EMADOC-1700519818-2925080
Committee for Medicinal Products for Human Use (CHMP)

Type II variation assessment report

Procedure No. EMA/VR/0000332196

Invented name: COMIRNATY

Common name: COVID-19 mRNA vaccine

Marketing authorisation holder (MAH): BioNTech Manufacturing GmbH

This application is in the area of: (Non-)Clinical

Note

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

Status of this report and steps taken for the assessment			
Current step	**Description**	**Planned date**	**Actual Date**
☐	Submission deadline	20 Feb 2026	13 Feb 2026
☐	Validation	9 Mar 2026	17 Feb 2026
☐	Start date	10 Mar 2026	10 Mar 2026
☐	PRAC Rapporteur AR	20 Apr 2026	20 Apr 2026
☐	PRAC comments	24 Apr 2026	n/a
☐	Updated PRAC Rapporteur AR	28 Apr 2026	28 Apr 2026
☐	CHMP comments	28 Apr 2026	28 Apr 2026
☐	PRAC outcome	5 May 2026	5 May 2026
☐	Start of CHMP written procedure	5 May 2026	5 May 2026
☒	CHMP Outcome	7 May 2026	7 May 2026

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1. Background information on the procedure

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, BioNTech Manufacturing GmbH submitted to the European Medicines Agency on 13 February 2026 an application for a variation.

The following changes were proposed:

Variation(s) requested		**Type**
C.12	C.12 Other variations not specifically covered elsewhere in this Annex which involve the submission of studies, including be to be d. bioequivalence studies, to the competent authority	Variation type II

Submission of the final report from study C4591009 listed as a category 3 study in the RMP. This is an observational PASS designed to assess safety events of interest (including myocarditis and pericarditis) among recipients of original monovalent Pfizer-BioNTech COVID-19 Vaccine, using data from administrative claims and electronic health records from data research partners participating in the Sentinel System.

The requested variation(s) proposed no amendments to the Product information.

2. Overall conclusion and impact on the benefit/risk balance

Comirnaty, an mRNA-based vaccine, is authorised for use in the European Union (EU) for the prevention of coronavirus disease 2019 (COVID-19) since December 2020.

This report covers the **final study report** of study **C4591009**, an observational post-authorisation safety study (PASS) designed to assess safety events of interest (including myocarditis and pericarditis) among recipients of original monovalent Pfizer-BioNTech COVID-19 Vaccine (i.e. Comirnaty) in the **United States**. This non-interventional study was designated as a post-marketing requirement to the Food and Drug Administration (FDA) and included as a category 3 study in the EU Risk Management Plan (RMP). In according with the agreed milestones per RMP, two monitoring/ interim reports have been submitted to the EMA between October 2022 and April 2024.

An increased risk of **myocarditis/ pericarditis** was observed following vaccination with a primary series dose or initial booster dose of original monovalent Comirnaty. In the primary series analysis, the highest hazard ratios (HRs) were observed among males aged 12 to 17 years (HR = 12.22; 95% CI, 5.51-27.11) and 18 to 24 years (HR = 3.63; 95% CI, 1.94-6.80) after dose 2, and among females aged 18 to 24 years after dose 2 (HR = 4.33; 95% CI, 1.65-11.40). In the booster dose analysis, the highest HRs were observed among males aged 12 to 17 years (HR = 4.92; 95% CI, 1.01-24.09), 18 to 24 years (HR = 5.16; 95% CI, 1.39-19.24), and 30 to 39 years (HR = 8.22; 95% CI, 0.95-71.27). In subgroup analysis among immunocompromised individuals, individuals with a history of COVID-19, and pregnant women, no increased risks of myocarditis/pericarditis were observed in either the primary series or booster dose analysis. In the sensitivity analysis using different risk intervals, the highest HR was for 1-7 days. Myocarditis and pericarditis are currently included in the EU SmPC of Comirnaty (sections 4.4 and 4.8). Section 4.4 states among others that myocarditis and pericarditis primarily occurred within 14 days, have been observed more often after the second vaccination, and more often in younger males. This is deemed sufficient. Based on the final results of this study no regulatory update is needed regarding this known risk.

An increased risk of **anaphylaxis** was observed following vaccination with a primary series dose (HR = 11.65; 95% CI, 5.51-24.65) or initial booster dose (HR = 1.69; 95% CI, 0.23-12.23) of original

monovalent Comirnaty. Hypersensitivity reactions and anaphylaxis are included in the EU SmPC of Comirnaty (sections 4.4 and 4.8). Based on the findings of this study no regulatory action is needed.

No increased risk regarding pregnancy outcomes was observed in the primary series and booster dose analysis. This is consistent with previous findings. The EU SmPC of Comirnaty states that Comirnaty can be used during pregnancy. This is deemed sufficient, no further action is needed.

A small increased prevalence of **small size for gestational age** was observed among infants born to pregnant women exposed to original monovalent Comirnaty (PR = 1.12; 95% CI, 1.07-1.17). The MAH postulated that this study could be more subject to outcome misclassification and confounding bias, since administrative claims data were used and not clinical data. In addition, this study did not adjust for variables like body mass index (BMI), race, ethnicity, socioeconomic status. This could be acceptable. However, to carefully monitor this issue further, the MAH is requested to discuss any new relevant emerging safety information regarding pregnancy and birth outcomes including small size for gestational age in the next PSUR, if applicable, in the context of routine pharmacovigilance activity.

The benefit-risk balance of COMIRNATY remains positive.

In addition, the MAH should submit the following safety data in the next PSUR:

- Within the context of routine pharmacovigilance, the MAH is requested to discuss, if applicable, any relevant emerging safety findings regarding pregnancy and birth outcomes including small size for gestational age.

3. Recommendations

Based on the review of the submitted data, this application regarding the following change:

Variation(s) requested		**Type**
C.12	C.12 Other variations not specifically covered elsewhere in this Annex which involve the submission of studies, including be to be d. bioequivalence studies, to the competent authority	Variation type II

Submission of the final report from study C4591009 listed as a category 3 study in the RMP; this is an observational post-authorisation safety study (PASS) designed to assess safety events of interest (including myocarditis and pericarditis) among recipients of original monovalent Comirnaty, using data from administrative claims and electronic health records from data research partners participating in the Sentinel System.

☒is recommended for approval

Amendments to the marketing authorisation

This variation leads to no amendments to the terms of Community Marketing Authorisation.

4. EPAR changes

The table in the 'Steps after' module of the EPAR will be updated as follows:

Scope

Please refer to the Recommendations section above

Summary

Please refer to Scientific Discussion “Comirnaty-VR-0000332196”.

Annex: Rapporteur’s assessment comments on the type II variation

5. Introduction

Comirnaty, an mRNA-based vaccine, is authorized for use in the EU for the prevention of coronavirus disease 2019 (COVID-19) since December 2020.

This report covers the **final study report** of study **C4591009**, an observational PASS designed to assess safety events of interest (including myocarditis and pericarditis) among recipients of original monovalent Pfizer-BioNTech COVID-19 Vaccine in the **United States**. This non-interventional study was designated as a post marketing requirement to the Food and Drug Administration (FDA) and included as a category 3 study in the EU Risk Management Plan (RMP).

6. Non-interventional Post-Authorisation Safety Study (PASS) results

Study C4591009: A Non-Interventional Post-Approval Safety Study of Pfizer-BioNTech BNT162b2 (original monovalent) COVID-19 Vaccine in the United States

6.1. Research questions and objectives

Primary objectives

Among the overall study population and subgroups of pregnant women, immunocompromised individuals, and individuals with a history of COVID-19:

1. In individuals aged 5 years and older: To estimate the RR of safety events of interest (including myocarditis/pericarditis) following receipt of a first, second, or third (if received within 2 months of the second dose) dose in a primary series of original monovalent Pfizer-BioNTech COVID-19 Vaccine compared with that among individuals with no receipt of any COVID-19 vaccine.
2. In individuals aged 6 months to 4 years: To estimate the RR of safety events of interest (including myocarditis/pericarditis) following receipt of a first, second, or third dose in a primary series of original monovalent Pfizer-BioNTech COVID-19 Vaccine compared with that among individuals with no receipt of any COVID-19 vaccine.
3. In individuals aged 5 years and older who have received 2 doses in a primary series of original monovalent Pfizer-BioNTech COVID-19 Vaccine: To estimate the RR of safety events of interest (including myocarditis/pericarditis) following a third dose (as an additional dose in a primary series or as a booster dose) of original monovalent Pfizer-BioNTech COVID-19 Vaccine received > 2 months after the second dose compared with that among individuals without a third dose of any COVID-19 vaccine[1].

Among pregnant women:

1. To estimate the birth prevalence and prevalence ratio (PR) of birth outcomes among infants born to pregnant women vaccinated with original monovalent Pfizer-BioNTech COVID-19 Vaccine compared with that among infants born to unvaccinated pregnant women.

[1] As specified in the SAP, the third dose was analyzed as part of the primary series with the first and second doses if received within 2 months of the second dose; the third dose was considered a booster dose if received > 2 months after the second dose in individuals aged 6 months to 4 years and all other age groups. The rationale for this differentiation (which was applied for all age groups) was that the safety of the third dose may depend on the timing between second and third doses.

Secondary objectives

Among the overall study population and subgroups of pregnant women, immunocompromised individuals, and individuals with a history of COVID-19:

1. To describe the proportion of individuals receiving original monovalent Pfizer-BioNTech COVID-19 Vaccine, stratified by number of doses
2. To describe – among individuals who have received a first dose of original monovalent Pfizer-BioNTech COVID-19 Vaccine – the timing and type of second dose of COVID-19 vaccine (original monovalent Pfizer-BioNTech COVID-19 Vaccine or other COVID-19 vaccine)
3. To describe baseline characteristics (demographics and comorbidities) of individuals who have received at least 1 dose of original monovalent Pfizer-BioNTech COVID-19 Vaccine and those with no record of COVID-19 vaccination of any type
4. To describe – among individuals who have received 2 doses of original monovalent Pfizer-BioNTech COVID-19 Vaccine – the timing and type of a third dose of COVID-19 vaccine (original monovalent Pfizer-BioNTech COVID-19 Vaccine or other COVID-19 vaccine)
5. To describe – among individuals aged 5 years and older who have received at least 2 doses in a primary series of original monovalent Pfizer-BioNTech COVID-19 Vaccine – baseline characteristics (demographics and comorbidities) of those who received a third dose (either as an additional dose in a primary series or as a booster dose) of original monovalent Pfizer-BioNTech COVID-19 Vaccine > 2 months after the second dose and those with no record of a third dose of COVID-19 vaccination of any type
6. Among pregnant women who have received 2 doses in a primary series of original monovalent Pfizer-BioNTech COVID-19 Vaccine: To estimate the RR of safety events of interest (including myocarditis/pericarditis) after receipt of a third dose (either as an additional dose in a primary series or as a booster dose) received > 2 months after the second dose of original monovalent Pfizer-BioNTech COVID-19 Vaccine compared with that among individuals with no receipt of a third dose of any COVID-19 vaccine

6.2. Research methods

PRAC Rapporteur comment:

Study protocol was already approved with FDA and EMA.

Please find in this section a summary of the research methods for information purposes only. Refer to **section 6.3.** for the results of the study.

Study design

This primary study design was a retrospective cohort design with concurrent unexposed comparators. In the general population, immunocompromised individuals, individuals with a history of COVID-19, and pregnant women, the study compared the incidence of **26 safety events of interest** ("general safety events," including myocarditis/pericarditis) among those who had received a first, second, or third dose in a primary series of original monovalent Pfizer-BioNTech COVID-19 Vaccine with the incidence among those who had no record of any COVID-19 vaccine in a concurrent time period. **Primary series analyses** included first and second doses as well as third doses received ≤ 2 months (≤ 60 days) after the second dose.

A separate **booster dose analysis** of general safety events was also performed within the general population, immunocompromised individuals, individuals with a history of COVID-19, and pregnant women. Among individuals who had received 2 doses of a primary series of original monovalent Pfizer-BioNTech COVID-19 Vaccine, the incidence of general safety events among those receiving an initial booster dose of original monovalent Pfizer-BioNTech COVID-19 Vaccine was compared with the incidence among those not receiving a subsequent dose of any COVID-19 vaccine. Initial booster doses were defined as third doses received > 2 months (> 60 days) after the second dose.

In addition to assessing general safety events, the study compared the incidence of **pregnancy outcomes** among pregnant women exposed to original monovalent Pfizer- BioNTech COVID-19 Vaccine with the incidence among pregnant women not exposed to any COVID-19 vaccine, in separate analyses for the primary series and for initial booster doses. Finally, the study compared the prevalence of birth outcomes among infants born to pregnant women who had received at least 1 dose of original monovalent Pfizer-BioNTech COVID-19 Vaccine during an exposure window of interest with that among infants born to pregnant women who had not received any COVID-19 vaccine during the same exposure window.

For safety analyses in the general population, immunocompromised individuals, and individuals with a history of COVID-19, individuals in the exposed cohorts were matched to individuals in the unexposed or comparator cohorts (in a variable ratio of up to 1:2) within data source on age, sex, US state, calendar time, and propensity score. For safety analyses in pregnant women, women in the exposed cohort were matched to the unexposed or comparator cohorts (in a ratio of 1:1) on maternal age, US geographic region, and estimated pregnancy start.

Cox proportional hazard models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) of general safety events and pregnancy outcomes. Modified Poisson regression was used to estimate prevalence ratios and 95% CIs of birth outcomes. Regression models were not adjusted for covariates, as confounding bias was addressed via propensity score matching (for analysis within the general population and subgroup analysis among immunocompromised individuals and individuals with a history of COVID-19) or inverse probability treatment (IPT) weighting (for analysis among pregnant women).

Setting

To be eligible for the study, exposures and comparator index dates were required to occur between 11 December 2020 (the first date of the Emergency Use Authorization [EUA] for original monovalent Pfizer-BioNTech COVID-19 Vaccine) and 18 April 2023 (the last date of the EUA for original monovalent Pfizer-BioNTech COVID-19 Vaccine).

The follow-up period for general safety events started on 11 December 2020 and ended on 18 April 2024 (1 year after the last date that original monovalent Pfizer-BioNTech COVID-19 Vaccine was authorized for use in the US). The follow-up period for pregnancy outcomes was from 12 December 2020 until 12 March 2024 (the pregnancy end date for the last eligible pregnancy), and the observation period for identifying birth outcomes was from 11 December 2020 until the last date of data available in each data source at the time of the final analysis (ranging from 04 April 2024 to 31 August 2024).

Subjects/Study populations

Safety analyses were limited to individuals who were within the ages authorized by the FDA to receive original monovalent Pfizer-BioNTech COVID-19 Vaccine. The age-based eligibility criteria were updated each time the EUA was amended to authorize younger individuals to be vaccinated.

For all safety analyses, individuals were required to be aged ≥ 6 months on the index date (i.e., date of cohort entry) and to be enrolled with continuous medical and pharmacy coverage for the longer of the following time periods: (1) from the first date that they were eligible to receive the vaccine (based on age) until the index date or (2) from 12 months before the index date until the index date[2].

Additional eligibility criteria were required for safety analyses in pregnant women. For all safety analyses, pregnant women were required to have an end-of-pregnancy event (i.e., live birth, stillbirth, spontaneous abortion, or ectopic pregnancy) recorded in the data sources, be aged between 12 and 55 years at the time of the end-of-pregnancy event, and have continuous health plan enrollment until the end of pregnancy.

For analyses of birth outcomes, pregnant women were also required to have a singleton live delivery that could be successfully linked to an infant and to have 30 days of continuous health plan enrollment after delivery. For analysis of major congenital malformations, ≥ 90 days of continuous enrollment from birth (or from birth until death, if the infant died before 90 days after birth) was required for linked infants. No minimum enrollment was required for linked infants for analysis of small size for gestational age.

For primary series and booster dose analyses in the general population, immunocompromised individuals, and individuals with a history of COVID-19, **Table 1** and **Table 2** present the numbers of individuals included in the matched, outcome-specific cohorts. Ranges are provided to summarize the cohort sizes across the outcome-specific cohorts, which were formed by excluding individuals with a history of each specific outcome before the index date.

Table 1. Number of individuals included in outcome-specific cohorts in primary series analysis in the general population, immunocompromised individuals, and individuals with a history of COVID-19

Population	Dose 1		Dose 2		Dose 3	
	Exposed (range N)	Unexposed (range N)	Exposed (range N)	Unexposed (range N)	Exposed (range N)	Unexposed (range N)
General population	6,982,505 to 7,036,223	13,316,402 to 13,431,771	5,658,225 to 5,702,994	10,727,955 to 10,821,065	31,531 to 31,752	63,049 to 63,491
Immunocompromised individuals	1,144,485 to 1,172,279	2,215,003 to 2,268,895	891,915 to 913,076	1,708,271 to 1,749,317	4,775 to 4,908	9,529 to 9,796
Individuals with a history of COVID-19	684,377 to 715,744	1,334,460 to 1,397,184	574,854 to 600,418	1,115,476 to 1,166,143	4,721 to 4,857	9,426 to 9,698

COVID-19 = coronavirus 2019.

Table 2. Number of individuals included in outcome-specific cohorts in booster dose analysis in the general population, immunocompromised individuals, and individuals with a history of COVID-19

Population	Exposed cohort (range N)	Comparator cohort (range N)
General population	2,074,831 to 2,092,944	3,405,758 to 3,438,945
Immunocompromised individuals	343,398 to 351,961	543,156 to 557,061
Individuals with a history of COVID-19	246,632 to 253,267	407,339 to 417,826

COVID-19 = coronavirus 2019.

For primary series and booster dose analysis of **general safety events** and **pregnancy outcomes** among pregnant women, **Table 3** and **Table 4** present ranges for the numbers of pregnancies included in

[2] Individuals aged < 1 year as of the index date were required to be enrolled with continuous medical and pharmacy coverage from birth until the index date.

the matched, outcome-specific cohorts. For analysis of general safety events, the sizes of the outcome-specific cohorts varied due to excluding individuals with a history of the outcome of interest before the index date. For analysis of pregnancy outcomes, the sizes of the outcome-specific cohorts varied due to differences in the outcome-specific exposure windows, as women who were vaccinated after the exposure window for the outcome of interest were not eligible for the exposed cohort.

Table 3. Number of pregnancies included in outcome-specific cohorts for primary series analysis of general safety events and pregnancy outcomes

Outcome	Dose 1		Dose 2		Dose 3	
	Exposed (range N)	Unexposed (range N)	Exposed (range N)	Unexposed (range N)	Exposed (range N)	Unexposed (range N)
General safety events	38,738 to 38,932	38,738 to 38,932	33,897 to 34,071	33,897 to 34,071	79 to 81	79 to 81
Pregnancy outcomes	32,559 to 55,416	32,559 to 55,416	13,096 to 30,460	13,096 to 30,460	20 to 45	20 to 45

COVID-19 = coronavirus 2019.

Table 4. Number of pregnancies included in outcome-specific cohorts for booster dose analysis of general safety events and pregnancy outcomes

Outcome	Exposed (range N)	Comparator (range N)
General safety events	15,001 to 15,079	15,001 to 15,079
Pregnancy outcomes	10 to 1,944	10 to 1,944

COVID-19 = coronavirus 2019.

For analysis of **birth outcomes**, **Table 5** presents the number of mother-infant pairs included in the analysis of birth outcomes for the primary series analysis, before and after matching.

Table 5. Number of mother-infant pairs eligible for primary series analysis of birth outcomes, before and after matching

Outcome-specific cohorts	Exposed cohort N	Unexposed cohort N
Major congenital malformations cohorts		
Before matching	13,218	198,512
After matching	13,201	13,201
Small size for gestational age		
Before matching	35,909	185,715
After matching	34,683	34,683

RPs = research partners.
Note: Analyses of birth outcomes were limited to the 4 RPs that had mother-infant linkage available (Carelon Research, CVS Health, HealthPartners, and Optum).

Variables and data sources

This study included secondary data from 5 research partners (RPs), all of which are participants in the FDA Sentinel System. For analyses of birth outcomes, data from only 4 RPs were included, as the fifth RP did not have mother-infant linkage available.

Receipt of the monovalent Pfizer-BioNTech COVID-19 Vaccine and other monovalent COVID-19 vaccines that were authorized or approved for use in the US during the study observation period were identified in data from claims, electronic health records (where available), and immunization registry data (where available), using procedure codes, pharmacy dispensing codes, or Centers for Disease Control Vaccine Administered codes.

General safety events, pregnancy outcomes, and birth outcomes were identified in claims and electronic health records data using diagnosis codes.

The following **general safety events** were assessed in the general population and among subgroups of interest:

- Cardiac events: myocarditis/pericarditis and acute myocardial infarction
- Neurologic events: acute disseminated encephalomyelitis, Bell's palsy, convulsions[3], encephalomyelitis/encephalitis, Guillan-Barré syndrome, narcolepsy, and transverse myelitis
- Haematologic events: deep vein thrombosis, disseminated intravascular coagulation, immune hemolytic anemia, immune thrombocytopenia, pulmonary embolism, thromboembolic events associated with thrombocytopenia, thrombotic thrombocytopenic purpura, venous thromboembolism, hemorrhagic stroke, and ischemic stroke
- Respiratory events: acute respiratory distress syndrome and vaccine-associated enhanced respiratory disease
- Other organ system events: anaphylaxis, appendicitis, Kawasaki disease, multisystem inflammatory syndrome[4], and myositis

Pregnancy outcomes (i.e. spontaneous abortion, stillbirth, and preterm birth) were identified in data from pregnant women. **Birth outcomes** (i.e. small size for gestational age and major congenital malformations) were identified in data from pregnant women and in linked infant data.

Within the general population and the sub cohorts, baseline characteristics of individuals eligible for the study were identified using diagnosis and procedure codes. These characteristics were included as variables in propensity scores. Such variables included demographic characteristics (e.g., age, sex), comorbidities (e.g., diabetes, hypertension, cardiovascular disease, history of COVID-19, immunocompromised status, obesity, pregnancy status), receipt of other vaccines, and healthcare utilization.

6.3. Results

6.3.1. Myocarditis/pericarditis

6.3.1.1. Primary series analysis

6.3.1.1.1. General population

In the **primary series analysis** within the general population, HR of myocarditis/pericarditis was 1.15 (95% CI, 1.03-1.30), as shown in **Figure 1.**

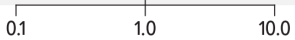
[3] Convulsions and Kawasaki disease were assessed only in individuals aged < 5 years and were not assessed in the subgroup analysis of pregnant women
[4] Multisystem inflammatory syndrome was assessed in individuals aged ≥ 6 months. Additionally, multisystem inflammatory syndrome in children (MIS-C) was assessed in individuals aged < 21 years and was not assessed in the subgroup analysis of pregnant women

6.3.1.1.2. Subgroups

In the **primary series analysis** among the *immunocompromised individuals*, HR of myocarditis/pericarditis was 0.87 (95% CI, 0.71-1.08), among *individuals with a history of COVID-19*, HR was 0.85 (95% CI, 0.64-1.13). Among *pregnant women*, no cases of myocarditis/pericarditis were observed in the exposed cohort, 2 cases were observed in the unexposed cohort [see **Figure 1**].

Figure 1. Incidence rates and hazard ratios of myocarditis/pericarditis, primary series analysis within the general population and among subgroups

	Exposed		Unexposed			
	Cases	IR (per 100,000 py)	Cases	IR (per 100,000 py)	HR (95% CI)	HR (95% CI)
General population	451	62.32	734	54.33		1.15 (1.03-1.30)
Subgroup						
Dose number						
Dose 1	208	52.31	413	55.57		0.95 (0.80-1.12)
Dose 2	242	74.64	318	52.63		1.42 (1.20-1.68)
Dose 3	1	55.40	3	84.37		0.67 (0.07-6.41)
Sex						
Male	277	80.60	407	63.23		1.29 (1.10-1.50)
Female	174	45.79	327	46.23		0.99 (0.82-1.19)
Age group						
6 months-4 years old	0	0	3	16.04		NaN
5-11 years old	8	16.00	7	7.47		1.91 (0.68-5.33)
12-17 years old	61	90.53	30	25.26		3.82 (2.45-5.97)
18-24 years old	62	115.19	42	40.69		2.88 (1.95-4.27)
25-29 years old	17	48.65	25	37.85		1.23 (0.66-2.28)
30-39 years old	44	49.24	53	31.67		1.55 (1.04-2.32)
40-49 years old	42	45.85	85	49.56		0.91 (0.63-1.32)
50-64 years old	80	51.15	186	64.27		0.80 (0.62-1.04)
≥ 65 years old	137	80.27	303	94.03		0.86 (0.70-1.05)
Calendar time						
Pre-delta era	263	56.98	483	55.78		1.04 (0.89-1.21)
Delta era	162	78.78	194	51.27		1.56 (1.26-1.92)
Omicron era	26	46.01	57	53.43		0.79 (0.49-1.26)
Immunocompromised individuals	125	105.59	274	122.54		0.87 (0.71-1.08)
Individuals with a history of COVID-19	70	93.60	154	107.87		0.85 (0.64-1.13)
Pregnant women	0	0	2	52.15		NaN



CI = confidence interval; COVID-19 = coronavirus disease 2019; HR = hazard ratio; IR = incidence rate; NaN = not a number (i.e., not estimable); py = person-years.

6.3.1.1.3. Other subgroups

Figure 2 shows the analysis stratified jointly by *age*, *sex* and *dose number*:

Among males, the highest HR estimates were observed among those aged 12 to 17 years (HR = 12.22; 95% CI, 5.51-27.11) and those aged 18 to 24 years (HR = 3.63; 95% CI, 1.94-6.80) after dose 2.

Among females, the highest HR estimates were observed among those aged 18 to 24 years after dose 2 (HR = 4.33; 95% CI, 1.65-11.40) and after dose 1 (HR = 2.88; 95% CI, 1.02-8.11).

The incidence rate (IR) of myocarditis/pericarditis after receipt of a second dose was 286.38 cases per 100,000 person-years (16.28 per 100,000 doses) in males aged 12 to 17 years, 242.82 cases per 100,000 person-years (13.84 cases per 100,000 doses) in males aged 18 to 24 years, and 101.90 cases per 100,000 person-years (5.80 cases per 100,000 doses) in females aged 18 to 24 years, see also Figure 2.

Figure 2. Incidence rates and HRs of myocarditis/pericarditis, primary series analysis among subgroups defined jointly by sex, age, and dose number

	Exposed		Unexposed			
	Cases	IR (per 100,000 py)	Cases	IR (per 100,000 py)	HR (95% CI)	HR (95% CI)
Males						
Dose 1						
6 months-4 years old	0	0.00	1	21.58		NaN
5-11 years old	2	14.83	3	11.89		1.00 (0.16-6.14)
12-17 years old	4	22.33	10	31.64		0.72 (0.22-2.30)
18-24 years old	12	85.58	15	55.31		1.56 (0.73-3.34)
25-29 years old	5	54.46	13	74.63		0.68 (0.24-1.91)
30-39 years old	12	50.92	18	40.66		1.21 (0.58-2.53)
40-49 years old	13	53.55	24	52.48		1.04 (0.53-2.05)
50-64 years old	25	60.45	54	69.93		0.86 (0.53-1.38)
≥ 65 years old	44	102.70	91	111.81		0.95 (0.66-1.37)
Dose 2						
6 months-4 years old	0	0.00	0	0.00		NaN
5-11 years old	3	25.09	3	13.33		1.59 (0.31-8.05)
12-17 years old	46	286.38	8	27.82		12.22 (5.51-27.11)
18-24 years old	28	242.82	15	67.23		3.63 (1.94-6.80)
25-29 years old	8	108.24	7	49.73		2.09 (0.75-5.81)
30-39 years old	18	94.33	16	44.35		2.26 (1.14-4.50)
40-49 years old	12	60.22	24	64.66		0.88 (0.44-1.78)
50-64 years old	15	44.31	36	57.71		0.81 (0.44-1.48)
≥ 65 years old	29	90.62	68	112.94		0.79 (0.51-1.22)
Females						
Dose 1						
6 months-4 years old	0	0.00	1	22.63		NaN
5-11 years old	2	15.41	1	4.13		4.00 (0.36-44.11)
12-17 years old	3	17.02	7	23.03		0.79 (0.20-3.09)
18-24 years old	9	58.25	6	20.41		2.88 (1.02-8.11)
25-29 years old	2	19.72	5	26.26		0.80 (0.16-4.12)
30-39 years old	8	31.33	10	21.01		1.48 (0.58-3.77)
40-49 years old	9	34.88	18	36.99		0.95 (0.42-2.11)
50-64 years old	18	40.39	55	66.99		0.60 (0.35-1.02)
≥ 65 years old	40	73.65	81	78.84		0.93 (0.64-1.37)
Dose 2						
6 months-4 years old	0	0.00	1	26.47		NaN
5-11 years old	1	8.69	0	0.00		NaN
12-17 years old	8	50.93	5	17.93		2.62 (0.85-8.11)
18-24 years old	13	101.90	6	24.72		4.33 (1.65-11.40)
25-29 years old	2	24.41	0	0.00		NaN
30-39 years old	6	28.47	9	22.93		1.15 (0.41-3.28)
40-49 years old	8	37.25	19	47.76		0.75 (0.32-1.73)
50-64 years old	21	57.68	39	57.99		1.00 (0.59-1.70)
≥ 65 years old	24	58.02	62	79.89		0.73 (0.45-1.17)

CI = confidence interval; HR = hazard ratio; IR = incidence rate; NaN = not a number (i.e., not estimable); py = person-years.
Notes: Third doses in the primary series are not included in this figure due to low case numbers. Results for third doses stratified jointly by age and sex are presented in Source Table 15.A8a.

6.3.1.2. Booster dose analysis

6.3.1.2.1. General population

In the **booster dose analysis** within the general population, HR of myocarditis/pericarditis was 1.09 (95% CI, 0.77-1.54), as shown in **Figure 3**.

6.3.1.2.2. Subgroups

In the **booster dose analysis** among the *immunocompromised individuals*, HR of myocarditis/ pericarditis was 0.66 (95% CI, 0.33-1.31), among *individuals with a history of COVID-19*, HR was 0.76 (95% CI, 0.33-1.71). Among *pregnant women*, no cases of myocarditis/pericarditis were observed in either the exposed cohort or the comparator (unexposed) cohort [see **Figure 3**].

6.3.1.2.3. Other subgroups

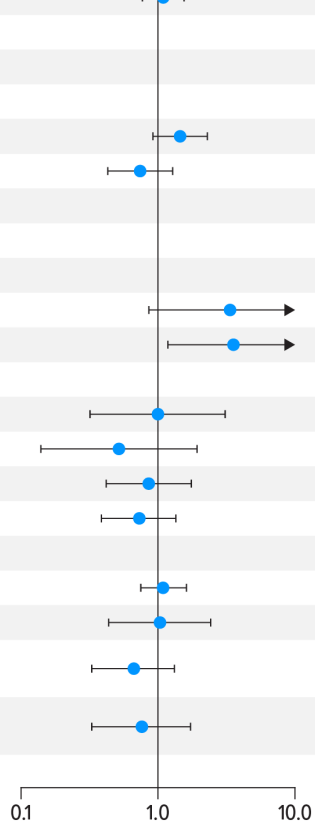
Figure 4 shows the analysis stratified jointly by *age* and *sex*:

In males, HR estimates were highest among those aged 12 to 17 years (HR = 4.92; 95% CI, 1.01-24.09), 18 to 24 years (HR = 5.16; 95% CI, 1.39-19.24), and 30 to 39 years (HR = 8.22; 95% CI, 0.95-71.27).

In females, few exposed cases (< 2) were observed among those aged 12 to 17 years, 18 to 24 years, 25 to 29 years, 30 to 39 years, and 40 to 49 years. HRs were inestimable among those aged 12 to 17 years, 25 to 29 years, and 30 to 39 years due to a lack of cases in the exposed or comparator cohorts. The HR among females aged 50 to 64 years was 1.36 (95% CI, 0.50-3.69).

Figure 3. Incidence rates and HRs of myocarditis/pericarditis, booster dose analysis within the general population and among subgroups

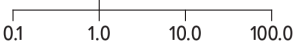
	Exposed		Comparator			
	Cases	IR (per 100,000 py)	Cases	IR (per 100,000 py)	HR (95% CI)	HR (95% CI)
General population	55	47.38	82	43.85		1.09 (0.77-1.54)
Subgroup						
Sex						
Male	36	67.72	39	45.46		1.45 (0.92-2.30)
Female	19	30.19	43	42.48		0.74 (0.43-1.28)
Age group						
6 months-4 years old	0	0	0	0		NaN
5-11 years old	0	0	1	8.98		NaN
12-17 years old	7	59.35	3	16.35		3.38 (0.86-13.30)
18-24 years old	10	122.00	5	36.79		3.53 (1.20-10.41)
25-29 years old	3	65.31	0	0		NaN
30-39 years old	5	36.84	9	40.50		1.00 (0.32-3.10)
40-49 years old	3	19.87	9	36.56		0.52 (0.14-1.93)
50-64 years old	12	42.76	22	48.45		0.86 (0.42-1.75)
≥ 65 years old	15	52.41	33	75.72		0.73 (0.39-1.35)
Calendar time						
Delta era	46	52.83	68	49.17		1.10 (0.75-1.61)
Omicron era	9	31.07	14	28.78		1.03 (0.44-2.41)
Immunocompromised individuals	12	61.30	28	91.78		0.66 (0.33-1.31)
Individuals with a history of COVID-19	9	63.52	18	78.36		0.76 (0.33-1.71)
Pregnant women	0	0	0	0		NaN



CI = confidence interval; HR = hazard ratio; IR = incidence rate; NaN = not a number (i.e., not estimable); py = person-years.
Note: The pre-Delta era is not included in this figure because a third dose of original monovalent Pfizer-BioNTech COVID-19 Vaccine was first authorized in August 2021, after the end of the pre-Delta era (31 May 2021).

Figure 4. Incidence rates and HRs of myocarditis/pericarditis, booster dose analysis among subgroups defined jointly by age and sex

	Exposed		Comparator			
	Cases	IR (per 100,000 py)	Cases	IR (per 100,000 py)	HR (95% CI)	HR (95% CI)
Males						
6 months-4 years old	0	0	0	0		NaN
5-11 years old	0	0	1	17.69		NaN
12-17 years old	7	120.84	2	21.98		4.92 (1.01-24.09)
18-24 years old	9	249.37	3	49.53		5.16 (1.39-19.24)
25-29 years old	2	96.50	0	0		NaN
30-39 years old	5	80.38	1	9.82		8.22 (0.95-71.27)
40-49 years old	2	28.62	5	43.95		0.58 (0.11-3.05)
50-64 years old	5	38.15	13	61.30		0.55 (0.19-1.56)
≥ 65 years old	6	48.95	14	75.65		0.71 (0.27-1.86)
Females						
6 months-4 years old	0	0	0	0		NaN
5-11 years old	0	0	0	0		NaN
12-17 years old	0	0	1	10.81		NaN
18-24 years old	1	21.80	2	26.54		1.00 (0.09-11.03)
25-29 years old	1	39.67	0	0		NaN
30-39 years old	0	0	8	66.42		NaN
40-49 years old	1	12.33	4	30.21		0.43 (0.05-3.87)
50-64 years old	7	46.79	9	37.19		1.36 (0.50-3.69)
≥ 65 years old	9	55.00	19	75.78		0.75 (0.33-1.66)



CI = confidence interval; HR = hazard ratio; IR = incidence rate; NaN = not a number (i.e., not estimable); py = person-years.

PRAC Rapporteur comment:

In the primary series analysis, HR of myocarditis/pericarditis within the general population was 1.15 (95% CI, 1.03-1.30). In subgroup analysis by age, sex, and dose number, HR estimates were highest after dose 2 among males aged 12 to 17 years (HR = 12.22; 95% CI, 5.51-27.11), males aged 18 to 24 years (HR = 3.63; 95% CI, 1.94-6.80). Among females, the highest HR estimates were observed aged 18 to 24 years after dose 2 (HR = 4.33; 95% CI, 1.65-11.40) and after dose 1 (HR = 2.88; 95% CI, 1.02-8.11).

In the booster dose analysis, HR of myocarditis/pericarditis within the general population was 1.09 (95% CI, 0.77-1.54), which is not significant. In subgroup analysis by age and sex, HR estimates were highest among males aged 12 to 17 years (HR = 4.92; 95% CI, 1.01-24.09), 18 to 24 years (HR = 5.16; 95% CI, 1.39-19.24), and 30 to 39 years (HR = 8.22; 95% CI, 0.95-71.27; not significant).

In subgroup analysis among immunocompromised individuals, individuals with a history of COVID-19, and pregnant women, no increased risks of myocarditis/pericarditis were observed in either the primary series or booster dose analysis.

Myocarditis and pericarditis are currently labelled in the EU SmPC of Comirnaty (section 4.4 and 4.8). Section 4.4 states among others that myocarditis and pericarditis have been observed more often after the second vaccination, and more often in younger males. Based on the final results of this study no regulatory update is needed regarding this known risk.

Refer to **section 6.3.5. Sensitivity analyses** using different risk intervals for myocarditis/ pericarditis.

6.3.2. Other general safety events

6.3.2.1. General population

For analysis within the **general population**, **Table 6** presents HRs for general safety events that were > 1.0 in the primary series and/or booster dose analysis. HR estimates for all other general safety events were ~1.0 or < 1.0 in both the primary series and booster dose analysis within the general population.

Table 6. HRs of general safety events that were > 1.0 in the primary series and/or booster dose analysis within the general population

General safety event	Primary series analysis HR (95% CI)	Booster dose analysis HR (95% CI)
Anaphylaxis	11.65 (5.51-24.65)	1.69 (0.23-12.23)
Guillain-Barré syndrome	1.19 (0.75-1.89)	0.46 (0.12-1.71)
Acute disseminated encephalomyelitis	0.92 (0.34-2.47)	1.41 (0.08-23.57)
Convulsions	0.90 (0.71-1.13)	1.14 (0.42-3.05)
Appendicitis	0.98 (0.92-1.04)	1.06 (0.90-1.24)
Kawasaki disease	0.59 (0.19-1.81)	2.00 (0.13-31.98)

CI = confidence interval; HR = hazard ratio

6.3.2.2. Immunocompromised individuals

For subgroup analysis among **immunocompromised individuals**, **Table 7** presents HRs for general safety events that were > 1.0 in the primary series and/or booster dose analysis. HR estimates for all other general safety events were ~ 1.0 or < 1.0 in both the primary series and booster dose analysis among immunocompromised individuals.

Table 7. HRs of general safety events that were > 1.0 in the primary series and/or booster dose analysis among immunocompromised individuals

General safety event	Primary series analysis HR (95% CI)	Booster dose analysis HR (95% CI)
Anaphylaxis	10.27 (3.52-29.95)	5.16 (0.53-50.41)
Convulsions	1.23 (0.64-2.34)	Not estimable due to zero events
Transverse myelitis	1.33 (0.55-3.26)	0.55 (0.06-5.39)
Guillain-Barré syndrome	0.31 (0.11-0.92)	1.33 (0.22-7.98)
Appendicitis	0.92 (0.79-1.06)	1.33 (0.93-1.91)

CI = confidence interval; HR = hazard ratio.

6.3.2.3. Individuals with a history of COVID-19

For subgroup analysis among **individuals with a history of COVID-19**, **Table 8** presents HRs for general safety events that were > 1.0 in the primary series and/or booster dose analysis. HR estimates for all other general safety events were ~ 1.0 or < 1.0 in both the primary series and booster dose analysis among individuals with a history of COVID-19.

Table 8. HR of general safety events that were > 1.0 in the primary series and/or booster dose analysis among individuals with a history of COVID-19

General safety event	Primary series analysis HR (95% CI)	Booster dose analysis HR (95% CI)
Guillain-Barré syndrome	1.21 (0.43-3.43)	1.41 (0.08-23.57)
Anaphylaxis	4.67 (1.21-18.05)	Not estimable with 1 case in exposed and 0 cases in comparator
Kawasaki disease	1.33 (0.22-7.98)	Not estimable due to zero counts
Bell's palsy	0.93 (0.77-1.11)	1.33 (0.92-1.93)
Narcolepsy	0.88 (0.73-1.08)	1.42 (0.97-2.08)
Transverse myelitis	0.67 (0.18-2.46)	1.41 (0.08-23.57)

CI = confidence interval; HR = hazard ratio.

6.3.2.4. Pregnant women

In the primary series and booster dose analysis among **pregnant women**, no cases or few cases of several general safety events were observed. For subgroup analysis among pregnant women, **Table 9** presents HRs for general safety events that were > 1.0 in the primary series and/or booster dose analysis.

Table 9. HRs of general safety events that were > 1.0 in the primary series and/or booster dose analysis among pregnant women

General safety event	Primary series analysis HR (95% CI)	Booster dose analysis HR (95% CI)
Narcolepsy	1.56 (0.55-4.40)	Not estimable with 1 event in exposed and no events in comparator
Immune thrombocytopenia	1.73 (0.83-3.59)	4.35 (0.42-44.71)
Pulmonary embolism	1.26 (0.52-3.07)	1.28 (0.12-13.84)
Myositis	1.23 (0.85-1.78)	0.50 (0.17-1.47)
Appendicitis	0.55 (0.23-1.35)	1.93 (0.21-17.76)

CI = confidence interval; HR = hazard ratio.

6.3.2.5. Age groups

In subgroup analysis by **age**, HR estimates for most general safety events were generally consistent across all age groups. However, some variation across age groups was observed for the following outcomes in either the *primary series* or *booster dose* analysis: acute myocardial infarction, Bell's palsy, Guillain-Barré syndrome, narcolepsy, hemorrhagic stroke, transverse myelitis, acute respiratory distress

syndrome, anaphylaxis, and vaccine-associated enhanced respiratory disease. Notably, in the primary series analysis, the HR of acute myocardial infarction among individuals aged 12 to 17 years was 5.58 (95% CI, 1.12-27.79), with 6 cases in the exposed cohort. In contrast, HR estimates were < 1.0 for individuals aged 18 to 64 years (HR = 0.63; 95% CI, 0.58-0.68) and those aged ≥ 65 years (HR = 0.60; 95% CI, 0.57-0.63). HRs were inestimable for individuals aged 6 months through 4 years and 5 to 11 years due to zero counts [see **Annex**].

PRAC Rapporteur comment:

Overall, HR estimates for most general safety events were ~1.0 or < 1.0 in the primary series and/or booster dose analysis within the general population and subgroups.

An increased risk of **anaphylaxis** was observed following vaccination with a primary series dose (HR = 11.65; 95% CI, 5.51-24.65) or initial booster dose (HR = 1.69; 95% CI, 0.23-12.23) of original monovalent Pfizer-BioNTech COVID-19 Vaccine. Hypersensitivity reactions and anaphylaxis are included in the EU SmPC of Comirnaty (section 4.4 and 4.8). Based on the findings of this study no regulatory action is needed.

Although HRs of some general safety events that were >1 (tables 5, 6, 7, 8 above), these were not statistically significant.

HR of acute myocardial infarction among individuals aged 12 to 17 years was 5.58 (95% CI, 1.12-27.79), (see Annex **Figure 9**), however, CI is wide with 6 cases only in the exposed cohort.

Please refer to section **Annex** reporting IRs and HRs of other general safety events in the primary series analysis, booster dose analysis among general population and subgroups.

6.3.3. Pregnancy outcomes

6.3.3.1. Primary series analysis

Table 10 presents the IRs and HRs in the **primary series** analysis of **pregnancy outcomes**, after pooling across doses 1, 2, and 3. Source Table 15.D6 [not reproduced here] presents the results by dose number. As shown in **Table 10**, HR estimates for all pregnancy outcomes were < 1.0 in the primary series analysis pooled across all doses.

Table 10. Incidence rates and HRs of pregnancy outcomes, primary series analysis, pooled across doses 1, 2, and 3

Exposure cohort	Number of pregnancies	Number of events[a]	IR per 100,000 PY[b]	Crude HR (95% CI)	sIPT-weighted HR (95% CI)
Spontaneous abortion					
Exposed	45,675	4,426	60,010.06	0.83 (0.73-0.93)	0.83 (0.73-0.93)
Unexposed	45,675	5,856	81,481.70	Reference group	Reference group
Stillbirth					
Exposed	85,921	154	718.48	0.65 (0.51-0.84)	0.66 (0.53-0.82)
Unexposed	85,921	234	1,338.10	Reference group	Reference group

Preterm birth					
Exposed	81,299	1,825	9,467.75	0.86 (0.80-0.92)	0.87 (0.81-0.94)
Unexposed	81,299	1,808	11,352.66	Reference group	Reference group

CI = confidence interval; COVID-19 = coronavirus disease 2019; HR = hazard ratio; IR = incidence rate; PY = person-years; sIPT = stabilized inverse probability of treatment.
a. Individuals were followed from the day after the index date until the earliest of the following: end-of-pregnancy event, latest gestational age at which an outcome could occur (20 weeks of gestation for spontaneous abortion; 37 weeks of gestation for preterm birth), or receipt of another dose of any COVID-19 vaccine. Individuals receiving an additional dose of original monovalent Pfizer-BioNTech COVID-19 Vaccine may have entered the subsequent dose cohort if they met all eligibility criteria.
b. IRs were calculated within the matched, outcome-specific cohorts without application of weights.

PRAC Rapporteur comment:

In the primary series analysis, HR estimates of spontaneous abortion, stillbirth and preterm birth were < 1.0.

6.3.3.2. Booster dose analysis

Table 11 presents the IRs of **pregnancy outcomes** in the **booster dose** analysis. Because of the low number of booster doses of original monovalent Pfizer-BioNTech COVID-19 Vaccine, HRs of pregnancy outcomes were not estimated. No or few cases of spontaneous abortion or stillbirth were observed in the exposed cohorts for the booster dose analysis. The IR of preterm birth was lower in the exposed cohort than in the comparator cohort.

Table 11. Incidence rates of pregnancy outcomes, booster dose analysis

Exposure cohort	Number of pregnancies[a]	Number of events	IR per 100,000 PY [b]
Spontaneous abortion			
Exposed	10	0	0.00
Comparator	10	1	123,456.79
Stillbirth			
Exposed	1,944	2	911.08
Comparator	1,944	2	972.95
Preterm birth			
Exposed	1,355	43	33,041.34
Comparator	1,355	53	41,993.50

COVID-19 = coronavirus disease 2019; HR = hazard ratio; IR = incidence rate; PY = person-years.
a. Individuals were followed from the day after the index date until the earliest of the following: end-of-pregnancy event, latest gestational age at which an outcome could occur (20 weeks of gestation for spontaneous abortion; 37 weeks of gestation for preterm birth), or receipt of another dose of any COVID-19 vaccine. Individuals receiving an additional dose of original monovalent Pfizer-BioNTech COVID-19 Vaccine may have entered the subsequent dose cohort if they met all eligibility criteria.
b. IRs were calculated within matched, outcome-specific cohorts without application of weights. Because of the low number of booster doses of original monovalent Pfizer-BioNTech COVID-19 Vaccine, HRs of pregnancy outcomes were not estimated.

PRAC Rapporteur comment:

In the booster dose analysis, HRs could not be estimated due to low number of booster dose exposed to pregnant women.

No event of spontaneous abortion was observed in the exposed cohort, 2 events of stillbirth were observed in the exposed cohort. IR of preterm birth was lower in the exposed cohort however, number of pregnant women exposed to booster dose was limited.

Overall, no increased risk regarding pregnancy outcomes was observed in the primary series and booster dose analysis. This is consistent with previous findings. The EU SmPC of Comirnaty states that Comirnaty can be used during pregnancy. This is deemed sufficient, no further action is needed.

6.3.4. Birth outcomes

Table 12 present the prevalences and prevalence ratios (PRs) of major congenital malformations and small size for gestational age among exposed and unexposed mother-infant pairs. The prevalence of major congenital malformations was similar between the exposed and unexposed cohorts (sIPT-weighted PR ~1.0). The PR estimate for small size for gestational age was > 1.0 (sIPT-weighted PR = 1.12; 95% CI, 1.07-1.17).

Table 12. Prevalence and prevalence ratios (95% CI) of major congenital malformations and small size for gestational age

Exposure cohort	Number of mother-infant pairs[a]	Number of events[b]	Prevalence per 100,000 pregnancies	Crude PR (95% CI)	sIPT-weighted PR (95% CI)
Major congenital malformations					
Exposed[c]	13,201	357	2,704.34	1.04 (0.90-1.20)	1.02 (0.88-1.18)
Unexposed	13,201	344	2,605.86	*Reference group*	*Reference group*
Small size for gestational age					
Exposed[c]	34,683	3,570	10,293.23	1.11 (1.06-1.16)	1.12 (1.07-1.17)
Unexposed	34,683	3,215	9,269.67	*Reference group*	*Reference group*

CI = confidence interval; LMP = first day of the last menstrual period; PR = prevalence ratio; RPs = research partners.
Note: Analyses of birth outcomes were limited to the 4 RPs that had mother-infant linkage available (Carelon Research, CVS Health, HealthPartners, and Optum).
a. To be eligible for analysis of small size for gestational age or major congenital malformation, pregnant women had to be continuously enrolled from the earlier of 11 December 2020 or 365 days before the index date (estimated pregnancy start) until 30 days after pregnancy and had to be linked to an infant. Additionally, to be eligible for analysis of major congenital malformations, pregnant women had to be linked to an infant who had continuous health plan enrollment from birth until 90 days after birth or from birth until death, if the infant died before 90 days of age (allowing for a 30-day grace period in infant enrollment after birth).
b. Small size for gestational age was assessed in maternal data and infant data from delivery until 30 days after delivery; major congenital malformations were assessed in maternal data from birth until 30 days after birth and in infants from birth until 365 days after birth.
c. For small size for gestational age analyses, the exposure window of interest was from 28 days before LMP through the end of pregnancy. For major congenital malformations analyses, the exposure window was from 28 days before LMP through the end of the first trimester.

PRAC Rapporteur comment:

Prevalence ratio (PR) of major congenital malformations was similar between the exposed and unexposed groups: sIPT-weighted PR ~1.0.

A small increased prevalence of small size for gestational age (SGA) was observed: PR = 1.12; 95% CI, 1.07-1.17. Refer to **section 6.3.6. MAH interpretation of key results** for discussion on SGA.

6.3.5. Sensitivity analyses

6.3.5.1. Primary series analysis, alternative risk window for myocarditis/pericarditis

For the **primary series** analysis, **Table 13** shows the results from sensitivity analyses for the cohort design with concurrent comparators, using the risk interval definitions for myocarditis/pericarditis of 1 to 7 days and 1 to 14 days. HR estimates of myocarditis/pericarditis were > 1.0 with all 3 risk interval

definitions (1 to 7, 1 to 14, and 1 to 21 days). However, HR was the highest in the sensitivity analysis using the risk interval definition of 1 to 7 days (HR = 1.61; 95% CI, 1.34-1.93).

Table 13. Incidence rates and HRs (95% CI) of myocarditis/pericarditis, sensitivity analysis with alternative risk interval definitions, primary series analysis

Risk interval definition	Exposed cohort		Unexposed cohort		HR (95% CI)
	Cases	IR (per 100,000 PY)	Cases	IR (per 100,000 PY)	
1 to 7 days (sensitivity analysis)	218	89.37	255	55.17	1.61 (1.34-1.93)
1 to 14 days (sensitivity analysis)	343	70.62	493	53.92	1.31 (1.14-1.50)
1 to 21 days (primary analysis)	451	62.32	734	54.33	1.15 (1.03-1.30)

CI = confidence interval; HR = hazard ratio; IR = incidence rate; PY = person-years.

6.3.5.1.1. Booster dose analysis, alternative risk window for myocarditis/pericarditis

For the **booster dose** analysis, **Table 14** reports the results from sensitivity analyses for the cohort design with concurrent comparators, using the risk interval definitions for myocarditis/pericarditis of 1 to 7 days and 1 to 14 days. HR estimates were > 1.0 with all 3 risk interval definitions (1 to 7, 1 to 14, and 1 to 21 days), with the highest HR observed using the sensitivity analysis risk interval definition of 1 to 7 days (HR = 1.81; 95% CI, 1.07-3.08).

Table 14. Incidence rates and HRs (95% CI) of myocarditis/pericarditis, sensitivity analysis with alternative risk interval definitions, booster dose analysis

Risk interval definition	Exposed cohort		Unexposed cohort		HR (95% CI)
	Cases	IR (per 100,000 PY)	Cases	IR (per 100,000 PY)	
1 to 7 days (sensitivity analysis)	29	72.88	27	41.44	1.81 (1.07-3.08)
1 to 14 days (sensitivity analysis)	42	53.45	57	44.61	1.20 (0.80-1.79)
1 to 21 days (primary analysis)	55	47.38	82	43.85	1.09 (0.77-1.54)

CI = confidence interval; HR = hazard ratio; IR = incidence rate; PY = person-years.

PRAC Rapporteur comment:

Using different risk intervals – 1 to 7, 1 to 14, 1 to 21 days – for myocarditis/ pericarditis, HR were above 1 for all 3 risk intervals with the highest HR for 1 to 7 days. The current warning in EU SmPC of Comirnaty states that myocarditis/ pericarditis primarily occurred within 14 days. This is deemed sufficient. No regulatory action is needed based on the findings of this study.

6.3.5.2. Cohort design with concurrent, unexposed comparators and quantitative bias analysis for outcome misclassification (myocarditis/pericarditis only)

Details of the results of this sensitivity analysis for both primary series and booster dose analyses are provided in the final CSR [not reproduced here]. The IRRs corrected for outcome misclassification were below the null. In the primary series analysis, the observed IRR was 1.14, whereas the corrected IRRs in the primary series analysis ranged from 0.55 to 0.70. In the booster dose analysis, the observed IRR was 1.08, whereas the corrected IRRs ranged from 0.52 to 0.66.

6.3.5.3. Secondary study design

These results are described in detail in the final CSR [not reproduced here]. Overall, the results of the analysis using the SCRI design (a secondary study design) were consistent with the results of the primary analysis, with a few exceptions. No increased risks of myocarditis/pericarditis were observed among subgroups of primary series or booster dose vaccinees among immunocompromised individuals (primary series HR = 0.87; 95% CI, 0.71-1.08; booster dose HR = 0.66; 95% CI, 0.33-1.31) or among those who had a history of COVID-19 (primary series HR = 0.85; 95% CI, 0.64-1.13; booster dose HR = 0.76; 95% CI, 0.33-1.71). However, the results of the SCRI design among immunocompromised individuals and individuals with a history of COVID-19 for primary series vaccination suggested elevated IRRs (IRR among immunocompromised individuals = 1.44; 95% CI, 0.86-2.47); IRR among individuals with a history of COVID-19 = 2.76; 95% CI, 1.48-5.52), with wide Cis.

Additionally, in subgroup analysis among pregnant women, the results of the SCRI design were generally consistent with those of the cohort design with concurrent unexposed comparators. However, 1 case of myocarditis/pericarditis was observed in the risk interval in the primary series analysis in the SCRI design (with an IRR estimate of < 1.0). In contrast, no exposed cases of myocarditis/pericarditis were observed in the cohort design.

6.3.6. MAH interpretation of key results

Myocarditis/pericarditis

The increased risk of myocarditis/pericarditis after receipt of original monovalent Pfizer-BioNTech COVID-19 Vaccine observed in the present study is consistent with other observational studies, which have reported the highest increased risk in young males after a second dose, and in the week after vaccination. Wong et al.[5] compared observed incidence rates of myocarditis/pericarditis in the 1 to 7 days after vaccinations occurring from 18 December 2020 to 25 December 2021 in 4 US administrative claims databases with expected rates from historical cohorts from the same data sources in 2019. Consistent with the results from this study, the highest observed to expected ratios were reported among men aged 18 to 25 years after the second dose, ranging from 8.57 to 21.85 across the data sources included in the analysis. The study by Goddard et al[6] reported an IRR of 6.94 (95% CI, 3.57-14.13) for dose 1 or dose 2 of original monovalent Pfizer-BioNTech COVID-19, 3.02 (95% CI, 1.03-8.33) for dose 1, and 14.34 for dose 2 (95% CI, 6.45-34.85).

The findings in this study regarding an increased risk of myocarditis/pericarditis are consistent with the US prescribing information (PI) and European Union (EU) SmPC for Pfizer-BioNTech COVID-19 Vaccine Comirnaty).

The increased risk of myocarditis/pericarditis after receipt of Pfizer-BioNTech COVID-19 Vaccine should be interpreted in the context of the benefits of the vaccine. Observational studies have previously reported an association between COVID-19 and an elevated risk of myocarditis/pericarditis. In a study conducted in the FDA Biologics Effectiveness and Safety (BEST) system, HR for myocarditis/pericarditis in the 0 to 41 days after a COVID-19 diagnosis, as compared with no COVID-19 diagnosis was 14.32 (95% CI, 7.98-25.69) among males aged 18 to 34 years, and was 4.70 (95% CI, 2.45-8.99) among males aged 35 to 49 years[7]. Similarly, in a study using the Premier HealthCare Database Special COVID-19 Release (a large, US hospital-based administrative database from > 900 hospitals) that was conducted between

[5] Wong HL, Hu M, Zhou CK, et al. Risk of myocarditis and pericarditis after the COVID-19 mRNA vaccination in the USA: a cohort study in claims databases. Lancet. 2022;399(10342):2191-99
[6] Goddard K, Lewis N, Fireman B, et al. Risk of myocarditis and pericarditis following BNT162b2 and mRNA-1273 COVID-19 vaccination. Vaccine. 2022;40(35):5153-59
[7] Layton JB, Fisher S, Lindaas A, et al. Evaluating the risk of adverse events after COVID-19 diagnosis. Final report. 13 December 2024. Available from: https://bestinitiative.org/wp-content/uploads/2025/01/BEST_Post-COVID-19_AE_2024.pdf. Accessed on: 2 December 2025

March 2020 and January 2021, the risk ratio comparing the incidence of myocarditis among individuals with a diagnosis of COVID-19 with the incidence among those without a diagnosis of COVID-19 was 15.7 (95% CI, 14.1-17.2), with a corresponding risk difference of 0.126 (0.112-0.140)[8].

Observational studies have also reported a higher risk of myocarditis/pericarditis after SARS-CoV-2 infection than after receipt of original monovalent Pfizer-BioNTech COVID-19 Vaccine or any mRNA COVID-19 vaccine (regardless of brand). In a study conducted in England using national registry data between 01 December 2020 and 24 August 2021, a self-controlled case series design was used to examine the associations of SARS-CoV-2 infection and receipt of original monovalent Pfizer-BioNTech COVID-19 Vaccine with the incidence of myocarditis and pericarditis[9]. For SARS-CoV-2 infection when using a 1 to 7 day risk window, IRRs were elevated for myocarditis (IRR = 21.08; 95% CI, 15.34-28.96), and for pericarditis (IRR = 4.85; 95% CI, 2.56-9.18). For receipt of a first dose of original monovalent Pfizer-BioNTech COVID-19 Vaccine, IRR of myocarditis was 1.45 (95% CI, 0.97-2.17) and IRR of pericarditis was 0.59 (95% CI, 0.32-1.07). For receipt of a second dose of original monovalent Pfizer-BioNTech COVID-19 Vaccine, IRRs were elevated for myocarditis (IRR = 1.75; 95% CI, 1.13-2.70) but not for pericarditis (IRR = 0.58; 95% CI, 0.33-1.04).

PRAC Rapporteur comment:

No new safety information on myocarditis and pericarditis was identified. Myocarditis and pericarditis are labelled in the EU SmPC (section 4.4, 4.8). No further action is needed.

Anaphylaxis

The increased risk of anaphylaxis after receipt of original monovalent Pfizer-BioNTech COVID-19 Vaccine observed in this study is also consistent with previous observational research.

Although the present study estimated an 11.7-fold increase in the hazard of anaphylaxis for a primary series dose and a 5.0-fold increase in the hazard for a booster dose , the comparators comprised an unexposed population without restricting to individuals with healthcare visits or exposure to medical products, likely leading to a lower estimate of the baseline incidence and as a result, a higher estimate of comparative risk. Notably, the incidence of anaphylaxis after receipt of original monovalent Pfizer-BioNTech COVID-19 Vaccine in this study was very rare in this study, with an incidence rate estimate of 137.28 cases per 100,000 person-years (3.76 per million doses) for primary series vaccination and 34.90 cases per 100,000 person-years (0.96 per million doses) for booster dose. These estimates are consistent with an estimate from the VSD, which previously reported an incidence of anaphylaxis of 4.8 cases per million doses of original Pfizer-BioNTech COVID-19 Vaccine based on chart-confirmed cases[10].

The findings in this study regarding an increased risk of anaphylaxis are consistent with the US PI and EU SmPC for Pfizer-BioNTech COVID-19 Vaccine (Comirnaty).

PRAC Rapporteur comment:

No new safety information on anaphylaxis was identified. Anaphylaxis is labelled in the EU SmPC (section 4.4, 4.8). No further regulatory action is needed.

The MAH noted a 5.0-fold increase in the hazard for a booster dose, however Fig. 15 showed HR = 1.69 (95% CI, 0.23-12.23) for a booster dose in the general population for anaphylaxis. The MAH is requested to clarify (**OC**). Note that Fig. 16 showed HR = 5.16 (95% CI, 0.53-50.41) for a booster dose in immunocompromised individuals.

[8] 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
[9] Patone M, Mei XW, Handunnetthi L, et al. Risks of myocarditis, pericarditis, and cardiac arrhythmias associated with COVID-19 vaccination or SARS-CoV-2 infection. Nat Med. 2022;28(2):410-22
[10] Klein NP, Lewis N, Goddard K, et al. Surveillance for Adverse Events After COVID-19 mRNA Vaccination. JAMA. 2021;326(14):1390-99

Small size for gestational age

An increased prevalence of small size for gestational age (SGA) among infants born to pregnant women who were exposed to Pfizer-BioNTech COVID-19 Vaccine has not previously been reported in the published literature. Four prior observational studies (summarized below) reported no association of small size for gestational age with receipt of mRNA vaccine during pregnancy.

In a population registry–based study in Ontario, Canada, that included data from 14 December 2020 through 31 December 2021, no increased hazard of infants being born small size for gestational age was observed after receipt of at least a first dose (HR = 0.98; 95% CI, 0.93-1.03; n = 76,589) or at least 2 doses of original monovalent Pfizer-BioNTech COVID-19 Vaccine during pregnancy (HR = 0.97; 95% CI, 0.92-1.04; n = 61,929)[11]. Similarly, a population-based study of births in Sweden and Norway occurring from 01 January 2021 to 15 January 2022 did not report increased prevalences of infants being born small size for gestational age after receipt of 1 dose of original monovalent Pfizer-BioNTech COVID-19 Vaccine during pregnancy (odds ratio [OR] = 1.01; 95% CI, 0.92-1.12; n = 134,041) or after receipt of 2 doses during pregnancy (OR = 0.97; 95% CI, 0.92-1.03; n = 147,695)[12]. In a study that included data from 15 December 2020 to 22 July 2021 for 40,627 pregnant women, the CDC's Vaccine Safety Datalink reported HR estimates of small size for gestational age that were ~1.0 or < 1.0 for receipt of 1 dose (HR = 0.92; 95% CI, 0.80-1.07) and receipt of 2 doses of any mRNA COVID-19 vaccine during pregnancy (HR = 0.98; 95% CI, 0.89-1.08)[13]. A subsequent study conducted by the VSD that included data from 01 June 2021 to 31 January 2022 for 55,591 pregnant women reported a hazard ratio of small size for gestational age of 1.06 (95% CI, 0.99-1.13) for receipt of ≥ 1 doses of mRNA COVID-19 vaccine during pregnancy[14].

The contrasting results from the 4 prior studies and this study can potentially be explained by the type of data available to identify small size for gestational age and pregnancy start (clinical data vs. administrative claims data) and differences in the confounders that were included in analyses. The studies conducted in the VSD, the Nordic countries, and Ontario, Canada, defined small size for gestational age as a birthweight < the 10th percentile for gestational age based on clinical data on birthweight and gestational age. In contrast, the algorithm used in this study was based on claims data only (requiring ≥ 1 ICD-10-CM diagnosis code for placental insufficiency, poor fetal growth, or small size for gestational age) and was an adaptation of an *International Classification of Diseases, Ninth Revision* (ICD-9)–based algorithm that had a Positive Predictive Value (PPV) of > 90%. However, a subsequent validation study of an algorithm that only included ICD-10 codes for small size for gestational age reported a very low PPV (35%). Additionally, the other studies had clinical data on Last Menstrual Period (LMP) date, whereas the present study assigned pregnancy start using an algorithm that was based on diagnosis and procedure codes in claims data. The other studies adjusted for prenatal care, race and ethnicity, and socioeconomic status, whereas the present study did not adjust for these variables because they were incompletely captured in the data sources. The other studies also had access to body mass index (BMI) information, which was not available in the data sources for this study, to more accurately capture obesity. Thus, the prior studies may have been less subject to outcome misclassification and confounding bias.

Although a slightly increased prevalence of small size for gestational age (IPT-weighted PR = 1.12; 95% CI, 1.07-1.17) was observed among infants born to pregnant women exposed to original monovalent Pfizer-BioNTech COVID-19 Vaccine, this finding should be interpreted within the context of the study's limitations and the benefits of vaccination for pregnant women for prevention of SARS-CoV-2

[11] Fell DB, Dimanlig-Cruz S, Regan AK, et al. Risk of preterm birth, small for gestational age at birth, and stillbirth after covid-19 vaccination during pregnancy: population based retrospective cohort study. BMJ. 2022;378:e071416
[12] Magnus MC, Ortqvist AK, Dahlqwist E, et al. Association of SARS-CoV-2 Vaccination During Pregnancy With Pregnancy Outcomes. JAMA. 2022;327(15):1469-77
[13] Lipkind HS, Vazquez-Benitez G, DeSilva M, et al. Receipt of COVID-19 Vaccine During Pregnancy and Preterm or Small-for-Gestational-Age at Birth - Eight Integrated Health Care Organizations, United States, December 15, 2020-July 22, 2021. MMWR Morb Mortal Wkly Rep. 2022;71(1):26-30
[14] Vesco KK, Denoble AE, Lipkind HS, et al. Obstetric Complications and Birth Outcomes After Antenatal Coronavirus Disease 2019 (COVID-19) Vaccination. Obstet Gynecol. 2024;143(6):794-802

infection. Observational studies have previously reported an association between SARS-CoV-2 infection or diagnosis of COVID-19 during pregnancy and increased risks of morbidity and mortality.

PRAC Rapporteur comment:

Published literature reported no association of small size for gestational age (SGA) with receipt of mRNA vaccine during pregnancy. In this study a small increased prevalence of SGA among infants born to pregnant women who were exposed to Pfizer-BioNTech COVID-19 Vaccine was observed: IPT-weighted PR = 1.12; 95% CI, 1.07-1.17. The MAH postulated that this study could be more subject to outcome misclassification and confounding bias, since administrative claims data were used and not clinical data. In addition, this study did not adjust for variables like BMI, race, ethnicity, socioeconomic status. This could be acceptable. However, to carefully monitor this issue further, the MAH is requested to discuss any new relevant emerging safety information regarding pregnancy and birth outcomes including SGA in the next PSUR, if applicable (Request for next PSUR, see **section 2. Overall conclusion and impact on the benefit/risk balance**).

6.3.7. MAH Overall conclusion on benefits and risks

Consistent with published observational studies as well as the US PI and the EU SmPC for Pfizer-BioNTech COVID-19 Vaccine, an increased risk of myocarditis/pericarditis was observed after receipt of a primary series dose or initial booster dose of original monovalent Pfizer-BioNTech COVID-19 Vaccine. In subgroup analysis among immunocompromised individuals, individuals with a history of COVID-19, and pregnant women, no increased risks of myocarditis/pericarditis were observed in either the primary series or booster dose analysis.

Also consistent with prior observational research, US PI, and EU SmPC, an increased risk of anaphylaxis was observed after receipt of a primary series dose or initial booster dose of original monovalent Pfizer-BioNTech COVID-19 Vaccine. Importantly, the incidence of anaphylaxis after receipt of original monovalent Pfizer-BioNTech COVID-19 Vaccine was extremely rare, equating to 3.76 cases per million doses in the primary series analysis and 0.96 cases per million doses in the booster dose analysis.

In safety analyses of pregnant women, a slightly elevated prevalence of small size for gestational age was observed among infants born to pregnant women exposed to original monovalent Pfizer-BioNTech COVID-19 Vaccine. However, no association between original monovalent Pfizer-BioNTech COVID-19 Vaccine and small size for gestational age has been reported in prior studies that have identified this outcome using clinical data on birthweight and gestational age, and residual confounding may have been present in this study.

Additionally, the incidences of certain general safety events were numerically higher among Pfizer-BioNTech COVID-19 Vaccine–exposed individuals in subgroup analyses of immunocompromised individuals (i.e., convulsions, transverse myelitis, and Guillain-Barré syndrome), individuals with a history of COVID-19 (i.e., Kawasaki disease, Bell's palsy, narcolepsy, and transverse myelitis), pregnant women (narcolepsy, immune thrombocytopenia, pulmonary embolism, and myositis), and specific age groups (i.e., acute myocardial infarction, Bell's palsy, Guillain-Barré syndrome, narcolepsy, hemorrhagic stroke, transverse myelitis, acute respiratory distress syndrome, anaphylaxis, and vaccine-associated enhanced respiratory disease). However, sample sizes were limited, and estimates were imprecise in many of the subgroup analyses; thus, associations with these outcomes cannot be confirmed. The results of other general safety events, pregnancy outcomes, and birth outcomes did not suggest increased risks associated with receipt of original monovalent Pfizer-BioNTech COVID-19 Vaccine.

Based on the results of this study, no new safety issues were identified, and the benefit-risk profile of the original monovalent Pfizer-BioNTech COVID-19 Vaccine remains unchanged.

PRAC Rapporteur comment:

Refer to **section 2. Overall conclusion and impact on the benefit/risk balance**.

7. Request for supplementary information

7.1. Major objections

Clinical aspects

None

7.2. Other concerns

Clinical aspects

1. Regarding anaphylaxis, the MAH noted a 5.0-fold increase in the hazard for a booster dose, however Fig. 15 showed HR = 1.69 (95% CI, 0.23-12.23) for a booster dose in the general population. The MAH is requested to clarify. Note that Fig. 16 showed HR = 5.16 (95% CI, 0.53-50.41) for a booster dose in immunocompromised individuals.

8. Assessment of the responses to the request for supplementary information

8.1. Major objections

Clinical aspects

None

8.2. Other concerns

Clinical aspects

Question 1
Regarding anaphylaxis, the MAH noted a 5.0-fold increase in the hazard for a booster dose, however Fig. 15 showed HR = 1.69 (95% CI, 0.23-12.23) for a booster dose in the general population. The MAH is requested to clarify. Note that Fig. 16 showed HR = 5.16 (95% CI, 0.53-50.41) for a booster dose in immunocompromised individuals.

Summary of the MAH's response

The MAH confirms that among the general population there was a 1.7-fold increase in the hazard ratio for a booster dose as shown in Fig. 15. The statement in Section 11.3 (Anaphylaxis) of the final report should read:

"*Although the present study estimated an 11.7-fold increase in the hazard of anaphylaxis for a primary series dose and a 1.7-fold increase in the hazard for a booster dose, the comparators comprised an unexposed population without restricting to individuals with healthcare visits or exposure to medical products, likely leading to a lower estimate of the baseline incidence and as a result, a higher estimate of comparative risk*".

Assessment of the MAH's response

The MAH's clarification is acceptable. Issue resolved.

Conclusion

☐Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☒No need to update overall conclusion and impact on benefit-risk balance

9. Annex

Other general safety events, primary series analysis

General population

Figure 5 presents IRs and HRs of other general safety events for the **primary series analyses** within the *general population*, pooled across all 3 doses. HR estimates were > 1.0 for anaphylaxis (HR = 11.65; 95% CI, 5.51-24.65) and Guillain-Barré syndrome (HR = 1.19; 95% CI, 0.75-1.89). As shown in **Figure 5**, HR estimates for the other general safety events in the general population were ~1.0 or < 1.0.

Figure 5. Incidence rates and HRs of other general safety events, primary series analysis within the general population

	Exposed		Unexposed			
	Cases	IR (per 100,000 py)	Cases	IR (per 100,000 py)	HR (95% CI)	HR (95% CI)
Cardiac						
Acute myocardial infarction	3,239	370.32	10,705	659.95		0.61 (0.58-0.63)
Neurologic						
Acute disseminated encephalomyelitis	6	0.52	15	0.71		0.92 (0.34-2.47)
Bells palsy	1,311	114.22	3,493	166.09		0.84 (0.78-0.89)
Convulsions	106	666.79	262	849.80		0.90 (0.71-1.13)
Encephalomyelitis/ encephalitis	101	8.80	300	14.26		0.73 (0.58-0.92)
Guillain-Barré syndrome	30	2.61	54	2.57		1.19 (0.75-1.89)
Narcolepsy	1,203	35.50	3,821	67.61		0.80 (0.75-0.86)
Transverse myelitis	17	1.48	36	1.71		1.02 (0.56-1.84)
Hematalogic						
Deep vein thrombosis	3,574	408.63	10,297	634.71		0.69 (0.66-0.72)
Disseminated intravascular coagulation	101	11.50	491	30.11		0.42 (0.34-0.52)
Immune hemolytic anemia	94	8.19	287	13.64		0.74 (0.58-0.94)
Immune thrombocytopenia	522	45.49	1,436	68.29		0.77 (0.69-0.85)
Pulmonary embolism	2,440	278.70	7,776	478.74		0.63 (0.60-0.66)
Thromboembolic events associated with thrombocytopenia	1,087	123.84	3,438	211.07		0.64 (0.60-0.69)
Thrombotic thrombocytopenic purpura	7	0.80	34	2.09		0.40 (0.18-0.91)
Venous thromboembolism	5,114	586.18	15,217	940.59		0.67 (0.65-0.69)
Hemorrhagic stroke	828	94.35	2,647	162.53		0.63 (0.59-0.69)
Ischemic stroke	2,536	290.91	7,919	489.91		0.64 (0.61-0.67)
Respiratory						
Acute respiratory distress syndrome	2,694	307.27	12,195	749.70		0.45 (0.43-0.46)
Vaccine-associated enhanced respiratory disease	10,766	223.40	128,403	1676.56		0.27 (0.27-0.28)
Other organ system						
Anaphylaxis	48	137.28	8	12.02		11.65 (5.51-24.65)
Appendicitis	1,462	127.42	3,389	161.23		0.98 (0.92-1.04)
Kawasaki disease	4	25.12	16	51.81		0.59 (0.19-1.81)
Multisystem inflammatory syndrome	23	2.00	138	6.56		0.35 (0.22-0.55)
Multisystem inflammatory syndrome in children	14	5.76	76	17.39		0.39 (0.22-0.70)
Myositis	7,600	157.50	25,946	338.02		0.87 (0.85-0.90)

CI = confidence interval; HR = hazard ratio; IR = incidence rate; py = person-years

Subgroups

Figure 6 presents IRs and HRs of other general safety events among *immunocompromised individuals* for the primary series analysis, pooled across all doses. HR estimates among immunocompromised individuals were > 1.0 for anaphylaxis (HR = 10.27; 95% CI, 3.52-29.95), convulsions (HR = 1.23; 95% CI, 0.64-2.34), and transverse myelitis (HR = 1.33; 95% CI, 0.55-3.26). The HR estimates of all other general safety events were ~ 1.0 or < 1.0.

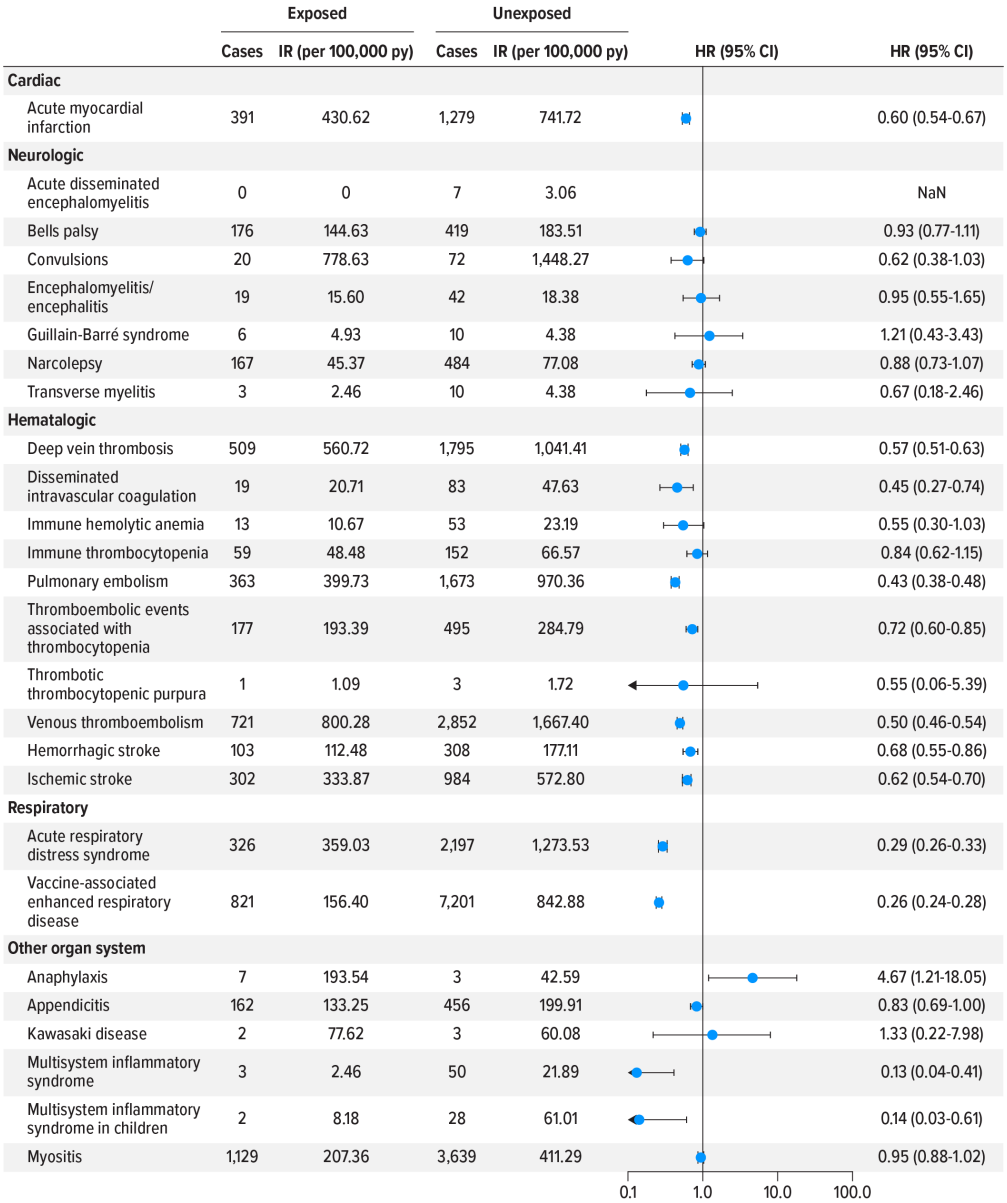
Figure 6. Incidence rates and HRs of other general safety events, primary series analysis among immunocompromised individuals

	Exposed		Unexposed			
	Cases	IR (per 100,000 py)	Cases	IR (per 100,000 py)	HR (95% CI)	HR (95% CI)
Cardiac						
Acute myocardial infarction	1,147	802.37	3,698	1,378.03		0.62 (0.58-0.66)
Neurologic						
Acute disseminated encephalomyelitis	0	0	5	1.41		NaN
Bells palsy	404	211.13	1,028	289.88		0.86 (0.77-0.97)
Convulsions	15	1,050.60	28	1,012.87		1.23 (0.64-2.34)
Encephalomyelitis/ encephalitis	42	21.89	164	46.12		0.57 (0.40-0.81)
Guillain-Barré syndrome	4	2.09	24	6.75		0.31 (0.11-0.92)
Narcolepsy	391	67.45	1,127	115.66		0.90 (0.79-1.02)
Transverse myelitis	8	4.17	18	5.06		1.33 (0.55-3.26)
Hematalogic						
Deep vein thrombosis	1,398	978.92	4,225	1,575.89		0.67 (0.63-0.71)
Disseminated intravascular coagulation	47	32.42	234	85.96		0.40 (0.29-0.55)
Immune hemolytic anemia	45	23.46	145	40.78		0.65 (0.46-0.91)
Immune thrombocytopenia	212	110.74	517	145.70		0.88 (0.75-1.04)
Pulmonary embolism	1,038	724.92	3,349	1,245.78		0.62 (0.57-0.66)
Thromboembolic events associated with thrombocytopenia	529	366.19	1,691	623.42		0.62 (0.56-0.68)
Thrombotic thrombocytopenic purpura	3	2.07	13	4.78		0.47 (0.13-1.68)
Venous thromboembolism	2,032	1,435.94	6,306	2,374.01		0.65 (0.61-0.68)
Hemorrhagic stroke	260	179.86	861	317.19		0.60 (0.52-0.69)
Ischemic stroke	799	562.16	2,565	961.39		0.62 (0.57-0.67)
Respiratory						
Acute respiratory distress syndrome	1,189	827.92	5,295	1,964.20		0.45 (0.42-0.48)
Vaccine-associated enhanced respiratory disease	4,606	569.17	37,119	2,865.00		0.39 (0.38-0.40)
Other organ system						
Anaphylaxis	21	366.97	4	36.27		10.27 (3.52-29.95)
Appendicitis	276	144.08	679	191.24		0.92 (0.79-1.06)
Kawasaki disease	1	69.82	5	180.15		0.43 (0.05-3.87)
Multisystem inflammatory syndrome	4	2.09	43	12.10		0.20 (0.07-0.57)
Multisystem inflammatory syndrome in children	1	6.32	10	34.29		0.20 (0.03-1.62)
Myositis	2,426	295.45	7,701	585.27		0.94 (0.89-0.99)

CI = confidence interval; HR = hazard ratio; IR = incidence rate; NaN = not a number (i.e., not estimable); py = person-years

Figure 7 presents the IRs and HRs of other general safety events for the primary series analysis among *individuals with a history of COVID-19*, pooled across all doses. HR estimates among individuals with a history of COVID-19 were > 1.0 for anaphylaxis (HR = 4.67; 95% CI, 1.21-18.05), Guillain-Barré syndrome (HR = 1.21; 95% CI, 0.43-3.43), and Kawasaki disease (HR = 1.33; 95% CI, 0.22-7.98). The HR estimates for other general safety events among individuals with a history of COVID-19 were ~1.0 or < 1.0.

Figure 7. Incidence rates and HRs of other general safety events, primary series analysis among individuals with a history of COVID-19

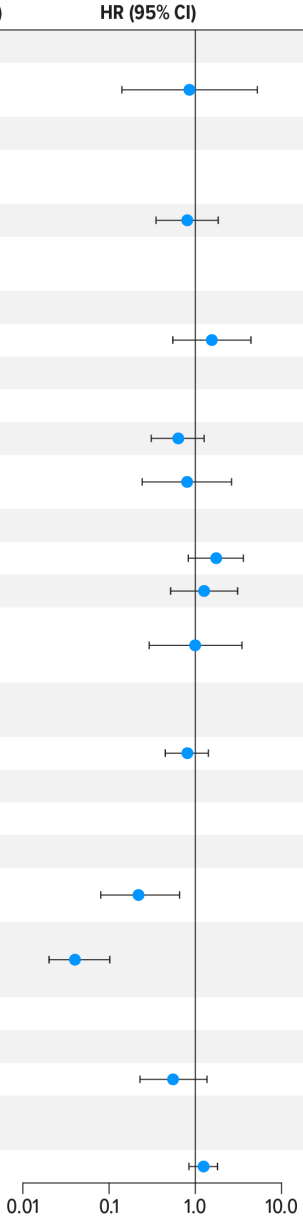


CI = confidence interval; HR = hazard ratio; IR = incidence rate; NaN = not a number (i.e., not estimable); py = person-years

Figure 8 presents the IRs and HRs for the primary series of other general safety events among *pregnant women*, pooled across all doses. No exposed cases of acute disseminated encephalomyelitis, encephalomyelitis / encephalitis, Guillain-Barré syndrome, transverse myelitis, immune hemolytic anemia, thrombotic thrombocytopenic purpura, hemorrhagic stroke, ischemic stroke, anaphylaxis, or multisystem inflammatory syndrome were observed, leading to not estimable HRs. HR estimates were > 1.0 for narcolepsy (HR = 1.56; 95% CI, 0.55-4.40), immune thrombocytopenia (HR = 1.73; 95% CI, 0.83-3.59), pulmonary embolism (HR = 1.26; 95% CI, 0.52-3.07), and myositis (HR = 1.23; 95% CI, 0.85-1.78). HR estimates for other general safety events among pregnant women were ~1.0 or < 1.0.

Figure 8. Incidence rates and HRs of other general safety events, primary series analysis among pregnant women

	Exposed		Unexposed			
	Cases	IR (per 100,000 py)	Cases	IR (per 100,000 py)	HR (95% CI)	HR (95% CI)
Cardiac						
Acute myocardial infarction	2	39.47	3	59.96		0.86 (0.14-5.16)
Neurologic						
Acute disseminated encephalomyelitis	0	0	0	0		NaN
Bells palsy	9	134.86	15	207.29		0.80 (0.35-1.81)
Encephalomyelitis/ encephalitis	0	0	1	13.81		NaN
Guillain-Barré syndrome	0	0	0	0.00		NaN
Narcolepsy	10	46.34	6	24.79		1.56 (0.55-4.40)
Transverse myelitis	0	0.00	0	0		NaN
Hematalogic						
Deep vein thrombosis	13	257.22	20	400.68		0.63 (0.31-1.26)
Disseminated intravascular coagulation	5	98.65	7	139.88		0.79 (0.24-2.59)
Immune hemolytic anemia	0	0	1	13.81		NaN
Immune thrombocytopenia	19	285.12	12	166.07		1.73 (0.83-3.59)
Pulmonary embolism	12	237.28	9	180.23		1.26 (0.52-3.07)
Thromboembolic events associated with thrombocytopenia	5	98.66	5	99.91		0.99 (0.29-3.45)
Thrombotic thrombocytopenic purpura	0	0	0	0		NaN
Venous thromboembolism	23	455.95	27	541.97		0.80 (0.45-1.41)
Hemorrhagic stroke	0	0	3	59.96		NaN
Ischemic stroke	0	0	2	40.00		NaN
Respiratory						
Acute respiratory distress syndrome	4	78.96	20	399.86		0.22 (0.08-0.65)
Vaccine-associated enhanced respiratory disease	6	18.08	165	423.10		0.04 (0.02-0.10)
Other organ system						
Anaphylaxis	0	0	0	0		NaN
Appendicitis	7	105.16	15	207.77		0.55 (0.23-1.35)
Multisystem inflammatory syndrome	0	0	0	0		NaN
Myositis	63	190.54	56	143.87		1.23 (0.85-1.78)



CI = confidence interval; HR = hazard ratio; IR = incidence rate; NaN = not a number (i.e., not estimable); py = person-years

Other subgroups (by age group, dose number, and RP)

Age group

For the primary series analysis within the general population, IRs and HRs of other **cardiac events** (excluding myocarditis/pericarditis) and **neurologic events** are presented by *age group* (pooled across all doses) in **Figure 9**. Results are presented for the **haematology system** in **Figure 10**. Results for the **respiratory and other organ systems** are presented in **Figure 11**.

In general, no or few cardiovascular, haematologic events, and neurologic events were observed among individuals aged 6 months to 4 years or aged 5 to 11 years.

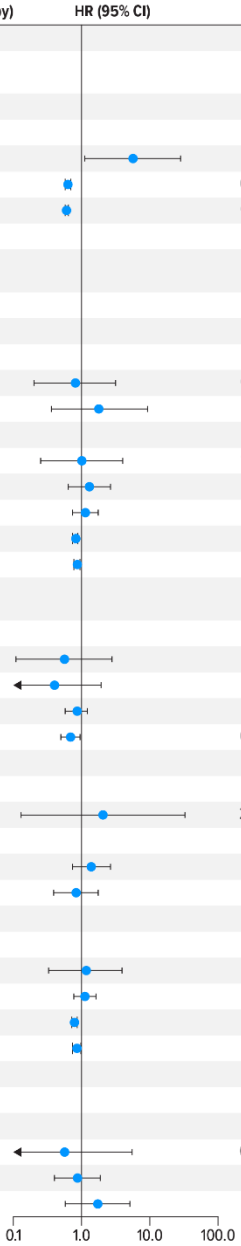
With some exceptions, HR estimates for most general safety events in all organ systems were generally consistent across all age groups. However, some variability was observed across age groups in the HR estimates for acute myocardial infarction, Bell's palsy, Guillain-Barré syndrome, narcolepsy, transverse myelitis, acute respiratory syndrome, and anaphylaxis.

As shown in **Figure 9**

- HR of acute myocardial infarction among individuals aged 12 to 17 years was 5.58 (95% CI, 1.12-27.79), with 6 cases in the exposed cohort. In contrast, HR estimates were < 1.0 for individuals aged 18 to 64 years (HR = 0.63; 95% CI, 0.58-0.68) and those aged ≥ 65 years (HR = 0.60; 95% CI, 0.57-0.63). HRs were inestimable for individuals aged 6 months to 4 years and 5 to 11 years due to zero counts.
- HR of Bell's palsy among individuals aged 6 months to 4 years was 1.00 (95% CI, 0.25-4.00) and HR estimates were < 1.0 among those aged 18 to 64 years (HR = 0.81; 95% CI, 0.74-0.88) and aged ≥ 65 years (HR = 0.85; 95% CI, 0.77-0.94). In contrast, HRs were > 1.0 for individuals aged 5 to 11 years (HR = 1.29; 95% CI, 0.63-2.64) and 12 to 17 years (HR = 1.12; 95% CI, 0.73-1.74).
- HR estimates of Guillain-Barré syndrome among individuals were > 1.0 for individuals aged 5 to 11 years (HR = 2.00; 95% CI, 0.13-31.98, with only 1 case and aged 18 to 64 years (HR = 1.38; 95% CI, 0.73- 2.59), but was < 1.0 for those aged ≥ 65 years (HR = 0.81; 95% CI, 0.39-1.71). HRs were inestimable for those aged 6 months to 4 years (with no exposed cases) and aged 12 to 17 years (with 2 exposed cases) due to the lack of unexposed cases in these age groups.
- HR estimates of narcolepsy were > 1.0 for individuals aged 5 to 11 years (HR = 1.14; 95% CI, 0.33-3.90) and aged 12 to 17 years (HR = 1.11; 95% CI, 0.77-1.60) but were < 1.0 for those aged 18 to 64 years (HR = 0.77; 95% CI, 0.71-0.84) and ≥ 65 years (HR = 0.84; 95% CI, 0.73-0.96). No exposed cases were observed among those aged 6 months to 4 years, and the HR was inestimable in this age group.
- HR estimate of transverse myelitis was > 1.0 for individuals aged ≥ 65 years (HR = 1.71; 95% CI, 0.58-5.10), but HR estimates were < 1.0 for individuals aged 12 to 17 years (HR = 0.55; 95% CI, 0.06-5.39, with only 4 cases) and aged 18 to 64 years (HR = 0.86; 95% CI, 0.40-1.84). No cases were observed among those aged 6 months to 4 years or aged 5 to 11 years, and HRs were inestimable in these age groups.

Figure 9. Incidence rates and HRs of other general safety events by age group, primary series analysis of cardiac and neurologic events

	Exposed		Unexposed		
	Cases	IR (per 100,000 py)	Cases	IR (per 100,000 py)	HR (95% CI)
Cardiac					
Acute myocardial infarction					
6 months-4 years old	0	0	0	0	NaN
5-11 years old	0	0	1	0.88	NaN
12-17 years old	6	7.41	2	1.41	5.58 (1.12-27.79)
18-64 years old	855	166.32	2,772	290.06	0.63 (0.58-0.68)
≥ 65 years old	2,378	1,150.45	7,930	2,047.52	0.60 (0.57-0.63)
Neurologic					
Acute disseminated encephalomyelitis					
6 months-4 years old	0	0	0	0	NaN
5-11 years old	0	0	0	0	NaN
12-17 years old	0	0	2	1.10	NaN
18-64 years old	3	0.45	8	0.65	0.79 (0.20-3.09)
≥ 65 years old	3	1.07	5	0.96	1.79 (0.36-8.97)
Bells palsy					
6 months-4 years old	3	18.64	7	22.43	1.00 (0.25-4.00)
5-11 years old	13	16.45	24	16.51	1.29 (0.63-2.64)
12-17 years old	33	31.46	70	38.34	1.12 (0.73-1.74)
18-64 years old	655	97.98	1,867	152.24	0.81 (0.74-0.88)
≥ 65 years old	607	217.33	1,525	294.66	0.85 (0.77-0.94)
Encephalomyelitis/ encephalitis					
6 months-4 years old	2	12.42	0	0	NaN
5-11 years old	2	2.53	8	5.51	0.55 (0.11-2.76)
12-17 years old	2	1.91	8	4.38	0.39 (0.08-1.88)
18-64 years old	41	6.13	111	9.05	0.83 (0.57-1.20)
≥ 65 years old	54	19.32	173	33.39	0.68 (0.50-0.93)
Guillain-Barré syndrome					
6 months-4 years old	0	0	0	0	NaN
5-11 years old	1	1.27	1	0.69	2.00 (0.13-31.98)
12-17 years old	2	1.91	0	0	NaN
18-64 years old	17	2.54	27	2.20	1.38 (0.73-2.59)
≥ 65 years old	10	3.58	26	5.02	0.81 (0.39-1.71)
Narcolepsy					
6 months-4 years old	0	0	2	3.28	NaN
5-11 years old	4	1.73	13	3.29	1.14 (0.33-3.90)
12-17 years old	51	16.77	116	23.84	1.11 (0.77-1.60)
18-64 years old	824	42.67	2,753	86.08	0.77 (0.71-0.84)
≥ 65 years old	324	36.43	937	62.03	0.84 (0.73-0.96)
Transverse myelitis					
6 months-4 years old	0	0	0	0	NaN
5-11 years old	0	0	0	0	NaN
12-17 years old	1	0.95	3	1.64	0.55 (0.06-5.39)
18-64 years old	10	1.50	25	2.04	0.86 (0.40-1.84)
≥ 65 years old	6	2.15	8	1.54	1.71 (0.58-5.10)



CI = confidence interval; HR = hazard ratio; IR = incidence rate; NaN = not a number (i.e., not estimable); py = person-years

Figure 10. Incidence rates and HRs of other general safety events by age group, primary series analysis of haematologic events

	Exposed		Unexposed			
	Cases	IR (per 100,000 py)	Cases	IR (per 100,000 py)	HR (95% CI)	HR (95% CI)
Hematologic						
Deep vein thrombosis						
6 months-4 years old	2	16.70	0	0		NaN
5-11 years old	2	3.29	3	2.65		1.15 (0.19-7.03)
12-17 years old	8	9.87	22	15.45		0.77 (0.34-1.77)
18-64 years old	1,368	266.30	3,893	407.67		0.71 (0.66-0.75)
≥ 65 years old	2,194	1,059.34	6,379	1,642.69		0.68 (0.65-0.71)
Disseminated intravascular coagulation						
6 months-4 years old	0	0	0	0		NaN
5-11 years old	2	3.29	7	6.18		0.60 (0.12-3.02)
12-17 years old	0	0	0	0		NaN
18-64 years old	36	6.99	171	17.85		0.42 (0.29-0.60)
≥ 65 years old	63	30.08	313	79.61		0.41 (0.31-0.54)
Immune hemolytic anemia						
6 months-4 years old	0	0	3	9.61		NaN
5-11 years old	1	1.27	2	1.38		0.78 (0.07-8.88)
12-17 years old	1	0.95	3	1.64		0.67 (0.07-6.41)
18-64 years old	40	5.98	103	8.39		0.93 (0.64-1.37)
≥ 65 years old	52	18.61	176	33.98		0.65 (0.47-0.89)
Immune thrombocytopenia						
6 months-4 years old	0	0	14	44.87		NaN
5-11 years old	6	7.60	21	14.45		0.74 (0.28-1.93)
12-17 years old	15	14.30	36	19.72		0.85 (0.46-1.58)
18-64 years old	230	34.41	673	54.88		0.73 (0.62-0.85)
≥ 65 years old	271	97.07	692	133.74		0.82 (0.71-0.95)
Pulmonary embolism						
6 months-4 years old	0	0	0	0		NaN
5-11 years old	0	0	0	0		NaN
12-17 years old	5	6.17	13	9.13		0.67 (0.23-1.92)
18-64 years old	986	191.82	2,946	308.26		0.67 (0.63-0.73)
≥ 65 years old	1,449	697.99	4,817	1,237.06		0.60 (0.56-0.63)
Thromboembolic events associated with thrombocytopenia						
6 months-4 years old	0	0	1	4.27		NaN
5-11 years old	0	0	0	0		NaN
12-17 years old	3	3.70	4	2.81		2.00 (0.40-9.91)
18-64 years old	274	53.20	879	91.78		0.62 (0.54-0.71)
≥ 65 years old	810	387.72	2,554	651.39		0.65 (0.60-0.70)
Thrombotic thrombocytopenic purpura						
6 months-4 years old	0	0	0	0		NaN
5-11 years old	0	0 (N/A)	0	0		NaN
12-17 years old	0	0 (N/A)	2	1.40		NaN
18-64 years old	1	0.19	15	1.57		0.13 (0.02-1.03)
≥ 65 years old	6	2.86	17	4.32		0.67 (0.26-1.73)
Venous thromboembolism						
6 months-4 years old	2	16.69	0	0		NaN
5-11 years old	2	3.29	3	2.65		1.15 (0.19-7.03)
12-17 years old	11	13.57	35	24.59		0.61 (0.30-1.21)
18-64 years old	2,012	392.33	5,820	610.61		0.70 (0.66-0.73)
≥ 65 years old	3,087	1,500.64	9,359	2,427.67		0.65 (0.62-0.68)
Hemorrhagic stroke						
6 months-4 years old	1	8.36	3	12.82		0.67 (0.07-6.41)
5-11 years old	1	1.64	9	7.94		0.20 (0.03-1.62)
12-17 years old	8	9.87	31	21.78		0.57 (0.25-1.27)
18-64 years old	216	41.94	642	67.04		0.69 (0.59-0.81)
≥ 65 years old	602	288.32	1,962	500.69		0.62 (0.56-0.68)
Ischemic stroke						
6 months-4 years old	0	0	4	17.07		NaN
5-11 years old	1	1.64	4	3.53		0.43 (0.05-3.87)
12-17 years old	3	3.70	9	6.32		0.49 (0.13-1.82)
18-64 years old	626	121.93	1,823	191.01		0.70 (0.63-0.76)
≥ 65 years old	1,906	932.18	6,079	1,587.65		0.63 (0.59-0.66)

CI = confidence interval; HR = hazard ratio; IR = incidence rate; NaN = not a number (i.e., not estimable); py = person-years

As shown in **Figure 11**

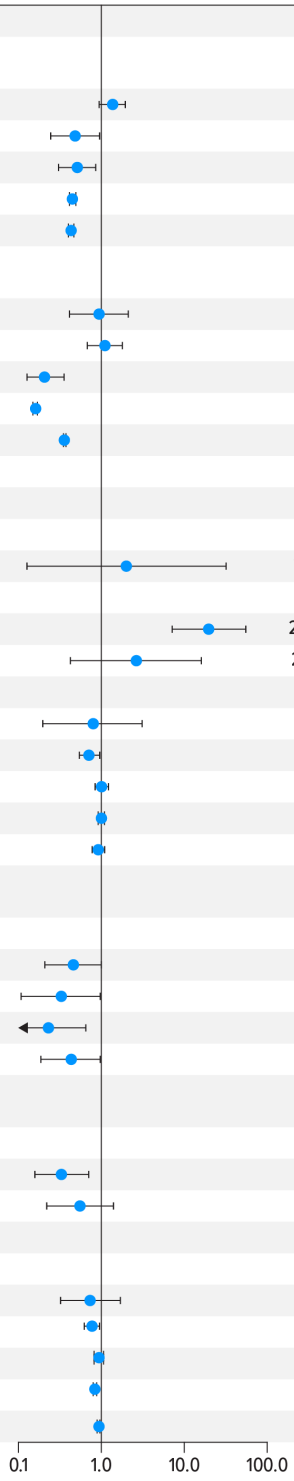
- HR for acute respiratory distress syndrome among individuals aged 6 months to 4 years was 1.37 (95% CI, 0.96-1.97), but HR estimates were < 1.0 among individuals aged 5 to 11 years (HR = 0.48;

95% CI, 0.25-0.94), 12 to 17 years (HR = 0.52; 95% CI, 0.31-0.85), 18 to 64 years (HR = 0.45; 95% CI, 0.42-0.49), and ≥ 65 years (HR = 0.43; 95% CI, 0.41-0.46).

- HR for anaphylaxis among individuals aged 18 to 64 years was 20.02 (95% CI, 7.17-55.93). HR estimates were lower among individuals aged 5 to 11 years (HR = 2.00; 95% CI, 0.13-31.98, with 1 exposed case) and individuals aged ≥ 65 years (HR = 2.64; 95% CI, 0.43-16.02, with 3 exposed cases). HRs were inestimable for those aged 6 months to 4 years (with no exposed cases) and those aged 12 to 17 years (with 3 exposed cases) because of the lack of unexposed cases in these age groups

Figure 11. Incidence rates and HRs of other general safety events by age group, primary series analysis of respiratory and other organ systems

	Exposed		Unexposed		
	Cases	IR (per 100,000 py)	Cases	IR (per 100,000 py)	HR (95% CI)
Respiratory					
Acute respiratory distress syndrome					
6 months-4 years old	50	419.22	78	334.44	1.37 (0.96-1.97)
5-11 years old	11	18.08	44	38.83	0.48 (0.25-0.94)
12-17 years old	20	24.69	75	52.69	0.52 (0.31-0.85)
18-64 years old	848	164.80	3,845	401.88	0.45 (0.42-0.49)
≥ 65 years old	1,765	846.93	8,153	2,085.66	0.43 (0.41-0.46)
Vaccine-associated enhanced respiratory disease					
6 months-4 years old	9	25.61	35	54.50	0.95 (0.42-2.11)
5-11 years old	29	7.94	84	13.96	1.10 (0.69-1.78)
12-17 years old	17	3.74	261	37.54	0.21 (0.13-0.35)
18-64 years old	2,719	99.74	55,891	1,303.22	0.16 (0.15-0.17)
≥ 65 years old	7,992	645.27	72,132	3,590.47	0.36 (0.35-0.37)
Other organ systems					
Anaphylaxis					
6 months-4 years old	0	0	1	108.62	NaN
5-11 years old	1	41.35	1	21.61	2.00 (0.13-31.98)
12-17 years old	3	92.18	0	0	NaN
18-64 years old	41	198.81	4	10.15	20.02 (7.17-55.93)
≥ 65 years old	3	36.55	2	12.67	2.64 (0.43-16.02)
Appendicitis					
6 months-4 years old	3	18.63	7	22.42	0.79 (0.20-3.09)
5-11 years old	72	91.22	230	158.35	0.72 (0.55-0.95)
12-17 years old	192	183.29	416	228.15	1.02 (0.85-1.22)
18-64 years old	950	142.17	2,155	175.85	1.01 (0.93-1.09)
≥ 65 years old	245	87.70	581	112.22	0.92 (0.79-1.08)
Multisystem inflammatory syndrome					
6 months-4 years old	0	0	6	19.22	NaN
5-11 years old	8	10.13	37	25.45	0.46 (0.21-1.00)
12-17 years old	4	3.81	20	10.95	0.33 (0.11-0.98)
18-64 years old	4	0.60	37	3.02	0.23 (0.08-0.65)
≥ 65 years old	7	2.50	38	7.34	0.43 (0.19-0.97)
Multisystem inflammatory syndrome in children					
6 months-4 years old	0	0	4	12.81	NaN
5-11 years old	8	9.65	50	33.02	0.33 (0.16-0.71)
12-17 years old	6	5.62	21	11.35	0.56 (0.22-1.40)
18-20 years old	0	0	1	1.44	NaN
Myositis					
6 months-4 years old	8	22.76	41	63.82	0.74 (0.33-1.68)
5-11 years old	132	36.19	549	91.38	0.78 (0.63-0.96)
12-17 years old	389	85.76	1,261	181.66	0.93 (0.82-1.05)
18-64 years old	4,579	167.95	16,346	380.82	0.84 (0.81-0.87)
≥ 65 years old	2,492	200.07	7,749	382.81	0.93 (0.89-0.98)



CI = confidence interval; HR = hazard ratio; IR = incidence rate; NaN = not a number (i.e., not estimable); py = person-years

Dose number

For the primary series analysis within the general population, IRs and HRs of other **cardiac events** (excluding myocarditis/pericarditis) and **neurologic events** are presented by *dose* number in **Figure 12**. Results are presented for the **haematology system** in **Figure 13** and for the **respiratory and other organ systems** in **Figure 14**.

Across all organ systems, HRs of several general safety events for third doses within the primary series were inestimable due to zero counts, and low case counts were observed for many of the events.

With some exceptions, HR estimates were consistent across doses 1 and 2. As shown in **Figure 12** and in **Figure 14**, differences were observed across dose 1 and dose 2 for the following general safety events:

- Acute disseminated encephalomyelitis: HR for dose 1 was 1.37 (95% CI, 0.36-5.17, with 4 exposed cases and 8 unexposed cases) and for dose 2 was 0.57 (95% CI, 0.12-2.75, with 2 exposed cases and 7 unexposed cases)
- Convulsions: HR for dose 1 was 0.76 (95% CI, 0.50-1.15, with 31 exposed cases and 107 unexposed cases) and for dose 2 was 1.05 (95% CI, 0.77-1.44, with 61 exposed cases and 117 unexposed cases)
- Guillain-Barré syndrome: HR for dose 1 was 1.51 (95% CI, 0.82-2.76, with 19 exposed cases and 30 unexposed cases) and for dose 2 was 0.88 (95% CI, 0.43-1.80, with 11 exposed cases and 24 unexposed cases)
- Transverse myelitis: HR for dose 1 was 1.13 (95% CI, 0.49-2.59, with 9 exposed cases and 20 unexposed cases) and for dose 2 was 0.91 (95% CI, 0.39-2.14, with 8 exposed cases and 16 unexposed cases
- Anaphylaxis: HR for dose 1 was 24.37 (95% CI, 7.52-79.02, with 38 exposed cases and 3 unexposed cases) and for dose 2 was 5.00 (95% CI, 1.57-15.94, with 10 exposed cases and 4 unexposed cases)

Figure 12. Incidence rates and HRs of other general safety events by dose number, primary series analysis of cardiac and neurologic events

	Exposed		Unexposed			
	Cases	IR (per 100,000 py)	Cases	IR (per 100,000 py)	HR (95% CI)	HR (95% CI)
Cardiac						
Acute myocardial infarction						
Dose 1	1,750	394.15	6,056	732.95		0.62 (0.59-0.66)
Dose 2	1,479	345.31	4,637	586.04		0.59 (0.56-0.63)
Dose 3	10	425.43	12	260.34		1.70 (0.72-4.03)
Neurologic						
Acute disseminated encephalomyelitis						
Dose 1	4	0.79	8	0.85		1.37 (0.36-5.17)
Dose 2	2	0.31	7	0.60		0.57 (0.12-2.75)
Dose 3	0	0	0	0		NaN
Bells palsy						
Dose 1	628	123.92	1,973	210.35		0.85 (0.77-0.93)
Dose 2	682	106.97	1,517	130.95		0.83 (0.75-0.91)
Dose 3	1	29.20	3	45.21		0.67 (0.07-6.41)
Convulsions						
Dose 1	31	485.28	107	862.88		0.76 (0.50-1.15)
Dose 2	61	799.74	117	792.90		1.05 (0.77-1.44)
Dose 3	14	744.06	38	1,034.19		0.73 (0.40-1.36)
Encephalomyelitis/ encephalitis						
Dose 1	55	10.85	171	18.22		0.79 (0.57-1.08)
Dose 2	45	7.05	128	11.04		0.67 (0.47-0.94)
Dose 3	1	29.18	1	15.05		2.00 (0.13-31.98)
Guillain-Barré syndrome						
Dose 1	19	3.75	30	3.20		1.51 (0.82-2.76)
Dose 2	11	1.72	24	2.07		0.88 (0.43-1.80)
Dose 3	0	0	0	0		NaN
Narcolepsy						
Dose 1	363	37.60	2,117	126.92		0.71 (0.63-0.81)
Dose 2	835	34.63	1,702	42.96		0.84 (0.77-0.92)
Dose 3	5	41.09	2	9.28		4.59 (0.88-23.84)
Transverse myelitis						
Dose 1	9	1.78	20	2.13		1.13 (0.49-2.59)
Dose 2	8	1.25	16	1.38		0.91 (0.39-2.14)
Dose 3	0	0	0	0		NaN

CI = confidence interval; HR = hazard ratio; IR = incidence rate; NaN = not a number (i.e., not estimable); py = person-years

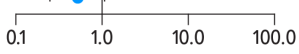
Figure 13. Incidence rates and HRs of other general safety events by dose number, primary series analysis of haematologic events

	Exposed		Unexposed			
	Cases	IR (per 100,000 py)	Cases	IR (per 100,000 py)	HR (95% CI)	HR (95% CI)
Hematologic						
Deep vein thrombosis						
Dose 1	1,899	427.75	5,881	711.68		0.68 (0.65-0.72)
Dose 2	1,670	389.89	4,409	557.14		0.70 (0.66-0.74)
Dose 3	5	212.93	7	152.02		1.27 (0.40-4.04)
Disseminated intravascular coagulation						
Dose 1	55	12.34	276	33.23		0.43 (0.32-0.57)
Dose 2	46	10.69	213	26.78		0.41 (0.30-0.56)
Dose 3	0	0	2	43.25		NaN
Immune hemolytic anemia						
Dose 1	41	8.09	153	16.30		0.75 (0.52-1.07)
Dose 2	53	8.31	134	11.56		0.74 (0.54-1.01)
Dose 3	0	0	0	0		NaN
Immune thrombocytopenia						
Dose 1	240	47.37	789	84.12		0.76 (0.65-0.89)
Dose 2	281	44.08	640	55.25		0.78 (0.68-0.90)
Dose 3	1	29.22	7	105.52		0.29 (0.04-2.32)
Pulmonary embolism						
Dose 1	1,364	306.96	4,446	537.44		0.65 (0.61-0.69)
Dose 2	1,071	249.77	3,325	419.62		0.60 (0.56-0.64)
Dose 3	5	212.54	5	108.39		2.00 (0.58-6.91)
Thromboembolic events associated with thrombocytopenia						
Dose 1	570	127.95	1,991	239.99		0.62 (0.56-0.68)
Dose 2	516	120.03	1,447	182.10		0.66 (0.60-0.73)
Dose 3	1	42.48	0	0		NaN
Thrombotic thrombocytopenic purpura						
Dose 1	4	0.90	20	2.41		0.43 (0.14-1.27)
Dose 2	3	0.70	14	1.76		0.37 (0.11-1.30)
Dose 3	0	0	0	0		NaN
Venous thromboembolism						
Dose 1	2,766	624.59	8,674	1,052.62		0.67 (0.65-0.70)
Dose 2	2,338	547.24	6,528	827.18		0.66 (0.63-0.69)
Dose 3	10	426.71	15	326.46		1.33 (0.60-2.97)
Hemorrhagic stroke						
Dose 1	456	102.38	1,493	179.98		0.67 (0.60-0.74)
Dose 2	370	86.08	1,148	144.50		0.60 (0.53-0.67)
Dose 3	2	84.89	6	129.94		0.67 (0.13-3.30)
Ischemic stroke						
Dose 1	1,317	297.63	4,482	544.37		0.63 (0.59-0.67)
Dose 2	1,214	284.38	3,428	434.75		0.65 (0.61-0.69)
Dose 3	5	212.90	9	195.54		1.25 (0.41-3.82)

CI = confidence interval; HR = hazard ratio; IR = incidence rate; NaN = not a number (i.e., not estimable); py = person-years

Figure 14. Incidence rates and HRs of other general safety events by dose number, primary series analysis of respiratory and other organ system

	Exposed		Unexposed			
	Cases	IR (per 100,000 py)	Cases	IR (per 100,000 py)	HR (95% CI)	HR (95% CI)
Respiratory						
Acute respiratory distress syndrome						
Dose 1	1,610	361.80	6,999	844.77		0.49 (0.47-0.52)
Dose 2	1,075	250.35	5,173	651.89		0.39 (0.36-0.41)
Dose 3	9	383.11	23	499.40		0.81 (0.37-1.78)
Vaccine-associated enhanced respiratory disease						
Dose 1	4,304	327.69	70,571	3,258.41		0.37 (0.36-0.38)
Dose 2	6,433	184.28	57,667	1,054.71		0.23 (0.22-0.24)
Dose 3	29	196.51	165	650.78		0.43 (0.28-0.65)
Other organ systems						
Anaphylaxis						
Dose 1	38	197.26	3	8.16		24.37 (7.52-79.02)
Dose 2	10	64.05	4	13.50		5.00 (1.57-15.94)
Dose 3	0	0	1	575.41		NaN
Appendicitis						
Dose 1	646	127.52	1,826	194.76		0.99 (0.90-1.09)
Dose 2	814	127.72	1,560	134.74		0.96 (0.88-1.05)
Dose 3	2	58.39	3	45.19		1.33 (0.22-7.98)
Kawasaki disease						
Dose 1	0	0	10	80.47		NaN
Dose 2	3	39.26	5	33.84		1.10 (0.26-4.63)
Dose 3	1	53.05	1	27.16		2.00 (0.13-31.98)
Multisystem inflammatory syndrome						
Dose 1	13	2.56	74	7.89		0.44 (0.24-0.82)
Dose 2	10	1.57	63	5.44		0.28 (0.14-0.55)
Dose 3	0	0	1	15.06		NaN
Multisystem inflammatory syndrome in children						
Dose 1	4	4.00	39	21.61		0.28 (0.10-0.81)
Dose 2	10	7.12	37	14.67		0.46 (0.23-0.94)
Dose 3	0	0	0	0		NaN
Myositis						
Dose 1	2,217	168.70	14,059	647.86		0.86 (0.82-0.91)
Dose 2	5,373	153.67	11,841	216.07		0.88 (0.85-0.91)
Dose 3	10	67.32	46	180.33		0.52 (0.25-1.06)



CI = confidence interval; HR = hazard ratio; IR = incidence rate; NaN = not a number (i.e., not estimable); py = person-years

Other general safety events, booster dose analysis

General population

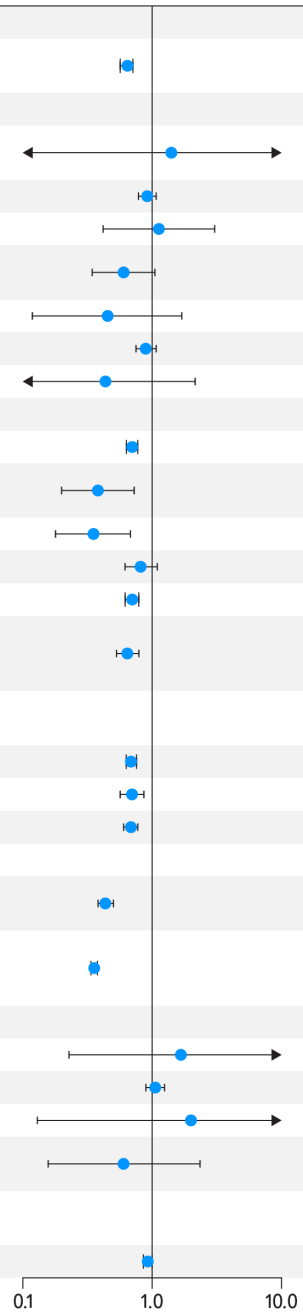
Figure 15 presents the IRs and HRs for the **booster dose analysis** of all other general safety events (excluding myocarditis/pericarditis) within the general population.

No cases or fewer than 4 cases of acute disseminated encephalomyelitis, Guillain-Barré syndrome, transverse myelitis, thrombotic thrombocytopenic purpura, anaphylaxis, Kawasaki disease, multisystem inflammatory syndrome, and multisystem inflammatory syndrome in children were observed in the exposed cohorts. Hazard ratios for thrombotic thrombocytopenic purpura and multisystem inflammatory syndrome in children were inestimable due to zero events in the exposed and/or comparator groups.

Hazard ratio estimates were > 1.0 for acute disseminated encephalomyelitis (HR = 1.41; 95% CI, 0.08-23.57), convulsions (HR = 1.14; 95% CI, 0.42-3.05), anaphylaxis (HR = 1.69; 95% CI, 0.23-12.23), appendicitis (HR = 1.06; 95% CI, 0.90-1.24), and Kawasaki disease (HR = 2.00; 95% CI, 0.13-31.98). Hazard ratios for all other general safety events were < 1.0.

Figure 15. Incidence rates and HRs of other general safety events, booster dose analysis within the general population

	Exposed		Comparator		
	Cases	IR (per 100,000 py)	Cases	IR (per 100,000 py)	HR (95% CI)
Cardiac					
Acute myocardial infarction	502	331.65	1,191	494.08	0.64 (0.57-0.71)
Neurologic					
Acute disseminated encephalomyelitis	1	0.46	1	0.29	1.41 (0.08-23.57)
Bells palsy	277	126.46	462	135.52	0.92 (0.79-1.07)
Convulsions	8	755.49	8	622.47	1.14 (0.42-3.05)
Encephalomyelitis/ encephalitis	18	8.21	47	13.78	0.60 (0.35-1.04)
Guillain-Barré syndrome	3	1.37	9	2.64	0.46 (0.12-1.71)
Narcolepsy	220	32.17	357	37.27	0.90 (0.76-1.08)
Transverse myelitis	2	0.91	7	2.05	0.44 (0.09-2.15)
Hematalogic					
Deep vein thrombosis	548	362.06	1,205	499.84	0.70 (0.64-0.78)
Disseminated intravascular coagulation	12	7.89	48	19.80	0.38 (0.20-0.72)
Immune hemolytic anemia	11	5.02	47	13.78	0.35 (0.18-0.68)
Immune thrombocytopenia	75	34.25	138	40.49	0.82 (0.62-1.09)
Pulmonary embolism	390	257.33	848	351.26	0.71 (0.63-0.80)
Thromboembolic events associated with thrombocytopenia	156	102.61	372	153.57	0.65 (0.54-0.79)
Thrombotic thrombocytopenic purpura	0	0	0	0	NaN
Venous thromboembolism	776	514.23	1,730	719.96	0.69 (0.64-0.76)
Hemorrhagic stroke	133	87.50	293	120.98	0.70 (0.57-0.86)
Ischemic stroke	399	264.58	871	362.78	0.69 (0.61-0.78)
Respiratory					
Acute respiratory distress syndrome	318	209.40	1,095	452.61	0.44 (0.39-0.50)
Vaccine-associated enhanced respiratory disease	1,238	120.21	5,115	368.21	0.36 (0.34-0.38)
Other organ system					
Anaphylaxis	2	34.90	2	21.24	1.69 (0.23-12.23)
Appendicitis	261	119.23	400	117.41	1.06 (0.90-1.24)
Kawasaki disease	1	94.23	1	77.68	2.00 (0.13-31.98)
Multisystem inflammatory syndrome	3	1.37	8	2.35	0.61 (0.16-2.33)
Multisystem inflammatory syndrome in children	0	0	4	5.78	NaN
Myositis	1,485	144.15	2,564	184.52	0.93 (0.87-1.00)



CI = confidence interval; HR = hazard ratio; IR = incidence rate; NaN = not a number (i.e., not estimable); py = person-years

Subgroups

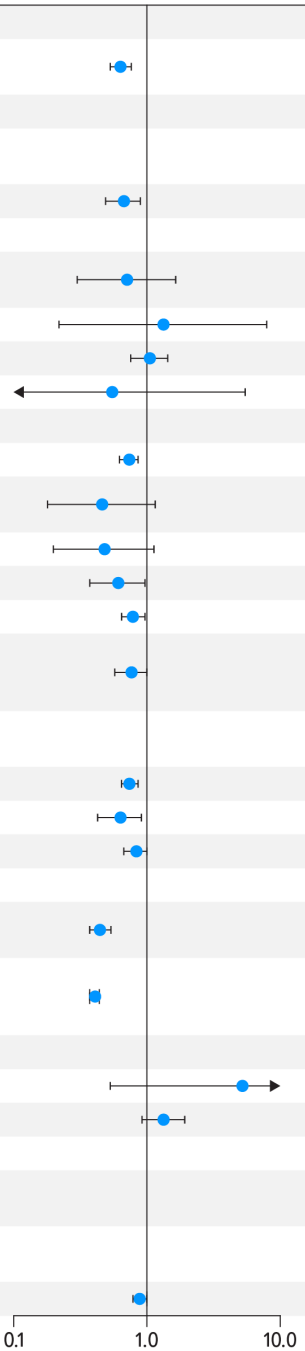
Figure 16 presents the IRs and HRs for the booster dose analysis of other general safety events among *immunocompromised individuals*. Between 0 and 4 cases of acute disseminated encephalomyelitis, convulsions, Guillain-Barré syndrome, transverse myelitis, thrombotic thrombocytopenic purpura, anaphylaxis, Kawasaki disease, multisystem inflammatory syndrome, and multisystem inflammatory syndrome in children were observed in the exposed cohorts. Hazard ratios for acute disseminated encephalomyelitis, convulsions, thrombotic thrombocytopenic purpura, Kawasaki disease, multisystem

inflammatory syndrome, and multisystem inflammatory syndrome in children were inestimable due to zero events in the exposed and/or comparator groups.

Hazard ratio estimates were > 1.0 for anaphylaxis (HR = 5.16; 95% CI, 0.53-50.41), Guillain-Barré syndrome (HR = 1.33; 95% CI, 0.22-7.98), narcolepsy (HR = 1.04; 95% CI, 0.76- 1.41), and appendicitis (HR = 1.33; 95% CI, 0.93-1.91). Hazard ratio estimates for all other general safety events were ~ 1.0 or < 1.0.

Figure 16. Incidence rates and HRs of other general safety events, booster dose analysis among immunocompromised individuals

	Exposed		Comparator			
	Cases	IR (per 100,000 py)	Cases	IR (per 100,000 py)	HR (95% CI)	HR (95% CI)
Cardiac						
Acute myocardial infarction	169	666.37	393	1,003.60		0.63 (0.53-0.76)
Neurologic						
Acute disseminated encephalomyelitis	0	0	0	0		NaN
Bells palsy	67	180.52	155	275.92		0.66 (0.49-0.88)
Convulsions	0	0	0	0		NaN
Encephalomyelitis/ encephalitis	8	21.50	18	31.96		0.70 (0.30-1.64)
Guillain-Barré syndrome	2	5.38	3	5.33		1.33 (0.22-7.98)
Narcolepsy	75	64.75	105	66.50		1.04 (0.76-1.41)
Transverse myelitis	1	2.69	3	5.33		0.55 (0.06-5.39)
Hematalogic						
Deep vein thrombosis	223	880.49	463	1,183.84		0.73 (0.62-0.86)
Disseminated intravascular coagulation	6	23.32	20	50.32		0.46 (0.18-1.15)
Immune hemolytic anemia	7	18.82	22	39.07		0.48 (0.20-1.12)
Immune thrombocytopenia	24	64.65	59	105.02		0.60 (0.37-0.96)
Pulmonary embolism	166	653.65	322	821.11		0.78 (0.65-0.95)
Thromboembolic events associated with thrombocytopenia	88	343.31	177	447.08		0.76 (0.58-0.98)
Thrombotic thrombocytopenic purpura	0	0	2	5.03		NaN
Venous thromboembolism	320	1,275.66	650	1,678.72		0.74 (0.65-0.85)
Hemorrhagic stroke	41	159.79	101	254.91		0.63 (0.43-0.90)
Ischemic stroke	150	595.13	270	694.03		0.82 (0.67-1.00)
Respiratory						
Acute respiratory distress syndrome	154	603.62	502	1,274.51		0.44 (0.37-0.53)
Vaccine-associated enhanced respiratory disease	602	354.16	2,116	946.49		0.41 (0.37-0.44)
Other organ system						
Anaphylaxis	3	311.34	1	65.57		5.16 (0.53-50.41)
Appendicitis	56	150.74	68	120.95		1.33 (0.93-1.91)
Kawasaki disease	0	0	0	0		NaN
Multisystem inflammatory syndrome	0	0	4	7.10		NaN
Multisystem inflammatory syndrome in children	0	0	2	44.91		NaN
Myositis	440	256.66	770	341.52		0.88 (0.78-0.99)



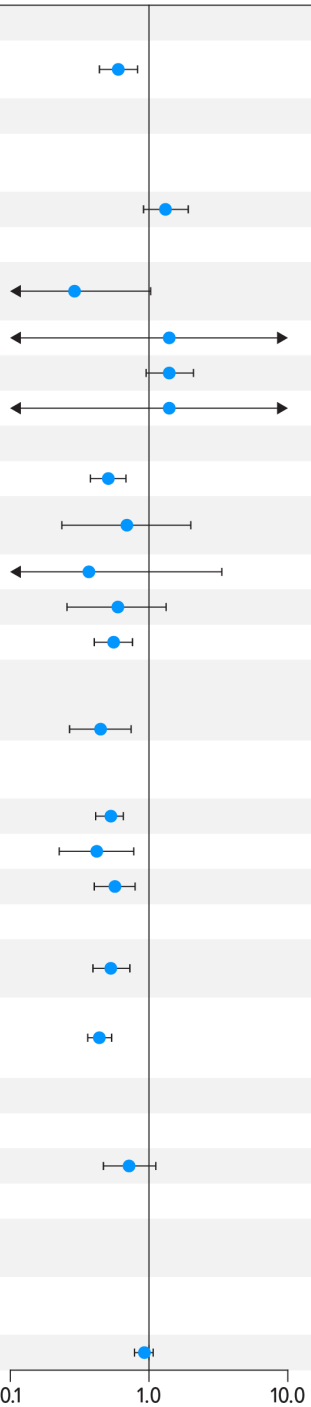
CI = confidence interval; HR = hazard ratio; IR = incidence rate; NaN = not a number (i.e., not estimable); py = person-years

Figure 17 presents the IRs and HRs for the booster dose analysis of other general safety events among *individuals with a history of COVID-19*. Between 0 and 4 cases of acute disseminated encephalomyelitis, convulsions, encephalomyelitis/encephalitis, Guillain-Barré syndrome, transverse myelitis, immune hemolytic anemia, thrombotic thrombocytopenic purpura, anaphylaxis, Kawasaki disease, multisystem inflammatory syndrome, and multisystem inflammatory syndrome in children were observed in the exposed cohort.

Hazard ratio estimates were > 1.0 for Bell's palsy (HR = 1.33; 95% CI, 0.92-1.93), Guillain-Barré syndrome (HR = 1.41; 95% CI, 0.08-23.57), narcolepsy (HR = 1.42; 95% CI, 0.97-2.08), and transverse myelitis (HR = 1.41; 95% CI, 0.08-23.57). Hazard ratios were inestimable for the remaining safety events due to zero events in the exposed and/or comparator groups.

Figure 17. Incidence rates and HRs of other general safety events, booster dose analysis among individuals with a history of COVID-19

	Exposed		Comparator		
	Cases	IR (per 100,000 py)	Cases	IR (per 100,000 py)	HR (95% CI)
Cardiac					
Acute myocardial infarction	62	335.49	149	501.38	0.61 (0.45-0.83)
Neurologic					
Acute disseminated encephalomyelitis	1	3.66	0	0	NaN
Bells palsy	52	190.67	64	148.56	1.33 (0.92-1.93)
Convulsions	1	762.20	0	0	NaN
Encephalomyelitis/ encephalitis	3	10.99	13	30.15	0.29 (0.08-1.02)
Guillain-Barré syndrome	1	3.66	1	2.32	1.41 (0.08-23.57)
Narcolepsy	54	57.37	58	42.47	1.42 (0.97-2.08)
Transverse myelitis	1	3.66	1	2.32	1.41 (0.08-23.57)
Hematalogic					
Deep vein thrombosis	65	351.69	196	659.50	0.51 (0.38-0.68)
Disseminated intravascular coagulation	5	26.76	11	36.62	0.69 (0.24-2.00)
Immune hemolytic anemia	1	3.66	4	9.28	0.37 (0.04-3.35)
Immune thrombocytopenia	8	29.35	21	48.76	0.59 (0.26-1.34)
Pulmonary embolism	57	308.15	155	521.03	0.56 (0.41-0.76)
Thromboembolic events associated with thrombocytopenia	20	107.28	65	216.84	0.45 (0.27-0.75)
Thrombotic thrombocytopenic purpura	0	0	0	0	NaN
Venous thromboembolism	101	550.46	288	976.07	0.53 (0.42-0.66)
Hemorrhagic stroke	14	75.08	47	156.77	0.42 (0.23-0.78)
Ischemic stroke	50	271.80	127	429.36	0.57 (0.41-0.80)
Respiratory					
Acute respiratory distress syndrome	62	334.33	177	593.53	0.54 (0.40-0.73)
Vaccine-associated enhanced respiratory disease	147	100.89	491	240.38	0.44 (0.37-0.54)
Other organ system					
Anaphylaxis	1	144.21	0	0	NaN
Appendicitis	31	113.80	66	153.35	0.73 (0.47-1.12)
Kawasaki disease	0	0	0	0	NaN
Multisystem inflammatory syndrome	0	0	2	4.64	NaN
Multisystem inflammatory syndrome in children	0	0	1	11.43	NaN
Myositis	274	184.74	478	230.40	0.93 (0.79-1.08)



CI = confidence interval; HR = hazard ratio; IR = incidence rate; NaN = not a number (i.e., not estimable); py = person-years

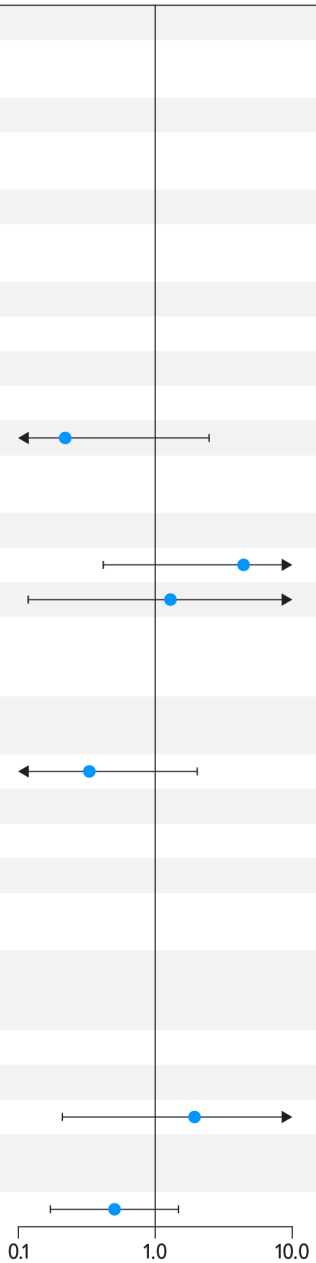
Figure 18 presents the IRs and HRs for the booster dose analysis of other general safety events among *pregnant women*. No cases were observed in the exposed and/or comparator cohorts for most general safety events leading to inestimable HRs.

Hazard ratio estimates were > 1.0 for immune thrombocytopenia (HR = 4.35; 95% CI, 0.42-44.71), pulmonary embolism (HR = 1.28; 95% CI, 0.12-13.84), and appendicitis (HR = 1.93; 95% CI, 0.21-

17.76). Hazard ratios were < 1.0 for all other general safety events (i.e., deep vein thrombosis, venous thromboembolism, and myositis).

Figure 18. Incidence rates and HRs of other general safety events, booster dose analysis among pregnant women

	Exposed		Unexposed			
	Cases	IR (per 100,000 py)	Cases	IR (per 100,000 py)	HR (95% CI)	HR (95% CI)
Cardiac						
Acute myocardial infarction	1	87.11	0	0		NaN
Neurologic						
Acute disseminated encephalomyelitis	0	0	0	0		NaN
Bells palsy	2	116.53	0	0		NaN
Encephalomyelitis/ encephalitis	0	0	0	0		NaN
Guillain-Barré syndrome	0	0	0	0		NaN
Narcolepsy	1	13.90	0	0		NaN
Transverse myelitis	0	0	0	0		NaN
Hematalogic						
Deep vein thrombosis	1	87.29	2	204.30		0.22 (0.02-2.48)
Disseminated intravascular coagulation	0	0	1	101.91		NaN
Immune hemolytic anemia	0	0	0	0		NaN
Immune thrombocytopenia	6	350.10	1	72.28		4.35 (0.42-44.71)
Pulmonary embolism	2	174.51	1	102.09		1.28 (0.12-13.84)
Thromboembolic events associated with thrombocytopenia	0	0	0	0		NaN
Thrombotic thrombocytopenic purpura	0	0	0	0		NaN
Venous thromboembolism	2	174.85	3	306.90		0.33 (0.06-1.98)
Hemorrhagic stroke	0		0	0		NaN
Ischemic stroke	2	174.27	0	0		NaN
Respiratory						
Acute respiratory distress syndrome	0	0	0	0		NaN
Vaccine-associated enhanced respiratory disease	2	15.09	0	0		NaN
Other organ system						
Anaphylaxis	0	0	0	0		NaN
Appendicitis	3	175.11	1	72.31		1.93 (0.21-17.76)
Multisystem inflammatory syndrome	0	0	0	0		NaN
Myositis	10	75.80	14	186.53		0.50 (0.17-1.47)



CI = confidence interval; HR = hazard ratio; IR = incidence rate; NaN = not a number (i.e., not estimable); py = person-years

Other subgroups (by age group and sex)

Age groups

For the booster dose analysis within the general population, IRs and HRs of **other cardiac events** (excluding myocarditis/pericarditis) and **neurologic events** are presented by age group in **Figure 19**.

Results are presented for the **haematology system** in **Figure 20**. Results for the **respiratory and other organ systems** are presented in **Figure 21**.

In general, across all organ systems, no or few exposed cases (< 5) were observed in the exposed cohorts for individuals aged 6 months to 4 years, 5 to 11 years, and 12 to 17 years for most general safety events.

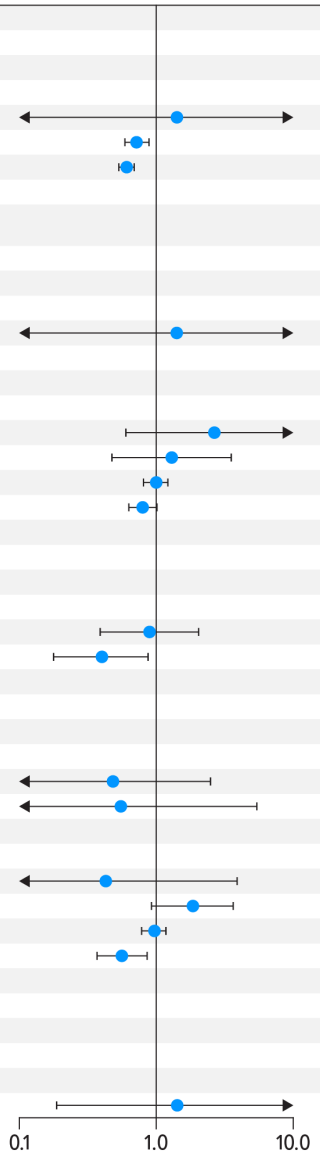
With some exceptions, HR estimates for most general safety events in all organ systems were generally consistent across all age groups. However, some variability across age groups was observed for Bell's palsy, narcolepsy, hemorrhagic stroke, acute respiratory distress syndrome, and vaccine-associated enhanced respiratory disease.

As shown in **Figure 19** [source CSR]:

- HR of Bell's palsy was > 1.0 for individuals aged 5 to 11 years (HR = 2.67; 95% CI, 0.60-11.91, with 4 exposed cases) and those aged 12 to 17 years (HR = 1.30; 95% CI, 0.48-3.54, with 7 exposed cases) but was ~1.0 or < 1.0 among individuals aged 18 to 64 years (HR = 0.99; 95% CI, 0.81-1.21) and those aged ≥ 65 years (HR = 0.80; 95% CI, 0.63-1.01). No cases were observed in the exposed or comparator cohorts among individuals aged 6 months to 4 years.
- HR of narcolepsy among individuals aged 12 to 17 years was 1.84 (95% CI, 0.93-3.66, with 19 exposed cases) but was ~1.0 or < 1.0 among individuals aged 5 to 11 years (HR = 0.43; 95% CI, 0.05-3.87, with 1 exposed case), 18 to 64 years (HR = 0.97; 95% CI, 0.79-1.18, with 167 cases exposed), and ≥ 65 years (HR = 0.56; 95% CI, 0.37-0.85, with 33 cases exposed). No cases were observed in the exposed or comparator cohorts among individuals aged 6 months to 4 years.

Figure 19. Incidence rates and HRs of other general safety events by age group, booster dose analysis of cardiac and neurologic events

	Exposed		Unexposed			
	Cases	IR (per 100,000 py)	Cases	IR (per 100,000 py)	HR (95% CI)	HR (95% CI)
Cardiac						
Acute myocardial infarction						
6 months-4 years old	0	0	0	0		NaN
5-11 years old	0	0	0	0		NaN
12-17 years old	1	6.44	1	4.16		1.41 (0.08-23.57)
18-64 years old	131	144.39	290	198.38		0.72 (0.59-0.89)
≥ 65 years old	370	1,001.17	900	1,619.37		0.61 (0.54-0.69)
Neurologic						
Acute disseminated encephalomyelitis						
6 months-4 years old	0	0	0	0		NaN
5-11 years old	0	0	0	0		NaN
12-17 years old	0	0	0	0		NaN
18-64 years old	1	0.77	1	0.49		1.41 (0.08-23.57)
≥ 65 years old	0	0	0	0		NaN
Bells palsy						
6 months-4 years old	0	0	0	0		NaN
5-11 years old	4	34.95	3	13.96		2.67 (0.60-11.91)
12-17 years old	7	30.80	10	28.75		1.30 (0.48-3.54)
18-64 years old	156	119.60	252	123.22		0.99 (0.81-1.21)
≥ 65 years old	110	204.50	197	248.37		0.80 (0.63-1.01)
Encephalomyelitis/encephalitis						
6 months-4 years old	0	0	0	0		NaN
5-11 years old	1	8.74	0	0		NaN
12-17 years old	0	0	0	0		NaN
18-64 years old	9	6.90	16	7.82		0.89 (0.39-2.03)
≥ 65 years old	8	14.86	31	39.04		0.40 (0.18-0.87)
Guillain-Barré syndrome						
6 months-4 years old	0	0	0	0		NaN
5-11 years old	0	0	0	0		NaN
12-17 years old	0	0	1	2.87		NaN
18-64 years old	2	1.53	5	2.44		0.48 (0.09-2.49)
≥ 65 years old	1	1.86	3	3.78		0.55 (0.06-5.39)
Narcolepsy						
6 months-4 years old	0	0	0	0		NaN
5-11 years old	1	2.38	4	5.65		0.43 (0.05-3.87)
12-17 years old	19	22.49	16	13.08		1.84 (0.93-3.66)
18-64 years old	167	41.75	263	47.26		0.97 (0.79-1.18)
≥ 65 years old	33	21.22	74	35.88		0.56 (0.37-0.85)
Transverse myelitis						
6 months-4 years old	0	0	0	0		NaN
5-11 years old	0	0	0	0		NaN
12-17 years old	0	0	1	2.87		NaN
18-64 years old	0	0	4	1.95		NaN
≥ 65 years old	2	3.72	2	2.52		1.41 (0.19-10.34)



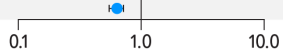
CI = confidence interval; HR = hazard ratio; IR = incidence rate; NaN = not a number (i.e., not estimable); py = person-years

As shown in **Figure 20** [source CSR]:

- HR for hemorrhagic stroke among individuals aged 12 to 17 years was 2.00 (95% CI, 0.33-12.28, with 3 exposed cases) and was < 1.0 among individuals aged 5 to 11 years (HR = 0.67; 95% CI, 0.07-6.41, with 1 exposed case), 18 to 64 years (HR = 0.70; 95% CI, 0.44-1.09, with 28 cases exposed), and ≥ 65 years (HR = 0.69; 95% CI, 0.54-0.87, with 101 cases exposed). No cases were observed in the exposed or comparator cohorts among individuals aged 6 months to 4 years.

Figure 20. Incidence rates and HRs of other general safety events by age group, booster dose analysis of haematologic events

	Exposed		Unexposed			
	Cases	IR (per 100,000 py)	Cases	IR (per 100,000 py)	HR (95% CI)	IR (95% CI)
Hematologic						
Deep vein thrombosis						
6 months-4 years old	0	0	0	0		NaN
5-11 years old	1	12.99	0	0		NaN
12-17 years old	2	12.88	5	20.81		0.48 (0.09-2.49)
18-64 years old	209	230.55	460	314.94		0.74 (0.63-0.88)
≥ 65 years old	336	907.58	740	1,327.82		0.68 (0.60-0.78)
Disseminated intravascular coagulation						
6 months-4 years old	0	0	0	0		NaN
5-11 years old	0	0	0	0		NaN
12-17 years old	0	0	1	4.16		NaN
18-64 years old	5	5.50	14	9.55		0.50 (0.18-1.40)
≥ 65 years old	7	18.66	33	58.34		0.33 (0.15-0.76)
Immune hemolytic anemia						
6 months-4 years old	0	0	0	0		NaN
5-11 years old	0	0	0	0		NaN
12-17 years old	0	0	1	2.87		NaN
18-64 years old	2	1.53	13	6.35		0.21 (0.05-0.95)
≥ 65 years old	9	16.72	33	41.56		0.42 (0.20-0.88)
Immune thrombocytopenia						
6 months-4 years old	0	0	0	0		NaN
5-11 years old	0	0	2	9.31		NaN
12-17 years old	4	17.60	0	0		NaN
18-64 years old	33	25.30	70	34.23		0.73 (0.48-1.12)
≥ 65 years old	38	70.71	66	83.26		0.84 (0.56-1.26)
Pulmonary embolism						
6 months-4 years old	0	0	0	0		NaN
5-11 years old	1	12.99	0	0		NaN
12-17 years old	0	0	0	0		NaN
18-64 years old	159	175.23	297	203.16		0.90 (0.74-1.09)
≥ 65 years old	230	619.33	551	985.13		0.62 (0.53-0.72)
Thromboembolic events associated with thrombocytopenia						
6 months-4 years old	0	0	0	0		NaN
5-11 years old	1	12.99	0	0		NaN
12-17 years old	0	0	0	0		NaN
18-64 years old	50	54.99	95	64.82		0.87 (0.61-1.23)
≥ 65 years old	105	280.60	277	491.20		0.58 (0.46-0.73)
Thrombotic thrombocytopenic purpura						
6 months-4 years old	0	0	0	0		NaN
5-11 years old	0	0	0	0		NaN
12-17 years old	0	0	0	0		NaN
18-64 years old	0	0	0	0		NaN
≥ 65 years old	0	0	0	0		NaN
Venous thromboembolism						
6 months-4 years old	0	0	0	0		NaN
5-11 years old	1	12.99	0	0		NaN
12-17 years old	2	12.88	5	20.81		0.48 (0.09-2.49)
18-64 years old	299	330.49	634	435.04		0.77 (0.67-0.89)
≥ 65 years old	474	1,289.75	1,091	1,974.02		0.65 (0.58-0.73)
Hemorrhagic stroke						
6 months-4 years old	0	0	0	0		NaN
5-11 years old	1	12.99	3	20.43		0.67 (0.07-6.41)
12-17 years old	3	19.31	2	8.32		2.00 (0.33-12.28)
18-64 years old	28	30.79	65	44.35		0.70 (0.44-1.09)
≥ 65 years old	101	270.16	223	395.76		0.69 (0.54-0.87)
Ischemic stroke						
6 months-4 years old	0	0	0	0		NaN
5-11 years old	0	0	1	6.81		NaN
12-17 years old	2	12.88	0	0		NaN
18-64 years old	101	111.46	173	118.51		0.95 (0.74-1.22)
≥ 65 years old	296	810.67	697	1,271.48		0.63 (0.55-0.72)



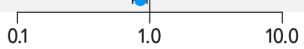
CI = confidence interval; HR = hazard ratio; IR = incidence rate; NaN = not a number (i.e., not estimable); py = person-years

As shown in **Figure 21** [source CSR]:

- HR of acute respiratory distress syndrome was > 1.0 in individuals aged 5 to 11 years (HR = 1.33; 95% CI, 0.22-7.98, with 2 exposed cases). HRs were < 1.0 among individuals aged 12 to 17 years (HR = 0.23; 95% CI, 0.03-1.91, with 1 exposed case), 18 to 64 years (HR = 0.62; 95% CI, 0.50-0.78), and ≥ 65 years (HR = 0.39; 95% CI, 0.33-0.45). No cases were observed in the exposed cohort among individuals aged 6 months to 4 years.
- HR for vaccine-associated enhanced respiratory disease was > 1.0 among individuals aged 5 to 11 years (HR = 1.15; 95% CI, 0.19-7.03, with 2 exposed cases) and was < 1.0 among individuals aged 12 to 17 years (HR = 0.38; 95% CI, 0.11-1.34, with 3 exposed cases), 18 to 64 years (HR = 0.43; 95% CI, 0.38-0.49, with 312 exposed cases), and ≥ 65 years (HR = 0.34; 95% CI, 0.32-0.37 with 921 cases exposed). No cases were observed in the exposed or comparator cohorts among individuals aged 6 months to 4 years.

Figure 21. Incidence rates and HRs of other general safety events by age group, booster dose analysis of respiratory and other system events

	Exposed		Unexposed			
	Cases	IR (per 100,000 py)	Cases	IR (per 100,000 py)	HR (95% CI)	HR (95% CI)
Respiratory						
Acute respiratory distress syndrome						
6 months-4 years old	0	0	3	523.99		NaN
5-11 years old	2	26.00	3	20.44		1.33 (0.22-7.98)
12-17 years old	1	6.44	7	29.14		0.23 (0.03-1.91)
18-64 years old	104	114.46	269	183.72		0.62 (0.50-0.78)
≥ 65 years old	211	565.23	813	1,445.73		0.39 (0.33-0.45)
Vaccine-associated enhanced respiratory disease						
6 months-4 years old	0	0	0	0		NaN
5-11 years old	2	3.80	4	4.66		1.15 (0.19-7.03)
12-17 years old	3	2.17	14	7.24		0.38 (0.11-1.34)
18-64 years old	312	49.97	1,097	131.50		0.43 (0.38-0.49)
≥ 65 years old	921	432.97	4,000	1,462.13		0.34 (0.32-0.37)
Other organ systems						
Anaphylaxis						
6 months-4 years old	0	0	0	0		NaN
5-11 years old	0	0	0	0		NaN
12-17 years old	0	0	1	109.86		NaN
18-64 years old	2	57.96	1	17.34		4.00 (0.36-44.11)
≥ 65 years old	0	0	0	0		NaN
Appendicitis						
6 months-4 years old	0	0	0	0		NaN
5-11 years old	15	131.22	26	121.14		1.13 (0.60-2.14)
12-17 years old	36	158.60	57	164.11		1.03 (0.68-1.58)
18-64 years old	166	127.37	266	130.18		1.00 (0.82-1.22)
≥ 65 years old	44	81.78	51	64.27		1.33 (0.88-2.00)
Multisystem inflammatory syndrome						
6 months-4 years old	0	0	0	0		NaN
5-11 years old	0	0	3	13.96		NaN
12-17 years old	0	0	3	8.62		NaN
18-64 years old	1	0.77	2	0.98		0.78 (0.07-8.88)
≥ 65 years old	2	3.72	0	0		NaN
Multisystem inflammatory syndrome in children						
6 months-4 years old	0	0	0	0		NaN
5-11 years old	0	0	1	4.7		NaN
12-17 years old	0	0	3	8.63		NaN
18-20 years old	0	0	0	0		NaN
Myositis						
6 months-4 years old	1	54.81	0	0		NaN
5-11 years old	22	41.78	43	50.14		1.03 (0.60-1.77)
12-17 years old	121	87.58	176	91.11		1.09 (0.86-1.39)
18-64 years old	926	148.49	1,579	189.53		0.96 (0.88-1.04)
≥ 65 years old	415	194.00	766	278.19		0.84 (0.74-0.95)



CI = confidence interval; HR = hazard ratio; IR = incidence rate; NaN = not a number (i.e., not estimable); py = person-years

PRAC Rapporteur comment:

Figure 21 shows that HR of appendicitis are generally consistent across all age groups (with exception of individuals aged 6 months – 4 years), but ~1.0 or > 1, however the results are not statistically significant (CI crossing 1).

Research partners (RPs) [source CSR p 204]

For the booster dose analysis of other general safety events within the general population, Source Table 15A.20 [not reproduced here; source pdf report body, p. 854] presents the IRs and HRs by RP. **Table 15** presents the HRs by RP for the general safety events for which some variability was observed across RPs. For the following general safety events, some variability was observed in HR estimates across RPs:

- Acute myocardial infarction: 4 RPs reported HRs < 1.0; 1 RP reported an HR of ~1.4
- Bell's palsy: 4 RPs reported HRs of < 1.0; 1 RP reported an HR of ~1.2
- Narcolepsy: 3 RPs reported HRs of < 1.0; 1 RP reported an HR of ~1.0; 1 RP reported an HR of ~1.3
- Thromboembolic events associated with thrombocytopenia: 3 RPs reported HRs of < 1.0; 1 RP reported an HR of ~1.0; 1 RP reported an HR of ~1.1
- Hemorrhagic stroke: 3 RPs reported HRs of < 1.0; 2 RPs reported HRs of ~1.2
- Ischemic stroke: 4 RPs reported HRs of < 1.0; 1 RP reported an HR of ~1.1
- Appendicitis: 1 RP reported HRs of < 1.0; 4 RPs reported HRs of ~1.1 to ~1.5
- Myositis: 4 RPs reported HRs of < 1.0; 1 RP reported an HR of ~1.2

Table 15. HRs of general safety events for which variability was observed across RPs in booster dose analysis, by RP

General safety event	RP1 HR (95% CI)	RP2 HR (95% CI)	RP3 HR (95% CI)	RP4 HR (95% CI)	RP5 HR (95% CI)
Acute myocardial infarction	0.52 (0.43-0.62)	0.31 (0.14-0.71)	0.77 (0.65-0.91)	0.64 (0.51-0.81)	1.37 (0.73-2.57)
Bell's palsy	0.94 (0.69-1.29)	1.24 (0.65-2.36)	0.91 (0.74-1.13)	0.90 (0.62-1.31)	0.57 (0.24-1.39)
Narcolepsy	0.66 (0.43-1.00)	1.26 (0.71-2.22)	1.02 (0.81-1.27)	0.82 (0.46-1.46)	0.38 (0.15-0.97)
Thromboembolic events associated with thrombocytopenia	0.63 (0.48-0.84)	1.11 (0.45-2.75)	0.58 (0.38-0.86)	0.67 (0.45-0.99)	1.00 (0.42-2.40)
Hemorrhagic stroke	0.47 (0.33-0.67)	1.16 (0.40-3.40)	0.70 (0.49-1.00)	1.20 (0.78-1.84)	0.80 (0.26-2.49)
Ischemic stroke	0.62 (0.51-0.76)	1.08 (0.51-2.28)	0.84 (0.69-1.02)	0.57 (0.44-0.75)	0.51 (0.18-1.45)
Appendicitis	1.44 (0.87-2.40)	1.25 (0.77-2.02)	0.95 (0.77-1.16)	1.08 (0.68-1.72)	1.46 (0.75-2.86)
Myositis	0.89 (0.75-1.04)	1.17 (0.93-1.48)	0.93 (0.85-1.02)	0.87 (0.72-1.04)	0.92 (0.64-1.32)

CI = confidence interval; HR = hazard ratio; RP = research partner.

PRAC Rapporteur comment:

With exception of acute myocardial infarction (AMI), HRs of RP2 were > 1 for some safety events, however none of the HR were statistically significant (CI crossing 1).

For appendicitis, HRs of 4 of the 5 RPs were > 1, but none of the HRs were statistically significant (CI crossing 1).