2 December 2021
EMA/PRAC/575791/2021
Pharmacovigilance Risk Assessment Committee (PRAC)

Signal assessment report on Myocarditis, pericarditis with Tozinameran (COVID-19 mRNA vaccine (nucleoside-modified) – COMIRNATY)

EPITT no: 19712

Procedure no: EMEA/H/C/005735/SDA/032.2

Administrative information

Confirmation assessment report	07/10/2021
Adoption of first PRAC recommendation	14/10/2021
Adoption of second PRAC recommendation	28/10/2021
Submission of data/responses from MAH	15/11/2021
Preliminary assessment report on additional data	23/11/2021
Deadline for comments	25/11/2021
Updated rapporteur assessment report	29/11/2021
Adoption of third PRAC recommendation	02/12/2021

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Administrative information

Active substance(s) (invented name)	Tozinameran - COVID-19 mRNA vaccine (nucleoside-modified) - COMIRNATY
Pharmaceutical form(s)	Concentrate for dispersion for injection (sterile concentrate)
Route(s) of administration	Intramuscular
Indication(s)	Active immunisation to prevent COVID-19 caused by SARS-CoV-2 virus
Marketing authorisation holder(s)	BioNTech Manufacturing GmbH
☒	Centralised
☐	Mutual recognition or decentralised
☐	National

Adverse event/reaction:	Myocarditis, pericarditis

Signal validated by:	SE
Date of circulation of signal validation report:	07 Oct 2021
Signal confirmed by:	NL
Date of confirmation:	07 Oct 2021
PRAC Rapporteur appointed for the assessment of the signal:	Menno van der Elst

Table of contents

Background

This signal was triggered by the MPA following the circulation of the preliminary results dated 5th October 2021 of a study entitled *SARS-CoV-2 vaccination and risk of pericarditis and myocarditis: Nordic nationwide cohort study of 20 million individuals*. The analyses were undertaken within a request from the Swedish government to the Medical Products Agency of in depth safety evaluation of covid-19 vaccines.

The report is based on a meta-analysis of data from Denmark, Finland, Norway and Sweden.

Myocarditis and pericarditis have been followed specifically due to the previous signal of these events.

1. Initial evidence

1.1. Signal validation

The preliminary analyses of the abovementioned study show that the occurrence of myocarditis is more frequent after the second vaccine dose, than after the first, and in younger men. Analyses are ongoing to further characterize these risks, which include similar analyses of pericarditis.

The previous PRAC recommendation was mainly based on data from spontaneous reporting. The new data, based on national population registers, linked to vaccination and health care registries in the respective countries, contribute with new information regarding the magnitude of risk for the two respective vaccines, including in different age strata.

Prompt evaluation on the need for updates on e.g. the product information for these respective vaccines is proposed.

The triggering MS noted that these data can be important for ongoing vaccination campaigns.

Based the preliminary results the triggering MS concluded regarding Comirnaty the following (summarised):

- 2nd dose is not strongly associated with myocarditis in the general Nordic populations.
- 2nd dose is associated with myocarditis in men 18-39 – however the absolute number of cases is still low.
- 1st and 2nd dose are associated with myocarditis in boys 12-17 – however the absolute number of cases is still low.
- Estimates in men 18-39 yrs are far from precise but are consistent over countries
- 2nd dose is associated with pericarditis in men 18-39
- SARS-CoV-2 infection is associated with myocarditis, more strongly in those 40 years and older

Evaluation of potential biases (*i.e.* ascertainment bias, residual confounding, confounding by age and by calendar-time) are still ongoing.

1.2. Signal confirmation

As the previous PRAC recommendation (July 2021) was mainly based on data from spontaneous reporting from outside the EEA, the new data, based on Scandinavian national population registers

linked to vaccination and health care registries in the respective countries, contribute with new information regarding the magnitude of risk for the two respective vaccines, including in different age strata although estimates in several strata are based on low numbers.

The current product information contains the following warning in SmPC section 4.4:

Myocarditis and pericarditis

Very rare cases of myocarditis and pericarditis have been observed following vaccination with Comirnaty. These cases have primarily occurred within 14 days following vaccination, more often after the second vaccination, and more often in younger men. Available data suggest that the course of myocarditis and pericarditis following vaccination is not different from myocarditis or pericarditis in general.

Healthcare professionals should be alert to the signs and symptoms of myocarditis and pericarditis. Vaccinees should be instructed to seek immediate medical attention if they develop symptoms indicative of myocarditis or pericarditis such as (acute and persisting) chest pain, shortness of breath, or palpitations following vaccination.

Healthcare professionals should consult guidance and/or specialists to diagnose and treat this condition.

Both myocarditis and pericarditis are currently listed in SmPC Section 4.8 as adverse reactions with frequency category *'Not known (cannot be estimated from the available data)'*.

In view of the new information on the magnitude of the risk and the current labelling lacking a frequency in section 4.8, the signal is confirmed and further assessment is warranted.

1.3. Proposed recommendation

The PRAC Rapporteur will perform an in-depth evaluation of the preliminary report which describes a meta-analysis of data from Denmark, Finland, Norway and Sweden, including the need for updates on *e.g.* the product information for these respective vaccines, as appropriate.

In parallel the MAH will be requested to discuss these new findings, including the need to amend the current labelling.

1.4. Adopted (first) PRAC recommendation

Having considered that new data on the known risk of myocarditis, pericarditis has become available from a preliminary report which describes a meta-analysis of data from Denmark, Finland, Norway and Sweden, the PRAC has recommended the following.

1. The PRAC Rapporteur for the COVID-19 mRNA Vaccine Comirnaty should perform an in-depth evaluation of the preliminary report and compile a List of Questions for the researchers and the MAH for the COVID-19 mRNA Vaccine Comirnaty (BioNTech Manufacturing GmbH), as appropriate. Considering that the results of the study are expected to become available starting with 25 October 2021 at the earliest, these Lists of Questions will be further discussed in the PRAC plenary 25-28 October.
2. The MAH for the COVID-19 mRNA Vaccine Comirnaty (BioNTech Manufacturing GmbH) should continuously monitor the emerging evidence on the association between COVID-19 mRNA vaccine Comirnaty and myocarditis and pericarditis arising from all available of sources (e.g. clinical studies, observational studies considering in various jurisdictions, company data bases).

3. The Agency will provide an updated expected to observed analysis considering the most recent EudraVigilance data and EEA exposure to COVID-19 vaccines including in the under 18 years old.

2. Additional evidence (second round of signal assessment procedure)

The assessment of additional data in the second round of this procedure (i.e. the assessment of the preliminary results dated 5th October 2021 of a study entitled SARS-CoV-2 vaccination and risk of pericarditis and myocarditis: Nordic nationwide cohort study of 20 million individuals) has been relocated to the Annex of this AR, since these preliminary results are superseded by a manuscript, supplemental information, tables and figures, on the final results from the Nordic meta-analysis of SARS-CoV-2 Vaccination and Myocarditis among 23 million residents, as circulated by MPA on 5 November 2021. These final results are assessed in section 3.1. below.

2.1. Adopted (second) PRAC recommendation

Considering the current EU product labelling for COVID-19 mRNA vaccines and the new data on the risk of myocarditis and pericarditis that have become available after the PRAC recommendation in July 2021, the PRAC has agreed that the MAH of COVID-19 mRNA vaccine Comirnaty (BioNTech Manufacturing GmbH) should provide by 15 November 2021 a review of the respective data from clinical studies, from the scientific literature and other data available in public domain (e.g. published data from Canada, Israel, US and other jurisdictions). The MAH should respond to the below List of Questions separately for myocarditis and pericarditis.

List of Questions:

1. The MAH should provide a risk estimation of myocarditis and pericarditis overall and per age groups (e.g. 5-11, 12-15, 16-17, 18-24, 25-29, 30-39, 40+ also depending on age groups used in studies), gender, vaccine dose(s) (i.e. first, second or booster).

2. The MAH should perform further characterisation of myocarditis and pericarditis, with focus on the following:

- Provide an estimation of the incidence of myocarditis and pericarditis, with the view to better characterize the current 'unknown' frequency in the product labelling.
- Discuss any plausible pathophysiological mechanism(s) of myocarditis and pericarditis observed after COVID-19 mRNA vaccine Comirnaty.
- Data on the characteristics, severity, duration and outcome of myocarditis and pericarditis after vaccination with Covid-19 mRNA vaccine Comirnaty.

3. Additional evidence (third round of signal assessment procedure)

3.1. Assessment of additional data submitted by the MAH

On 15 November 2021 the MAH submitted their response to the PRAC Assessment Report Signal Assessment Report on Myocarditis, pericarditis dated 29 October 2021, which is reviewed below.

PRAC's recommendations and questions in ***bold italics*** are followed by the MAH's responses in plain text.

2. QUERIES

Considering the current EU product labelling for COVID-19 mRNA vaccines and the new data on the risk of myocarditis and pericarditis that have become available after the PRAC recommendation in July 2021, the PRAC has agreed that the MAH of COVID-19 mRNA vaccine Comirnaty (BioNTech manufacturing GmbH) should provide by 15 November 2021 a review of the respective data from clinical studies, from the scientific literature and other literature in the public domain (e.g. published data from Canada, Israel, US and other jurisdictions). The MAH should respond to the below List of Questions separately for myocarditis and pericarditis.

List of Questions:

Question 1

The MAH should provide a risk estimation of myocarditis and pericarditis overall and per age groups (e.g. 5-11, 12-15, 16-17, 18-24, 25-29, 30-39, 40+ also depending on age groups used in studies), gender, vaccine dose(s) (i.e. first, second or booster).

Question 2

The MAH should perform further characterization of myocarditis and pericarditis, with focus on the following:

- ***Provide an estimation of the incidence of myocarditis and pericarditis, with the view to better characterize the current 'unknown' frequency in the product labelling.***
- ***Discuss any plausible pathophysiological mechanism(s) of myocarditis and pericarditis observed after COVID-19 mRNA vaccine Comirnaty.***
- ***Data on the characteristics, severity, duration and outcome of myocarditis and pericarditis after vaccination with COVID-19 mRNA vaccine Comirnaty.***

Summary of MAH RESPONSE

In response to the PRAC request dated 29 October 2021, the MAH conducted cumulative reviews of relevant clinical epidemiological, non-clinical and post-marketing data in order to determine whether there is new or significant information to suggest the risk has changed.

Clinical Trial Data

There were 4 cases of myocarditis and pericarditis in the pivotal study, C4591001, to the cut-off date of 31 August 2021, are presented below:

1. The first case was reported in <18-year-old who originally received placebo, and then received two (2) doses of BNT162b2 (30µg). This participant developed myocarditis 3 days after the second dose of BNT162b2 (30µg), which resolved 2 days later; was considered a serious adverse event by the investigator but was not considered related to vaccine.
2. The second case was reported in a 20-29-year-old who was randomized to received placebo, and developed myocarditis with right retroatrial inflammation 6 days after the second dose of placebo, which resolved 1 day later. It was mild in severity and was not considered related to vaccine by the investigator.
3. The third case was reported in a 50-59-year-old participant who originally received placebo and then received two (2) doses of BNT162b2 (30µg). This participant developed pericarditis 152 days after the second dose of BNT162b2 (30µg) and was still ongoing at the time of the data cutoff date. This was reported as a serious adverse event by the investigator but considered not related to vaccine.
4. The fourth case was reported in a 60-69-year-old participant randomized to receive BNT162b2 (30µg). This participant developed pericarditis 29 days after the second dose of BNT162b2 (30µg), which resolved 217 days later. This event was considered serious by the investigator but was not considered related to vaccine.

No incidence was calculated due to the crossover nature of the study. Up to 31 August 2021, a **total of 44,699 subjects** received at least one dose of BNT162B2 in this trial.

Comment PRAC Rapporteur:

Of the 4 cases reported in the pivotal clinical trial, two of the cases were reported in subjects who originally received placebo, but developed myocarditis/pericarditis after receiving two doses of Comirnaty (crossover), and the third case were reported in a subject randomized to receive Comirnaty.

Therefore, the number of cases of myocarditis/pericarditis reported from clinical trials is 3 in the active group and 1 in the placebo group.

It is agreed that based on these 4 cases exclusively no causal relation with the vaccine or accurate ADR incidence can be concluded. Nevertheless, the PRAC Rap notes that the current frequency category in 4.8 (frequency unknown) does not adequately represent the currently increasing body of evidence gathered in the post-marketing phase based on evidence from observational studies.

See comments below.

Epidemiological Data

Observed Versus Expected Analyses

Please refer to Appendix 5.1 Observed versus Expected Analyses for Adverse Events of Special Interest of the SMSR 11 for updated analyses of myocarditis and myocarditis/pericarditis by age, gender, and vaccine dose for the EEA and US using a range of background incidence rate estimates. The age-groups provided for the O/E in the SMSR for myocarditis and myocarditis/pericarditis were selected based on the availability of reported vaccine administration information and background rates from ACCESS. The relevant O/E analyses were included as Annex, but are summarized here.

Comment PRAC Rap:

The O/E analyses for myocarditis in European Economic Area (EEA, Table 1), US (Table 2) using a 14-day risk window are shown below. The O/E ratios for 21-day risk window were slightly lower (not reproduced here).

Table 3 shows the O/E Analysis of Myocarditis/Pericarditis combined in EEA Countries. The O/E ratios for US were roughly 3-fold lower (not reproduced here).

Table 1. Observed to Expected (O/E) Analysis of Myocarditis in European Economic Area Countries, 14-day Risk Window, Cumulative Period

			Low				Mid				High			
Stratification	Person Years	Obs Cases	Bkgd rate[a,i]	Exp Cases	O/E Ratio	95% CI	Bkgd rate[ii]	Exp Cases	O/E Ratio	95% CI	Bkgd rate[iii]	Exp Cases	O/E Ratio	95% CI
Males ≤17 years	523,319	250	0.48	2.5	99.525	87.569, 112.657	4.40	23.0	10.857	9.553, 12.290	8.26	43.2	5.784	5.089, 6.547
Males 18-24 years	615,187	430	2.77	17.0	25.234	22.905, 27.735	4.40	27.1	15.886	14.420, 17.461	20.20	124.3	3.460	3.141, 3.803
Males 25-49 years	2,785,474	521	2.48	69.1	7.542	6.908, 8.218	4.40	122.6	4.251	3.894, 4.632	14.97	417.0	1.249	1.144, 1.361
Males 50-59 years	1,299,455	106	1.66	21.6	4.914	4.023, 5.943	4.40	57.2	1.854	1.518, 2.242	8.48	110.2	0.962	0.788, 1.163
Males 60-69 years	978,729	52	2.37	23.2	2.242	1.674, 2.940	4.40	43.1	1.208	0.902, 1.583	4.80	47.0	1.107	0.827, 1.452
Males 70+ years	1,569,054	40	2.58	40.5	0.988	0.706, 1.346	4.40	69.0	0.579	0.414, 0.789	3.82	59.9	0.667	0.477, 0.909
Females ≤17 years	590,126	44	0.08	0.5	93.201	67.720, 125.117	4.40	26.0	1.695	1.231, 2.275	1.42	8.4	5.251	3.815, 7.049
Females 18-24 years	693,722	75	0.74	5.1	14.610	11.492, 18.314	4.40	30.5	2.457	1.933, 3.080	4.55	31.6	2.376	1.869, 2.978
Females 25-49 years	3,141,067	213	0.72	22.6	9.418	8.196, 10.772	4.40	138.2	1.541	1.341, 1.763	3.97	124.7	1.708	1.486, 1.954
Females 50-59 years	1,465,343	82	0.97	14.2	5.769	4.588, 7.161	4.40	64.5	1.272	1.012, 1.579	3.46	50.7	1.617	1.286, 2.008
Females 60-69 years	1,103,673	30	1.48	16.3	1.837	1.239, 2.622	4.40	48.6	0.618	0.417, 0.882	4.20	46.4	0.647	0.437, 0.924
Females 70+ years	1,769,359	34	0.96	17.0	2.002	1.386, 2.797	4.40	77.9	0.437	0.302, 0.610	4.83	85.5	0.398	0.276, 0.556
Overall, dose 1	8,470,034	635	1.34	113.5	5.595	5.168, 6.047	4.40	372.7	1.704	1.574, 1.842	6.27	531.1	1.196	1.104, 1.292
Overall, dose 2	8,064,472	1,237	1.34	108.1	11.447	10.818, 12.103	4.40	354.8	3.486	3.295, 3.686	6.27	505.6	2.446	2.312, 2.587
Overall, dose 3	NA	6	1.34	NA	NA	NA	4.40	NA	NA	NA	6.27	NA	NA	NA

a. Background rate per 100,000 person years

Table 2. Observed to Expected (O/E) Analysis of Myocarditis in the United States, 14-day Risk Window, Cumulative Period

			Low				Mid				High			
Stratification	**Person Years**	**Obs Cases**	**Bkgd rate[a,i]**	**Exp Cases**	**O/E Ratio**	**95% CI**	**Bkgd rate[ii]**	**Exp Cases**	**O/E Ratio**	**95% CI**	**Bkgd rate[iii]**	**Exp Cases**	**O/E Ratio**	**95% CI**
Males ≤17 years	291,308	41	0.48	1.4	29.322	21.042, 39.778	4.40	12.8	3.199	2.295, 4.339	8.26	24.1	1.704	1.223, 2.312
Males 18-24 years	391,310	48	2.77	10.8	4.428	3.265, 5.871	4.40	17.2	2.788	2.056, 3.696	20.20	79.0	0.607	0.448, 0.805
Males 25-49 years	1,534,803	44	2.48	38.1	1.156	0.840, 1.552	4.40	67.5	0.652	0.473, 0.875	14.97	229.8	0.192	0.139, 0.257
Males 50-59 years	710,154	8	1.66	11.8	0.679	0.293, 1.337	4.40	31.2	0.256	0.111, 0.504	8.48	60.2	0.133	0.057, 0.262
Males 60-69 years	670,299	8	2.37	15.9	0.504	0.217, 0.992	4.40	29.5	0.271	0.117, 0.534	4.80	32.2	0.249	0.107, 0.490
Males 70+ years	745,662	9	2.58	19.2	0.468	0.214, 0.888	4.40	32.8	0.274	0.125, 0.521	3.82	28.5	0.316	0.144, 0.600
Females ≤17 years	328,497	4	0.08	0.3	15.221	4.147, 38.971	4.40	14.5	0.277	0.075, 0.709	1.42	4.7	0.858	0.234, 2.196
Females 18-24 years	441,264	8	0.74	3.3	2.450	1.058, 4.827	4.40	19.4	0.412	0.178, 0.812	4.55	20.1	0.398	0.172, 0.785
Females 25-49 years	1,730,735	32	0.72	12.5	2.568	1.756, 3.625	4.40	76.2	0.420	0.287, 0.593	3.97	68.7	0.466	0.319, 0.657
Females 50-59 years	800,812	10	0.97	7.8	1.287	0.617, 2.367	4.40	35.2	0.284	0.136, 0.522	3.46	27.7	0.361	0.173, 0.664
Females 60-69 years	755,869	9	1.48	11.2	0.805	0.368, 1.527	4.40	33.3	0.271	0.124, 0.514	4.20	31.7	0.283	0.130, 0.538
Females 70+ years	840,853	6	0.96	8.1	0.743	0.273, 1.618	4.40	37.0	0.162	0.060, 0.353	4.83	40.6	0.148	0.054, 0.322
Overall, dose 1	4,829,930	76	1.34	64.7	1.174	0.925, 1.470	4.40	212.5	0.358	0.282, 0.448	6.27	302.8	0.251	0.198, 0.314
Overall, dose 2	4,021,903	150	1.34	53.9	2.783	2.356, 3.266	4.40	177.0	0.848	0.717, 0.995	6.27	252.2	0.595	0.503, 0.698
Overall, dose 3	389,733	1	1.34	5.2	0.191	0.005, 1.067	4.40	17.1	0.058	0.001, 0.325	6.27	24.4	0.041	0.001, 0.228

a. Background rate per 100,000 person years

Table 3. Observed to Expected (O/E) Analysis of Myocarditis/Pericarditis in European Economic Area Countries, Cumulative Period

Stratification	Bkgd rate[a,iv]	14-Day Risk Window					21-Day Risk Window				
		Obs Cases	PY	Exp Cases	O/E Ratio	95%CI	Obs Cases	PY	Exp Cases	O/E Ratio	95%CI
Males ≤17 years	16.77	283	523,319	87.8	3.225	2.860, 3.623	297	779,575	130.7	2.272	2.021, 2.545
Males 18-24 years	54.88	507	615,187	337.6	1.502	1.374, 1.638	538	918,489	504.1	1.067	0.979, 1.161
Males 25-49 years	43.53	751	2,785,474	1,212.5	0.619	0.576, 0.665	848	4,162,610	1,812.0	0.468	0.437, 0.501
Males 50-59 years	25.25	175	1,299,455	328.1	0.533	0.457, 0.618	205	1,944,178	490.9	0.418	0.362, 0.479
Males 60-69 years	26.50	90	978,729	259.4	0.347	0.279, 0.427	108	1,464,663	388.1	0.278	0.228, 0.336
Males 70+ years	24.58	97	1,569,054	385.7	0.252	0.204, 0.307	121	2,348,681	577.3	0.210	0.174, 0.250
Females ≤17 years	1.39	65	590,126	8.2	7.924	6.116, 10.100	73	879,095	12.2	5.974	4.683, 7.512
Females 18-24 years	6.42	125	693,722	44.5	2.807	2.336, 3.344	138	1,035,743	66.5	2.075	1.744, 2.452
Females 25-49 years	7.61	493	3,141,067	239.0	2.062	1.884, 2.253	553	4,694,007	357.2	1.548	1.422, 1.683
Females 50-59 years	10.23	182	1,465,343	149.9	1.214	1.044, 1.404	211	2,192,371	224.3	0.941	0.818, 1.077
Females 60-69 years	13.38	74	1,103,673	147.7	0.501	0.393, 0.629	88	1,651,641	221.0	0.398	0.319, 0.491
Females 70+ years	13.26	86	1,769,359	234.6	0.367	0.293, 0.453	102	2,648,512	351.2	0.290	0.237, 0.353
Overall, dose 1	18.68	1,184	8,470,034	1,582.2	0.748	0.706, 0.792	1,368	12,668,265	2,366.4	0.578	0.548, 0.610
Overall, dose 2	18.68	1,732	8,064,472	1,506.4	1.150	1.096, 1.205	1,901	12,051,301	2,251.2	0.844	0.807, 0.883
Overall, dose 3	18.68	13	NA	NA	NA	NA	14	NA	NA	NA	NA

a. Background rate per 100,000 person years (PY)

Comment PRAC Rapporteur:

The MAH provided an updated O/E analyses stratified by age, and gender, for EEA and US separately, for Myocarditis only and Myocarditis/Pericarditis combined, using 14- and 21-day risk windows, and low-/mid- and high background incidence rates.

Generally, the results are consistent with previous findings, with the difference that the number of cases and vaccine exposure in the younger age groups have increased, leading to somewhat more precision in the estimates.

Based on the O/E analyses presented above (Table 1, Table 2 and Table 3) it is noted that although the absolute number of cases in males is higher, the background incidence in males is also higher. Consequently, the O/E ratios above 1 do not really differ that much between males and females. This aspect is currently not reflected in the current wording in SmPC section 4.4. On the other hand, the numbers of female cases shown here, but also in the epidemiological studies cited by the MAH (as well as those conducted by VAC4EU and EPI-PHARE) are low, especially in the younger females, which raises the question regarding robustness of these estimates. The MAH should commit to remain closely evaluating the risk estimates in females, and in case more (robust, stable) data would become available, provide a proposal for refined/adjusted the wording in Section 4.4, as appropriate.

Incidence of Myocarditis and Pericarditis

The MAH has conducted literature reviews of myocarditis and pericarditis risk after BNT162b2 vaccination or SARS-CoV-2 infection, as summarized below. Overall, risk varied widely depending on the study methodology, definition of study population, length of follow-up period, and definitions of myocarditis and pericarditis used. Studies consistently reported higher risk after Dose 2 and among younger males (<30 years) post-vaccination, as well as higher risk after COVID-19 infections when compared with reported rates for individuals without COVID-19 infection or after vaccination.

Studies from Israel, US, and Australia reported the incidence of myocarditis following BNT162b2 vaccination for all ages combined. A real-world study using integrated health care data in Israel included 884,828 persons who received BNT162b2 vaccine and estimated the risk of myocarditis/pericarditis following COVID-19 vaccination compared with unvaccinated persons.[v] Vaccination was associated with an elevated risk of myocarditis (risk ratio [RR], 3.24; 95% confidence interval [CI], 1.55 to 12.44; excess risk [ER], 27 events per million persons; 95% CI, 10 to 46). SARS-CoV-2 infection was also associated with an increased risk of myocarditis (RR, 18.28; 95% CI, 3.95 to 25.12; ER, 110 events per million persons; 95% CI, 56 to 158). Vaccination non-significantly increased the risk of pericarditis as well (RR 1.27; 95% CI, 0.68 to 2.31; ER, 10 events per million persons; 95% CI, -16 to 34). SARS CoV-2 infection posed higher and significant risk of pericarditis (RR, 5.39; 95% CI, 2.22 to 23.58; ER, 109 events per million persons; 95% CI, 49 to 169).

The Vaccine Safety Datalink,[vi] which includes 8 data-contributing US health plans comprising 12,506,658 people of all ages and representing 3.6% of the US population, reported the incidence of myocarditis/pericarditis treated in ED or hospital settings within 21 days post vaccination and compared it to 22 to 42 days after either dose 1 or 2. The rate of events post-vaccination (any dose) was 131.7/million person-years compared with 106.9/million person-years in the comparison interval (adjusted rate ratio 1.18 [95% CI 0.79-1.79]). The dose-specific myocarditis/pericarditis rates among individuals 12-39 years were 70.4/million person-years post-dose 1 (vs. 35.0/million in comparison interval) and 221.3/million post-dose 2 (vs. 44.6/million in comparison interval).[vi]

Two additional studies reported myocarditis and pericarditis frequency following BNT162b2 vaccination for all ages combined of 10 (95% CI 6.1-15.4) per million for myocarditis and 18 (95% CI 13.-25.5) per million for pericarditis in a US healthcare system,[vii] and 13.5 cases of myocarditis and/or pericarditis per million doses in Australia.[viii]

Studies from Israel and surveillance data in the United States have provided age- and dose-specific estimates. One study from Israel,[ix] conducted as part of ongoing national surveillance and without involvement from the Sponsor, evaluated the relative risk of post-vaccination myocarditis with respect to comparator populations. This retrospective analysis of medically reviewed cases of myocarditis identified through passive and active surveillance for the period 20 December 2020 through 31 May 2021 found an overall standardized incidence ratio of 5.34 after a second dose using a 30-day risk window compared to 2017-2019 rates, driven mostly by the standardized incidence rate (SIR) in males under 30 years of age (Table 4). Elevated SIRs were not observed after Dose 1 in any age/sex category (95% CI included 1). The highest absolute risk was observed after the second dose among male recipients between the ages of 16 and 19 years: 150.7 per million persons. In males after the second dose, the incidence of myocarditis decreased with age: estimated at 109 per million for those between the ages of 20-24 years, 70 for those 25-29 years, 37 for those 30-39 years of age, 12 for those 40-49 years, and 2 for those 50 years or older. Among females the incidence after the second dose was 10 per million for those 16-19 years, 22 per million for those 20-24 years, 0 (no case reported) for those 25-29 years, 2 for those 30-39 years of age, 5 for those 40-49 years, and 2 for those 50 years or older. This study did not include information about vaccinees 12 to 15 years of age.

Table 4. Ratios Comparing Rates of Myocarditis Diagnoses within 21 Days Post Dose 1 and 30 Days Post Dose 2 of Vaccine Compared with Historical Periods and Unvaccinated Individuals

Age and Sex	Standardized Incidence Rate Ratio[a] (95% CI)		Rate Ratio[b] (95% CI)
	Dose 1	Dose 2	Dose 2
Overall	1.42 (0.92 – 2.10)	5.34 (4.48 – 6.40)	2.35 (1.10 – 5.02)
16-19 Year			
Male	1.62 (0.32 – 4.72)	13.60 (9.30, 19.20)	8.96 (4.50, 17.83)
Female	0	6.74 (0.76, 24.35)	2.95 (0.42, 20.91)
20-24 year			
Male	2.14 (0.69 – 5.00)	8.53 (5.57, 12.50)	6.13 (3.16, 11.88)
Female	2.37 (0.03-13.20)	10.76 (3.93, 23.43)	7.56 (1.47, 38.96)
25-29 Year			
Male	1.39 (0.28 – 4.05)	6.96 (4.25, 10.75)	3.58 (1.82, 7.01)
Female	0	2.54 (0.03, 14.14)	0
⩾30 Year			
Male	1.23 (0.59 – 2.26)	2.90 (1.98, 4.09)	1.00 (0.61, 1.64)
Female	1.42 (0.29 – 4.15)	2.44 (0.98, 4.09)	0.82 (0.33, 2.02)

a. In comparison with 2017-2019 rates
b. In comparison to matched unvaccinated comparator (11 January to 31 May 2021)
Source:[ix].

Another study[x] searched the database of Clalit Health Services, the largest health care organization in Israel, for diagnoses of myocarditis in patients who had received at least one dose of the BNT162b2 mRNA vaccine. The estimated incidence per million persons who had received at least one dose of vaccine was 21.3 cases (95% CI, 15.6-27.0). The highest incidence of myocarditis (106.9 per million; 95% CI, 69.3-144.6) was reported in male patients between the ages of 16 and 29 years and in those aged 30 years or older (21.1 per million, 95% CI 11.9–30.4). The incidence in females was substantially lower, 3.4 (95% CI 0–10) per million among younger female adults aged 16-29 years and 2.0 (95% CI 0–4.8) per million in those aged 30 years or older.[x]

Information about myocarditis and perimyocarditis by age has been reported by the Israeli Ministry of Health as part of their overall COVID-19 Vaccine monitoring (Figure 1).[xi] Among males the reporting rate of myocarditis was lower for individuals 12 to 15 years of age than for individuals 16 to 19 years of age for both dose 1 (1/196,398=0.51 vs 3/261,112=1.15 per 100,000 doses) and dose 2 (11/158,541=6.94 vs 37/226,452=16.34 per 100,000 doses), with rates for both doses declining thereafter with age. Among females the rate was lowest for individuals 30+ years of age for dose 2 (8/2,045,584= 0.39 per 100,000 doses) and highest for those 20-24 years of age (6/246,129=2.44/100,000 doses). Compared to dose 2, risk does not appear higher after dose 3 for either males or females (Males; age 12-15: 0 cases; age 16-19: 6/108,504=5.53 cases/100,000 doses; age 20-24: 6/155,935=3.85/100,000 doses; age 25-29: 1/148,410=0.67/100,000 doses; age 30+:12/1,502,119=0.80/100,000 doses; Females; ages 12-29: 0 cases; age 30+: 2/1,599,973=0.13/100,000 doses).

Figure 1. Myocarditis and perimyocarditis cases reported to the Israel Ministry of Health following COVID-19 mRNA vaccination

Myocarditis & perimyocarditis cases
and number of vaccinees by age group and sex

Proactive surveillance. All cases reported in Israel Dec. 2020 - Oct. 28th, 2021[1]

Sex	Age group	1st dose (0-21 days following vaccination)		2nd dose (0-30 days following vaccination)		3rd dose (0-30 days following vaccination)	
		Number of vaccinees	Number of myocarditis cases reported	Number of vaccinees	Number of myocarditis cases reported	Number of vaccinees	Number of myocarditis cases reported
Female	12-15	209,738	0	170,858	1	331	0
	16-19	256,231	0	225,444	2	110,713	0
	20-24	277,498	1	246,129	6	158,554	0
	25-29	258,791	0	232,457	2	143,623	0
	30+	2,176,128	*2	2,045,584	*8	1,599,973	2
Male	12-15	196,398	1	158,541	11	326	0
	16-19	261,112	3	226,452	**37	108,504	6
	20-24	286,615	6	255,116	26	155,935	6
	25-29	267,766	3	242,308	20	148,410	1
	30+	2,024,131	6	1,910,901	28	1,502,119	12

[1] Not including 5 cases after 1st dose and 4 cases after 2nd dose at ages 30+ that were ruled out as not myocarditis by clinical committee.
*One case received Moderna
** One case – first dose Pfizer, second dose Moderna
For 2,548 individuals without gender information there were zero cases reported.

Source:xi

The Vaccine Adverse Event Reporting System (VAERS) has information on the number of myocarditis cases within 7 days of vaccination per million second doses from spontaneous reports in the US. A similar pattern was observed as in Israel 30 days post second dose, although rates were lower due in part to the length of the risk window.[xii,xiii] Among males aged 12-29 years, myocarditis reporting rates were 40.6 per million second doses of mRNA vaccines administered; the reporting rate was 2.4 per million second doses for males aged >=30 years.[xiii] The reporting rate among females was 4.2 per million second doses for 12-29 years and 1.0 per million for >=30 years. Myocarditis rates were higher after dose 2, and among 16-17 year olds for both males (69.1/million second doses) (**Figure 2**) and females (7.9/million second doses) (**Figure 3**).

Figure 2. Reporting rates (per million doses) of myocarditis in VAERs - Males

Vaccine Adverse Event Reporting System (VAERS):
Reporting rates (per 1 million doses administered) of myocarditis among males after mRNA COVID-19 vaccines, 7-day risk period (N=797)*

- **169,740,953** doses of mRNA vaccine administered to males (dose 1 and dose 2) *
- Reporting rates exceed background incidence**

Highest % is among males aged 16-17 years: 0.007%

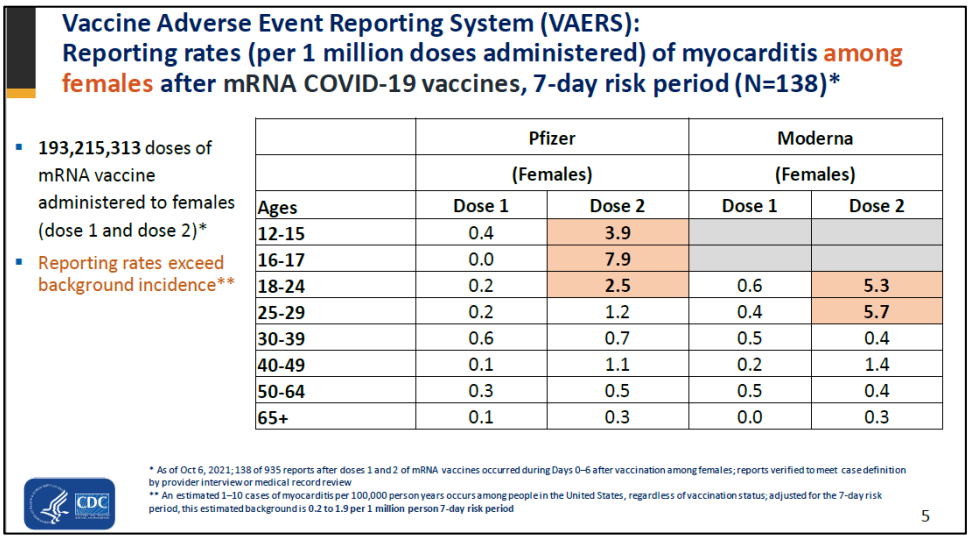
	Pfizer (Males)		Moderna (Males)	
Ages	Dose 1	Dose 2	Dose 1	Dose 2
12-15	4.2	39.9		
16-17	5.7	69.1		
18-24	2.3	36.8	6.1	38.5
25-29	1.3	10.8	3.4	17.2
30-39	0.5	5.2	2.3	6.7
40-49	0.3	2.0	0.2	2.9
50-64	0.2	0.3	0.5	0.6
65+	0.2	0.1	0.1	0.3

* As of Oct 6, 2021, 797 of 935 reports after doses 1 and 2 of mRNA vaccines occurred during Days 0–6 after vaccination among males; reports verified to meet case definition by provider interview or medical record review
** An estimated 1–10 cases of myocarditis per 100,000 person years occurs among people in the United States, regardless of vaccination status; adjusted for the 7-day risk period, this estimated background is 0.2 to 1.9 per 1 million person 7-day risk period

4

Source[xii]

Figure 3. Reporting rates (per million doses) of myocarditis in VAERs - Females



	Pfizer (Females)		Moderna (Females)	
Ages	Dose 1	Dose 2	Dose 1	Dose 2
12-15	0.4	3.9		
16-17	0.0	7.9		
18-24	0.2	2.5	0.6	5.3
25-29	0.2	1.2	0.4	5.7
30-39	0.6	0.7	0.5	0.4
40-49	0.1	1.1	0.2	1.4
50-64	0.3	0.5	0.5	0.4
65+	0.1	0.3	0.0	0.3

Source[xii]

Reported rates of myocarditis are higher after SARS-CoV-2 infection than rates reported after vaccination. In one hospital-based study, individuals with a COVID-19 diagnosis had 7-37 times the risk of myocarditis compared to those without COVID-19[xiv] depending on age-group, with risk ranging from 77/100,000 in individuals 25-39 years to 238/100,000 among 75+ years; the risk was 133/100,000 among individuals under 16 years of age.[xiv] A study of United States[xv] medical claims that included 70,288 COVID-19 patients (53% hospitalized, 5% ICU) reported the incidence of acute myocarditis overall was 100/100,000 within 30 days after the index diagnosis.[xv]

It is important to note that data described above reflect rates from different regions, source data (*e.g.* spontaneous reports, registries, administrative), and using different methodologies. This could explain, at least partially, the variability in the reported rates between studies. Therefore, an integrated or side-by-side analysis is not appropriate, and it is not possible to use the available data to provide a single estimate of risk. Overall, in aggregate, the studies reported higher risk after dose 2 compared to dose 1, and among younger males compared to older males or females of any age post-vaccination. Risk was lower for individuals 12-15 years, higher for 16-19 years, and generally declining thereafter with age. Reported risk for myocarditis after COVID-19 infections was higher when compared with reported rates for individuals without COVID-19 infection or after vaccination. The MAH will continue to monitor the literature and safety data for myocarditis and pericarditis by age, sex, and dose.

Comment PRAC Rapporteur:

The MAH has conducted literature reviews of myocarditis and pericarditis risk after BNT162b2 vaccination or SARS-CoV-2 infection, as summarized above.

Overall, risk varied depending on the study methodology, definition of study population, length of follow-up period, and definitions of myocarditis and pericarditis used.

Observational studies consistently reported higher risk after Dose 2 and among younger males (<30 years) post-vaccination, as well as higher risk after COVID-19 infections when compared with reported rates for individuals without COVID-19 infection or after vaccination.

In addition to the literature cited by the MAH, the Rapporteur has recently been notified of **two further studies** by the **EMA/VAC4EU** (retrospective, multi-database, cohort study) and **EPI-PHARE**

- Scientific Interest Group (GIS) ANSM-CNAM (matched case-control study in the FR national health data system (SNDS)), which are briefly summarised below in Sections 3.5 and 3.6 of this AR.

The MAH noted that the data described above reflect rates from different regions, source data (*e.g.* spontaneous reports, registries, administrative), and using different methodologies, which could explain, at least partially, the variability in the reported rates between studies. Hence it is recognized that an integrated or side-by-side analysis is not appropriate.

Nevertheless, although challenging, the available data from the increasing number of published observational studies, all point in the same direction and can be used to provide a better estimate of risk, *i.e.* as currently described with ADR frequency 'unknown' in the product information.

For instance based on the studies cited by the MAH:

- Two studies reported myocarditis and pericarditis frequency following BNT162b2 vaccination for **all ages combined of 10 (95% CI 6.1-15.4) per million for myocarditis** and 18 (95% CI 13.-25.5) per million for pericarditis in a US healthcare system,[xvi] and 13.5 cases of myocarditis and/or pericarditis per million doses in Australia.[xvii]
- Information about myocarditis and perimyocarditis by age has been reported by the Israeli Ministry of Health as part of their overall COVID-19 Vaccine monitoring (Figure 1). [xviii] Among males the reporting rate of myocarditis was lower for individuals 12 to 15 years of age than for individuals 16 to 19 years of age for both dose 1 (1/196,398=0.51 vs 3/261,112=1.15 per 100,000 doses) and dose 2 (11/158,541=6.94 vs 37/226,452=**16.34 per 100,000 doses**), with rates for both doses declining thereafter with age.

Based on the currently available body of evidence from clinical trials and post-marketing observational studies the incidence of myocarditis ranged from **0.1-1.6 per 10,000**, hence a frequency category **Very Rare < 1 per 10,000** in the SmPC section 4.8 would be more appropriate. The rationale for the frequency category could be explained in sub-section *c "Description of selected adverse reactions"*. *I.e.* a footnote could be considered noting that the incidence of myocarditis in the younger males was at the high end of the range and would be closer to frequency category rare (≥1/10.000, <1/1.000)

In addition, the current wording should be further refined. The current product information section 4.4 mentions: ***Very rare*** *cases of myocarditis and pericarditis have been observed following vaccination with Comirnaty. These cases have primarily occurred within 14 days following vaccination, more often after the second vaccination, and more often in younger* ***men.***

It is proposed to remove and replace '**men**' (which implies adults only) by '**males**', as also cases have been observed in adolescent males aged below 18 years.

Nonclinical Data

An established mechanism for myocarditis or pericarditis has not been determined. Pfizer continues to monitor data from clinical trials, information gathered from pharmacovigilance databases, and literature for information that would potentially inform on a plausible mechanism.

Assessment of plausible pathophysiological mechanisms for the relationship between the COVID-19 mRNA vaccine and myocarditis or pericarditis has included database searches (such as Pharmapendium and OFF-X), epitope mimicry assessments, and literature reviews. Although there are rare reports of vaccine-associated myocarditis (eg, influenza vaccines) and extensive reporting on smallpox vaccine-associated myocarditis, no pathophysiological cause has been identified. Underlying genetic

predisposition to myocarditis may contribute to post-vaccination-associated myocarditis, but there is little in the published literature to support such a conclusion at this time.

Direct toxicities generally manifest consistently in clinical trials. Therefore, a direct effect of the mRNA vaccine or the expressed spike protein on the heart would have been expected to occur more frequently and been identified in clinical trials; as such, this mechanism is considered less likely. The nonclinical safety assessment of BNT162 vaccine candidates included 2 GLP repeat dose toxicity studies and a GLP developmental and reproductive toxicity study. There were no effects on the heart in any of these studies. Further, distribution of vaccine to the heart was not identified in rats administered an IM dose of a modRNA-LNP encoding luciferase (as a surrogate protein). Circulating levels of spike protein post-vaccination have not been well studied. The expressed spike protein antigen is anticipated to remain membrane bound or presented in association with MHC and would likely have limited systemic distribution. One report investigated circulating levels of spike protein after vaccination with mRNA-1273 (Moderna COVID-19 vaccine), but levels were shown to be very low after the first vaccination and undetectable after the second vaccination.[xix] Biodistribution studies using a modRNA-LNP encoding luciferase (surrogate protein) identified luciferase expression only in the region of the IM administration and in the liver. Liver luciferase expression is consistent with LNP distribution and most likely reflects local mRNA expression of the protein and not distribution of luciferase from systemic exposure of secreted luciferase. Therefore, systemic exposure of Spike protein with binding to ACE2 in any tissues, potentially initiating off-target immune responses, would be not be expected. Further, ACE2 expression is low in the heart relative to other tissues.[xx] There is limited reporting that ACE2 may be upregulated in the heart after COVID-19 infection (see below and Chen et al, 2020[xxi]). Data suggests that patients exhibiting clinical signs of myocarditis or pericarditis after vaccination are not SARS-CoV-2 infected based on a negative qPCR test.

Indirect mechanisms (i.e., immune-related) and non-vaccine associated (e.g., microbial, toxic, etc.) mechanisms have also been assessed as potential causes for reported post-COVID mRNA vaccine myocarditis. Immune-mediated mechanisms include hypersensitivity myocarditis, autoimmune myocarditis, and immune-associated exacerbation of subclinical/asymptomatic myocarditis. Hypersensitivity myocarditis is generally characterized by circulating eosinophilia and eosinophil infiltrates in endomyocardial biopsies. Some reports in the literature have demonstrated eosinophils within the endomyocardial biopsies from patients who developed myocarditis after vaccination. However, most reports and cases examined by Pfizer are not associated with either peripheral eosinophilia or eosinophilic infiltrates in endomyocardial biopsies from affected patients. Myocarditis and pericarditis have been associated with auto-immune diseases such as Lupus[xxii], although these diseases tend to occur more frequently in females compared with males.[xxiii] Vaccines have been associated with transient autoimmune disorders such as Guillain-Barre syndrome. However, the data suggest that myocarditis reported after COVID-19 mRNA vaccine administration is unlikely to be the result of autoimmunity. This is based on the predominantly mild and transient nature of the myocarditis clinically and the lack significant lymphocytic infiltrates or presence of immune complexes (by immunohistochemistry) in endomyocardial biopsies.[ix] Although the microscopic findings in endomyocardial biopsies were not suggestive of a cellular immune response, the potential risk for molecular mimicry as a cause for myocarditis/pericarditis was evaluated internally. Peptide sequences from the spike protein antigen of Comirnaty were compared against human peptides by homology search. There were no matches against human peptides to the spike peptides of greater than or equal to 9 mers. Matches for smaller peptides were similar to what has been reported previously.[xxiv] However, these matches would not explain the predominance of younger males associated with myocarditis. Exacerbation of subclinical/asymptomatic myocarditis related to COVID-19 mRNA vaccination innate immune activation is a possible explanation which is consistent with both the sex

and age groups affected, as well as the transient nature of the finding clinically. However, there are no data internally or within the literature to support this hypothesis.

In published reports evaluated by Pfizer, viral serology for other main cardiotropic viruses were negative in patients exhibiting clinical signs of myocarditis or pericarditis.

In performing a comprehensive evaluation of potential mechanisms for myocarditis or pericarditis, to date, Pfizer has uncovered nothing of substance from the nonclinical perspective to identify a potential root cause of myocarditis or pericarditis as to consider it an established mechanism. Further, animal models of myocarditis or pericarditis are not well established and therefore would not serve as a viable model to perform additional nonclinical assessments.

Comment PRAC Rapporteur:

The MAH's evaluation discussion of potential pathophysiological mechanisms is accepted.

At the moment no clear mechanism can be established based on the available evidence. The following aspects were highlighted:

- Although there are rare reports of vaccine-associated myocarditis (*e.g.* influenza vaccines) and extensive reporting on smallpox vaccine-associated myocarditis, no pathophysiological cause has been identified. Underlying genetic predisposition to myocarditis may contribute to post-vaccination-associated myocarditis, but there is little in the published literature to support such a conclusion at this time.
- Four cases in the pivotal clinical (2 in placebo and 2 in vaccine arm; none of which were vaccine-related by investigator) did not indicate direct toxicity (*i.e.* a direct effect of the mRNA vaccine or the expressed spike protein on the heart).
- No effects on the heart in any of the preclinical study program were observed (including 2 GLP repeat dose toxicity studies and a GLP developmental and reproductive toxicity study).
- Biodistribution studies using a modRNA-LNP encoding luciferase (surrogate protein) identified luciferase expression only in the region of the IM administration and in the liver. Liver luciferase expression is consistent with LNP distribution and most likely reflects local mRNA expression of the protein and not distribution of luciferase from systemic exposure of secreted luciferase. Systemic exposure of Spike protein with binding to ACE2 in any tissues, potentially initiating off-target immune responses, would not be expected.
- ACE2 expression is lower in the heart relative to other tissues
- The potential risk for molecular mimicry as a cause for myocarditis/pericarditis was evaluated by the MAH internally. Peptide sequences from the spike protein antigen of Comirnaty were compared against human peptides by homology search. There were no matches against human peptides to the spike peptides of greater than or equal to 9 mers. Matches for smaller peptides were similar to what has been reported previously.[xxv] However, these matches would not explain the predominance of younger males associated with myocarditis. Exacerbation of subclinical/asymptomatic myocarditis related to COVID-19 mRNA vaccination innate immune activation is a possible explanation which is consistent with both the sex and age groups affected, as well as the transient nature of the finding clinically.
- In published reports evaluated by MAH, viral serology for other main cardiotropic viruses were negative in patients exhibiting clinical signs of myocarditis or pericarditis. Consequently, a causal role of the vaccine is an at least reasonable possibility, in absence of these alternative etiologies.

Within the context of routine pharmacovigilance the MAH should continue to scrutinise any relevant safety findings and published scientific literature regarding the pathophysiological mechanism.

Post-marketing Data

Estimated Exposure and Use Patterns

Approximately 1,958,966,949 doses of BNT162b2 were shipped worldwide from the receipt of the first temporary authorisation for emergency supply on 01 December 2020 through 28 October 2021, corresponding to approximately 1,584,774,361 estimated administered doses. In the EU-EEA region, approximately 541,004,490 doses of BNT162b2 were shipped in the EU-EEA countries from the receipt of the first conditional marketing authorisation approval on 21 December 2020 through 28 October 2021, corresponding to 427,393,547 estimated administered doses. The top 3 EU-EEA countries by the cumulative number of administered doses are Germany, France and Italy.

Detailed methodology and analysis of exposure data, including analyses by geographic region, dose number and patient age group is provided in the Summary Monthly Safety Reports (SMSR).

Overview of Cumulative Post-Marketing Safety Database

As of 28 October 2021, there was a total of 564,284 cumulative reports received from post-marketing data sources for PF-07302048 (BNT162b2), as per the methodology described in the SMSR[1]. This dataset was used to retrieve cases potentially indicative of myocarditis and pericarditis, as described below.

Cumulative Post-Marketing Safety Database Review of Myocarditis and Pericarditis

As "myocarditis and pericarditis" is a safety concern for BNT162b2, analysis of new information collected from the post-marketing data sources is provided in the monthly SMSRs, Section 9.5. The SMSR evaluation provides detailed information on the interval potentially relevant cases[2], with separate discussion provided for myocarditis and pericarditis cases, as well as sub-group analyses by age, medical confirmation, and Brighton Collaboration Level assessment.

For the purpose of this response, the MAH conducted a cumulative analysis of myocarditis and pericarditis covering up to and including 28 October 2021(as of 29 October 2021), including separate summaries by condition (myocarditis, pericarditis), age group and gender using the same search criteria as the SMSR.

The cumulative descriptive analysis of post-marketing cases of myocarditis and pericarditis, by age strata and gender is provided in **ANNEX 2** to this AR (not all tables are reproduced here).

Table 5. Overview of Post-Marketing Cases Reporting Myocarditis and Pericarditis

Ae group	Female		Male		Gender Unk		TOTAL
	Total	BC1[b]	Total	BC1	Total	BC1	Total

[1] This refers also to post-EUA/conditional marketing authorisation approval data sources. Only cases having a complete workflow cycle in the safety database (meaning that they went to Distribution or Closed workflow status at least once) have been included. This approach will prevent the inclusion of cases initially received and not fully processed since cases in early steps of the workflow process may still undergo changes and not accurately reflect final data.
[2] MedDRA Search criteria: PTs Autoimmune myocarditis; Eosinophilic myocarditis; Giant cell myocarditis; Hypersensitivity myocarditis; Immune-mediated myocarditis; Myocarditis; Autoimmune pericarditis, Pericarditis; Pericarditis adhesive; Pericarditis constrictive; Pleuropericarditis.

Table 5. Overview of Post-Marketing Cases Reporting Myocarditis and Pericarditis

Myocarditis							
5-11 years	0	-	1	0	0	-	1
12-15 years	31	3	189	12	4	0	224
16-17 years	38	6	281	40	3	0	322
18-24 years	163	7	711	85	9	0	883
25-29 years	98	6	308	32	5	0	411
30-39 years	207	10	436	41	5	0	648
≥ 40 years	554	33	669	51	10	0	1233
Age unk	62	0	151	7	171	1	384
Total	**1153**	**65**	**2746**	**268**	**207**	**1**	**4106**
Pericarditis							
5-11 years	0	-	0	-	0	-	0
12-15 years	26	0	68	1	0	-	94
16-17 years	30	1	61	1	0	-	91
18-24 years	153	0	260	0	2	0	415
25-29 years	155	0	187	0	4	0	346
30-39 years	315	0	332	3	10	0	657
≥ 40 years	772	1	730	6	9	0	1511
Age unk	55	0	81	0	47	0	183
Total	**1506**	**2**	**1719**	**11**	**72**	**0**	**3297**

b. In order to provide a more specific analysis the MAH, starting with cases reported on 1 October 2021 forward, limited the BC criteria classification to cases of myocarditis and pericarditis that are both medically confirmed and having a time to onset ≤ 21 days. BC assessment of Pericarditis has been conducted only for cases reported starting 15 July 2021, the date of publishing of BC criteria for Pericarditis. Prior to that date cases were assessed based on acute and chronic classification.

In order to retrieve the most relevant data on the characteristics, severity, duration and outcome of myocarditis and pericarditis after vaccination with BNT162b2, as per the PRAC request, the MAH has conducted a tailored and detailed review of the myocarditis and pericarditis medically confirmed cases assessed as Brighton Collaboration Level 1,[xxvi] as these cases provide the highest level of diagnostic confirmation. However, the BC classification does not account for aspects which would inform on the causal association with the vaccine administration, such as time to onset, patient medical history and alternative aetiologies, and these were therefore reviewed separately.

BC level 1 - Myocarditis

Brighton Collaboration (BC) assessment of cases is shown in Table 6. Of the total 4106 reported cases of Myocarditis, there were 334 cases (8.1% of myocarditis dataset, 0.06% of the cumulative dataset) assessed as BC level 1, where the case narratives reflected either a positive biopsy or positive findings on a cardiac MRI or an Echocardiogram associated with elevated Troponin pointing to a confirmed Myocarditis. The majority of this confirmed Myocarditis cluster of cases involved males (268) in addition to 65 females and 1 case of unreported gender.

The age of the patients ranged from 12-85 years old (MN:31.7). Additionally, these cases reflected a time-to-onset (TTO) (less than 21 days)- and a dose sequence (post second dose Comirnaty received)-dependent pattern of event occurrence. Specifically, 176 cases occurred after the second injection while 97 cases occurred after the first. There were 209 cases occurring on or before 21 days post vaccination while 18 cases occurred between 22 to 30 days, 17 between 31 to 100 days, and the rest of an unknown latency.

France was the most frequently reporting country (129) in this BC level 1 cluster of cases followed by Germany (45), Spain (33) and the US (21). The most common age segment of patients in this cluster was 18-24 years of age (92) cases. Nineteen of the BC level 1 cases had history of COVID-19 infection, 14 had history of Myocarditis and 2 cases had history of Pericarditis.

All of the cases were assessed as serious adverse events. The most common cause of seriousness was hospitalization. There were five cases with fatal outcome 3 males and 1 female majority from Japan (3), 1 from Israel and 1 from Sweden ranging in age between 50 to 85 years of age (MN:72.4). All BC level 1 cases with fatal outcome reported a medical history, which included DM, prostatic hyperplasia, plasma cell myeloma, thyroid neoplasm, dyslipidaemia, cerebral infarction and oesophageal oedema. No autopsy has been performed for any of these cases to confirm that Myocarditis was the cause of death. Only one of the cases with fatal outcome had a positive COVID-19 test result or was exposed to COVID-19 infection prior to vaccine administration.

Table 6. BC Assessment of Cases of Myocarditis Through 28 October 2021

Brighton Collaboration Level	Number of cases
BC 1	334
BC 2	143
BC 3	62
BC 4	2624
BC 5	20

Comment PRAC Rapporteur:

Generally, the updated (covering up to and including 28 Oct 2021) cumulative review of BC level 1 Myocarditis did not identify new safety findings:

The majority of cases were males (268) in addition to 65 females and 1 case of unreported gender. The age of the patients ranged from 12-85 years old (mean:31.7). More cases (n=176) occurred after the 2nd injection, while 97 cases occurred after the first. There were 209 cases occurring on or before 21 days post vaccination while 18 cases occurred between 22 to 30 days, 17 between 31 to 100 days, and the rest of an unknown latency.

The most common cause of seriousness was hospitalization. There were five cases with fatal outcome 3 males and 1 female majority from Japan (3), 1 from Israel and 1 from Sweden ranging in age between 50 to 85 years of age. All BC level 1 cases with fatal outcome reported a medical history, which included DM, prostatic hyperplasia, plasma cell myeloma, thyroid neoplasm, dyslipidaemia, cerebral infarction and oesophageal oedema.

In addition the MAH also provided an comprehensive cumulative overview of relevant data (*i.e.* characteristics, severity, duration and outcome) of all (not only BC 1) myocarditis cases following vaccination with Comirnaty, by age stratum.

Subjects aged 5-11 years: There was 1 medically confirmed case involving a patient who experienced myocarditis, leading to hospitalization 4 days after Dose 2, with an unknown clinical outcome.

MS1 comment (endorsed by PRAC Rapporteur):

The MAH provided a cumulative review of relevant data, and included a medically confirmed case of myocarditis involving a patient who experienced myocarditis, leading to hospitalization 4 days after dose 2, with an unknown clinical outcome. This case is not consistent with earlier observations of myocarditis, and in view of the recent approval of Comirnaty for children aged 5 to 11 years, additional data on the outcome of this case is expected.

Only the data for age groups 12-15 years (Table 7) and 16-17 years (Table 8) are reproduced here.

Table 7. Myocarditis in Subjects aged 12-15 years (N=224)

Characteristics		Female No. of Cases	Male No. of Cases	Unknown No. of Cases
No. of Cases		31	189	4
Medically Confirmed	Yes	29	151	3
	No	2	38	1
Country of occurrence (≥10 occurrences)	Hong Kong	9	38	0
	Germany	3	27	3
	US	0	25	0
	France	5	18	0
	Japan	4	9	0
	Israel	0	10	0
Relevant PT	Myocarditis[Error! Reference source not found.]	31	189	4
Hospitalization Required/prolonged	Yes	20	146	3
	No	11	43	1
Relevant suspect dose	Dose 1	7	44	1
	Dose 2	20	124	2
	Unknown	4	21	1
Time to Onset n=170	≤ 24 hours	2	7	0
	1-5 days	12	118	3
	6-13 days	6	9	0
	14-21 days	2	5	0
	22-48 days	1	5	0
	Unknown	8	45	1
Event Outcome	Not resolved	3	31	1
	Resolved	10	52	0
	Resolving	7	52	0
	Unknown	11	54	3
Duration of event[Error! Reference source not found.] n=15, median=4	Up to 3 days	0	6	0
	4-6 days	2	4	0
	7-10 days	2	1	0

a. All serious occurrences.
b. For those cases where the event resolved.

Table 8. Myocarditis in Subjects aged 16-17 years (N=322)

Characteristics		Female No. of Cases	Male No. of Cases	Unknown No. of Cases
No. of Cases		38	281	3
Medically Confirmed	Yes	29	198	3
	No	9	83	0
Country of occurrence (≥10 occurrences)	Germany	5	70	0
	France	5	28	0
	Australia	2	22	1
	Israel	0	24	1
	US	3	21	0
	Spain	2	18	0
	Italy	6	10	1
	Japan	1	11	0
	UK	4	8	0
	Austria	1	9	0
Relevant PT	Myocarditis[Error! Reference source not found.]	38	281	3
Hospitalization Required/prolonged	Yes	28	242	1
	No	10	40	2
Relevant suspect dose	Dose 1	14	55	0
	Dose 2	15	178	2
	Dose 3	0	1	0
	Unknown	9	47	1
Time to Onset n=248	≤ 24 hours	3	13	0
	1-5 days	23	143	0
	6-13 days	3	33	1
	14-21 days	2	8	1
	22-52 days	2	16	0
	Unknown	5	68	1
Event Outcome	Fatal	0	1	0
	Not resolved	9	68	0
	Resolved	10	66	0
	Resolved with sequelae	0	4	0
	Resolving	17	81	1
	Unknown	2	61	2
Duration of event[Error! Reference source not found.] n=36, median=4	Up to 3 days	3	13	0
	4-6 days	1	8	0
	7-10 days	1	7	0
	11-20 days	1	2	0

a. All serious occurrences.
b. For those cases where the event resolved.

Comment PRAC Rapporteur:

These data on characteristics/demographic, clinical disease course and outcome are consistent with earlier observations. Although cases are considered serious due to the required hospitalization, in cases <18 years of age the duration of the event (where reported to be resolved) was between 3 to 20 days (median 4 days).

However, it is noted that still in a considerable number of cases no information on the duration of event, or whether the events were resolved is available. The MAH is expected to keep the clinical course, severity, outcome, sequelae under close monitoring in both spontaneous reports and ongoing

and planned observational studies. The Rapporteur should be notified immediately in case of unexpected findings or trends.

A similar picture was observed in the cases above 18 years, with a median duration of event between 3 to 6 days.

Based on the above review the current wording in the SmPC section 4.4 regarding disease course is still considered adequate

BC level 1 - Pericarditis

Brighton Collaboration (BC) assessment of pericarditis reports is shown in Table 9. Of the total reported cases of Pericarditis, there were 13 cases (0.4% of the pericarditis dataset, 0.002% of the cumulative dataset) assessed as BC level 1. The majority of this confirmed Pericarditis diagnosis cluster of cases were males (11) in addition to 2 females. The age of the patients ranged from 15-93 years old (MN:44.3).

Additionally, these cases reflected a TTO (less than 21 days)- and a dose sequence (post second vaccination)-dependent pattern of event occurrence. Specifically, 6 cases occurred after the second injection while 4 cases occurred after the first, 1 after the booster and 1 without a reported dose sequence. There were 12 cases occurring on or before 21 days post vaccination while 1 case had an unknown latency.

France was the most frequently reporting country (6) in this BC level 1 cluster of cases. The most common age segment of patients in this cluster was above 40 years of age (7) cases. One of the BC level 1 cases had history of COVID-19 infection and 1 case of Pericarditis. All of the cases were assessed as serious adverse events. The most common cause of seriousness was hospitalization. None of these cases had a fatal outcome.

Table 9. BC Assessment of Cases of Pericarditis Through 28/Oct/2021

Brighton Collaboration Level	Number of cases
BC 1	13
BC 2	33
BC 3	18
BC 4	2454
BC 5	None

Comment PRAC Rapporteur:

Generally, the updated (covering up to and including 28 Oct 2021) cumulative review of BC level 1 pericarditis cases did not identify new safety information:

Of the total reported cases of Pericarditis, there were 13 cases (0.4% of the pericarditis dataset, 0.002% of the cumulative dataset) assessed as BC level 1. The majority of this confirmed Pericarditis diagnosis cluster of cases were males (11) in addition to 2 females. The age of the patients ranged from 15-93 years old (MN:44.3).

These cases reflected a TTO (less than 21 days)- and a dose sequence (post second vaccination)-dependent pattern of event occurrence. Specifically, 6 cases occurred after the second injection while 4 cases occurred after the first, 1 after the booster and 1 without a reported dose sequence. There were 12 cases occurring on or before 21 days post vaccination while 1 case had an unknown latency.

The most common age segment of patients in this cluster was above 40 years of age (7) cases. One of the BC level 1 cases had history of COVID-19 infection and 1 case of Pericarditis. All of the cases were assessed as serious adverse events. The most common cause of seriousness was hospitalization. None of these cases had a fatal outcome.

In addition the MAH also provided an comprehensive cumulative overview of relevant data (*i.e.* characteristics, severity, duration and outcome) of all (not only BC 1) pericarditis cases following vaccination with Comirnaty, by age stratum. Only the data for age groups 12-15 years (Table 10) and 16-17 years (Table 11) are reproduced here. There were no cases of pericarditis in the age group 5-11 years.

Table 10. Pericarditis in Subjects aged 12-15 years (N=94)

Characteristics		Female No. of Cases	Male No. of Cases	Unknown No. of Cases
No. of Cases		26	68	0
Medically Confirmed	Yes	23	62	0
	No	3	6	0
Country of occurrence (≥10 occurrences)	Hong Kong	6	24	0
	Australia	7	9	0
	Italy	9	4	0
Relevant PT**Error! Reference source not found.**	Pericarditis	26	68	0
Hospitalization Required/prolonged	Yes	5	24	0
	No	21	44	0
Relevant suspect dose	Dose 1	7	18	0
	Dose 2	10	38	0
	Unknown	9	12	0
Time to Onset n=53	≤ 24 hours	2	2	0
	1-5 days	6	25	0
	6-13 days	0	7	0
	14-21 days	4	3	0
	22-31 days	1	3	0
	Unknown	13	28	0
Event Outcome	Not resolved	10	11	0
	Resolved	2	15	0
	Resolved with sequelae	0	1	0
	Resolving	3	15	0
	Unknown	11	26	0
Duration of event**Error! Reference source not found.** n=5, median=6	Up to 3 days	0	1	0
	4-6 days	0	2	0
	7-25 days	1	1	0

a. All serious occurrences.
b. For those cases where the event resolved.

Table 11. Pericarditis in Subjects aged 16-17 years (N=91)

Characteristics		Female No. of Cases	Male No. of Cases	Unknown No. of Cases
No. of Cases		30	61	0
Medically Confirmed	Yes	25	49	0
	No	5	12	0
Country of occurrence (≥5 occurrences)	Australia	7	16	0
	France	11	8	0
	Italy	7	5	0
	US	1	4	0
Relevant PT[Error! Reference source not found.]	Pericarditis	30	61	0
Hospitalization Required/prolonged	Yes	9	29	0
	No	21	32	0
Relevant suspect dose	Dose 1	11	19	0
	Dose 2	12	24	0
	Unknown	7	18	0
Time to Onset n=61	≤ 24 hours	2	3	0
	1-5 days	10	23	0
	6-13 days	5	8	0
	14-21 days	3	2	0
	22-37 days	2	3	0
	Unknown	8	22	0
Event Outcome	Not resolved	8	13	0
	Resolved	3	11	0
	Resolving	13	17	0
	Unknown	6	20	0
Duration of event[Error! Reference source not found.] n=6, median=19	Up to 3 days	0	1	0
	4-6 days	1	0	0
	7-43 days	1	3	0

c. All serious occurrences.
d. For those cases where the event resolved.

Comment PRAC Rapporteur:

These data on characteristics/demographic, clinical disease course and outcome are consistent with earlier observations. Although cases are considered serious due to the required hospitalization, in cases <18 years of age the duration of the event (when reported) was between 3 to 43 days (median 6-19 days). A similar picture was observed in the cases above 18 years, with a median duration of event between 7 to 13 days (data not reproduced here).

As with the myocarditis cases, also still in a considerable number of pericarditis cases no information on the duration of event, or whether the events were resolved is available. The MAH is expected to keep the clinical course, severity, outcome, sequelae under close monitoring in both spontaneous reports and ongoing and planned observational studies. The Rapporteur should be notified immediately in case of unexpected findings or trends.

Based on the above review the current wording in the SmPC section 4.4 regarding disease course is still considered adequate.

Myocarditis and Pericarditis (ages 12-15)

Out of the total 7403 cumulative cases reported for Myocarditis and Pericarditis, there were 224 cases reported in subjects aged 12-15 years old reported to Myocarditis and 94 cases reported to Pericarditis in this age group. Of the Myocarditis cases 15 were classified as BC level 1, 9 cases as BC level 2, 132 cases as BC level 4 and 1 case as BC level 5. The majority of this age cluster were males 189 in addition to 31 females and the rest with unreported gender. The most common cause of seriousness was hospitalization. None of the cases in this age group had a fatal outcome. One had history of Myocarditis, 1 with cardiac murmur and 1 with congenital heart disease. The most commonly reporting country in this age group was Hong Kong (31 cases). For Pericarditis assessed for BC classification, 1 case was assessed as BC level 1, 6 cases as BC level 2, and the rest as BC level 4. The overall cases were 43 males and 16 females. The most common cause for seriousness was hospitalization. None of the cases of Pericarditis in this age group had a fatal outcome. Two cases had a medical history of Pericarditis and 1 case of COVID-19 infection. The most commonly reporting country in this age group was Hong Kong (17 cases).

Comment PRAC Rapporteur:

See previous comments.

Summary of Myocarditis and Pericarditis BC level 1

It is worth noting that the majority of the BC level 1 cases of Myocarditis and Pericarditis during the aforementioned reporting period lacked proper accounting of case duration, , outcome, concomitant medication and/or investigative measures to exclude alternate aetiologies such as viral infection, cardiovascular disorder, all of which precluded proper medical assessment of causality between the event occurrence and vaccine administration. The assessment of cases continues to point to a gender (male)-, age (higher for 16-19 year olds)-, TTO (less than 21 days)- and dose-dependent (post second vaccination) pattern of occurrence in Myocarditis as listed in the SmPC and the same for Pericarditis albeit in a higher age demographic.

Given this cluster of cases for confirmed Myocarditis and pericarditis constituted the minority of the total reported cases throughout the cumulative period (approximatively 5% of myocarditis and pericarditis cases, or 0.06% of the cumulative vaccine dataset), this analysis does not result in changing the MAH's position stated in the product label regarding the risk of Myocarditis or Pericarditis.

Comment PRAC Rapporteur:

Also see comments above regarding all (not only BC 1) reported myocarditis and pericarditis cases. The MAH's conclusions regarding BC 1 cases are noted.

Post-marketing Safety Summary

Overall, the review of the safety database found that the reporting of myocarditis and pericarditis cases increased with expanded vaccination campaign that now approached approximately 2 billion doses. However, these cases represent a minority of the overall vaccine post-marketing dataset (1.3%).

A minority of cases (10%) qualify for BC level 1 classification, and thus with a high degree of diagnostic accuracy. Even in these cases where myocarditis or pericarditis diagnosis is confirmed, causality assessment was not possible for most of these cases due to lack of proper accounting of case

duration, severity, outcome, concomitant medications and/or investigative measures to exclude alternate aetiologies such as viral infections, cardiovascular disorders. These limitations of the post-marketing data are important factors that preclude proper medical assessment of causality between the event occurrence and vaccine administration. The assessment of cases continues to point to a gender (male)-, age (higher for 16-19 year olds)-, TTO (less than 21 days)- and dose-dependent (post second vaccination) pattern of occurrence in Myocarditis as listed in the SmPC and the same for Pericarditis albeit a higher age demographic.

Comment PRAC Rapporteur:

The MAH's general conclusion is endorsed that assessment of cases continues to point to a gender (male), age (higher for 16-19 year olds), TTO (less than 21 days) and dose dependent (post second vaccination) pattern of occurrence in Myocarditis as listed in the SmPC and the same for Pericarditis albeit a higher age demographic.

The limitations as noted by the MAH are acknowledged.

Risk Management Strategy

The EU RMP includes a detailed description of the additional pharmacovigilance activities and their milestones to monitor and characterise the risk of myocarditis and pericarditis and a summary is presented herein. Studies C4591021(EU), C4591038 (former C4591021 sub-study) (EU), C4591011 (US), C4591012 (US), and C4591009 (US) will describe the incidence of myocarditis/pericarditis following Comirnaty vaccination overall, and stratified by age group, gender, race/ethnicity (if feasible), dose, and risk interval using structured information and following case confirmation via medical record review where feasible. To assess the magnitude of risk, these studies include comparative methods (self-controlled analyses, and analyses involving a separate comparator group).

Relative risk (RR) estimates from comparative analyses will be obtained overall and stratified by the same factors as described above when supported by sufficient cell counts.

To evaluate long-term outcomes, myocarditis/pericarditis-specific analytic endpoints in currently planned or ongoing studies C4591009, C4591011, C4591012, C4591021 and C4591038 (former C4591021 substudy) will assess the natural history of post-vaccination myo-/pericarditis, e.g., recovery status (medical record review) and/or identification of serious cardiovascular outcomes (structured data) within 1 year of myo-/pericarditis diagnosis among individuals vaccinated with COMIRNATY as well as individuals not vaccinated with a COVID-19 vaccine.

In addition, a long-term primary data collection study is C4591036 (former Pediatric Heart Network (PHN), to evaluate the clinical course, risk factors, long-term sequelae, and quality of life of post-vaccine myocarditis/pericarditis over a 5-year period.

Finally, study C4591021 will also estimate the time trend, in relation to DHPC letter dissemination, of the proportion of individuals who received real-world clinical assessments for myocarditis/pericarditis following Comirnaty vaccination.

For complete details, please refer to the EU RMP.

MAH Discussion and Conclusion

In the large, controlled, pivotal study C4591001, myocarditis and pericarditis cases have been reported infrequently, and no imbalance was seen between placebo and active arm for events of myocarditis or

pericarditis events. Efforts are ongoing to evaluate the background rate of troponin abnormalities in healthy study participants prior to vaccination, to inform whether or not troponin may represent a useful biomarker for presence of subclinical myocarditis or pericarditis (if such conditions exist).

The comprehensive evaluation of potential mechanisms for myocarditis or pericarditis found, to date, there is nothing of substance from the nonclinical perspective to identify a potential root cause to consider an established mechanism. Further, animal models of myocarditis or pericarditis are not well established and therefore do not serve as a viable model to perform additional nonclinical assessments.

In the interpretation of the epidemiology data, it is important to note that data described above reflect rates from different regions, different data sources (e.g. spontaneous reports, registries, administrative), and using different methodologies. This could explain, at least partially, the variability in the reported rates between studies. Therefore, an integrated or side-by-side analysis is not appropriate, and it is not possible to use the available data to provide a single estimate of risk. Overall, in aggregate, the studies reported higher risk after Dose 2 compared to Dose 1, and among younger males compared to older males or females of any age post-vaccination. Risk was lower for individuals 12-15 years, higher for 16-19 years, and generally declining thereafter with age. Reported risk for myocarditis after COVID-19 infections was higher when compared with reported rates for individuals without COVID-19 infection or after vaccination.

The review of the post-marketing cases of myocarditis found that although the number of cases increases as the vaccine exposure increases, the profile of cases remains largely unchanged. Within this profile, a minority of cases (10%) qualify for BC level 1 classification, and thus provide a high degree of diagnostic accuracy. Even in these cases where myocarditis or pericarditis diagnosis is confirmed, the review of data to assess causality reveals that cases lack proper accounting of case duration, severity, outcome, concomitant medication and/or investigative measures to exclude alternate aetiologies such as viral infections or cardiovascular disorders. These limitations of the post-marketing data are important factors that preclude proper medical assessment of causality between the event occurrence and vaccine administration.

According to the EU SmPC Guideline[xxvii] and aligned Pfizer methodology for estimation of ADR frequencies, the estimation of the frequency of an adverse reaction depends on the data source, the quality of data collection and causality evaluation. Furthermore, the frequency of adverse reactions should be derived from pooled placebo-controlled studies if these data are available and the databases are sufficiently large to be informative and be represented by crude incidence rates. Furthermore, the guidance clarifies that frequencies based on reporting rates from a spontaneous reporting system should not be used to assign frequency category.[xxvii]

The EU SmPC provides ADR frequency aligned with the above guidance, with CIOMS ADR frequency categories based on the C4591001, as the largest, controlled clinical trial, and most representative of the safety profile of the vaccine. However, the use of the C4591001 study results, as per the EU SmPC dataset, or the updated analyses described in section 3.2 are not appropriate to support a frequency for myocarditis and pericarditis since the case particulars do not support a relationship with the vaccination in all cases, and the fact that patients in placebo arm also reported relevant events further confounds the assessment of how informative the clinical trial rates are to adequately inform the HCP and patient on the magnitude of this risk. Although additional epidemiological data are emerging as described in Section 0, it is notable that the results vary by type of study, region, data source (spontaneous reporting versus chart review), and thus, no integrated analysis can be produced to reliably estimate the frequency of the ADR.

Additionally, several post-marketing studies are ongoing or planned to further characterize this risk (see Section 0 and the EU RMP). Until such data become available, the frequency of 'Not known' best represents the level of knowledge regarding the frequency of this ADR in the individuals receiving vaccination with BNT162B2.

Overall, no new or significant information regarding myocarditis or pericarditis became available. The reported data continues to align with the information presented in the EU SmPC. Therefore, no changes to the product information or risk management strategy are warranted. Myocarditis and pericarditis are important identified risks in the EU RMP and subject to close monitoring and extensive pharmacovigilance activities, routine and additional. The positive benefit risk of the BNT162B2 vaccine remains unchanged and favourable.

Comment PRAC Rapporteur:

See previous comments regarding ADR frequency and refinement of SmPC section 4.4 wording.

It is noted that also randomised clinical trials have limitations as is outlined in the SmPC Guidance:

'Furthermore, the frequency of adverse reactions should be derived from pooled placebo-controlled studies ***if these data are available and the databases are sufficiently large to be informative and be represented by crude incidence rates.****'*

A vaccine exposure of 20,000 subjects in the pivotal RCT may not be sufficient, also considering the representation of the population below 18 years-of-age.

Post-scriptum

The MAH is grateful for the chance to review the draft manuscript entitled "SARS-CoV-2 vaccination and Myocarditis in a Nordic Cohort Study of 23 Million Residents" by Karlstad *et al.* The above conclusions remain unchanged after the review of the article. The data reflecting the risk of Myocarditis following the receipt of BNT162b2 vaccine demonstrated in this manuscript are consistent with the information already reported in the Comirnaty EU SmPC (*i.e.* sections 4.4 and 4.8) denoting an age-, gender-, dose sequence and latency-dependent pattern of event occurrence occurring most commonly in younger males following the second dose within the first 14 days post administration. While it is worth noting that key limitations in the manuscript, as recognized by the Authors, are based on event detection stemming from hospital admission or discharge primary and secondary codes without access to the main reason for hospitalization, cardiac imaging, troponin values or description on hospital length of stay, the incidence rate of Myocarditis reflected following vaccination with Comirnaty is not higher than the reported data from other studies as described in the Epidemiology section. As per the MAH's post authorization safety analysis, cases of Myocarditis typically tend to respond to standard of care, which generally includes precautionary admission to hospital, and with very rare incidence of life-threatening reaction. Notable in the manuscript is the higher rate of these events in subjects receiving doses of different vaccines. Interchange of vaccine products and myocarditis/pericarditis are closely monitored by MAH.

It is the MAH's conclusion that this manuscript does not provide any new significant information on the risk of Myocarditis/pericarditis following vaccination with Comirnaty as described in the EU SmPC and the benefit risk balance of the BNT162b2 vaccine. These events will continue to be monitored and analyzed in real time for further evaluation.

Comment PRAC Rapporteur:

The MAH's position is noted.

The MAH noted the higher rate of these events in subjects receiving doses of different vaccines. Interchange of vaccine products and myocarditis/pericarditis are closely monitored by MAH. This is endorsed.

See *Section 3.3 Assessment of additional data submitted by MPA (i.e. Nordic study)* of this AR for the PRAC Rapporteur's review of the paper of Karlstad *et al.*

3.2. Discussion on MAH responses

The MAH provided an updated cumulative review (up to 28 Oct 2021) to in response to the PRAC's List of Questions.

Overall

The MAH's general conclusion is endorsed that assessment of cases continues to point to a gender (male), age (higher for 16-19 year olds)-, TTO (less than 21 days)- and dose-dependent (post second vaccination) pattern of occurrence in Myocarditis as listed in the SmPC and the same for Pericarditis albeit a higher age demographic.

Myocarditis

The updated cumulative review of BC level 1 Myocarditis cases did not identify new safety information:

- The majority of cases were males (268) in addition to 65 females and 1 case of unreported gender. The age of the patients ranged from 12-85 years old (MN:31.7). More cases (n=176) occurred after the 2nd injection, while 97 cases occurred after the first. There were 209 cases occurring on or before 21 days post vaccination while 18 cases occurred between 22 to 30 days, 17 between 31 to 100 days, and the rest of an unknown latency.
- The most common cause of seriousness was hospitalization. There were five cases with fatal outcome 3 males and 1 female majority from Japan (3), 1 from Israel and 1 from Sweden ranging in age between 50 to 85 years of age. All BC level 1 cases with fatal outcome reported a medical history, which included DM, prostatic hyperplasia, plasma cell myeloma, thyroid neoplasm, dyslipidaemia, cerebral infarction and oesophageal oedema.

In addition to evaluation of BC level 1 cases the MAH also provided a comprehensive cumulative overview of relevant data (*i.e.* characteristics, severity, duration and outcome) of all (not only BC 1) myocarditis cases following vaccination with Comirnaty by age stratum. Data on characteristics/demographic, clinical disease course and outcome are consistent with earlier observations. Although cases are considered serious due to the required hospitalization in cases <18 years of age the duration of the event (when reported) was between 3 to 20 days (median 4 days). A similar picture was observed in the cases above 18 years, with a median duration of event between 3 to 6 days.

However, it is noted that still in a considerable number of cases no information on the duration of event, or whether the events were resolved is available. The MAH is expected to keep the clinical course, severity, outcome, sequelae under close monitoring in both spontaneous reports and ongoing and planned observational studies. The Rapporteur should be notified immediately in case of unexpected findings or trends.

Pericarditis

The updated cumulative review of BC level 1 pericarditis cases did not identify new safety information:

- Of the total reported cases of Pericarditis, there were 13 cases (0.4% of the pericarditis dataset, 0.002% of the cumulative dataset) assessed as BC level 1. The majority of this confirmed Pericarditis diagnosis cluster of cases were males (11) in addition to 2 females. The age of the patients ranged from 15-93 years old (MN:44.3).
- These cases reflected a TTO (less than 21 days)- and a dose sequence (post second vaccination)-dependent pattern of event occurrence. Specifically, 6 cases occurred after the second injection while 4 cases occurred after the first, 1 after the booster and 1 without a reported dose sequence. There were 12 cases occurring on or before 21 days post vaccination while 1 case had an unknown latency.
- The most common age segment of patients in this cluster was above 40 years of age (7) cases. One of the BC level 1 cases had history of COVID-19 infection and 1 case of Pericarditis. All of the cases were assessed as serious adverse events. The most common cause of seriousness was hospitalization. None of these cases had a fatal outcome.

In addition to evaluation of BC level 1 cases the MAH also provided a comprehensive cumulative overview of relevant data (*i.e.* characteristics, severity, duration and outcome) of all (not only BC 1) pericarditis cases following vaccination with Comirnaty, by age stratum. These data are consistent with earlier observations. Although cases are considered serious due to the required hospitalization, in cases <18 years of age the duration of the event (when reported) was between 3 to 43 days (median 6-19 days). A similar picture was observed in the cases above 18 years, with a median duration of event between 7 to 13 days.

As with the myocarditis cases, also still in a considerable number of pericarditis cases no information on the duration of event, or whether the events were resolved is available. The MAH is expected to keep the clinical course, severity, outcome, sequelae under close monitoring in both spontaneous reports and ongoing and planned observational studies. The Rapporteur should be notified immediately in case of unexpected findings or trends.

Characteristics, severity, outcome

Based on the above reviews of characteristics, severity, duration and outcome of myocarditis and pericarditis the current wording in the SmPC section 4.4 regarding disease course is still considered adequate.

Pathophysiological mechanism

At the moment no clear mechanism can be established based on the available evidence. The following aspects were highlighted:

- Although there are rare reports of vaccine-associated myocarditis (e.g. influenza vaccines) and extensive reporting on smallpox vaccine-associated myocarditis, no pathophysiological cause has been identified. Underlying genetic predisposition to myocarditis may contribute to post-vaccination-associated myocarditis, but there is little in the published literature to support such a conclusion at this time.

- Four cases in the pivotal clinical (2 in placebo and 2 in vaccine arm; none of which were vaccine-related by investigator) did not indicate direct toxicity (*i.e.* a direct effect of the mRNA vaccine or the expressed spike protein on the heart).
- No effects on the heart in any of the preclinical study program were observed (including 2 GLP repeat dose toxicity studies and a GLP developmental and reproductive toxicity study).
- Biodistribution studies using a modRNA-LNP encoding luciferase (surrogate protein) identified luciferase expression only in the region of the IM administration and in the liver. Liver luciferase expression is consistent with LNP distribution and most likely reflects local mRNA expression of the protein and not distribution of luciferase from systemic exposure of secreted luciferase. Systemic exposure of Spike protein with binding to ACE2 in any tissues, potentially initiating off-target immune responses, would be not be expected.
- ACE2 expression is lower in the heart relative to other tissues
- The potential risk for molecular mimicry as a cause for myocarditis/pericarditis was evaluated by the MAH internally. Peptide sequences from the spike protein antigen of Comirnaty were compared against human peptides by homology search. There were no matches against human peptides to the spike peptides of greater than or equal to 9 mers. Matches for smaller peptides were similar to what has been reported previously.[xxviii] However, these matches would not explain the predominance of younger males associated with myocarditis. Exacerbation of subclinical/asymptomatic myocarditis related to COVID-19 mRNA vaccination innate immune activation is a possible explanation which is consistent with both the sex and age groups affected, as well as the transient nature of the finding clinically.
- In published reports evaluated by MAH, viral serology for other main cardiotropic viruses were negative in patients exhibiting clinical signs of myocarditis or pericarditis. Consequently, a causal role of the vaccine is an at least reasonable possibility, in absence of these alternative etiologies.

Within the context of routine Pharmacovigilance the MAH should continue to scrutinise any relevant safety findings and published scientific literature regarding the pathophysiological mechanism.

Regarding ADR frequency in SmPC section 4.8

The PRAC Rapporteur considers that the frequency assignment **unknown is not accepted**.

The PRAC Rap notes that the current frequency category in 4.8 (frequency unknown) does not adequately represent the current body of evidence gathered in the post-marketing phase based on **observational studies**.

The difficulty in accurately estimating ADR frequencies from post-marketing sources is acknowledged (*e.g.* due to absence of accurate denominator data, potential underestimation of actual cases). However the MAH's proposal of Frequency category *'Unknown'* is **not accepted,** as this does not provide useful guidance for the prescriber or patient and may lead to falsely underestimate the relevance of this risk.

The MAH has cited guidance which refers to labelling the absolute numbers of cases and ADR frequencies based on spontaneous reporting systems **exclusively**. This is not entirely applicable to the current situation as the MAH has referred to several post-marketing sources, including well-conducted observational studies (hence not spontaneous reporting systems exclusively) that have provided frequency estimates of myocarditis and pericarditis following vaccination, albeit variable in different

patient populations/jurisdictions. However, it should be noted that the variability margins can be taken into account in the representation in the ADR table in SmPC section 4.8, because the frequency designations are represented as ranges.

In addition to the literature cited by the MAH, the Rapporteur has been notified of **two further studies** by the **EMA/VAC4EU** (retrospective, multi-database, cohort study) and **EPI-PHARE** - Scientific Interest Group (GIS) ANSM-CNAM (matched case-control study in the FR national health data system (SNDS)), which are briefly summarised below in **Sections 3.5 and 3.6** of this AR. Full reports are included in **ANNEX 3 and 4**, respectively.

Based on the currently available combined body of evidence from clinical trials and post-marketing Observational studies the incidence for myocarditis ranged from **0.1 to 1.6 per 10,000**, hence a frequency category **Very Rare < 1 per 10,000** in the SmPC section 4.8 would be more appropriate. Note that this would also be more in line with the wording already present in **SmPC section 4.4**. The rationale for the frequency category could be explained in sub-section *c "Description of selected adverse reactions"*. *I.e.* a footnote could be considered noting that the incidence of myocarditis after the second dose in the younger males was at the high end of the range and would be closer to frequency category rare (≥1/10.000, <1/1.000)

Regarding refinement of SmPC section 4.4

In addition, the current wording should be further refined. The current product information section 4.4 mentions: ***Very rare*** *cases of myocarditis and pericarditis have been observed following vaccination with Comirnaty. These cases have primarily occurred within 14 days following vaccination, more often after the second vaccination, and more often in younger* ***men.***

It is proposed to remove and replace '**men**' (which implies adults only) by '**males**', as also cases have been observed in adolescent males aged below 18 years.

Request for further adjustment of SmPC section 4.4 when more robust data become available

Based on the O/E analyses presented by the MAH (Table 1, Table 2 and Table 3) it is noted that although the absolute number of cases in males is higher, the background incidence in males is also higher. Consequently, the O/E ratios above 1 do not really differ that much between males and females. This aspect is currently not reflected in the current wording in SmPC section 4.4. On the other hand, the numbers of female cases shown here, but also in the epidemiological studies cited by the MAH (as well as those conducted by VAC4EU and EPI-PHARE) are low, especially in the younger females, which raises the question regarding robustness of these estimates.

The MAH should commit to remain closely evaluating the risk estimates in females, and in case more (robust, stable) data would become available, provide a proposal for refined/adjusted the wording in SmPC section 4.4, as appropriate.

3.3. Assessment of additional data submitted by MPA (i.e. Nordic study)

Data is summarized below. Supplementary material has not been reproduced in this AR.

Study Title:

SARS-CoV-2 Vaccination and Myocarditis in a Nordic Cohort Study of 23 Million Residents

Authors: *Karlstad O[1], *Hovi P[2], *Husby A[3,4], Härkäben T[2], Selner RM[1], Pihlström N[5], Hansen JV[3], Gunnes N[1,7], Sundström A[8], Wohlfahrt J[3], Nieminen T[9], Grünewald M[5], Gulseth HL[1], *Hviid A[3,10] and *Ljung [R8,11].

*Drs. Karlstad, Hovi, and Husby and Profs. Hviid and Ljung contributed equally.

Affiliation:

1. Norwegian Institute of Public Health, Department of Chronic Diseases Oslo, Norway
2. Finnish Institute for Health and Welfare, Dept of Public health and Welfare, Helsinki, Finland
3. Statens Serum Institut, Dept of Epidemiology Research, Copenhagen, Denmark
4. Imperial College London, Dept of Epidemiology and Biostatistics, London, United Kingdom
5. Swedish Medical Products Agency, Division of Licensing, Uppsala, Sweden
6. Finnish Institute for Health and Welfare, Health Security, Helsinki, Finland
7. Norwegian Research Centre for Women's Health, Oslo University Hospital, Oslo, Norway
8. Swedish Medical Products Agency, Division of Use and information, Uppsala, Sweden
9. Finnish Institute for Health and Welfare, Information Services, Helsinki, Finland
10. Pharmacovigilance Research Center, Department of Drug Design and Pharmacology, University of Copenhagen, Copenhagen, Denmark
11. Karolinska Institutet, Institute of Environmental Medicine, Stockholm, Sweden

ABSTRACT

Background:

Reports of myocarditis in young males occurring after SARS-CoV-2 mRNA vaccination have emerged.

Methods:

We conducted nationwide cohort studies in Denmark, Finland, Norway and Sweden according to a common protocol and combined results by meta-analysis. We retrieved SARS-CoV-2 vaccinations, hospital diagnoses of myocarditis or pericarditis, and covariates from national registers. We followed all residents 12 years and older from December 27, 2020, until an incident myocarditis or pericarditis, censoring or end-of-study (October 5, 2021). Poisson regression yielded adjusted incidence rate ratios (RRs) and excess rates with 95% confidence intervals (CIs), comparing rates in 28-day and 7-day periods following vaccination with unvaccinated rates.

Results:

Among 23.1 million individuals, (82% vaccinated by end-of-study) we identified 1092 myocarditis and 1154 pericarditis events. Within the 28-day period, second-dose vaccinations with BNT162b2 and mRNA-1273 were associated with higher risk of myocarditis, adjusted RRs 1.86 (95% CI, 1.5-2.3) and 7.2 (5.3-9.8), respectively. In males 16-24 years of age RRs were 5.4 (3.8 to 7.6) and 14.2 (8.4 to 23.8), and excess events 5.7 (3.6 to 7.5) and 18.8 (9.6 to 28.0) per 100,000 vaccinations,

respectively. RRs for the 7-day period were higher. For pericarditis, results pointed in the same direction.

Conclusion:

First- and second-dose vaccinations with mRNA vaccines were associated with higher risk of myocarditis and pericarditis. Associations were strongest for myocarditis in young males after second vaccination: our data are compatible with between 4 and 8 excess events in 28 days per 100,000 after BNT162b2, and between 10 and 28 per 100,000 after mRNA-1273.

INTRODUCTION

The European Medicines Agency (EMA) has approved four vaccines against SARS-CoV-2: BNT162b2 (Pfizer–BioNTech), mRNA-1273 (Moderna), AZD1222 (AstraZeneca), and Ad26.COV2.S (Janssen). The Nordic countries have primarily used the two mRNA vaccines BNT162b2 and mRNA-1273. These vaccines have proven to be efficient and safe, but cases of myocarditis or pericarditis during the first weeks after vaccination have been reported.[1]

Case reports and surveillance data from the United States indicate an increased risk of myocarditis after vaccination with an mRNA vaccine, higher after second dose and higher in young men.[2–7] Israeli data on risk of myocarditis after vaccination with BNT162b2 have shown a higher risk after a second dose and a higher risk in young men.[8,9] Surveillance data from Canada indicates a higher increase of myocarditis after mRNA-1273 than after BNT162b2.10

In nationwide cohort studies in Denmark, Finland, Norway and Sweden, we evaluated the risks of myocarditis and pericarditis following SARS-CoV-2 vaccination in a combined population of 23.1 million individuals. High-quality nationwide registers allowed us to calculate exact unvaccinated and vaccinated person-time at risk for each individual to evaluate the risk by vaccine product, vaccination number, sex, and age.

METHODS

SETTING AND DATA SOURCES

We conducted population-based cohort studies in four Nordic countries (Denmark, Finland, Norway and Sweden) comprising linked data from nationwide health registers on SARS-CoV2 vaccination, myocarditis and pericarditis diagnoses and other covariates (**Suppl Methods**). All Nordic residents are assigned a unique personal identifier at birth or immigration, which we used for linking data between registers. All Nordic countries have universal and tax-financed healthcare systems and reporting to national registers is mandatory, providing near-complete follow-up of all residents over time.[11] Each cohort study was analyzed according to a common protocol and results combined by use of meta-analyses.

Comment PRAC Rapporteur:

Within the supplementary materials details have been provided regarding quality, validity and completeness of the relevant characteristics and outcome variables (*e.g.* vaccination information, COVID testing results, comorbidities). The authors confirmed that vaccination data recorded in the respective registries is complete and accurate, as well as the data on the outcomes.

STUDY POPULATION

We included 23,124,459 million persons aged 12 years and older, consisting of all residents in any of the countries on January 1, 2017, alive and still residing within the country on December 27, 2020. We excluded XXaround20,000XX persons with any myocarditis or pericarditis in inpatient or outpatient hospital care from January 1, 2017, to December 26, 2020 (**Suppl Methods**). [In the supplementary methods it is stated: *"In total, XXX were excluded, whereof 3706 from Denmark, XXX from Finland, 4864 from Norway, and 8477 from Sweden."*].[3]

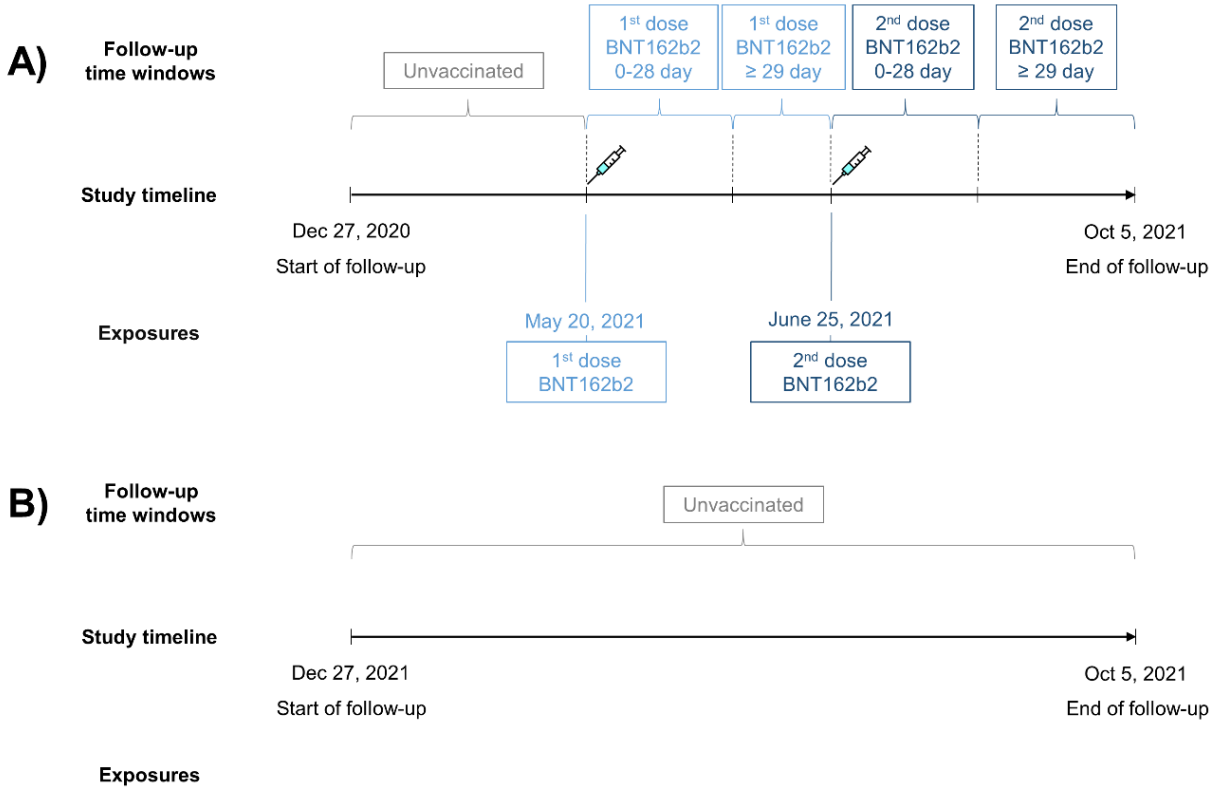
SARS-COV-2 VACCINATION

The Nordic countries implemented national vaccination campaigns against SARS-CoV-2 from December 27, 2020, providing free vaccinations to all residents. Phased distribution plans were implemented prioritizing vaccination of individuals at highest risk of COVID-19 complications, firstly nursing home residents, and subsequently healthcare workers, older age groups, medical risk groups, and finally the youngest age groups. Denmark, Finland and Norway almost exclusively used mRNA vaccines after full or partial discontinuing use of AZD1222 in March 2021 due to reported serious adverse events.[12,13]

Sweden used AZD1222 for a majority of those 65 years and older and mRNA vaccines in other age groups. Ad26.COV2.S has seen very limited use. The Nordic countries have vaccinated 4 to 6 times more individuals with BNT162b2 than with mRNA-1273. We studied risk of myocarditis and pericarditis in 28-day risk periods after administration date of the first and second dose of BNT162b2, mRNA-1273 and AZD1222 (Figure 4).

[3] As provided to the European Medicines Agency.

Figure 4: SCHEMATIC ILLUSTRATION OF FOLLOW-UP TIME WINDOWS IN THE COHORT STUDY FOR AN INDIVIDUAL WHO WAS A) VACCINATED WITH A FIRST DOSE ON MAY 20, 2021, A SECOND DOSE ON JUNE 25, 2021, AND WAS FOLLOWED UNTIL END OF FOLLOW-UP ON OCTOBER 5TH, 2021, B) NOT VACCINATED AND FOLLOWED UNTIL END OF FOLLOW-UP ON OCTOBER 5TH, 2021.



Comment PRAC Rapporteur:

The authors confirm that the reference group is defined as all person time from December 27, 2020 until the (possibly) first vaccination, i.e. a few of months. Hence, the duration of the study is quite short. People who do not get vaccinated during the study period contribute all their person-time to the reference group.

The exposure time (main analysis: 0-28 days after vaccination) is by definition after the reference time: this means that everyone who is exposed has to 'survive' until this period, without an event. Since the outcome is rare, this is considered acceptable.

A post exposure window is defined in the methods, however, no results have been shown regarding these time periods. In the authors' discussion it is mentioned that "Potentially, future research utilizing post risk time comparison time will provide help in excluding time-dependent unmeasured confounding".

MYOCARDITIS AND PERICARDITIS

We defined incident outcome events as the date of first admission for myocarditis or pericarditis from December 27, 2020, and onwards. The primary outcome was a main or secondary diagnosis of myocarditis at discharge from inpatient hospital care. Secondary outcomes included a main or secondary diagnosis of pericarditis (inpatient hospital care), and a main or secondary diagnosis of either condition (myocarditis or pericarditis) combined from either inpatient or outpatient hospital care.

COVARIATES

We used the following covariates for adjustment and stratification: sex, age, calendar time (categories below), healthcare worker status, nursing home resident, and five comorbidities (pulmonary disease, renal disease, autoimmune disease, cardiovascular disease or diabetes, and cancer) defined by diagnoses before start of follow-up. We also adjusted for verified SARS-CoV-2 infection before December 27, 2020, while infection after this date was a censoring event. We defined SARS-CoV-2 as the sample date of a positive reverse transcription polymerase chain reaction or lateral flow test. Testing has been free and easily available in all counties since summer of 2020.

Comment PRAC rapporteur:

Although adjustment of the results using the covariates mentioned may correct for some biases, a thorough discussion of possible sources of selection bias is currently missing. *I.e.* were the **baseline characteristics and risk factors** of myocarditis/ pericarditis evenly distributed between vaccinated *vs.* unvaccinated people? A table detailing baseline characteristics of the vaccinated and unvaccinated groups would be helpful. A sensitivity analysis excluding people without any COVID-19 vaccination might also be helpful to diminish bias, and help interpretation of findings.

Further, the number of covariates included is limited. No co-medications that are potential risk factors for myocarditis have been incorporated, such as medication to treat cancer, antibiotics (such as penicillin and sulfonamide drugs), diuretics (such as furosemide and hydrochlorothiazide), and medication for epilepsy.

Also, no time-dependent adjustments were made, but only adjustments for covariates measured at baseline.

The authors discussed ascertainment bias as follows: "Ascertainment bias, whereby increased focus on myocarditis as an adverse event after mRNA vaccination has resulted in more subclinical cases being diagnosed, cannot be ruled out. However, it is unlikely to fully explain the difference between the two mRNA vaccines or the differences between age groups. The background incidence rates of both myocarditis and pericarditis are similar in Denmark, Finland, and Sweden, whereas in Norway the rate of myocarditis is lower and the rate of pericarditis higher. However, the combined rates of myocarditis and pericarditis are very similar across the countries." This is endorsed.

Regarding potential confounding by age and by calendar-time: analyses have been stratified by sex and age groups (12-15, 16-24, 25-39 and 40+), however, findings in children 12-15 years are limited because of relatively few exposed individuals as vaccination in this age group had only recently started in most countries at the time the study was performed. Adjustment for calendar-time did not change the results substantially.

In summary, residual bias /confounding may be present in the study because of selection bias (vaccinated versus unvaccinated people), limited adjustment for covariates and lack of time-dependent adjustments.

STATISTICAL ANALYSIS

We took advantage of the longitudinal information in our national cohorts to calculate exact unvaccinated and vaccinated person-time at risk for each individual. We started follow-up on December 27, 2020, coinciding with the start of the vaccination campaign in all four countries. Censoring events were defined as the first occurrence of a positive test for SARS-CoV-2 infection, receiving Ad26.COV2.S vaccine, receiving a third dose of any SARS-CoV-2 vaccine, emigration, death,

or country-specific end-of-study (latest October 5, 2021). Individuals contributed person-time as unvaccinated until the first vaccination. After each first- or second-dose vaccination, individuals contributed with person-time in a main risk period of interest defined as day 0 up to and including day 28. The resulting follow-up periods and numbers of myocarditis and pericarditis cases were aggregated for all individuals according to vaccination status (unvaccinated, risk period after first-dose vaccination, and risk period after second-dose vaccination).

We used Poisson regression on the number of cases to estimate incidence rate ratios (RRs) with 95% confidence intervals (CIs) comparing rates in the main risk periods after vaccination to rates in unvaccinated periods. We took potential confounding factors into account by direct adjustment in three models: Model 1: adjustment for sex and age (12-15, 16-19, 20-24, 25-29, 30-39, 40-64, 65+ years); model 2: adjustment as in model 1 with additional adjustment for healthcare worker status, nursing home resident, and the comorbidities above; model 3: adjustment as in model 2 with additional adjustment for calendar periods (December-March, April-June, July-end). Model 2 was used to estimate adjusted RRs in our main analyses; models 1 and 3 were used as sensitivity analyses. We include subgroup results according to sex and age (12-15, 16-24, 25-39 and 40+ years). We conducted the analyses with SAS 9.4 (Denmark, Sweden), R version 3.6.3 (Finland), and Stata 16.0 (Norway).

META-ANALYSES

Meta-analyses of the IRR estimates were based on random-effects models implemented using mixmeta package[14] of R[15]. We tested homogeneity of country-specific estimates using the Cochran Q test,[16] calculated the pooled incidence rates (IRs) using the sum of events and person years in the countries and the pooled excess rates using the pooled IR and IRR estimates. For the CIs we utilized the delta method assuming independence of the IR and IRR estimates.

SARS-COV2 INFECTION AND MYOCARDITIS

In a complementary analysis we studied incident myocarditis within 28 days following SARS-CoV-2 infection. Using the analytic approach as above and with the sample date of the first positive test after August 1, 2020, defining the exposure start.

SUPPLEMENTARY ANALYSES

We studied risk of myocarditis or pericarditis in a shorter 7-day risk window. Among events after vaccination, we calculated median time from vaccination to outcome (admission date). Further, we analyzed short-term outcomes among myocarditis cases using the Kaplan-Meier estimator, by estimating the proportion of cases discharged day 4 or later, and the proportion of cases who died within 28 days of the admission date.

ETHICS

The study was conducted according to ethical and legal requirements of each country (**Supplementary Methods**).[17]

Comment PRAC Rapporteur:

Statistical analyses are considered appropriate.

RESULTS

Within the four Nordic countries in the study, 23,124,459 residents were followed from December 27, 2020, to Oct 5, 2021, at the latest; 17,384,090 (75.2%) had received two doses and 1,494,826 (6.5 %) had received one dose only of SARS-CoV-2 vaccines by end-of-study (**Table 1**).

TABLE 1 NUMBER OF INDIVIDUALS CONTRIBUTING TO UNEXPOSED AND EXPOSED PERSON-TIME BY VACCINE TYPE AND VACCINE SCHEDULE. VACCINATION IN THE NORDIC COUNTRIES (DENMARK, FINLAND, NORWAY, SWEDEN) FROM DECEMBER 27, 2020, TO OCTOBER 5, 2021. MEN AND WOMEN COMBINED.

	12+	12-15	16-24	25-39	40+
	N	N	N	N	N
Population at start-of-follow-up	23,124,459	1,238,017	2,675,978	5,047,011	14,163,453
Unvaccinated by end-of-follow-up	4,244,591	739,344	651,800	1,288,624	1,564,823
Vaccine schedule					
At least first dose AZD1222	1,356,758	99	38,436	152,072	1,166,151
Only first dose AZD1222	178,124	78	12,456	45,196	120,394
AZD1222—AZD1222	765,770	<5	4623	22,719	738,427
AZD1222—BNT162B2	363,263	6	19,494	75,238	268,525
AZD1222 —mRNA-1273	49,601	14	1863	8919	38,805
At least first dose BNT162B2	15,120,821	413,076	1,687,593	2,837,074	1,0183,078
Only first dose BNT162B2	1,012,661	202,764	276,129	240,322	293,446
BNT162B2—BNT162B2	13,489,266	209,002	1,282,384	2,343,495	9,654,385
BNT162B2—mRNA-1273	616,914	1309	129,045	253,155	233,405
BNT162B2—AZD1222	1980	<5	35	102	1842
At least first dose mRNA-1273	2,398,951	85,253	297,911	768,079	1,247,708
Only first dose mRNA-1273	301,655	30,782	80,900	111,498	78,475
mRNA-1273—BNT162B2	92,965	18,943	20,308	30,565	23,149
mRNA-1273—mRNA-1273	2,004,059	35,524	196,685	625,989	1,145,861
mRNA-1273—AZD1222	272	<5	18	27	223
Other combinations	2386	0	180	1069	1137

Comment PRAC Rapporteur:

It is understood that around 20,000 persons (exact number seems unknown) were excluded with any myocarditis or pericarditis in inpatient or outpatient hospital care from January 1, 2017, to December 26, 2020. In the Supplementary Methods it is mentioned that "In total, XXX were excluded, whereof 3706 from Denmark, XXX from Finland, 4864 from Norway, and 8477 from Sweden."[4]

The authors did not provide details regarding the participant flow, or number eligible vaccinated and unvaccinated subjects [*i.e.* a clear accounting of study subjects who entered each stage of study (*e.g.*

[4] As provided to the European Medicines Agency.

numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing followed and analysed) with an explanation for non-participation at every stage].

MYOCARDITIS AND PERICARDITIS DURING FOLLOW-UP

During the 28-day risk-periods following vaccination and during unvaccinated periods experienced by our study participants (6.7 million person-years in total), we observed 1092 incident myocarditis cases and 1154 incident pericarditis cases. Incidence rates of myocarditis during unvaccinated time was 9.7 per 100,000 person-years for men, and 4.2 for women (**Table 2**). Among 16- to 24-year-old, incidence rates were 18.7 for men and 4.4 for women. Incidence rates of pericarditis increased with increasing age.

TABLE 2. MYOCARDITIS WITHIN 28 DAYS OF RECEIPT OF FIRST AND SECOND DOSE OF SARS-COV-2 VACCINE, ACCORDING TO SEX AND AGE. INCIDENCE RATE RATIOS AND EXCESS CASES.

Data from 2021-10-29 Nordic tables.xlsx

Table 2 Comments to Tommi(on 2021-10-29 Nordic Tables.xlsx (copied below):

- number of countries column needed. – This information is in Supplemental figure already

Subgroup, exposure	Events	1000 PYR	IR per 1000 PYR	IRR (95%CI)	Excess in 28 days (95%CI)
Men, 12+					
Unvaccinated	520	5355.1	0.097	1	0
AZD1222	6	43	0.139	2.55 (1.11-5.85)	0.65 (0.02-1.28)
BNT162B2	71	562	0.126	1.43 (1.11-1.83)	0.29 (0.11-0.47)
mRNA-1273	13	93.7	0.139	1.45 (0.84-2.52)	0.33 (-0.11-0.77)
AZD1222—AZD1222	(<5)	29.2	...	1.29 (0.31-5.33)	0.12 (-0.48-0.72)
BNT162B2—BNT162B2	93	501.9	0.185	2.21 (1.77-2.77)	0.78 (0.57-0.99)
BNT162B2—mRNA-1273	34	24.1	1.409	16.22 (10.99-23.94)	10.14 (6.72-13.56)
mRNA-1273—mRNA-1273	58	73.7	0.787	9.11 (6.91-12.0)	5.38 (3.98-6.77)
Men, 12-15					
Unvaccinated	19	449.1	0.042	1	0
BNT162B2	(<5)	12	...	10.00 (1.93-51.70)	1.13 (-0.45-2.71)
mRNA-1273	0	3.3	0	...	...
BNT162B2—BNT162B2	(<5)	6.6	...	16.41 (2.30-117.00)	2.19 (-0.86-5.24)
BNT162B2—mRNA-1273	0	0	0	...	...
mRNA-1273—mRNA-1273	(<5)	0.6	4.814	89.05 (21.23-373.49)	36.51 (-4.81-77.82)
Men, 16-24					
Unvaccinated	149	797.2	0.187	1	0
BNT162B2	25	64.2	0.39	2.24 (1.46-3.44)	1.66 (0.79-2.52)
mRNA-1273	(<5)	11.6	...	2.90 (1.05-7.97)	1.74 (-0.20-3.67)
BNT162B2—BNT162B2	40	43.8	0.913	5.35 (3.75-7.64)	5.69 (3.87-7.52)
BNT162B2—mRNA-1273	17	4.8	3.561	32.7 (17.34-61.80)	26.48 (13.88-39.07)
mRNA-1273—mRNA-1273	16	6.1	2.637	14.16 (8.41-23.82)	18.8 (9.56-28.04)
Men, 25-39					
Unvaccinated	147	1445.9	0.102	1	0
BNT162B2	17	109.6	0.155	1.62 (0.93-2.80)	0.45 (-0.00-0.91)
mRNA-1273	(<5)	30.8	...	1.24 (0.39-3.91)	0.15 (-0.56-0.86)
BNT162B2—BNT162B2	20	86.6	0.231	2.26 (1.31-3.91)	0.99 (0.38-1.60)
BNT162B2—mRNA-1273	15	9.9	1.517	21.82 (11.87-40.12)	11.10 (5.48-16.73)
mRNA-1273—mRNA-1273	28	23.4	1.196	13.53 (8.85-20.68)	8.49 (5.33-11.65)
Men, 40+					

Unvaccinated	205	2662.9	0.077	1	0
AZD1222	6	39.3	0.153	2.33 (1.01-5.41)	0.67 (-0.01-1.35)
BNT162B2	27	376	0.072	0.94 (0.63-1.41)	-0.03 (-0.27-0.20)
mRNA-1273	6	48.2	0.125	1.90 (0.84-4.29)	0.45 (-0.10-1.0)
AZD1222AZD1222	(<5)	28.6	...	1.24 (0.30-5.18)	0.10 (-0.53-0.74)
BNT162B2—BNT162B2	31	364.9	0.085	1.08 (0.74-1.58)	0.05 (-0.18-0.28)
BNT162b2—mRNA-1273	(<5)	9.4	...	3.54 (0.85-14.79)	1.17 (-0.58-2.91)
mRNA-1273—mRNA-1273	11	43.6	0.252	3.45 (1.87-6.34)	1.38 (0.49-2.26)
Women, 12+					
Unvaccinated	210	4953.3	0.042	1	0
AZD1222	(<5)	64.1	...	1.87 (0.58-6.03)	0.17 (-0.13-0.46)
BNT162B2	35	573.2	0.061	1.47 (1.02-2.12)	0.15 (0.02-0.28)
mRNA-1273	(<5)	90.5	...	1.45 (0.35-5.97)	0.05 (-0.13-0.23)
AZD1222—AZD1222	(<5)	31.6	...	1.67 (0.40-6.97)	0.19 (-0.30-0.69)
BNT162B2—BNT162B2	30	528.7	0.057	1.26 (0.77-2.05)	0.09 (-0.08-0.26)
BNT162B2—mRNA-1273	(<5)	19.5	...	9.03 (2.97-27.42)	1.40 (0.01-2.79)
mRNA-1273—mRNA-1273	9	73.1	0.123	3.61 (1.83-7.10)	0.68 (0.20-1.16)
Women, 12-15					
Unvaccinated	(<5)	334.1	...	1	0
BNT162B2	0	8.7	0	...	...
mRNA-1273	(<5)	3.3	...	...	...
BNT162B2—BNT162B2	0	6.2	0	...	...
BNT162B2—mRNA-1273	0	0	0	...	...
mRNA-1273—mRNA-1273	(<5)	0.8	...	...	...
Women, 16-24					
Unvaccinated	31	708.8	0.044	1	0
BNT162B2	(<5)	63.4	...	1.98 (0.56-7.01)	0.18 (-0.13-0.49)
mRNA-1273	0	10.8	0	...	...
BNT162B2—BNT162B2	5	46	0.109	2.73 (1.05-7.13)	0.53 (-0.02-1.08)
BNT162B2—mRNA-1273	(<5)	4.2	...	71.70 (15.10-340)	3.57 (-1.38-8.52)
mRNA-1273—mRNA-1273	0	6.3	0	...	...
Women, 25-39					
Unvaccinated	37	1014.2	0.036	1	0
BNT162B2	(<5)	82.2	...	2.38 (0.82-6.91)	0.22 (-0.05-0.49)
mRNA-1273	0	22	0	...	...
BNT162B2—BNT162B2	5	73.4	0.068	2.27 (0.86-6.02)	0.29 (-0.04-0.63)
BNT162B2—mRNA-1273	0	0.8	0	...	...
mRNA-1273—mRNA-1273	(<5)	17.8	...	6.12 (1.85-20.2)	1.08 (-0.17-2.33)
Women, 40+					
Unvaccinated	136	2546.2	0.053	1	0
AZD1222	(<5)	52.9	...	2.03 (0.62-6.64)	0.221 (-0.135-0.577)
BNT162B2	27	392.7	0.069	1.38 (0.91-2.10)	0.14 (-0.02-0.31)
mRNA-1273	(<5)	48.6	...	4.68 (0.60-36.45)	0.12 (-0.13-0.38)
AZD1222AZD1222	(<5)	30	...	1.71 (0.41-7.17)	0.21 (-0.31-0.73)
BNT162B2—BNT162B2	20	389.2	0.051	1.02 (0.63-1.66)	0.01 (-0.187-0.20)
BNT162B2—mRNA-1273	(<5)	7.6	...	7.96 (1.84-34.38)	1.77 (-0.71-4.25)
mRNA-1273—mRNA-1273	(<5)	44.6	...	3.05 (1.11-8.38)	0.46 (-0.05-0.97)

Abbreviations: PYR follow-up time in person years, IR crude incidence rate, IRR adjusted incidence rate ratio (Model 2: Adjusted for age group, sex, previous SARS-CoV-2 infection, healthcare worker, nursing home resident, comorbidity variables). For other models see **Supplemental Figure and Supplement Tables**).

VACCINATION AND MYOCARDITIS

During the 28-day risk period, we observed 106 and 123 myocarditis cases following first- and second-dose vaccinations with BNT162b2, respectively, and 15 and 67 following mRNA-1273, respectively.

Adjusted RRs comparing the 28-day risk periods following first- and second-dose vaccinations to unvaccinated periods were 1.4 (95%CI, 1.1 to 1.7) and 1.9 (95%CI, 1.5 to 2.3) for BNT162b2 and 1.2 (95%CI, 0.7 to 1.9) and 7.2 (95%CI, 5.3 to 9.8) for mRNA-1273. In males, following the first and second dose, adjusted RRs were 1.5 (95%CI, 1.1 to 1.8) and 2.2 (95%CI, 1.8 to 2.8) for BNT162b2, and 1.5 (95%CI, 0.8 to 2.5) and 9.1 (95%CI, 6.9 to 12) for mRNA-1273.

In males, 16-24 years of age, the adjusted RR was 5.4 (95%CI, 3.8 to 7.6) for a second dose of BNT162b2 and 14.2 (95%CI, 8.4—23.8) for mRNA-1273. For females, the comparative adjusted IRRs were lower (**Table 2).**

Among all males, the excess number of events per 100,000 vaccinated in the 28-day risk periods were 0.3 (95%CI, 0.1 to 0.5) and 0.8 (95%CI, 0.6 to 1.0) following first and second doses for BNT162b2, and 0.3 (95%CI, -0.1 to 0.8) and 5.4 (95%CI, 4.0 to 6.8) following first and second doses for mRNA-1273. The excess number of events for females were low (**Table 2**).

Among males 16–24 years, the excess number of events per 100,000 vaccinated in the 28-day risk periods following first and second doses were 1.7 (95%CI, 0.8 to 2.5) and 5.7 (95%CI, 3.9 to 7.5) for BNT162b2 and 1.7 (95%CI, -0.2 to 3.7) and 18.8 (95%CI, 9.6 to 28.0) for mRNA-1273.The corresponding excess number of events for males 25 to 39 years of age were somewhat lower (**Table 2**).

In a mixed schedule (BNT162b2—mRNA-1273), close to 40 cases (34 males) occurred following the second dose. In males 16-24 years, 17 cases occurred, with an excess number of events of 26.5 (95%CI, 13.9 to 39.1) (Table 2).

VACCINATION AND PERICARDITIS

Pericarditis in males followed a similar pattern by vaccine product and age as for myocarditis but with lower RRs. Pericarditis was rare in females 12–39 years. In men 16–24 years, the excess number of events within the 28-day risk periods was 7.0 per 100,000 vaccinated (95%CI, 1.4 to 12.7).

VACCINATION AND MYOCARDITIS OR PERICARDITIS COMBINED

IRRs of myocarditis or pericarditis combined in males 16–24 years were close to those of myocarditis (**Table 3**). In males 25–39 years the RRs were generally lower. In females 16–24 years the IRRs were similar to those of males of the same age, however, with wider confidence intervals.

TABLE 3. MYOCARDITIS AND PERICARDITIS COMBINED WITHIN 28 DAYS OF RECEIPT OF FIRST AND SECOND DOSE OF SARS-COV-2 VACCINE, ACCORDING TO SEX AND AGE. INCIDENCE RATE RATIOS AND EXCESS CASES.
Data from 2021-10-29 Nordic tables.xlsx (Table5)

lab	Events	1000 PYR	IR per 1000 PYR	IRR (95%CI)	Excess in 28 days (95%CI)
Men, 12+					
Unvaccinated	1393	5355	0.26	1	0
AZD1222	18	43	0.418	1.50 (0.93-2.41)	1.07 (-0.06-2.20)
BNT162B2	214	562	0.381	1.39 (1.21-1.61)	0.83 (0.50-1.15)
mRNA-1273	30	93.7	0.32	1.17 (0.82-1.68)	0.36 (-0.41-1.13)
AZD1222—AZD1222	10	29.2	0.342	1.23 (0.65-2.33)	0.494 (-0.90-1.89)
BNT162B2—BNT162B2	239	501.8	0.476	1.77 (1.48-2.11)	1.59 (1.17-2.00)
BNT162B2—mRNA-1273	57	24.1	2.362	8.02 (6.06-10.63)	15.9 (11.7-20.03)
mRNA-1273—mRNA-1273	101	73.7	1.371	5.18 (4.05-6.63)	8.49 (6.76-10.22)
Men, 12-15					
Unvaccinated	26	353	0.074	1	0
BNT162B2	(<5)	9.1	...	9.13 (2.83-29.5)	3.01 (0.03-5.99)
mRNA-1273	(<5)	3.3	...	4.62 (0.557-38.4)	1.85 (-1.93-5.63)
BNT162B2—BNT162B2	5	6.6	0.763	19.5 (5.24-72.8)	5.55 (0.670-10.43)
BNT162B2—mRNA-1273	(<5)	0	...	...	...
mRNA-1273—mRNA-1273	(<5)	0.6	...	73.4 (18.3-294)	36.43 (-4.80-77.65)
Men, 16-24					
Unvaccinated	271	797.2	0.34	1	0
BNT162B2	42	64.2	0.655	1.99 (1.44-2.76)	2.50 (1.38-3.62)
mRNA-1273	7	11.6	0.605	2.20 (1.03-4.67)	2.53 (0.07-4.99)
BNT162B2—BNT162B2	64	43.8	1.46	4.36 (3.30-5.74)	8.63 (6.40-10.86)
BNT162B2—mRNA-1273	24	4.8	5.027	19 (11.7-31)	36.5 (21.9-51.2)
mRNA-1273—mRNA-1273	24	6.1	3.956	12.24 (7.93-18.91)	27.86 (16.66-39.06)
Men, 25-39					
Unvaccinated	345	1445.8	0.239	1	0
BNT162B2	43	109.6	0.392	1.62 (1.02-2.56)	1.15 (0.226-2.07)
mRNA-1273	12	30.8	0.39	1.63 (0.914-2.92)	1.16 (-0.0891-2.41)
BNT162B2—BNT162B2	48	86.5	0.555	2.41 (1.71-3.39)	2.49 (1.56-3.41)
BNT162B2—mRNA-1273	27	9.9	2.731	11.1 (7.28-17.05)	19.07 (11.83-26.30)
mRNA-1273—mRNA-1273	46	23.4	1.964	8.18 (5.97-11.20)	13.23 (9.36-17.09)
Men, 40+					
Unvaccinated	746	2662.9	0.28	1	0
AZD1222	16	39.3	0.407	1.30 (0.79-2.16)	0.728 (-0.534-1.99)
BNT162B2	125	376	0.332	1.10 (0.91-1.33)	0.24 (-0.21-0.68)
mRNA-1273	10	48.2	0.208	0.74 (0.40-1.39)	-0.55 (-1.94-0.83)
AZD1222—AZD1222	10	28.6	0.35	1.13 (0.60-2.13)	0.30 (-1.23-1.83)

BNT162B2—BNT162B2	122	364.9	0.334	1.09 (0.90-1.33)	0.22 (-0.23-0.67)
BNT162B2—mRNA-1273	6	9.4	0.636	2.30 (1.02-5.20)	2.76 (-0.05-5.56)
mRNA-1273—mRNA-1273	28	43.6	0.643	2.25 (1.54-3.29)	2.74 (1.43-4.05)
Women, 12+					
Unvaccinated	618	4953.3	0.125	1	0
BNT162B2	96	573	0.167	1.16 (0.93-1.44)	0.174 (-0.07-0.42)
mRNA-1273	22	90.5	0.243	1.96 (1.28-3.00)	0.91 (0.36-1.47)
BNT162B2—BNT162B2	102	529	0.193	1.27 (0.95-1.68)	0.31 (-0.03-0.65)
BNT162B2—mRNA-1273	15	19.5	0.77	6.53 (3.83-11.11)	5.00 (2.43-7.58)
mRNA-1273—mRNA-1273	30	73.1	0.41	3.10 (1.91-5.04)	2.13 (1.23-3.04)
Women, 12-15					
Unvaccinated	6	334.1	0.018	1	0
BNT162B2	0	8.7	0	...	...
mRNA-1273	(<5)	3.3	...	12.4 (1.16-142)	2.16 (-2.10-6.42)
BNT162B2—BNT162B2	0	6.2	0	...	...
BNT162B2—mRNA-1273	0	0	0	...	...
mRNA-1273—mRNA-1273	(<5)	0.8	...	54.4 (4.93-599)	9.75 (-9.37-28.87)
Women, 16-24					
Unvaccinated	67	708.8	0.095	1	0
BNT162B2	7	63.4	0.11	1.18 (0.54-2.58)	0.13 (-0.44-0.70)
mRNA-1273	(<5)	10.8	0.37	6.34 (2.26-17.8)	2.39 (0.00-4.78)
BNT162B2—BNT162B2	10	46	0.217	2.41 (1.23-4.73)	01.00 (0.21-1.74)
BNT162B2—mRNA-1273	5	4.2	1.18	21.19 (7.85-57.2)	8.63 (1.05-16.20)
mRNA-1273—mRNA-1273	6	6.3	0.953	21.05 (8.72-50.82)	6.96 (1.38-12.54)
Women, 25-39					
Unvaccinated	93	1273.5	0.073	1	0
BNT162B2	12	105.3	0.114	2.09 (1.13-3.88)	0.46 (0.09-0.82)
mRNA-1273	6	27.8	0.216	6.50 (2.71-15.56)	1.40 (0.26-2.54)
BNT162B2—BNT162B2	17	87.2	0.195	3.02 (1.27-7.17)	1 (0.36-1.64)
BNT162B2—mRNA-1273	5	7.6	0.656	12.33 (4.51-33.67)	4.62 (0.55-8.70)
mRNA-1273—mRNA-1273	9	21.4	0.42	6.44 (3.24-12.80)	2.72 (0.91-4.53)
Women, 40+					
Unvaccinated	452	2546.1	0.178	1	0
AZD1222	10	52.9	0.189	1.39 (0.73-2.65)	0.44 (-0.34-1.12)
BNT162B2	77	392.7	0.196	1.07 (0.84-1.37)	0.10 (-0.24-0.44)
mRNA-1273	11	48.6	0.226	1.45 (0.80-2.64)	0.54 (-0.25-1.32)
AZD1222—AZD1222	(<5)	30	0.133	0.73 (0.27-1.99)	-0.37 (-1.80-1.06)
BNT162B2—BNT162B2	75	389.2	0.193	1.05 (0.82-1.34)	0.07 (-0.28-0.42)
BNT162B2—mRNA-1273	5	7.6	0.66	4.33 (1.77-10.6)	3.89 (0.32-7.46)
mRNA-1273—mRNA-1273	14	44.6	0.314	1.88 (1.10-3.21)	1.13 (0.22-2.03)

Abbreviations: PYR follow-up time in person years, IR crude incidence rate, IRR adjusted incidence rate ratio (Model 2: Adjusted for age group, sex, previous SARS-CoV-2 infection, healthcare worker, nursing home resident, comorbidity variables).

SARS-COV-2 INFECTION AND MYOCARDITIS

During the 28-day risk period after a positive SARS-CoV-2 test there were 67 myocarditis cases. Excess events of myocarditis were 5.4 (95%CI, 3.7 to 7.1) per 100,000 diagnosed infected in all males, and 3.7 (95%CI, 1.1 to 6.4) in males 25–39 years. In females these numbers were similar.

SUPPLEMENTARY ANALYSES

IRRs and excess rates slightly attenuated, when Model1 was complemented by other covariates (Model2) and further attenuated when calendar time was added (Model3). When estimating RRs of myocarditis risk following second dose of mRNA-1273 in men 16–24 years, adjustment for calendar time (model3) yielded unstable estimates with wide 95% CIs.

Heterogeneity of the analyses across countries was not statistically significant, and we thus present the results as pooled four-country estimates of risk ratios and excess rates.

We also evaluated a 7-day risk period. Of the 228 myocarditis cases in the 28-day risk-window after a second dose of mRNA 145 vaccination, events occurred within the first week, yielding higher IRRs **(Table 3).** The excess events, per 100,000 vaccinated, during 7-day risk-window represented the majority of excess events during the 28-day risk-window.

In males 12–39 years, at least 75% of the cases were admitted to hospital within 10 days of vaccination. Comorbid conditions did not differ markedly between vaccinated and unvaccinated cases**.** Length of stay did not markedly differ between vaccinated and unvaccinated cases.

DISCUSSION

This study of 23.1 million individuals shows higher rates of myocarditis and pericarditis within 28 days following vaccination with SARS-CoV-2 mRNA vaccines when compared to unvaccinated. These associations were strongest within the first 7 days, were increased for all combinations of mRNA vaccines and were more pronounced after the second dose. A second dose of mRNA-1273, either after mRNA-1273 or BNT162b2 as a first dose, had the highest risk. Young males aged 16-24 years had the highest increased risk.

We confirm a higher risk after a second dose and a higher risk in young men.[8–10,18,19] Excess events within 28 days in young males of 5.7 per 100,000 after a second-dose vaccination with BNT162b2 and 18.8 after a second-dose vaccination with mRNA-1273 are higher than previously reported.[2,8,19] Our finding of a higher risk of myocarditis after mRNA-1273 than after BNT162b2 in young males is supported by surveillance data from Canada and the US.[3,10]

STRENGTHS AND LIMITATIONS

The main strengths of our study include the population-based cohort design in four Nordic countries, the large sample size, complete follow-up, and independent ascertainment of vaccinations and diagnoses from nationwide registers to which reporting is mandatory. The findings in the meta-analyses are supported by consistent findings across all four countries, despite some country-specific differences in data sources, SARS-CoV-2 transmission, testing activities, and vaccination schedules.

There are also some limitations of the study. We defined myocarditis and pericarditis as an inpatient hospital admission with a corresponding main or secondary discharge diagnosis. Diagnostic codes have been shown to have a 85% positive predictive value male patients below the age of 60.[20] Thus, without access to data on clinical measures like troponin levels, diagnostic imaging results, or endomyocardial biopsy we studied myocarditis as diagnosed in clinical practice and could therefore not assess how many of these patients fulfil all criteria for a myocarditis diagnosis.21 However, median length-of-stay was 4-5 days for both unvaccinated and vaccinated cases indicative of sufficient time for adequate diagnostic procedures.

We were able to present analyses stratified by sex in younger ages, however, our findings in children 12-15 years are limited to relatively few exposed individuals as vaccination in this age group has just recently started in most countries.

Ascertainment bias, whereby increased focus on myocarditis as an adverse event after mRNA vaccination has resulted in more subclinical cases being diagnosed, cannot be ruled out. However, it is unlikely to fully explain the difference between the two mRNA vaccines or the differences between age groups. The background incidence rates of both myocarditis and pericarditis are similar in Denmark, Finland, and Sweden, whereas in Norway the rate of myocarditis is lower and the rate of pericarditis higher. However, the combined rates of myocarditis and pericarditis are very similar across the countries.

We show increased risks of myocarditis after COVID-19 compared to those unexposed to neither SARS-CoV-2 infection nor vaccination. COVID-19 related myocarditis is associated with severe disease, and more frequent in older subjects. Therefore, estimates of myocarditis risk with COVID-19 will be dependent on the testing strategy, appearing less frequent the more mild or pauci-symptomatic cases are diagnosed. We limited our follow-up to a time period of most large-scale testing. The risk of myocarditis after vaccination was highest in the younger age groups, whereas the risk of myocarditis after SARS-CoV-2 infection decreased with decreasing age.

The two mRNA vaccines have been utilized according to their availability during 2021. Further, vaccination was first provided for the elderly and for the younger age groups only later. The implementation has thus varied across age and calendar months and across countries. The background incidence rate of myocarditis fluctuates with infectious-disease burden, usually higher during the fall and winter.[22] Moreover, differences in lockdown measures affecting the spread of SARS-CoV-2 and other viruses, could also affect the background incidence rate in both the unvaccinated and the vaccinated. Most of the younger age groups were vaccinated in July, August and September, and very few during the spring. However, adjustment for calendar-time did not change the results substantially. Potentially, future research utilizing post risk time comparison time will provide help in excluding time-dependent unmeasured confounding.

In this Nordic cohort study of 23.1 million individuals 12 years and older, the risk of myocarditis was higher within 28 days of vaccination compared to unvaccinated with both BNT162b2 and mRNA-1273, higher after second than first dose. The risk was more pronounced after the second dose of mRNA-1273 than after the second dose of BNT162b2. The risk was highest in males 16-24 years with 4 to 8 excess events within 28 days per 100,000 vaccinees after a second dose of BNT162b2 and 10 to 28 excess events after second dose of mRNA-1273.

REFERENCES

1. European Medicines Agency (EMA). COVID-19 mRNA Vaccines Comirnaty and Spikevax: risk of myocarditis pericarditis. July 19 2021 [Internet]. 2021;Available from: https://www.ema.europa.eu/en/medicines/dhpc/covid-19-mrna-vaccines-comirnaty-spikevax-risk-myocarditis-pericarditis

2. Klein NP, Lewis N, Goddard K, et al. Surveillance for Adverse Events After COVID-19 mRNA Vaccination. JAMA [Internet] 2021 [cited 2021 Sep 6];Available from: https://jamanetwork.com/journals/jama/fullarticle/2784015

3. Klein N. Myocarditis Analyses in the Vaccine Safety Datalink: Rapid Cycle Analyses and "Head-to-Head" Product Comparisons. CDC Advisory Committee on Immunization Practices (ACIP) Meeting October 21,

2021 [Internet]. 2021;Available from: https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-10-20-21/08-COVID-Klein-508.pdf

4. Montgomery J, Ryan M, Engler R, et al. Myocarditis Following Immunization With mRNA COVID-19 Vaccines in Members of the US Military. JAMA Cardiology [Internet] 2021 [cited 2021 Aug 16];Available from: https://jamanetwork.com/journals/jamacardiology/fullarticle/2781601

5. Su JR. Myopericarditis following COVID-19 vaccination: Updates from the Vaccine Adverse Event Reporting System (VAERS). CDC Advisory Committee on Immunization Practices (ACIP) Meeting October 21, 2021 [Internet]. 2021;Available from: https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-10-20-21/07-COVID-Su-508.pdf

6. Wong H-L. Surveillance Updates of Myocarditis/Pericarditis and mRNA COVID-19 Vaccination in the FDA BEST System. FDA Vaccines and Related Biological Products Advisory Committee 14 October, 2021 [Internet]. 2021;Available from: https://www.fda.gov/media/153090/download

7. Shimbakuro T. COVID-19 Vaccine Safety Updates. CDC Advisory Committee on Immunization Practices (ACIP) Meeting October 21, 2021. [Internet]. 2021 [cited 2021 Oct 20];Available from: https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-10-20-21/06-COVID-Shimabukuro-508.pdf

8. Witberg G, Barda N, Hoss S, et al. Myocarditis after Covid-19 Vaccination in a Large Health Care Organization. New England Journal of Medicine [Internet] 2021 [cited 2021 Oct 8];Available from: https://www.nejm.org/doi/full/10.1056/NEJMoa2110737

9. Mevorach D, Anis E, Cedar N, et al. Myocarditis after BNT162b2 mRNA Vaccine against Covid-19 in Israel. New England Journal of Medicine [Internet] 2021;Available from: https://www.nejm.org/doi/full/10.1056/NEJMoa2109730

10. Government of Ontario, Canada. Ontario Recommends the use of Pfizer-BioNTech COVID-19 Vaccine for Individuals Aged 18-24 Years Old. September 29, 2021 [Internet]. 2021 [cited 2021 Sep 29];Available from: https://news.ontario.ca/en/statement/1000907/ontario-recommends-the-use-of-pfizer-biontech-covid-19-vaccine-for-individuals-aged-18-24-years-old

11. Laugesen K, Ludvigsson JF, Schmidt M, et al. Nordic Health Registry-Based Research: A Review of Health Care Systems and Key Registries. Clinical Epidemiology 2021;13:533–54.

12. Pottegård A, Lund LC, Karlstad Ø, et al. Arterial events, venous thromboembolism, thrombocytopenia, and bleeding after vaccination with Oxford-AstraZeneca ChAdOx1-S in Denmark and Norway: population based cohort study. BMJ 2021;373:n1114.

13. Schultz NH, Sørvoll IH, Michelsen AE, et al. Thrombosis and Thrombocytopenia after ChAdOx1 nCoV-19 Vaccination. New England Journal of Medicine 2021;384:2124–30.

14. Sera F, Armstrong B, Blangiardo M, Gasparrini A. An extended mixed-effects framework for meta-analysis. Statistics in Medicine 2019;38(29):5429–44.

15. R Core Team. The R Project for Statistical Computing [Internet]. R Foundation for Statistical Computing, Vienna, Austria; 2021. Available from: https://www.r-project.org/

16. Cochran WG. The comparison of percentages in matched samples. Biometrika 1950;37(3–4):256–66.

17. Ludvigsson JF, Håberg SE, Knudsen GP, et al. Ethical aspects of registry-based research in the Nordic countries. Clinical Epidemiology 2015;7:491–508.

18. Dagan N, Barda N, Balicer RD. Adverse Effects after BNT162b2 Vaccine and SARS-CoV-2 Infection, According to Age and Sex. New England Journal of Medicine [Internet] 2021;Available from: https://www.nejm.org/doi/10.1056/NEJMc2115045

19. Barda N, Dagan N, Ben-Shlomo Y, et al. Safety of the BNT162b2 mRNA Covid-19 Vaccine in a Nationwide Setting. New England Journal of Medicine 2021;385:1078–90.

20. Sundbøll J, Adelborg K, Munch T, et al. Positive predictive value of cardiovascular diagnoses in the Danish National Patient Registry: a validation study. BMJ Open 2016;6(11):e012832.

21. The Brighton Collaboration. Myocarditis/Pericarditis Case Definition (Myocarditis_Version_1.5.0_16.July.2021) [Internet]. 2021. Available from: https://brightoncollaboration.us/myocarditis-case-definition-update/

22. Arola A, Pikkarainen E, Sipilä JO, Pykäri J, Rautava P, Kytö V. Occurrence and Features of Childhood Myocarditis: A Nationwide Study in Finland. Journal of the American Heart Association 2017;6(11):e005306.

3.4. Rapporteur's Discussion on results from Nordic study

Karlstad *et al.* conducted nationwide cohort studies in Denmark, Finland, Norway and Sweden according to a common protocol and combined results by meta-analysis. They retrieved SARS-CoV-2 vaccinations, hospital diagnoses of myocarditis or pericarditis, and covariates from national registers. All residents 12 years and older were followed from December 27, 2020, until an incident myocarditis or pericarditis, censoring or end-of-study (October 5, 2021). Poisson regression yielded adjusted incidence rate ratios (RRs) and excess rates with 95% confidence intervals (CIs), comparing rates in 28-day and 7-day periods following vaccination with unvaccinated rates.

The non-interventional cohort study in the Nordic registries evaluating the risk of myocarditis and pericarditis following immunisation with COVID-19 vaccines is a welcomed addition to data from previous spontaneous reporting from outside the EEA. The new data, based on Scandinavian national population registers linked to vaccination and health care registries in the respective countries, contribute with new information regarding the magnitude of risk for the two respective vaccines, including in different age strata although estimates in several strata are based on low numbers.

There are some limitations to the study:

- The reference group is defined as all person time from December 27, 2020 until the (possibly) first vaccination, i.e. a few of months. Hence, the duration of the study is quite short.
- The authors did not provide details regarding the participant flow, or number eligible vaccinated and unvaccinated subjects.
- People who do not get vaccinated during the study period contribute all their person-time to the reference group, which may lead to selection bias.
- The exposure time (main analysis: 0-28 days after vaccination) is by definition after the reference time: this means that everyone who is exposed has to 'survive' until this period, without an event.
- A post exposure window is defined in the methods, however, no results have been shown regarding these time periods.
- Residual bias /confounding may be present because of selection bias (vaccinated versus unvaccinated people), limited adjustment for covariates (e.g. no adjustment for co-mediation) and lack of time-dependent adjustments.

However, these nationwide studies are considered helpful in further quantifying risks of myocarditis or pericarditis in relation to SARS-CoV-2 vaccinations.

The study results show that among 23.1 million individuals, (82% vaccinated by end-of-study) 1092 myocarditis and 1154 pericarditis events were identified.

During the 28-day risk-periods following vaccination and during unvaccinated periods experienced by the study participants (6.7 million person-years in total), 1092 incident myocarditis cases were observed. Incidence rates of myocarditis during unvaccinated time was 9.7 per 100,000 person-years for men, and 4.2 for women. Among 16- to 24-year-old, incidence rates were 18.7 for men and 4.4 for women.

Incidence rates of myocarditis within 28 days after first- and second-dose BNT162B2 vaccination was 12.6 and 18.5 per 100,000 person-years for men, and 6.1 and 5.7 per 100,000 person-years for women. Among 16- to 24-year-old, incidence rates were 39 and 91,3 per 100,000 person-years for men and <frequency unknown> and 10.9 per 100,000 person-years for women.

Adjusted RRs comparing the 28-day risk periods following first- and second-dose vaccinations to unvaccinated periods were 1.4 (95%CI, 1.1 to 1.7) and 1.9 (95%CI, 1.5 to 2.3) for BNT162b2. In males, following the first and second dose, adjusted RRs were 1.4 (95%CI, 1.1 to 1.8) and 2.2 (95%CI, 1.8 to 2.8) for BNT162b2. In females, following the first and second dose, adjusted RRs were 1.5 (95%CI, 1.0 to 2.1) and 1.3 (95%CI, 0.8 to 2.1) for BNT162b2. In males, 16-24 years of age, the adjusted RR was 5.4 (95%CI, 3.8 to 7.6) for a second dose of BNT162b2. In females, 16-24 years of age, the adjusted RR was 2.7 (95%CI, 1.1 to 7.1) for a second dose of BNT162b2.

Among all males, the excess number of events per 100,000 vaccinated in the 28-day risk periods were 0.3 (95%CI, 0.1 to 0.5) and 0.8 (95%CI, 0.6 to 1.0) following first and second doses for BNT162b2. Among males 16–24 years, the excess number of events per 100,000 vaccinated in the 28-day risk periods following first and second doses were 1.7 (95%CI, 0.8 to 2.5) and 5.7 (95%CI, 3.9 to 7.5) for BNT162b2. Among all females, the excess number of events per 100,000 vaccinated in the 28-day risk periods were 0.2 (95%CI, 0.0 to 0.3) and 0.1 (95%CI, 0.0 to 0.3) following first and second doses for BNT162b2. Among females 16–24 years, the excess number of events per 100,000 vaccinated in the 28-day risk periods following first and second doses were 0.2 (95%CI, 0.1 to 0.5) and 0.5 (95%CI, 0.0 to 1.1) for BNT162b2.

Incidence rates of pericarditis during unvaccinated time was 10.2 per 100,000 person-years for men, and 4.8 for women.

Incidence rates of pericarditis within 28 days after first- and second-dose BNT162B2 vaccination was 16.7 and 17.7 per 100,000 person-years for men, and 7.5 and 8.1 per 100,000 person-years for women.

In males, following the first and second dose, adjusted RRs were 1.3 (95%CI, 1.0 to 1.7) and 1.4 (95%CI, 1.1 to 1.8) for BNT162b2. In females, following the first and second dose, adjusted RRs were 1.3 (95%CI, 0.9 to 1.7) and 1.5 (95%CI, 1.1 to 2.1) for BNT162b2. For both men and women, RRs were highest in the younger age groups (16-39 years); around a 2-fold or 3-fold increase.

Among all males, the excess number of events per 100,000 vaccinated in the 28-day risk periods were 0.3 (95%CI, 0.0 to 0.6) and 0.4 (95%CI, 0.2 to 0.6) following first and second doses for BNT162b2. Among males 16–24 years, the excess number of events per 100,000 vaccinated in the 28-day risk periods following first and second doses were 0.1 (95%CI, 0.4 to 0.5) and 1 (95%CI, 0.2 to 1.8) for BNT162b2. Among all females, the excess number of events per 100,000 vaccinated in the 28-day risk periods were 0.1 (95%CI, 0.0 to 0.3) and 0.2 (95%CI, 0.0 to 0.4) following first and second doses for BNT162b2. Among females 16–24 years, the excess number of events per 100,000 vaccinated in the

28-day risk periods following first and second doses were 0.1 (95%CI, 0.1 to 0.4) and 0.1 (95%CI, 0.0 to 0.4) for BNT162b2.

Comments EMA received 22 Nov 2021

On 22 November a slide set with a summary and appraisal for the Nordic study was received by the Rapporteur, which is summarised below. The results of the Nordic and EPI-PHAR FR studies seem to converge overall, this is also supported by the use of two different study designs with different strengths and limitations.

Main Results:

- 75.2% of study population with two doses by end of study period
- 1092 incident myocarditis and 1154 incident pericarditis cases in the study period
- Incidence of myocarditis during unvaccinated time: 9.7/100,000 (men) and 4.2/100,000 (women); 18.7 and 4.4 resp. among 16-24-year-olds. Incidence of pericarditis increased with age
- Adjusted RRs for **myocarditis** (28-day risk period): 1.4 (95%CI, 1.1 to 1.7) and 1.9 (95%CI, 1.5 to 2.3) for BNT162b2 and 1.2 (95%CI, 0.7 to 1.9) and 7.2 (95%CI, 5.3 to 9.8) for mRNA-1273
    - Males after first and 2nd dose: 1.5 (95%CI, 1.1 to 1.8) and 2.2 (95%CI, 1.8 to 2.8) for BNT162b2, and 1.5 (95%CI, 0.8 to 2.5) and 9.1 (95%CI, 6.9 to 12) for mRNA-1273, resp.
    - Males 16-24: 5.4 (95%CI, 3.8 to 7.6) for 2nd dose of BNT162b2 and 14.2 (95%CI, 8.4—23.8) for mRNA-1273. Females: IRRs lower (Supp. analysis)
    - Males: excess number of events/100,000 vaccinated 0.3 (95%CI, 0.1 to 0.5) after first and 0.8 (95%CI, 0.6 to 1.0) after 2nd dose for BNT162b2, and 0.3 (95%CI, -0.1 to 0.8) and 5.4 (95%CI, 4.0 to 6.8) for mRNA-1273. Excess number in females low. In 16–24 years males: 1.7 (95%CI, 0.8 to 2.5) and 5.7 (95%CI, 3.9 to 7.5) for BNT162b2 and 1.7 (95%CI, -0.2 to 3.7) and 18.8 (95%CI, 9.6 to 28.0) for mRNA-1273. Lower for 25-39 years of age
    - Mixed schedule (BNT162b2—mRNA-1273): 34 cases in males after 2nd dose incl. 17 cases in 16-24 years, with excess number of events 26.5 (95%CI, 13.9 to 39.1)
- **Pericarditis**: similar pattern as myocarditis in males but lower IRRs. Rare in females 12–39 years. In men 16–24, excess number of events in 28-day risk period 7.0/100,000 vaccinated (95%CI, 1.4 to 12.7)
- **Myocarditis + pericarditis**: IRRs in males 16–24 years close to those of myocarditis, generally lower for 25–39 years. Females 16–24 years: IRRs similar to males of same age but wider CIs
- **SARS-COV-2 infection and myocarditis**: 67 cases during 28-day risk period after positive test. Excess events 5.4/100,000 (95%CI, 3.7 to 7.1) in males, similar in females
- Risk of myocarditis after vaccination highest in the younger age groups, whereas risk after SARS-CoV-2 infection decreased with decreasing age

- **Supplementary analyses**
    - Unstable estimates with wide 95% CIs for myocarditis after 2nd dose of mRNA-1273 in men 16–24 years
    - Sensitivity analysis shows that excess events/100,000 during the 7-day risk window represented the majority of excess events
    - >75% male cases 12–39 years admitted to hospital within 10 days of vaccination. Comorbid conditions and length of stay did not differ markedly between vaccinated and unvaccinated cases

Strengths

- Well-conducted pharmacoepidemiological study, capturing the entire national population in the 4 countries with a total study population >23 million
- Common protocol used in the 4 national studies
- Completeness of data: reporting to nationwide registers is mandatory
- Heterogeneity in meta-analysis not statistically significant (despite some country differences in data sources, transmission, testing, vaccination schedules)
- Clearly defined washout period (e.g., exclusion of myocarditis/pericarditis cases in inpatient/ outpatient hospital care from Jan. 2017 to Dec. 26, 2020) and case definition for outcome events
- Appropriate adjustments for likely confounders
- Sensitivity analyses
- Calculation of the number of excess cases in the vaccinated population important from a public health/policy perspective

Limitations

- Outcomes defined as inpatient hospital admission with main or secondary discharge diagnosis (PPV 85% for male patients <60 years). However, no clinical data (e.g., troponin, imaging results) available to complement diagnosis (but non-differential median length-of-stay by vaccination status)
- Limited exposure data for children 12-15
- According to authors ascertainment bias cannot be ruled out (but similar background incidence rates in the 4 countries)
- As in other COVID-19 vaccine observational safety studies, risk estimates are affected by national vaccination strategies (implementation varying by age and calendar months and across countries), testing strategies, non-pharmaceutical interventions, and COVID-19 epidemiology.
- Potential time-dependent unmeasured confounding
- Potential issue of comparability between vaccinated/unvaccinated groups could have been addressed using an additional self-controlled design which would allow adjusting for temporal variations in baseline incidence

Authors' conclusion

- This study of 23.1 million individuals shows higher rates of myocarditis and pericarditis within 28 days following vaccination with SARS-CoV-2 mRNA vaccines when compared to unvaccinated. These associations were strongest within the first 7 days, were increased for all combinations of mRNA vaccines and were more pronounced after the second dose. A second dose of mRNA-1273, either after mRNA-1273 or BNT162b2 as a first dose, had the highest risk. Young males aged 16-24 years had the highest increased risk.
- Excess events within 28 days in young males of 5.7 per 100,000 after a second-dose vaccination with BNT162b2 and 18.8 after a second-dose vaccination with mRNA-1273 are higher than previously reported. Our finding of a higher risk of myocarditis after mRNA-1273 than after BNT162b2 in young males is supported by surveillance data from Canada and the US

Comment PRAC Rapporteur:

The EMA's summary and critical appraisal of the study from Karlstad *et al.* is appreciated and endorsed.

3.5. Assessment of additional data submitted by EMA /VAC4EU

Abstract

Title:
Rapid Safety Assessment of SARS-CoV-2 vaccines in EU Member States using electronic health care datasources-Myocarditis and pericarditis

Authors and contributor:
Prof. dr. M.C.J.M. Sturkenboom, University Medical Center Utrecht, The Netherlands.
Dr. CE Duran, UMC Utrecht, The Netherlands
Drs. J Riera, UMC Utrecht, The Netherlands
Dr. D Messina, Agenzia Regionale di Toscana, Italy
Dr. O Paoletti, Agenzia Regionale di Toscana, Italy
Dr. J Overbeek, PHARMO institute, the Netherlands
Dr. K Swart-Polinder, PHARMO institute, the Netherlands
Dr. Consuelo Huerta, Spanish Agency of Medicines and Medical Devices (AEMPS)
Dr. Mar Martín-Pérez, Spanish Agency of Medicines and Medical Devices (AEMPS)
Dr. Patricia García-Poza, Spanish Agency of Medicines and Medical Devices (AEMPS)
Dr. Patrick Souverein, Utrecht University, the Netherlands
Dr. Satu Siiskonen, Utrecht University, the Netherlands

Rationale and background:
PRAC is currently assessing the risk of myocarditis/pericarditis associated with COVID-19 vaccines following reports with mRNA platform vaccines in young adults and children.

Primary objective
To estimate the incidence rate of myocarditis/pericarditis (MYO/PERI) in children and adults across different study periods and study populations, prior to vaccination and following vaccination by age group, and by data source.

Secondary objectives
The secondary objectives for the rapid assessment studies is:
To assess the incidence rate of myocarditis and pericarditis the following subgroups

- persons with the presence of co-morbidities elevating the risk of serious COVID-19
- persons with a history of diagnosed COVID-19 disease
- age groups (0-4, 5-11, 12-17, 18-24, 25-29, and in 10-year categories above

Study design:
A retrospective, multi-database, cohort study, conducted during the study period ranging from December 1, 2020, to the latest availability of data.

Population:
All subjects in the source population in the participating data sources who were in follow-up for at least 365 days on December 1, 2020 or were born into the cohort during the study period, and for whom vaccination data would be able to be obtained/linked.

Variables:
Variables of interest are:

- Person-time: birth and death dates as well as periods of observation.
- Events: dates of medical and/or procedure and/or prescription/dispensing codes to identify AESI, COVID-19, and at-risk medical conditions.
- Vaccines: vaccine brands and doses

Data sources:
A total of more than 20 million subjects were included in the study population from ARS Tuscany, BIFAP Spain and CPRD, UK. BIFAP subpopulations were followed from various regions, some could link primary care data to hospital data and/or COVID-registry data or had only primary care data. These subpopulations and their rates are reported separately. For CPRD we present only vaccination data, as the event rates did not pass quality control and need to be revisited, they will be updated for the next round.

Results

Study population
The study population comprised 3.147.663 from ARS-Tuscany, 2.949.955 from BIFAP regions that could link to hospitalization and 5.339.434 of BIFAP sources that could link between GP and COVID register. CPRD had more than 12 million subjects, for which we could analyse the vaccination data. Mean age was around 50 years of age in all data sources, except for CPRD were the mean was at 45 years of age. Event data from CPRD are not reported here as they did not pass quality control. They will be reported next time, PHARMO could only access GP data, and is not included in this analysis.

COVID-19 Vaccination

Table 1: Overview of vaccinations by data source

	Pfizer		Moderna		AstraZeneca		Janssen		Unknown	
	N	%	N	%	N	%	N	%		
ARS	1235571	69.2%	170324	9.5%	321922	18%	56859	3.2%		
BIFAP PC-HOSP	353067	65.7%	73846	13.7%	78600	14.6%	31992	6%		
BIFAP PCCOVID	2752487	70%	438571	11.2%	537001	13.7%	201399	5.1%	229	0%
CPRD	1712221	32.7%	26163	0.5%	3499628	66.8%				
Total	6.053.346		708.904		4.437.151		290.250		229	

The most frequently used vaccines were Pfizer COVID-19 vaccine (Comirnaty) and AstraZeneca (Vaxzevria). There were relatively low number of vaccinations in BIFAP PCHOSP, since one region was censored before start of vaccination. The different countries have used different vaccination strategies. The Janssen vaccine was not used in the UK. The majority of persons in the UK received the AstraZeneca COVID-19 vaccine, which was less than 20% of all COVID-19 vaccines in Italy and Spain. In those countries the majority of subjects received the Pfizer vaccine. The UK also had much longer distances between COVID-19 vaccine doses, both for AstraZeneca as well as for Pfizer, the distance was less for Moderna. In Italy and Spain, Pfizer and Moderna COVID-19 vaccine doses were given rapidly (within a month) after each other, whereas AstraZeneca second dose COVID-19 vaccine also was prolonged to almost 3 months.

Covid-19 disease
There are a total of 1,215,768 persons who had a recorded COVID-19 disease during the study period.

Impact of COVID-19 on rates of myocarditis and pericarditis (combined)

COVID-19 disease increased the rate of myocarditis and pericarditis especially in younger age groups

Incidence rates of myocarditis and/or pericarditis in vaccinated
In this report we provided the rates of myocarditis and pericarditis post-vaccination and compare them with age specific background rates. We also include the excel sheets with detailed data and stratified data on incidence rates. We observed that myocarditis rates post-vaccination were very rare, whereas pericarditis was more frequent. To have more ability to detect elevations we combined myocarditis and pericarditis in the comparison.

The comparison of incidence shows that there is excess incidence of myocarditis and pericarditis in younger adult age groups, and this is more frequent in persons vaccinated with the Pfizer COVID-19 vaccine (Comirnaty). We did not formally test the significance of the elevation as that was not the purpose of this analysis.

Limitations
Our data have limitations, although age stratification is done and we compared rates in persons without prior COVID-19, confounding may remain. We therefore pursue with a Self-Controlled Risk Interval Study, which should be able to deal with the within person confounding and will apply post-vaccination risk windows and dose analysis. We may not have captured all cases, which is why we used various databanks in BIFAP, those GP linked to COVID registry and the GPs who could link to hospital data.

Due to the rapidity of the required response, quality control could not be finalized and CPRD rates were not included. We will continue quality control after the delivery of this report, updates of the data will be made in November.

Conclusions
Based on the descriptive analysis and comparison of incidence rates of myocarditis and pericarditis we conclude that COVID-19 disease itself increased the rates of myocarditis & pericarditis and that there is an excess rate of myocarditis and pericarditis in younger persons without prior COVID-19 disease, who are vaccinated with the mRNA platform COVID-19 vaccines, in particular Comirnaty, which was also most widely used. A formal association assessment will require a design that controls for confounding such as the SCRI, which is initiated. Because of the limited power in the younger age groups, meta-analysis of the data with the Nordic data might be beneficial.

Comment PRAC Rapporteur:

This retrospective, multi-database, cohort study, conducted during the study period ranging from December 1, 2020, to the latest availability of data is welcomed.

The limitations of the study are acknowledged. In addition, the authors noted that a total of 1,215,768 persons had a recorded COVID-19 disease during the study period. Note that especially during the initial phases of the pandemic, COVID testing frequency and capacity was not at the same level as the current situation. Consequently, it cannot be excluded that children and adolescents may have had an asymptomatic COVID-19 (relatively more often than the older age groups) and may have not been tested at all.

The authors' conclusions are endorsed that based on the descriptive analysis and comparison of incidence rates of myocarditis and pericarditis:

- COVID-19 disease itself increased the rates of myocarditis & pericarditis

- There is an excess rate of myocarditis and pericarditis in younger persons without prior COVID-19 disease, who are vaccinated with the mRNA platform COVID-19 vaccines, in particular Comirnaty, which was most widely used.

It is noted that in their conclusions the authors make no distinction in risk estimates following vaccination by gender.

3.6. Assessment of additional data submitted by FR: EPI-PHARE Study based on data from the French national health data system (SNDS)

Study title:

EPI-PHARE_Association of myocarditis and pericarditis with mRNA COVID-19 vaccines in France

Study based on data from the French national health data system (SNDS)

Dated: 08 November 2021

Authors: Le Vu S, Bertrand M, Jabagi M-J, Botton J, Drouin J, Baricault B, Bouillon K, Semenzato L, Weill A, Dray-Spira R, Zureik M

Affiliation: *EPI-PHARE - Scientific Interest Group (GIS) ANSM-CNAM,* www.epi-phare.fr

Contact: Prof. Mahmoud Zureik, Director

Summary

Since July 2021, cases of myocarditis and pericarditis have been regarded as adverse side effects potentially arising from vaccination against COVID-19 using messenger RNA vaccines (Pfizer-BioNTech or Moderna), particularly in young men. More recent data suggest that the risk of myocarditis and pericarditis might be higher with the Moderna vaccine, particularly after the second dose, than with the Pfizer-BioNTech vaccine. The aim of this study was to measure the link between the Pfizer-BioNTech and Moderna vaccines and the risk of myocarditis and pericarditis among all persons aged 12-50 in France.

A matched case-control study was conducted using data from the national health data system (SNDS), chain-linked to data from the national databases for Covid-19 vaccination (VAC-SI) and testing (SI-DEP). All cases of hospitalisation for myocarditis and pericarditis recorded in France between 15 May and 31 August 2021 involving patients between the ages of 12 and 50 were included. Each case was matched with 10 controls of the same age, gender and *département* of residence. The relative risk of hospitalisation for myocarditis and pericarditis was compared for persons exposed to the Pfizer-BioNTech and Moderna vaccines and those not exposed, by gender and by age group, using conditional models of logistic regression adjusted to account for history of myocarditis or pericarditis in the last 5 years, infection with SARS-CoV-2 in the previous month, and the deprivation index.

Across the whole of France, a total of 919 cases of myocarditis (median age 26, 21% women) and 917 cases of pericarditis (median age 34, 38% women) were recorded in the 12-50 age group during the study period. These cases were matched with 9190 controls (for myocarditis) and 9170 controls (for pericarditis).

Overall, vaccination with the Pfizer BioNTech and Moderna vaccines was associated with an increase in the risk of hospitalisation for myocarditis and pericarditis in the 7 days following vaccination. The association with the risk of myocarditis appears to be particularly strong among young men below the age of 30, especially after the second dose of the Moderna vaccine (an adjusted Odds Ratio (OR) of 79.8 with a 95% confidence interval [29.8-213.4]), with excess cases in the order of 132 per million doses administered in this age group. To a lesser extent, the Pfizer-BioNTech vaccine also appears to be associated with an increased risk of myocarditis among men under the age of 30 (OR 2.1 [1.3-3.5] with 3 excess cases per million doses for the first dose; OR 10.9 [7.6-15.8] and 27 excess cases per million doses for the second dose), and an association with the first dose of the Moderna vaccine, albeit not a statistically significant one, cannot be ruled out (OR 2.1 [0.6-7.3]) on account of a lack of

statistical power. Although the incidence of myocarditis is lower than it is among men, this risk also increases among young women below the age of 30 following the second dose of both vaccines (OR 11.4 [4.5-28.6] and 4 excess cases per million doses for Pfizer-BioNTech; 40.6 [9.9-166.4] and 37 excess cases per million doses for Moderna). The risk of pericarditis also appears to be greater after the Moderna vaccine for persons under the age of 30, particularly after the second dose for men (OR 15.0 [3.3-68.4] and 18 excess cases per million doses) and after the first dose for women (OR 27.9 [2.4-328.0] and 6 excess cases per million doses).

The clinical prognosis for these cases of myocarditis and pericarditis appears to be broadly positive, with hospitalisation lasting for between 2 and 4 days on average. During the period studied, no deaths were reported among the cases of hospitalisation for myocarditis or pericarditis following vaccination.

Furthermore, multivariate analysis suggests that infection with SARS-CoV-2 within the last month is also associated with cases of myocarditis (OR 7.9 [5.0-12.3]) and pericarditis (OR 3.9 [2.3-6.6]).

In conclusion, this study confirms the existence of a risk of myocarditis and pericarditis in the 7 days following vaccination against Covid-19 with mRNA vaccines (Pfizer BioNTech and Moderna) among persons aged 12-50, particularly young people under the age of 30. This risk is higher with the Moderna vaccine. Nevertheless, the number of cases which can be attributed to vaccines is small in relation to the number of doses administered. This study also confirms the positive clinical prognosis for cases of myocarditis and pericarditis arising after vaccination.

Comments PRAC Rapporteur:

The study conducted in France provides a welcome addition to the body of evidence regarding the occurrence of myocarditis and pericarditis following COVID-19 vaccination.

In general the authors' conclusion is endorsed that this study confirms the existence of a risk of myocarditis and pericarditis in the 7 days following vaccination against Covid-19 with mRNA vaccines (Pfizer BioNTech and Moderna) among persons aged 12-50, particularly young people under the age of 30. This risk seems higher with the Moderna vaccine.

Nevertheless, the number of cases which can be attributed to vaccines is small in relation to the number of doses administered.

This study also reports a favorable clinical prognosis for cases of myocarditis and pericarditis occurring after vaccination.

3.7. Rapporteur's proposed recommendation

See comments above in the respective sections.

Based on review of the submitted data the benefit-risk balance remains unchanged.

Nevertheless, the MAH should adequately address the following:

Regarding ADR frequency in SmPC 4.8

The PRAC Rapporteur considers that the current frequency assignment **unknown is not accepted**.

The PRAC Rap notes that the current frequency category in 4.8 (frequency unknown) does not adequately represent the current body of evidence gathered in the post-marketing phase based on **observational studies**.

For instance based on the studies cited by the MAH:

- Two studies reported myocarditis and pericarditis frequency following BNT162b2 vaccination for **all ages combined of 10 (95% CI 6.1-15.4) per million for myocarditis** and **18 (95% CI 13.-25.5) per million for pericarditis** in a US healthcare system,[xxix] and 13.5 cases of myocarditis and/or pericarditis per million doses in Australia.[xxx]
- Information about myocarditis and perimyocarditis by age has been reported by the Israeli Ministry of Health as part of their overall COVID-19 Vaccine monitoring (proactive for myocarditis). [xxxi] Among males the reporting rate of myocarditis was lower for individuals 12 to 15 years of age than for individuals 16 to 19 years of age for both dose 1 (1/196,398=0.51 vs 3/261,112=1.15 per 100,000 doses) and dose 2 (11/158,541=6.94 vs 37/226,452=**16.34 per 100,000 doses**), with rates for both doses declining thereafter with age.

Based on the currently available combined body of evidence from clinical trials and post-marketing observational studies as cited by the MAH the incidence of myocarditis ranged from **0.1 to 1.6 per 10,000**, hence a frequency category **Very Rare < 1 per 10,000** in the SmPC section 4.8 would be more appropriate.

Note that this is would also be more in line with the wording already present in **SmPC section 4.4**. The rationale for the frequency category could be explained in sub-section *c "Description of selected adverse reactions"*. *I.e.* a footnote could be considered noting that the incidence of myocarditis in the younger males was at the high end of the range and would be closer to frequency category rare (≥1/10.000, <1/1.000)

Regarding refinement of SmPC section 4.4

In addition, the current wording should be further refined. The current product information section 4.4 mentions: ***Very rare*** *cases of myocarditis and pericarditis have been observed following vaccination with Comirnaty. These cases have primarily occurred within 14 days following vaccination, more often after the second vaccination, and more often in younger* ***men.***

It is proposed to remove and replace '**men**' (which implies adults only) by '**males**', as also cases have been observed in adolescent males aged below 18 years.

Request for further adjustment of SmPC section 4.4 when more robust data become available

Based on the O/E analyses presented by the MAH (Table 1, Table 2 and Table 3) it is noted that although the absolute number of cases in males is higher, the background incidence in males is also higher. Consequently, the O/E ratios above 1 do not really differ that much between males and females. This aspect is currently not reflected in the current wording in SmPC section 4.4. On the other hand, the numbers of female cases shown here, but also in the epidemiological studies cited by the MAH (as well as those conducted by VAC4EU and EPI-PHARE) are low, especially in the younger females, which raises the question regarding robustness of these estimates.

The MAH should commit to remain closely evaluating the risk estimates in females, and in case more (robust, stable) data would become available, provide a proposal for refined/adjusted the wording in SmPC section 4.4, as appropriate.

Characteristics, severity, outcome

Based on the above reviews of characteristics, severity, duration and outcome of myocarditis and pericarditis the current wording in the SmPC section 4.4 regarding disease course is still considered adequate. Nevertheless in a considerable number of cases no information on the duration of event, or whether the events were resolved is available. The MAH is expected to keep the clinical course, severity, outcome, sequelae under close monitoring in both spontaneous reports and ongoing and planned observational studies. The Rapporteur should be notified immediately in case of unexpected findings or trends.

3.7.1. PRAC Rapporteur proposed product information update

Deleted text in ~~Strike through~~, New text in **Bold**.

Summary of Product Characteristics (SmPC)

Section 4.4 Warnings and Precautions

Myocarditis and pericarditis

Very rare cases of myocarditis and pericarditis have been observed following vaccination with Comirnaty. These cases have primarily occurred within 14 days following vaccination, more often after the second vaccination, and more often in younger ~~men~~ **males**. Available data suggest that the course of myocarditis and pericarditis following vaccination is not different from myocarditis or pericarditis in general.

Healthcare professionals should be alert to the signs and symptoms of myocarditis and pericarditis. Vaccinees should be instructed to seek immediate medical attention if they develop symptoms indicative of myocarditis or pericarditis such as (acute and persisting) chest pain, shortness of breath, or palpitations following vaccination.

Healthcare professionals should consult guidance and/or specialists to diagnose and treat this condition.

The risk of myocarditis after a third dose of Comirnaty has not yet been characterised.

Section 4.8 Side effects

Cardiac disorders

[Frequency] ~~Not known~~**Very rare**: myocarditis[d], pericarditis[d]

Description of selected adverse reactions

Myocarditis / Pericarditis

Based on observational studies the incidence of myocarditis and pericarditis ranges from 0.1-1.6 per 10,000 persons, which corresponds to frequency category *Very Rare* (< 1 per 10,000). The incidence of myocarditis in younger males was at the high end of the range and corresponds to the frequency category *Rare* (≥1/10.000, <1/1.000).

The **Patient Information Leaflet** should be amended accordingly:

Section 2

Very rare cases of myocarditis (inflammation of the heart muscle) and pericarditis (inflammation of the lining outside the heart) have been reported after vaccination with Comirnaty. The cases have primarily occurred within two weeks following vaccination, more often after the second vaccination, and more often occurred in younger ~~men~~ **males**. Following vaccination, you should be alert to signs of myocarditis and pericarditis, such as breathlessness, palpitations and chest pain, and seek immediate medical attention should these occur.

Section 4

~~Not known (cannot be estimated from the available data)~~ **Rare side effects: may affect up to 1 in 10,000 people**

- inflammation of the heart muscle (myocarditis) or inflammation of the lining outside the heart (pericarditis) which can result in breathlessness, palpitations or chest pain

3.8. Comments from other PRAC members and MAH(s)

Full endorsement without addition comments were received by: **Member State (MS)1, MS2**

Comment PRAC Rapporteur: The endorsements are noted.

MS3

The PRAC Rapps AR is endorsed. However, we have two additional comments:

According to the MAH, four cases of myocarditis and pericarditis were reported in the pivotal clinical trial (2 in placebo and 2 in vaccine arm). Two of the cases were reported in subjects who originally received placebo, but developed myocarditis/pericarditis after receiving two doses of Comirnaty (crossover), and the third case were reported in a subject randomized to receive Comirnaty.

Therefore, the correct number of cases of myocarditis/pericarditis reported from clinical trials is 3 in the active group and 1 in the placebo group. The AR should be amended accordingly.

The MAH provided a cumulative review of relevant data, and included a medically confirmed case of myocarditis involving a patient who experienced myocarditis, leading to hospitalization 4 days after dose 2, with an unknown clinical outcome. This case is not consistent with earlier observations of myocarditis, and in view of the recent approval of Comirnaty for children aged 5 to 11 years, additional data on the outcome of this case is expected.

Comment PRAC Rapporteur:

The additional comments/ corrections are acknowledged.

MS4

The PRAC Rapporteur's AR is generally endorsed. However, MS4 has some additional comments.

Based on the vast amount of data available, the proposal to update the current frequency (unknown) is fully supported.

We would however like to highlight that multiple studies showed an increased risk of myocarditis for Spikevax as compared to Comirnaty. The observational studies, which the proposed update for Comirnaty is based on, did not include risk estimates for Spikevax, and hence a direct comparison is not possible.

Based on the data available for Spikevax, in the signal AR for Spikevax, we propose an update of the frequency to "very rare" for myocarditis with an addition to highlight that the risk is higher in younger men (frequency "rare"). This results in the same frequency categories for Spikevax and Comirnaty, despite the robust data from multiple sources indicating an increased risk for Spikevax vs Comirnaty.

Therefore, we propose to reflect a frequency based on the same data for the Comirnaty and the Spikevax. Based on the lower exposure for Spikevax (i.e. less studies estimating the risk), we consider that the Nordic cohort study (Karlstad et al., 2021) provides robust estimates allowing an estimation of frequency for both the Comirnaty and the Spikevax.

In the Nordic cohort study (Karlstad et al., 2021), following the second dose of Spikevax, in males 16-24 years, the excess number of cases of myocarditis was 18.8 (95% CI 9.56 – 28.04) per 100,000 doses. As no absolute numbers (cases per doses) were provided we propose to use the excess cases estimates to provide a frequency. For Spikevax, this would result in a frequency of approximately 1.9/ 10,000 (rare) for males in this age stratum. For Comirnaty, the excess number of cases of myocarditis was 5.69 (95% CI 3.87 – 7.52) per 100,000 vaccinated, which would result in a frequency of approximately 0.7/10,000 (very rare). Referring to the same data would allow to highlight the possible differences in the risk between the two mRNA vaccines.

Therefore, MS4 proposes the below amendments to the SmPC [for Comirnaty].

Section 4.8 Side effects

Cardiac disorders

[Frequency] ~~Not known~~ **Very rare**: myocarditis[d], pericarditis[d]

Description of selected adverse reactions

Myocarditis / Pericarditis
Based on observational studies the incidence of myocarditis and pericarditis ranges from 0.1-1.6 per 10,000 persons, which corresponds to frequency category *Very Rare* (< 1 per 10,000). ~~**The incidence of myocarditis in younger males was at the high end of the range and corresponds to the frequency category *Rare* (≥1/10.000, <1/1.000).**~~
A Nordic cohort study of 23.1 million individuals from DK, FI, NO and SE estimated the excess number of cases of myocarditis to 5.69 (95% CI 3.87 – 7.52) per 100,000 vaccinated for males 16 – 24 years old. Although the risk is higher in younger males (See section 4.4), the frequency remains within the frequency category "Very rare".

Comment PRAC Rapporteur:

The proposal of MS4 is **not endorsed**. However in the **updated** recommendation we have included more details including the results from the recent EU studies. Also see MS5 comments.

It is acknowledged that the possible differences in the height of the risk between the two mRNA vaccines that has been observed in several studies is important information to communicate with health care professionals, but in our view this cannot be addressed via the SmPC of Comirnaty. We do feel that a statement in the product information of Spikevax would be appropriate, *e.g.* as has been included in the FDA prescribing information of Spikevax

We do not agree to include numbers from the unpublished Nordic study in the product information, as this gives an incomplete picture and is prone to updates with more data becoming available. Should the PRAC decide to include incidences this should be based on all available data (*i.e.* EU and non-EU studies)

Generally, comparative statements regarding adverse reaction frequencies comparing different products, should be avoided in the SmPC of a particular product.

For all EU and non-EU observational studies currently available some degree of uncertainty remains regarding the impact of unmeasured confounding between the vaccinated and unvaccinated populations, let alone between populations that have received different vaccines.

Moreover, the variation in incidence estimates depending on the age, gender, population, particular study, even for the same product, renders it very hard to accurately reflect these observed differences/trend between products in the SmPC. The fact that the ranges of estimates partially overlap between the different vaccines, and the ADR frequency categories used in the SmPC section 4.8 have wide margins (10-fold steps between categories), makes it very hard to accurately representing these observed differences.

The MS4 proposal to provide as justification (in section 4.8 c description of selected adverse reactions) risk estimates as *excess* number of cases per 100,000 vaccinated persons is, although scientifically correct, not endorsed, as frequency category assignment should be based on **crude incidence rates**, as stated the SmPC Guidance.

[If the choice of the frequency category is based on different sources, the category representing the highest frequency should be chosen unless a more specific method has been applied and thus resulted in an estimate of clearly higher validity, e.g. a pooled analysis across suitable studies.

Adverse reactions from clinical trials:

…

Frequency should represent crude incidence rates (and not differences or relative risks calculated against placebo or other comparator).

Adverse reactions from safety studies:

The choice of the frequency category to which any adverse reaction will be assigned is based on the point estimate of the crude incidence rate derived from a study designed in such a way that specific adverse events occurring in patients within a defined observation period would have been detected and reasonably attributed to the medicinal product. In this situation, it is possible to calculate a point estimate of the crude incidence rate using standard statistical methods. In cases where the original information is expressed as an incidence density (denominator expressed as person-time), an appropriate transformation into an incidence proportion should be performed for choosing the frequency category. Normally, incidence proportions for the most representative exposure period (e.g. 1 week, 3 months, 1 year) should be used to derive the frequency category. However, this may not be appropriate if the hazard function increases over time; in this case, the adverse reaction and its frequency pattern, when clinically relevant, should be properly described in section c).

The frequency category to be chosen for each adverse reaction should not be based on differences calculated against a comparator. However, when data are derived from a study with a non-exposed group and the rate difference attributed to the medicinal product is smaller than the baseline or background incidence rate, and if the adverse reaction is considered important, the background incidence may be provided (e.g. in section c).]

MS5

In large, we agree with the assessment by the PRAC rapporteur and the need to update the PI. However, we have some additional comments, including a proposal for a more detailed update of the PI, given that there currently is a substantially larger data set available than at the time of deciding the current wording (See below).

Clinical Safety

Evaluation of myocarditis and pericarditis cases:

- When presenting some of the data, and particularly in summaries, myocarditis and pericarditis are lumped together. This is unfortunate, as these are not the same diseases, and *e.g.* the clear sex difference in both natural and vaccine induced occurrence of myocarditis, is not at all obvious for pericarditis. Thus, we find it important to analyse these entities separately.
- We note that for myocarditis only BC level 1 cases are primarily reviewed. However, for future reviews, we find it important that also BC level 2 cases are closely considered in the analysis, as cases assessed as BC level 2 add valuable information regarding myocarditis risk after vaccination.

Comment PRAC Rapporteur:

Note the entities has been analysed separately and all BC levels are included. **ANNEX 2** of the AR contains *CUMULATIVE Analysis of the Safety Database (through 28 October 2021) of Post-Authorization Reports of Myocarditis and Pericarditis following the Administration of PF-07302048 (BNT162b2)*. Tables 12 to 18 list the details of all BC level myocarditis, and Table 19 to 25 the details of all BC level pericarditis cases.

Regarding subsequent outcomes for those developing vaccine induced myocarditis/pericarditis:

We acknowledge that there is a continued lack of knowledge regarding potential underlying mechanisms as well as of long-term outcomes of both vaccine induced diseases. Continued work is important.

We note in the conclusion from *e.g.* the French study, stating: *the study confirms the positive clinical prognosis for cases of myocarditis and pericarditis arising after vaccination*.

We find it too early to draw such conclusions, particularly considering the so far short follow up time analysed. The sentence in the current SmPC: *'Available data suggest that the course of myocarditis and pericarditis following vaccination is not different from myocarditis or pericarditis in general.* Is not optimal, given the substantial uncertainties regarding long-term consequences, as well as the fact that there are some serious cases also observed in the short term. This is a very important issue for further follow up.

Comment PRAC Rapporteur:

The comment regarding uncertainty of severity, clinical course and outcome is endorsed, as is already reflected in the PRAC Rapporteur's conclusion: *'…in a considerable number of cases no information on the duration of event, or whether the events were resolved is available. The MAH is expected to keep the clinical course, severity, outcome, sequelae under close monitoring in both spontaneous reports and ongoing and planned observational studies. The Rapporteur should be notified immediately in case of unexpected findings or trends.'*

At this moment we do not see any grounds to alter the already including statement: *Available data suggest that the course of myocarditis and pericarditis following vaccination is not different from myocarditis or pericarditis in general.*

Additional comments 27 November 2021

We have tried to get an understanding of the studies referred to in the Rapporteur's proposed recommendation (Section 3.7), being the basis for the proposed revision of the ADR frequency in section 4.8 and the added text regarding observational studies. In section 3.7, it is stated:

*The PRAC Rap notes that the current frequency category in 4.8 (frequency unknown) does not adequately represent the current body of evidence gathered in the post-marketing phase based on **observational studies**. For instance based on the studies cited by the MAH:*

- *Two studies reported myocarditis and pericarditis frequency following BNT162b2 vaccination for **all ages combined of 10 (95% CI 6.1-15.4) per million for myocarditis** and 18 (95% CI 13.-25.5) per million for pericarditis in a US healthcare system,[xxxii] and 13.5 cases of myocarditis and/or pericarditis per million doses in Australia.[xxxiii]*
- *Information about myocarditis and perimyocarditis by age has been reported by the Israeli Ministry of Health as part of their overall COVID-19 Vaccine monitoring.[xxxiv] Among males the reporting rate of myocarditis was lower for individuals 12 to 15 years of age than for individuals 16 to 19 years of age for both dose 1 (1/196,398=0.51 vs 3/261,112=1.15 per 100,000 doses) and dose 2 (11/158,541=6.94 vs 37/226,452=**16.34 per 100,000 doses**), with rates for both doses declining thereafter with age.*

*Based on the currently available combined body of evidence from clinical trials and post-marketing observational studies as cited by the MAH the incidence of myocarditis ranged from **0.1 to 1.6 per 10,000**, hence a frequency category **Very Rare < 1 per 10,000** in the SmPC section 4.8 would be more appropriate.*

In the AR, we have not been able to find a summary of the US (Diaz GA et al. JAMA. 2021;326(12):1210) or Australian (Pepe S, Gregory AT, Denniss AR. Heart Lung Circ. 2021;30(10):1425-9) studies referred to in the first bullet point, which appears to be the bases for the lower range proposed in the additional text for section 4.8 of the SmPC. The articles were however submitted by the MAH, and some points are worth noting:

Pepe S, Gregory AT, Denniss AR. Heart Lung Circ. 2021;30(10):1425-9.

We would not refer to this as a study, is seems more like a review article. Nevertheless, the figure of estimated frequency in Australia given in the bullet point above is reflected in the article and seems to come from the following paragraph:

In Australia, to 11 July 2021, the Department of Health Therapeutic Goods Administration (TGA) has received 50 reports of suspected myocarditis and/or pericarditis out of 288 total adverse event reports after 3.7 million doses of Pfizer mRNA COVID-19 vaccine [32]. These reported cases of temporally associated possible myocarditis/ pericarditis and their clinical course are being evaluated and may be an overestimate of the incidence; however, if all these events are confirmed as likely vaccination complications, this represents an incidence of 13.5 per million doses administered.

Thus, the reference in bullet 1 to *13.5 cases of myocarditis and/or pericarditis per million doses in Australia* seems based on spontaneously reported data, in relation to the estimation of vaccine doses administered. We do not find that an appropriate source for frequency estimation, and propose this reference is being removed from discussion supporting the frequencies in the PI.

Comment PRAC Rapporteur:

The comment is endorsed that this paper is more a review of published reporting rates from spontaneous reporting sources and should not be used to support frequencies in the PI.

Diaz et al : JAMA. 2021;326(12):1210

This study was undertaken based on data from forty hospitals in 4 US states that were part of the Providence health care system and used the same electronic medical record (EMR). Among 2 000 287 individuals receiving at least 1 COVID-19 vaccination, 58.9% were women, the median age was 57 years (interquartile range [IQR], 40-70 years), 76.5% received more than 1 dose, 52.6% received the BNT162b2 vaccine (Pfizer/BioNTech), 44.1% received the mRNA-1273 vaccine (Moderna), and 3.1% received the Ad26.COV2.S vaccine (Janssen/Johnson&Johnson). Twenty individuals had vaccine-related myocarditis (1.0 [95% CI, 0.61-1.54] per 100 000) and 37 had pericarditis (1.8 [95% CI, 1.30-2.55] per 100 000).

The estimation in the last sentence above seems to be a summary of all cases of myocarditis and pericarditis respectively, for the three vaccines together, and irrespective of first or second dose. For myocarditis, there were 11 cases for Spikevax, 9 cases for Comirnaty and none for the Janssen vaccine. For pericarditis, there were 12 cases for Spikevax, 23 (Comirnaty), and 2 (Janssen).

Thus, the lower range proposed for the PI, for both *myocarditis and pericarditis*, of 0.1/ 10,000 persons, seems based on combined data on *myocarditis* for the two mRNA vaccines. Furthermore, the figure stated in the bullet above for pericarditis (0.18 / 10 000 persons), appears based on data for the three vaccines combined. This raises two questions on the appropriateness of i) adding data to the SmPC based on combined vaccine data, ii) to use the lower range for myocarditis for also pericarditis, even if the occurrence of pericarditis was nearly twice as high.

Further, it is noted that the population included in this study only partly seems presentative for the total population approved for Comirnaty as the median age in the study was 57 years (IQR 40-70 years), and given the clear age-dependent risk for myocarditis particularly. Finally, the total number of myocarditis cases following use of Comirnaty in this study (n=9) makes the estimations quite uncertain.

We would have appreciated also including the Nordic and French data sets in the discussion of estimation of the absolute risk of myocarditis as well as pericarditis, although it is acknowledged that the results from these studies are not presented in the same way and that presentation of excess number of cases (as in both of these studies) is not the usual way of estimating frequencies (will underestimate the actual frequency). Further, time windows and exposure metrics may also not be entirely similar, which makes frequency assessment somewhat challenging. Nevertheless, both of these are well conducted studies with large data sets. In relation to the two publications discussed above, these studies are considered more robust, and also of more relevance, given that the lower age groups, where the risk is largest, are well represented in these materials.

Even if estimated ranges when considering the Nordic and French data as well in the end will be roughly similar as to those proposed already, given the scrutiny this AR will get when published, we suggest broadening and focusing on the most robust data when supporting the PI-updates. If maintaining reference to e.g. Diaz et al, for the frequency estimation, it would be desirable to present and discuss the strengths and limitations of this study as well. Preferably, the revised PI should in such case include the age ranges where these data have been obtained.

Comment PRAC Rapporteur:

The comment regarding the paper of Diaz *et al.* is endorsed.

The strength of the study is that included hospital data in US from around 2 million persons receiving at least 1 COVID-19 vaccination, but it has the limitations as noted above. Within the updated

recommendation we have highlighted the uncertainties of the lower end of the range and included the results from the recent EU studies in support of the proposed frequency category.

Summary of Product Characteristics, Package Leaflet and Labelling

Section 4.4:

We note that only minor changes are proposed for the current wording, which is based on the review of a limited number of spontaneously reported cases, which were available by the end of June 2021. However, at present, the available data have increased substantially since then. For instance, it can clearly be concluded that there is an increased risk of myocarditis and pericarditis following vaccination with Comirnaty. The present text is very vague by stating 'cases have been observed', which we do not find adequate anymore. A revision should be made (see below).

Further, we suggest revising the wording related to time to onset with some more detail. The reason is that, although the current wording 'within 14 days' is not incorrect, there is a notable number of cases (both among the spontaneously reported, as well as in e.g. the Nordic data), occurring within just a few days. Further, we have been informed by HCPs, that they misunderstand the current statement; interpreting it as there is little risk after the first 14 days. We therefore propose to revise the wording on TTO. See below (proposed addition **in bold underlined**; wording to be removed – ~~strikethrough~~):

Section 4.4 Warnings and Precautions

Myocarditis and pericarditis

There is an increased risk for ~~Very rare cases of~~ myocarditis and pericarditis ~~have been observed~~ following **vaccination with Comirnaty**. ~~These~~ **These conditions** ~~cases~~ **can develop within just a few days after vaccination** and have primarily occurred within 14 days ~~following vaccination~~. **They have** more often **been observed** after the second vaccination, and more often in younger ~~men~~ **males.**

Available data suggest that the course of myocarditis and pericarditis following vaccination is not different from myocarditis or pericarditis in general.

Comment PRAC Rapporteur:

The MSs helpful suggestions for further refinement of the wording of SmPC Section 4.4 are endorsed.

Regarding the proposed addition to section 4.8

We support the MS4 comments regarding the proposed addition of further detail on this issue in section 4.8, and to add specifically data from the Nordic study.

Furthermore, for the first paragraph, we suggest giving some more details regarding the types of studies which this evaluation is based on e.g by the following wording (proposed addition in **bold, underlined**):

Description of selected adverse reactions

Myocarditis / Pericarditis

Based on observational studies including **nationwide health registers, or other electronic health care data sources in various European countries** the incidence of myocarditis and pericarditis ranges from 0.1-1.6 per 10,000 persons, which corresponds to frequency category Very Rare (< 1 per

10,000). The incidence of myocarditis in younger males was at the high end of the range and corresponds to the frequency category Rare (≥1/10.000, <1/1.000).

Finally, we support considering the MS4 proposal for Spikevax of adding a sentence regarding lack of knowledge regarding myo/pericarditis risk in the peadiatric population, although the somewhat different situations in terms of approved age ranges need to be taken into account as well.

Comment PRAC Rapporteur:

Also see MS4 comments and updated recommendation.

The suggested addition regarding the types of studies on which this evaluation is based is endorsed, albeit in a slightly more concise wording, as follows:

Based on observational studies **within and outside Europe** ~~including **nationwide health registers, or other electronic health care data sources in various European countries**~~ the incidence of myocarditis and pericarditis ranges from 0.1-1.6 per 10,000 persons, which corresponds to frequency category Very Rare (< 1 per 10,000). The incidence of myocarditis in younger males was at the high end of the range and corresponds to the frequency category Rare (≥1/10.000, <1/1.000).

Addition of a statement regarding lack of knowledge regarding myo/pericarditis risk in the peadiatric population below 12 years-of-age, is not supported.

MS6

Please find below some comments for both Signal pARs regarding mRNA COVID-19 vaccines and myo/pericarditis signal:

- We concur with the Rapporteur regarding not to include data from Nordic registry. An overall estimate or an interval estimated with all available data would be fine for us.
- Regarding wording for 4.4, we would support MS4 proposal. There are many uncertainties regarding children administration and we consider it is important this should be reflected in the SmPC to be known for other stakeholders.

Comment PRAC Rapporteur:

The comments of endorsment are noted.

3.9. Updated rapporteur's proposed recommendation

Based on review of the submitted data the benefit-risk balance remains unchanged.

Nevertheless, the MAH should adequately address the following:

Regarding ADR frequency in SmPC 4.8

The PRAC Rapporteur considers that the current frequency assignment **Not known** is **not accepted**.

The PRAC Rap notes that the current frequency category in 4.8 (frequency unknown) does not adequately represent the current body of evidence gathered in the post-marketing phase based on **observational studies** including nationwide health registers, or other electronic health care data sources in various non-European and European countries.

For instance based on the studies and literature (including reviews from spontaneous reporting systems) cited by the MAH the lowest and highest estimates were:

- A study by Diaz *et al.* conducted on data from 40 US hospitals including 2 million person who receiving at least 1 COVID-19 vaccination, 58.9% were women, the median age was 57 years (interquartile range [IQR], 40-70 years), 76.5% received more than 1 dose, 52.6% received the BNT162b2 vaccine (Pfizer/BioNTech), 44.1% received the mRNA-1273 vaccine (Moderna), and 3.1% received the Ad26.COV2.S vaccine (Janssen/Johnson&Johnson) reported myocarditis and pericarditis frequency following BNT162b2 vaccination for all ages combined of 0.10 (95% CI 0.061-0.154) per 10,000 for myocarditis and 0.18 (95% CI 0.13-0.255) per 10.000 for pericarditis in a US healthcare system,[xxxv]However these are very rough estimates and have limitations as they are based on data for the three vaccines together, and irrespective of first or second dose. For myocarditis, there were 11 cases for Spikevax, 9 cases for Comirnaty and none for the Janssen vaccine. For pericarditis, there were 12 cases for Spikevax, 23 (Comirnaty), and 2 (Janssen). Further, it is noted that the population included in this study only partly seems representative for the total population approved for Comirnaty as the median age in the study was 57 years (IQR 40-70 years), and given the clear age-dependent risk for myocarditis particularly. Finally, the total number of myocarditis cases following use of Comirnaty in this study (n=9) makes the estimations quite uncertain.
- Information about myocarditis and perimyocarditis by age has been reported by the Israeli Ministry of Health as part of their overall COVID-19 Vaccine monitoring (proactive). [xxxvi] Among males the reporting rate of myocarditis was lower for individuals 12 to 15 years of age than for individuals 16 to 19 years of age for both dose 1 (1/196,398=0.051 vs 3/261,112=0.115 per 10,000 doses) and dose 2 (11/158,541=0.0694 vs 37/226,452=**1.634 per 10,000 doses**), with rates for both doses declining thereafter with age.

The **Nordic cohort study** of 23.1 million individuals from DK, FI, NO and SE by Karlstadt *et al.* confirmed a higher risk after a second dose of Comirnaty and a higher risk in young men. **Excess events** within 28 days in young males of **0.57 [95% CI 0.39 – 0.75] per 10,000** after a second-dose vaccination with BNT162b2. Among females 16–24 years, the excess number of events per 10,000 vaccinated in the 28-day risk periods following first and second doses were 0.02 (95%CI, 0.01 to 0.05) and 0.05 (95%CI, 0.00 to 0.10) for BNT162b2.

The **EPI-PHARE** matched case-control study based on data from the French national health data system (SNDS) concluded that the Pfizer-BioNTech vaccine appears to be associated with an increased risk of myocarditis among men under the age of 30 (OR 10.9 [7.6-15.8] and **0.265 [95% CI 0.255-**

0.275] excess cases per 10,000 doses within 7 days following the second dose). Although the incidence of myocarditis is lower than it is among men, this risk also increases among young women below the age of 30 within 7 days following the second dose (OR 11.4 [4.5-28.6] and 0.043 [95% CI 0.037 – 0.045] excess cases per 10,000 doses for Pfizer-BioNTech).

The results from these recent EU studies are presented as excess number of cases which will underestimate the actual frequency. Further, time windows [28 *vs* 7 days] and exposure metrics may also not be entirely similar, which makes frequency assessment somewhat challenging. Nevertheless, both of these are well conducted studies with large data sets. In relation to some of the publications cited by the MAH, these studies are considered robust, and also of more relevance, given that the lower age groups, where the risk is largest, are well represented in these materials.

The **VAC4EU** retrospective, multi-database, cohort study, conducted during the study period ranging from December 1, 2020 observed the highest excess incidence rates **[per person-years]** of myocarditis or pericarditis as background post-vaccination in persons without COVID19:
ARS Tuscany: in males 18-24yrs: 121 per 100,000 person-years; in females 30-39yrs: 48 per 100,000 person-years
BIFAP PCHOSP: in males 18-24yrs: 152 per 100,000 person-years; in females 40-49yrs: 22 per 100,000 person-years
BIFAP PC-COVID: In males 12-17yrs: 49 per 100,000 person-years; in females 12-17yrs: 32 per 100,000 person-years.
The results from the VAC4EU study are shown here, but as the excess incidence rates are presented per person-years they are not readily compatible with the other EU studies, or ADR frequency category in the SmPC.

Based on the currently available combined body of evidence from clinical trials and post-marketing observational studies as cited by the MAH and recent nationwide health registers, or other electronic health care data sources in various European countries the incidence of myocarditis ranged from **0.1 to 1.6 per 10,000**, hence a frequency category **Very Rare < 1 per 10,000** in the SmPC section 4.8 would be more appropriate.

Note that this is would also be more in line with the wording already present in **SmPC section 4.4**. The rationale for the frequency category could be explained in sub-section *c "Description of selected adverse reactions"*. *I.e.* a footnote could be considered noting that the incidence of myocarditis in the younger males was at the high end of the range and would be closer to frequency category rare (≥1/10.000, <1/1.000)

Regarding refinement of SmPC section 4.4

In addition, the current wording should be further refined. The current product information section 4.4 mentions: ***Very rare*** *cases of myocarditis and pericarditis have been observed following vaccination with Comirnaty. These cases have primarily occurred within 14 days following vaccination, more often after the second vaccination, and more often in younger* ***men.***

It is proposed to remove and replace '**men**' (which implies adults only) by '**males**', as also cases have been observed in adolescent males aged below 18 years.

Further suggestions of MS are endorsed. See below.

Request for further adjustment of SmPC section 4.4 when more robust data become available

Based on the O/E analyses presented by the MAH (Table 1, Table 2 and Table 3) it is noted that although the absolute number of cases in males is higher, the background incidence in males is also

higher. Consequently, the O/E ratios above 1 do not really differ that much between males and females. This aspect is currently not reflected in the current wording in SmPC section 4.4. On the other hand, the numbers of female cases shown here, but also in the epidemiological studies cited by the MAH (as well as those conducted by VAC4EU and EPI-PHARE) are low, especially in the younger females, which raises the question regarding robustness of these estimates.

The MAH should commit to remain closely evaluating the risk estimates in females, and in case more (robust, stable) data would become available, provide a proposal for refined/adjusted the wording in SmPC section 4.4, as appropriate.

Characteristics, severity, outcome

Based on the above reviews of characteristics, severity, duration and outcome of myocarditis and pericarditis the current wording in the SmPC section 4.4 regarding disease course is still considered adequate. Nevertheless in a considerable number of cases no information on the duration of event, or whether the events were resolved is available. The MAH is expected to keep the clinical course, severity, outcome, sequelae under close monitoring in both spontaneous reports and ongoing and planned observational studies. The Rapporteur should be notified immediately in case of unexpected findings or trends.

3.9.1. PRAC Rapporteur proposed product information update

Deleted text in ~~Strike through~~, New text in **Bold**.

Summary of Product Characteristics (SmPC)

Section 4.4 Warnings and Precautions

Myocarditis and pericarditis

There is an increased risk for ~~Very rare cases of~~ myocarditis and pericarditis ~~have been observed~~ following vaccination with Comirnaty. These ~~cases~~ **conditions can develop within just a few days after vaccination and** have primarily occurred within 14 days ~~following vaccination,~~ **They have been observed** more often after the second vaccination, and more often in younger ~~men~~ **males.**

Available data suggest that the course of myocarditis and pericarditis following vaccination is not different from myocarditis or pericarditis in general.

Healthcare professionals should be alert to the signs and symptoms of myocarditis and pericarditis. Vaccinees should be instructed to seek immediate medical attention if they develop symptoms indicative of myocarditis or pericarditis such as (acute and persisting) chest pain, shortness of breath, or palpitations following vaccination.

Healthcare professionals should consult guidance and/or specialists to diagnose and treat this condition.

The risk of myocarditis after a third dose of Comirnaty has not yet been characterised.

Section 4.8 Side effects

Cardiac disorders

[Frequency] ~~Not known~~**Very rare**: myocarditis[d], pericarditis[d]

Description of selected adverse reactions

Myocarditis / Pericarditis

Based on observational studies within and outside Europe the incidence of myocarditis and pericarditis ranges from 0.1-1.6 per 10,000 persons, which corresponds to frequency category *Very Rare* (< 1 per 10,000). The incidence of myocarditis in younger males was at the high end of the range and corresponds to frequency category *Rare* (≥1/10.000, <1/1.000).

The **Patient Information Leaflet** should be amended accordingly:

Section 2

~~Very rare cases~~ **There is an increased risk** of myocarditis (inflammation of the heart muscle) and pericarditis (inflammation of the lining outside the heart) ~~have been reported~~ after vaccination with Comirnaty. The**se conditions can develop within just a few days after vaccination and** ~~cases~~ have primarily occurred within two weeks**.** ~~following vaccination,~~ **They have been observed** more often after the second vaccination, and more often ~~occurred~~ in younger ~~men~~ **males**. Following vaccination, you should be alert to signs of myocarditis and pericarditis, such as breathlessness, palpitations and chest pain, and seek immediate medical attention should these occur.

Section 4

~~Not known (cannot be estimated from the available data)~~ **Rare side effects: may affect up to 1 in 10,000 people**

- inflammation of the heart muscle (myocarditis) or inflammation of the lining outside the heart (pericarditis) which can result in breathlessness, palpitations or chest pain

3.10. Adopted (third) PRAC recommendation

Having considered the available evidence from large observational studies in and outside the EEA, as well as the data provided by the Marketing Authorisation Holder (MAH), the PRAC has agreed that the MAH for COVID-19 mRNA vaccine (nucleoside-modified) Comirnaty (BioNTech Manufacturing GmbH) should submit by Monday 6 December (by 9am CET time) a variation to amend the product information as described below (new text underlined):

Summary of Product Characteristics

Section 4.4 – Special warnings and precautions for use:

Myocarditis and pericarditis

There is an increased risk ~~Very rare cases~~ of myocarditis and pericarditis ~~have been observed~~ following vaccination with Comirnaty. These ~~cases~~ conditions can develop within just a few days after vaccination, and ~~cases~~ have primarily occurred within 14 days ~~following vaccination~~. They have been observed more often after the second vaccination, and more often in younger ~~men~~ males (see section 4.8). Available data suggest that the course of myocarditis and pericarditis following vaccination is not different from myocarditis or pericarditis in general.

Healthcare professionals should be alert to the signs and symptoms of myocarditis and pericarditis. Vaccinees should be instructed to seek immediate medical attention if they develop symptoms indicative of myocarditis or pericarditis such as (acute and persisting) chest pain, shortness of breath, or palpitations following vaccination.

Healthcare professionals should consult guidance and/or specialists to diagnose and treat this condition.

The risk of myocarditis after a third dose of Comirnaty has not yet been characterised.

Section 4.8 Undesirable effects

SOC cardiac disorders:

[Frequency] ~~Not known~~ Very rare: Myocarditis[d], Pericarditis[d]

Description of selected adverse reactions

Myocarditis

The increased risk of myocarditis after vaccination with Comirnaty is highest in younger males (see section 4.4).

Two large European pharmacoepidemiological studies have estimated the excess risk in younger males following the second dose of Comirnaty. One study showed that in a period of 7 days after the second dose there were about 0.265 (95% CI 0.255 - 0.275) extra cases of myocarditis in 12-29 year old males per 10,000 compared to unexposed persons. In another study, in a period of 28 days after the second dose there were 0.57 [95% CI 0.39 – 0.75] extra cases of myocarditis in 16-24 year old males per 10,000 compared to unexposed persons.

Package leaflet:

Section 2 – What you need to know before you receive Comirnaty

Warning and precautions

There is an increased risk ~~Very rare cases~~ of myocarditis (inflammation of the heart muscle) and pericarditis (inflammation of the lining outside the heart) ~~have been reported~~ after vaccination with Comirnaty (see section 4). These conditions can develop within just a few days after vaccination and have primarily occurred within 14 days. They have been observed more often after the second vaccination, and more often ~~occurred~~ in younger ~~men~~ males. Following vaccination, you should be alert to signs of myocarditis and pericarditis, such as breathlessness, palpitations and chest pain, and seek immediate medical attention should these occur.

Section 4 - Possible side effects

~~Not known (cannot be estimated from the available data)~~ Very rare side effects: may affect up to 1 in 10,000 people

- inflammation of the heart muscle (myocarditis) or inflammation of the lining outside the heart (pericarditis) which can result in breathlessness, palpitations or chest pain.

4. Annexes

ANNEX 1

ANNEX 2 – Additional data included in MAH response

ANNEX 3

ANNEX 4

[i] Willame C, Dodd C, Gini R, et al. Background rates of Adverse Events of Special Interest for monitoring COVID-19 vaccine, NL PHARMO HOSP. Available from: http://www.encepp.eu/phact_links.shtml. Updated March 2021. Accessed 27 August 2021.

[ii] Elfström P, Hamsten A, Montgomery SM, et al. Cardiomyopathy, pericarditis and myocarditis in a population-based cohort of inpatients with coeliac disease. J Intern Med. 2007;262(5):545-54. DOI: 10.1111/j.1365-2796.2007.01843.x.

[iii] Willame C, Dodd C, Gini R, et al. Background rates of Adverse Events of Special Interest for monitoring COVID-19 vaccine, IT_ARS. Available from: http://www.encepp.eu/phact_links.shtml. Updated March 2021. Accessed 27 August 2021.

[iv] Willame C, Dodd C, Gini R, et al. Background rates of Adverse Events of Special Interest for monitoring COVID-19 vaccine, ES_BIFAP_PCHOSP. Available from: http://www.encepp.eu/phact_links.shtml. Updated March 2021. Accessed 27 August 2021.

[v] Barda N, Dagan N, Ben-Shlomo Y, et al. Safety of the BNT162b2 mRNA Covid-19 Vaccine in a Nationwide Setting. N Engl J Med. 2021;385(12):1078-90.

[vi] Klein NP, Lewis N, Goddard K, et al. Surveillance for Adverse Events After COVID-19 mRNA Vaccination. JAMA. 2021

[vii] Diaz GA, Parsons GT, Gering SK, et al. Myocarditis and Pericarditis After Vaccination for COVID-19. JAMA. 2021;326(12):1210-2.

[viii] Pepe S, Gregory AT, Denniss AR. Myocarditis, Pericarditis and Cardiomyopathy After COVID-19 Vaccination. Heart Lung Circ. 2021;30(10):1425-9.

[ix] Mevorach D, Anis E, Cedar N, et al. Myocarditis after BNT162b2 mRNA Vaccine against Covid-19 in Israel. N Engl J Med. 2021.

[x] Witberg G, Barda N, Hoss S, et al. Myocarditis after Covid-19 Vaccination in a Large Health Care Organization. N Engl J Med. 2021

[xi] Israel Ministry for Health https://www.gov.il/en/departments/publications/reports/safety-results-from-nationwide-booster-campaign

[xii] Oster M, mRNA COVID-19 Vaccine-Associated Myocarditis. VACCINES AND RELATED BIOLOGICAL PRODUCTS ADVISORY COMMITTEE Meeting Date: 26 October 2021. Available at: https://www.fda.gov/media/153514/download. Accessed Nov 5, 2021

[xiii] Gargano JW, Wallace M, Hadler SC, et al. Use of mRNA COVID-19 Vaccine After Reports of Myocarditis Among Vaccine Recipients: Update from the Advisory Committee on Immunization Practices - United States, June 2021. MMWR Morb Mortal Wkly Rep. 2021;70(27):977-82.

[xiv] Boehmer TK, Kompaniyets L, Lavery AM, et al. Association Between COVID-19 and Myocarditis Using Hospital-Based Administrative Data - United States, March 2020-January 2021. MMWR Morb Mortal Wkly Rep. 2021;70(35):1228-32

[xv] Murk W, Gierada M, Fralick M, et al. Diagnosis-wide analysis of COVID-19 complications: an exposure-crossover study. CMAJ. 2021;193(1):E10-E8.

[xvi] Diaz GA, Parsons GT, Gering SK, et al. Myocarditis and Pericarditis After Vaccination for COVID-19. JAMA. 2021;326(12):1210-2.

[xvii] Pepe S, Gregory AT, Denniss AR. Myocarditis, Pericarditis and Cardiomyopathy After COVID-19 Vaccination. Heart Lung Circ. 2021;30(10):1425-9.

[xviii] Israel Ministry for Health https://www.gov.il/en/departments/publications/reports/safety-results-from-nationwide-booster-campaign

[xix] Ogata AF, Cheng C-A, Desjardins M, et al. Circulating SARS-CoV-2 vaccine antigen detected in the plasma of mRNA-1273 vaccine recipients. Clin Infect Dis. 2021;ciab465.

[xx] The Human Protein Atlas. Online. Available from: https://www.proteinatlas.org/ENSG00000130234-ACE2/tissue. Accessed 20 Sep 2021.

[xxi] Chen L, Li X, Chen M, et al. The ACE2 expression in human heart indicates new potential mechanism of heart injury among patients infected with SARS-CoV-2. Cardiovasc Res. 2020;116(6):1097-1100.

[xxii] Tschöpe C, Ammirati E, Bozkurt B, et al. Myocarditis and inflammatory cardiomyopathy: current evidence and future directions. Nat Rev Cardiol 2021;18:169–93.

[xxiii] Ngo ST, Steyn FJ, McCombe PA. Gender differences in autoimmune disease. Front Neuroendocrinol. 2014;35(3):347-69.

[xxiv] Kanduc D, Shoenfeld Y. Molecular mimicry between SARS-CoV-2 spike glycoprotein and mammalian proteomes: implications for the vaccine. Immunologic Research 2020;68(5):310–13.

[xxv] Kanduc D, Shoenfeld Y. Molecular mimicry between SARS-CoV-2 spike glycoprotein and mammalian proteomes: implications for the vaccine. Immunologic Research 2020;68(5):310–13.

[xxvi] BC classification of Myocarditis _Version 1.5.0 https://brightoncollaboration.us/myocarditis-case-definition-update/

[xxvii] A Guideline on Summary of Product Characteristics (SmPC) September 2009 https://ec.europa.eu/health/sites/default/files/files/eudralex/vol-2/c/smpc_guideline_rev2_en.pdf

[xxviii] Kanduc D, Shoenfeld Y. Molecular mimicry between SARS-CoV-2 spike glycoprotein and mammalian proteomes: implications for the vaccine. Immunologic Research 2020;68(5):310–13.

[xxix] Diaz GA, Parsons GT, Gering SK, et al. Myocarditis and Pericarditis After Vaccination for COVID-19. JAMA. 2021;326(12):1210-2.

[xxx] Pepe S, Gregory AT, Denniss AR. Myocarditis, Pericarditis and Cardiomyopathy After COVID-19 Vaccination. Heart Lung Circ. 2021;30(10):1425-9.

[xxxi] Israel Ministry for Health https://www.gov.il/en/departments/publications/reports/safety-results-from-nationwide-booster-campaign

[xxxii] Diaz GA, Parsons GT, Gering SK, et al. Myocarditis and Pericarditis After Vaccination for COVID-19. JAMA. 2021;326(12):1210-2.

[xxxiii] Pepe S, Gregory AT, Denniss AR. Myocarditis, Pericarditis and Cardiomyopathy After COVID-19 Vaccination. Heart Lung Circ. 2021;30(10):1425-9.

[xxxiv] Israel Ministry for Health https://www.gov.il/en/departments/publications/reports/safety-results-from-nationwide-booster-campaign

[xxxvi] Israel Ministry for Health https://www.gov.il/en/departments/publications/reports/safety-results-from-nationwide-booster-campaign