Tomita S. IgA Nephropathy with Gross Hematuria Following COVID-19 mRNA Vaccination. Internal Medicine. 2022:8787-21.

Nohynek and Wilder 2022
Nohynek H, Wilder-Smith A. Does the World Still Need New Covid-19 Vaccines? NEJM. 2022 Jun 2;386(22):2140-2

Noseda et al 2021
Noseda R, Ripellino P, Ghidossi S, Bertoli R, Ceschi A. Reporting of Acute Inflammatory Neuropathies with COVID-19 Vaccines: Subgroup Disproportionality Analyses in VigiBase. Vaccines (Basel). 2021;9(9):1022.

Notghi et al 2021
Notghi A, Atley J, Silva M. Lessons of the month 1: Longitudinal extensive transverse myelitis following AstraZeneca COVID-19 vaccination. Clin Med (Lond). 2021;21(5): e535-8.

Nyberg et al 2022
Nyberg T, Ferguson NM, Nash SG, Webster HH, Flaxman S, Andrews N, Hinsley W, Bernal JL, Kall M, Bhatt S, Blomquist P. Comparative analysis of the risks of hospitalisation and death associated with SARS-CoV-2 omicron (B. 1.1. 529) and delta (B. 1.617. 2) variants in England: a cohort study. The Lancet. 2022 Apr 2;399(10332):1303-12.

Ohayon A et al
Myocarditis Following COVID-19 Vaccinations: A Systemic Review. 13th International Congress on Autoimmunity - Kenes group

Olbricht et al 1993
Olbricht CJ, Stark E, Helmchen U, Schulze M, Brunkhorst R, Koch KM. Glomerulonephritis associated with inflammatory demyelinating polyradiculoneuropathy: a case report and review of the literature. Nephron. 1993;64(1):139-41.

Oldstone 2014
Oldstone MBA. Molecular mimicry: its evolution from concept to mechanism as a cause of autoimmune diseases. Monoclon Antib Immunodiagn Immunother. 2014 Jun;33(3):158-65. doi: 10.1089/mab.2013.0090.

O'Leary ST et al 2021
Myocarditis After SARS-CoV-2 Vaccination: True, True, and… Related?. Pediatrics September 2021; 148 (3): e2021052644. 10.1542/peds.2021-052644

Oliver and Zarnke 2021
Oliver LC, Zarnke AM. Sarcoidosis: An Occupational Disease? Chest. 2021;160(4):1360-1367. doi: 10.1016/j.chest.2021.06.003.

Oo et al 2021
Oo, W. M., P. Giri,A. de Souza Journal of Neuroimmunology 2021 360.

Osowicki et al 2021
Osowicki, J., H. Morgan, A. Harris, N. W. Crawford, J. P. Buttery,L. Kiers Annals of Neurology 2021 90(5): 856-858.

Othman et al 2022
Othman M, Baker AT, Gupalo E, Elsebaie A, Bliss CM, Rondina MT et. al. To clot or not to Othman M, Baker AT, Gupalo E, Elsebaie A, Bliss CM, Rondina MT, Lillicrap D, Parker AL. To clot or not to clot? Ad is the question—Insights on mechanisms related to vaccine-induced thrombotic thrombocytopenia. J Thrombosis and Haemostasis. 2021;19(11):2845-56.

Oth and Ritz 1998
Orth SR, Ritz E: The nephrotic syndrome. N Engl J Med 338: 1202–11, 1998.

Oyibo 2021
Oyibo SO. Subacute thyroiditis after receiving the adenovirus-vectored vaccine for coronavirus disease (COVID-19). Cureus. 2021 Jun 29;13(6).

Pagenkopf et al 2021
Pagenkopf C, Sudmeyer M. A case of longitudinally extensive transverse myelitis following vaccination against COVID-19. J Neuroimmunol; 2021;358:577606.

Palla et al 2021
Palla P, Vergadis C, Sakellariou S, Androutsakos T. Autoimmune hepatitis after COVID-19 vaccination: A rare adverse effect?. Hepatology. 2021 15.

Park DY et al 2022
A systematic review of case reports and case series. Clin Cardiol. 2022 Jun 2. doi: 10.1002/clc.23828. Epub ahead of print. PMID: 35652390.

Park et al 2021
Park HS, Byun Y, Byeon SH, Kim SS, Kim YJ, Lee CS et al. Retinal hemorrhage after sars-cov-2 vaccination Journal of Clinical Medicine 2021 10(23).

Park et al 2021
Park K, Miyake S, Tai C, Tseng M, Andeen NK, Kung VL. Letter regarding: "A case of gross hematuria and IgA nephropathy flare-up following SARS-CoV-2 vaccination". Kidney International Reports. 2021 Aug 1;6(8):2246-7.

Park S et al 2022
A Case of Myocarditis Presenting With a Hyperechoic Nodule After the First Dose of COVID-19 mRNA Vaccine. J Korean Med Sci. 2022 Apr 25;37(16):e131. doi: 10.3346/jkms.2022.37.e131. PMID: 35470603; PMCID: PMC9039195.

Parra-Lucares A et al 2021
Cardiomyopathy Associated with Anti-SARS-CoV-2 Vaccination: What Do We Know? Viruses. 2021 Dec 13;13(12):2493. doi: 10.3390/v13122493. PMID: 34960761; PMCID: PMC8708989.

Parrino et al 2021
Parrino D, Frosolini A, Gallo C, De Siati RD, Spinato G, De Filippis C. Tinnitus following COVID-19 vaccination: report of three cases, International Journal of Audiology. 2021. DOI: 10.1080/14992027.2021.1931

Parry et al 2021
Parry H, McIlroy G, Bruton R et al. Antibody responses after first and second Covid-19 vaccination in patients with chronic lymphocytic leukaemia. Blood Cancer J. 2021;11:136.

Patel et al 2019
Patel P, Walborn A, Rondina M, Fareed J, Hoppensteadt D. Markers of Inflammation and Infection in Sepsis and Disseminated Intravascular Coagulation. Clin Appl Thromb Hemost. 2019;25:1076029619843338.

Paterson 1960
Paterson PY (1960). Transfer of allergic encephalomyelitis in rats bymeans of lymph node cells. J ExpMed 111: 119–36.

Patone et al 2021
Patone M, Handunnetthi L, Saatci D, Pan J, Katikireddi SV, Razvi S et al. Neurological complications after first dose of COVID-19 vaccines and SARS-CoV-2 infection. Nat Med. 2021;27(12):2144-53.

Pede et al 2021
Pede FD, Covolo A, Sala ED, Gadaleta G, Gojani C, Laudadio M et al. A case of Guillain-Barré syndrome after COVID-19 vaccination. Journal of the Neurological Sciences. 2021;429 (119860).

Pedrazini et al 2022
Pedrazini, M.C., da Silva, M.H. and Groppo, F.C., 2022. L-lysine in herpesvirus reactivation after ChAdOx1 nCoV-19 vaccine (AZD1222): Minor literature review and case report. *Dermatologic Therapy*, *35*(3), p.e15291.

Pereira et al 2021
Pereira DAG, Teixeira EPP, Lopes ACM, Sarmento RJP, Lopes APC. Lipschütz Ulcer: An Unusual Diagnosis that Should Not be Neglected. Rev Bras Ginecol Obstet. 2021;43(5):414-416. doi: 10.1055/s-0041-1729147.

Perez Y et al 2021
Myocarditis Following COVID-19 mRNA Vaccine: A Case Series and Incidence Rate Determination. Clin Infect Dis. 2021 Nov 3:ciab926. doi: 10.1093/cid/ciab926. Epub ahead of print. PMID: 34734240; PMCID: PMC8767838.

Permezel et al 2022
Permezel F, Borojevic B, Lau S, de Boer HH. Acute disseminated encephalomyelitis (ADEM) following recent Oxford/AstraZeneca COVID-19 vaccination. Forensic Sci Med Pathol. 2022;18:74–79. doi.org/10.1007/s12024-021-00440-7.

Perna F et al 2022
Rapid resolution of severe pericardial effusion using anakinra in a patient with COVID-19 vaccine-related acute pericarditis relapse: a case report. Eur Heart J Case Rep. 2022 Mar 18;6(4):ytac123. doi: 10.1093/ehjcr/ytac123. PMID: 35445166; PMCID: PMC8992233.

Pettoello et al 2021
Pettoello M. Viewpoint of the European Pediatric Societies over Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Vaccination in Children Younger Than Age 12 Years Amid Return to School and the Surging Virus Variants. *J Pediatr*. 2021; 239 (250-251.e2).

Pfrepper et al 2021
Pfrepper C, Holstein K, Konigs C, Heller C, Krause M, Olivieri M et al. Consensus Recommendations for Intramuscular COVID-19 Vaccination in Patients with Hemophilia. Hamostaseologie. 2021;41(3):190-6.

Pham et al 2021
Pham A, Anoroff D, Thompson J. Maternal COVID-19, vaccination safety in pregnancy, and evidence of protective immunity. Journal of Allergy and Clinical Immunology. 2021; 148 (3): 728-31.

Phylactou et al 2021
Phylactou M, Li JP, Larkin DF. Characteristics of endothelial corneal transplant rejection following immunisation with SARS-CoV-2 messenger RNA vaccine. British Journal of Ophthalmology. 2021 1;105(7):893-6.

Pick et al 2020
Pick J, Nickels S, Salmann F, Finger RP, Schuster AK. Incidence of retinal artery occlusion in Germany. Acta Ophthalmol. 2020;98(5):e656-7.

Pillay J et al 2022
Myocarditis and Pericarditis following COVID-19 Vaccination: Evidence Syntheses on Incidence, Risk Factors, Natural History, and Hypothesized Mechanisms. medRxiv 2022.02.28.22271643; doi: https://doi.org/10.1101/2022.02.28.22271643

Pisani D et al 2021
Pisani D, Leopardi G, Viola P, Scarpa A, Ricciardiello F, Cerchiai N, Astorina A, Chiarella G. Audiovestibular Disorders after COVID-19 Vaccine: Is there an association? Otolaryngology Case Reports. 2021 Nov 1; 21:100384.

Pisani et al 2022
Pisani D, Gioacchini FM, Viola P, Scarpa A, Astorina A, Re M, et al. Audiovestibular Disorders after COVID-19 Vaccine: Is There an Association? Audiol Res. 2022;12(3):212-23. doi: 10.3390/audiolres12030024.

Pitkanen et al 2021
Pitk¨anen HH, Jouppila A, Helin T, Dulipati V, Kotimaa J, Meri S; COVID-19 adenovirus vaccine triggers antibodies against PF4 complexes to activate complement and platelets, Thromb Res.2021;208:129-37.

Pla Peris et al. 2022
Pla Peris B, Merchante Alfaro AÁ, Maravall Royo FJ, Abellán Galiana P, Pérez Naranjo S, González Boillos M. Thyrotoxicosis following SARS-COV-2 vaccination: a case series and discussion. Journal of Endocrinological Investigation. 2022 May;45(5):1071-7.

Plasse et al 2021
Plasse R, Nee R, Gao S, Olson S. Acute kidney injury with gross hematuria and IgA nephropathy after COVID-19 vaccination. Kidney international. 2021 Oct;100(4):944.

Pohl et al 2004
Pohl D, Rostasy K, Reiber H, Hanefeld F. CSF characteristics in early-onset multiple sclerosis. Neurology. 2004;63:1966-67.

Ponnatt et al 2021
Ponnatt TS, Lilley CM, Mirza KM. Hemophagocytic lymphohistiocytosis. Arch Pathol Lab Med. 2021 Aug. doi: 10.5858/arpa.2020-0802-RA.

Pouria and Bharratt 2008
Pouria S, Barratt J. Secondary IgA nephropathy. InSeminars in nephrology 2008 Jan 1 (Vol. 28, No. 1, pp. 27-37). WB Saunders.

Power JR et al 2022
Myocarditis following COVID-19 vaccination: incidence, mechanisms, and clinical considerations. Expert Rev Cardiovasc Ther. 2022 Apr;20(4):241-251. doi: 10.1080/14779072.2022.2066522. Epub 2022 Apr 18. PMID: 35414326; PMCID: PMC9115793.

Pradhan et al 1999
Pradhan S, Gupta RP, Shashank S et al. (1999). Intravenous immunoglobulin therapy in acute disseminated encephalomyelitis. J Neurol Sci 165: 56–61.

Prentice et al 2021
Prentice R, Rentsch C, Al-Ani A, Zhang E, Johnson D, Halliday J et al. SARS-CoV-2 vaccination in patients with inflammatory bowel disease. GastroHep, An International Journal of Gastroenterology and Hepatology. 2021; 3 (4);212-28.

Psichogiou et al 2021
Psichogiou M, Samarkos M, Mikos N, Hatzakis A. Reactivation of Varicella Zoster Virus after Vaccination for SARS-CoV-2. Vaccines (Basel). 2021;9(6):572. doi:10.3390/vaccines9060572.

Qiao et al 2021
Qiao Y, Lopes de Abreu AJ, Dias CZ, Meng X, Ferreira RV, Pereira RG, Julian GS, Yin W. Safety profile of COVID-19 vaccines in pregnant and postpartum women in brazil. medRxiv 2021.12.14.21267777; doi: https://doi.org/10.1101/2021.12.14.21267777.

Rademacher et al 2021
Rademacher JG, Tampe B, Korsten P. First Report of Two Cases of Löfgren's Syndrome after SARS-CoV-2 Vaccination-Coincidence or Causality? Vaccines (Basel). 2021;9(11):1313. doi: 10.3390/vaccines9111313.

Rafaniello C et al 2022
Disentangling a Thorny Issue: Myocarditis and Pericarditis Post COVID-19 and Following mRNA COVID-19 Vaccines. Pharmaceuticals. 2022; 15(5):525. https://doi.org/10.3390/ph15050525

Rahim et al 2021
Rahim SE, Lin JT, Wang JC. A case of gross hematuria and IgA nephropathy flare-up following SARS-CoV-2 vaccination. Kidney international. 2021 Jul 1;100(1):238.

Rahman et al, 2022
Rahman et al. Risk of serious adverse events after the BNT162b2, CoronaVac, and ChAdOx1 vaccines in Malaysia: A self-controlled case series study, Vaccine, https://doi.org/10.1016/j.vaccine.2022.05.075

Rashidi-Alavijeh et al 2021
Rashidi-Alavijeh J, Frey A, Passenberg M, Korth J, Zmudzinski J, Anastasiou OE et al. Humoral Response to SARS-Cov-2 Vaccination in Liver Transplant Recipients–A Single-Center Experience. MDPI Journals; Vaccines 2021, 9(7), 738.

Rathberger et al 2021
Rathberger K, Hausler S, Wellman S, Weigl M, Langhammer F, Bazzano V et al. SARS-CoV-2 in pregnancy and possible transfer of immunity: assessment of peripartal maternal and neonatal antibody levels and a longitudinal follow-up. Journal of Perinatal Medicine. 2021.

RCOG 2021
Royal College of Obstetricians and Gynaecologists (RCOG). Coronavirus (COVID-19) Infection in Pregnancy Guidance Version 1.0: Published 30 June 2021 Available from https://www.rcog.org.uk/globalassets/documents/guidelines/2021-06-30-coronavirus-COVID-19-vaccination-in-pregnancy.pdf

Rehak and Wiedmann 2010
Rehak M, Wiedemann P. Retinal vein thrombosis: pathogenesis and management.J Thromb Haemost. 2010;8: 1886–94

Rela et al 2021
Rela M, Jothimani D, Vij M, Rajakumar A, Rammohan A. Auto-immune hepatitis following COVID vaccination. Journal of Autoimmunity. 2021 1;123:102688.

Rinaldi et al 2021
Rinaldi V, Bellucci G, Sforza M, Catania C, Rossini E, De Carolis L, et al. Suspected acute disseminated encephalomyelitis (ADEM) after ChAdOx1 nCoV-19 vaccine: A case report. Journal of the Neurological Sciences.2021;429.

Rinaldi et al 2022
Rinaldi V, Bellucci G, Romano A, Bozzao A, Salvetti M. ADEM after ChAdOx1 nCoV-19 vaccine: A case report. Multiple Sclerosis Journal. 2022;28(7):1151-1154. doi:10.1177/13524585211040222.

Ritchie et al 2020
Ritchie H, Mathieu E, Rodés-Guirao L, Appel C, Giattino C, Ortiz-Ospina E et al. (2020) - "Coronavirus Pandemic (COVID-19)". Published online at OurWorldInData.org. Available at : https://ourworldindata.org/grapher/share-people-vaccinated-covid?country=High+income~Upper+middle+income~Lower+middle+income~Low+income

Rivers et al 1933
Rivers TM, Sprunt DH, Berry GP (1933). Observations on attempts to produce acute disseminated encephalomyelitis in monkeys. J Exp Med 58: 39–53.

Rivière et al 2014
Rivière S, Galicier L, Coppo P, Marzac, C, Aumont, C, Lambotte O et al. Reactive hemophagocytic syndrome in adults: A retrospective analysis of 162 patients. Am. J. Med. 2014, 127, 1118–25.

Roberts 2021
Roberts LL. Iga nephropathy after receiving the Pfizer COVID-19 vaccine: A case report. Journal of the American Society of Nephrology. 2021:89-90.

Rocco et al 2021
Rocco A, Sgamato C, Compare D, Nardone G. Autoimmune hepatitis following sars-cov-2 VACCINE: MAY not be a casualty. Journal of Hepatology. 2021;75(3):728-9.

Rodriguez et al 1993
Rodriguez M, Karnes WE, Bartleson JD et al. (1993). Plasmapheresis in acute episodes of fulminant CNS inflammatory demyelination. Neurology 43: 1100–04.

Rogers et al 2022
Rogers A, Rooke E, Morant S, Guthrie G, Doney A, Duncan A, et al. Adverse events and overall health and well-being after COVID-19 vaccination: interim results from the VAC4COVID cohort safety study. BMJ Open 2022 12(6).

Roman et al 2021
Román GC, Gracia F, Torres A, Palacios A, Gracia K, Harris D. Acute Transverse Myelitis (ATM): Clinical Review of 43 Patients With COVID-19-Associated ATM and 3 PostVaccination ATM Serious Adverse Events With the ChAdOx1 nCoV-19 Vaccine (AZD1222). Frontiers in Immunology. 2021;12. Available from: https://www.embase.com/search/results?subaction=viewrecord&id=L634953914&from=export, http://dx.doi.org/10.3389/fimmu.2021.653786.

Román et al 2021
Román GC, Gracia F, Torres A, Palacios A, Gracia K, Harris D. Acute Transverse Myelitis (ATM):Clinical Review of 43 Patients With COVID-19-Associated ATM and 3 Post-Vaccination ATM Serious Adverse Events With the ChAdOx1 nCoV-19 Vaccine (AZD1222). Frontiers in Immunology 2021.12:879.

Rothacker 2016
Rothacker K.M., Walsh J.P. (2016) Acute and Subacute Thyroiditis. In: Vitti P., Hegedus L. (eds) Thyroid Diseases. Endocrinology. Springer, Cham. https://doi.org/10.1007/978-3-319-29195-6_9-1.

Rowhani-Rahbar A et al 2012
Biologically plausible and evidence-based risk intervals in immunization safety research, Vaccine, Volume 31, Issue 1, 2012, Pages 271-277, ISSN 0264-410X, https://doi.org/10.1016/j.vaccine.2012.07.024.

Rowhani-Rahbara et al 2012
Rowhani-Rahbara A, Kleina NP, Dekker CL, Edward KM, Marchant CD, Vellozzi C, et al. Biologically plausible and evidence-based risk intervals in immunization safety research. Vaccine. 2012;31;271-7.

Ryan et al 2019
Ryan A. Frisbie, Alexis K. Warren, Tyler B.S. Risma, Michael D. Abramoff. Eye Rounds.org April 1, 2019.

Sadoghi et al 2019
Sadoghi B, Stary G, Wolf P, Komericki P. Ulcus vulvae acutum Lipschütz: a systematic literature review and a diagnostic and therapeutic algorithm. Journal of The European Academy of Dermatology and Venerology. 2019; 34(7): 1432-39.

Saha et al 2018
Saha MK, Julian BA, Novak J, Rizk DV. Secondary IgA nephropathy. Kidney international. 2018 Oct 1;94(4):674-81.

Sahlas et al 2000
Sahlas DJ, Miller SP, Guerin M et al. (2000). Treatment of acute disseminated encephalomyelitis with intravenous immunoglobulin. Neurology 54: 1370–72.

Sakaguchi et al 1995
Sakaguchi S, Sakaguchi N, Asano M, Itoh M, Toda M. Immunologic self-tolerance maintained by activated T cells expressing IL-2 receptor alpha-chains (CD25). Breakdown of a single mechanism of self-tolerance causes various autoimmune diseases. J Immunol. 1995;155:11511164.

Sanidas et al 2021
Sanidas E, Papadopoulos D, Mantzourani M, Velliou M, Anastasiou T, Fotsali A. Abstract P266: Hypertensive Response In Recently COVID-19 Vaccinated Patients. Hypertension. 2021;78:AP266.

Schaubschlager et al 2022
Schaubschlager T, Rajora N, Diep S, Kirtek T, Cai Q, Hendricks AR, Shastri S, Zhou XJ, Saxena R. De novo or recurrent glomerulonephritis and acute tubulointerstitial nephritis after COVID-19 vaccination: A report of six cases from a single center. Clinical Nephrology. 2022.

Scheuermeyer FX et al 2022
Atrial fibrillation as a precursor of mRNA-1273 SARS-CoV-2 vaccine-induced pericarditis. CJEM. 2022 Mar;24(2):230-232. doi: 10.1007/s43678-021-00250-4. Epub 2022 Jan 17. PMID: 35038138; PMCID: PMC8761835.

Schönborn et al 2022
Schönborn L, M.D. et.al; SARS-CoV-2 Infection in Patients with a History of VITT, N Engl J Med. 2022;387(1):88-90.

Schwarz et al 2001
Schwarz S, Mohr A, Knauth M, Wildemann B, Storch-Hagenlocher B. Acute disseminated encephalomyelitis: a follow-up study of 40 adult patients. Neurology. 2001;56:1313-8.

Seales and Greer 1991
Seales D, Greer M (1991). Acute hemorrhagic leukoencephalitis. A successful recovery. Arch Neurol 48: 1086–88.

See et al 2021
See I, Su JR, Lale A, Woo EJ, Guh AY, Shimabukuro TT et al. US case reports of cerebral venous sinus thrombosis with thrombocytopenia after Ad26. COV2. S vaccination, March 2 to April 21, 2021. Jama. 2021;325(24):2448-56.

Sejvar et al 2007
Sejvar JJ, Kohl KS, Bilynsky R, Blumberg D, Cvetkovich T, Galama J, et al. Encephalitis, myelitis and acute disseminated encephalomyelitis (ADEM): Case definitions and guidelines for collection, analysis and presentation of immunization safety data. Vaccine. 2007;25:57715792.

Sejvar et al 2011
Sejvar JJ, Kohl KS, Gidudu J, Amato A, Bakshi N, Baxter R et al. Guillain-Barré syndrome and Fisher syndrome: case definitions and guidelines for collection, analysis, and presentation of immunization safety data. Vaccine. 2011;29(3):599-612.

Sepahvand et al 2021
Sepahvand M, Yazdi N, Rohani M, Emamikhah M. Radiology Case Reports. 2022;17(2): 303-5. Available from: https://www.embase.com/search/results?subaction=viewrecord&id=L2015735187&from=export. http://dx.doi.org/10.1016/j.radcr.2021.10.053

Serban et al 2021
Serban A, Mihai A, Dima A, Balaban D, Jinga M, Jurcut C. The impact of the COVID-19 pandemic on patients with primary Sjögren syndrome. Rheumatology International 2021; 41 1933–40.

Sethi et al 2016
Sethi S, Haas M, Markowitz GS, D'Agati VD, Rennke HG, Jennette JC, et al. Mayo clinic/renal pathology society consensus report on pathologic classification, diagnosis, and reporting of GN. Journal of the American Society of Nephrology. 2016 May 1;27(5):1278-87.

Sexson Tejtel SK et al 2022
Myocarditis and pericarditis: Case definition and guidelines for data collection, analysis, and presentation of immunization safety data. Vaccine. 2022 Mar 1;40(10):1499-1511. doi: 10.1016/j.vaccine.2021.11.074. Epub 2022 Jan 31. PMID: 35105494.

Sfriso et al 2018
Sfriso P, Bindoli S, Galozzi P. Adult-Onset Still's Disease: Molecular Pathophysiology and Therapeutic Advances. Drugs. 2018 1;78(12):1187–95.

Shahar et al 2002
Shahar E, Andraus J, Savitzki D et al. (2002). Outcome of severe encephalomyelitis in children: effect of high-dose methylprednisolone and immunoglobulins. J Child Neurol 17: 810–14.

Shamriz et al 2018
Shamriz O, Tal Y, Gross M. Autoimmune Inner Ear Disease: Immune Biomarkers, Audiovestibular Aspects, and Therapeutic Modalities of Cogan's Syndrome. J Immunol Res. 2018;2018:1498640. doi: 10.1155/2018/1498640.

Shao et al 2021
Shao, S. C., C. H. Wang, K. C. Chang, M. J. Hung, H. Y. Chen,S. C. Liao. Emerging Infectious Diseases 2021 27(12): 3175-8.

Sharbatdaran A et al 2022
A rare case of COVID-19 vaccine-induced myopericarditis in a young adult. Radiology Case Reports Volume 17, Issue 6, June 2022, Pages 1916-1920
https://doi.org/10.1016/j.radcr.2022.03.039

Shasha et al 2022
Shasha D, Bareket R, Sikron FH. Real-world safety data for the Pfizer BNT162b2 SARS-CoV-2 vaccine: historical cohort study. Clin Microbiol Infect. 2022;28(1):130-134. doi:10.1016/j.cmi.2021.09.018.

Shimizu et al 2021
Shimizu M, Ogaki K, Nakamura R, Kado E, Nakajima S, N. Kurita, et al. An 88-year-old woman with acute disseminated encephalomyelitis following messenger ribonucleic acid-based COVID-19 vaccination. eNeurologicalSci. 2021;25.

Shukla AK et al 2022
Sarcoidosis presenting as bilateral optic neuritis after ChAdOx1 nCoV-19 vaccination. Monaldi Arch Chest Dis. 2022 Jun 8. doi: 10.4081/monaldi.2022.2279. Epub ahead of print. PMID: 35678536.

Sidhu et al 2021
Sidhu S, Orpiano C, Klein D, Staffetti J, Alkurdi B. S3674 Drug-Induced Autoimmune Liver Disease (DIAILD). Official journal of the American College of Gastroenterology| ACG. 2021 1;116:S1500.

Simone et al 2021
Simone AM, Monti G, Amidei S, Costa M, Vaghi L, Devetak M, et al. Acute disseminated encephalomyelitis associated with anti-myelin oligodendrocyte glycoprotein (MOG-IGG) antibody in a patient with recent vaccination against SARS-CoV-2. J Neurol Sci. 2021;429:118167. doi: 10.1016/j.jns.2021.118167.

Simwanza et al 2022
Simwanza J, Hines J, Sinyange D, Mulenga C, Hanyinza S. et al, medRxiv 2022.05.06.22274701; doi: https://doi.org/10.1101/2022.05.06.22274701

Singh et al 2022
Singh, J., A. More, S. B. Shetty, P. Chaskar,A. Sen. Herpes simplex virus retinitis following ChAdOx1 nCoV- 19 (Covishield) vaccination for SARS CoV 2: A case report Ocular Immunology and Inflammation 2022.

Singh Malhotra et al 2021
Singh Malhotra H, Gupta P, Prabhu V, Garg RK, Dandu, Agarwal V. COVID-19 vaccinationassociated myelitis. QJM : monthly journal of the Association of Physicians. 2021.

Singh R et al 2021
Acute Cardiac Events After ChAdOx1 nCoV-19 Corona Virus Vaccine: Report of Three Cases. American journal of therapeutics https://doi.org/10.21203/rs.3.rs-891077/v2

Sivji et al 2022
Sivji M, MV V, Pratap T, Abdul Jalal MJ. Acute disseminated encephalomyelitis post-SARS-COV-2 vaccination with Chadox1 nCov-19 (AZD1222) – A rare case report. Eastern Journal of Medical Sciences. 2022;7(2):47-50. doi.org/10.32677/ejms.v7i2.3365.

Sobue et al 2021
Sobue T, Fukuda H, Matsumoto T, Lee B, Ito S, Iwata S. The background occurrence of selected clinical conditions prior to the start of an extensive national vaccination program in Japan. PLoS One 2021 16(8): e0256379.

Soboleva et al 2022
Soboleva K, Shankar NK, Yadavalli M, Ferreira C, Foskett N, Putsepp K, et al. Geographical distribution of TTS cases following AZD1222 (ChAdOx1 nCoV-19) vaccination. The Lancet Global Health 2022;10;1; e33-e34. https://doi.org/10.1016/S2214-109X(21)00545-3

Sokolowska et al 2021
Sokolowska M, Eiwegger T, Ollert M, Torres MJ, Barber D, Giacco S et al. EAACI statement on the diagnosis, management and prevention of severe allergic reactions to COVID-19 vaccines. Allergy 2021;76:1629-39.

Soleimani et al 2021
Soleimani B, Turaga S, Khan D, Davies C, Duodu Y, Botcherby E et al. Syndrome of cerebral venous sinus thrombosis and thrombocytopenia after vaccination for COVID-19. 2021. 10.21203/rs.3.rs-439289/v1.

Sonawane et al 2021
Sonawane N; Yadav D; Rao K, Annaji. Retinal Vein Occlusion following COVID-19 Vaccination 14th Congress of the Asia-Pacific Vitreo-Retina Society (APVRS) - VIRTUAL

Soraci L et al 2022
COVID-19 Vaccines: Current and Future Perspectives. Vaccines (Basel). 2022 Apr 13;10(4):608. doi: 10.3390/vaccines10040608. PMID: 35455357; PMCID: PMC9025326.

Sozen, M et al. 2021
Sözen M, Topaloğlu Ö, Çetinarslan B, Selek A, Cantürk Z, Gezer E, Köksalan D, Bayraktaroğlu T. COVID-19 mRNA vaccine may trigger subacute thyroiditis. Human Vaccines & Immunotherapeutics. 2021 Dec 2;17(12):5120-5.

Speeckaert et al 2021
Speeckaert R, Lambert J, Puig L, et al. Vaccinations in Patients Receiving Systemic Drugs for Skin Disorders: What Can We Learn for SARS-Cov-2 Vaccination Strategies?.Drugs R 2021;D 21:341–50.

Spillane and Wells 1964
Spillane JD, Wells CE. The neurology of Jennerian vaccination. A clinical account of the neurological complications which occurred during the smallpox epidemic in south wales in 1962. Brain. 1964;87:1-44.

Sriphrapradang 2016
Sriphrapradang C, Bhasipol A. Differentiating Graves' disease from subacute thyroiditis using ratio of serum free triiodothyronine to free thyroxine. Annals of medicine and surgery. 2016 Sep 1;10:69-72.

Stasiak and Lewiński 2021
Stasiak and Lewiński. New aspects in the pathogenesis and management of subacute thyroiditis. Rev Endocr Metab Disord 22, 1027–1039 (2021). https://doi.org/10.1007/s11154-021-09648-y

Stevens et al 2022
Stevens KI, Frangou E, Shin JI, Anders HJ, Bruchfeld A, et al. Perspective on COVID-19 vaccination in patients with immune-mediated kidney diseases: consensus statements from the ERA-IWG and EUVAS. Nephrology Dialysis Transplantation. 2022.

Stohler et al 2019
Stohler NA, Reinau D, Jick SS, Bodmer D, Meier CR. A study on the epidemiology of tinnitus in the United Kingdom. Clin Epidemiol. 2019;11:855-71.

Stowe et al 2022
Stowe J, Andrews N, Kirsebom F, Ramsay M, Lopez Bernal J. Effectiveness of COVID-19 vaccines against Omicron and Delta hospitalisation: test negative case-control study. medRxiv 2022.04.01.22273281; doi: https://doi.org/10.1101/2022.04.01.22273281

Stratton et al 1994
Stratton KR, Howe CJ, Johnston RB Jr., editors. Adverse Events Associated with Childhood Vaccines: Evidence Bearing on Causality. Washington (DC): National Academies Press (US); 1994. 3, Neurologic Disorders. Available from: https://www.ncbi.nlm.nih.gov/books/NBK236298/

Stricker et al 1992
Stricker RB, Miller RG, Kiprov DD (1992). Role of plasmapheresis in acute disseminated (postinfectious) encephalomyelitis. J Clin Apher 7: 173–9.

Suri et al 2021
Suri V, Pandey S, Singh J, Jena A. BMJ case reports 2021 14(10).

Suwa et al 1999
Suwa K, Yamagata T, Momoi MY, Kawakami A, Kikuchi Y, Miyao M, et al. Acute relapsing encephalopathy mimicking acute necrotizing encephalopathy in a 4-year-old boy. Brain Dev. 1999;21:554-8.

Swanson et al 2021
Swanson PA, Padilla M, Hoyland W, McGlinchey K, Fields PA, Bibi S, et al. AZD1222/ChAdOx1 nCoV-19 vaccination induces a polyfunctional spike protein-specific TH1 response with a diverse TCR repertoire. Sci Transl Med. 2021;13(620). Available online at: https://www.science.org/doi/10.1126/scitranslmed.abj7211.

Tang et al 2021
Tang W.R., Hsu C.W., Lee C.C., Huang W.L., Lin C.Y., Hsu Y.T et al. A Case Report of Posttransplant Lymphoproliferative Disorder After AstraZeneca Coronavirus Disease 2019 Vaccine in a Heart Transplant Recipient. Transplantation Proceedings. 2021.

Tang et al 2021
Tang LV, Hu Y. Hemophagocytic lymphohistiocytosis after COVID-19 vaccination, J Hematol Oncol. 2021;14(1):87. doi: 10.1186/s13045-021-01100-7.

Tapdia et al 2022
Tapdia M, Kumar A, Singh VK, Pathak A, Joshi D. Post ChAdOx1 nCoV-19 vaccination frontal lobe syndrome. Neurol Sci 43. 2022;43:4099–101. doi.org/10.1007/s10072-022-06086-9.

Taylor and Hughes 1989
Taylor, W.A. and Hughes, R.A.C. (1989) T lymphocyte activation antigens in GBS and CIDP. J. Neuroimmunol. 24, 33-9.

Temiz et al 2022
Temiz SA, Abdelmaksoud A, Wollina U, Kutlu O, Dursun R, Patil A et al. Cutaneous and Allergic reactions due to COVID-19 vaccinations: A review. J Cosmet Dermatol. 2022 (1):4-12.

Tenembaum et al 2002
Tenembaum S, Chamoles N, Fejerman N. Acute disseminated encephalomyelitis: a long-term follow-up study of 84 pediatric patients. Neurology. 2002;59:1224-31.

Tenembaum et al 2007
Tenembaum S, Chitnis T, Ness J, Hahn JS, International Pediatric MS Study Group. Acute disseminated encephalomyelitis. Neurology. 2007;68(Suppl 2):S23-S36.

Terpos et al 2021
Terpos E, Gavriatopoulou M, Stathopoulos IN, Briasoulis A, Gumeni S, Malandrakis P,et al. Poor neutralizing antibody responses in 106 patients with WM after vaccination against SARS-CoV-2: a prospective study. Blood Adv. 2021;5(21):4398–405. doi: https://doi.org/10.1182/bloodadvances.2021005444

Thakur et al 2021
Thakur K, Tamborska A, Wood G, McNeil E, Roh D, Akpan I et al. Clinical review of cerebral venous thrombosis in the context of COVID-19 vaccinations: Evaluation, management, and scientific questions. J Neurol Sci. 2021 15;427:117532.

Thaler et al 2021
Thaler J, Ay C, Gleixner KV, Hauswirth AW, Cacioppo F, Grafeneder J et al. Successful treatment of vaccine-induced prothrombotic immune thrombocytopenia (VIPIT). J Thromb Haemost. 2021 Apr 20. doi: 10.1111/jth.15346. Epub ahead of print. PMID: 33877735.

The Netherlands Pharmacovigilance Centre Lareb 2022
The Netherlands Pharmacovigilance Centre Lareb. Overview menstrual disorders after COVID-19 vaccination – Update. 2022 May.

Theiler et al 2021
Theiler R, Wick M, Mehta R, Weaver A, Virk A, Swift M et al. Pregnancy and birth outcomes after SARS-CoV-2 vaccination in pregnancy. American Journal of Obstetrics & Gynecology MFM. 2021 ; 3(6): 100467

Tijmes et al 2021
Tijmes, SJ. Lebron D. Annual Meeting Assembly and Technical Exhibition of the American Academy of Physical Medicine and Rehabilitation (AAPMR). 2021;187.

Timmermans et al 2022
Timmermans SA, Busch MH, Abdul-Hamid MA, Frenken LAM, Aarnoudse AJ, Paassen PV. Primary Podocytopathies After COVID-19 Vaccination. Kidney International Reports. 2022 Apr;7(4):892.

Torres PA et al 2015
Rhabdomyolysis: pathogenesis, diagnosis, and treatment. Ochsner J. 2015 Spring; 15(1):58-69. PMID: 25829882; PMCID: PMC4365849.

Tracking SARS-CoV-2 variants
WHO Tracking SARS-CoV-2 variants. Available at: https://www.who.int/en/activities/tracking-SARS-CoV-2-variants

Trujillo et al 2020
Trujillo Gittermann LM, Valenzuela Feris SN, von Oetinger Giacoman A. Relation between COVID-19 and Guillain-Barré syndrome in adults. Systematic review. Neurologia (Engl Ed). 2020;35(9):646-54.

Truong D T et al 2022
Clinically Suspected Myocarditis Temporally Related to COVID-19 Vaccination in https://doi.org/10.1161/CIRCULATIONAHA.121.056583Circulation. 2022;145:345–356

Tseng et al 2021
Tseng PT, Chen TY, Sun YS, Chen YW, Chen JJ, The reversible tinnitus and cochleopathy followed first-dose AstraZeneca COVID-19 vaccination, QJM: An International Journal of Medicine, Volume 114, Issue 9, September 2021, Pages 663–664, https://doi.org/10.1093/qjmed/hcab210

Tsetsos N et al 2021
Tsetsos N, Poutoglidis A, Vlachtsis K, Kilmpasanis A, Gougousis S. Sudden sensorineural hearing loss following the second dose of COVID-19 vaccine. Cureus. 2021 Aug 25;13(8).

Tsilingiris D et al 2021
Potential implications of lipid nanoparticles in the pathogenesis of myocarditis associated with the use of mRNA vaccines against SARS-CoV-2. Metabol Open. 2022 Mar;13:100159. doi: 10.1016/j.metop.2021.100159. Epub 2021 Dec 17. PMID: 34938983; PMCID: PMC8677426.

Tuekprakhon et al 2022
Tuekprakhon A, Nutalai R, Dijokaite-Guraliuc A, Zhou D, Ginn HM, Selvaraj M et al. Antibody escape of SARS-CoV-2 Omicron BA.4 and BA.5 from vaccine and BA.1 serum. Cell 2022; 185 (14), 2422-2433. Available online at: https://doi.org/10.1016/j.cell.2022.06.005.

Tun et al 2021
Tun GS, Gleeson D, Al-Joudeh A, Dube A. Immune-mediated hepatitis with the Moderna vaccine, no longer a coincidence but confirmed. Journal of Hepatology. 2021 5.

Uzoma et al. 2022
Uzoma M. Abstract# 1185161: Thyroiditis Related to mRNA-Based SARS-CoV-2 Vaccination: A Case Series. Endocrine Practice. 2022;28(5):S158.

VAC4COVID Study 2022
What is the VAC4COVID Study? MEMO Research, 2022, Available from: https://vac4covid.com/

van den Berg and Weening 2004
van den Berg JG, Weening JJ. Role of the immune system in the pathogenesis of idiopathic nephrotic syndrome. Clin Sci(Lond) 2004; 107: 125–36.

van Rooji et al 2018
van Rooij J, Lucas EH, Geerards AJ, Remeijer L, Wubbels R. Corneal transplantation for Fuchs endothelial dystrophy: A comparison of three surgical techniques concerning 10 year graft survival and visual function. PLoS One. 2018 5;13(10):e0203993.

Varona et al 2021
Varona JF, García-Isidro M, Moeinvaziri M, Ramos-López M, Fernández-Domínguez M. Primary adrenal insufficiency associated with Oxford-AstraZeneca ChAdOx1 nCoV-19 vaccine-induced immune thrombotic thrombocytopenia (VITT). Eur J Intern Med. 2021;91:90-92. doi: 10.1016/j.ejim.2021.06.025.

Vasileiou et al 2021
Vasileiou E, Simpson CR, Robertson C, Shi T, Kerr S, Utkarsh A, et al. Effectiveness of first dose of COVID-19 vaccines against hospital admissions in Scotland: National prospective cohort study of 5.4 million people. Lancet. 2021;397:1646-57. Published Online April 23, 2021 https://doi.org/10.1016/ S0140-6736(21)00677-2.

Vasileiou et al 2021
Vasileiou E, Simpson CR, Robertson C, Shi T, Kerr S, Agrawal U, et al. Effectiveness of first dose of COVID-19 vaccines against hospital admissions in Scotland: national prospective cohort study of 5.4 million people. 2021;[preprint]. www.ed.ac.uk/files/atoms/files/scotland_firstvaccinedata_preprint.pdf.

Vasileiou V et al. 2021
Recurring subacute thyroiditis after SARS-CoV-2 mRNA vaccine: A case report. Case Rep Womens Health. 2022 Jan;33:e00378. doi: 10.1016/j.crwh.2021.e00378. Epub 2021 Dec 28. PMID: 34976747; PMCID: PMC8713417.

Vegezzi et al 2021
Vegezzi E, Ravaglia S, Buongarzone G, Bini P, Diamanti L, Gastaldi M et al. Acute myelitis and ChAdOx1 nCoV-19 vaccine: Casual or causal association?. Neuroimmunol. 2021 Oct 15;359:577686. doi: 10.1016/j.jneuroim.2021.577686.

Ventura et al 2021
Ventura F, John JS, Al-Saadi YI, Stevenson HL, Khan K. S2841 Autoimmune Hepatitis: Possible Relation to the Pfizer-BioNTech COVID-19 Vaccine?. Official journal of the American College of Gastroenterology ACG. 2021 Oct 1;116:S1180.

Vinzamuri et al 2021
Vinzamuri S, Pradeep TG, Kotian R. Bilateral paracentral acute middle maculopathy and acute macular neuroretinopathy following COVID-19 vaccination. Indian J Ophthalmol. 2021;69(10):2862-4.

Vismara et al 2020
Vismara SA, Lava SAG, Kottanattu L, Simonetti GD, Zgraggen L, Clericetti CM, et al. Lipschütz's acute vulvar ulcer: a systematic review. Eur J Pediatr. 2020;179(10):1559-1567. doi: 10.1007/s00431-020-03647-y. Epub 2020 15. PMID: 32296983

Vogel et al 2021
Vogel TP, Top KA, Karatzios C, Hilmers DC, Tapia LI, Moceri P et al. Multisystem inflammatory syndrome in children and adults (MIS-C/A): Case definition & guidelines for data collection, analysis, and presentation of immunization safety data. Vaccine. 2021;39(22):3037-49.

Vojdani and Kharrazian 2020
Vojdani A, Kharrazian D. Potential antigenic cross-reactivity between SARS-CoV-2 and human tissue with a possible link to an increase in autoimmune diseases. Clin Immunol. 2020;217:108480.

Vojdani et al 2020
Vojdani, A.; Kharrazian, D. Potential antigenic cross-reactivity between SARS-CoV-2 and human tissue with a possible link to an increase in autoimmune diseases. Clin. Immunol. 2020, 217, 108480

Von Woon et al 2022
Von Woon E, Male V. Effect of COVID-19 vaccination on menstrual periods in a prospectively recruited cohort. MedRxiv. 2022 Jan.

Vuille-Lessard et al 2021
Vuille-Lessard É, Montani M, Bosch J, Semmo N. Autoimmune hepatitis triggered by SARS-CoV-2 vaccination. Journal of autoimmunity. 2021 1;123:102710.

Wang AYL 2022
Modified mRNA-Based Vaccines Against Coronavirus Disease 2019. Cell Transplant. 2022 Jan-Dec;31:9636897221090259. doi: 10.1177/09636897221090259. PMID: 35438579; PMCID: PMC9021518.

Wang et al 1996
Wang PN, Fuh JL, Liu HC et al. (1996). Acute disseminated encephalomyelitis in middle-aged or elderly patients. Eur Neurol 36: 219–23.

Wang et al 2001
Wang Y, Wang YP, Tay YC, Harris DC. Role of CD8(+) cells in the progression of murine adriamycin nephropathy. Kidney Int 2001; 59: 941--49.

Wang et al 2022
Wang S, Mortazavi J, Hart JE, Hankins JA, Katuska LM et al. A prospective study of the association between SARS-CoV-2 infection and COVID-19 vaccination with changes in usual menstrual cycle characteristics. Am J Obstet Gynecol. 2022 Jul:S0002-9378(22)00539-7.

Wang H et al 2022
Wang H, Zhao S, Wang S, Zheng Y, Wang S, Chen H, Pang J, Ma J, Yang X, Chen Y. Global magnitude of encephalitis burden and its evolving pattern over the past 30 years. Journal of Infection. 2022;84(6):777-87.

Wang M et al 2022
Wang M, Meta-Analysis of Risk of Myocarditis After Messenger RNA COVID-19 Vaccine. Am J Cardiol. 2022 Mar 15;167:155-157. doi: 10.1016/j.amjcard.2021.12.007. Epub 2022 Jan 19. PMID: 35063268; PMCID: PMC8767906.

Watad et al 2021
Watad A, De Marco G, Mahajna H, Druyan A, Eltity M, Hijazi N et al. Immune-Mediated Disease Flares or New-Onset Disease in 27 Subjects Following mRNA/DNA SARS-CoV-2 Vaccination. Vaccines (Basel). 2021;9(5):435. doi: 10.3390/vaccines9050435.

Watson & Barnsley et al 2022
Watson OJ, Barnsley G, Toor J, Hogan AB, Winskill P, Ghani AC. Global impact of the first year of COVID-19 vaccination : a mathematical modelling study. The Lancet. 2022. DOI:https://doi.org/10.1016/S1473-3099(22)00320-6

Weitzman et al 2021
Weitzman D, Shavit O, Stein M, Cohen R, Chodick G, Shalev V et al. A population based study of the epidemiology of Herpes Zoster and its complications. Journal of Infection. 2013. ;67(5):463-9.

Whitaker et al 2022
Whitaker HJ, Tsang RSM, Byford R, Andrews NJ, Sherlock J, Sebastian Pillai P, Williams J, Button E, Campbell H, Sinnathamby M, Victor W, Anand S, Linley E, Hewson J, DArchangelo S, Otter AD, Ellis J, Hobbs RFD, Howsam G, Zambon M, Ramsay M, Brown KE, de Lusignan S, Amirthalingam G, Lopez Bernal J. Pfizer-BioNTech and Oxford AstraZeneca COVID-19 vaccine effectiveness and immune response amongst individuals in clinical risk groups. J Infect. 2022 May;84(5):675-83.

Whiteley et al 2022
Whiteley et al. AssociationofCOVID-19vaccinesChAdOx1 andBNT162b2withmajorvenous,arterial,or thrombocytopenicevents:A population based cohort study of 46million adults in England PLoSMed19(2): e1003926.https://doi.org/10.1371/journal. pmed.1003926

Whitely et al 2022
Whiteley et al. AssociationofCOVID-19vaccinesChAdOx1 andBNT162b2withmajorvenous,arterial,or thrombocytopenicevents:A population based cohort study of 46million adults in England PLoSMed19(2): e1003926.https://doi.org/10.1371/journal. pmed.1003926

WHO Coronavirus (COVID-19) Dashboard
WHO Coronavirus (COVID-19) Dashboard With Vaccination Data Available at : https://www.who.int/emergencies/diseases/novel-coronavirus-2019?adgroupsurvey={adgroupsurvey}&gclid=EAIaIQobChMInYPDnLfQ-QIVQx0rCh1A2wfTEAAYASAAEgLFn_D_BwE

WHO - interim guidance 2021
Guidance for clinical case management of thrombosis with thrombocytopenia syndrome (TTS) following vaccination to prevent coronavirus disease (COVID-19) Interim guidance 19 July 2021, WHO reference number: WHO/2019-nCoV/TTS/2021.1)

WHO 2021
https://www.who.int/publications/i/item/causality-assessment-aefi-user-manual-2019. Assessed on 09 December 2021.

Wichova H et al 2021
Wichova H, Miller ME, Derebery MJ. Otologic manifestations after COVID-19 vaccination: the house ear clinic experience. Otology & Neurotology. 2021 Oct;42(9):e1213.

Willame et al 2021
Willame C, Dodd C, Gini R, Duran CE, Ehrenstein V, Thomsen RM et al. Background rates of Adverse Events of Special Interest for monitoring COVID-19 vaccines, an ACCESS study. D3-Draft Final Report. 2021;(2.0). DOI: 10.5281/zenodo.5255870.

Willame et al 2021 [B]
Willame C, Dodd C, Gini R, Duran CE, Ehrenstein V, Thomsen RM et al. Background rates of Adverse Events of Special Interest for monitoring COVID-19 vaccines, an ACCESS study. D3-Draft Final Report. 2021;(2.0). DOI: 10.5281/zenodo.5255870.

Willame et al. 2021
Willame C, Dodd C, Gini R, et al. Background rates of Adverse Events of Special Interest for monitoring COVID-19 vaccines. European Network of Centres for Pharmacoepidemiology

and Pharmacovigilance; 2021. Available from: http://www.encepp.eu/documents/ACCESS_Report_BGR_20210430_v.1.2.pdf accessed 23 February 2022.

Wolfson et al 2021
Wolfson AR, Robinson LB, Li L, McMahon AE, Cogan AS, Fu X et al. First-dose mRNA COVID-19 vaccine allergic reactions: limited role for excipient skin testing. J Allergy Clin Immunol Pract. (2021). 9:3308.e3–20.e3

Won T et al 2022
Increased Interleukin 18-Dependent Immune Responses Are Associated With Myopericarditis After COVID-19 mRNA Vaccination. Front Immunol. 2022 Feb 18;13:851620. doi: 10.3389/fimmu.2022.851620. PMID: 35251049; PMCID: PMC8894592.

Wong and Scott 2010
Wong TY, Scott IU. Clinical practice. Retinal-vein occlusion. N Engl J Med 2010; 363:2135-44.

Wu et al 2021
Wu HH, Kalra PA, Chinnadurai R. New-Onset and Relapsed Kidney Histopathology Following COVID-19 Vaccination: A Systematic Review. Vaccines. 2021 Nov;9(11):1252.

Xinxue Liu et al. 2022
Liu X, Munro AP, Feng S, Janani L, Aley PK, Babbage G, Baxter D, Bula M, Cathie K, Chatterjee K, Dejnirattisai W. Persistence of immunogenicity after seven COVID-19 vaccines given as third dose boosters following two doses of ChAdOx1 nCov-19 or BNT162b2 in the UK: Three month analyses of the COV-BOOST trial. Journal of Infection. 2022.

Xu et al 2021
Xu SL, Chen, Corrales C. Annual Meeting Assembly and Technical Exhibition of the American Academy of Physical Medicine and Rehabilitation (AAPMR). 2021;375.

Yamaguchi et al 1992
Yamaguchi M, Ohta A, Tsunematsu T, Kasukawa R, Mizushima Y, Kashiwagi H, et al. Preliminary criteria for classification of adult Still's disease. J Rheumatol. 1992;19(3):424–30.

Yamout et al 2021
Yamout, BI, Zakaria M, Inshasi J, Al-Jumah M, Zeineddine M, Dahdaleh M et al. MENACTRIMS practice guideline for COVID-19 vaccination in patients with multiple sclerosis. Multiple Sclerosis and Related Disorders 2021 56.

Yanir Y et al 2022
Yanir Y, Doweck I, Shibli R, Najjar-Debbiny R, Saliba W. Association between the BNT162b2 messenger RNA COVID-19 vaccine and the risk of sudden sensorineural hearing loss. JAMA Otolaryngology–Head & Neck Surgery. 2022 Apr 1;148(4):299-306.

Yapici-Eser et al 2021
Yapici-Eser H, Koroglu YE, Oztop-Cakmak O, Keskin O, Gursoy A, Gursoy-Ozdemir Y. Neuropsychiatric symptoms of COVID-19 explained by SARS-CoV-2 proteins' mimicry of human protein interactions. Frontiers in human neuroscience. 2021;23:15:656313.

Yen et al 2021
Yen CC, Lin SY, Chen SC, Chiu YW, Chang JM, Hwang SJ. COVID-19 Vaccines in Patients with Maintenance Hemodialysis. J. Pers. Med. 2021;11:789. https://doi.org/10.3390/jpm11080789.

Yoon et al 2018
Yoon HY, Kim HM, Kim YJ, Song JW. Prevalence and incidence of sarcoidosis in Korea: a nationwide population-based study. Respir Res. 2018;19(1):158. https://doi.org/10.1186/s12931-018-0871-3.

Zan et al 2022
Zan J, Ma J, Man Q, Liu X, Yu D, Zhang Y, et al 2022. Safety evaluation of COVID-19 vaccine in patients with IgA nephropathy or IgA vasculitis nephritis. Kidney international reports. 2022 Jun 1;7(6):1435-6.

Zhao and Wu 2022
Zhao Y, Wu X. Influence of COVID-19 vaccines on endocrine system. Endocrine. 2022:1–6. doi: 10.1007/s12020-022-03119-3.

Zhou et al 2022
Zhou T, Fronhoffs F, Dold L, Strassburg CP, Weismüller TJ. New-onset autoimmune hepatitis following mRNA COVID-19 vaccination in a 36-year-old woman with primary sclerosing cholangitis–should we be more vigilant?. Journal of Hepatology. 2022 1;76(1):218-20.

Zhu et al 2007
Zhu J, Huang X, Yang Y. Innate Immune Response to Adenoviral Vectors Is Mediated by both Toll-Like Receptor-Dependent and -Independent Pathways. ASM Journals Journal of Virology. 2007; 81(7).