EMADOC-1700519818-2492155
Committee for Medicinal Products for Human Use (CHMP)

Type II variation assessment report

Procedure No. EMA/VR/0000302705

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 RMP

Note

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

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Status of this report and steps taken for the assessment			
Current step	**Description**	**Planned date**	**Actual Date**
☐	Submission deadline	30 Oct 2025	30 Sept 2025
☐	Validation	17 Nov 2025	1 Oct 2025
☐	Start date	18 Nov 2025	18 Nov 2025
☐	PRAC Rapporteur AR	22 Dec 2025	16 Dec 2025
☐	PRAC comments	2 Jan 2026	n/a
☐	CHMP comments	5 Jan 2026	n/a
☐	Updated PRAC Rapporteur AR	6 Jan 2026	6 Jan 2026
☐	PRAC outcome	13 Jan 2026	13 Jan 2026
☐	Start of CHMP written procedure	13 Jan 2026	13 Jan 2026
☐	Request for Supplementary Information	15 Jan 2026	15 Jan 2026
☐	Submission of Responses	10 Feb 2026	10 Feb 2026
☐	Re-start date	11 Feb 2026	11 Feb 2026
☐	PRAC Rapporteur AR	20 Mar 2026	18 Mar 2026
☐	PRAC comments	26 Mar 2026	26 Mar 2026
☐	CHMP comments	27 Mar 2026	27 Mar 2026
☐	Updated PRAC Rapporteur AR	30 Mar 2026	n/a
☐	PRAC outcome	8 Apr 2026	8 Apr 2026
☐	Start of CHMP written procedure	8 Apr 2026	8 Apr 2026
☒	CHMP Outcome	10 Apr 2026	10 Apr 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 30 September 2025 an application for a variation.

The following changes were proposed:

Variation(s) requested		Type
C.I.13	C.I.13 Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	Variation type II

Submission of the final report, protocol amendment #6 and SAP amendment #5 for the non-interventional study C4591021, listed as a category 3 PASS in the RMP. This is a post conditional approval active surveillance study among individuals in Europe receiving the Pfizer BioNTech Coronavirus Disease 2019 (COVID-19) vaccine. The RMP version 15.1 has also been submitted.

The requested variation(s) proposed amendments to the amendments to the Risk Management Plan (RMP).

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

Comirnaty is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2 virus, in individuals 6 months of age and older.

C4591021 is a post-authorisation safety study (PASS) that assessed the risk of 37 prespecified AESIs in individuals of all ages (including pregnant individuals) in the general European population who received $\geq$1 dose of Comirnaty. C4591021 is a category 3 commitment in the risk management plan (RMP) and a post-marketing requirement to the FDA. A total of 5 interim study reports have been submitted to the EMA and the FDA every 6 months beginning in September 2021 through March 2024.

The study confirmed associations between Comirnaty and previously identified risks of rare events (i.e. anaphylaxis and myocarditis/pericarditis).

The findings demonstrate an association between Comirnaty vaccination and subacute thyroiditis and an association with hypermenorrhoea in GP-based data sources.

In December 2021 Subacute thyroiditis has been unconfirmed as signal [EPITT reference 19753]. In contrast to previous findings reported in the PSUR and 5th interim study report, the analysis in this final study report of PASS C4591021 found an increase in risk on subacute thyroiditis in CPRD, SIDIAP and NHR.-As a result following on a request from the PRAC, the MAH provided a comprehensive review of available data on subacute thyroiditis including the most recent cases reported after January 2024, relevant scientific literature, and a discussion on strengths and limitations of the results from PASS C4591021. At this moment the cumulative evidence is inconclusive and insufficient to establish causal relation between Comirnaty and subacute thyroiditis, and no update of the product information is warranted, provided subacute thyroiditis will be continue to be monitored using routine pharmacovigilance.

Hypermenorrhoea is currently labelled in the approved product information.

Although some cardiovascular events, such as arrhythmia and acute cardiovascular injury, coronary artery disease, and heart failure, showed very minor elevations during 365 days of follow-up, it is believed this may be due to selection bias in the unvaccinated individuals that remained unvaccinated during the 365 days follow-up.

No association between Comirnaty vaccination and adverse pregnancy AESIs or neonatal AESIs were found, except a small elevation of preterm birth and foetal growth restriction, most likely due to residual confounding by COVID-19 or gestational age.

A lower frequency of reported imaging in both vaccinated and unvaccinated individuals following the issuance of the Direct Healthcare Professional Communication (addressing the risk of myo/pericarditis) was observed.

The results demonstrated that the majority of the AESI were not associated with Comirnaty vaccine.

The PRAC concludes that, in general no new important safety information could be identified.

Within this variation no changes to the marketing authorisation, product information, or RMP summary of safety concerns are being proposed. The requested amendments of the RMP are consequential of the finalisation of the study and are accepted. RMP version 16.0 is acceptable.

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:

- Acute cardiovascular injury
- Subacute thyroiditis
- Pregnancy outcomes including foetal growth restriction and preterm birth

The benefit-risk balance of COMIRNATY remains positive.

3. Recommendations

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

Variation(s) requested		**Type**
C.I.13	C.I.13 Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	Variation type II

Submission of the final report, protocol amendment #6 and SAP amendment #5 for the non-interventional study C4591021, listed as a category 3 PASS in the RMP. This is a post-conditional approval active surveillance study among individuals in Europe receiving Comirnaty. The RMP is updated to version 16.0.

☒is recommended for approval.

Amendments to the marketing authorisation

The Variation leads to no amendments to the terms of the Community Marketing Authorisation.

The variation requires amendments to the Risk Management Plan.

In view of the data submitted with the variation, amendments to Annex(es) and to the Risk Management Plan

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-0000302705".

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

5. Introduction

The MAH provided a clinical overview in support of the submission of a Type II variation to describe clinical study data as well as Risk Management Plan changes (proposal to remove the aRMM of the DHPC letter for myocarditis and pericarditis from RMP) for Comirnaty, a prophylactic, mRNA vaccine indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2, developed by BioNTech and Pfizer.

This clinical overview has been used as backbone for this assessment report, supplemented by [a selection of] relevant details on the evaluated outcomes, as included in the full Final Clinical Study Report.

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

6.1. Study C4591021

Category 3 PASS: Post Conditional Approval Active Surveillance Study Among Individuals in Europe Receiving the Pfizer-BioNTech Coronavirus Disease 2019 (COVID-19) Vaccine.

PASS information

Title	Post Conditional Approval Active Surveillance Study Among Individuals in Europe Receiving the Pfizer-BioNTech Coronavirus Disease 2019 (COVID-19) Vaccine
Protocol number	C4591021
Version identifier of the study report	V1.0
Date	10 September 2025
EU Post Authorization Study (PAS) register number	EUPAS41623
Active substance	BNT162b2
Medicinal product	COVID-19 messenger ribonucleic acid (mRNA) vaccine is a nucleoside-modified ribonucleic acid (modRNA) encoding the viral spike glycoprotein S of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)
Product reference	EMEA/H/C/005735
Procedure Number	EMA/VR/0000XXXXXX
Marketing Authorization Holder (MAH)	BioNTech Manufacturing GmbH
Joint PASS	No
Research question and objectives	The research question addressed by this study is: Is there an increased risk of select adverse events of special interest (AESI) after being

	vaccinated with the Pfizer-BioNTech COVID-19 vaccine? **Objectives** ***Primary study objective*** To determine whether an increased risk of prespecified AESI exists following the administration of at least one dose of the Pfizer-BioNTech COVID-19 vaccine using two approaches: (a) a matched cohort design comparing risk in vaccinated and unvaccinated individuals and (b) a self-controlled risk interval (SCRI) design. ***Secondary study objectives*** • To estimate the incidence rates of prespecified AESI among individuals who receive at least one dose of the Pfizer-BioNTech COVID-19 vaccine using a cohort study design. • To describe the incidence rates and determine whether an increased risk of prespecified AESI exists following the administration of at least one dose of the Pfizer-BioNTech COVID-19 vaccine compared with a matched comparator group with no COVID-19 vaccination within sub-cohorts of interest (i.e., individuals who are immunocompromised, individuals who are frail or have comorbidities, individuals diagnosed with previous COVID-19 infection, and age-specific groups) in Europe using a cohort study design and/or a SCRI design. • To determine whether an increased risk of prespecified AESI exists following the administration of at least one dose of the Pfizer-BioNTech COVID-19 vaccine compared with no COVID-19 vaccination, in pregnant people and their neonates using a cohort study design. To characterise utilisation patterns of Pfizer-BioNTech COVID-19 vaccine among individuals within Europe, including estimating the proportion of individuals receiving the vaccine; two-dose vaccine completion rate and distribution of time gaps between the first and second doses; and demographics and clinical characteristics of recipients, overall and among sub-cohorts of interest, such as individuals who are immunocompromised, elderly, or have specific comorbidities.
Countries of study	Italy (IT), The Netherlands (NL), Norway (NO), Spain (ES), United Kingdom (UK)

Authors	Daniel Weibel Assistant Professor University Medical Center Utrecht Miriam Sturkenboom Professor University Medical Center Utrecht Alejandro Arana Senior Director Epidemiology RTI Health Solutions On behalf of the Vaccine Monitoring Collaboration for Europe (VAC4EU) Consortium research team

6.1.1. Milestones

Milestone	Planned/actual date
Registration in the EU PAS Register	25 June 2021
Start of data collection	30 September 2021
Study end date	31 December 2023
End of data collection	31 March 2025[2]
Progress report [1]	30 September 2021
Interim report 1	31 March 2022
Interim report 2	30 September 2022
Interim report 3	31 March 2023
Interim report 4	30 September 2023
Interim report 5	31 March 2024
Final study report	30 September 2025

[1] Data will not be provided in the progress report.
[2] Date when analytic tables will be ready and maximising the length of period for AESI validation

6.1.2. Rationale and background

The novel coronavirus, SARS-CoV-2, the cause of COVID-19, resulted in a global pandemic that was declared on 11 March 2020. The Pfizer-BioNTech COVID-19 vaccine, BNT162b2, tozinameran (Comirnaty) an mRNA-based vaccine, received conditional marketing authorisation (CMA) by the European Commission on 21 December 2020, for the prevention of COVID-19. The nucleoside-modified mRNA in original BNT162b2 and variant adapted BNT162b2 is formulated in LNPs, which enable delivery of the RNA into host cells to allow expression of the SARS-CoV-2 S antigen. The vaccine elicits both neutralizing antibody and cellular immune responses to the S antigen, which contributes to protection against COVID-19. Comirnaty does not contain the virus itself and cannot cause COVID-19.

The Pfizer-BioNTech vaccine is indicated for active immunization to prevent COVID-19 caused by SARS-CoV-2 virus, in individuals 6 months of age and older.

At the time of CMA, the safety of the Pfizer-BioNTech COVID-19 vaccine had been investigated in clinical studies conducted in the United States, Europe, Turkey, South Africa, and South America and included over 43,000 individuals aged 16 years and older. The overall safety profile of the vaccine was found to be favourable in the trial setting. Reported adverse reactions from unblinded data (i.e., from the overall trial population) on participants aged 16 years and older who received 2 doses of Pfizer-BioNTech COVID-19 vaccine 21 days apart after 2 months of follow-up included pain at the injection site, fatigue, headache, muscle pain, chills, joint pain, fever, injection site swelling, injection site redness, nausea, malaise, and lymphadenopathy. The safety database revealed an imbalance of cases of Bell's palsy (4 in the vaccine group and 0 in the placebo group).[1] However, currently available information is insufficient to determine a causal relationship with the vaccine. Severe allergic reactions had been reported following receipt of the Pfizer-BioNTech COVID-19 vaccine in mass vaccination campaigns outside clinical trials in various countries.

At the time of first introduction of the Pfizer-BioNTech vaccine, rapid uptake was expected. Public health authorities identified priority populations for vaccination based on health care or essential worker status, comorbidities, and age and therefore the vaccine was initially provided to vulnerable groups at higher risk for COVID-19 infection and COVID-19 complications.[2] Initial authorization was only for adults and older adolescents (16+ years), both by the EMA (conditional marketing authorization) and the FDA (emergency use authorization [EUA]). However, Comirnaty's authorization expanded progressively from adults to adolescents, then to younger children and infants, with dose adjustments and schedules tailored correspondingly for these age groups. Comirnaty accounted for the majority of COVID-19 vaccine doses distributed in EU/EEA countries (about 67.3% of doses distributed by mid-2021).

Routine safety monitoring and additional activities have been conducted, with PSURs prepared initially every 6 months, thereafter every 12 months and now every 2 years. The PRAC assessed various safety issues after the roll out of the vaccine.[3] They are included in Table 1 below.

Table 1. Safety Issues Discussed by PRAC

Appendix 5. Safety Issue	Appendix 6. Earliest PRAC Discussion / Reporting Date	Appendix 7. Notes
Allergic Reactions and Anaphylaxis	December 2020 – January 2021	Addressed initially in risk management plan and early monitoring.
Local Reactions (Swelling, Redness, Pain)	December 2020	Included at first authorisation, consistently monitored.
Paraesthesia / Hypoesthesia	December 2020	Included early among neurological side effects.
Pregnancy and Breastfeeding	Ongoing from December 2020	Regularly reviewed, no negative effects identified on pregnancy and breastfeeding to date.
Myocarditis and Pericarditis	July 2021 (initial); October 2021 (formal listing)	Rare but confirmed risk, especially in younger males post-second dose; product updates made.
Facial Paralysis (Bell's Palsy)	Early 2021 (case reports August 2021)	Recognized as rare side effect after review.
Lymphadenopathy	Early 2021	Observed early after rollout, listed in safety profile.
Heavy Menstrual Bleeding	October 2022	Added as potential side effect after thorough signal evaluation.
Erythema Multiforme	Early 2022	Included after case reports raised concern.
Facial Swelling (Dermal Fillers)	2021	Recognized and added as side effect.
Glomerulonephritis	2023	Discussed as a safety signal with reported cases; ongoing monitoring; causality unconfirmed.
Hemophagocytic Lymphohistiocytosis (HLH)	Ongoing through PSUR cycles (latest mid-2023 to 2024)	No new safety information identified; cumulative evidence to be reviewed continuously.
Idiopathic Inflammatory Myopathies/Myositis	From 2023	Rising case reports reviewed; included as AESI (Adverse Event of Special Interest) and monitored in PASS studies.
Small Fiber Neuropathy (SFN)	Under review in latest PSUR cycles	MAH requested to provide cumulative evidence; causality assessment ongoing.
Postmenopausal Bleeding	Ongoing review, no causal link established	Continued monitoring without confirmed link.
Amenorrhoea (Absence of Menstruation)	Ongoing review, no causal link established	Continued monitoring without confirmed link.
Other Rare Immunological/Inflammatory Conditions	Throughout ongoing monitoring	Includes various signals like idiopathic inflammatory myopathies, myositis, SFN, HLH with no conclusive updates yet.

Based on Caplanusi et al.[3]

Because of the relatively short pre-authorisation period and limited number of participants in clinical studies, efficient and timely monitoring of the safety of the vaccine was a necessary part of the pharmacovigilance program in Europe and elsewhere. C4591021 is a post-authorisation safety study (PASS) that assessed the risk of 37 prespecified AESIs in individuals of all ages (including pregnant individuals) in the general European population who received ≥1 dose of the Pfizer-BioNTech vaccine. C4591021 is a category 3 commitment in the EU Risk Management Plan and a postmarketing requirement to the FDA. A total of 5 interim study reports have been submitted to the EMA and the FDA every 6 months beginning in September 2021 through March 2024.

PRAC Rapporteur's comment:

Previous PRAC assessment [updated AR dated 06 Jun 2024] of the **5th interim report** concluded:

- *No additional characterisation of the AESIs is warranted*
- *No new important safety information could be identified.*

In summary,

- *The incidence rates of AESIs were generally very low in the risk intervals studied and were comparable with available published background incidence rates from previous studies in unvaccinated cohorts.*
- *The divergence in cumulative incidence observed for several of the cardiovascular [CV] events with long risk windows (e.g. 365 days) resulted in small increases in risk in some of the data sources. According to the MAH these increases could be explained by a number of factors:*

a) Some of these CV events have presented with mild symptoms that did not require immediate medical attention, and vaccinated individuals may have sought medical attention more frequently than those who were unvaccinated (healthy vaccinee effect).

b) Differences in the composition of the unvaccinated cohort as follow-up progresses. Unvaccinated individuals were censored in the unvaccinated cohort if they were vaccinated and were then followed up in the vaccinated cohort from that time point. Consequently, the individuals who remained in the unvaccinated cohort were those who were never vaccinated and who were possibly less likely seek medical attention at all if it was not urgently needed.

c) These differences may have been minimal earlier in follow-up, however, may have become more pronounced as follow-up progressed.

- *Results for CVST, Bell's Palsy and glomerulonephritis all showed no evidence of an increased risk in the vaccinated cohort based on adjusted HRs.*
- *Adjusted HRs for secondary amenorrhea were slightly elevated in EpiChron and CPRD Aurum.*
- *For hypermenorhea, only the adjusted HR in Epichron was slightly elevated. [Heavy menstrual bleeding is considered an ADR and is stated with frequency 'not known' in the currently approved Comirnaty PI].*
- *The MAH's commitment to continue to monitor and further refine these events for inclusion in the final study report is noted.*

For the Final Report due 20 Dec 2024 [due date change was accepted] the MAH should address the following:

- *[**Outstanding request** from previous 4th interim report, regarding the evaluation of the effectiveness of the DHPC on myocarditis/pericarditis July 2021] The MAH should discuss and clearly describe the criteria used to evaluate the effectiveness of the DHPC.*
- *The MAH committed to continue to monitor and thoroughly discuss acute cardiovascular injury in the final report.*
- *No consistent differences in the adjusted HRs for Bell's palsy between interim reports 4 and 5 were observed. The MAH committed to investigate (and discuss in the final report) whether more specific identification codes were used in the algorithm in PHARMO may have led to the lower adjusted HR.*
- *No differences in the adjusted HRs for secondary amenorrhoea and between interim reports 4 and 5 were observed, except in EpiChron for secondary amenorrhoea and PHARMO for hypermenorrhoea. The MAH committed to further refine the case identification algorithm that includes ICPC and ICD10 codes for these menstrual events for the final report.*

6.1.3. Research question and objectives

The research question addressed by this study was:

Is there an increased risk of select AESIs after being vaccinated with the Pfizer-BioNTech COVID-19 vaccine?

Primary Study Objective

To determine whether an increased risk of prespecified AESIs exists following the administration of at least one dose the Pfizer-BioNTech COVID-19 vaccine using two approaches: (a) a cohort design comparing risk in vaccinated and non-vaccinated individuals and (b) a self-controlled risk interval (SCRI) design.

Secondary Study Objectives

- To estimate the incidence rates of prespecified AESI among individuals who receive at least one dose of the Pfizer-BioNTech COVID-19 vaccine using a cohort study design;
- To describe the incidence rates and determine whether an increased risk of prespecified AESI exists following the administration of at least one dose the Pfizer-BioNTech COVID-19 vaccine compared with a matched comparator group with no COVID-19 vaccination within subcohorts of interest (i.e., individuals who are immunocompromised, individuals who are frail and have comorbidities, individuals diagnosed with previous COVID-19 infection, and age-specific groups) in Europe using a cohort study design and/or a SCRI design;
- To determine whether an increased risk of prespecified AESI exists following the administration of at least one dose of the Pfizer-BioNTech COVID-19 vaccine compared with no COVID-19 vaccination, in pregnant people and their neonates using a cohort study design;
- To characterise utilisation patterns of Pfizer-BioNTech COVID-19 vaccine among individuals within Europe, including estimating the proportion of individuals receiving the vaccine; two-dose vaccine completion rate and distribution of time gaps between the first and second doses; and demographics and clinical characteristics of recipients, overall and among subcohorts of interest, such as individuals who are immunocompromised, elderly, or have specific comorbidities;

- To assess the effectiveness of the Direct Healthcare Professional Communication (DHPC) about the risk of myocarditis and pericarditis associated with COVID-19 mRNA vaccine use and describe the rate of cardiac imaging use for vaccinated and unvaccinated individuals in this study population each calendar month during the study period, before and after distribution of the DHPC.

PRAC Rapporteur's Comment

No difference observed from the final approved protocol.

For evaluation of the effectiveness of the DHPC see *Section 6.2*.

6.1.4. Amendments and updates to the protocol

The following amendments have been made to the protocol:

Amendment number	Date	Section of protocol changed	Summary of amendment/update	Reason
6	22 July 2025	4. Abstract; 6. Milestones	Revised end of data collection date from 30 September 2024 to 31 March 2025. Revised final study report date from 20 December 2024 to 30 September 2025	To provide additional time to fully complete data collection activities, including validation of select AESIs. To allow sufficient time to prepare final study report and to comply with requirement to submit report within 6 months of end of data collection for studies that include paediatric data.
6	22 July 2025	3. Responsible Parties	Additions and removals of staff members at participating institutions	Personnel changes
6	22 July 2025	3. Responsible Parties	IDIAP JGol removed from list of country coordinating investigators	To have only one country coordinating investigator per country. EpiChron serves as the coordinating institution for the study in Spain
6	22 July 2025	Throughout	DAP (data access provider) changed to DEAP (data expert and access partner)	To reflect the change in VAC4EU name for partners
6	22 July 2025	9.1 Study design	Removed 'race' from list of time-invariant confounders	To reflect the unavailability of this variable in the data sources
6	22 July 2025	9.2.1.2. Self-controlled risk interval design	Changed criteria from 'full accrual of data' in the risk and control intervals to 'at least one day accrual of data'	To reflect the decision to reduce the need for full accrual to increase the number of eligible individuals
6	22 July 2025	9.2.2.1. Cohort and SCRI designs	Clarification that the look back period for diabetes type 1 is only for the cohort design	For clarity
6	22 July 2025	9.3.2.1 Safety outcomes	Replaced a hyperlink	HMA-EMA Catalogues website replaced the previous EU PAS Register and ENCePP Resource Database

Amendment number	Date	Section of protocol changed	Summary of amendment/update	Reason
6	22 July 2025	9.3.2.2. Outcome identification and validation, by data source	Description of positive predictive value (PPV) calculation	To provide details of the PPV calculation method
6	22 July 2025	9.4.1	Headings; 9.4.1.1, 9.4.3.1, 9.4.4.1, were removed	Considered redundant
6	22 July 2025	9.4.1	9.4.1 ARS Toscana (IT) updated	For clarity
6	22 July 2025	9.9 Limitations of the research methods	Edited text	For clarity
5	15 May 2024	4. Abstract 6 Milestones	Revised end of data collection date from 31 Mar 2024 to 30 Sep 2024 to correspond to new final study report date of 20 Dec 2024	This change to the end of data collection date was inadvertently excluded from Sections 4 and 6 and not mentioned in Section 5 under Amendments and Updates in Protocol Amendment #4
5	15 May 2024	4. Abstract, 9.2.Setting	ARS Toscana (IT) cannot participate in the study until further notice	Due to the ongoing revision of the procedure for data access in the Tuscany Region, ARS must suspend its activities concerning the re-use of data until the revision is complete.
5	15 May 2024	9.6.1 Case report forms/data collection tools/electronic data record	Deleted sentence indicating that CRFs need to be signed	CRFs will not be collected and therefore it will not be possible to verify if they are signed in the QC process
5	15 May 2024	9.7.4 Description of cardiac imaging use before and after the issue of the direct healthcare professional communication (DHPC)	Calculation of rates, rate ratios and 95% CI for the evaluation and interpretation of results and conclusions on effectiveness of the DHPC	To address European Medicines Agency (EMA) request to discuss and clearly state the success criteria for evaluation of effectiveness of the DHPC
5	15 May 2024	9.9 Limitations of the research methods	Description of the strong assumption needed for a formal estimation of the effectiveness of the DHPC using cardiac imaging procedures	Importance of describing the limitations of the proposed analysis in the assessment of the effectiveness of the DHPC
5	15 May 2024	Table 1 and Table 3	Removed AESIs: severe COVID-19 and anosmia, ageusia	Request from EMA to remove these AESIs that were inadvertently forgotten
5	15 May 2024	3 Responsible parties	Updated country teams	To list current team members
5	15 May 2024	LIST OF ABBREVIATIONS	Removed abbreviations that only appear once or not at all in the text and added new ones	To be conform with Pfizer style guide

Amendment number	Date	Section of protocol changed	Summary of amendment/update	Reason
5	15 May 2024	6 Milestones	End of data collection modified to 30 September 2024	To reflect the modified timelines and the date when analytic tables will be ready. This maximises the length of period for AESI validation

PRAC Rapporteur's Comment

The most recent amendments 5 and 6 are accepted. There are no substantial amendments and updates to the study protocol after the start of data collection had impact on the validity of study results as initially planned in the final endorsed study protocol.

Full details of the study research methods described in the study protocol C4591021 (version 6.0; dated 18 Oct 2023) have been assessed and are accepted in a previously separate procedure EMEA/H/C/005735/MEA/017.7.

As the final protocol has been endorsed previously, the research methods will only be described briefly, and not commented on.

6.1.5. Research methods

Study design and Setting

This was a retrospective study using a cohort design involving data from multiple electronic healthcare databases in 5 European countries. In addition to the cohort analysis, for a subset of the study endpoints, a SCRI design was used to assess risk.

Study Population

Inclusion Criteria

Cohort Design

Individuals needed to meet all the following inclusion criteria to be eligible for inclusion in the cohort study:

- Have a minimum of 12 months (or from birth if enrolled in the data source at birth) of active enrolment and history in one of the selected data sources to ensure adequate characterisation of medical history; this criterion may be met after the start of the study period.
- No history of vaccination with a COVID-19 vaccine before time zero.

At any point in time, vaccinated individuals may have differed from the remaining population in characteristics that may determine their risk of AESI. Measured baseline characteristic differences were adjusted for analytically.

For the study of pregnancy outcomes, the cohort was restricted to pregnant women.

Self-Controlled Risk Interval Design

For analyses of outcomes assessed with the SCRI design, the following criteria were required. Note that the study population for each outcome-specific analysis would thus be different.

- Have received at least one dose of the Pfizer-BioNTech COVID-19 vaccine.
- Have experienced an event during the risk or control interval.
- Have at least one day accrual of data in the risk and control intervals.

Exclusion Criteria

Cohort and Self-Controlled Risk Interval Designs

- Have a diagnosis for the specific AESI under study within 1 year before time zero (to distinguish the recording of previous events from true new events) except for the event diabetes type 1 in the cohort design for which the look back period will be any time before time zero. Note: Time zero corresponds to the day of vaccination (ie, a 42-day risk interval means that individuals are followed from the day of vaccination to the 41st day); refer to Module 5.3.5.1 C4591021 Appendix 16.1.1, Protocol Section 9.1.1 for further details.
- Individuals having any specified contraindication to vaccination or being part of a group not recommended for vaccination in the jurisdiction of the study were analysed separately.

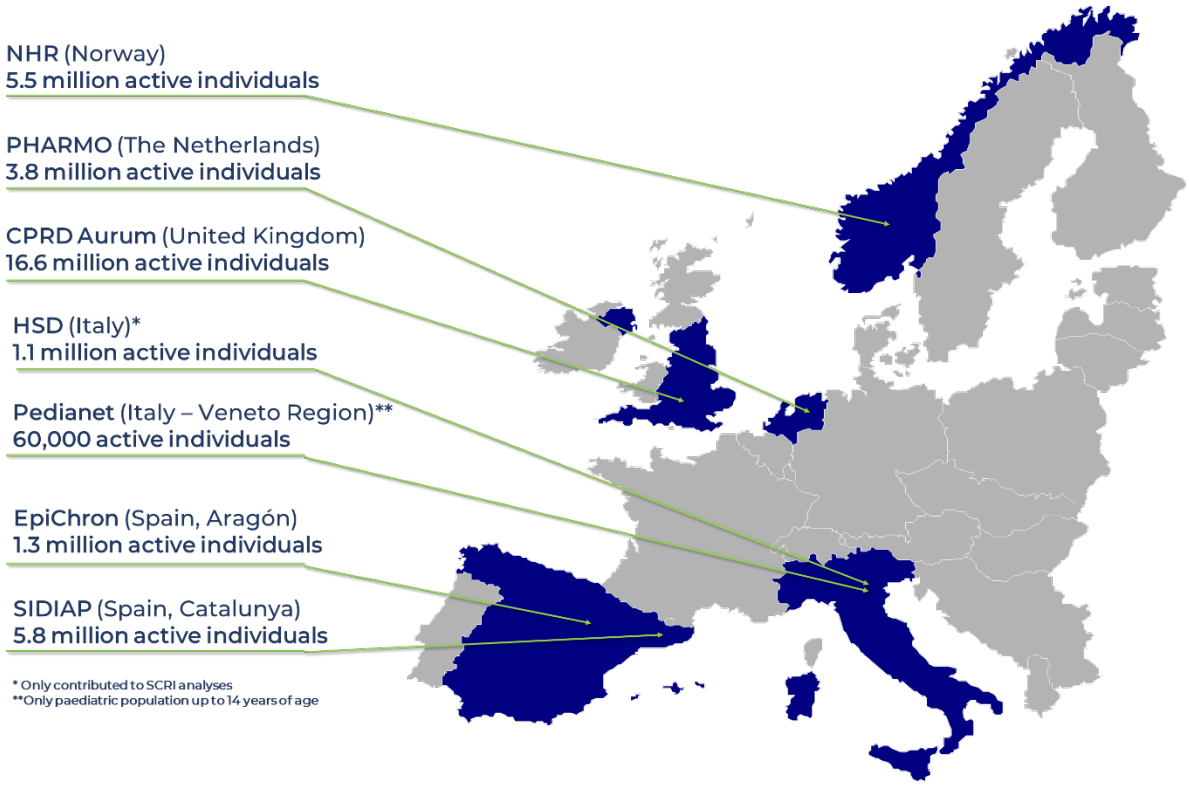
Data Sources and Collection Process

The study planned to use data from 8 European electronic healthcare data sources in Italy, the Netherlands, Norway, Spain and part of the UK (England and Northern Ireland). However, 1 data source in Italy, Agenzia Regionale di Sanità della Toscana (ARS Toscana), only contributed to the first and second interim reports due to national and regional re-assessment of regulations affecting its ability to provide public data for PASS studies. Therefore, this final report contains data from 7 European electronic healthcare data sources. The selected data sources and two-letter country codes are provided below:

- Agenzia Regionale di Sanità della Toscana (ARS Toscana) ([Tuscany Regional Health Agency])(IT)]
    - Note: ARS only contributed to the first and second interim reports
- Pedianet (IT)
- Health Search Database (HSD) (IT)
- PHARMO Institute for Drug Outcomes Research (PHARMO) (NL)
- The Norwegian Health Registers (NHR) (NO)
- EpiChron Research Group on Chronic Diseases at the Aragon Health Sciences Institute (EpiChron) (ES)
- Sistema d'Informació per el Desenvolupament de la Investigació en Atenció Primària (SIDIAP) [Information System for the Development of Primary Care Research] (ES)
- Clinical Practice Research Datalink (CPRD) (UK)

Figure 1 shows the location and number of active individuals in each data source.

Figure 1. Location and Number of Active Individuals in Each Data Source



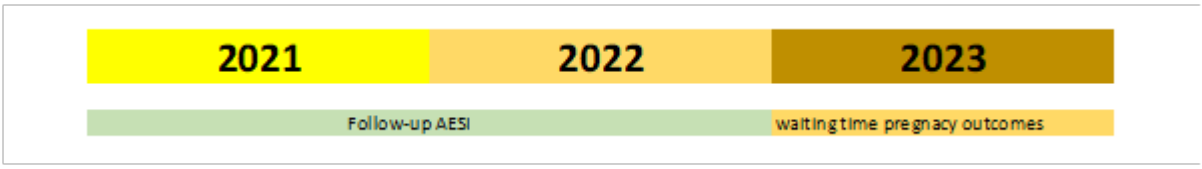
Study Period and Follow-up

The study period for both the cohort and SCRI designs started on the date of administration of the first dose of the Pfizer-BioNTech COVID-19 vaccine in each country participating in the study (Table 2) and ended on the date of the latest data availability. The study period was two years for AESIs (Figure 2). The specific risk windows for acute and non-acute events have been described in the SAP. For the pregnancy outcomes in women who became pregnant during the two-year study period, these women were followed up for an additional year (Figure 2).

Table 2. Date of Administration of First Dose of Pfizer-BioNTech COVID-19 Vaccine and Dates of Data Collection for This Report

Country (Data source)	Date of First Dose Administrated	Data Source Start and End Date for Use of Data
Italy (Pedianet, HSD)	27 December 2020	Pedianet: 31 May 2021– 31 December 2022 HSD: 01 January 2021– 30 June 2023
The Netherlands (PHARMO)	08 January 2021	GP data: 06 January 2021– 30 June 2023 Hospital data: 06 January 2021–31 December 2022
Norway (NHR)	27 December 2020	01 January 2021– 31 December 2022
Spain (EpiChron, SIDIAP)	27 December 2020	EpiChron: 27 December 2020– 31 July 2023 SIDIAP: 01 January 2021– 30 June 2023
England and Northern Ireland (CPRD Aurum)	08 December 2020	08 December 2020–07 June 2023

Figure 2. Study Period and Follow Up Periods



Variables and data sources

Exposure was based on recorded prescription, dispensing, or administration of the Pfizer-BioNTech COVID-19 vaccine. Outcomes were identified in the data sources with algorithms based on codes for diagnoses and free text. The selected adverse events of special interest (AESIs) were based initially on the ACCESS project but the list has been extended with new AESIs and the code lists have been reviewed and tagged as narrow and possible codes on the descendant code level.

Main statistical methods

The following risk estimates were estimated for the AESIs:

- Matched and adjusted incidence rates (IRs), hazard ratios (HRs) and risk differences (RDs) for all AESIs during their specific risk windows in individuals who had received ≥1 dose and matched unvaccinated individuals.
- The IRs for AESIs during their specific risk windows after each dose (doses 1 to 4).
- The number of cases and risk estimates (IR, Kaplan-Meier (KM) for all AESI in the matched vaccinated and unvaccinated cohorts, overall and by subgroups.
- The matched and adjusted cumulative incidence (1- KM) curves for all AESI in the matched vaccinated and unvaccinated cohorts, taking the AESI-specific risk windows into consideration.
- Pooled relative risk estimates (HRs, 95% CIs) for AESIs overall, by subgroups and sensitivity analyses.

Analyses for direct healthcare professional communication (DHPC)

The monthly rate of ≥1 cardiac imaging procedure (cardiac magnetic resonance or echocardiogram) during the study period from January 2021 to December 2022 were estimated per 10,000 person-years (PY) in the vaccinated and unvaccinated cohorts. In addition, the rate before and after the direct healthcare professional communication was issued (19 July 2021) was estimated overall and by age group in the vaccinated and unvaccinated cohorts, and incidence rate ratios were calculated comparing the period after the DHPC with the period before.

PRAC Rapporteur comment:

See *Section 6.2 Direct Healthcare Professional Communication*, below.

Validation of events analyses

For case validation, case definitions for AESIs by the Brighton Collaboration and the Coalition of Epidemic Preparedness and Innovation (CEPI) were used. Cases were assigned Brighton Collaboration levels of diagnostic certainty, which follow the following classification:

Level 1 of certainty (definitive case);
Level 2 of certainty (probable case);
Level 3 of certainty (possible case);
Level 4: Data collected insufficient to meet any of the three levels of certainty, but the diagnosis was recorded;
Level 5: An alternative diagnosis was found to explain the clinical illness, and thus it is not a case.

The positive predictive values (PPVs) and exact 95% CI for the AESIs that underwent clinical validation were calculated as follows:

$$\frac{\text{Number of true positives}}{\text{Number of true positives + number of false positives}}$$

Limitations of the research methods

Limitations due to observation periods and death dates

Several limitations in this study relate to the structure of the data sources and the mechanisms for determining the start and end of follow-up. In Spain (SIDIAP and EpiChron), the Netherlands (PHARMO), Italy (PEDIANET and HSD), and the United Kingdom (CPRD Aurum), data were primarily derived from general practitioner (GP) databases whereas the Norwegian Health Registries (NHR) also includes specialist healthcare. In these settings, inclusion in the study population is contingent upon registration with a participating GP practice, and follow-up ends upon deregistration.

The data sources in the Netherlands, Spain, Italy and part of the UK (England and Northern Ireland) are dynamic, and the data collection period, catchment area and overlap between databases differ. Data are recorded at the contributing general practices daily for clinical purposes and processed to create monthly, quarterly or yearly data sources which are then made available for observational research. In these data sources GP practices and individuals can opt out of data collection for research purposes. In Italy, Pedianet includes data from paediatricians, and follow-up typically ends when children transition to adult care around age 14, this is where HSD begins.

The quality of data for deaths varied across the data sources. In PHARMO, SIDIAP, HSD, and PEDIANET, deaths are recorded by GPs or paediatricians when informed, which may lead to underreporting. PEDIANET had very few deaths (≤5), consistent with low paediatric mortality in Italy. EpiChron and NHR had complete death data via public registries. CPRD Aurum used a validated algorithm based on GP records. The same algorithm was shown to have high sensitivity (98%) in the CPRD GOLD database, minimising impact of imprecise dates.[72] Across all data sources, delays in deregistration following migration or death may result in individuals erroneously appearing as still under observation, unvaccinated, and without recorded AESIs. This is more likely to happen in the unvaccinated, than in the vaccinated, because the vaccinated at least have a recording health care contact of vaccination. This misclassification could lead to spurious associations in cohort analyses.

Low numbers of recorded deaths prior to follow-up were observed in Norway, EpiChron, and PEDIANET. In NHR, this was due to incomplete 2018 mortality data, leading to exclusion of this data source from sensitivity analyses using historical controls. The low number of deaths in Pedianet reflects its paediatric population. EpiChron included only individuals alive after 01 January 2020 and those that enrolled in the data source after, i.e., newborns and new enrolments. Because of the selection on death (EpiChron) and incompleteness in NHR, NHR and EpiChron were excluded from the pre-COVID-19 and COVID-19 historical cohort analyses.

Exposure measurement error

The identification of COVID-19 vaccine exposure in this study was based on a range of data sources, including pharmacy dispensing records, general practice records, immunisation registries, medical records, and other secondary sources. In NHR, EpiChron, CPRD Aurum, PEDIANET, and SIDIAP, COVID-19 vaccination data were transferred automatically from the point of administration to the respective databases. Vaccination data were generally complete in SIDIAP, CPRD Aurum, NHR, and Pedianet, due to integration with national or regional registries. In contrast, PHARMO and HSD had fragmented or incomplete records. HSD lacked automated vaccine reporting and was excluded from the main analysis but included in SCRI design. PHARMO data were inconsistently recorded across providers and sources, requiring a hierarchical approach to improve reliability.

Findings from the EMA-tendered COVID-19 Vaccine Monitoring study, which benchmarked vaccine uptake against ECDC figures, confirmed good uptake and recording in NHR, Pedianet, SIDIAP, and CPRD Aurum. However, PHARMO showed some delays in recording of vaccines for people aged 50-59, potentially causing exposure misclassification, but eventually good uptake was reached for all age groups., further supporting concerns about exposure misclassification in this data source. However, the delays were believed to be a problem during the pandemic only and should no longer influence the current study.

Limitations on outcome measurement

The data sources in this study varied by type of data source (GP, record linkage), and also the type of databases that could be linked varied (GP, emergency room, discharge diagnosis, outpatient specialists), as well as the vocabularies that were used to identify the events. For example, in EpiChron and NHR, data from visits to emergency rooms and hospitalisations were available, which may have resulted in a detection bias, i.e. higher number of events being recorded compared with the other data sources in this study. This was confirmed by the standardised incidence rates for most AESIs, which were often higher in NHR and EpiChron than in other data sources, except for those that are primarily diagnosed by GPs, e.g., menstrual disorders, chilblains, which were not captured in NHR. Another limitation was the inability to identify cardiac imaging events in PHARMO and NHR. In both data sources, no specific procedure codes were available, and it was not possible to text mine for these events in patients' hospital discharge letters. Consequently, the impact of the DHPC on cardiac imaging after COVID-19 vaccination could not be assessed in either data source.

As with all studies using routinely collected healthcare data, outcome misclassification is a potential limitation. AESIs were identified using operational definitions based on diagnostic codes and algorithms, which are subject to information bias due to diagnostic errors, recording inaccuracies, and misclassification. Variability in data availability and coding vocabularies across data sources further contributes to heterogeneity in the completeness and validity of AESI definitions and covariates. To mitigate this, all AESI definitions and covariates underwent dual medical review and refinement by a dedicated VAC4EU task force. Additionally, nine rare and most severe AESIs were prioritised for validation of a sample of cases across data sources using modified Brighton Collaboration level of diagnostic certainty criteria.

The results showed that in each data source the number of validated cases was relatively low, and the level of certainty varied substantially across data sources, resulting in diverse patterns for all PPVs. This variability of PPVs was mainly due to available source data for validation in each data source. In data sources which had only access to GP medical records and were manually reviewed (i.e., SIDIAP and CPRD Aurum), most cases were classified as level 4 (diagnosis but no further information) and therefore PPVs based on a strict definition for all AESIs were low. However, when combined with additional levels of certainty, the PPVs substantially increased (level 4a: diagnosis by specialists, although there was insufficient information to satisfy the complete case definition). This suggests that

cases were identified in this study, but that there were insufficient data available during the validation process to meet the level of certainty of 1 to 3. This does not mean that the cases were not cases, but they could not be definitively ascertained.

The results from data sources with access to in-hospital data for validation e.g., EpiChron and NHR, showed higher strict PPVs for AESIs, indicating that information, such as results of tests and imaging was available for validation. Overall, the study did not observe substantial differences (measured by overlapping confidence intervals) in the PPV between the vaccinated and unvaccinated individuals. While small sample sizes for validation in each data source. may drive this observation, these findings support that misclassification is mostly non-differential within each data source, and for this reason the HR was not corrected. An attenuation of the HR was expected, but the assessment of HRs in data sources with the highest PPV did not change the conclusions. Absolute incidence rates may vary substantially depending on the healthcare setting captured, e.g., general practice, emergency room, or hospital, and the level of misclassification. For instance, anaphylaxis is typically diagnosed in emergency room settings, and if such data were not captured, the absolute risk may have been underestimated. This was also observed in the ACCESS study, which demonstrated that AESI rates vary significantly depending on the type of data source used.[73] In this PASS age standardisation was conducted within data sources, based on the population of 2020 for the unvaccinated historical and the unvaccinated controls. This means that within data source comparisons over time were not confounded by age, but not between data sources or with external references.

Misclassification may become differential if awareness of specific safety concerns influences diagnostic behaviour. For example, anaphylaxis was recognised early in the vaccination campaigns as a potential risk, and mitigation strategies, e.g., 15-minute observation period post-vaccination, were implemented promptly. Such cases may have been managed on-site and not recorded in routine healthcare data. Similarly, myocarditis and pericarditis following mRNA vaccination were identified in Israel and the US before being confirmed in Europe in July 2021.[19, 20, 22, 74, 75] However, no evidence of increased diagnostic activity was observed following the regulatory DHPC, probably because most individuals had already received their second dose by that time and the majority of cases had already occurred. The results from a systematic review showed that issuing a DHPC has differing success rates.[76]

Temporal changes unrelated to vaccination may also affect AESI rates. These include shifts in coding practices (e.g., the introduction of MIS), changes in healthcare access during the COVID-19 pandemic period and evolving risk factors such as SARS-CoV-2 infection itself, which was associated with increased risk for several cardiovascular and coagulation-related AESIs. To explore these effects, two historical comparator cohorts were used, one from the pre-pandemic period (2018 and 2019), with normal healthcare access; and one from the early pandemic period (01 January 2020 to 30 November 2020), during lockdown and wild-type virus circulation. These historical comparator cohorts provided a valuable instrument for comparison with the periods before and during the pandemic period. Forest plots illustrate conveniently the differences and comparison, and interpretation was possible and further described in the results and discussion sections. Additionally, quarterly age-standardised incidence rates in unvaccinated individuals were analysed to assess longitudinal trends.

Limitations on covariates

Information on comorbidity and comedications was based on the nature of the data sources, e.g., capturing only GP prescriptions or dispensing, or also hospital, emergency room or outpatient specialist prescriptions or dispensing, but consistent look-back periods were applied across data sources, i.e., 10 years for comorbidity and 12 months for comedications and healthcare utilisation. Moreover, comparisons between vaccinated individuals were conducted within each data source in the SCRI analyses, and so it is reasonable to expect non-differential misclassification. Demographic information on age and sex was available, but data on ethnicity, social economic status, lifestyle indicators, e.g.,

smoking, BMI, were not complete, but the levels of completeness were not different between vaccinated and unvaccinated individuals.

Confounding

Confounding is inherent in every observational study since exposures are targeted to certain groups by indication. During the COVID-19 pandemic, there were many factors that could influence the probability of exposure and occurrence and detection of events. This probability also varied over time due to vaccination roll out schemes and lock downs. In this study confounding was mitigated by the study design. Several important covariates that could determine exposure were matched on, e.g., age, comorbidity, pregnancy status, as well as calendar time in the main analysis. The comparison of balance, using the absolute standardised differences (ASDs) showed that most covariates were generally well balanced, except for healthcare utilisation. Propensity scores for exposures, which is an appropriate method to control for confounding in comparative analyses of low numbers of events were calculated. Therefore, IPTW-adjusted effect estimates for all AESIs were presented. However, not all potential confounders were available in some databases, which may have resulted in residual confounding. Hence, self-controlled risk interval (SCRI) analyses were also performed, where individuals acted as their own controls, and thus, automatically controlling for both measured and unmeasured time-invariant confounders to assess residual confounding. Since it was not possible to rule out that the SCRI may have suffered from time varying confounding within a person, such as COVID-19, direct effect estimates were obtained, since sensitivity analyses for comparison with the results from the main analyses were also performed. Since the pooled adjusted HRs from these sensitivity analyses were generally similar to the pooled adjusted HRs from the main analyses, it would seem that residual confounding, if any, was minimal. For the pregnancy outcomes SCRI could not be conducted, nor did we estimate direct effects, this may have caused residual confounding by COVID-19 for preterm birth and FGR.

Censoring and selection bias

A key limitation of the comparison between the Pfizer–BioNTech COVID-19 vaccine cohort and concurrent unvaccinated cohorts is the potential for selection bias, particularly due to differential loss to follow-up, also known as informative censoring. This type of bias may arise when censoring is influenced by exposure and shares common causes with the outcome. In this study, participants were censored when they deviated from the treatment strategy defined at baseline.

In the vaccinated cohort, censoring due to receipt of a non–Pfizer–BioNTech COVID-19 vaccine was relatively infrequent. This form of censoring is not expected to have introduced substantial bias. In contrast, censoring the concurrent unvaccinated cohort primarily occurred when individuals received any COVID-19 vaccine. This may be associated with factors such as age and comorbidities, characteristics that are also linked to the risk of AESIs. As a result, younger and healthier individuals may have remained unvaccinated for longer, potentially leading to an overestimation of the relative risk of AESIs in the vaccinated cohorts, despite matching on age and CDC scores. Alternatively, individuals who remained unvaccinated may have been lost to follow-up, and moved to other areas, e.g. students, which would also result in underestimated recording of outcomes.

Notably, differences in follow-up duration between vaccinated and unvaccinated individuals were observed with indications of non-proportional hazards emerging early in the follow-up period (within 45 to 90 days post-baseline). This suggests that selection bias may have influenced the results, particularly for AESIs with longer risk windows, e.g., 180 or 365 days. In contrast, analyses focusing on shorter risk windows are likely to be less affected.

To mitigate this bias, the main analysis employed pairwise censoring, whereby both members of a matched pair were censored if one deviated from the assigned exposure status. However, residual bias

may persist if unvaccinated individuals remained unvaccinated for reasons related to their underlying risk profile or because of loss-to-follow-up.

Comparisons using historical control cohorts are expected to be less susceptible to this form of selection bias, as censoring due to vaccination does not occur. Similarly, the SCRI design is inherently less affected by informative censoring, as comparisons are made within individuals over time.

Limitations of the meta-analysis

The meta-analysis method applied uses the estimates and uncertainty around the hazard ratio (HR) directly in deriving the pooled estimate. This implies that DEAPs without a valid estimate of the HR (due to the presence of zero events or lack of model convergence), do not contribute to the analysis: This is reflected in the pooled event counts, which sum only those event counts from DEAPs with a valid HR estimate. An advantage of this approach is that we can obtain pooled HR estimates without the need for exact event counts per DEAP, which, in the case of small event counts, are masked due to disclosure control. However, a disadvantage of this approach is that DEAPs which record zero events in vaccinated and/or unvaccinated individuals do not contribute to the pooled result, which may in some circumstances lead to an underestimation of the treatment effect.[77] This could result in overestimation of the combined estimates when one or more data sources are excluded from the meta-analyses due to zero events in the risk window, but with events in the control window, or the other way around.

PRAC Rapporteur's Assessment

The various limitations as (comprehensively) discussed by the MAH are acknowledged.

6.1.6. Results

Participants

A total of 18,475,392 individuals received a first dose of Pfizer-BioNTech COVID-19 vaccine during the study period. Among these, 12,398,589 (67.11%) individuals were eligible for matching, and 32.89% individuals were excluded because of receipt of a COVID-19 vaccine other than the Pfizer-BioNTech COVID-19 vaccine before the first Pfizer-BioNTech COVID-19 vaccine or not having had 12 months of continuous enrolment in the data source. A total of 48,439 pregnant women who had received ≥1 dose of the Pfizer-BioNTech COVID-19 vaccine were included in the vaccinated cohort before matching.

Of the 12,398,589 vaccinated individuals eligible for matching, 11,496,929 (92.73%) were matched to unvaccinated individuals. A total of 26,696 of the 48,439 (55.11%) vaccinated, pregnant women could be matched to unvaccinated, pregnant women.

Among the 12,398,589 individuals who received a first dose of the Pfizer-BioNTech COVID-19 vaccine, 84.9% received a second dose of the same vaccine, but with variation between data sources. Overall, 34.8% of those with a first dose, also had a third dose. Only 9% of those with a first dose also received a fourth dose of Pfizer-BioNTech COVID-19 vaccine during the follow-up period and 0.1% a fifth dose.

The median age of the matched vaccinated and unvaccinated cohorts was lowest in Pedianet (10 years) and highest in PHARMO (48 years).

PRAC Rapporteur's Comment

In the full Final Clinical Study report the MAH provided comprehensive details of the results regarding:

- attrition table for the matched vaccinated and unvaccinated cohorts and sub-cohorts, historical matched cohorts and pregnancy cohort by data source and overall
- Cohort follow-up and reasons for censoring for the matched vaccinated and unvaccinated cohorts by data source
- baseline demographics, lifestyle variables and healthcare resource utilisation by data source
- censoring due to prior AESIs

These details are not reproduced in this assessment report.

Overview of Safety

An overview of the number of events, person years (PY) and incidence rates for each of the core AESIs in the matched vaccinated and unvaccinated cohorts, as well propensity score adjusted HRs and RDs by data source are summarised in Table 3 on the following pages. The core AESIs include risks identified in the risk management plan, risks discussed as safety signals by the PRAC, as well as cardiovascular and circulatory AESI and death. Results of interest have been shaded and bolded.

PRAC Rapporteur comment:

The Final Clinical Study Report provides comprehensive detail per outcome and data source as follows:

- Pooled analyses (Forest plots) in the overall, historical cohorts and sensitivity analyses,
- Age-standardised Incidence rates in unvaccinated individuals, standardised to the data source specific population in 2020

Only a selection of these detailed data are reproduced in this assessment report, *i.e.* the AESIs/results of interest which were either requested by PRAC following previous assessment of the 5th interim study report, or those which showed a consistently increased risk (*i.e.* rows shaded in tables 3 and 4 below). For details refer to from **pages 40-58** (of this AR).

Table 3. Summary of Number of Events, Person-Years (PY), and Incidence Rates for Each of the Core AESI in the Vaccinated and Unvaccinated Cohorts and the Adjusted Hazard Ratio (HR) and Rate Difference (RD) by Data Source

	Vaccinated			Unvaccinated				
Adverse event of special interest	**Events (n)**	**PY**	**Incidence rate (95% CI)**	**Events (n)**	**PY**	**Incidence rate (95% CI)**	**Adjusted HR**	**Adjusted RD**
Autoimmune diseases								
Idiopathic thrombocytopenia								
Pedianet	0	1,009	0 (0, 36.56)	0	1,009	NE	NE	NR (NR, NR)
PHARMO	<5	NR	0.18 (0.02, 0.67)	<5	NR	0.37 (0.14, 0.98)	0.40 (0.07, 2.18)	NR (NR, NR)
NHR	23	237,527.10	0.97 (0.61, 1.45)	37	237,463.60	1.56 (0.89, 2.74)	0.62 (0.31, 1.24)	-0.06 (-0.16, 0.05)
EpiChron	<5	NR	0.88 (0.24, 2.25)	8	45,611.70	1.75 (0.62, 4.96)	0.48 (0.11, 2.04)	-0.10 (-0.35, 0.15)
SIDIAP	29	236,132.10	1.23 (0.82, 1.76)	29	236,122.40	1.23 (0.75, 2.01)	0.95 (0.51, 1.77)	-0.01 (-0.09, 0.08)
CPRD Aurum	8	236,940.40	0.34 (0.15, 0.67)	7	236,940.30	0.30 (0.13, 0.68)	1.14 (0.39, 3.35)	0.01 (-0.03, 0.04)
Thrombosis thrombo-cytopenia syndrome								
Pedianet	0	395.60	0 (0, 93.25)	0	395.60	NE	NE	NR (NR, NR)
PHARMO	<5	NR	0.23 (0.01, 1.29)	0	43,189.50	NE	NE	NR (NR, NR)
NHR	11	114,883.60	0.96 (0.48, 1.71)	9	114,878.90	0.78 (0.32, 1.92)	1.22 (0.42, 3.58)	0.01 (-0.03, 0.04)
EpiChron	<5	NR	0.99 (0.12, 3.57)	<5	NR	1.48 (0.48, 4.59)	0.57 (0.09, 3.43)	NR (NR, NR)
SIDIAP	10	102,777.70	0.97 (0.47, 1.79)	8	102,776	0.78 (0.36, 1.69)	1.59 (0.59, 4.26)	0.02 (-0.02, 0.06)
CPRD Aurum	0	97,332.20	0 (0, 0.38)	0	97,332.20	NE	NE	NR (NR, NR)
Myositis								
Pedianet	0	6,654.30	0 (0, 5.54)	0	6,654.30	NE	NE	NR (NR, NR)
PHARMO	<5	NR	0.06 (0.02, 0.16)	<5	NR	0.02 (0, 0.11)	2.86 (0.32, 25.73)	NR (NR, NR)
NHR	156	786,184	1.98 (1.69, 2.32)	129	785,495.40	1.64 (1.28, 2.11)	1.21 (0.90, 1.64)	0.31 (-0.28, 0.90)
EpiChron	7	228,391.20	0.31 (0.12, 0.63)	5	228,391.30	0.22 (0.09, 0.53)	1.23 (0.39, 3.89)	0.05 (-0.21, 0.31)
SIDIAP	177	1,036,534.50	1.71 (1.47, 1.98)	171	1,036,317	1.65 (1.36, 2.01)	0.97 (0.76, 1.25)	0.01 (-0.43, 0.45)
CPRD Aurum	33	1,158,054.10	0.28 (0.20, 0.40)	35	1,158,046.10	0.30 (0.20, 0.45)	0.89 (0.53, 1.50)	-0.01 (-0.17, 0.15)
Cardiovascular system								
Acute cardiovascular injury including microangiopathy								
Pedianet	22	6,609.30	33.29 (20.86, 50.40)	20	6,608.60	30.26 (18.72, 48.92)	1.11 (0.59, 2.11)	3.26 (-16.73, 23.24)
PHARMO	10,759	612,629.90	175.62 (172.32, 178.97)	6,249	614,895.60	101.63 (98.34, 105.03)	**1.55 (1.49, 1.61)**	**61.06 (56.33, 65.79)**
NHR	23,150	805,183	287.51 (283.82, 291.24)	17,115	669,264.10	255.73 (249.95, 261.64)	**1.13 (1.10, 1.16)**	**40.28 (33.09, 47.47)**
EpiChron	2,420	224,759.20	107.67 (103.42, 112.05)	2,159	224,481.80	96.18 (90.13, 102.63)	1.05 (0.97, 1.13)	7.04 (-0.64, 14.71)
SIDIAP	16,601	1,019,100.80	162.90 (160.43, 165.40)	13,011	989,885.80	131.44 (128.03, 134.94)	**1.27 (1.23, 1.30)**	**40.45 (36.18, 44.72)**
CPRD Aurum	4,350	1,149,560.50	37.84 (36.72, 38.98)	3,557	1,148,967.50	30.96 (29.62, 32.35)	**1.16 (1.10, 1.22)**	**5.92 (4.16, 7.69)**
Arrhythmia								
Pedianet	18	6,618.60	27.20 (16.12, 42.98)	19	6,617.60	28.71 (17.50, 47.10)	0.96 (0.49, 1.90)	-0.93 (-19.98, 18.12)

Table 3. Summary of Number of Events, Person-Years (PY), and Incidence Rates for Each of the Core AESI in the Vaccinated and Unvaccinated Cohorts and the Adjusted Hazard Ratio (HR) and Rate Difference (RD) by Data Source

	Vaccinated			Unvaccinated				
Adverse event of special interest	**Events (n)**	**PY**	**Incidence rate (95% CI)**	**Events (n)**	**PY**	**Incidence rate (95% CI)**	**Adjusted HR**	**Adjusted RD**
PHARMO	8,130	617,811	131.59 (128.75, 134.49)	4,693	619,512	75.75 (72.93, 78.68)	**1.55 (1.48, 1.62)**	**45.11 (40.98, 49.23)**
NHR	18,588	806,420	230.50 (227.20, 233.84)	14,630	699,399.20	209.18 (204.06, 214.43)	**1.10 (1.07, 1.14)**	**27.67 (21.22, 34.13)**
EpiChron	1,848	225,660	81.89 (78.20, 85.71)	1,560	225,499.70	69.18 (64.11, 74.65)	**1.10 (1.01, 1.20)**	**6.26 (-0.39, 12.90)**
SIDIAP	13,475	1,023,160.80	131.70 (129.49, 133.94)	10,601	999,018.10	106.11 (103.06, 109.25)	**1.26 (1.22, 1.30)**	**32.21 (28.36, 36.05)**
CPRD Aurum	2,766	1,153,067.80	23.99 (23.10, 24.90)	2,199	1,152,728.80	19.08 (18.08, 20.13)	**1.18 (1.10, 1.26)**	**4.42 (3.06, 5.79)**
Heart failure								
Pedianet	0	6,654.30	0 (0, 5.54)	0	6,654.30	NE	NE	NR (NR, NR)
PHARMO	1,752	630,623.80	27.78 (26.50, 29.11)	1,203	630,916.60	19.07 (17.64, 20.61)	**1.34 (1.23, 1.47)**	**8.27 (6.32, 10.21)**
NHR	3,892	795,644.50	48.92 (47.39, 50.48)	4,673	763,414.80	61.21 (58.29, 64.28)	0.79 (0.75, 0.84)	-12.07 (-15.76, -8.39)
EpiChron	886	227,405.60	38.96 (36.44, 41.61)	972	227,145.30	42.79 (38.71, 47.30)	0.86 (0.76, 0.97)	-5.31 (-10.43, -0.18)
SIDIAP	5,124	1,032,288.90	49.64 (48.29, 51.02)	4,366	1,022,305.90	42.71 (40.73, 44.78)	**1.31 (1.24, 1.38)**	**14.82 (12.41, 17.24)**
CPRD Aurum	710	1,156,913.60	6.14 (5.69, 6.61)	787	1,156,636.50	6.80 (6.19, 7.48)	0.86 (0.76, 0.97)	-0.47 (-1.24, 0.30)
Stress cardiomyopathy								
Pedianet	0	6,654.30	0 (0, 5.54)	0	6,654.30	NE	NE	NR (NR, NR)
PHARMO	8	633,498.20	0.13 (0.05, 0.25)	8	633,500.70	0.13 (0.05, 0.32)	0.97 (0.30, 3.14)	< 0.01 (-0.14, 0.13)
NHR	<5	NR	0.05 (0.01, 0.13)	<5	NR	0.05 (0.01, 0.24)	0.99 (0.16, 6.20)	0.02 (-0.04, 0.08)
EpiChron	6	228,394.70	0.26 (0.10, 0.57)	6	228,393.90	0.26 (0.09, 0.74)	0.90 (0.24, 3.33)	-0.06 (-0.36, 0.24)
SIDIAP	44	1,036,706.40	0.42 (0.31, 0.57)	39	1,036,590.80	0.38 (0.23, 0.63)	1.19 (0.67, 2.13)	0.06 (-0.19, 0.31)
CPRD Aurum	9	1,158,129.40	0.08 (0.04, 0.15)	<5	NR	0.03 (0.01, 0.08)	3 (0.81, 11.15)	0.05 (-0.01, 0.11)
Coronary artery disease								
Pedianet	0	6,654.30	0 (0, 5.54)	0	6,654.30	NE	NE	NR (NR, NR)
PHARMO	2,050	629,441.20	32.57 (31.17, 34.01)	1,281	629,877.20	20.34 (18.88, 21.91)	**1.48 (1.35, 1.61)**	**10.47 (8.44, 12.51)**
NHR	5,672	801,645.80	70.75 (68.92, 72.62)	5,048	751,073.30	67.21 (64.22, 70.34)	1.06 (1, 1.11)	5.79 (2.07, 9.52)
EpiChron	323	227,915.30	14.17 (12.67, 15.80)	382	227,825.70	16.77 (14.27, 19.70)	0.81 (0.66, 0.98)	-0.99 (-3.96, 1.97)
SIDIAP	2,106	1,034,981.60	20.35 (19.49, 21.24)	1,717	1,031,304.40	16.65 (15.44, 17.95)	**1.25 (1.14, 1.36)**	**4.66 (3.14, 6.17)**
CPRD Aurum	953	1,156,054.60	8.24 (7.73, 8.78)	772	1,155,917.10	6.68 (6, 7.44)	**1.19 (1.05, 1.34)**	**0.90 (0.05, 1.75)**
Myocarditis (1–21 days)								
Pedianet	0	538.60	0 (0, 68.49)	0	538.60	NE	NE	NR (NR, NR)
PHARMO	12	58,621.60	2.05 (1.06, 3.58)	8	58,621.80	1.36 (0.68, 2.73)	**1.29 (0.52, 3.20)**	**0.03 (-0.06, 0.11)**
NHR	17	148,726.70	1.14 (0.67, 1.83)	19	148,712.50	1.28 (0.73, 2.23)	0.89 (0.43, 1.86)	-0.01 (-0.06, 0.05)
EpiChron	<5	NR	1.13 (0.23, 3.31)	<5	NR	0.38 (0.05, 2.68)	**2.79 (0.29, 26.88)**	**NR (NR, NR)**
SIDIAP	9	136,030	0.66 (0.30, 1.26)	7	136,028.90	0.51 (0.25, 1.08)	**1.31 (0.48, 3.54)**	**0.01 (-0.02, 0.05)**
CPRD Aurum	12	131,251.20	0.91 (0.47, 1.60)	<5	NR	0.30 (0.11, 0.81)	**2.89 (0.92, 9.02)**	**0.03 (< 0.01, 0.07)**
Pericarditis (1–21 days)								
Pedianet	<5	NR	18.55 (0.47, 103.38)	0	539	NE	NE	NR (NR, NR)
PHARMO	<5	NR	0.34 (0.04, 1.23)	0	58,635	NE	NE	NR (NR, NR)

Table 3. Summary of Number of Events, Person-Years (PY), and Incidence Rates for Each of the Core AESI in the Vaccinated and Unvaccinated Cohorts and the Adjusted Hazard Ratio (HR) and Rate Difference (RD) by Data Source

	Vaccinated			Unvaccinated				
Adverse event of special interest	**Events (n)**	**PY**	**Incidence rate (95% CI)**	**Events (n)**	**PY**	**Incidence rate (95% CI)**	**Adjusted HR**	**Adjusted RD**
NHR	55	148,660.10	3.70 (2.79, 4.82)	36	148,631	2.42 (1.60, 3.67)	**1.52 (0.93, 2.48)**	**0.08 (< 0.01, 0.16)**
EpiChron	7	26,471.40	2.64 (1.06, 5.45)	8	26,471.30	3.02 (1.07, 8.55)	0.89 (0.24, 3.21)	-0.07 (-0.29, 0.15)
SIDIAP	46	135,949.30	3.38 (2.48, 4.51)	32	135,943.40	2.35 (1.48, 3.75)	**1.44 (0.81, 2.54)**	**0.06 (-0.03, 0.15)**
CPRD Aurum	23	131,235.70	1.75 (1.11, 2.63)	13	131,235.80	0.99 (0.51, 1.91)	**1.62 (0.74, 3.52)**	**0.04 (-0.02, 0.10)**
Myocarditis or pericarditis (1–21 days)								
Pedianet	<5	NR	18.57 (0.47, 103.49)	0	538.40	NE	NE	NR (NR, NR)
PHARMO	14	58,619.80	2.39 (1.31, 4.01)	8	58,620	1.36 (0.68, 2.73)	**1.53 (0.64, 3.68)**	**0.04 (-0.04, 0.13)**
NHR	70	148,624.10	4.71 (3.67, 5.95)	49	148,583.30	3.30 (2.31, 4.71)	**1.42 (0.93, 2.18)**	**0.09 (-0.01, 0.18)**
EpiChron	10	26,470.10	3.78 (1.81, 6.95)	9	26,470.10	3.40 (1.32, 8.79)	1.11 (0.36, 3.48)	-0.02 (-0.26, 0.22)
SIDIAP	53	135,936.20	3.90 (2.92, 5.10)	38	135,929.70	2.80 (1.85, 4.22)	**1.41 (0.84, 2.34)**	**0.07 (-0.02, 0.17)**
CPRD Aurum	34	131,224.60	2.59 (1.79, 3.62)	16	131,225.10	1.22 (0.69, 2.17)	**1.99 (1.02, 3.91)**	**0.07 (0.01, 0.14)**
Circulatory system								
Coagulation disorders: thromboembolism								
Pedianet	0	699.50	0 (0, 52.74)	0	699.50	NE	NE	NR (NR, NR)
PHARMO	269	75,418.10	35.67 (31.53, 40.19)	245	75,418.30	32.49 (28.11, 37.54)	0.99 (0.82, 1.19)	-0.06 (-0.56, 0.44)
NHR	1,178	179,265.20	65.71 (62.01, 69.58)	1,306	177,862.30	73.43 (68.28, 78.96)	0.89 (0.81, 0.98)	-0.58 (-1.09, -0.06)
EpiChron	198	32,849.80	60.27 (52.17, 69.28)	252	32,844.90	76.72 (64.82, 90.82)	0.76 (0.61, 0.94)	-1.56 (-2.90, -0.22)
SIDIAP	818	169,821.90	48.17 (44.92, 51.59)	1,069	169,509.70	63.06 (58.21, 68.32)	0.82 (0.74, 0.91)	-0.77 (-1.25, -0.30)
CPRD Aurum	265	167,818.60	15.79 (13.95, 17.81)	326	167,813.50	19.43 (17.06, 22.12)	0.77 (0.64, 0.91)	-0.35 (-0.59, -0.11)
Single organ cutaneous vasculitis								
Pedianet	0	700.50	0 (0, 52.66)	0	700.50	NE	NE	NR (NR, NR)
PHARMO	<5	NR	0.13 (0, 0.73)	<5	NR	0.40 (0.13, 1.23)	0.40 (0.04, 3.83)	NR (NR, NR)
NHR	16	182,763.10	0.88 (0.50, 1.42)	15	182,744.50	0.82 (0.38, 1.78)	1.06 (0.42, 2.64)	0.01 (-0.05, 0.07)
EpiChron	<5	NR	0.60 (0.07, 2.17)	0	33,217.60	NE	NE	NR (NR, NR)
SIDIAP	<5	NR	0.17 (0.04, 0.51)	<5	NR	0.17 (0.06, 0.54)	1.13 (0.22, 5.69)	< 0.01 (-0.02, 0.03)
CPRD Aurum	<5	NR	0.06 (0, 0.33)	<5	NR	0.24 (0.09, 0.63)	0.21 (0.02, 1.92)	NR (NR, NR)
Cerebral venous sinus thrombosis								
Pedianet	0	700.50	0 (0, 52.66)	0	700.50	NE	NE	NR (NR, NR)
PHARMO	<5	NR	0.13 (0, 0.73)	<5	NR	0.40 (0.06, 2.81)	0.32 (0.02, 5.11)	NR (NR, NR)
NHR	8	182,791	0.44 (0.19, 0.86)	<5	NR	0.05 (0.01, 0.39)	8.01 (1, 64.03)	0 (0, NR)
EpiChron	<5	NR	0.30 (0.01, 1.68)	0	33,217.10	NE	NE	NR (NR, NR)
SIDIAP	<5	NR	0.12 (0.01, 0.42)	7	171,801.50	0.41 (0.16, 1.03)	0.32 (0.06, 1.75)	NR (NR, NR)
CPRD Aurum	<5	NR	0.12 (0.01, 0.43)	5	168,407.80	0.30 (0.12, 0.71)	0.39 (0.07, 1.99)	0 (0, NR)
Hepato-gastrointestinal and renal system								

Table 3. Summary of Number of Events, Person-Years (PY), and Incidence Rates for Each of the Core AESI in the Vaccinated and Unvaccinated Cohorts and the Adjusted Hazard Ratio (HR) and Rate Difference (RD) by Data Source

	Vaccinated			Unvaccinated				
Adverse event of special interest	**Events (n)**	**PY**	**Incidence rate (95% CI)**	**Events (n)**	**PY**	**Incidence rate (95% CI)**	**Adjusted HR**	**Adjusted RD**
Glomerulonephritis								
Pedianet	0	3,696.40	0 (0, 9.98)	0	3,696.40	NE	NE	NR (NR, NR)
PHARMO	40	382,678.90	1.05 (0.75, 1.42)	53	382,676.80	1.38 (0.94, 2.04)	0.66 (0.39, 1.12)	-0.29 (-0.67, 0.08)
NHR	92	526,171.70	1.75 (1.41, 2.14)	109	525,586.70	2.07 (1.57, 2.75)	0.85 (0.60, 1.21)	-0.18 (-0.57, 0.20)
EpiChron	18	140,087.90	1.28 (0.76, 2.03)	31	140,080.50	2.21 (1.32, 3.71)	0.55 (0.27, 1.10)	0.07 (-0.33, 0.48)
SIDIAP	163	693,708.70	2.35 (2, 2.74)	154	693,439.10	2.22 (1.77, 2.79)	1.16 (0.88, 1.52)	0.20 (-0.09, 0.49)
CPRD Aurum	62	734,439.10	0.84 (0.65, 1.08)	47	734,438.30	0.64 (0.45, 0.90)	1.26 (0.83, 1.92)	0.07 (-0.09, 0.22)
Skin and mucous membrane bone and joints								
Erythema multiforme								
Pedianet	0	1,008.80	0 (0, 36.57)	0	1,008.80	NE	NE	NR (NR, NR)
PHARMO	<5	NR	0.37 (0.10, 0.94)	<5	NR	0.28 (0.09, 0.86)	1.44 (0.32, 6.46)	0.02 (-0.03, 0.07)
NHR	<5	NR	0.13 (0.03, 0.37)	9	237,590.40	0.38 (0.16, 0.88)	0.33 (0.08, 1.37)	-0.03 (-0.08, 0.01)
EpiChron	<5	NR	0.66 (0.14, 1.92)	<5	NR	0.22 (0.03, 1.56)	2.87 (0.29, 28.09)	NR (NR, NR)
SIDIAP	17	236,174.10	0.72 (0.42, 1.15)	12	236,166.80	0.51 (0.24, 1.05)	1.34 (0.56, 3.23)	0.01 (-0.05, 0.07)
CPRD Aurum	7	236,948.40	0.30 (0.12, 0.61)	12	236,947.90	0.51 (0.27, 0.93)	0.52 (0.20, 1.38)	-0.03 (-0.07, 0.02)
Reproductive system								
Secondary amenorrhoea								
Pedianet	<5	NR	5.33 (0.65, 19.27)	<5	NR	2.67 (0.38, 18.93)	NA	NA
PHARMO	0	122,666.40	0 (0, 0.30)	0	122,666.40	NE	NE	NR (NR, NR)
NHR	137	155,531.60	8.81 (7.40, 10.41)	132	155,405.80	8.49 (6.63, 10.88)	1.03 (0.77, 1.39)	-0.27 (-1.71, 1.17)
EpiChron	5	45,485.20	1.10 (0.36, 2.57)	5	45,484.50	1.10 (0.46, 2.64)	0.85 (0.25, 2.95)	0.01 (-0.73, 0.75)
SIDIAP	1,812	216,311.50	83.77 (79.96, 87.72)	1,601	215,746.40	74.21 (69.53, 79.20)	1.04 (0.96, 1.13)	2.16 (-1.12, 5.45)
CPRD Aurum	2,382	264,299.30	90.13 (86.54, 93.82)	1,636	264,376.70	61.88 (58.42, 65.55)	1.33 (1.24, 1.43)	9.75 (7.20, 12.30)
Hypermenorrhoea								
Pedianet	<5	NR	8.02 (1.65, 23.43)	<5	NR	10.69 (3.22, 35.51)	NA	NA
PHARMO	1,639	119,566.20	137.08 (130.52, 143.88)	990	119,678.70	82.72 (77.01, 88.86)	**1.46 (1.34, 1.59)**	**21.41 (16.74, 26.09)**
NHR	2,731	149,898.30	182.19 (175.42, 189.15)	2,568	147,543.60	174.05 (165.12, 183.47)	1.05 (0.98, 1.12)	6.72 (0.29, 13.15)
EpiChron	903	43,827.30	206.04 (192.81, 219.92)	531	43,875.60	121.02 (107.83, 135.83)	**1.50 (1.32, 1.72)**	**34.66 (24.51, 44.82)**
SIDIAP	2,906	214,757.80	135.32 (130.44, 140.33)	2,345	213,824.40	109.67 (103.90, 115.76)	**1.13 (1.06, 1.21)**	**9.15 (5.10, 13.20)**
CPRD Aurum	3,622	261,586.80	138.46 (133.99, 143.05)	2,891	261,501.80	110.55 (105.91, 115.40)	**1.18 (1.12, 1.24)**	**11.54 (8.18, 14.91)**
Other								
Anaphylaxis								

Table 3. Summary of Number of Events, Person-Years (PY), and Incidence Rates for Each of the Core AESI in the Vaccinated and Unvaccinated Cohorts and the Adjusted Hazard Ratio (HR) and Rate Difference (RD) by Data Source

	Vaccinated			Unvaccinated				
Adverse event of special interest	**Events (n)**	**PY**	**Incidence rate (95% CI)**	**Events (n)**	**PY**	**Incidence rate (95% CI)**	**Adjusted HR**	**Adjusted RD**
Pedianet	0	28.70	0 (0, 3.67)	0	28.70	NE	NE	NR (NR, NR)
0.01 (0, 0.06)	0.87 (0.05, 13.97)	NR (NR, NR)	0.01 (0, 0.05)	<5	NR			
NHR	63	9,736	0.18 (0.14, 0.23)	<5	NR	0.04 (0.01, 0.14)	**15.54 (5.66, 42.71)**	**NA**
EpiChron	<5	NR	0.04 (0.02, 0.13)	<5	NR	0.04 (0.01, 0.14)	0.97 (0.20, 4.83)	NA
SIDIAP	6	8,796.40	0.02 (0.01, 0.04)	0	8,796.50	NE	NE	NR (NR, NR)
CPRD Aurum	10	7,585.20	0.04 (0.02, 0.07)	6	7,585.20	0.02 (0.01, 0.05)	**1.53 (0.56, 4.23)**	**NA**
Multisystem inflammatory syndrome								
Pedianet	0	1,009	0 (0, 36.56)	0	1,009	NE	NE	NR (NR, NR)
PHARMO	<5	NR	0.18 (0.02, 0.67)	<5	NR	0.09 (0.01, 0.65)	1.77 (0.16, 19.51)	NR (NR, NR)
NHR	185	237,306.80	7.80 (6.71, 9)	229	237,115	9.66 (7.94, 11.75)	0.80 (0.63, 1.02)	-0.20 (-0.46, 0.07)
EpiChron	17	45,602.10	3.73 (2.17, 5.97)	6	45,602.40	1.32 (0.52, 3.31)	2.70 (0.94, 7.74)	0.24 (-0.05, 0.53)
SIDIAP	13	236,184.50	0.55 (0.29, 0.94)	34	236,182	1.44 (0.87, 2.38)	0.48 (0.23, 1.02)	-0.08 (-0.16, 0.01)
CPRD Aurum	<5	NR	0.17 (0.05, 0.43)	<5	NR	0.08 (0.02, 0.34)	2.80 (0.51, 15.38)	0 (0, NR)
Death (any causes)								
Pedianet	<5	NR	1.50 (0.04, 8.37)	0	6,654.80	NE	NE	NR (NR, NR)
PHARMO	3,613	635,840.40	56.82 (54.98, 58.71)	4,897	635,077.60	77.11 (74.12, 80.22)	0.64 (0.61, 0.67)	-20.15 (-23.79, -16.51)
NHR	6,907	794,220.20	86.97 (84.93, 89.04)	14,059	787,968.30	178.42 (173.17, 183.83)	0.48 (0.46, 0.50)	-85.34 (-91.65, -79.02)
EpiChron	1,513	229,849.20	65.83 (62.55, 69.23)	2,472	228,830.50	108.03 (101.13, 115.40)	0.58 (0.53, 0.63)	-35.94 (-43.64, -28.23)
SIDIAP	8,005	1,046,913.60	76.46 (74.80, 78.16)	20,375	1,039,227.90	196.06 (191.42, 200.81)	0.63 (0.61, 0.65)	-41.92 (-46.38, -37.45)
CPRD Aurum	1,714	1,162,095.60	14.75 (14.06, 15.46)	5,570	1,158,683.20	48.07 (46.31, 49.90)	0.29 (0.27, 0.31)	-24.77 (-26.52, -23.02)

From C4591021 Final Study Report, Table 7. "Summary of number of events, person-years (PY), and incidence rates for each of the core AESI in the vaccinated and unvaccinated cohorts and the adjusted hazard ratio (HR) and rate difference (RD) by data source"

NA: not available; NE: not estimated, but bootstrap confidence intervals will be provided in final report; NR: not reportable due to obligation to mask number of events when less than 5.

PRAC Rapporteur's Comment

Detailed discussion of outcomes/AESIs/results of interest which were either requested by PRAC following previous assessment of the 5th interim study report, or those which showed a consistently increased risk is provided below.

Main results

This final report is based on healthcare data from 7 population-based sources across 5 European countries: Pedianet and HSD (Italy), PHARMO (Netherlands), NHR (Norway), EpiChron and SIDIAP (Spain), and CPRD Aurum (United Kingdom). Data from HSD (Italy) were included exclusively in the self-controlled risk interval (SCRI) analysis due to concerns about exposure misclassification linked to the registration practices of the Pfizer–BioNTech COVID-19 vaccine in GP settings within the HSD coverage area, which could have resulted in vaccinated individuals being classified as unvaccinated.

The observation period encompassed the timeframe during which individuals could receive up to 5 doses of the Pfizer–BioNTech COVID-19 vaccine, following the implementation of extended booster campaigns in many countries from late summer 2022. During this period, only the original Comirnaty formulation was available, and paediatric doses had been authorised.

Incidence rates and hazard ratios for AESIs

To inspect temporal trends in incidence, age-standardised incidence rates in unvaccinated individuals were estimated by quarter. This was performed using the 2018-2019 and 2020 historical controls and the unvaccinated individuals in the matched cohort for 2021-2022. Unvaccinated individuals in 2021 and 2022 were censored when vaccinated, which reduced the size of the cohort for 2022. This is reflected in rapid rate reductions and spikes. For NHR and EpiChron, historical controls were biased since data on death were not available in NHR, for 2018/2019 and EpiChron excluded all persons who were not alive on 01 January 2020. The rates for these data sources only started at the start of the study period (vaccination roll out) in December 2020. All rates were standardised to the age distribution within the data source on 01 January 2020, to allow for cross-period comparisons. However, since the standard distribution for weighting is specific to the data source, age differences between data sources could confound results in comparisons between data sources. Comparison of the incidence rates between vaccinated and unvaccinated individuals showed that:

1. Most AESIs were very rare or rare. Rare: may affect up to 1 in 1,000 people; Very rare: may affect up to 1 in 10,000 people.
2. Many incidence rates had seasonal patterns since (viral) infections were important risk factors, underlining the importance of matching on calendar time, which was done in the matched cohort;
3. Incidence rates of many serious AESIs were higher in NHR, EpiChron, and SIDIAP since these data sources were linked to hospital discharge databases, and emergency room visits (not in SIDIAP); rates were lower in GP-based data sources (especially PHARMO), where information from the hospital was not available for the whole period that information from the GP data source was available;
4. Incidence rates of several events changed during the COVID-19 pandemic (Q2 2020 and onwards) when healthcare access was restricted.

Within the main matched cohort, IRs were estimated in vaccinated and unvaccinated individuals and adjusted for inverse probability of treatment weighting (IPTW), and excess incidence and excess risk estimates could be obtained. Many sensitivity and subgroup analyses were conducted to support interpretation of the matched cohort results and to further examine subgroups of interest. A summary of the core AESIs, in addition to other AESIs for the main comparisons with adjusted hazard ratios (HRs) pooled across data sources and the results from the SCRI analyses are provided in Table 4. Together these results answer the primary study objectives. Results of interest have been shaded and bolded.

Table 4. Summary of Pooled Analyses by AESI in the Matched Cohort and SCRI Analyses

	Matched cohort analyses					SCRI analyses			
	Risk window (days)	**Events vac n**	**Events unvac n**	**Adjusted HR (95% CI)**	**I^2 (95% CI)**	**Events in risk window**	**Events in control window**	**IRR (95% CI)**	**I^2 (95% CI)**
Identified risks in risk management plan									
Myocarditis	21	<55	<44	**1.32 (0.74-2.34)**	0 (0-0.79)	ND	ND	ND	ND
	7	<26	<24	1.14 (0.40-3.28)	0 (0-0.85)	ND	ND	ND	ND
	14	<44	<38	1.20 (0.61-2.40)	0 (0-0.79)	ND	ND	ND	ND
Myocarditis or pericarditis	21	181	120	**1.49 (1.22-1.81)**	0 (0-0.79)	<586	<426	**1.15 (0.99-134)**	0 (0-0.71)
	7	75	57	**1.32 (0.91-1.90)**	0 (0-0.79)	<240	<172	**1.39 (1.01-1.93)**	0.24 (0-0.68)
	14	137	100	**1.36 (1.13-1.64)**	0 (0-0.79)	<416	<306	**1.19 (1.06-1.35)**	0 (0-0.75)
Pericarditis	21	131	89	**1.46 (1.13-1.87)**	0 (0-0.85)	ND	ND	ND	ND
	7	<55	<43	**1.27 (0.97-1.64)**	0 (0-0.85)	ND	ND	ND	ND
	14	99	75	**1.31 (0.90-1.90)**	0 (0-0.85)	ND	ND	ND	ND
Anaphylaxis	1	<83	<21	**2.52 (0.27-23.28)**	0.79 (0.44-0.92)	<130	<296	**7.69 (3.71-15.94)**	0.79 (0.49-0.91)
AESIs identified as signals and discussed by PRAC									
idiopathic thrombocytopenia	42	<70	<86	0.77 (0.50-1.17)	0 (0-0.79)	<272	<225	0.91 (0.76-1.09)	0 (0-0.79)
TTS	15	<26	<22	1.24 (0.44-3.46)	0 (0-0.9)	<71	<58	0.91 (0.60-1.39)	0 (0-0.90)
Glomerulonephritis	180	375	394	0.92 (0.62-1.38)	0.51 (0-0.82)	ND	ND	ND	ND
Erythema multiforme	42	<39	<43	0.87 (0.35-2.14)	0.24 (0-0.69)	ND	ND	ND	ND
Multi inflammatory syndrome	42	<225	<279	1.11 (0.42-2.96)	0.57 (0-0.84)	ND	ND	ND	ND
Hypermenorrhoea	183	11,801	9,325	**1.24 (1.02-1.51)**	0.92 (0.84-0.96)	ND	ND	ND	ND
Secondary amenorrhoea	183	4336	3374	1.14 (0.90-1.44)	0.86 (0.66-0.94)	ND	ND	ND	ND
Myositis	365	<378	<345	1.05 (0.86-1.29)	0 (0-0.79)	ND	ND	ND	ND
AESIs prespecified and discussed in the literature									
Death (all causes)	365	21,752	47,373	0.50 (0.34-0.76)	0.99 (0.99-0.99)	ND	ND	ND	ND
Acute cardiovascular injury	365	57,302	42,111	**1.22 (1.04-1.42)**	0.98 (0.96-0.98)	ND	ND	ND	ND
Arrhythmia	365	44,825	33,702	**1.22 (1.05-1.42)**	0.97 (0.95-0.98)	ND	ND	ND	ND
Coronary artery disease	365	11,104	9,200	1.14 (0.87-1.50)	0.93 (0.87-0.96)	ND	ND	ND	ND
Stress cardiomyopathy	365	<72	<63	1.23 (0.77-1.96)	0 (0-0.79)	ND	ND	ND	ND
Heart failure	365	12,364	12,001	1.01 (0.73-1.38)	0.98 (0.97-0.99)	ND	ND	ND	ND
Other AESI									
Subacute thyroiditis	**365**	**<57**	**<37**	**1.89 (1.20-2.96)**	0 (0-0.85)	ND	ND	ND	ND
Acute aseptic arthritis	42	<3,418	<3,055	1.13 (0.99-1.30)	0.60 (0.02-0.84)	16,235	12,227	0.99 (0.88-1.11)	0.91 (0.83-0.95)
Diabetes mellitus-1	365	1,317	1,219	1.05 (0.89-1.24)	0.26 (0-0.70)	ND	ND	ND	ND
Generalised convulsions	42	1,578	1,488	1.04 (0.09-1.20)	0.11 (0-0.86)	<5,551	<4,228	0.98 (0.89-1.09)	0.60 (0.01-0.84)
Coagulation disorders	28	2,728	3,198	0.85 (0.76-0.95)	0.37 (0-0.76)	10,711	8,602	0.93 (0.88-0.98)	0.51 (0-0.81)
Acute liver injury	365	547	546	1.07 (0.69-1.66)	0.56 (0-0.84)	ND	ND	ND	ND
Acute pancreatitis	365	1,507	1,420	1.05 (0.88-1.25)	0.37 (0-0.77)	ND	ND	ND	ND
Acute kidney injury	365	9,335	10,305	0.92 (0.74-1.16)	0.96 (0.94-0.98)	ND	ND	ND	ND

Table 4. Summary of Pooled Analyses by AESI in the Matched Cohort and SCRI Analyses

	Matched cohort analyses					SCRI analyses			
	Risk window (days)	**Events vac n**	**Events unvac n**	**Adjusted HR (95% CI)**	**I^2 (95% CI)**	**Events in risk window**	**Events in control window**	**IRR (95% CI)**	**I^2 (95% CI)**
Rhabdomyolysis	365	<286	<368	0.77 (0.59-1.01	0 (0-0.79)	ND	ND	ND	ND
Acute disseminated encephalomyelitis	42	NA	NA	NA	NA	<11	<10	1.39 (0.01-318)	0 (NA)
Bell's palsy	42	468	477	0.96 (0.88-1.05)	0 (0-0.79)	<1806	<1444	0.93 (0.83-1.04)	0.24 (0-0.68)
CVST	28	<23	<22	0.74 (0.06-8.83)	0.57 (0-0.86)				
GBS	42	<25	<26	1.05 (0.27-4.13)	0.21 (0-0.88)	<122	<106	0.91 (0.67-1.25)	0 (0-0.79)
Meningoencephalitis	42	<83	100	0.84 (0.55-1.27)	0 (0-0.79)	338	302	0.82 (0.70-0.96)	0 (0-0.79)
Transverse myelitis	42	<10	<10	1.57 (0.16-15.62)	0 (NA)	<29	<30	0.83 (0.51-1.37)	0 (0-0.85)
Narcolepsy	42	<30	37	0.54 (0.09-3.31)	0.37 (0-0.80)	<81	<71	0.76 (0.38-1.53)	0.27 (0-0.73)
ARDS	365	282	1280	0.27 (0.11-0.63)	0.83 (0.60-0.92)	ND	ND	ND	ND
Chilblain like lesions	42	<187	<206	0.81 (0.45-1.44)	0.60 (0-0.85)	ND	ND	ND	ND
SOCV	28	<31	<30	0.82 (0.30-2.25)	0 (0-0.85)	<94	<72	1.01 (0.85-1.19)	0 (0-0.85)

From C4591021 Final Study Report, Table 10. “Summary of pooled analyses by AESI in the matched cohort and SCRI analyses”
ND: not done; Sudden death could not be accurately assessed.

PRAC Rapporteur comment:

Detailed data below are only reproduced in this assessment report for the outcomes/AESIs/results of interest which were either requested by PRAC following previous assessment of the 5th interim study report, or those which showed a consistently increased risk.

Anaphylaxis

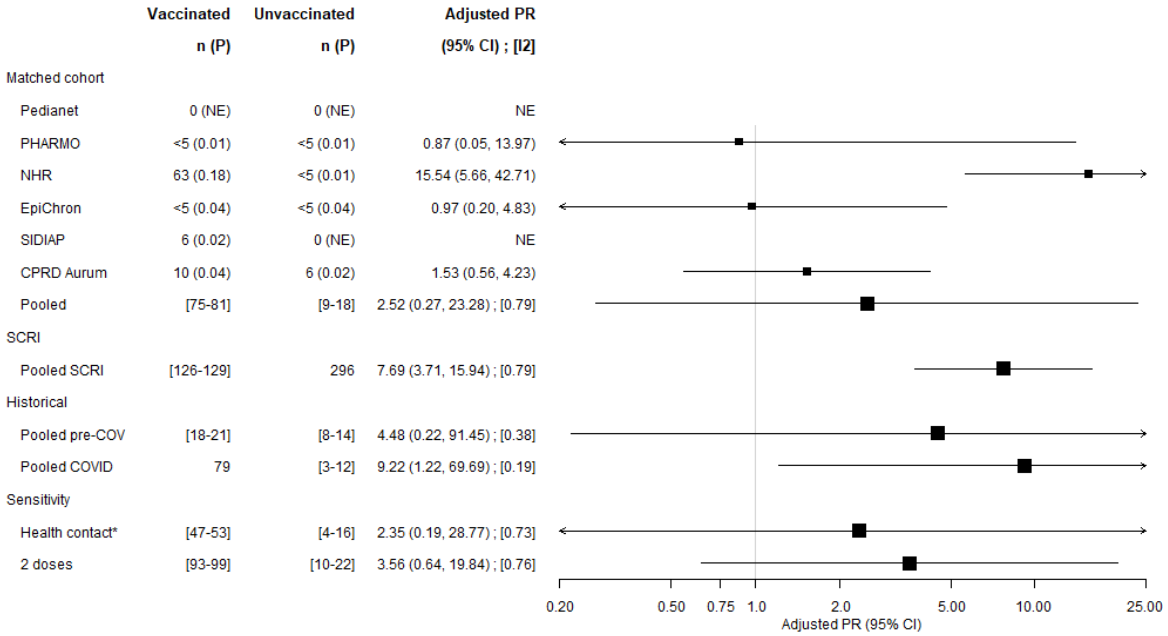
Prevalence rates of anaphylaxis were very low but were highest in the vaccinated cohort in NHR (0.18/10,000 PY) (Table 4, above).

The propensity score adjusted PRs for anaphylaxis in the primary analysis were elevated in NHR and CPRD Aurum but with wide 95% CIs (Table 4, above). The results of the SCRI and historical cohort analyses showed substantial heterogeneity between data sources, and therefore the pooled estimates should be interpreted with caution (Figure 3). The results for the other sensitivity analyses in the matched cohort did not differ from the result for the pooled main analysis, but also should be interpreted with caution, since there was substantial heterogeneity, and mostly based on NHR data.

There were more events identified in the SCRI analyses, which was conducted in the unmatched vaccinated cohort during post-vaccination risk and control windows, and these analyses showed an elevated pooled IRR with large heterogeneity but consistent elevations of rates. (Standalone section 15 [not reproduced in this AR]): in CPRD IRR was 5.09, 95% CI 2.60-9.99, in EpiChron 5.38, (95% CI: 2.48-11.66), in PHARMO: 3.06, (95% CI: 0.39-24.13), and in SIDIAP IRR=7.66, (95% CI: 3.88-15.13).

The results for the stratified analyses in the matched cohort by data source (Appendix Figure 1 [not reproduced in this AR]) show that almost all cases in NHR occurred in females, 62 out of the 63 cases occurred in individuals who were frail or had comorbidities, who had been targeted first with COVID-19 vaccination. The pooled adjusted PRs for anaphylaxis were higher in immunocompromised individuals: PR= 10.44 (95% CI: 0.01-7759.39), with very wide confidence intervals and heterogeneity.

Figure 3. Pooled analyses for anaphylaxis in the overall, SCRI, and historical cohorts and sensitivity analyses



NE: not estimable; *no healthcare contact in 7 days prior to time zero; two doses within 6 weeks

MAH discussion

Anaphylaxis within one day of vaccination was primarily associated with the Pfizer-BioNTech vaccine in NHR, where the adjusted hazard ratio was 15.54 (95% CI: 5.66–42.71), mostly in females and the subgroup of individuals with comorbidities. These cases likely occurred early in the vaccination rollout, consistent with CDC reports from December 2020.[25] Interim guidance was issued by public health agencies, including screening, observation periods, and immediate treatment protocols.[26] The CDC reported about 4.8 confirmed anaphylaxis cases per million Pfizer doses, nearly all occurring within 30 minutes and predominantly in women.[25] Findings in NHR aligned with these early case series. Although the positive predictive value for anaphylaxis was low across data sources, including NHR, confidence intervals overlapped between vaccinated and unvaccinated individuals in NHR, which means the effect would be to potentially attenuate the observed HR.

PRAC Rapporteur comment:

Anaphylaxis is already labelled a adverse reaction. No new safety information was identified.

Myocarditis, pericarditis and myocarditis or pericarditis (21 days)

Age standardised incidence rates of myocarditis, pericarditis, and myocarditis or pericarditis in unvaccinated individuals are presented in Figure 4. A seasonal pattern was observed, except in 2020/2021. The rates varied between data sources, based on the type of healthcare setting in which events could be identified and the age of the cohorts (lowest in Pedianet and CPRD Aurum). In PHARMO, the International Classification of Primary Care (ICPC) codes in the GP data source could not distinguish between myocarditis and pericarditis, which is why the incidence of myocarditis was relatively high in this data source and pericarditis low. Pericarditis could be identified in hospital data, but these data were not available for the whole population, which is why the risk for pericarditis in PHARMO was relatively low. The cumulative incidence curves for these outcomes showed an increased cumulative incidence in the vaccinated cohorts (Appendix Figure 2, Appendix Figure 3, Appendix Figure 4 [not reproduced in this AR]).

The pooled adjusted HR in the main matched cohort analysis showed a slightly elevated risk for myocarditis alone within 21 days of time zero (Figure 5). The pooled adjusted HRs for the comparisons with the historical cohorts showed an increased risk, which was higher in the comparisons with the pre-COVID-19 historical cohorts than with the COVID-19 period historical cohorts. When the cohort was restricted to individuals with at least two vaccine doses, the pooled HRs for risk of myocarditis increased as this analysis also included events occurring with 21 days of dose 2. The stratified analyses of the matched cohort analysis showed that the HR for myocarditis within 1-21 days of time zero for the matched vaccinated and unvaccinated cohorts were consistently higher in males (pooled adjusted HR: 1.80 95% CI: 0.88-3.66) than females (0.83, 95% CI: 0.28-2.49). (*Post hoc* pooling analysis). The HRs varied by age in individual data sources but not so much in the pooled HR. The direct effect analysis of the vaccine resulted in a pooled HR of 1.43, 95% CI: 0.67-3.07. No adjusted HRs were available for the pregnant women sub-cohort.

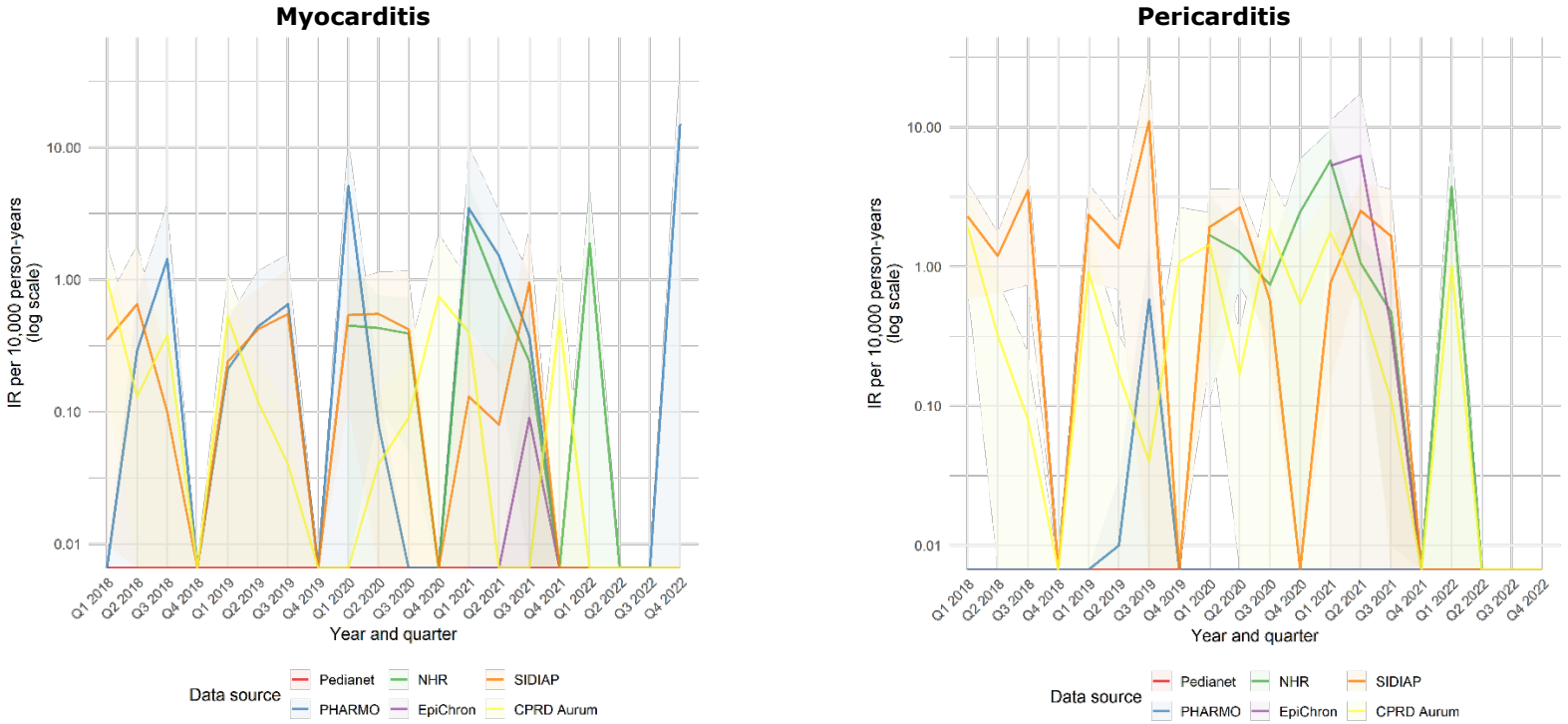
The pooled adjusted HR for pericarditis in the main matched cohort within 21 days of time zero showed an elevation of risk (Figure 5). When the analyses were restricted to individuals with at least two doses, the pooled HR for risk of pericarditis within 21 days after dose 1 increased from 1.46 (95% CI: 1.13-1.87) to 1.57 (95% CI: 1.48-1.66), showing the effect of dose 2. Restriction of the cohort to those without healthcare contact in the 7 days before time zero also resulted in an increased HR (2.19, 95% CI: 1.71-2.80). The subgroup analyses within 21 days after time zero are shown in Appendix Figure 6 [not reproduced in this AR]. The patterns observed in the subgroups were heterogeneous across data sources. Pooled adjusted HRs in these subgroup analyses showed a higher HR in males

(HR=1.87, 95% CI: 0.99-3.53) than females (HR=1.02, 95% CI 0.57-1.81) (*Post hoc* pooling analysis). The pooled HR was highest in the age category 50-59 years (HR=2.44, 95% CI 1.10-5.43) and elevated in both males and females. The direct effect analysis of the vaccine resulted in a pooled HR of 1.51 (95% CI: 1.08-2.10) of pericarditis within 21 days. Estimates could not be produced for pregnant women.

The pooled adjusted HR for *myocarditis or pericarditis* in the main matched cohort within 21 days of time zero showed an elevation of risk (HR=1.49, 95% CI: 1.22-1.81) (Figure 5). When the analyses were restricted to individuals with at least two doses, the pooled HR for risk of myocarditis or pericarditis within 21 days after dose 1 increased from 1.49 to 1.67 showing the effect of dose 2. Restriction of the cohort to those without healthcare contact in the 7 days before time zero also resulted in an increased HR (1.86, 95% CI: 1.42-2.43). Comparison with 2018/2019 historic controls showed an increase in HR, whereas comparisons with controls in the COVID-19 period, showed a decrease in HR. The direct effect analysis of the vaccine resulted in a pooled HR of 1.59 (95% CI: 1.09-2.30) (*Post hoc* pooling analysis). The subgroup analyses within 21 days after time zero for myocarditis or pericarditis are shown in Appendix Figure 7 [not reproduced in this AR]. The patterns observed in the subgroups were heterogeneous across data sources. Pooled adjusted HRs in these subgroup analyses showed a higher HR in males HR=1.99 (95% CI: 1.25-3.15) than females HR=0.96 (95% CI: 0.58-1.58). Subgroup analyses showed elevated risks in younger males, with a pooled HR of 2.32 (95% CI: 1.74–3.10) in those aged 18–29 and 2.37 (95% CI: 0.31–18.14) in those aged 30–39. (*Post hoc* pooling analysis). Estimates could not be produced for pregnant women.

Pooled analysis for myocarditis or pericarditis using the self-controlled risk interval (SCRI) design showed an IRR of 2.05 (95% CI: 0.8–5.27) in males aged 18–29 years for myocarditis or pericarditis, and a pooled IRR of 1.18 (95% CI: 0.94–1.46) in females aged 18–29 years (*Post hoc* pooling analysis).

Figure 4. Incidence rates by quarter from Q1 2018 to Q4 2022 for myocarditis, pericarditis and myocarditis, and pericarditis in unvaccinated individuals, standardised to the age in the data source specific population in 2020, by data sources



Myocarditis or pericarditis

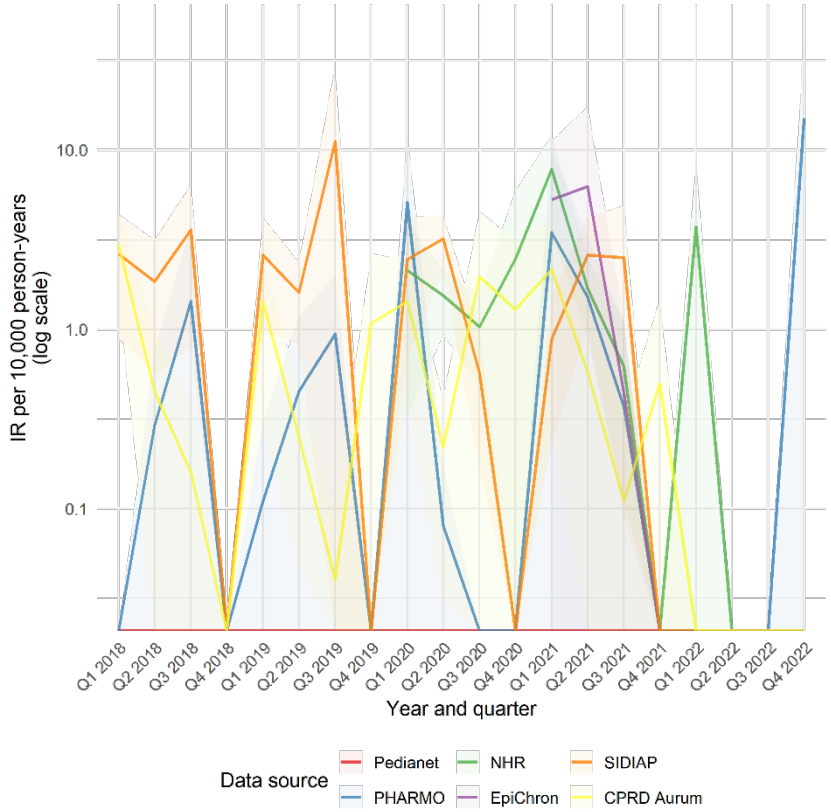


Figure 5. Pooled analyses for myocarditis, pericarditis, and myocarditis or pericarditis (21 days) in the main cohort, historical cohorts and sensitivity analyses

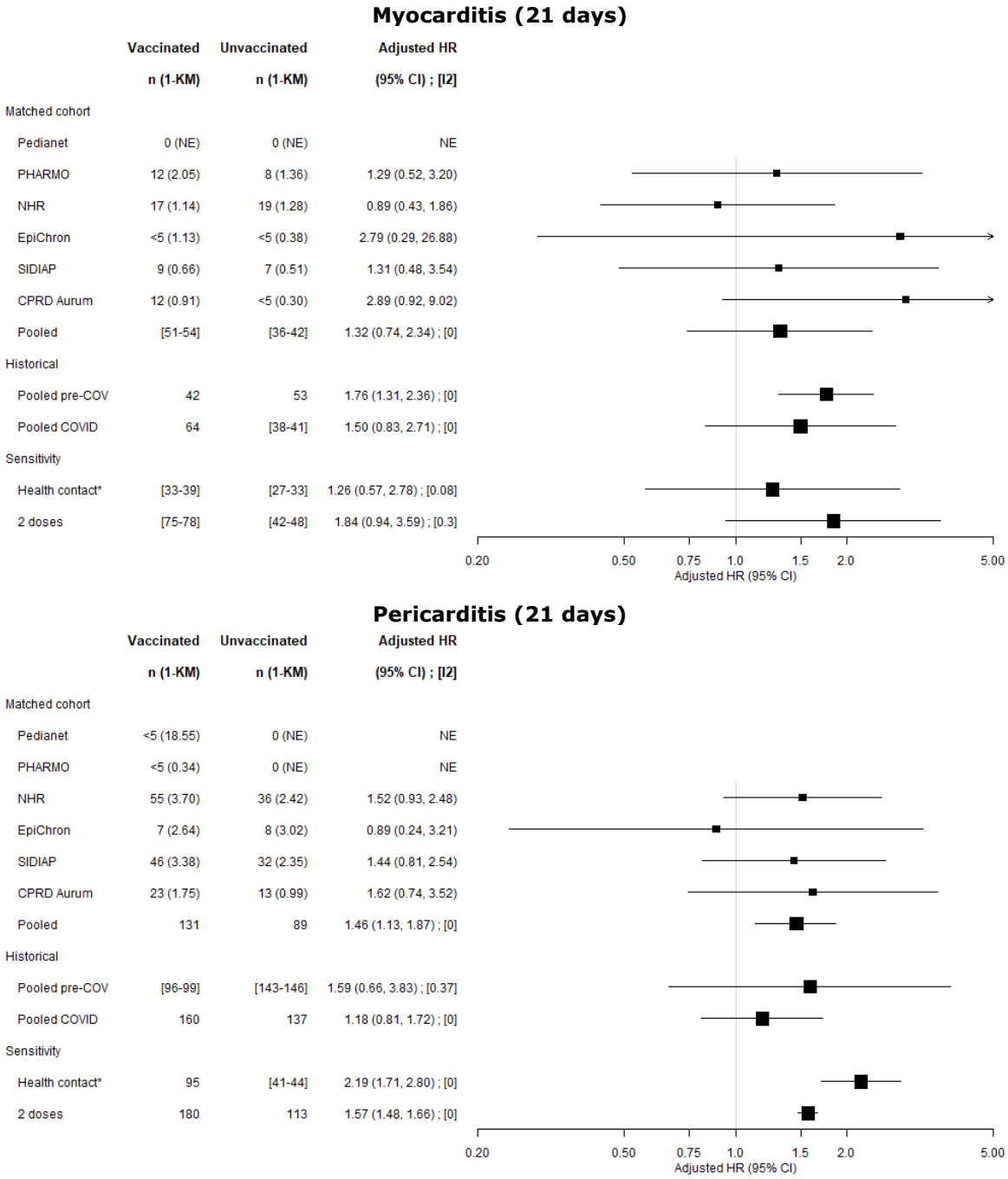
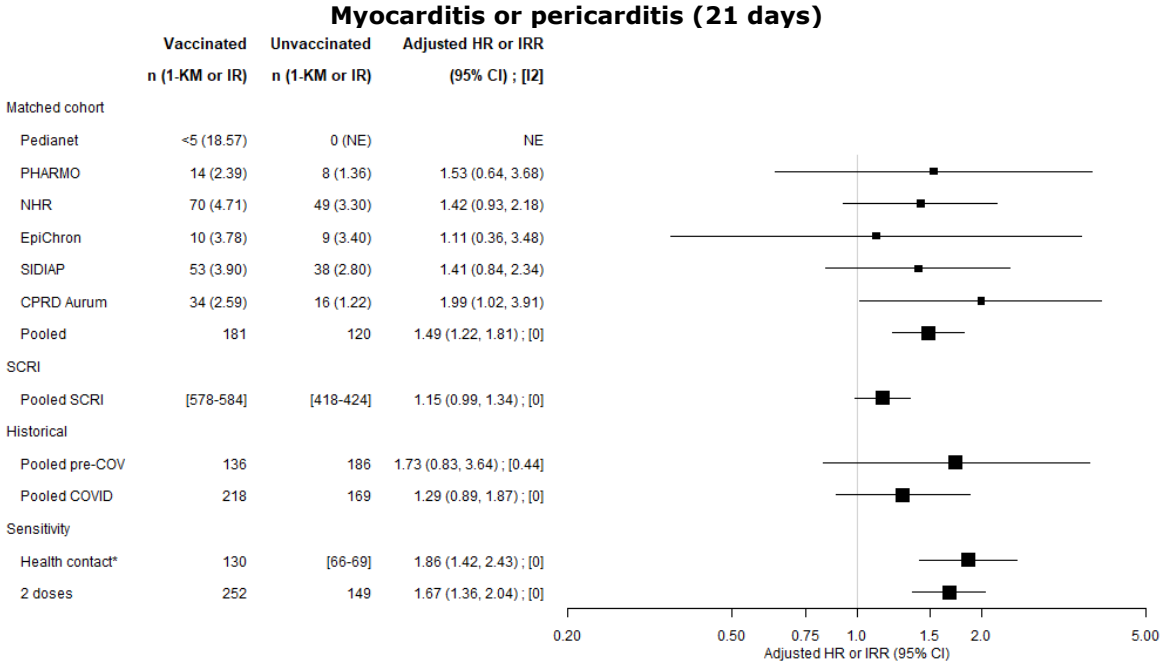


Figure 5. Pooled analyses for myocarditis, pericarditis, and myocarditis or pericarditis (21 days) in the main cohort, historical cohorts and sensitivity analyses



MAH discussion

Results show increased risks for myocarditis and pericarditis, with varying results across risk windows, sensitivity analyses, and subgroup analyses (Figure 5, above).

The overall hazard ratio (HR) for myocarditis and pericarditis was based on the 21-day risk window following the first dose. In individuals who received two doses within six weeks, the pooled adjusted HR increased to 1.67 (95% CI: 1.36–2.04) when considering risk windows after both doses. Subgroup analyses showed elevated risks in younger males, with a pooled HR of 2.32 (95% CI: 1.74–3.10) in those aged 18–29 and 2.37 (95% CI: 0.31–18.14) in those aged 30–39. SCRI analyses supported these findings, showing a pooled incidence rate ratio (IRR) of 2.06 (95% CI: 0.48–8.79) in males aged 18–29 and 1.16 (95% CI: 0.75–1.81) in females of the same age group.

Although the analyses were not dose-specific, these findings are consistent with evidence from the literature, which shows an increased risk, especially in the 7-day period after dose 2, in young males.[19-22] Results from a meta-analysis showed that, compared with unvaccinated groups or unvaccinated time periods, the highest attributable risk of myocarditis or pericarditis was observed after the second dose of the Pfizer-BioNTech COVID-19 vaccine in boys aged 12-17 years (10.18 per 100 000 doses [95% CI: 0.50-19.87]) and in young men aged 18-24 years (attributable risk, 20.02 per 100 000 doses [95% CI: 10.47-29.57]) for the mRNA-1273 vaccine.[23]

The PPV values for myocarditis and pericarditis were below 80% in most data sources and did not differ between vaccinated and unvaccinated cohorts. This means that absolute risks and rates were overestimated, and relative risks were attenuated.[24] The PPV did not differ between the vaccinated and unvaccinated cohorts, which means we can predict the direction. Most of the published studies did not apply case validation and therefore may also have suffered from misclassification.

PRAC Rapporteur comment:

The study showed that the identified risks of myocarditis, and pericarditis were associated and in line with existing evidence for the Pfizer-BioNTech COVID-19 vaccine profile and the literature. Myocarditis and Pericarditis are labeled in the currently approved product information.

Age standardised incidence rates of myocarditis, pericarditis, and myocarditis or pericarditis in unvaccinated individuals (in Figure 4) showed a seasonal pattern, except in 2020/2021.

Overall, a seasonal pattern in incidence rates was observed for many of the evaluated outcomes, probably because (viral) infections were important risk factors, underlining the importance of matching on calendar time, which was done in the matched cohort.

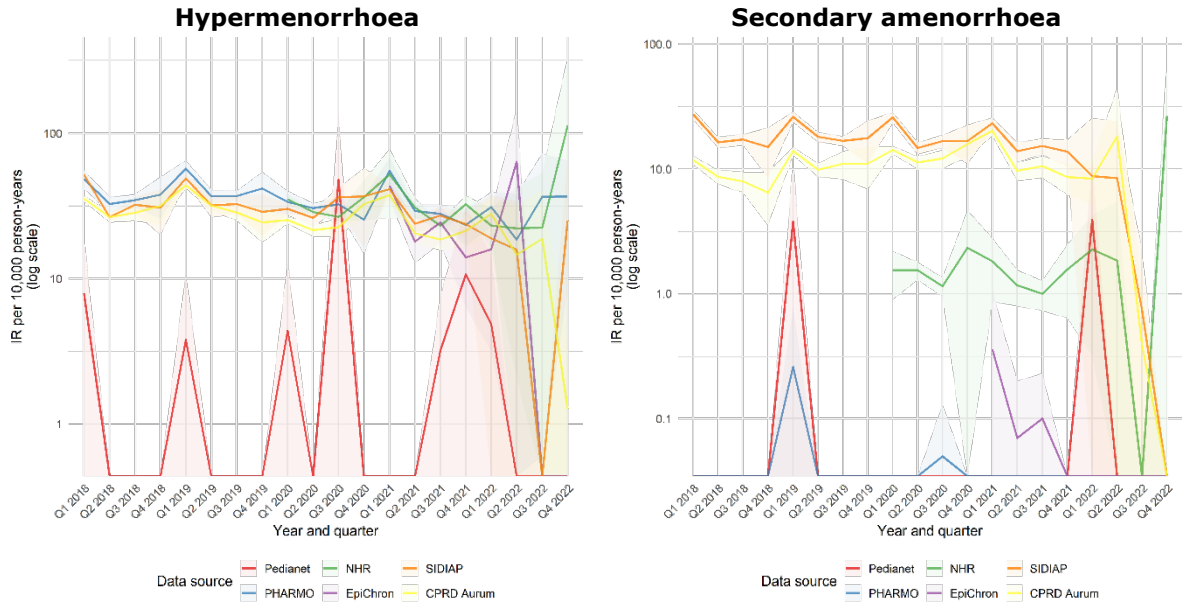
Myocariditis and pericarditis are currently labelled. No new safety information was identified.

Hypermenorrhoea and Secondary amenorrhoea

Previous PRAC request following 5th interim report: *No differences in the adjusted HRs for secondary amenorrhoea and between interim reports 4 and 5 were observed, except in EpiChron for secondary amenorrhoea and PHARMO for hypermenorrhoea. The MAH committed to further refine the case identification algorithm that includes ICPC and ICD10 codes for these menstrual events for the final report.*

Figure 6 shows the age standardised quarterly incidence rates of hypermenorrhoea and secondary amenorrhoea in individuals unvaccinated for COVID-19. Except for Pedianet (pediatric data source), rates were relatively stable, with clear patterns of higher rates in GP-based data sources, but no clear seasonal or COVID-19 related patterns.

Figure 6. Age-standardised incidence rates for hypermenorrhoea and secondary amenorrhoea in unvaccinated individuals, standardised to the data source specific population in 2020, by data sources



The pooled analysis in the main matched cohort for hypermenorrhoea in women of age showed that results were heterogeneous between data sources (I^2=0.92), therefore the pooled HR should be interpreted cautiously (Figure 7). The HRs were elevated in all data sources. The HRs were also

consistently elevated in the different sensitivity analyses, except in the analysis with the historical COVID-19-cohorts. The HRs for hypermenorrhoea, varied across age groups in the stratified analyses, but with imprecise estimates (Appendix Figure 20). Younger age groups in females (12-15 years) seemed to have slightly higher risks (pooled HR=1.42, 95% CI: 0.75-2.69) than other age groups, although the HRs were elevated across all female age groups (*Post-hoc* pooling analysis).

The adjusted HRs for *secondary* amenorrhoea within 183 days of time zero were around 1 in NHR and SIDIAP and elevated in CPRD Aurum (HR=1.33, 95% CI: 1.24-1.43). Pedianet data cannot be assessed since it only includes children up till 14 years of age. The pooled analysis in the main matched cohort analysis and the sensitivity analyses showed the HRs for secondary amenorrhoea were only very slightly elevated (Figure 8). There was no evidence of heterogeneity in the different sensitivity analyses and the pooled HRs were only very slightly elevated. In NHR, the 16–17 years age groups had an elevated risk HR=5.01, 95% CI: 1.71-14.69) but this was not in other data sources (Appendix Figure 21 [not reproduced in this AR]). In SIDIAP the risk of secondary amenorrhoea was elevated in pregnant women (HR=1.98, 95% CI: 1.41-2.78), which is probably based on recording of health status and not evidence of morbidity.

Figure 7. Pooled analyses for hypermenorrhoea in in the overall and historical cohorts and sensitivity analyses

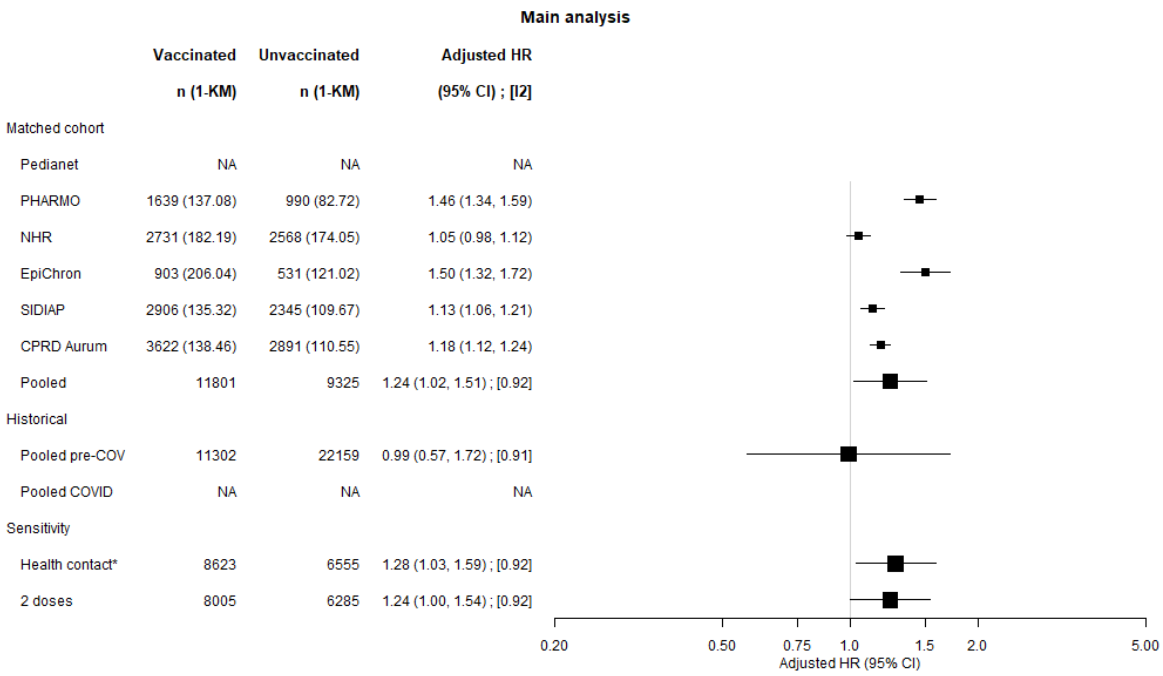
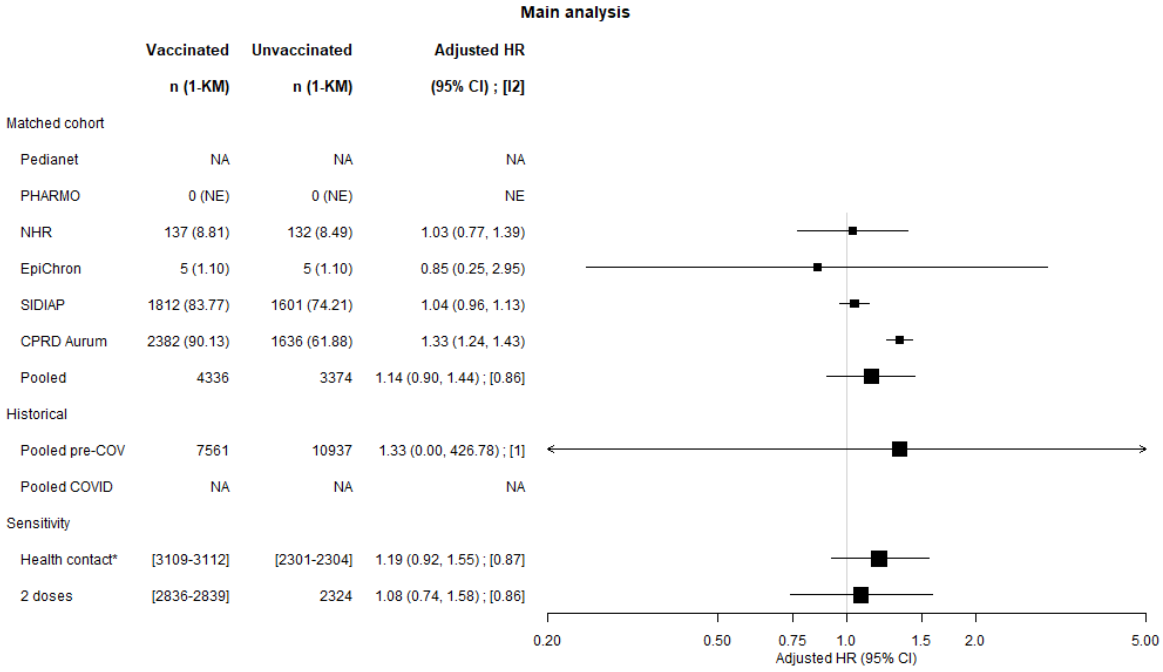


Figure 8. Pooled analyses for secondary amenorrhoea in in the overall cohort, historical cohorts and sensitivity analyses



MAH discussion

Hypermenorrhoea was reviewed by PRAC in October 2022, following accumulating evidence suggesting a possible causal link with mRNA COVID-19 vaccines.[33] The EMA proposed immune-mediated vascular effects and coagulation changes as plausible mechanisms. A 2024 systematic review supported the possibility of menstrual changes post-vaccination, though most were mild and short-lived.[34, 35] This study found associations in GP-based data sources but not in NHR, where GP diagnoses were absent. Adjusted HRs were 1.18 (95% CI: 1.12–1.24) in CPRD Aurum, 1.59 (95% CI: 1.39–1.82) in EpiChron, 1.46 (95% CI: 1.34–1.59) in PHARMO, and 1.13 (95% CI: 1.06–1.21) in SIDIAP. Associations were stronger in younger girls aged 12–15 and 16–17 and declined with age in all data sources, except CPRD where adjusted HRs remain similar across age groups.

Secondary amenorrhoea, defined as no menstruation for ≥90 days, was discussed by PRAC in June 2022.[36] PRAC concluded there was insufficient evidence to establish a causal link between the Pfizer-BioNTech COVID-19 vaccine and secondary amenorrhoea. This study showed no association, except for CPRD Aurum, where the adjusted hazard ratio was 1.33 (95% CI: 1.24–1.43). The overall pooled HR was 1.13 (95% CI: 0.85–1.51). Neither of the events were validated, therefore the direction of bias cannot be predicted.

PRAC Rapporteur comment:

For *Hypermenorrhoea* the study found associations in GP-based data sources but not in NHR, where GP diagnoses were absent. Adjusted HRs were 1.18 (95% CI: 1.12–1.24) in CPRD Aurum, 1.59 (95% CI: 1.39–1.82) in EpiChron, 1.46 (95% CI: 1.34–1.59) in PHARMO, and 1.13 (95% CI: 1.06–1.21) in SIDIAP. Associations were stronger in younger girls aged 12–15 and 16–17 and declined with age in all data sources, except CPRD where adjusted HRs remain similar across age groups. Hypermenorrhoea is currently labelled in the approved product information. No new safety information was identified.

For *secondary amenorrhoea*, the overall pooled HR was not increased: 1.13 (95% CI: 0.85–1.51). This is in line with the conclusion of the previous signal procedure [EPITT ref. 19784, dated 10 Jun 2022].

Based on the currently available evidence from the current PASS no causal relation between Comirnaty and amenorrhoea can be concluded.

Acute cardiac injury and Arrhythmia

Outstanding PRAC request following 5th interim report: *The MAH committed to continue to monitor and thoroughly discuss acute cardiovascular injury in the final report.*

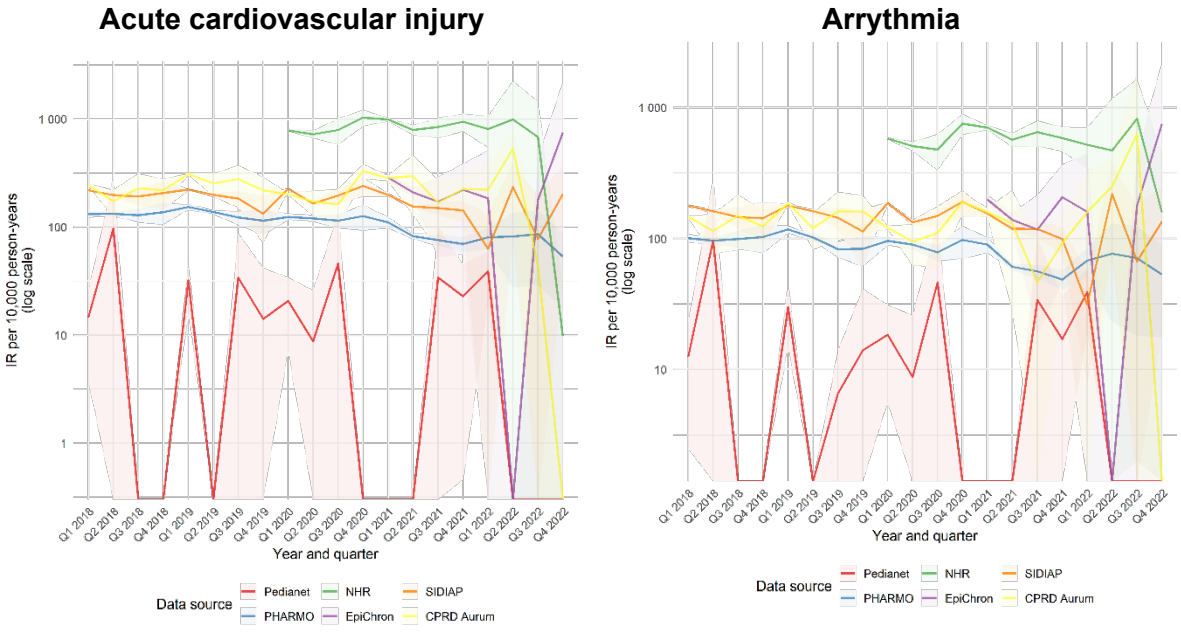
Cardiovascular system

Figure 9 shows the age-standardised incidence rates for different cardiovascular AESIs in unvaccinated individuals. ACI, a composite of all cardiovascular AESIs, showed a low and spiky rate in Pedianet. In SIDIAP, EpiChron and PHARMO the rates of ACI decreased between Q4-2020 and Q4 2021, while in NHR the rates remained stable.

Arrhythmia was the major component of ACI, for which age-standardised rates in unvaccinated individuals were highest in NHR, probably because of the healthcare settings, with low seasonality, but reductions during COVID-19 period were seen in the other data sources.

Incidence rates for heart failure in unvaccinated individuals were quite stable over the period assessed, with small reductions in PHARMO during the COVID-19 pandemic period, which was not observed in the other data sources.

Figure 9. Age-standardised incidence rates for cardiovascular AESIs in unvaccinated individuals, standardised to the data source specific population in 2020, by data source



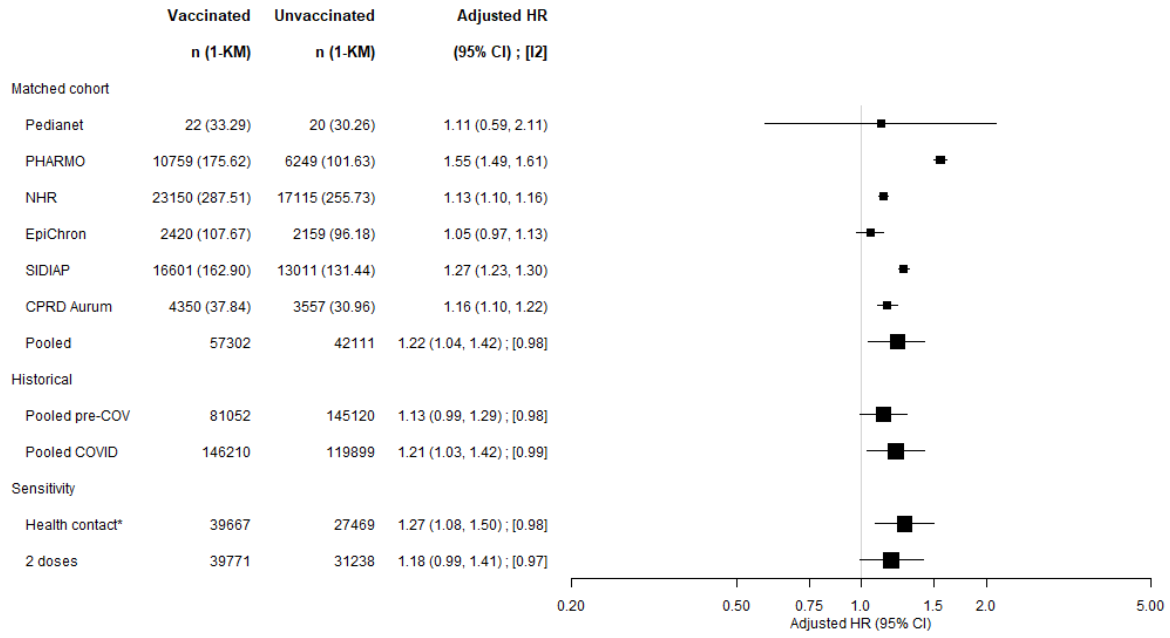
Acute cardiovascular injury (ACI)

ACI was assessed over 365 days of follow-up. The cumulative incidence curves of ACI showed that the divergence of incidences starts around day 60 during follow-up in most of the data sources, except in EpiChron (Appendix Figure 24 [not reproduced in this AR]).

Data source-specific adjusted HRs were consistently elevated, except in EpiChron (Figure 10). The pooled adjusted HR was slightly elevated (pooled HR 1.22, 95% CI: 1.04-1.42), with large heterogeneity between data sources (I^2 = 0.98) even if all pointed in same direction. The pooled adjusted HR from the main matched cohort analysis was comparable with the pooled adjusted HRs in various sensitivity analyses, which showed a consistently small increased HR.

The adjusted HR was slightly higher in females than in males in PHARMO, but not in the other data sources (Appendix Figure 25). The pooled adjusted HR in immunocompromised and individuals who were frail or had comorbidities sub-cohorts showed similar HRs compared with the main pooled adjusted HR=1.19, 95% CI: 1.02-1.39 (Post-hoc pooled analysis). The HR for the pregnant sub cohort was similar to the main result (pooled adjusted HR: 0.86 (0.51–1.44).

Figure 103. Pooled analyses for acute cardiovascular injury in the overall and, historical cohorts and sensitivity analyses



NE: not estimable; *no healthcare contact in 7 days prior to time zero; two doses within 6 weeks

MAH discussion

Cardiovascular events, listed as AESIs by the SPEAC project due to their known link to SARS-CoV-2 infection,[39] were not specifically discussed by PRAC but were reported in literature.[40] A Swedish study found a reduced cardiovascular risk post-vaccination, especially after dose three (HRs: 0.69–0.81). Slightly increased risks were observed for extrasystoles: adjusted HR = 1.17 (95% CI: 1.06–1.28) after dose one and adjusted HR 1.22 (95% CI: 1.10–1.36) after dose two, mainly in the elderly and males. Transient ischaemic attack showed a modest increase (adjusted HR: 1.13, 95% CI: 1.05–1.23), but no association was found for stroke or arrhythmias.[41].

In this PASS study, cardiovascular risk was assessed over a 365-day period post-dose one. A composite outcome of acute cardiovascular injury showed a consistent, small increase in risk (adjusted HR =1.22, 95% CI: 1.04-1.42). However, there was a potential selection bias since most unvaccinated individuals were censored after 60 days due to COVID-19 vaccination, leaving only few unvaccinated which may suffer from loss to follow-up (see *Section 11.3 Limitations*). The direct effect estimate for acute cardiovascular injury rose from: adjusted HR 1.22 (95% CI: 1.04–1.42 to 1.27 (95% CI: 1.09–1.49). Similar small increases, and censoring of unvaccinated was seen for arrhythmia, coronary artery

disease, and stress cardiomyopathy, but no association was found with heart failure. The events were not validated; therefore, the direction of bias cannot be predicted.

PRAC Rapporteur comment

The consistent, small increase in risk of composite outcome of acute cardiovascular injury (currently in Final report: adjusted HR =1.22, 95% CI: 1.04-1.42) was previously observed and discussed in the most recent 5th interim study report.

The MAH postulated that potential selection bias cannot be fully excluded considering:

- Some of these CV events have presented with mild symptoms that did not require immediate medical attention, and vaccinated individuals may have sought medical attention more frequently than those who were unvaccinated (healthy vaccinee effect).
- Differences in the composition of the unvaccinated cohort as follow-up progresses. Unvaccinated individuals were censored in the unvaccinated cohort if they were vaccinated and were then followed up in the vaccinated cohort from that time point. Consequently, the individuals who remained in the unvaccinated cohort were those who were never vaccinated and who were possibly less likely seek medical attention at all if it was not urgently needed.
- These differences may have been minimal earlier in follow-up, however, may have become more pronounced as follow-up progressed.

At this moment no new safety information is identified based on the data presented in the Final report (**Request for next PSUR.** See *Section 2. Overall conclusion and impact on the benefit/risk balance*).

Nerves and central nervous system, including Bell's Palsy

Outstanding PRAC request following 5th interim report: *No consistent differences in the adjusted HRs for Bell's palsy between interim reports 4 and 5 were observed. The MAH committed to investigate (and discuss in the final report) whether more specific identification codes were used in the algorithm in PHARMO may have led to the lower adjusted HR.*

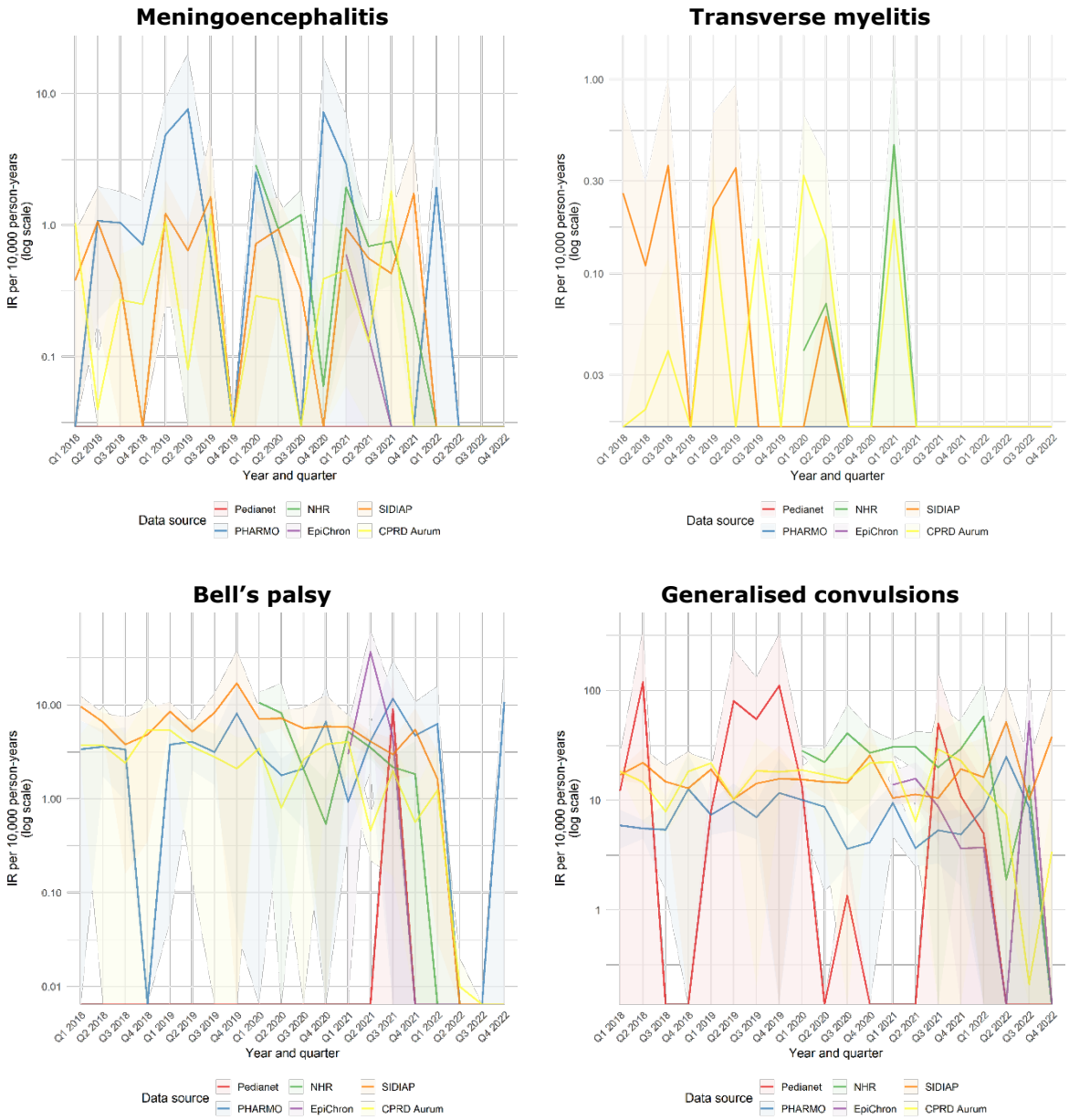
Figure 11 shows the incidence rates from Q1 2018 to Q4 2022 for the peripheral nerves and central nervous system AESIs: meningoencephalitis, transverse myelitis, Bell's palsy, and generalised convulsions in unvaccinated individuals. Meningoencephalitis was very rare, and showed seasonal variation, across all data sources, transverse myelitis incidence was very rare, and diagnoses could not be identified in PHARMO or PEDIANET, while other data sources showed seasonal variation, Bell's Palsy was also very rare with less seasonal variation and a reduction during 2020. Generalised convulsions peaked with seasons in Pedianet and may be related to vaccination for childhood diseases in other data sources rates were more stable.

The results for the main matched analysis for meningoencephalitis, transverse myelitis, Bell's palsy, and generalised convulsions were very consistent. The adjusted HRs varied across data sources, but the pooled adjusted HR was around 1 for generalised convulsions (1.04, 95% CI: 0.90-1.20) but with a highly imprecise adjusted HR in NHR of 10.26 (1.31-80.16) in children 5-11 years of age: meningoencephalitis (adjusted HR: 0.84, 95% CI: 0.55-1.27), Bell's palsy (adjusted HR: 0.96, 95% CI: 0.88-1.05), and transverse myelitis (adjusted HR: 1.57, 95% CI: 0.16-15.62) (Appendix Figures 47 to 50).

The pooled IRRs in the SCRI analysis, which was conducted in the all-vaccinated cohort, were IRR 0.82 (95% CI: 0.70-0.96) for meningoencephalitis; IRR 0.83, (95% CI: 0.51-1.37) for transverse myelitis;

and IRR 0.98, (95% CI: 0.89-1.09) for generalised convulsions. The HRs for the historical cohorts and the sensitivity analyses were mostly consistent with the matched cohort HR.

Figure 11. Incidence rates by quarter from Q1 2018 to Q4 2022 for nerves and central nervous system AESIs in unvaccinated individuals standardised to the data source specific population in 2020, by data source



MAH discussion

Generalised convulsions or seizures

Generalised convulsions or seizures have been reported as rare adverse events following Pfizer-BioNTech COVID-19 vaccination, primarily in individuals with pre-existing epilepsy.[53] New-onset seizures are uncommon and may be triggered by post-vaccination fever in susceptible individuals.[54] A SCCS analysis in Hong Kong found no association.[55] This PASS observed no increased risk of generalised convulsions from both the matched cohort and SCRI analyses and the sensitivity analyses. ADEM has been temporally associated with Pfizer-BioNTech COVID-19 vaccination in isolated cases. The results from an SCCS in the England and Northern Ireland did not show an association with mRNA

vaccines but the point estimate had very wide 95% CIs.[56] In this study the association could not be estimated because there were very few cases.

Bell's palsy

Case reports and a systematic review identified Pfizer-BioNTech COVID-19 vaccine as one of the most commonly reported vaccines in cases of Bell's palsy, with its onset ranging from 1 to 48 days post-vaccination.[57] A case-control study did not find a statistically significant association between recent Pfizer-BioNTech COVID-19 vaccination and Bell's palsy (adjusted odds ratio 0.84, 95% CI: 0.37–1.90).[58, 59] Some population-based studies suggested a slight increase in risk, particularly after the first dose and among older age groups, but the findings are inconsistent.[57] This PASS showed no association between Pfizer-BioNTech COVID-19 vaccine and Bell's palsy, and this was consistent across the different sensitivity analyses and subgroups.

Cerebral venous sinus thrombosis (CVST)

Reports and case series describe some instances of cerebral venous sinus thrombosis (CVST) following Pfizer-BioNTech COVID-19 vaccination, but these are very rare.[58, 59] An SCCS study in New Zealand found no association.[59] No association between vaccination and CVST was observed in this PASS, although the risk increased in the immunocompromised subgroup, with very wide confidence intervals (pooled adjusted HR: 4.00; 95% CI: 0.45-35.78), based on data from NHR only.

Guillain-Barré syndrome (GBS)

Published results from comparative cohort and SCCS analyses on Guillain-Barré syndrome (GBS) consistently show no increase, and even a decrease, in risk after vaccination with Pfizer-BioNTech COVID-19 vaccine, including when recipients are compared with those who received adenoviral vector COVID-19 vaccine or had had a SARS-CoV-2 infection itself. The results from a large systematic review showed a reduction of risk.[60] In this PASS there was no consistent association in the results from different sensitivity analyses, SCRI, and subgroup analyses. The broad PPV for GBS in the vaccinated cohorts was 50% in CPRD Aurum, 56% in SIDIAP and 67% in NHR.

Meningoencephalitis

There have been rare reports of meningoencephalitis and related conditions following vaccination with the Pfizer-BioNTech COVID-19 vaccine. In this study no association between Pfizer-BioNTech COVID-19 vaccination and meningoencephalitis was found in the matched comparative cohort or the SCRI analysis. In some younger age groups, the risks were elevated but the 95% CIs were very wide. Transverse myelitis occurrence has been reported after various vaccines, including COVID-19 vaccines.[61] Pharmacovigilance data from the Netherlands show that about half of the transverse myelitis reports after COVID-19 vaccination involved the Pfizer-BioNTech COVID-19 vaccine, reflecting its widespread use.[62] The results from observational cohort and SCCS studies did not show a statistically significant increased risk of transverse myelitis associated with Pfizer-BioNTech COVID-19 vaccination compared with background rates. In this PASS a small increase in the pooled adjusted HR was observed, but with wide confidence intervals, whereas the SCRI design did not show an elevated risk. Narcolepsy has been associated with Pfizer-BioNTech COVID-19 vaccine in case reports, but this PASS found no association in the matched cohort or SCRI analyses, or in the sensitivity and subgroup analyses.[63]

PRAC Rapporteur comment

No associations were observed for for the peripheral nerves and central nervous system AESIs meningoencephalitis, transverse myelitis, Bell's palsy, and generalised convulsions in unvaccinated individuals.

At the time of marketing authorization approval the safety database revealed an imbalance of cases of Bell's palsy with four in the vaccine group and none in the placebo group.[1] However, currently available information is insufficient to determine a causal relationship with the vaccine.

The final report of this PASS showed no association between Pfizer-BioNTech COVID-19 vaccine and Bell's palsy (adjusted HR: 0.96, 95% CI: 0.88-1.05), and this was consistent across the different sensitivity analyses and subgroups.

Subacute Thyroiditis

Subacute thyroiditis was not included in the list of signals published by Caplanusi et al.[11] and therefore, it was not pre-classified for evaluation as a signal identified by the PRAC for this study. However, Pfizer-BioNTech evaluated this AESI at the request of the PRAC in 2022 and reevaluated it again in 2024.[12]

Figure 12 shows that the incidence of subacute thyroiditis in unvaccinated individuals from Q1 2018 to Q4 2022 was very low with slight seasonal variation.

Figure 13 shows the pooled adjusted HR was elevated for the association between Pfizer-BioNTech COVID-19 vaccine and subacute thyroiditis (adjusted HR =1.89, 95% CI: 1.20-2.96). Sensitivity analyses with the unvaccinated historical controls showed a lower point estimate. The results for the sensitivity analyses among those with no healthcare contact in the previous 7 days of time zero and those with at least 2 doses of the vaccine show similar results to those seen with the overall cohort. Subgroup analyses could only be conducted meaningfully in NHR due to the low numbers of events in the other data sources (Appendix Figure 53 [not reproduced in this AR]). The results showed that the adjusted HR seemed higher in those who were frail or had comorbidities, and immunocompromised individuals as well as those who had prior COVID-19 infection. However, all estimates were imprecise and should be interpreted with caution. No events were observed in pregnant women.

Figure 12. Incidence rates by quarter from Q1 2018 to Q4 2022 for subacute thyroiditis in unvaccinated individuals standardised to the data source specific population in 2020, by data sources

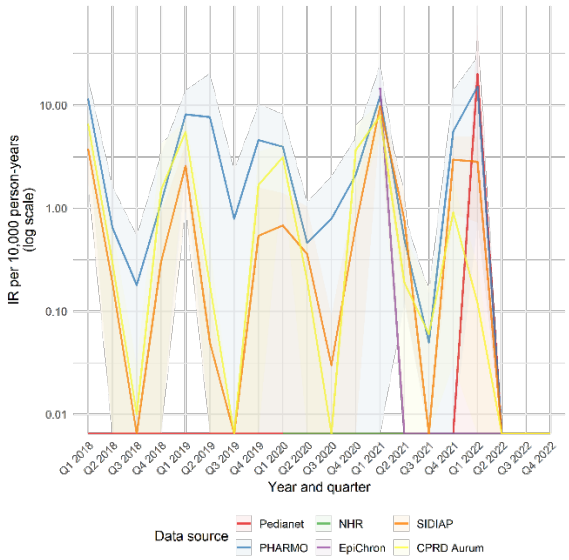
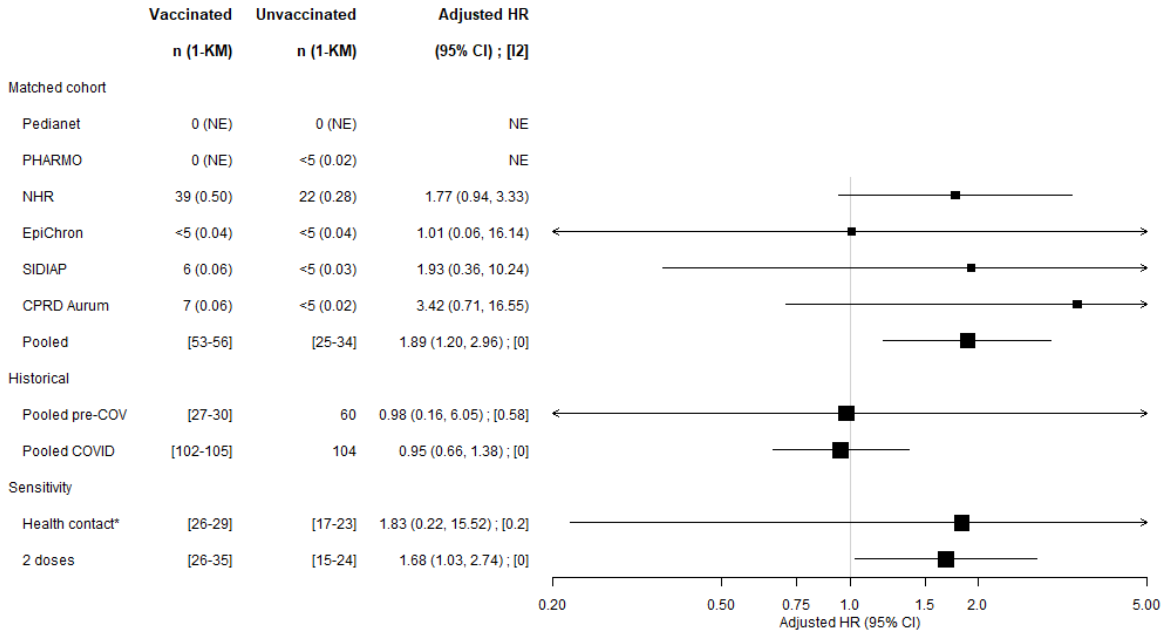


Figure 13. Pooled Analyses for Subacute Thyroiditis in the Overall and Historical Cohorts and Sensitivity Analyses



NE: not estimable; *no healthcare contact in 7 days prior to time zero; two doses within 6 weeks

MAH discussion

Subacute thyroiditis occurrence after receipt of Pfizer-BioNTech COVID-19 vaccination has been reported in the literature.[42] Pfizer-BioNTech evaluated this AESI at the request of the PRAC in 2022 and again in 2024,[12] but it was not included in the list of signals published by Caplanusi et al.[11] No large-scale comparative studies exist to the best of the MAH's knowledge, but this study found a small, consistent increase in risk in CPRD, SIDIAP and NHR. In NHR, with increases in females and some age categories. The pooled direct effect had an adjusted HR of 2.71 (95% CI: 1.65–4.45).

PRAC Rapporteur's Comment

In contrast to previous findings reported in the PSUR and 5th interim study report, the analysis in this final study report of PASS C4591021 found a small, consistent increase in risk on *subacute thyroiditis* in CPRD, SIDIAP and NHR. In NHR, with increases in females and some age categories. The pooled adjusted HR was elevated for the association between Pfizer-BioNTech COVID-19 vaccine and *subacute thyroiditis* (adjusted HR =1.89, 95% CI: 1.20-2.96). The MAH should discuss whether an update of the product information is warranted, or justify otherwise (**Request for Supplementary Information**).

It is acknowledged that the results should be interpreted cautiously for the following reasons:

- The pooled adjusted HR (risk window of 365 days) from the matched cohort analysis is based a limited number of events (n<57 vaccinated *vs.* n<37 unvaccinated), resulting in wide 95% confidence intervals (Table 5 and Figure 13).
- The impact of COVID can not be excluded as the number events in the (historical) pooled COVID cohort (n=105, Fig 13) was higher than the pre-COVID cohort (n=60)
- The results showed that the adjusted HR seemed higher in those who were frail or had comorbidities, and immunocompromised individuals as well as those who had prior COVID-19 infection. However, all estimates were imprecise.
- In addition, the background incidence of subacute thyroiditis in unvaccinated subjects from Q1 2018 to Q4 2022 was very low with slight seasonal variation (Figure 12).

Note that previously in Dec 2021 Subacute thyroiditis has been unconfirmed as signal [EPITT reference 19753]. In the most recent PSUR (uAR dated 26 June 2025) subacute thyreoditis has been (re)evaluated and refuted as signal upon request by the Saudi Food and Drug Authority.

Previously, in the most recent PSUR it was concluded:

Subacute thyroiditis, also known as De Quervain's thyroiditis or granulomatous thyroiditis, is the most common cause of painful thyroiditis. Subacute thyroiditis, presumed to be caused by viral infections or post-viral inflammatory responses, generally develops 2 to 8 weeks following viral upper respiratory tract infections and cases tend to increase during virus outbreaks.

It has been hypothesised that viral antigens in vaccines may trigger inflammation in the thyroid, similar to an infectious agent. This evaluation of subacute thyroiditis coincident with BNT162b2 vaccination provided information from several data sources, such as clinical trial data, the MAH's safety database data, disproportionality analyses, literature review, and observed to expected analyses.

The placebo-controlled clinical trial data did not provide supportive evidence of a causal association between BNT162b2 and subacute thyroiditis, although it is acknowledged that uncommon AEs may not occur in clinical trials, even when participants number in the thousands.

A cumulative safety database search of the MAH's global safety database through 31 December 2023 as of 7 January 2024 was conducted using MedDRA (Version 26.1) to identify cases with PT: Thyroiditis subacute. A total of 349 cases (0.017% of total 2,003,153 cases for BNT162b2 vaccines) were retrieved. Out of these 349, (286, 81.9%) were spontaneous, (61, 17.5%) were literature, and 1 each were solicited and clinical study cases. Cases included females (260, 74.5%) and males (84, 24.1%) and sex unknown/no data (5, 1.4 %). The patients ranged in age from 23-95 years (mean = 47.9 years). Of these 349, there were 212 serious cases (60.7%) and 137 (39.3%) cases were non-serious.

The number of reported post-authorisation subacute thyroiditis cases that did not include alternative explanations or confounding factors was relatively low (72 cases) when taking into consideration the

unprecedented number of doses of BNT162b2 that have been administered worldwide and the number of AEs reported to the safety database. While the large population study of AESIs in >1.3 million individuals was not designed to compare the incidence of subacute thyroiditis between non-vaccinated individuals and those vaccinated with BNT162b2, the low number of subacute thyroiditis reports following BNT162b2 administration (1 per 100,000 doses after dose 1, 0 per 100,000 after Dose 2) is reassuring even though it does not prove a lack of association. Likewise, the smaller cohort studies did not provide comparative incidences of subacute thyroiditis in vaccinated vs unvaccinated cohorts, rather they provided clinical descriptions of subacute thyroiditis presentation and course. The disproportionality analysis in the published literature was inconsistent with that in the MAH's safety database, although limitations of this signal detection exercise, such as potential masking of signals, is acknowledged. The O/E analyses and interim results of the non-interventional PASS (C4591021) are also not supportive of a relationship between BNT162b2 and subacute thyroiditis.

In summary, there is not sufficient evidence to conclude that BNT162b2 administration causes subacute thyroiditis and, therefore, no product labelling changes are warranted. Routine pharmacovigilance activities have not revealed any new significant safety information up to the DLP of the current PSUR and this topic will continue to be monitored with routine pharmacovigilance.

Request for Supplementary information:

The MAH is requested to clarify an apparent discrepancy in pooled adjusted HRs. The pooled adjusted HR stated in the Figure 13 Forest plot (adjusted HR =1.89, 95% CI: 1.20-2.96) is different from the one mentioned in the MAH's discussion included in the full CSR (adjusted HR =2.71 (95% CI: 1.65–4.45).

In our view, the currently observed increase in risk on *subacute thyroiditis* in CPRD, SIDIAP and NHR, adds to the cumulative evidence regarding this suspected adverse reaction. The MAH is requested to discuss whether this finding alters previous conclusions regarding the causal relation between Comirnaty and subacute thyroiditis, or justify otherwise.

If applicable, any consequences to the product information should be discussed taking into account

- The findings including strengths and limitations of the current study
- Any relevant well-documented cases supportive of causality reported after January 2024
- Any relevant publications from scientific literature

Pregnancy outcomes

A total of 26,696 of the 48,439 (55.11%) vaccinated, pregnant women were matched with unvaccinated, pregnant women in the analyses of the pregnancy and neonatal AESIs. In both the vaccinated and unvaccinated cohorts, there were no pregnancies in Pedianet (a paediatric data source), 915 pregnancies in PHARMO, 12,062 pregnancies in NHR, 974 pregnancies in EpiChron, 10,212 pregnancies in SIDIAP, and 2,533 pregnancies in CPRD Aurum.

Appendix Table 11 [not reproduced in this AR] provides an overview of the prevalence rates for maternal and neonatal outcomes. For the outcomes maternal death, microcephaly, and termination of pregnancy for foetal anomaly, either zero or <5 events were identified in all data sources. Data on preterm birth were not available in EpiChron because 89.8% of pregnancy start dates were imputed

using the pregnancy algorithm, resulting in unreliable gestational age calculations for preterm birth (*i.e.*, birth before 37 weeks).

Maternal pregnancy outcomes

The prevalence of gestational diabetes was consistent between data sources, and ranged between 3-5% in unvaccinated, and was consistently lower in the vaccinated cohorts than unvaccinated cohorts with a pooled adjusted PR of 0.76, (95% CI: 0.69-0.85) (Appendix Table 11 and Appendix Figure 54 [not reproduced in this AR]). The comparison with historical controls showed no elevation of the HR.

The prevalence of preeclampsia varied highly between data sources with the lowest prevalence in CPRD Aurum (Appendix Table 11 [not reproduced in this AR]). It was consistently higher in the matched pregnant cohorts among unvaccinated individuals. The prevalence rate ratios and differences do not suggest any association between the vaccine and pre-eclampsia. The pooled analyses showed the adjusted PR was 0.70 (95% CI: 0.55-0.89) (Appendix Figure 55 [not reproduced in this AR]).

Neonatal pregnancy outcomes

The prevalence of foetal growth restriction (FGR) varied across the different data sources (Appendix Table 11 [not reproduced in this AR]). The prevalence was highest in NHR and SIDIAP. The prevalence ratios and differences showed a small elevation (PR_{adj} 1.22 (95% CI: 1.07-1.38) mostly based on the PHARMO, NHR and SIDIAP data, but not in EpiChron (Appendix Figure 56 [not reproduced in this AR]). Comparison with historic controls showed a slightly higher risk compared with 2018/2019 historic controls and lower adjusted PRR when compared with 2020 historic controls.

The prevalence rates for recorded spontaneous abortion were heterogeneous across the data sources and between vaccinated and unvaccinated pregnant women and PR varied between 0.70 and 1.25%. The pooled adjusted prevalence rate ratios and differences do not suggest an association between the vaccine and spontaneous abortion 0.93, (95% CI: 0.70-1.23) (Appendix Figure 57 [not reproduced in this AR]). Comparison with historical controls showed a slightly higher risk when compared with 2018/2019 historical controls and lower adjusted PRR when compared with 2020 historical controls.

Very few stillbirths occurred during the study, with prevalences less than 1% (Appendix Table 11 [not reproduced in this AR]). The pooled analysis for stillbirth showed no evidence of an increase in prevalence of stillbirth following maternal vaccination 1.02, (95% CI: 0.69-1.51) (Appendix Figure 58 [not reproduced in this AR]).

The prevalence of preterm birth varied across the data sources, In PHARMO and NHR the adjusted PR was elevated, but this was not observed in other data sources (Appendix Table 11 [not reproduced in this AR]), and the adjusted pooled PR was 1.25, 95% CI: 0.98-1.59) (Appendix Figure 59). No direct effect was estimated for the vaccine. COVID-19 and gestational age may residually confound this effect.

The prevalences of major congenital anomalies, based on single codes only, varied across the databases. There were 0 zero events in both cohorts in PHARMO and EpiChron, and the unvaccinated cohort in CPRD Aurum; there were [1-4] events in the vaccinated cohort in CPRD Aurum. In NHR there were 11 and 16 events in the vaccinated and unvaccinated cohorts, respectively, and 20 and 14, respectively in SIDIAP (Appendix Table 11 [not reproduced in this AR]). The prevalence rate ratios showed a lowering of prevalence in NHR and an elevation in SIDIAP, with wide 95% CIs (Appendix Figure 60 [not reproduced in this AR]). The pooled adjusted prevalence ratio was 1.01, (95% CI: 0.01-94.77). Less than five microcephaly events were identified in SIDIAP, and none in the other data sources, therefore no meaningful comparative estimates could be calculated (Appendix Table 11 [not reproduced in this AR]).

Neonatal death was only identified in NHR, and the prevalence was similar in the vaccinated and unvaccinated pregnant cohorts 1.16, (95% CI: 0.35-3.78). Less than five pregnancy terminations for foetal anomalies were reported in NHR (vaccinated cohort) and CPRD Aurum (unvaccinated cohort) with none in the other data sources and therefore no meaningful comparative estimates could be calculated.

MAH Discussion

Pregnancy and maternal outcomes were studied in a separate matched cohort and showed no increased risk for most the outcomes, which is in line with published literature.[67] Foetal Growth Restriction [FGR] and preterm birth showed small increases in risk, but this could be due to residual confounding by COVID-19, as many COVID-19 events were associated with these outcomes, and we did not estimate a direct effect.[68] In addition to residual confounding by COVID-19, we suspect there may be residual confounding due to gestational age, because gestational age was not a matching factor. Adjustment was done through IPTW, but not in NHR where the estimates for preterm birth and FGR were higher.

PRAC Rapporteur comment:

Pregnancy and maternal outcomes showed no increased risk for most of the outcomes, which is in line with published literature.[67] The MAH noted that *Foetal Growth Restriction [FGR]* [PR_{adj} 1.22 (95% CI: 1.07-1.38] and *preterm birth* [PR_{adj} 1.25, 95% CI: 0.98-1.59)] showed small increases in risk, and postulated that this could be due to residual confounding by COVID-19, as many COVID-19 events were associated with these outcomes. This could be acceptable. Nevertheless in the next PSUR, within the context of routine pharmacovigilance, the MAH is requested to discuss any relevant emerging safety issues regarding pregnancy outcomes including foetal growth restriction and preterm birth, if applicable (**Request for next PSUR.** See *Section 2. Overall conclusion and impact on the benefit/risk balance*).

6.2. Direct Healthcare Professional Communication

Outstanding PRAC request *from previous 4th and 5th interim report, regarding the evaluation of the effectiveness of the DHPC on myocarditis/pericarditis July 2021: The MAH should discuss and clearly describe the criteria used to evaluate the effectiveness of the DHPC.*

MAH response:

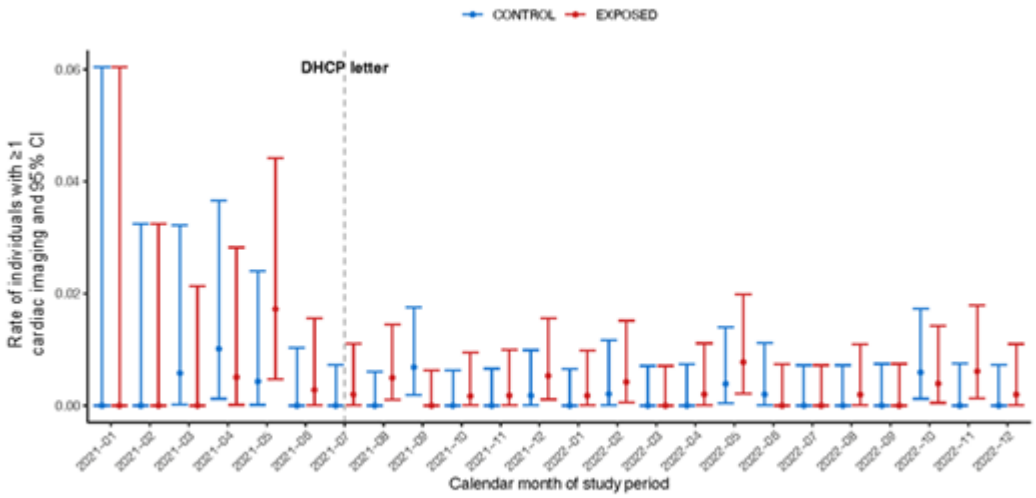
On 19 July 2021, a Direct Healthcare Professional Communication (DHPC) was issued to inform healthcare practitioners about the identified risk of myocarditis and pericarditis associated with COVID-19 mRNA vaccination. The healthcare practitioners were informed that they should be alert to the signs and symptoms of myocarditis and pericarditis and that they should advise vaccinated individuals to seek immediate attention should they experience chest pain, shortness of breath or palpitations.

A total of 15,639–15,793 (a range is provided due to masking of events) cardiac imaging events were recorded in EpiChron, SIDIAP, and CPRD Aurum. No cardiac imaging events were identified in PHARMO or NHR and one event was identified in Pedianet.

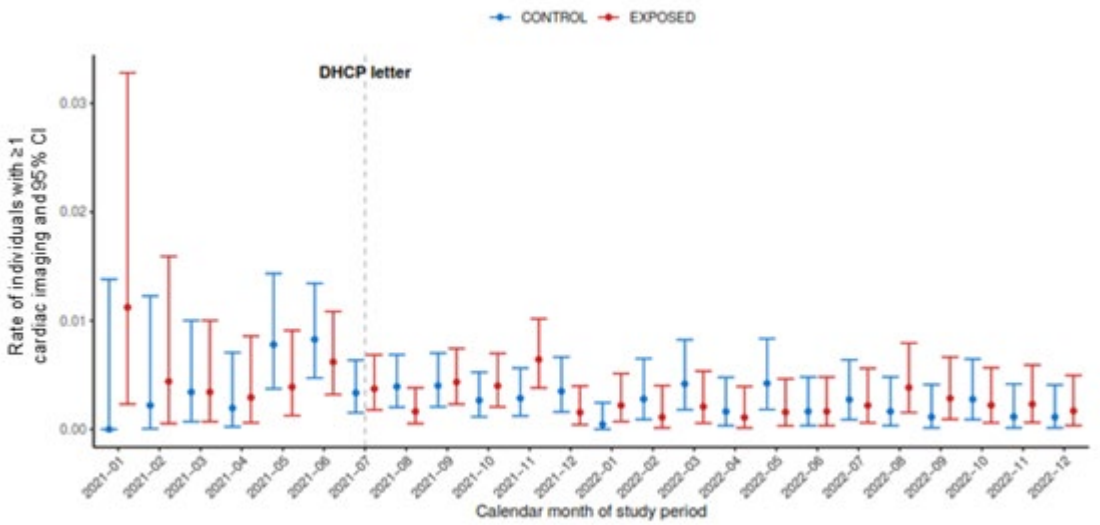
The incidence rate of recorded cardiac imaging was higher before the issuance of the DHPC than after in both the vaccinated and unvaccinated cohorts in EpiChron, SIDIAP, and CPRD Aurum (Figure 14). Incidence rate ratios for cardiac imaging, comparing rates after with rates before the issuance of the DHPC letter were consistently below 1 in the vaccinated and unvaccinated cohorts in the 3 data sources that captured this information (Table 5).

Figure 14. Evolution of Rates of Individuals Undergoing At Least One Cardiac Imaging Event Before and After the Issue of the Direct Healthcare Professional Communication (DHPC)

EpiChron



SIDIAP



CPRD Aurum

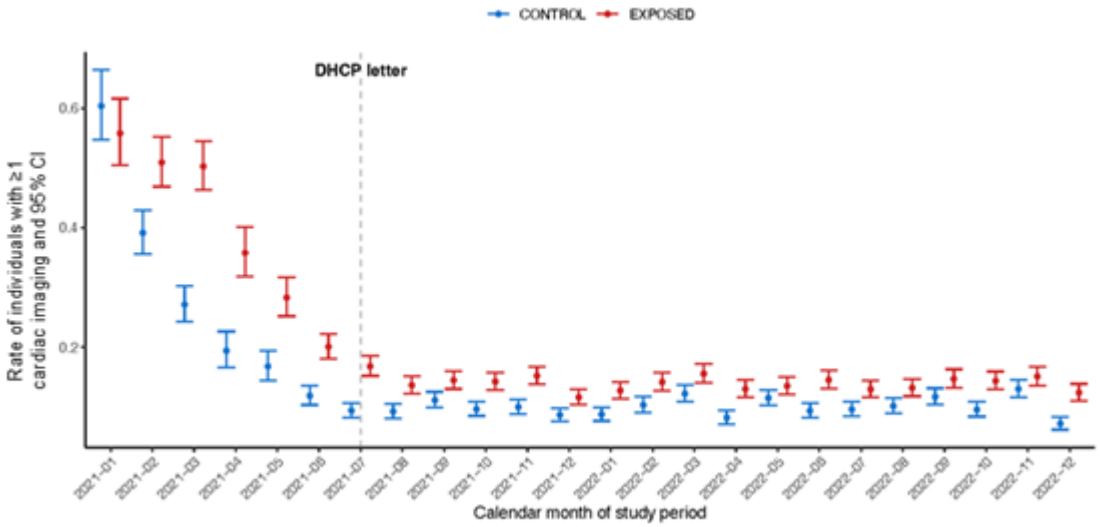


Table 5. Rate Ratios for Matched Vaccinated and Unvaccinated Individuals Undergoing ≥1 Cardiac Imaging Procedure Comparing After With Before the Direct Healthcare Professional Communication (DHPC) Issuance by Data Source

	EpiChron IRR (95% CI)	SIDIAP IRR (95% CI)	CPRD Aurum IRR (95% CI)
Vaccinated	0.46 (0.19, 1.14)	0.55 (0.36, 0.84)	0.35 (0.33, 0.37)
Unvaccinated	0.38 (0.12, 1.17)	0.45 (0.30, 0.68)	0.37 (0.34, 0.39)

MAH's interpretation

The analysis of cardiac imaging before and after the introduction of the DHPC demonstrated that the incidence rates of recorded cardiac imaging were higher before the issuance of the DHPC than after in both the vaccinated and unvaccinated cohorts in three data sources that included such information. Incidence rate ratios were consistently below 1 in both vaccinated and unvaccinated cohorts in all three data sources. Some likely reasons for these results include:

1. Pre-existing heightened clinical vigilance: Before the DHPC issue date (19 July 2021), there may have already been increased awareness and clinical suspicion of myocarditis and pericarditis in the context of COVID-19 vaccinations, especially as early safety signals and case reports emerged as well as the publication of the study by Barda et al.[10] Healthcare providers may have been proactively ordering cardiac imaging based on initial reports, which may have resulted in elevated imaging rates before official communications.
2. Public and media attention prior to DHPC: Media coverage and patient awareness of concerns about myocarditis and pericarditis in relation to vaccines may have prompted more individuals to seek medical evaluation even before the formal communication about safety was disseminated. EMA began its safety assessments of myocarditis events in April 2021 following cases reported in Israel. Public and social media attention increased from around spring 2021 and onward, especially as myocarditis cases were highlighted as a rare adverse event after mRNA COVID-19 vaccination, mainly in younger males after the second dose.
3. Decline in imaging post-DHPC due to clearer clinical guidance: Once the DHPC was released, healthcare professionals received specific criteria and guidance to identify and manage suspected myocarditis and pericarditis cases. This clarity may have led to more targeted and judicious use of cardiac imaging, avoiding unnecessary tests following the official advice.
4. During 2021 and 2022, the uptake of the first COVID-19 booster dose among young adults in Europe (specifically those aged 18-24) was relatively modest compared with older age groups. According to the European Centre for Disease Prevention and Control (ECDC) data reported as of 21 August 2022, the median booster dose uptake among adults aged over 18 years in EU/EEA countries was about 64.7%, but uptake among younger adults aged 18-24 was lower.[11]
5. Lower numbers of susceptible individuals: by the summer of 2021, most adults had already received two doses of the Pfizer vaccine, and most cases of vaccine associated myocarditis may have already occurred.

Although this analysis does not provide evidence that any of these factors are causal, collectively they may explain the observed pattern of cardiac imaging demonstrated from this study.

PRAC Rapporteur's Comment

In order to evaluate the impact/effectiveness of the DHPC regarding myocarditis and pericarditis the MAH analysed the monthly rate of ≥1 cardiac imaging procedure per 10,000 person-years (PY) in the vaccinated and unvaccinated cohorts, before and after the introduction of the DHPC. The analysis demonstrated that the incidence rates of recorded cardiac imaging were higher before the issuance of the DHPC than after in both the vaccinated and unvaccinated cohorts in three data sources that included such information.

The exact cause(s) for this observation remain unclear, but the possible explanations postulated by the MAH appear plausible, such as:

- Increased awareness and clinical suspicion of myocarditis and pericarditis in the context of COVID-19 vaccinations, especially as early safety signals and case reports emerged as well as the publication of the study by Barda et al.[10] HCPs may have been proactively ordering cardiac imaging based on initial reports, which may have resulted in elevated imaging rates before official communications.
- Public and media attention prior to DHPC

- Decline in imaging post-DHPC due to clearer clinical guidance: Once the DHPC was released, healthcare professionals received specific criteria and guidance to identify and manage suspected myocarditis and pericarditis cases.
- During 2021 and 2022, the uptake of the first COVID-19 booster dose among young adults in Europe (specifically those aged 18-24) was relatively modest compared with older age groups
- Lower numbers of susceptible individuals: by the summer of 2021, most adults had already received two doses of the Pfizer vaccine, and most cases of vaccine associated myocarditis may have already occurred.

Considering the current level of awareness regarding myo/pericarditis following mRNA COVID19 vaccines (both HCP and publicly), routine risk minimisation is currently considered sufficient to remind HCPs and patient to be alert to the signs and symptoms, and to counsel patients to seek immediate medical attention should they experience chest pain, shortness of breath, or palpitations.

6.3. MAH Overall Discussion

MAH Overall conclusion in Clinical Overview

According to the MAH this study showed that the identified risks of anaphylaxis, myocarditis, and pericarditis were associated and in line with existing evidence for the Pfizer-BioNTech COVID-19 vaccine profile and the literature, as described above. This study added substantial information on the safety of the vaccine for many AESIs for which case reports have been published and those that have been discussed by the PRAC, as described for each AESI, and in several subpopulation analyses and stratified sex and age analyses. No associations were identified except for subacute thyroiditis and hypermenorrhoea. The results from these study analyses were supported by multiple sensitivity analyses such as using different historical controls, excluding persons with a healthcare contact in the 7 days before time zero and the restriction to those with a completed 2 dose schedule as per the licensed sequence (within 6 weeks). Although cardiovascular events showed very minor elevations during 365 days of follow-up, it is believed this could be due to bias in the unvaccinated individuals who did not get vaccinated and remained in the unvaccinated cohort during the long follow-up.

Pregnancy and maternal outcomes were studied in a separate matched cohort and showed no increased risk for most of the outcomes, which is in line with published literature.[9] Foetal growth restriction (FGR) and preterm birth showed small increases in risk, but this could be due to residual confounding by COVID-19, as many COVID-19 events were associated with these outcomes.

MAH's Benefits and Risks Conclusions

The results from Study C4591021 do not alter the benefit-risk profile of the Pfizer-BioNTech COVID-19 vaccine. This study added substantial information on the safety of the vaccine for many AESIs for which case reports have been published and those that have been discussed by the PRAC, as described for each AESI, and in several subpopulation analyses and stratified sex and age analyses. No associations were identified except for subacute thyroiditis and hypermenorrhoea. These two topics have been subject to signal assessments which did not reveal a risk, although heavy menstrual bleeding is an ADR listed in Section 4.8 in the SmPC. Anaphylaxis was an identified risk and myocarditis/pericarditis is an important identified risk in the RMP. Analysis of the DHPC letter for myocarditis/pericarditis supports the proposal to remove this additional Risk Minimization Measure from the EU Risk Management Plan. While the rates of cardiac imaging were higher prior to the issuance of the DHPC letter, the rationale to inform HCPs about the identified risk of myocarditis and pericarditis associated with COVID-19 mRNA vaccine, to remind them to be alerted about the signs and symptoms and to counsel patients to seek immediate medical attention should they experience chest

pain, shortness of breath, or palpitations still likely had utility. The unprecedented attention given to all signals and risks associated with the COVID-19 vaccine campaign caused heightened awareness of risks at timepoints that were before the typical notification processes for HCPs, such as with a DHPC. However, the overall intention of the DHPC was met between the notifications from regulators regarding their evaluation of safety signals and actions to undertake in the interim, as well as the media attention given to the risks, as outlined in the data output from C4591021; therefore, the DHPC can be removed from the RMP at this time. The study does not provide any new information that would impact the benefit-risk profile of the Pfizer-BioNTech COVID-19 vaccine.

Interpretation

This study showed that the identified risks of anaphylaxis, myocarditis, and pericarditis were associated and in line with existing evidence for the Pfizer-BioNTech COVID-19 vaccine profile and the literature, as described above. This study added substantial information on the safety of the vaccine for many AESIs for which case reports have been published and those that have been discussed by PRAC, as described for each AESI, and in several subpopulation analyses and stratified sex and age analyses. No associations were identified except for subacute thyroiditis and hypermenorrhoea. The results from these study analyses were supported by multiple sensitivity analyses such as using different historical controls, excluding persons with a healthcare contact in the 7 days before time zero and the restriction to those with a completed 2 dose schedule as per the licensed sequence (within 6 weeks). Although cardiovascular events showed very minor elevations during 365 days of follow-up, it is believed this could be due to bias in the unvaccinated individuals who did not get vaccinated and remained in the unvaccinated cohort during the long follow-up. For preterm birth and FGR we noted a very small elevation, most likely caused by residual confounding by COVID-19.

PRAC Rapporteur's Comment

The MAH's interpretation of the results is accepted.

Generalisability

The generalisability of the study findings depends on the type of results. Findings related to Pfizer-BioNTech COVID-19 vaccine utilisation and subject characterisation apply to the populations included in the study from the different countries and populations. An all-vaccinated population was distinguished for which utilisation patterns were described, and the matched populations in which the main comparisons were conducted. Most of the eligible vaccinated individuals could be matched to an unvaccinated individual at baseline. This means that the results are generalisable to a large population in the countries studied. Moreover, the study analysed data were analysed in dedicated subgroups, for which information is often is not available, informing the benefit- -risk assessment in those subgroups risk.

PRAC Rapporteur's Comment

The discussion on the generalisability of results is accepted, taking into account data source, characteristics of the study population, inclusion and exclusion criteria, previous studies, and literature.

6.3.1. Conclusion

This large post-authorisation safety study of the Pfizer-BioNTech COVID-19 vaccine evaluated data from seven data sources in five European countries, to assess the risk for 37 distinct AESIs, and an additional 8 pregnancy and neonatal AESIs. The study confirmed associations between Pfizer-BioNTech COVID-19 vaccine and previously identified risks of rare events. The findings demonstrate a small and consistent association between Pfizer-BioNTech COVID-19 vaccination and subacute thyroiditis and an association with hypermenorrhoea in GP-based data sources. Although some cardiovascular events, such as arrhythmia and acute cardiovascular injury, coronary artery disease, and heart failure, showed very minor elevations during 365 days of follow-up, it is believed this may be due to bias in the unvaccinated individuals that remained unvaccinated during the 365 days follow-up. No association between Pfizer-BioNTech COVID-19 vaccination and adverse pregnancy AESIs or neonatal AESIs were found, except a small elevation of preterm birth and foetal growth restriction FGR, most likely due to residual confounding by COVID-19 or gestational age. A lower frequency of reported imaging in both vaccinated and unvaccinated individuals following the issuance of the DHPC was observed. The results demonstrated that the majority of the AESI were not associated with the Pfizer-BioNTech COVID-19 vaccine.

PRAC Rapporteur's Comment

The MAH's main conclusion(s) derived from the study and on its evaluation of the impact of the results is endorsed that the benefit-risk balance of the Pfizer-BioNTech COVID-19 vaccine remains **unchanged**.

Nevertheless, see *Section 9 Request for supplementary information* and *Section 2. Overall conclusion and impact on the benefit/risk balance*).

7. Risk management plan

The MAH submitted an updated RMP version **15.1** with this application.

Rationale for submitting an updated RMP (**v 15.1**): This comprehensive RMP update, which is based on the previously approved RMP v 15.0, encompasses a Type II variation related to the submission of the final report for study C4591021. In addition, the update includes the proposal to remove the DHPC letter (aRMM) which was implemented for the important identified risk of myocarditis and pericarditis.

At the time of opinion version 15.1 was up version to major version **16.0**.

The (main) proposed RMP changes were the following:

RMP Part/Module	**RMP v ~~15.0~~ ~~1~~ 16.0 Major Changes**
PART I PRODUCT(S) OVERVIEW	
	~~Editorial changes~~Updated to ~~remove Comirnaty and Comirnaty Original/Omicron BA.4/BA.5 presentations as approved with EMA/VR/0000236983~~ include the new presentations 30mcg (JN.1 & KP.2) refrigerated vials and the new LP.8.1 variant adapted vaccine~~.~~
PART II *SAFETY SPECIFICATION*	
PART II.Module SI Epidemiology of the Indication(s) and Target Populations	~~Editorial changes made.~~Updated to include the new LP.8.1 variant adapted vaccine
PART II.Module SII Non-Clinical Part of the Safety Specification	No changes made.
PART II.Module SIII Clinical Trial Exposure	No changes made.

RMP Part/Module	RMP v ~~15.0~~ ~~1~~ 16.0 Major Changes
PART II.Module SIV Populations Not Studied in Clinical Trials	No changes made.
PART II.Module SV Post-Authorisation Experience	Updated as of 18 ~~December~~ June 2025~~4~~.
PART II.Module SVI Additional EU Requirements for the Safety Specification	No changes made.
PART II.Module SVII Identified and Potential Risks	SVII.3: Post Marketing data from the safety database for the important identified risk of myocarditis and pericarditis updated as of 18 ~~December~~ June 2024~~5~~.
PART II.Module SVIII Summary of the Safety Concerns	No changes made.
PART III PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)	
III.1 Routine Pharmacovigilance activities.	~~Editorial changes in~~ Part III.1 ~~updated and removal of Comirnaty and Comirnaty original/Omi BA.4/BA.5 presentations as approved with EMA/VR/0000236983~~ to include the new presentations 30mcg (JN.1 & KP.2) refrigerated vials and the new LP.8.1 variant adapted vaccine.
III.2 Additional Pharmacovigilance Activities and III.3 Summary Table of Additional Pharmacovigilance Activities	~~Key objectives, design and study population of study C4591048 aligned according to protocol amendment #6~~. Updated to remove studies C4591021 and C4591038 and to revise frequency of progress reports from every 6 months to every 12 months of study C4591036.
PART IV PLANS FOR POST AUTHORISATION EFFICACY STUDIES	
	No changes made.
PART V RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)	
V.1 Routine Risk Minimisation Measures V.2 Additional Risk Minimisation Measures V.3 Summary of Risk Minimisation Measures	Updated based on the changes made in Part II and PART III. Updated to include the justification that supports the proposal to remove the DHPC communication for myocarditis and pericarditis.
PART VI SUMMARY OF THE RISK MANAGEMENT PLAN	
I The Medicine and What It Is Used For II Risks Associated With the Medicine and Activities to Minimise or Further Characterise the Risks	Editorial changes made. Updated based on the changes made in PART II, III and V.
PART VII. ANNEXES TO THE RISK MANAGEMENT PLAN	
~~Annex 4 Updated Multisystem inflammatory syndrome (MIS) specific Adverse Drug Reaction Follow-Up Form included~~. Annex 2 and 3: removal of studies C4591021 and C4591038 Annex 6 Proposal to remove the DHPC communication Annex 8: Changes to reflect the updates.	

In *Section V.2. Additonal Risk Minimisation Measures* the MAH's justification to remove the DHPC was as follows:

Removal of additional risk minimisation activities

On 19 July 2021, a Direct Healthcare Professional Communication (DHPC) was issued to inform healthcare practitioners about the identified risk of myocarditis and pericarditis associated with COVID-19 mRNA vaccination.

The effectiveness of the additional risk minimization measure (aRMM) was evaluated by estimating the time trend, in relation to the dissemination of the DHPC letter, of the proportion of individuals who received real-world clinical assessment for myocarditis/pericarditis following Comirnaty vaccination as an outcome of PASS C4591021.

While the rates of cardiac imaging were higher prior to the issuance of the DHPC letter, the rationale to inform healthcare practitioners about the identified risk of myocarditis and pericarditis associated with COVID-19 mRNA vaccine, to remind them to be alert to the signs and symptoms, and to counsel patients to seek immediate medical attention should they experience chest pain, shortness of breath, or palpitations, was still effective. The unprecedented attention given to all signals and risks associated with the COVID-19 vaccine campaign caused heightened awareness of risks at timepoints that were before the typical notification processes for healthcare practitioners, such as with a DHPC. However, the overall intention of the DHPC was met between the notifications from regulators regarding their evaluation of said signals and actions to undertake in the interim, as well as the media attention given to the risks, as outlined in the data output from C4591021.

Therefore, the MAH proposes to remove the DHPC from the RMP at this time.

PRAC Rapporteur's Comment

No changes are proposed regarding the *Summary of Safety concerns*, which is **accepted**.

The proposed RMP updates are consequential of the finalisation of EU Study C4591021 (former ACCESS/VAC4EU) and its substudy C4591038 [to assess the natural history of post-vaccination myo-/pericarditis], and are **accepted**.

Note that the final report of substudy C4591038 has been assessed in a separate procedure [EMA/VR/0000282346 uAR dated 23 Sep 2025] in which the MAH noted that the removal of study C4591038 from the RMP will be addressed at the next regulatory opportunity with an RMP update.

The removal of the 'historic' DHPC as additional risk minimisation measure [issued in in July 2021] to notify HCPs of the risks of myo- and pericarditis is **accepted**. The effectiveness of the additional risk minimization measure (aRMM) was evaluated by estimating the time trend, in relation to the dissemination of the DHPC letter, of the proportion of individuals who received real-world clinical assessment for myocarditis/pericarditis following Comirnaty vaccination as an outcome of PASS C4591021 see section 6.2.

Currently, routine risk minimisation is considered sufficient to remind HCPs and patient to be alert to the signs and symptoms, and to counsel patients to seek immediate medical attention should they experience chest pain, shortness of breath, or palpitations.

7.1. Overall conclusion on the RMP

☒The changes to the RMP are acceptable.

8. Request for supplementary information

8.1. Major objections

None

8.2. Other concerns

Clinical aspects

Regarding *Subacute thyroiditis*.

1. The MAH is requested to clarify an apparent discrepancy in the pooled adjusted HRs. The HR stated in the Figure 13 Forest plot (adjusted HR =1.89, 95% CI: 1.20-2.96) is different from the one mentioned in the MAH's discussion included in the full CSR (adjusted HR =2.71 (95% CI: 1.65–4.45).

2. In our view, the currently observed small, consistent increase in risk on subacute thyroiditis in CPRD, SIDIAP and NHR, adds to the cumulative evidence regarding this suspected adverse reaction. The MAH is requested to discuss whether this finding alters previous conclusions regarding the causal relation between Comirnaty and subacute thyroiditis, or justify otherwise.

   If applicable, any consequences to the product information should be discussed taking into account
   - ✓ The findings including strengths and limitations of the current study
   - ✓ Any relevant well-documented cases supportive of causality reported after January 2024
   - ✓ Any relevant publications from scientific literature

RMP aspects

None

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

9.1. Other concerns

Clinical aspects

Question 1

The MAH is requested to clarify an apparent discrepancy in the pooled adjusted HRs. The HR stated in the Figure 13 Forest plot (adjusted HR =1.89, 95% CI: 1.20-2.96) is different from the one mentioned in the MAH's discussion included in the full CSR (adjusted HR =2.71 (95% CI: 1.65–4.45).

Summary of the MAH's response

The apparent discrepancy highlighted by EMA in the reporting of the results for SAT (*i.e.*, pooled adjusted HR =1.89, 95% CI: 1.20-2.96) versus that referenced in the discussion section (*i.e.*, pooled direct effect adjusted HR = 2.71, 95% CI: 1.65–4.45) are two separate analyses. The pooled adjusted HR of 1.89 (95% CI: 1.20-2.96) shown in the results and the Forest Plot is the result of the main matched cohort analysis. The pooled adjusted direct effect HR of 2.71 (95% CI: 1.65–4.45) is from the pooled direct effect analysis which isolates the effect of the vaccine from that of potential COVID-19 infection. Therefore, this is not a discrepancy, but two different results. These analyses are pre-specified in both the protocol and statistical analysis plan.

Assessment of the MAH's response

The MAH's clarification is accepted. **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

Question 2

In our view, the currently observed small, consistent increase in risk on subacute thyroiditis in CPRD, SIDIAP and NHR, adds to the cumulative evidence regarding this suspected adverse reaction. The MAH is requested to discuss whether this finding alters previous conclusions regarding the causal relation between Comirnaty and subacute thyroiditis, or justify otherwise.

If applicable, any consequences to the product information should be discussed taking into account

- ***The findings including strengths and limitations of the current study***
- ***Any relevant well-documented cases supportive of causality reported after January 2024***
- ***Any relevant publications from scientific literature***

Summary of the MAH's response

For data **up to 31 December 2023**, please refer to the previous SAT safety signal evaluation submitted to the Saudi Arabia Health Authority (Appendix 1, not reproduced here, as it has been reviewed previously in the most recent PSUR. The results and conclusions are briefly summarized below).

PRAC Rapporteur assessment comment:

This safety signal evaluation requested by the Saudi Arabia Health Authority covering cumulative data up to **31 Dec 2023** has previously been assessed in the most recent (7th) PSUR (PSUSA/00010898/202412, covering 19 Dec 2023 through 18 Dec 2024).

In summary, the PRAC concluded [at the time of the 7th PSUR] that there is not sufficient evidence to conclude that COMIRNATY administration causes SAT and, therefore, no product labelling changes are warranted. This topic will continue to be monitored with routine pharmacovigilance.

For more recent data see below.

As requested, the MAH provided a signal evaluation report covering new information covering the period from **01 January 2024 to 12 December 2025**, which is summarized below.

Brief Introduction

Subacute granulomatous thyroiditis (SAT) is characterized by neck pain or discomfort, a tender diffuse goiter, and a predictable course of thyroid function evolution. Hyperthyroidism is typically the presentation followed by euthyroidism, hypothyroidism, and ultimately restoration of normal thyroid function.[1]

SAT is presumed to be caused by a viral infection or a postviral inflammatory process. Many patients have a history of an upper respiratory infection prior to the onset of thyroiditis (typically two to eight weeks beforehand). The disease is thought to have a seasonal incidence (higher in summer), and clusters of cases have been reported in association with Coxsackievirus, mumps, measles, adenovirus, SARS-CoV-2, and other viral infections. Therefore, a thorough medical history in the 2-8 weeks preceding onset of symptoms is important for differential diagnosis.[1]

The epidemiology of SAT is not well characterized, with variable reported incidence among studies (*e.g.* 2.4/100,000/year in a Danish cohort[2], approximately 10 per 100,000 person-years in Korean cohort during COVID-19[3]). The best available incidence data for SAT comes from the Rochester Epidemiology Project in Olmsted county, Minnesota. Between 1970 and 1997, 94 patients with SAT were identified. They report an incidence of 12.1 cases per 100,000/year with a higher incidence in females than in males (19.1 and 4.1 per 100,000/year, respectively). It is most common in young adulthood (24 per 100,000/year) and middle age (35 per 100,000/year), and it decreases in frequency with increasing age.[1] However, these incidence data are not necessarily representative of the EU region.

PRAC Rapporteur's assessment comment:

The MAH's summary of risk factors and epidemiology is accepted. It is acknowledged that thorough exclusion of alternative etiologies is essential for causality assessment considering known causes or risk factors such as viral infections or a post-viral inflammatory process. Irrespective of vaccination status, many subacute granulomatous thyroiditis (SAT) patients have a history of an upper respiratory infection prior to the onset of thyroiditis (typically two to eight weeks beforehand). The disease is thought to have a seasonal incidence (higher in summer), and clusters of cases have been reported in association with Coxsackievirus, mumps, measles, adenovirus, SARS-CoV-2, and other viral infections.

Safety Database Search

Methods

A safety database search of the Pfizer global safety database from **1 January 2024 through 12 Dec 2025** (as of 17 Dec 2025) was conducted using MedDRA (Version 28.1) to identify cases with PT: *Thyroiditis subacute* reported for the Pfizer-BioNTech COVID-19 vaccine (Search included all Monovalent and Bivalent formulations: BNT162B2; BNT162B2 MULTIVALENT NOS; BNT162B2 OMI XBB.1.5; BNT162B2, BNT162B2 OMI BA.1; BNT162B2, BNT162B2 OMI BA.4-5; BNT162b2 Omi KP.2; BNT162b2 Omi JN.1; BNT162b2 Omi LP.8.1).

PRAC Rapporteur's assessment comment:

As requested the current database review is focusing on the most recent relevant well-documented cases supportive of causality reported **after January 2024**.

Results

From 1 Jan 2024 through 12 Dec 2025, **17 new cases** were retrieved from Pfizer's global safety database. Of those, 12 were female, 4 male and 1 unknown. Mean age was 52.3 years. Regarding case outcome, 8 were recovered/recovered with sequelae/recovering, 5 were not recovered and in 4 cases the outcome was unknown. The countries of origin were as follows: Japan (4 cases), Turkey (4 cases), United States (3 cases), Germany (2 cases), Poland (2 cases), Italy (1 case) and Portugal (1 case). In addition, 9 cases were from literature and 8 were spontaneous.

A case-by-case review revealed 7 cases with insufficient information, 5 with alternative explanation such as a preceding viral infection or other confounders, and 5 remaining cases. In interpreting these remaining case reports the MAH noted that it is useful to consider that none of these cases sufficiently excluded a prior viral infection in the 2-8 weeks preceding the symptom onset, which is a major confounder introducing uncertainty about case causality. In one of those 5 remaining cases the manufacturer is not specified. These 5 cases are presented below:

1. **Case 2024000XXXXX** is a literature case [4] describing a 31-year-old female that presented with anterior neck pain and palpitation, and a heart rate of up to 150 beats per minute. The symptoms began 15 days after the second dose BNT162b2. She had two doses of the COVID-

19 mRNA vaccine. She had no family history of thyroid disease or any other chronic illness. She did not disclose any previous COVID-19 medical history. Thyroid function tests revealed hyperthyroxinemia, with serum TSH suppressed and FT4 levels elevated. ESR and CRP were also elevated. Thyroid ultrasound revealed diffuse hypoechoic echotexture of the thyroid gland, as well as decreased blood flow and thyroid scintigraphy with 99 mTc-pertechnetate showed markedly decreased thyroid uptake, consistent with thyroiditis. Indomethacin 25 mg/12 h and propranolol 20 mg/12 h treatment were initiated. After 23 days, all laboratory tests returned to normal. All symptoms resolved completely.

PRAC Rapporteur's comment:

Based on a TTO of 15 days after the second dose and lack of underlying medical conditions, causality is considered **possible** (WHO-UMC scaling), but no information is available whether previous COVID-19 or other infections were definitely excluded.

2. **Case PV2024000XXXXX** is a literature case [5] describing a 32-year-old female patient with excessive sweating and severe pain located in the anterior neck region that limited the palpation of the thyroid gland. The patient had no known history of chronic disease and had been breastfeeding for 10 months. There was no known history of allergy, autoimmune disease, thyroid disease, or previous upper respiratory tract infection. The patient had received the first dose of BNT162b2 on 28 April 2021, 1 month before presentation. Three days after the vaccination, she started to feel complaints of neck pain, arthralgia, and fever exceeding 38 °C. On presentation at the internal medicine clinic, the COVID-19 RT-PCR test was found to be negative and paracetamol and antibiotic were prescribed. Despite the intermittent use of paracetamol, the neck pain did not regress and the complaints of palpitations and sweating increased. The patient lost 7 kg in 3 weeks. On physical examination, there was tenderness and swelling in both thyroid lobes, more prominently in the right thyroid lobe with palpation. The other systemic examinations were unremarkable. A diagnosis of thyrotoxicosis was reported as well as elevated ESR and CRP levels. Thyroid Ultrasound revealed diffuse swelling of both thyroid glands and patchy hypoechoic areas with a lack of flow color on Doppler US in both thyroid lobes, especially in the right lobe. The diagnosis of SAT was confirmed and methylprednisolone 16 mg/day and propranolol 20 mg twice a day were prescribed. Three weeks after the initiation of steroid treatment, significant improvement was observed in clinical and laboratory examinations.

PRAC Rapporteur's comment:

Based on a TTO of 3 days after the first dose and lack of underlying chronic disease, allergy, or preceding upper respiratory infection including COVID-19 (PCR-test negative), causality is considered **possible** (WHO-UMC scaling). However, the TTO of 3 days after the first dose seems rather short, considering that, irrespective of vaccination, SAT patients often report an upper respiratory infection typically 2 to 8 weeks prior to the onset of thyroiditis.

3. **Case PV2024000XXXXX** is a literature case [6] describing a 39-year-old male healthcare worker presented with four weeks history of symptoms: fullness of the anterior neck, odynophagia, enlarged cervical lymph nodes, palpitations, anxiety and weight loss. Onset of symptoms was two days after the second dose of BNT162b2. There was no recent history of upper respiratory system infection or COVID-19 infection. Initial workup was significant for a TSH of 0.020 uIU/mL (n 0.45-5.330 uIU/mL), free T4 of 2.42 ng/mL (n 0.45-1.80 ng/mL) and

total T3 225.4 pg/mL (n 87-179 pg/mL). There was no evidence of leukocytosis. Ultrasound of the thyroid gland was unremarkable for nodules or hyperemia. Autoimmune thyroid disease was ruled out with negative levels of thyroid stimulating immunoglobulin, thyroid receptor antibody and anti-microsomal antibody. Thyroid scintigraphy was significant for abnormally low uptake, consistent with SAT. Clinical and biochemical improvements (TSH 4.193 uIU/mL; free T4 0.98 ng/dL) were seen after 5 months.

PRAC Rapporteur's comment:

Based on a TTO of 2 days after second dose and lack of preceding upper respiratory infections including COVID-19 (but no test results reported), causality is considered **possible** (WHO-UMC scaling).

4. **Case PV2024000XXXXX** is a literature case [4] describing a 40-year-old female. She complained of neck pain, palpitation and sweating for approximately 2 weeks. Laboratory tests revealed overt hyperthyroidism, compared to normal thyroid function tests 18 days prior. Her previous medical history was unremarkable. She had a mild case of COVID-19 that did not necessitate hospitalisation one year before her vaccination. She had received the second dose of BNT162b2 15 days prior to the SAT diagnosis with a prior dose given 2 months before. Laboratory results showed a suppressed TSH levels, with elevated FT4 and FT3 levels. ESR and CRP were also elevated. Thyroid ultrasound revealed heterogeneity in the thyroid parenchyma, bilateral multiple hypoechoic areas and decreased blood flow. The thyroid gland was found to have reactive lymph nodes, the largest of which was 11 × 7 mm in size. The patient was diagnosed with SAT based on clinical symptoms and laboratory tests. Treatment with indomethacin 25 mg/12 h and propranolol 20 mg/12 h was started. All laboratory tests and symptoms were completely resolved 33 days after the diagnosis.

PRAC Rapporteur's comment:

Based on a TTO of 2 months after first dose and 15 days after second dose and unremarkable medical history, including a mild case of COVID-19 that did not necessitate hospitalisation one year before her vaccination, causality is considered **possible** (WHO-UMC scaling). Case might be confounded by (mild) preceding SARS-CoV-2 infection.

5. **Case PV2024000XXXXX** is a literature case [7] describing an 82-year-old male with no relevant past medical history. He received the 3rd dose of anti-SARS-CoV-2 mRNA vaccine (Manufacturer not mentioned). 10 days later he was admitted to the hospital with epigastric pain, nausea and vomiting and episodes of palpitations. On admission he had no fever and was hemodynamically stable, cardiopulmonary auscultation without alterations, non-pathological abdomen, without oedema. During his hospitalization, the patient had a regular narrow complex tachycardia episode, heart rate >180 bpm, hypotension, sweating and epigastric pain. Electrical cardioversion was performed with reversion to sinus rhythm, heart rate 84 bpm. Negative troponin, no changes in the hepatobiliary profile, negative amylase. Abdominopelvic CT scan without important changes. Echocardiogram without significant changes. Laboratory showed TSH 0.04 with T4L 1.54. Negative anti-thyroid antibodies, negative TRAbs, thyroid ultrasound with enlargement of the gland. Thyroid scintigraphy with near absence of radiopharmaceutical uptake in relation to probable SAT. Started thiamazole and propranolol, with symptomatic control.

PRAC Rapporteur's comment:

Based on a TTO of 10 days after the 3rd dose and 15 days after second dose, unremarkable medical history, and no reported fever (hence active infection), causality is considered **possible** (WHO-UMC scaling). It is unknown whether preceding infections, including asymptomatic SARS-CoV-2 have been excluded.

Routine statistical reports

To support routine signal detection activities, in addition to non-statistical surveillance, the MAH generates statistical calculations, including EB05 scores.

EB_{05} is the lower 90% posterior interval of empirical Bayes geometric mean (EBGM), an empirical Bayesian implementation of the observed-to-expected (O/E) reporting frequencies. The MAH uses an $EB_{05} > 2$ as threshold of disproportionate reporting ("statistic of disproportionate reporting or "SDR").

On cumulative review, through 30 Nov 2025, EB05 values observed for the PT *Thyroiditis subacute* are in Table 6.

Table 6.EB05 by Vaccine Product

Product	**EB05**
BNT162b2 Monovalent Original	1.162
BNT162b2 Bivalent Omicron BA.1	0.390
BNT162b2 Bivalent Omicron BA.4/BA.5	0.958
BNT162b2 Multivalent NOS	-
BNT162b2 Monovalent Omicron XBB.1.5	0.214
BNT162b2 Monovalent Omicron JN.1	-
BNT162b2 Monovalent Omicron KP.2	0.325
BNT162b2 Monovalent Omicron LP.8.1	-

All EB05 values are less than the commonly utilized threshold of 2.

PRAC Rapporteur's comment:

No signal of disproportionate reporting was observed in the MAH's routine statistical analysis. All EB05 values are less than the commonly utilized threshold of 2.

MAH Conclusion

While there were 5 new well documented cases (1 case with manufacturer unknown) reporting SAT in Pfizer's safety database with a plausible temporal relationship, it is necessary to consider that some of these cases do not sufficiently exclude a prior viral infection in the 2-8 weeks preceding the symptom onset, which is a major and common confounder. This is also supported by the fact that there was no signal of disproportionate reporting for all variants in Pfizer's global safety database, as presented above.

PRAC Rapporteur's comment:

In summary

From 1 Jan 2024 through 12 Dec 2025, **17 new cases** were retrieved from Pfizer's global safety database. Of those, 12 were female, 4 male and 1 unknown. Mean age was 52.3 years. Regarding case outcome, 8 were recovered/recovered with sequelae/recovering, 5 were not recovered and in 4 cases the outcome was unknown. The countries of origin were as follows: Japan (4 cases), Turkey (4 cases), United States (3 cases), Germany (2 cases), Poland (2 cases), Italy (1 case) and Portugal (1 case). In

addition, 9 cases were from literature and 8 were spontaneous.

The MAH stated that case-by-case review revealed 7 cases with insufficient information, 5 with alternative explanation such as a preceding viral infection or other confounders, and **5 remaining cases**.

Following review (see above) of the **5 remaining** well-documented literature cases the PRAC Rapporteur considers that the causal relation between vaccination and SAT is **possible** (WHO-UMC scaling) based on a plausible TTO varying between 2 days and 2 months, and unremarkable medical history. Nevertheless, although in some cases fever, upper respiratory or SARS-CoV-2 (PCR test negative) infection has been excluded, in most of these cases it is not known whether prior viral infections in the 2-8 weeks preceding the symptom onset [which is a major confounder] have been exhaustively excluded, which hampers definite conclusions regarding causality.

No signal of disproportionate reporting was observed in the MAH's routine statistical analysis. All EB05 values are less than the commonly utilized threshold of 2.

In general, assessment of causality for this type of event based on individual spontaneous cases is challenging due to the challenges of excluding a number of relevant viral infections that play an important role in the development of this event. Therefore, the additional 5 supportive cases are not considered to provide sufficient evidence for causal association, and a coincidental finding cannot be excluded either.

Literature

A search of literature was conducted to identify new articles from January 2024 through December 2025 describing BNT162b2 and the SAT in the Medline and Embase databases. The search retrieved 69 articles, 7 of which were considered relevant to subacute thyroiditis.

Large Population-based Studies

Hviid A, Svalgaard IB. Safety of BNT162b2 mRNA COVID-19 Vaccine Batches: A Nationwide Cohort Study. Pharmacoepidemiol Drug Saf. 2025 Sep;34(9):e70207. doi: 10.1002/pds.70207. PMID: 40814857; PMCID: PMC12355449.[8]

Hviid *et al.* conducted a nationwide, population-based cohort study in Denmark to evaluate whether early, small batches of the BNT162b2 mRNA COVID-19 vaccine were associated with higher rates of serious adverse events compared with later, larger batches. The study included individuals vaccinated with BNT162b2 between 27 December 2020 and 25 April 2023, encompassing 9,983,728 administered doses across 52 predefined vaccine batches. Batches were grouped based on prior pharmacovigilance reporting rates and matched 1:1 on age, sex, and vaccination priority group. Participants were followed for 28 days after vaccination. Outcomes included 27 predefined serious adverse events of special interest (identified using ICD-10 hospital discharge diagnoses), two negative control outcomes, and all-cause mortality.

SAT was included among the prespecified adverse events. SAT events were rare, with fewer than five cases observed across comparisons. Overall, the study found no clinically meaningful differences in serious adverse event rates between vaccine batch groups.

The authors concluded that this large, nationwide analysis provides reassurance regarding the safety of BNT162b2 vaccine batches and the article does not support an association between COVID-19 vaccination and an increased risk of SAT within the 28-day post-vaccination period.

Bea S, Ahn HY, Woo J, Shin JY, Cho SW. Effect of COVID-19 Vaccination on Thyroid Disease

in 7 Million Adult and 0.2 Million Adolescent Vaccine Recipients. J Clin Endocrinol Metab. 2025 Aug 7;110(9):e3109-e3116. doi: 10.1210/clinem/dgae858. PMID: 39657695.[9]

The authors (Bea S *et al.*) conducted a large population-based analysis to evaluate the incidence of thyroid disorders following COVID-19 vaccination, including SAT, using routinely collected healthcare data in South Korea. The study assessed thyroid-related outcomes after vaccination using a self-controlled case series design, comparing incidence during post vaccination risk windows with baseline periods within the same individuals.

SAT was included as a prespecified outcome. Incidence rate ratios for SAT were not significantly elevated after either the first or second COVID-19 vaccine dose [IRRs with (95% CI) for SAT were 1.27 (0.94-1.72) for the first dose and 1.32 (0.96-1.80) for the second dose].

The authors concluded that COVID-19 vaccination was not associated with an increased risk of most thyroid diseases, including SAT based on the absence of statistically significant incidence rate ratio elevations for the evaluated outcomes. The findings contribute to increasing evidence and strengthen the safety profile of Covid-19 vaccines in relation to thyroid health.

Duskin-Bitan H, Robenshtok E, Peretz A, Beckenstein T, Tsur N, Netzer D, Cohen AD, Saliba W, Shimon I, Gorshtein A. Subacute Thyroiditis Following COVID-19 and COVID-19 Vaccination. Endocr Pract. 2024 Aug;30(8):731-736. doi: 10.1016/j.eprac.2024.05.001. Epub 2024 May 8. PMID: 38729568.[10]

Duskin-Bitan et al. conducted a large, population-based matched case-control study to evaluate whether COVID-19 infection or COVID-19 vaccination is associated with the development of new-onset SAT. Using electronic health record data from a nationwide healthcare system of Israel, the authors identified patients with newly diagnosed SAT and matched them to controls by age, sex, and other relevant characteristics. Exposures of interest included documented SARS-CoV-2 infection and receipt of COVID-19 vaccines within defined time windows prior to SAT diagnosis.

The analysis found no statistically significant association between COVID-19 vaccination and SAT at 30-, 60-, or 90-day intervals preceding diagnosis (adjusted odds ratios 0.97 (95% CI, 0.81-1.15) within 30 days, 1.10 (95% CI, 0.93-1.24) within 60 days, and 1.10 (95% CI, 0.97-1.25) within 90 days). Similarly, no association was observed between prior SARS-CoV-2 infection and subsequent SAT. These findings were consistent across multiple analytic windows and adjusted models. While SAT cases had higher use of anti-inflammatory and symptomatic treatments, reflecting standard clinical management, vaccination status did not differ meaningfully between cases and controls.

Overall, this study provides robust population-level evidence that neither COVID-19 vaccination nor COVID-19 infection is associated with an increased risk of SAT.

Hassan NAIF, Toraih EA, Shebl MA, Usmani A, Arafa AOG, Elnouty MM, Laraib-Ijaz A, Atwal U, Gir D, Samuel HAO, Hassanin M, Salim N, Shah J, Hazimeh Y, Aiash H. Risk of thyroid dysfunction after COVID-19 vaccination: meta-analysis of 11 million individuals. Ann Med Surg (Lond). 2025 Oct 27;87(12):8789-8802. doi: 10.1097/MS9.0000000000004186. PMID: 41377406; PMCID: PMC12688942.[11]

Hassan *et al.* conducted a large systematic review and meta-analysis of 21 studies to evaluate the risk of thyroid dysfunction following COVID-19 vaccination, synthesizing evidence from observational studies comparing vaccinated and unvaccinated individuals. The analysis included data from more than 11 million individuals across multiple countries and vaccine platforms and assessed a range of thyroid outcomes, including thyroiditis, hyperthyroidism, hypothyroidism, and Graves' disease.

Across pooled analyses, no increased overall risk of thyroid dysfunction or thyroiditis was observed among vaccinated individuals compared with unvaccinated controls. For overall thyroid dysfunction,

pooled relative risk estimate was RR 0.27, (95% CI 0.14-0.51). While a small relative increase in new-onset hyperthyroidism was noted (RR 1.85, 95% CI 1.84-1.86), absolute event rates were low. Importantly, outcomes related to thyroiditis, which encompassed SAT, did not differ significantly between groups. The authors emphasized that findings for specific thyroid subtypes should be interpreted cautiously due to heterogeneity across studies and outcome definitions.

Overall, this meta-analysis provides high-level evidence that COVID-19 vaccination is not associated with an increased risk of thyroiditis, including SAT, at the population level.

Cheng KL, Yu WS, Wang YH, Ibarburu GH, Lee HL, Wei JC. Long-Term Thyroid Outcomes After COVID-19 Vaccination: A Cohort Study of 2 333 496 Patients From the TriNetX Network. J Clin Endocrinol Metab. 2025 Sep 16;110(10):e3366-e3375. doi: 10.1210/clinem/dgaf064. PMID: 39883558.[12]

Cheng *et al.* evaluated long-term thyroid outcomes following COVID-19 vaccination using a large, population-based retrospective cohorts with extended follow-up to assess incident thyroid disorders, including SAT.

The study used the TriNetX database, including 1,166,748 vaccinated and 1,166,748 unvaccinated individuals. No significant difference in the risk of SAT was observed between the groups over follow-up periods of 3, 6, 9, and 12 months (hazard ratios ranged from 0.70 to 1.07; all 95% CIs included 1.00). While differences were observed for other thyroid outcomes such as an increased risk of hypothyroidism at later follow up, this did not implicate SAT and were interpreted as requiring continued clinical monitoring rather than indicating a vaccine related safety signal. Overall, this large comparative study provides reassuring population-level evidence that COVID-19 vaccination is not associated with an increased incidence of SAT over long-term follow up.

PRAC Rapporteur's assessment comment:

In none of the 5 highlighted *Large Population-based Studies* an increased risk on SAT was observed in vaccinated individuals.

Case Series and Case Reports

Vikram Jeet Singh Gill, Hongxiu Luo, #1697016 mRNA (SARS-CoV-2) vaccine-induced hyperthyroidism - Learnings Based on the Meta-Analysis, Endocrine Practice, Volume 30, Issue 5, Supplement, 2024, Pages S139-S140, ISSN 1530-891X, https://doi.org/10.1016/j.eprac.2024.03.040.[13]

Gill *et al.* reported cases of thyroid dysfunction following mRNA SARS-CoV-2 vaccination, including SAT, in a clinical report published in Endocrine Practice. The article describes patients who developed thyrotoxicosis after COVID-19 vaccination, with etiologies including SAT and Graves' disease, highlighting the need to distinguish inflammatory thyroiditis from autoimmune hyperthyroidism in the post-vaccination setting.

Patients with SAT presented with neck pain, systemic symptoms, elevated inflammatory markers, and biochemical thyrotoxicosis, consistent with classic SAT. Symptom onset occurred within a short interval following mRNA vaccination, supporting a temporal relationship. Diagnostic evaluation differentiated SAT from Graves' disease using clinical features, laboratory findings, and imaging when available. Management followed standard approaches, including anti-inflammatory therapy for SAT, with improvement over follow-up and, in some cases, a transient hypothyroid phase.

The authors discussed potential immune-mediated mechanisms by which mRNA vaccination might trigger thyroid inflammation in susceptible individuals, while emphasizing that such events appear to be rare. Overall, this report supports a temporal association between mRNA COVID-19 vaccination and

SAT but remains descriptive and lacks a comparator group.

PRAC Rapporteur assessment comment:

This publication is a conference abstract. It is understood that based on a temporal association between mRNA COVID-19 vaccination and SAT a causal role of vaccination is possible, but lack of sufficient detail (*e.g.* regarding relevant medical history or exclusion of alternative etiologies) precludes firm conclusions.

Kumar N, Zeki DF, Zilbermint M. Subacute Thyroiditis Due to COVID-19 Vaccine. J Community Hosp Intern Med Perspect. 2024 Jan 12;14(1):57-61. doi: 10.55729/2000-9666.1301. PMID: 38482090; PMCID: PMC10932489.[14]

Kumar *et al.* described a single case of SAT temporally associated with mRNA Covid-19 vaccine in an elderly patient. The report involved a 90-year-old woman who developed symptoms consistent with SAT approximately 19 days after receiving the second dose of mRNA SARS-CoV-2 vaccine. The patient had no known prior thyroid disease.

Clinical evaluation showed thyrotoxicosis, with suppressed TSH and elevated free thyroid hormone levels. Thyroid imaging supported a diagnosis of destructive inflammatory thyroiditis rather than autoimmune hyperthyroidism. No alternative infectious or inflammatory trigger was clearly identified at the time of presentation.

The patient was treated with systemic corticosteroids, resulting in clinical improvement. The authors discussed potential immune mediated mechanisms as a possible explanation for the temporal relationship, while acknowledging the limitation of single patient observations.

PRAC Rapporteur's assessment comment:

Based on a temporal association (TTO of 19 days after 2nd dose) and exclusion SARS-CoV-2 infection (test negative) causality is considered possible in this case. However, although the patient had no history of thyroid disease, her past medical history was significant for Parkinson's disease, atrial flutter, hypertension, depression and mild hyponatremia. No AEs were reported following her first dose which was administered 5 months prior.

Literature MAH Conclusion

The available literature includes multiple large population-based studies, a meta-analysis with more than 11 million individuals, and case series investigating SAT following COVID-19 vaccination. These large studies were designed to evaluate thyroid outcomes after vaccination and generally demonstrated that SAT events following COVID-19 vaccination were rare and not increased when compared with background rates or unvaccinated controls. The smaller cohort studies, case series and single case reports primarily provided descriptive clinical information on SAT cases occurring temporally after vaccination. These reports lacked comparator groups and did not provide incidence estimates. Overall, based on the literature review, there is no evidence to support an association between Comirnaty and SAT.

PRAC Rapporteur's assessment comment:

The MAH's conclusion is endorsed that based on the review of available scientific literature, there is no evidence to support an association between Comirnaty and SAT.

PASS C4591021

According to the MAH the C4591021 study demonstrated an elevated pooled adjusted hazard ratio for SAT of 1.89, (95% CI: 1.20-2.96), however the individual databases showed wide confidence intervals. The results for the sensitivity analyses among those with no healthcare contact in the previous 7 days of time zero and those with at least 2 doses of the vaccine show similar results to those seen with the overall cohort. Results using historical controls did not demonstrate an elevated risk. The results showed that the adjusted HR for SAT seemed higher in those who were frail or had comorbidities, and immunocompromised individuals as well as those who had prior COVID-19 infection. However, all estimates were imprecise and should be interpreted with caution. No events were observed in pregnant women.

The strengths of C4591021 include its large size (>12 million vaccinated) which included individuals from multiple European countries that were highly representative of the underlying population. The study included a heterogeneous group of individuals of all ages, persons with comorbid conditions, the immunocompromised, and pregnant women, and evaluated the risk of 37 AESIs using multiple study designs and sensitivity analyses.

Limitations of C4591021 comprise those that are inherent in all non-interventional studies. Those limitations have been previously discussed in detail in the final study report. These include limitations due to observation periods; exposure measurement error; outcome misclassification; limitations on the quality of covariates; residual confounding; censoring and selection bias.

Regarding the AESI of SAT, as the PRAC noted, 1) the evaluation was based on a limited number of cases, 57 in vaccinated and 37 in unvaccinated individuals resulting in wide 95 % confidence intervals and reduced precision of the estimate; 2) the potential confounding effect of COVID-19 infection should be considered as a higher number of SAT cases was observed in the historical COVID-19 period (104 cases) compared to pre-COVID-19 period (60 cases); and 3) the background incidence of SAT from Q1 2018 through Q4 2022 was very low with little seasonal variation (i.e., the indicated rarity of background rates in the databases and the seasonal variation pose additional challenges). Therefore, caution is warranted when interpreting the estimate for SAT.

PRAC Rapporteur assessment comment:

The MAH's discussion of strengths and limitations of the C4591021 PASS is accepted.

MAH Overall conclusion

Based on the new data reviewed since the last signal evaluation and taking into account the results from study C4591021, the MAH considers that SAT is a potential risk. The risk is considered to be not important because SAT is a self-limiting disease with limited clinical impact, potentially occurring very rarely (as also indicated by the low number of events among large studies), that does not significantly affect the drug's benefit-risk balance or have public health implications that require focused pharmacovigilance and risk minimization. No changes to the RMP or Product information are considered necessary. This topic will continue to be monitored using Routine Pharmacovigilance.

PRAC Rapporteur assessor's comment:

The MAH provided a comprehensive review of the most recent available evidence on *subacute thyroiditis* as requested.

Following review of the submitted data the MAH's conclusion is endorsed that at this moment the cumulative evidence is inconclusive and insufficient to establish causal relation between Comirnaty and SAT. At this moment no update of the product information is warranted, provided SAT will be continue to be monitored using routine pharmacovigilance. **Issue resolved.**

In summary:

Safety database review

From 1 Jan 2024 through 12 Dec 2025, **17 new cases** were retrieved from Pfizer's global safety database. Of those, 12 were female, 4 male and 1 unknown. Mean age was 52.3 years. Regarding case outcome, 8 were recovered/recovered with sequelae/recovering, 5 were not recovered and in 4 cases the outcome was unknown. The countries of origin were as follows: Japan (4 cases), Turkey (4 cases), United States (3 cases), Germany (2 cases), Poland (2 cases), Italy (1 case) and Portugal (1 case). In addition, 9 cases were from literature and 8 were spontaneous.

The MAH stated that case-by-case review revealed 7 cases with insufficient information, 5 with alternative explanation such as a preceding viral infection or other confounders, and **5 remaining cases**.

Following review (see above) of the **5 remaining** well-documented literature cases the PRAC Rapporteur considers that the causal relation between vaccination and SAT is **possible** (WHO-UMC scaling) based on a plausible TTO varying between 2 days and 2 months, and no other risk factors reported in the medical history. Nevertheless, although in some of these cases fever, upper respiratory or SARS-CoV-2 (PCR test negative) infection has been excluded, in most of these cases it is not known whether prior viral infections in the 2-8 weeks preceding the symptom onset [which is a major confounder] have been exhaustively excluded, which hampers definite conclusions regarding causality.

In general, assessment of causality for this type of event based on individual spontaneous cases is challenging due to the challenges of excluding a number of relevant viral infections that play an important role in the development of this event. Therefore, the additional 5 supportive cases are not considered to provide sufficient evidence for causal association, and a coincidental finding cannot be excluded either.

Scientific literature

Based on review of the available scientific literature there is no evidence to support an association between Comirnaty and SAT. The publications include multiple large population-based studies, a meta-analysis with more than 11 million individuals, and case series investigating SAT following COVID-19 vaccination. These large studies were designed to evaluate thyroid outcomes after vaccination and generally demonstrated that SAT events following COVID-19 vaccination were rare and not increased when compared with background rates or unvaccinated controls. The smaller descriptive cohort studies, case series and single case reports showed that based on a temporal association causality is considered possible, but these reports lacked comparator groups and did not provide incidence estimates.

PASS C4591021 demonstrated an elevated pooled adjusted hazard ratio for SAT of 1.89, (95% CI: 1.20-2.96), however the individual databases showed wide confidence intervals. The results for the sensitivity analyses among those with no healthcare contact in the previous 7 days of time zero and those with at least 2 doses of the vaccine show similar results to those seen with the overall cohort. Results using historical controls did not demonstrate an elevated risk. The results showed that the adjusted HR for SAT seemed higher in those who were frail or had comorbidities, and immunocompromised individuals as well as those who had prior COVID-19 infection. However, all estimates were imprecise and should be interpreted with caution. No events were observed in pregnant women.

The strengths of PASS C4591021 include its large size (>12 million vaccinated) which included individuals from multiple European countries that were highly representative of the underlying population. The study included a heterogeneous group of individuals of all ages, persons with comorbid conditions, the immunocompromised, and pregnant women, and evaluated the risk of 37 AESIs using multiple study designs and sensitivity analyses.

Limitations of C4591021 include those that are inherent to the non-interventional design, *i.e.* limitations due to observation periods; exposure measurement error; outcome misclassification; limitations on the quality of covariates; residual confounding; censoring and selection bias.

As previous noted by the PRAC, 1) the evaluation was based on a limited number of cases, 57 in vaccinated and 37 in unvaccinated individuals resulting in wide 95 % confidence intervals and reduced precision of the estimate; 2) the potential confounding effect of COVID-19 infection should be considered as a higher number of SAT cases was observed in the historical COVID-19 period (104 cases) compared to pre-COVID-19 period (60 cases); and 3) the background incidence of SAT from Q1 2018 through Q4 2022 was very low with little seasonal variation (*i.e.*, the indicated rarity of background rates in the databases and the seasonal variation pose additional challenges).

Assessment of the MAH's response

Conclusion

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