EMA/440372/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report for paediatric studies submitted in accordance with article 46 of regulation (EC) No 1901/2006, as amended

Comirnaty

Common name: COVID-19 mRNA Vaccine (nucleoside modified)

Procedure no.: EMEA/H/C/005735/P46/067

Marketing authorisation holder (MAH): BioNTech Manufacturing GmbH

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Status of this report and steps taken for the assessment			
Current step	**Description**	**Planned date**	**Actual Date**
☐	Start of procedure	17 July 2023	17 July 2023
☐	CHMP Rapporteur Assessment Report	21 Aug 2023	16 Aug 2023
☐	CHMP members comments	04 Sept 2023	04 Sept 2023
☐	Updated CHMP Rapporteur Assessment Report	07 Sept 2023	n/a
☒	CHMP adoption of conclusions:	14 Sept 2023	14 Sept 2023

Administrative information

Procedure resources	
Rapporteur:	**Name: Filip Josephson**

List of abbreviations

Abbreviation	Definition
ACIP	Advisory Committee on Immunization Practices
AE	adverse event
AIDS	acquired immunodeficiency syndrome
ARI	acute respiratory infection
BMI	body mass index
CAIR	California Immunization Registry
CCI	Charlson comorbidity index
cCCI	classic Charlson comorbidity index
CHF	congestive heart failure
CHIP	Children's Health Insurance Program
CI	confidence interval
CLIA	Clinical Laboratory Improvement Amendments
COPD	chronic obstructive pulmonary disease
COVID-19	coronavirus disease 2019
DCT	data collection tool
ED	emergency department
EHR	electronic health record
EUA	emergency use authorisation
FDA	Food and Drug Administration
GEE	generalized estimating equation
HIV	human immunodeficiency virus
HR	hazard ratio
ICD	International Classification of Diseases
ICU	intensive care unit
IEC	Independent Ethics Committee
IRB	Institutional Review Board
KPSC	Kaiser Permanente Southern California
LOE	lack of efficacy
LOS	length of stay
LTCF	long term care facility
mRNA	messenger RNA
NLP	Natural Language Processing
OR	odds ratio
PAC	Post Authorisation Commitment
PCR	polymerase chain reaction
PHI	protected health information
RT-PCR	reverse transcriptase polymerase chain reaction
RSV	respiratory syncytial virus
SAE	serious adverse event
SARS-CoV-2	severe acute respiratory syndrome coronavirus – 2
SAP	statistical analysis plan
SDIR	San Diego Immunization Registry
SOC	standard of care
TND	Test negative design
VE	vaccine effectiveness
WGS	whole genome sequencing
WHO	World Health Organization

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1. Introduction

On 21st of June 2023, the MAH submitted a completed paediatric study C4591014 (Kaiser) for BNT162b2, in accordance with Article 46 of Regulation (EC) No 1901/2006, as amended.

These data are also submitted as part of the post-authorisation measures.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that C4591014 (Kaiser) is a stand-alone study.

2.2. Information on the pharmaceutical formulation used in the study

BNT162b2 is a modified RNA vaccine that encodes the full-length, membrane-anchored S glycoprotein of SARS-CoV-2 with two introduced proline mutations to lock it in the prefusion conformation. The formulation (doses and primary vaccination schedule) differs for the various age groups in the study, the recommendations according to the SmPC at the time of the study were employed.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- C4591014 (Kaiser)

2.3.2. Clinical study

C4591014 (Kaiser)

Description

A retrospective database study using Kaiser Permanente Southern California (KPSC) electronic health records to evaluate the effectiveness of BNT162b2 in a real-world setting.

The primary objective was to evaluate the effectiveness of 2 doses of BNT162b2 >7 days after the second dose against hospitalisation for acute respiratory infection (ARI) due to SARS-CoV-2 infection using a test-negative design (TND). Stratification by age group was requested in alignment with the rolling authorisations. TND studies are considered a robust type of observational study for evaluating vaccine effectiveness (VE) against infectious respiratory diseases. The TND is a case-control study where all included subjects are required to be tested for the disease of interest. Previous exposures (e.g., vaccines) are compared between disease-positive "cases" and disease- negative "controls" to evaluate whether the exposures are associated with disease-negative status (i.e., protective). Individuals are enrolled from a group of subjects presenting for medical care with a common clinical presentation (e.g., ARI) to ensure that cases and controls are enrolled from the same source population. As a result, the main advantages of the TND are that it helps to avoid bias due to

(unmeasured) healthcare-seeking behaviour, including the propensity to test for infection, and its ease of access to controls that are representative of the source population.

Methods

Study participants

Inclusion criteria

Individuals met the following inclusion criteria to be eligible for inclusion in the study:

1. KPSC Individuals eligible to receive BNT162b2 who were admitted to the hospital (primary objective and some secondary objectives) with acute respiratory infection after 14 December 2020 (date of first vaccinations at KPSC), and who received a PCR test for SARS-CoV-2.
2. For secondary objectives estimating VE against ED admission, the TND included KPSC individuals eligible to receive BNT162b2 who presented to the ED with ARI without a subsequent hospitalisation within 14 days after 14 December 2020, and who received a PCR test for SARS-CoV-2.
3. We included membership requirement of 1 year prior to index date (except in the >6 month to 4 years old cohort, where individuals <1 year old did not have the 1-year membership requirement), which was defined as the date of hospitalisation or ED admission (allowing 31-day administrative gap), to facilitate accurate capture of comorbid conditions.

Exclusion Criteria

1. Individuals who received only another newly licensed or investigational SARS-CoV-2 vaccine or COVID-19 prophylactic agent other than COVID-19 vaccine prior to hospitalisation (or ED, for secondary objective).
2. If index date was within 7 days of 2nd dose or within 14 days of all other dosing regimens from vaccination date.

Setting

Kaiser Permanente Southern California (KPSC) is a large integrated healthcare delivery system that covers more than 4.7 million members in Southern California (United States).

Treatments

In this non-interventional retrospective study, the study participants had received either zero, one, two or three doses of BNT162b2.

Objectives and endpoints

The primary objective of the study was to estimate vaccine effectiveness (VE) of 2 doses of BNT162b2 vaccine against ARI requiring hospitalisation due to SARS-CoV-2 infection among KPSC members eligible for vaccination. VE was evaluated using a TND, including all KPSC individuals eligible for vaccination who were admitted to the hospital with an ARI after 14 December 2020 (date of first vaccinations at KPSC), and who received a PCR test for SARS-CoV-2.

Secondary and exploratory objectives were designed *a priori* to examine VE by the number of doses, as well as against ED admission, specific variants, durability, age cutoffs to align with regulatory

authorisations/approvals, and other populations of interest. The table below outlines primary, secondary, and exploratory objectives for the current study for the TND design.

Table 1: TND Study Design Proposed Objectives

Test-Negative Design	
Objectives	**Endpoints**
Primary:	Primary:
1. To estimate the effectiveness of 2 doses of BNT162b2 against hospitalisation for ARI due to SARS-CoV-2 infection.	VE calculated as 1 minus the OR comparing the odds of being vaccinated with 2 doses with BNT162b2 for hospitalised cases and controls, multiplied by 100.
Secondary:	Secondary:
1. To estimate the effectiveness of 2 doses of BNT162b2 against ED admission (without subsequent hospitalisation) for ARI due to SARS-CoV-2 infection.	VE calculated as 1 minus the OR comparing the odds of being vaccinated with 2 doses BNT162b2 for ED cases and controls, multiplied by 100.
2. To describe the effectiveness of only 1 dose of BNT162b2 (i.e., partially vaccinated) against hospitalisation for ARI due to SARS-CoV-2 infection.	VE calculated as 1 minus the OR comparing the odds of being partially vaccinated with BNT162b2 (only 1 dose) for hospitalised cases and controls, multiplied by 100.
3. To describe the effectiveness of only 1 dose of BNT162b2 (i.e., partially vaccinated) against ED admission (without subsequent hospitalisation) for ARI due to SARS-CoV-2 infection.	VE calculated as 1 minus the OR comparing the odds of being partially vaccinated with BNT162b2 (only 1 dose) for ED cases and controls, multiplied by 100.
4. To describe the effectiveness of ≥1 dose of BNT162b2 (i.e., ever vaccinated) against hospitalisation for ARI due to SARS-CoV-2 infection.	VE calculated as 1 minus the OR comparing the odds of ever being vaccinated (≥1 dose) with BNT162b2 for hospitalised cases and controls, multiplied by 100.
5. To describe the effectiveness of ≥1 dose of BNT162b2 (i.e., ever vaccinated) against ED admission (without subsequent hospitalisation) for ARI due to SARS-CoV-2 infection.	VE calculated as 1 minus the OR comparing the odds of ever being vaccinated (≥1 dose) with BNT162b2 for ED cases and controls, multiplied by 100.
6. To describe the effectiveness of >2 doses of BNT162b2 against hospitalisation for ARI due to SARS-CoV-2 infection.	VE calculated as 1 minus the OR comparing the odds of >2 doses with BNT162b2 for hospitalised cases and controls, multiplied by 100.
7. To describe the effectiveness of >2 doses of BNT162b2 against ED admission (without subsequent hospitalisation) for ARI due to SARS-CoV-2 infection.	VE calculated as 1 minus the OR comparing the odds of >2 doses with BNT162b2 for ED cases and controls, multiplied by 100.
8. To further describe the effectiveness of BNT162b2 against hospitalisation and ED admission stratified by prevalent or important viral strains	BNT162b2 VE estimates stratified by virus variant (as determined by genome sequencing) and select descriptive analyses described above by number of doses received
9. To evaluate the effectiveness of BNT162b2 against severe hospitalisation-related outcomes (e.g., ICU admission, mechanical ventilation, and death)	BNT162b2 VE estimates against severe outcomes including ICU admission, mechanical ventilation, and death by number of doses received.

10. To evaluate overall and variant-specific effectiveness of BNT162b2 against SARS-CoV- 2 infections and COVID-19 related hospital admissions by time since vaccination (by month)	Monthly VE estimates between variants of interest using independent Z tests of log hazard ratios.
Tertiary/Exploratory:	Tertiary/Exploratory:
1. Compare VE of models stratified by relevant vaccination phase time periods to understand how VE may change as vaccinated patient risk profiles or variants change over time.	BNT162b2 VE estimates by vaccination phase
2. To estimate the effectiveness of 1, ≥1, 2 or >2 doses of BNT162b2 against hospitalisation or ED for ARI due to SARS-CoV-2 infection.	VE calculated as 1 minus the OR comparing the odds of have >2, 2, 1, or ≥1 doses of BNT162b2 for hospitalised and ED cases and controls, multiplied by 100.
3. To further describe the effectiveness of BNT162b2 against hospitalisation and ED admission stratified by various patient characteristics (eg, age, sex, race/ethnicity, chronic medical conditions, history of SARS-CoV-2 infection, long-term care facility residence, pregnancy status, and receipt of influenza vaccine).	BNT162b2 VE estimates by time between first and second dose among those who received 2 doses
4. To describe the proportion of hospitalised and ED patients with ARI where SARS-CoV-2 was identified.	Proportion of ARI hospitalisations where SARS-CoV-2 is identified.
5. To summarize the proportion of patients who receive 0, 1, 2, or >2 doses of BNT162b2 among hospitalised and ED patients.	Proportion of patients who receive 0, 1, 2, or >2 doses of BNT162b2
6. To summarize the time between administration of the first and second dose of BNT162b2 among patients who received 2 doses and between the second and third dose of BNT162b2 among patients who received 3 doses	Average and median time between receipt of the first and second dose BNT162b2 among patients who received two doses and between second and third dose BNT162b2 among patients who received 3 doses.
7. To summarize the time since vaccination with BNT162b2 (most-recent dose) since vaccinations at KPSC began	Average and median time between 14 December 2020 and receipt of last dose among patients receiving BNT162b2 stratified by total number of doses received.
8. To describe demographic, clinical, and laboratory characteristics (i.e., viral strain) and disease severity of any BNT162b2 vaccine failures	Describe age, gender, race/ethnicity, clinical characteristics, and severity (ICU admission, ventilator, death) of any patients who received BNT162b2 and test positive for SARS-CoV-2 stratified by total number of doses received
9. To describe COVID-19 disease severity for vaccinated and unvaccinated cases in the TND design	Describe disease severity for vaccinated and unvaccinated cases (eg, average hospital LOS, 30- day readmission, the proportion requiring ICU admission or mechanical ventilation, death) stratified by total number of doses received

Sample size

No formal sample size calculations were undertaken as data were retrieved from a retrospective database. The TND analysis was event-driven based on the number of cases identified. Study sample size was based on the primary endpoint (BNT162b2 VE against ARI requiring hospitalisation where SARS-CoV-2 was identified in the TND study). The required sample size was dependent on i) the proportion of all-cause ARI requiring hospitalisation caused by SARS-CoV-2 (which determined the number of cases identified and the ratio of cases to controls in the primary analysis), ii) the average uptake of BNT162b2 in the study population over the duration of the study, and iii) the assumed VE of the specific COVID-19 vaccine against ARI requiring hospitalisation where SARS-CoV-2 was identified.

Randomisation and blinding (masking)

Not relevant for the retrospective study in question.

Statistical Methods

Test Negative Design Analyses

The analyses below were done separately for the primary population of hospitalised individuals as well as the secondary population of individuals with ED encounters. Further, they were stratified by age groups of interest in alignment with FDA authorisations and approvals over time. Individuals were included in the analyses regardless of prior COVID-19 infection status.

Descriptive Analyses

The proportion of hospitalised and ED individuals with ARI where SARS-CoV-2 was identified, as well as the proportion of individuals who received 0, 1, 2, and >2 doses of BNT162b2 were reported. We provided the average and median time between receipt of the first and second dose of BNT162b2 among individuals who received 2 doses, between receipt of the first to second and second to third dose of BNT162b2 among individuals who received 3 doses, as well as between 14 December 2020 (beginning of vaccinations at KPSC) and receipt of last dose of BNT162b2. Finally, we described age, gender, race/ethnicity, clinical characteristics, and severity (ICU admission, ventilator, death) by vaccination status, variant and among those PCR + for SARS-CoV-2.

Estimated Crude (Unadjusted) VE

Odds of having received BNT162b2 for cases and test-negative controls were constructed and compared using ORs and 95% CIs. VE was calculated as 1−OR multiplied by 100. Corresponding 95% CIs were calculated using the Wald method. Any VE estimates that resulted in a 95% confidence interval width greater than 50 percentage points were deemed imprecise and should be interpreted with caution. These results were included in tables and figures for completeness, but removed from the interpretation of results, similar to other COVID-19 vaccine effectiveness studies.

Estimating Adjusted VE

In addition to constructing crude VE estimates, logistic regression modelling to assess BNT162b2 VE after adjustment for potentially confounding factors was performed. Findings from the Phase 3 studies, expert opinion, and published studies of clinical/biologic factors were used to identify covariates for inclusion in the model. These were assessed for their availability and ability for adjusting crude results, including an examination of their distributions and missingness. Bivariate associations of potential confounders with the outcome, exposure, and each other were examined. For those with suggestions of imbalance with either exposure or outcome, the association between exposure and outcome was stratified by categories of the potential confounder to look for differences across strata (potential effect

modification) and influence on summary estimates of association (confounding). The variables were ultimately selected based on a combination of the a priori decisions and a qualitative assessment of the empirical relationships. The results of the multivariable model corroborated the knowledge gained from the stratified analyses. A 2-sided alpha of 0.05 was used for logistic regression modelling. Corresponding 95% CIs were calculated using the Wald method. Similar to other COVID-VE reports throughout the pandemic, VE estimates that resulted in a 95% confidence interval width greater than 50 percentage points were considered imprecise. As a result these estimates were not included in the interpretation of the results.44,45 A GEE estimator was used with a robust sandwich variance estimator to account for clustering introduced by variables measured at the neighbourhood level.

Variables

Outcomes and Exposures

Cases: Cases were defined as those with any positive KPSC laboratory-confirmed PCR test from a sample collected within 14 days prior to hospital admission through 3 days after a hospital admission (primary objective and some secondary) or ED encounter (secondary objectives) with an ARI code.

Controls: Controls were defined as those with laboratory confirmed negative COVID-19 (negative COVID-19 test collected within 14 days prior to hospital admission through 3 days after a hospital admission for (primary objective and some secondary) or ED encounter for secondary objectives with an ARI code and no positive COVID-19 tests within 14 days prior to encounter.

Exposure Definition: The exposure of interest was history of vaccination with BNT162b2. For the primary objective, individuals were considered vaccinated if they have documented evidence of receiving the second dose of BNT162b2 ≥7 days before index date (i.e., date of hospitalisation or ED admission). Five levels of exposure variables were assessed:

1. Initial 2-dose vaccination series defined as 2 doses of BNT162b2 received with ≥7 days between receipt of the 2nd dose and the index date. This group served as the "exposed" group evaluated in the primary objective. Individuals who received only 1 dose or 2 doses of BNT162b2 with <7 days between receipt of the 2nd dose and the index date were excluded from analysis.
2. Partially vaccinated defined as 1 dose (only) of BNT162b2 received with ≥14 days between receipt of the 1st dose and the index date. This group served as the "exposed" group for a secondary endpoint. Individuals who received 2 doses or 1 dose of BNT162b2 with <14 days between receipt of the 1st dose and the index date were excluded from analysis.
3. Ever vaccinated defined as ≥1 dose of BNT162b2 received with ≥14 days between index date and receipt of the 1st dose. Individuals who received 1 dose of BNT162b2 received with <14 days between receipt of the 1st dose and the index date were excluded from analysis.
4. Greater than 2 doses defined as receiving >2 doses of BNT162b2 with ≥14 days between receipt of the last dose and the index date.
5. Unvaccinated defined as never received BNT162b2 as of index date. This group served as the reference exposure group (i.e., 'unexposed' group) in most VE analyses.

The 2-dose exposure group was considered for the primary objective, while the partially (1 dose), ever vaccinated (≥1 dose) and additional (>2 doses) groups were considered in secondary objectives.

Outside Vaccinations

To obtain information about vaccination that occurs outside of the KPSC healthcare system, KPSC established a partnership with 7 national pharmacy chains as well as the data exchange with the California Immunization Registry (CAIR). This partnership allows KPSC members to receive influenza and other vaccines outside of KPSC pharmacies. Starting 30 December 2020, a bidirectional data exchange was established with CAIR, thereby allowing capture of vaccinations received outside of KPSC. CAIR bidirectionality brings together a partnership between electronic medical records, the public health department, and pharmacies. Doses administered outside of KPSC were recorded in the electronic health record as, for example, "Covid-19 vaccine, Pfizer, external administration."

In California, COVID-19 vaccination providers are required to report COVID-19 doses administered within 24 hours of administration to their local immunisation registry.

Covariates

Individual-level and neighbourhood-level factors were considered for analysis. These are factors that either were identified as important covariates in previous work, have been identified in other risk factor literature, or were variables that might be associated with the exposure as well as outcome (i.e., prior positive SARS-CoV-2 PCR test, etc). We also included calendar time as a covariate in our models to adjust for phase in vaccine rollout, testing practice changes, social distancing impacts, surges, and potential changes in clinical treatments.

Table 2: Factors to be considered in models

Demographics	Comorbidities	Care utilization prior to test	Neighborhood characteristics	COVID-history	Individual risk indicators
Age	Cardiac disease	Outpatient encounters	Population density	Prior negative PCR tests	HCW occupation
Sex	Organ transplant	Inpatient encounters	Median income	Prior positive PCR tests	Long-term care resident
Race/ethnicity	Diabetes with A1C	ED encounters	Neighborhood deprivation index	Prior negative serology tests	
	COPD	Influenza vaccination	Education	Prior positive serology tests	
	Renal disease	Pneumococcal vaccination	Medical Center		
	BMI	Virtual encounters			
	Malignancy				
	Hypertension				
	Charlson Comorbidity Index/Sun Pediatric Comorbidity Index				
	Sedentary vs. Active				
	Immunocompromised				

The Charlson Comorbidity Index (CCI) is a validated measure of 1-year mortality risk. The CCI sums 17 comorbidities which are weighted from 1 to 6, with 6 representing the most severe morbidity based on ICD-10 codes and age.

Among individuals <18 years the Sun Paediatric Comorbidity Index is used as a validated summary measure of disease burden. The index sums paediatric specific conditions which are each assigned weights ranging from 1 to 5.

The Neighbourhood Deprivation Index (NDI) is a validated scale to assess 20 socioeconomic neighbourhood factors that are indicators of community health outcomes. The index includes 7 domains: poverty, occupation, housing, employment, education, racial composition, and residential stability. A higher NDI score indicates increased health risk for the area.

Results

Recruitment

The study periods for analysis were varied by age group based on evolving age-based authorisations from the FDA. As such, the study periods were:

- for adults 18 years of age and older: 14 December 2020 – 31 August 2022;
- 12-17 years of age 10 May 2021 to 31 August 2022;
- 5-11 years of age; 29 October 2021 to 31 August 2022, and
- ≥6 months to 4 years of age 23 July 2022 – 7 April 2023.

Baseline data

Patient characteristics and outcomes of individuals 12-17 years of age hospitalised with an ARI 10 May 2021 - 31 August 2022 with a SARS-COV-2 test result: TND analysis

Between 10 May 2021 to 31 August 2022, there were 393 KPSC individuals 12-17 years of age with an ARI hospitalisation and SARS-CoV-2 PCR test included in the analysis. The mean age was 14.8 years (standard deviation (SD) 1.64) and median was 15 years. About half (52.2%) were Hispanic and a quarter (25.2%) White. Individuals who were a normal or healthy weight (up to 85th percentile) had a higher proportion of vaccination (68.4%) than unvaccinated (31.6%). Fifty-four percent (53.9%) of individuals were male. The most common comorbidity was chronic obstructive pulmonary disease (23.7%) and 14% were immunocompromised. The majority (61.1%) of individuals had a Charlson Comorbidity Index of zero. Almost all individuals had received a pneumococcal vaccine (95.2%) and 50.6% had received a flu vaccine in the past 12 months.

Forty-eight percent (48.3%) of individuals were unvaccinated, 2.8% had received 1 dose of BNT162b2, 37.9% had received 2 doses, and 10.9% had received 3 doses. Race/ethnicity, body mass index, and clinical outcomes were generally similar among the unvaccinated and individuals vaccinated with 1, 2, or 3 doses. Individuals who received 3 doses had a higher proportion of hypertension (14.0%, p-value 0.0044) and were immunocompromised (20.9%, p-value 0.5295). The proportion of unvaccinated individuals receiving a flu shot in the past 12 months was 32.1% and among vaccinated individuals, flu shots in the group based on the number of BNT162b2 were 1 dose: 63.6%; 2 doses: 66.4%; 3 doses: 74.4%.

Among 149 individuals (37.9%) individuals with 2 doses of BNT162b2, the mean age was 14.9 years (SD 1.60) and median was 15 years. Forty-four (44.3%) were Hispanic and a 28.2% White. Fifty-four percent (54.4%) of individuals were male. The most common comorbidity was chronic obstructive pulmonary disease (24.2%) and 13.4% were immunocompromised. The majority (60.4%) of individuals had a CCI of zero. Almost all individuals had received a pneumococcal vaccine (95.3%) and 66.4% had received a flu vaccine in the past 12 months.

Table 3: Study C4591014: Patient and clinical characteristics of adolescents 12-17 years of age hospitalised 10 May 2021 - 31 August 2022 due to acute respiratory infection with a PCR SARS-CoV-2 test by vaccination status: Test Negative Design

	Unvaccinated (N=190) 48.3%	1 dose BNT162b2 (N=11) 2.8%	2 doses BNT162b2 (N=149) 37.9%	3 doses BNT162b2 (N=43) 10.9%	Total (N=393)	P value
Age						0.1291
Mean (SD)	14.6 (1.66)	15.3 (1.95)	14.9 (1.60)	15.1 (1.56)	14.8 (1.64)	
Median	15	16	15	15	15	
Sex						0.6984
Male	104 (54.7%)	<6 (N/A)	81 (54.4%)	23 (53.5%)	212 (53.9%)	
Female	86 (45.3%)	7 (63.6%)	68 (45.6%)	20 (46.5%)	181 (46.1%)	
Race/ethnicity						0.2201
Asian	<6 (N/A)	<6 (N/A)	16 (10.7%)	<6 (N/A)	25 (6.4%)	
Black	27 (14.2%)	<6 (N/A)	20 (13.4%)	7 (16.3%)	55 (14.0%)	
Hispanic	105 (55.3%)	8 (72.7%)	66 (44.3%)	26 (60.5%)	205 (52.2%)	
Other	<6 (N/A)	<6 (N/A)	<6 (N/A)	<6 (N/A)	8 (2.0%)	
Pacific Islander	<6 (N/A)	<6 (N/A)	<6 (N/A)	<6 (N/A)	<6 (N/A)	
White	49 (25.8%)	<6 (N/A)	42 (28.2%)	7 (16.3%)	99 (25.2%)	
Body-mass index, kg/m2						0.1651
Underweight (<18.5)	38 (20.0%)	<6 (N/A)	29 (19.5%)	10 (23.3%)	78 (19.8%)	
Normal or healthy weight (18.5-24.9)	60 (31.6%)	<6 (N/A)	63 (42.3%)	23 (53.5%)	150 (38.2%)	
Overweight (25.0-29.9)	34 (17.9%)	<6 (N/A)	25 (16.8%)	<6 (N/A)	62 (15.8%)	
Obese, class 1 (30.0-34.9)	28 (14.7%)	<6 (N/A)	14 (9.4%)	<6 (N/A)	47 (12.0%)	
Obese, class 2-3 (≥35.0)	28 (14.7%)	<6 (N/A)	14 (9.4%)	<6 (N/A)	50 (12.7%)	
Unknown	<6 (N/A)	<6 (N/A)	<6 (N/A)	<6 (N/A)	6 (1.5%)	
Comorbidities						
Hypertension	<6 (N/A)	<6 (N/A)	6 (4.0%)	6 (14.0%)	16 (4.1%)	0.0044
Congestive heart failure	<6 (N/A)	<6 (N/A)	<6 (N/A)	<6 (N/A)	<6 (N/A)	0.8389
Myocardial infarction	<6 (N/A)	<6 (N/A)	<6 (N/A)	<6 (N/A)	<6 (N/A)	
Peripheral vascular disease	13 (6.8%)	<6 (N/A)	8 (5.4%)	<6 (N/A)	27 (6.9%)	0.5457
Cerebrovascular disease	<6 (N/A)	<6 (N/A)	<6 (N/A)	<6 (N/A)	7 (1.8%)	0.2515
Diabetes						0.1293
Diabetes with unknown glycated haemoglobin	<6 (N/A)	<6 (N/A)	<6 (N/A)	<6 (N/A)	<6 (N/A)	
Diabetes with glycated haemoglobin <7.5%	<6 (N/A)	<6 (N/A)	<6 (N/A)	<6 (N/A)	<6 (N/A)	
Diabetes with glycated haemoglobin ≥7.5%	<6 (N/A)	<6 (N/A)	<6 (N/A)	<6 (N/A)	<6 (N/A)	
No diabetes diagnosis	188 (98.9%)	10 (90.9%)	144 (96.6%)	40 (93.0%)	382 (97.2%)	
Chronic obstructive pulmonary disease	42 (22.1%)	<6 (N/A)	36 (24.2%)	12 (27.9%)	93 (23.7%)	0.8533
Renal disease	<6 (N/A)	<6 (N/A)	<6 (N/A)	<6 (N/A)	8 (2.0%)	0.0257
Malignancy	14 (7.4%)	<6 (N/A)	16 (10.7%)	7 (16.3%)	39 (9.9%)	0.2327
Organ transplant	<6 (N/A)	<6 (N/A)	<6 (N/A)	<6 (N/A)	<6 (N/A)	0.0945
Immunocompromised	24 (12.6%)	<6 (N/A)	20 (13.4%)	9 (20.9%)	55 (14.0%)	0.5295
Charlson comorbidity index						0.2598
0	122 (64.2%)	6 (54.5%)	90 (60.4%)	22 (51.2%)	240 (61.1%)	
1	45 (23.7%)	<6 (N/A)	36 (24.2%)	10 (23.3%)	93 (23.7%)	
2	10 (5.3%)	<6 (N/A)	7 (4.7%)	<6 (N/A)	21 (5.3%)	
3	<6 (N/A)	<6 (N/A)	8 (5.4%)	<6 (N/A)	14 (3.6%)	
≥4	10 (5.3%)	<6 (N/A)	8 (5.4%)	6 (14.0%)	25 (6.4%)	
COVID-19 History						
Any previous positive SARS-CoV-2 PCR test	22 (11.6%)	<6 (N/A)	16 (10.7%)	8 (18.6%)	51 (13.0%)	0.0059
Any previous positive SARS-CoV-2 serology	<6 (N/A)	<6 (N/A)	<6 (N/A)	<6 (N/A)	<6 (N/A)	0.0214
Previous COVID-19 in past 12 months						0.0211
PCR	17 (8.9%)	<6 (N/A)	12 (8.1%)	<6 (N/A)	38 (9.7%)	
Rapid antigen	<6 (N/A)	<6 (N/A)	<6 (N/A)	<6 (N/A)	<6 (N/A)	
Self-reported antigen	<6 (N/A)	<6 (N/A)	<6 (N/A)	<6 (N/A)	<6 (N/A)	
None	173 (91.1%)	7 (63.6%)	137 (91.9%)	38 (88.4%)	355 (90.3%)	
Previous COVID-19 within 90 days						0.2556
PCR	<6 (N/A)	<6 (N/A)	<6 (N/A)	<6 (N/A)	7 (1.8%)	
Rapid antigen	<6 (N/A)	<6 (N/A)	<6 (N/A)	<6 (N/A)	<6 (N/A)	
Self-reported antigen	<6 (N/A)	<6 (N/A)	<6 (N/A)	<6 (N/A)	<6 (N/A)	
None	188 (98.4%)	17 (100.0%)	139 (97.9%)	42 (97.7%)	386 (98.2%)	
Previous Vaccination						
Received flu shot in past 12 months	61 (32.1%)	7 (63.6%)	99 (66.4%)	32 (74.4%)	199 (50.6%)	<.0001
Received pneumococcal vaccine	183 (96.3%)	9 (81.8%)	142 (95.3%)	40 (93.0%)	374 (95.2%)	0.155
Received shingles vaccine	<6 (N/A)	<6 (N/A)	<6 (N/A)	<6 (N/A)	<6 (N/A)	
Outcomes						
Death at 30 days	<6 (N/A)	<6 (N/A)	<6 (N/A)	<6 (N/A)	<6 (N/A)	0.4192
Hospital readmission 30 days	17 (8.9%)	<6 (N/A)	26 (17.4%)	<6 (N/A)	51 (13.0%)	0.0593
Hospital LOS, Mean (SD)	15.8 (20.98)	8.5 (5.09)	12.4 (14.33)	11.9 (13.30)	13.9 (17.70)	0.6761
ICU Admission	60 (31.6%)	<6 (N/A)	53 (35.6%)	11 (25.6%)	129 (32.8%)	0.4822
ICU LOS, Mean (SD)	7.2 (11.34)	3.4 (3.21)	7.4 (10.61)	6.1 (5.74)	7.0 (10.42)	0.8030
Mechanical ventilation	<6 (N/A)	<6 (N/A)	<6 (N/A)	<6 (N/A)	10 (2.5%)	0.8402

Sixty-eight percent (68.4%) of individuals were negative for SARS-CoV-2. A higher proportion of females had an infection during the Omicron period (62.0%). Comorbidities and previous vaccination history were similar among the variant periods.

Table 4: Study C4591014: Patient and clinical characteristics of adolescents 12-17 years of age hospitalised 10 May 2021 to 31 August 2022 due to acute respiratory infection with a SARS-CoV-2 PCR test by predominant circulating variant time period: Test Negative Design

	Negative (N=269) 68.4%	Pre-Delta (N=2) 0.5%	Delta (N=51) 13.0%	Omicron (N=71) 18.1%	Total (N=393)	P value
Age						0.0304
Mean (SD)	14.8 (1.63)	14.0 (2.83)	15.4 (1.44)	14.5 (1.72)	14.8 (1.64)	
Median	15	14	15	15	15	
Sex						0.0274
Male	153 (56.9%)	<6 (N/A)	31 (60.8%)	27 (38.0%)	212 (53.9%)	
Female	116 (43.1%)	<6 (N/A)	20 (39.2%)	44 (62.0%)	181 (46.1%)	
Race/ethnicity						0.0339
Asian	17 (6.3%)	<6 (N/A)	<6 (N/A)	7 (9.9%)	25 (6.4%)	
Black	42 (15.6%)	<6 (N/A)	<6 (N/A)	8 (11.3%)	55 (14.0%)	
Hispanic	131 (48.7%)	<6 (N/A)	31 (60.8%)	42 (59.2%)	205 (52.2%)	
Other	8 (3.0%)	<6 (N/A)	<6 (N/A)	<6 (N/A)	8 (2.0%)	
Pacific Islander	<6 (N/A)	<6 (N/A)	<6 (N/A)	<6 (N/A)	<6 (N/A)	
White	71 (26.4%)	<6 (N/A)	14 (27.5%)	14 (19.7%)	99 (25.2%)	
Body-mass index, kg/m2						<.0001
Underweight (<18.5)	58 (21.6%)	<6 (N/A)	<6 (N/A)	15 (21.1%)	78 (19.8%)	
Normal or healthy weight (18.5-24.9)	109 (40.5%)	<6 (N/A)	13 (25.5%)	27 (38.0%)	150 (38.2%)	
Overweight (25.0-29.9)	43 (16.0%)	<6 (N/A)	9 (17.6%)	10 (14.1%)	62 (15.8%)	
Obese, class 1 (30.0-34.9)	25 (9.3%)	<6 (N/A)	8 (15.7%)	14 (19.7%)	47 (12.0%)	
Obese, class 2-3 (≥35.0)	31 (11.5%)	<6 (N/A)	16 (31.4%)	<6 (N/A)	50 (12.7%)	
Unknown	<6 (N/A)	<6 (N/A)	<6 (N/A)	<6 (N/A)	6 (1.5%)	
Comorbidities						
Hypertension	12 (4.5%)	<6 (N/A)	<6 (N/A)	<6 (N/A)	16 (4.1%)	0.8553
Congestive heart failure	<6 (N/A)	<6 (N/A)	<6 (N/A)	<6 (N/A)	<6 (N/A)	0.5059
Myocardial infarction	<6 (N/A)	<6 (N/A)	<6 (N/A)	<6 (N/A)	<6 (N/A)	
Peripheral vascular disease	22 (8.2%)	<6 (N/A)	<6 (N/A)	<6 (N/A)	27 (6.9%)	0.2008
Cerebrovascular disease	<6 (N/A)	<6 (N/A)	<6 (N/A)	<6 (N/A)	7 (1.8%)	0.7042
Diabetes						0.9257
Diabetes with unknown glycated haemoglobin	<6 (N/A)	<6 (N/A)	<6 (N/A)	<6 (N/A)	<6 (N/A)	
Diabetes with glycated haemoglobin <7.5%	<6 (N/A)	<6 (N/A)	<6 (N/A)	<6 (N/A)	<6 (N/A)	
Diabetes with glycated haemoglobin ≥7.5%	<6 (N/A)	<6 (N/A)	<6 (N/A)	<6 (N/A)	<6 (N/A)	
No diabetes diagnosis	262 (97.4%)	<6 (N/A)	50 (98.0%)	68 (95.8%)	382 (97.2%)	
Chronic obstructive pulmonary disease	72 (26.8%)	<6 (N/A)	7 (13.7%)	13 (18.3%)	93 (23.7%)	0.1061
Renal disease	6 (2.2%)	<6 (N/A)	<6 (N/A)	<6 (N/A)	8 (2.0%)	0.7126
Malignancy	30 (11.2%)	<6 (N/A)	<6 (N/A)	7 (9.9%)	39 (9.9%)	0.4351
Organ transplant	<6 (N/A)	<6 (N/A)	<6 (N/A)	<6 (N/A)	<6 (N/A)	0.8784
Immunocompromised	41 (15.2%)	<6 (N/A)	<6 (N/A)	11 (15.5%)	55 (14.0%)	0.3088
Charlson comorbidity index						0.4854
0	154 (57.2%)	<6 (N/A)	38 (74.5%)	47 (66.2%)	240 (61.1%)	
1	66 (24.5%)	<6 (N/A)	11 (21.6%)	15 (21.1%)	93 (23.7%)	
2	16 (5.9%)	<6 (N/A)	<6 (N/A)	<6 (N/A)	21 (5.3%)	
3	11 (4.1%)	<6 (N/A)	<6 (N/A)	<6 (N/A)	14 (3.6%)	
≥4	22 (8.2%)	<6 (N/A)	<6 (N/A)	<6 (N/A)	25 (6.4%)	
COVID-19 History						
Any previous positive SARS-CoV-2 PCR test	43 (16.0%)	<6 (N/A)	<6 (N/A)	8 (11.3%)	51 (13.0%)	0.0166
Any previous positive SARS-CoV-2 serology	<6 (N/A)	<6 (N/A)	<6 (N/A)	<6 (N/A)	<6 (N/A)	0.8784
Previous COVID-19 in past 12 months						0.0808
PCR	31 (11.5%)	<6 (N/A)	<6 (N/A)	7 (9.9%)	38 (9.7%)	
Rapid antigen	<6 (N/A)	<6 (N/A)	<6 (N/A)	<6 (N/A)	<6 (N/A)	
Self-reported antigen	<6 (N/A)	<6 (N/A)	<6 (N/A)	<6 (N/A)	<6 (N/A)	
None	238 (88.5%)	<6 (N/A)	51 (100.0%)	64 (90.1%)	355 (90.3%)	
Previous COVID-19 within 90 days						0.7225
PCR	6 (2.2%)	<6 (N/A)	<6 (N/A)	<6 (N/A)	7 (1.8%)	
Rapid antigen	<6 (N/A)	<6 (N/A)	<6 (N/A)	<6 (N/A)	<6 (N/A)	
Self-reported antigen	<6 (N/A)	<6 (N/A)	<6 (N/A)	<6 (N/A)	<6 (N/A)	
None	263 (97.8%)	<6 (N/A)	51 (100.0%)	70 (98.6%)	386 (98.2%)	
Previous Vaccination						
Received flu shot in past 12 months	148 (55.0%)	<6 (N/A)	15 (29.4%)	35 (49.3%)	199 (50.6%)	0.0102
Received pneumococcal vaccine	256 (95.2%)	<6 (N/A)	48 (94.1%)	68 (95.8%)	374 (95.2%)	0.9636
Received shingles vaccine	<6 (N/A)	<6 (N/A)	<6 (N/A)	<6 (N/A)	<6 (N/A)	
Outcomes						
Death at 30 days	<6 (N/A)	<6 (N/A)	<6 (N/A)	<6 (N/A)	<6 (N/A)	0.8497
Hospital readmission 30 days	40 (14.9%)	<6 (N/A)	<6 (N/A)	10 (14.1%)	51 (13.0%)	0.0818
Hospital LOS, Mean (SD)	13.9 (18.37)	16.0 (15.56)	16.5 (19.06)	11.6 (13.71)	13.9 (17.70)	0.2833
ICU Admission	104 (38.7%)	<6 (N/A)	9 (17.6%)	16 (22.5%)	129 (32.8%)	0.0031
ICU LOS, Mean (SD)	7.4 (10.91)	N/A	11.9 (10.37)	2.0 (3.06)	7.0 (10.42)	0.0008
Mechanical ventilation	9 (3.3%)	<6 (N/A)	<6 (N/A)	<6 (N/A)	10 (2.5%)	0.4449

Patient characteristics and outcomes among individuals 5-11 years of age with an emergency department or urgent care visit due to an ARI 29 October 2021 –31 August 2022 with a SARS-o-2 test result: TND Analysis

There were only 355 children aged 5-11 years of age with a hospital admission between 29 October 2021 to 31 August 2022. Among these hospitalisations, there were 71 who were SARS-CoV-2 positive and 275 that were SARS-COV-2 negative. There were 53 children hospitalised with ARI and tested positive for SARS-CoV-2 that were unvaccinated and 14 who had received two doses. Due to the small sample size and number of events, VE for hospitalisation could not be calculated. As an alternative, VE estimates against emergency department and urgent care were calculated for the monovalent vaccine. There were 4,606 children 5-11 years of age between 29 October 2021 to 31 August 2022 with an ED or UC visit due to an ARI diagnosis with a SARS-CoV-2 test who were included in the analysis dataset. The mean age was 7.6 years (SD 2.03), and median age was 7 years. About fifty-four percent (53.5%) of the individuals were male. Over half (56.7%) were Hispanic and 17.5% were White. Over half (55.4%) had a normal or healthy weight.

About half of the individuals had a Sun Paediatric Comorbidity Index of 0 (52.1%) and 25.7% had an index of 1. Approximately twelve percent (12.4%) had a previous positive SARS-CoV-2 PCR test. A little over half of the encounters were in urgent care (56.5%, 2,601).

The majority of individuals were unvaccinated (74.1%), 4.3% had received 1 dose, 20.5% had received 2 doses of BNT162b2, and 1.1% had received 3 doses.

Among the 944 (20.5%) children who had received 2 doses of BNT162b2, the mean age was 8.0 years (SD 1.99) and median age was 8 years. Fifty-four percent (53.9%) of the individuals were male. About half (49.7%) were Hispanic and 17.5% were White. Over half (57%) had a normal or healthy weight. Forty-seven percent (47.2%) of the individuals had a Sun Paediatric Comorbidity Index of 0 and 26.8% had an index of 1. Twelve percent (12%) had a previous positive SARS-CoV-2 PCR test. Over half of the encounters were in urgent care (59.3%, 560).

Half of the individuals had a negative SARS-CoV-2 test (50%), while 3.4% had an infection during the Delta period and 46.6% had an infection during the Omicron period. There were a higher proportion of negative controls who had a previous positive SARS-CoV-2 test (16.8%) compared with individuals during pre-Delta (0%), Delta (n<6), or Omicron (8.3%) (p-value <0.0001).

Table 5: Study C4591014: Patient and clinical characteristics of children 5-11 years of age with an emergency room or urgent care visit 1 November 2021 – 2 September 2022 due to acute respiratory infection with a SARS-CoV-2 test by vaccination status: Test-negative design

	Unvaccinated (N=3413) 74.0%	1 dose BNT162b2 (N=196) 4.3%	2 doses BNT162b2 (N=944) 20.5%	3 doses BNT162b2 (N=53) 1.2%	Total (N=4606)	P value
Age						<0.0001
Mean (SD)	7.4 (2.02)	7.9 (2.07)	8.0 (1.99)	7.9 (1.98)	7.6 (2.03)	
Median	7	8	8	8	7	
Sex						0.4218
Male	1809 (53%)	111 (56.6%)	509 (53.9%)	33 (62.3%)	2462 (53.5%)	
Female	1604 (47%)	85 (43.4%)	435 (46.1%)	20 (37.7%)	2144 (46.5%)	
Race/ethnicity						<0.0001
Asian	205 (6%)	29 (14.8%)	163 (17.3%)	17 (32.1%)	414 (9%)	
Black	378 (11.1%)	12 (6.1%)	74 (7.8%)	0 (0%)	464 (10.1%)	
Hispanic	2004 (58.7%)	116 (59.2%)	469 (49.7%)	22 (41.5%)	2611 (56.7%)	
Other/Unknown	216 (6.3%)	17 (8.7%)	73 (7.7%)	<6 (N/A)	311 (6.8%)	
White	610 (17.9%)	22 (11.2%)	165 (17.5%)	9 (17%)	806 (17.5%)	
Body-mass index, kg/m2						0.2212
Underweight (<5th Percentile)	158 (4.6%)	7 (3.6%)	30 (3.2%)	0 (0%)	195 (4.2%)	
Normal or healthy weight (5th up to 85th Perce	1883 (55.2%)	97 (49.5%)	538 (57%)	32 (60.4%)	2550 (55.4%)	
Overweight (85th up to 95th Percentile)	535 (15.7%)	33 (16.8%)	148 (15.7%)	7 (13.2%)	723 (15.7%)	
Obese, class 1 (95th Percentile - 100th Percen	801 (23.5%)	59 (30.1%)	221 (23.4%)	14 (26.4%)	1095 (23.8%)	
Unknown	36 (1.1%)	0 (0%)	7 (0.7%)	0 (0%)	43 (0.9%)	
Sun Pediatric Comorbidity Index						0.0065
0	1832 (53.7%)	96 (49%)	446 (47.2%)	24 (45.3%)	2398 (52.1%)	
1	861 (25.2%)	55 (28.1%)	253 (26.8%)	17 (32.1%)	1186 (25.7%)	
2	383 (11.2%)	18 (9.2%)	127 (13.5%)	9 (17%)	537 (11.7%)	
3	141 (4.1%)	16 (8.2%)	50 (5.3%)	0 (0%)	207 (4.5%)	
≥4	196 (5.7%)	11 (5.6%)	68 (7.2%)	<6 (N/A)	278 (6%)	
COVID-19 History						0.0218
Any previous positive SARS-CoV-2 PCR test	434 (12.7%)	12 (6.1%)	113 (12%)	10 (18.9%)	569 (12.4%)	
Encounter Type						0.0514
Emergency Department	1522 (44.6%)	82 (41.8%)	384 (40.7%)	17 (32.1%)	2005 (43.5%)	
Urgent Care	1891 (55.4%)	114 (58.2%)	560 (59.3%)	36 (67.9%)	2601 (56.5%)	

Adjusted models are adjusted for age, sex, race/ethnicity, BMI, Charlson, prior flu and pneumo vaccination, month of encounter and prior positive test (3 indicators for pre-Delta, Delta, and Omicron-era positive, yes/no, so later variants couldn't appear in models of earlier variants).

Table 6: Study C4591014: Patient and clinical characteristics of children 5-11 years of age with an emergency room or urgent care visit 1 November 2021 to 31 August 2022 due to acute respiratory infection with a SARS-CoV-2 PCR by predominant circulating variant time period: Test Negative Design

	Negative (N=2303) 50.0%	Pre-Delta (N=0) 0.0%	Delta (N=155) 3.4%	Omicron (N=2148) 46.6%	Total (N=4606)	P value
Age						<0.0001
Mean (SD)	7.2 (1.98)	N/A	155	2148	4606	
Median	7	N/A	8.1 (2.16)	7.9 (2.01)	7.6 (2.03)	
Sex						0.0104
Male	1205 (52.3%)	0 (0.0%)	69 (44.5%)	1188 (55.3%)	2462 (53.5%)	
Female	1098 (47.7%)	0 (0.0%)	86 (55.5%)	960 (44.7%)	2144 (46.5%)	
Race/ethnicity						<0.0001
Asian	200 (8.7%)	0 (0.0%)	12 (7.7%)	202 (9.4%)	414 (9%)	
Black	176 (7.6%)	0 (0.0%)	21 (13.5%)	267 (12.4%)	464 (10.1%)	
Hispanic	1347 (58.5%)	0 (0.0%)	78 (50.3%)	1186 (55.2%)	2611 (56.7%)	
Other/Unknown	158 (6.9%)	0 (0.0%)	8 (5.2%)	145 (6.8%)	311 (6.8%)	
White	422 (18.3%)	0 (0.0%)	36 (23.2%)	348 (16.2%)	806 (17.5%)	
Body-mass index, kg/m2						0.4374
Underweight (<5th Percentile)	95 (4.1%)	0 (0.0%)	<6 (N/A)	96 (4.5%)	195 (4.2%)	
Normal or healthy weight (5th up to 85th Perce	1271 (55.2%)	0 (0.0%)	81 (52.3%)	1198 (55.8%)	2550 (55.4%)	
Overweight (85th up to 95th Percentile)	386 (16.8%)	0 (0.0%)	24 (15.5%)	313 (14.6%)	723 (15.7%)	
Obese, class 1 (95th Percentile - 100th Percen	531 (23.1%)	0 (0.0%)	45 (29%)	519 (24.2%)	1095 (23.8%)	
Unknown	20 (0.9%)	0 (0.0%)	<6 (N/A)	22 (1%)	43 (0.9%)	
Sun Pediatric Comorbidity Index						0.0493
0	1174 (51%)	0 (0.0%)	98 (63.2%)	1126 (52.4%)	2398 (52.1%)	
1	594 (25.8%)	0 (0.0%)	40 (25.8%)	552 (25.7%)	1186 (25.7%)	
2	279 (12.1%)	0 (0.0%)	10 (6.5%)	248 (11.5%)	537 (11.7%)	
3	109 (4.7%)	0 (0.0%)	<6 (N/A)	93 (4.3%)	207 (4.5%)	
≥4	147 (6.4%)	0 (0.0%)	<6 (N/A)	129 (6%)	278 (6%)	
COVID-19 History						<0.0001
Any previous positive SARS-CoV-2 PCR test	387 (16.8%)	0 (0.0%)	<6 (N/A)	179 (8.3%)	569 (12.4%)	
Encounter Type						<0.0001
Emergency Department	824 (35.8%)	0 (0.0%)	62 (40%)	1119 (52.1%)	2005 (43.5%)	
Urgent Care	1479 (64.2%)	0 (0.0%)	93 (60%)	1029 (47.9%)	2601 (56.5%)	

Patient characteristics and outcomes among individuals ≥6 months-4 years of age with an emergency department, urgent care or outpatient visit due to an ARI 23 July 2022 – 7 April 2023 with a SARS-COV-2 test result: TND Analysis

There were 1273 children ≥6 months to 4 years that had an ARI hospitalisation and 1191 were tested for SARS-CoV-2. Only 82 children were positive for SARS-CoV-2, of which 78 were unvaccinated. Due to the timing of the FDA authorisation in this age group, the sample size and number of hospitalisations were too low to calculate a VE against hospitalisation, despite extending the time period to 7 April 2023. As an alternative, VE against ED, UC and OP visits was calculated for this age group. There were 24,729 individuals ≥6 months-4 years with an ED, UC or OP due to ARI with a SARS-CoV-2 test between 23 July 2022 to 7 April 2023. The mean age was 2.0 (SD 1.4) and median age was 2.0 years. Over half (54%) of the individuals were male. Over half (55.7%) were Hispanic and 19.7% were White. The majority of individuals had a Sun Paediatric Comorbidity Index of 0 (45.2%) or 1 (23.3%). About nineteen percent (18.7%) of individuals had a previous positive SARS-CoV-2 test. A

little under half of the individuals were seen in the emergency department (46.8%), 29.5% in urgent care and 23.7% at an outpatient visit. The majority of individuals were unvaccinated (92.1%), 1.6% had received 1 dose of BNT162b2, 3.8% had received 2 doses, and 2.6% had received 3 doses (which is the recommended primary series for this age group).

Among 634 (2.6%) individuals ≥6 months-4 years who received 3 doses of BNT162b2, the mean age was 2.4 (SD 1.17) and median age was 2 years. Over half (54.6%) of the individuals were male. Thirty-nine (38.6%) were Hispanic and 29.5% were White. The majority of individuals had a Sun Paediatric Comorbidity Index of 0 (45.9%) or 1 (24.6%). Nineteen percent (19.1%,) of individuals had a previous positive SARS-CoV-2 test, and thirty-three percent (33.4%) were seen in the emergency department.

The majority (90.0%) of individuals had a negative SARS-CoV-2 test. Race and ethnicity and the Sun Paediatric Comorbidity Index were similar between individuals with negative and positive tests.

Individuals who had a negative test during the study period had a previous positive SARS-CoV-2 test 19.8% of the time and those individuals who had a positive test had a previous positive SARS-CoV-2 test 8.4% of the time.

Due to the time period of eligibility for vaccination, Omicron was the only predominant variant.

Table 7: Study C4591014: Patient and clinical characteristics of children >6 months to 4 years of age with emergency department, outpatient, or urgent care visits 23 July 2022 – 7 April 2023 due to acute respiratory infection with a SARS-CoV2 PCR test by vaccination status: Test Negative Design

	Unvaccinated (N=22,765) 92.1%	1 dose BNT162b2 (N=387) 1.6%	2 doses BNT162b2 (N=943) 3.8%	3 doses BNT162b2 (N=634) 2.6%	Total (N=24,729)	P value
Age						<0.0001
Mean (SD)	2.0 (1.40)	2.3 (1.41)	2.5 (1.35)	2.4 (1.17)	2.0 (1.40)	
Median	2	3	3	2	2	
Sex						0.7051
Male	12258 (54%)	198 (56.4%)	461 (52.8%)	346 (54.6%)	13263 (54%)	
Female	10428 (46%)	153 (43.6%)	412 (47.2%)	288 (45.4%)	11281 (46%)	
Race/ethnicity						<0.0001
Asian	2102 (9.3%)	74 (21.1%)	191 (21.9%)	139 (21.9%)	2506 (10.2%)	
Black	2044 (9%)	20 (5.7%)	41 (4.7%)	39 (6.2%)	2144 (8.7%)	
Hispanic	12849 (56.6%)	182 (51.9%)	396 (45.4%)	245 (38.6%)	13672 (55.7%)	
Other/Unknown	1289 (5.7%)	25 (7.1%)	48 (5.5%)	24 (3.8%)	1386 (5.6%)	
White	4402 (19.4%)	50 (14.2%)	197 (22.6%)	187 (29.5%)	4836 (19.7%)	
Sun Pediatric Comorbidity Index						0.7969
0	10281 (45.3%)	149 (42.5%)	379 (43.4%)	291 (45.9%)	11100 (45.2%)	
1	5254 (23.2%)	88 (25.1%)	210 (24.1%)	156 (24.6%)	5708 (23.3%)	
2	4046 (17.8%)	66 (18.8%)	149 (17.1%)	99 (15.6%)	4360 (17.8%)	
3	1508 (6.6%)	22 (6.3%)	61 (7%)	40 (6.3%)	1631 (6.6%)	
≥4	1597 (7%)	26 (7.4%)	74 (8.5%)	48 (7.6%)	1745 (7.1%)	
COVID-19 History						0.0879
Any previous positive SARS-CoV-2 PCR test	4204 (18.5%)	81 (23.1%)	178 (20.4%)	121 (19.1%)	4584 (18.7%)	
Encounter Type						<0.0001
Emergency Department	10784 (47.5%)	133 (37.9%)	358 (41%)	212 (33.4%)	11487 (46.8%)	
Urgent Care	6651 (29.3%)	111 (31.6%)	271 (31%)	201 (31.7%)	7234 (29.5%)	
Outpatient	5251 (23.1%)	107 (30.5%)	244 (27.9%)	221 (34.9%)	5823 (23.7%)	

Table 8: Study C4591014: Patient and clinical characteristics of children >6 months to 4 years of age emergency department, outpatient, or urgent care visits 23 July 2022 – 21 February 2023 due to acute respiratory infection with a SARS-CoV-2 PCR test by predominant circulating variant time period: Test Negative Design

	Negative (N=22,266) 90.0%	Predelta (N=0) 0%	Delta (N=0) 0%	Omicron (N=2,463) 10.0%	Total (N=24,729)	P value
Age						<0.0001
Mean (SD)	2.1 (1.38)	N/A	N/A	1.4 (1.40)	2.0 (1.40)	
Median	2	N/A	N/A	1	2	
Sex						0.1403
Male	11980 (54.2%)	0 (0.0%)	0 (0.0%)	1283 (52.6%)	13263 (54%)	
Female	10126 (45.8%)	0 (0.0%)	0 (0.0%)	1155 (47.4%)	11281 (46%)	
Race/ethnicity						0.0645
Asian	2229 (10.1%)	0 (0.0%)	0 (0.0%)	277 (11.4%)	2506 (10.2%)	
Black	1961 (8.9%)	0 (0.0%)	0 (0.0%)	183 (7.5%)	2144 (8.7%)	
Hispanic	12297 (55.6%)	0 (0.0%)	0 (0.0%)	1375 (56.4%)	13672 (55.7%)	
Other/Unknown	1250 (5.7%)	0 (0.0%)	0 (0.0%)	136 (5.6%)	1386 (5.6%)	
White	4369 (19.8%)	0 (0.0%)	0 (0.0%)	467 (19.2%)	4836 (19.7%)	
Sun Pediatric Comorbidity Index						<0.0001
0	9965 (45.1%)	0 (0.0%)	0 (0.0%)	1135 (46.6%)	11100 (45.2%)	
1	5285 (23.9%)	0 (0.0%)	0 (0.0%)	423 (17.4%)	5708 (23.3%)	
2	3853 (17.4%)	0 (0.0%)	0 (0.0%)	507 (20.8%)	4360 (17.8%)	
3	1442 (6.5%)	0 (0.0%)	0 (0.0%)	189 (7.8%)	1631 (6.6%)	
≥4	1561 (7.1%)	0 (0.0%)	0 (0.0%)	184 (7.5%)	1745 (7.1%)	
COVID-19 History						<0.0001
Any previous positive SARS-CoV-2 PCR test	4379 (19.8%)	0 (0.0%)	0 (0.0%)	205 (8.4%)	4584 (18.7%)	
Encounter Type						<0.0001
Emergency Department	10184 (46.1%)	0 (0.0%)	0 (0.0%)	1303 (53.4%)	11487 (46.8%)	
Urgent Care	6755 (30.6%)	0 (0.0%)	0 (0.0%)	479 (19.6%)	7234 (29.5%)	
Outpatient	5167 (23.4%)	0 (0.0%)	0 (0.0%)	656 (26.9%)	5823 (23.7%)	

BNT162b2 effectiveness results

Adolescents 12-17 years of age

There were a limited number of acute respiratory infection hospitalisations (N = 393) among PCR tested individuals 12-17 years of age between 10 May 2020 – 31 August 2022: Unvaccinated 190, 1 dose 11, 2 dose 149 and 3 dose 43. As a result, there was limited ability to calculate reliable VE estimates. The overall adjusted vaccine effectiveness of 2 doses of BNT162b2 against hospitalisation due to SARS-CoV-2 among individuals 12-17 years of age who were diagnosed with an acute respiratory infection was 55% (95% CI: 23-74).

During the Delta period, adjusted BNT162b2 effectiveness against hospitalisation due to SARS-CoV-2 was 92% (95% CI: 71-98) for two doses and due to timing of the recommendation for a booster and the change in circulating variant, a 3-dose estimate could not be calculated. An Omicron estimate was deemed imprecise due to small sample size.

Table 9: Age 12-17 Enrollment flowchart by vaccine status, SARS-CoV-2 Test Status and Variant

	Positive test				Negative test				Total
	Pre-Delta	Delta	Omicron	Overall	Pre-Delta	Delta	Omicron	Overall	
Unvaccinated	<6	45	32	78	10	50	52	112	190
1 dose	0	<6	<6	<6	0	<6	<6	9	11
2 doses	<6	<6	29	34	0	60	55	115	149
3 doses	0	<6	9	10	0	<6	32	33	43
Overall	<6	51	71	124	10	115	144	269	393

Table 10: Study C4591014: Unadjusted and adjusted Pfizer-BioNTech's BNT162b2 effectiveness against hospitalisation 10 May 2020 – 31 August 2022 among adolescents 12-17 years of age due to ARI stratified by predominant circulating variant time period: Test Negative Design

Dose and time since last dose to hospitalization	Unadjusted VE PreDelta	Adjusted VE PreDelta	Unadjusted VE Delta	Adjusted VE Delta	Unadjusted VE Omicron	Adjusted VE Omicron	Unadjusted VE Overall	Adjusted VE Overall
1 dose overall			72 (-158- 97)	80 (-159- 98)	67 (-191- 96)	82 (-87- 98)	68 (-52- 93)	79 (-6- 96)
1 dose ≤3 months			72 (-158- 97)	81 (-156- 99)	67 (-191- 96)	82 (-89- 98)	68 (-52- 93)	79 (-7- 96)
1 dose >3 months								
2 dose overall			93 (78- 98)	92 (71- 98)	6 (-78- 50)	10 (-88- 57)	58 (31- 74)	55 (23- 74)
2 dose ≤3 months			96 (66- 99)	95 (56-100)			90 (59- 98)	91 (57- 98)
2 dose >3 months			90 (67- 97)	90 (50- 98)	6 (-78- 50)	10 (-90- 57)	46 (11- 67)	37 (-13- 65)
3 dose overall					54 (-8- 81)	32 (-87- 75)	56 (7- 80)	53 (-17- 81)
3 dose ≤3 months					74 (6- 93)	64 (-46- 91)	71 (13- 91)	65 (-22- 90)
3 dose >3 months					25 (-117- 74)	-31 (-369- 63)	34 (-82- 76)	8 (-206- 72)

Estimates with greater than 50 percentage points for the 95% CI should be interpreted with caution due to high level of imprecision in the estimate.
Adjusted models are adjusted for age, sex, race/ethnicity (Hispanic, White, and Other), Child BMI Category, Pediatric Comorbidity Score and prior flu.

Children 5-11 years of age

The number of hospitalisations among individuals 5-11 years of age was extremely small (N=346) and VE could not be calculated against hospitalisation. There were 71 individuals with a SARS-CoV-2 positive result of which 53 individuals were unvaccinated and 14 had received two doses of BNT162b2.

As an alternative to calculating VE against hospitalisation, BNT162b2 effectiveness against ARI-associated ED or UC visits from 29 October 2021 to 31 August 2022 was calculated among individuals 5-11 years of age.

The Omicron variant rapidly overtook the Delta variant as the dominant SARS-CoV-2 strain in the US in December 2021, only two months after the BNT162b2 vaccine was authorised for use in individuals 5-11 years of age. As a result, BNT162b2 VE against Delta could not be calculated and the overall estimate for this age group was limited to the Omicron circulating variant. The adjusted BNT162b2 effectiveness of 2 doses of BNT162b2 against ARI-associated ED or UC visits due to SARS-CoV-2 among individuals 5-11 years of age was 44% (95% CI: 34-53) and of 3 doses was 77% (95% CI: 55-88). The effectiveness of 2 doses of BNT162b2 was 56% (95% CI: 45-65) at less than 3 months but fell to 32% (95% CI: 15-45) after 3 months since vaccination. VE was restored with a booster dose 75% (95% CI: 52-87) within 3 months since vaccination.

Table 11: Age 5-11 Enrollment Flowchart by Vaccine Status, SARS-CoV-2 Test Status, and Variant

	Total	Excluded		Total	Excluded
Emergency Department and Urgent Care Encounters with an ARI diagnosis 10/29/2021-8/31/2022	500,187		Hospitalizations with an ARI Diagnosis 10/29/21-8/31/22	63,668	
Had a COVID-19 lab in the 14 days prior to admission through 3 days after discharge	205,042	295,145	Had a COVID-19 lab in the 14 days prior to admission through 3 days after discharge	34,692	28,976
Enrolled continously for the 6 months prior to admission	159,649	45,393	Enrolled continously for the 6 months prior to admission	28,439	6,253
Non-Pfizer COVID vaccine prior to admission were excluded	107,248	52,401	Non-Pfizer COVID vaccine prior to admission were excluded	15,916	12,523
Age 5-11	13,647	93,601	Age 5-11	355	15,561
Days between COVID vaccine doses too close together/doses not within the dates of age guidelines were excluded	13,258	389	Days between COVID vaccine doses too close together/doses not within the dates of age guidelines were excluded	346	9
Test Positives	2,303		Test Positives	71	
Test Negatives	10,955		Test Negatives	275	
Test Negatives Selected	2,303	8,652	Test Negatives Selected	N/A	
Final Study Population	4,606		Final Study Population	N/A	

	Positive test				Negative test				Total
	Pre-Delta	Delta	Omicron	Overall	Pre-Delta	Delta	Omicron	Overall	
Unvaccinated	0	149	1638	1787	0	145	1481	1626	3413
1 dose	0	6	87	93	0	8	95	103	196
2 doses	0	0	410	410	0	<6	532	534	944
3 doses	0	0	13	13	0	0	40	40	53
Overall	0	155	2148	2303	0	155	2148	2303	4606

Number of ARI-associated hospitalizations by SARS-COV-2 status October 29, 2021 – August 31, 2022 in individuals aged 5-11 years of age

	Test Positive		
Doses	No	Yes	Total
0	202	53	255
1	13	0	13
2	58	14	72
3	<6	<6	6
Total	275	71	346

Table 12: Study C4591014 Unadjusted and adjusted vaccine effectiveness of Pfizer-BioNTech's BNT162b2 against emergency department or urgent care visits 29 October 2021 - 31 August 2022 due to acute respiratory infection among children 5 -11 years of age stratified by predominant circulating variant time period

Dose and time since last dose to event	Unadjusted VE PreDelta	Adjusted VE PreDelta	Unadjusted VE Delta	Adjusted VE Delta	Unadjusted VE Omicron	Adjusted VE Omicron	Unadjusted VE Overall	Adjusted VE Overall
1 dose overall			25 (-116-74)	51 (-69-86)	15 (-15-38)	30 (3-50)	16 (-13-38)	31 (5-50)
1 dose ≤3 months			14 (-155-71)	44 (-99-84)	18 (-15-41)	32 (2-52)	18 (-13-40)	31 (3-51)
1 dose >3 months					16 (-92-63)	35 (-55-73)	22 (-75-65)	40 (-43-74)
2 dose overall					32 (20-41)	44 (34-53)	32 (21-41)	44 (34-53)
2 dose ≤3 months					47 (34-58)	56 (44-65)	48 (35-58)	56 (45-65)
2 dose >3 months					15 (-4-30)	32 (15-45)	15 (-4-30)	31 (15-45)
3 dose overall					71 (46-85)	77 (55-88)	71 (46-85)	76 (54-88)
3 dose ≤3 months					69 (43-84)	75 (52-87)	69 (43-84)	75 (52-87)
3 dose >3 months								

Estimates with greater than 50 percentage points for the 95% CI should be interpreted with caution due to high level of imprecision in the estimate.
Adjusted models are adjusted for age, sex, race/ethnicity, Child BMI Category, Pediatric Comorbidity Score, and prior covid pcr.

Children ≥6 months to 4 years of age

Similar to the other paediatric age groups, there were limited ARI hospitalisations (N = 1273) who were tested for SARS-CoV-2 among those >6 months to 4 years of age. Among the 1273 ARI hospitalisations with a SARS-CoV-2 test, there were 82 individuals who tested positive. The majority (n = 78) of the SARS-CoV-2 positive hospitalisations were among individuals who were unvaccinated.

The recommendation for vaccination among individuals ≥6 months to 4 years of age came in May of 2022 and the primary series was 3 doses. As a result, the time period for evaluation for this analysis was extended to 23 July 2022 (date of first ≥6 month to 4 years of age vaccination at KPSC) through 07 April 2023 for this age group and included ED, UC or OP visits. The overall two dose BNT162b2 effectiveness was 45% (95% CI: 25-59).

Table 13: Age ≥6mo-4yr Enrollment Flowchart by Vaccine Status, SARS-CoV-2 Test Status, and Variant

	Total	Excluded		Total	Excluded
Emergency Department, Oupatient, and Urgent Care Encounters with an ARI diagnosis 7/23/2022-4/7/2023	1,339,414		Hospitalizations with an ARI Diagnosis 7/23/22-4/7/23	47,991	
Had a COVID-19 lab in the 14 days prior to admission through 3 days after discharge	275,559	1,063,855	Had a COVID-19 lab in the 14 days prior to admission through 3 days after discharge	28,769	19,222
Enrolled continously for the 6 months prior to admission	224,042	51,517	Enrolled continously for the 6 months prior to admission	23,706	5,063
Non-Pfizer COVID vaccine prior to admission were excluded	128,840	95,202	Non-Pfizer COVID vaccine prior to admission were excluded	10,401	13,305
Age ≥6 months - 4 years old	24,730	104,110	Age ≥6 months - 4 years old	1,278	9,123
Days between COVID vaccine doses too close together/doses not within the dates of age guidelines were excluded/>3 doses	24,544	186	Days between COVID vaccine doses too close together/doses not within the dates of age guidelines were excluded	1,273	<6
Test Positives	2,438		Test Positives	82	
Test Negatives	22,106		Test Negatives	1,191	

	Positive test				Negative test				Total
	Pre-Delta	Delta	Omicron	Overall	Pre-Delta	Delta	Omicron	Overall	
Unvaccinated	0	0	2316	2316	0	0	20370	20370	22686
1 dose	0	0	37	37	0	0	314	314	351
2 doses	0	0	46	46	0	0	827	827	873
3 doses	0	0	39	39	0	0	595	595	634
Overall	0	0	2438	2438	0	0	22106	22106	24544

Number of ARI-associated hospitalizations by SARS-COV-2 status July 23, 2022 – April 7, 2023 in individuals aged ≥6 months to 4 years of age

	Test Positive		
Doses	No	Yes	Total
0	1101	78	1179
1	19	<6	20
2	41	<6	43
3	30	<6	31
Total	1191	82	1273

Table 14: Study C4591014: Unadjusted and adjusted Pfizer-BioNTech's BNT162b2 effectiveness against emergency department, outpatient, or urgent care visits 23 July 2022 - 21 February 2023 due to acute respiratory infection among children ⩾6 months to 4 years of age during Omicron: Test Negative Design micron

Dose and time since last dose to event	Unadjusted VE Omicron	Adjusted VE Omicron
1 dose overall	-4 (-44- 25)	-8 (-52- 23)
1 dose ≤2 months	-40 (-99- 1)	-23 (-77- 14)
1 dose >2 months	69 (17- 89)	47 (-44- 81)
2 dose overall	51 (34- 64)	45 (25- 59)
2 dose ≤2 months	45 (21- 62)	49 (27- 65)
2 dose >2 months	61 (34- 77)	31 (-19- 60)
3 dose overall	43 (20- 59)	7 (-30- 33)
3 dose ≤2 months	48 (18- 67)	32 (-9- 57)
3 dose >2 months	36 (-1- 60)	-39 (-122- 13)

Estimates with 95% CIs with greater than 50 percentage should be interpreted with caution with caution due to the high level of imprecision in the estimate.
Adjusted for age, sex, race/ethnicity, Pediatric Comorbidity Score and prior covid PCR.
Note: Due to timing of Pfizer-BioNTech's BNT162b2 recommendation for >6 months to 4 years (May 2022), VE could only be calculated during Omicron period.

MAH discussion (related to the paediatric population)

Key results

Paediatric BNT162b2 effectiveness was limited in KPSC due to the timing of the recommendations and the low prevalence of hospitalisation. This is in line with other observational studies in these age groups which are limited to reporting less severe outcomes, (i.e., infection). We included VE against emergency department and urgent care visits for 5-11 years of age and emergency department, urgent care and outpatient visits for >6 months to 4 years showing effectiveness at 2 doses.

Limitations

There were several limitations to take into consideration when interpreting the findings. The study was observational, and therefore cannot establish causal relationships between vaccination and COVID-19 outcomes. Although both a full cohort and test-negative design analyses were planned, as the pandemic evolved, biases that could not be controlled using the cohort design prevented executing the cohort analysis beyond the first year of the study. The most significant bias was introduced by changes in testing and health-seeking behaviour as the COVID-19 pandemic progressed that differed based on vaccination status. The test-negative design restricted the study population to those who have a SARS-CoV-2 test, thereby minimizing biases caused by health-seeking behaviour, including the propensity to test.

While we used a test-negative design and statistical methods to control for confounding, there may be unmeasured confounding. To address differences in SARS-CoV-2 testing behaviours, patterns, and other characteristics between the vaccinated and unvaccinated, we adjusted vaccine effectiveness estimates to account for confounding. We did not have data on occupation or adherence to non-pharmaceutical interventions, such as mask wearing or social distancing, which could also affect SARS-CoV-2 testing.

We compared cases and test-negative controls from the same variant time periods to balance testing availability, infection rates, and other inputs that may affect health behaviours and SARS-CoV-2 testing. However, it is possible that hospital admission practices changed during the study period. For example, if more individuals with less severe infection were admitted during the Omicron period, as reported by CDC the vaccine effectiveness estimates could be biased downward. Due to the timeframe in which vaccines became available to the paediatric population and the smaller sample size, we were

unable to compare paediatric cases to test-negative controls from the same variant period. In addition, VE estimates that resulted in a 95% confidence interval width greater than 50 percentage points were deemed non-reportable due to imprecision.

Due to the timeframe in which vaccines became available to the paediatric population and the predominant circulating variant, many of the paediatric VE analyses in KPSC required adjustment. Due to the small number of hospitalisations among the paediatric population, VE could only be calculated for adolescents 12-17 years of age during the Delta time period.

Among those 5-11 years of age, VE was calculated against ED and UC visits. Among those >6 months to 4 years, VE was calculated against ED, UC and OP visits and the study time period was extended through 07 April 2023 to capture as many children as possible. Both 5-11 years of age and >6 months to 4 years of age VE were only calculated during omicron study period. It should also be noted that the number of people with a history of prior infection increased over time and that this may be non-differentially distributed between vaccinated and unvaccinated individuals. This may be especially true among children, who received vaccinations later into the course of the pandemic. This could bias VE estimates downward towards the null. The impact of prior infection on VE was evaluated in stratified analysis and was accounted for as a covariate in adjusted VE analyses. Because prior infection can act as an effect modifier, simple adjustment may lead to biased VE estimates.

Immunocompromising status and comorbidities were not time-varying in the analyses, but rather based on health records in the year prior to the patient's index date. This may create misclassification bias depending on changing status throughout the entire study period.

Further, prior infection may be underestimated in this study because data was limited to what was available in the patient's record. There was a systematic mechanism to report SARS-CoV-2 testing that was administered outside the system or through at-home tests, but not all may have been reported. Furthermore, underreporting may have occurred because not all infected individuals are tested for SARS-CoV-2.

Key strata were deemed vital in understanding VE as the pandemic evolved including circulating variant, number of doses and time since last dose. Unfortunately, there were many instances where VE could not be calculated reliably when stratified by these or in combination with other subpopulations of interest such as age or immunocompromising status. Any VE estimates that resulted in a 95% confidence interval width greater than 50 percentage points were deemed unstable due to imprecision and need to be interpreted with caution.

There were some variables that were deemed important to adjust for at the initiation of the study period that were either unavailable in the data set or not reliably captured to be included in the analysis. Sequencing was included in all the studies, but results for every patient were unavailable. As a result, VE analyses were stratified by the predominant circulating variant at the time in the country.

This may lead to some misclassification bias, especially during times when variants were changing or when multiple variants were co-circulating. Although valuable data, the overall VE was comparable to other studies and was consistent across these three studies.

The TND study may be subject to selection bias. The proportion of individuals requiring hospitalisation due to COVID-19 decreased over time. It is possible that some cases were hospitalised or had ED admissions "with COVID-19" rather than "for COVID-19." This could result in spurious findings of waning VE against severe outcomes if vaccine breakthroughs were only incidental infections among individuals admitted to the hospital for something other than COVID-19. We restricted the analysis to only individuals admitted with a diagnosis of acute respiratory infection, however, it is possible that milder cases were included in the analysis and biased the vaccine effectiveness downwards. The

decreasing case severity over time may have also made VE estimates from the different variant-predominant periods less comparable

Interpretation

Collectively, these analyses demonstrate that BNT162b2 was effective at preventing SARS-CoV-2 hospitalisation and ED visits in the real-world setting and support the efficacy seen in the clinical trials. BNT162b2 was effective across all paediatric age groups studied and across multiple predominant circulating variant time periods. The data in these analyses confirm the need for booster dosing to maintain protection, as VE appeared to wane over time and was restored with subsequent boosters. Although BNT162b2 was effective during all variant time periods, VE was substantially lower during the Omicron variant time period, underscoring the need for adapted vaccines to match the circulating strain. The overall benefit risk profile remains favourable for BNT162b2 vaccination for the prevention of severe SARS-CoV-2 infection.

Generalizability

This observational study used real-world data to estimate the effectiveness of the vaccine in routine clinical care. KPSC is a large, integrated healthcare system that is representative of the socioeconomic, racial, and ethnic diversity of the area's population. The test-negative study design reduced bias in health-seeking behaviours, however, generalizability of the results was limited to individuals who had access to healthcare services and received SARS-CoV-2 testing. The results were not generalizable to variants or time periods of variant circulation not included in the study.

Conclusions

BNT162b2 was effective across all paediatric age groups studied across multiple clinically important predominant circulating variant time periods. The data in these analyses also confirm the need for booster dosing to maintain protection, as VE appeared to wane over time and was restored with subsequent boosters. Differences seen in VE based on predominating circulating variants suggest the potential need for adapted vaccines to match the circulating strain.

2.3.3. Discussion on clinical aspects

This report contains the final study results for study C4591014 (Kaiser), a non-interventional, retrospective, category 3 RMP study, investigating the real-world effectiveness of BNT162b2, that was due 30 June 2023. While the scope of the total study is much broader and contains a large amount of data for an adult population, this report only concerns the paediatric portion of the study.

The primary objective of the study was to in estimate the effectiveness of 2 doses of BNT162b2 against hospitalisation for acute respiratory infection (ARI) due to SARS-CoV-2 infection using a test-negative design. However, this endpoint proved to be difficult for the age group 12-17 years old due to the limited number of acute respiratory infection hospitalisations, and practically impossible for the age groups 6 months – 11 years of age due to limited sample size, the timing of the recommendations, changes in circulating virus strains and other factors listed under "Limitations" in the subheading "MAH discussion".

For the age group 12-17 years of age, the overall adjusted vaccine effectiveness of 2 doses of BNT162b2 against hospitalisation due to SARS-CoV-2 among individuals 12-17 years of age who were diagnosed with an acute respiratory infection was 55% (95% CI: 23-74). However, there were large differences between the VE against hospitalisation due to SARS-CoV-2 during the Delta-variant period (92%, 95% CI: 71-98) and the overall VE, corroborating previous findings that the efficacy of the original BNT162b2 was considerably lower against the Omicron-variant.

For the age group 5-11 years of age, the investigators chose to calculate BNT162b2 effectiveness against ARI-associated ED or UC visits as an alternative to VE against covid-mediated hospitalisation. Due to the timing of the recommendation for vaccination in this age group, BNT162b2 VE against Delta could not be calculated and the overall estimate for this age group was limited to the Omicron circulating variant. The adjusted BNT162b2 effectiveness of 2 doses of BNT162b2 against ARI-associated ED or UC visits due to SARS-CoV-2 among individuals 5-11 years of age was 44% (95% CI: 34-53) and of 3 doses was 77% (95% CI: 55-88). The effectiveness of 2 doses of BNT162b2 was 56% (95% CI: 45-65) at less than 3 months but fell to 32% (95% CI: 15-45) after 3 months since vaccination. VE was restored with a booster dose 75% (95% CI: 52-87) within 3 months since vaccination.

Similar to the other paediatric age groups, for the cohort >6 months to 4 years of age, the limited number of ARI hospitalisations prompted the investigators to instead calculate VE for ED, UC or OP visits. The investigators write that: "the recommendation for vaccination among individuals ≥6 months to 4 years of age came in May of 2022 and the primary series was 3 doses. As a result, the time period for evaluation for this analysis was extended to 23 July 2022 (date of first ≥6 month to 4 years of age vaccination at KPSC) through 07 April 2023 for this age group and included ED, UC or OP visits. The overall two dose BNT162b2 effectiveness was 45% (95% CI: 25-59)". The unadjusted VE for three doses (completed primary series) is stated to be 48%.

In total, the real-world data provided in this procedure generally corroborate what has been previously shown in controlled clinical trials with regard to the key findings: the original formulation was highly effective in preventing COVID-mediated ARI hospitalisation during the Delta-circulating period, however, efficacy dropped considerably during the Omicron-wave. The study also corroborates that immunity wanes within a couple of months, but is boosted upon administration of a booster dose (at least, for the 12-17 years age group that had chance to be boosted).

The drawbacks of any non-interventional, retrospective study render it difficult to draw more conclusions than these stated above.

3. CHMP overall conclusion and recommendation

The MAH has completed a clinical study investigating the real-world effectiveness of BNT162b2 in a paediatric population. Although the number of hospitalisations were too low to estimate a reliable estimate for these age cohorts, the real-world data provided in this procedure generally corroborate what has been previously shown in controlled clinical trials with regard to the key findings: the original formulation was highly effective in preventing COVID-mediated acute respiratory infection hospitalisation during the Delta-circulating period, however, efficacy dropped considerably during the Omicron-wave. The study also corroborates that immunity wanes within a couple of months but is boosted upon administration of a booster dose (at least, for the 12-17 years age group that had chance to be boosted).

☒ **Fulfilled:**

No regulatory action required.