# NON-INTERVENTIONAL (NI) STUDY
# FINAL REPORT

## 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?<br><br>**Objectives**<br><br>***Primary study objective***<br><br>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.<br><br>***Secondary study objectives***<br><br>• 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.<br><br>• 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.<br><br>• 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<br>Assistant Professor<br>University Medical Center Utrecht<br><br>Miriam Sturkenboom<br>Professor<br>University Medical Center Utrecht<br><br>Alejandro Arana<br>Senior Director Epidemiology<br>RTI Health Solutions<br><br>On behalf of the Vaccine Monitoring Collaboration for Europe (VAC4EU) Consortium research team |

## Marketing Authorization Holder

| | |
|---|---|
| **Marketing Authorization Holder** | BioNTech Manufacturing GmbH<br>An der Goldgrube 12<br>55131 Mainz<br>Germany |
| **MAH contact person** | Constanze Blume |

## TABLE OF CONTENTS

## LIST OF IN-TEXT TABLES



## LIST OF IN-TEXT FIGURES

## Annex 1. List of stand-alone documents

Appendix 1. SIGNATURES

Standalone document.

Appendix 2. PROTOCOL

Standalone document.

Appendix 3. INVESTIGATORS AND CORRESPONDING INDEPENDENT ETHICS COMMITTEES (IECs) OR INSTITUTIONAL REVIEW BOARDS (IRBs)

Refer to **Section 3 Investigators** and **Section 5 Milestones**

Appendix 3.1. List of Investigators by Country

Refer to **Section 3 Investigators**

Appendix 3.2. List of Independent Ethics Committee (IEC) or Institutional Review Board (IRB) and Corresponding Protocol Approval Dates

Refer to **Section 5 Milestones**

Appendix 4. STATISTICAL ANALYSIS PLAN

Standalone document.

Appendix 5. SAMPLE CASE REPORT FORM (CRF) / DATA COLLECTION TOOL (DCT)

Validation data collection form.

Standalone document.

Appendix 6. SAMPLE STANDARD SUBJECT INFORMATION SHEET AND INFORMED CONSENT DOCUMENT (ICD)

Not applicable.

Appendix 7. LIST OF SUBJECT DATA LISTINGS

Not applicable.

Appendix 8. ADDITIONAL DOCUMENTS

Appendix 8.1. AESI VALIDATION PLAN

Standalone document.

Appendix 8.2: APPENDIX TABLES AND FIGURES

Standalone document

# Appendix 8.3: CODE LIST

Standalone document

## 1. ABSTRACT (STAND-ALONE DOCUMENT)

## 2. LIST OF ABBREVIATIONS

| Abbreviation | Definition |
|---|---|
| ACCESS | vACcine Covid-19 monitoring readinESS |
| ACI | acute cardiovascular injury |
| ADEM | acute disseminated encephalomyelitis |
| AESI | adverse events of special interest |
| AIH | autoimmune hepatitis |
| ARDS | acute respiratory distress syndrome |
| ASD | absolute standardised difference |
| BMI | body mass index |
| CAD | coronary artery disease |
| CDC | Centers for Disease Control and Prevention |
| CI | confidence interval |
| CMA | conditional marketing authorisation |
| COVID-19 | Coronavirus disease 2019 |
| CPRD Aurum | Clinical Practice Research Datalink Aurum |
| CVST | cerebral venous sinus thrombosis |
| DEAP | data expert and access partner |
| DHPC | Direct Healthcare Professional Communication |
| DM-1 | diabetes mellitus |
| DSRU | Drug Safety Research Unit |
| ECDC | European Centre for Disease Prevention and Control |
| EEA | European Economic Area |
| EMA | European Medicines Agency |
| EpiChron | EpiChron Research Group on Chronic Diseases at the Aragon Health Sciences Institute (Spain) |
| ES | Spain |
| EU | European Union |
| FDA | Food and Drug Administration |
| FGR | foetal growth restriction |
| GACVS | Global Advisory Committee on Vaccine Safety |
| GBS | Guillain-Barré syndrome |
| GP | general practitioner |
| HLH | Hemophagocytic lymphohistiocytosis |
| HPV | human papilloma virus |
| HR | hazard ratio |
| HSD | Health Search Database (Italy) |
| ICD | International Classification of Diseases |
| ICD-9 | International Classification of Diseases, 9th Revision |
| ICD-10 | International Classification of Diseases, 10th Revision |
| IPTW | inverse probability of treatment weighting |
| IR | incidence ratio |
| IRB | institutional review board |
| IRR | incidence rate ratio |
| IT | Italy |

| Abbreviation | Definition |
|---|---|
| ITP | idiopathic thrombocytopenia |
| JCVI | Joint Committee on Vaccination and Immunisation |
| KM | Kaplan-Meier |
| MAH | marketing authorisation holder |
| MIS | multisystem inflammatory syndrome |
| MIS-C | multisystem inflammatory syndrome in children |
| mRNA | messenger ribonucleic acid |
| NA | not available |
| ND | not done |
| NE | not estimable |
| NHR | Norway Health Registries |
| NR | not reportable |
| NSAIDs | non-steroidal anti-inflammatory drugs |
| PASS | post-authorisation safety study |
| PHARMO | PHARMO Institute for Drug Outcomes Research or PHARMO Data Network (Netherlands) |
| PPV | positive predictive value |
| PR | prevalence rates |
| PRAC | Pharmacovigilance Risk Assessment Committee |
| PRR | prevalence rate ratios |
| PS | propensity score |
| PSUR | periodic safety update reports |
| PY | person-years |
| QC | quality control |
| RD | rate difference |
| RMP | risk management plan |
| RTI | RTI Health Solutions |
| SAP | statistical analysis plan |
| SARS-CoV-2 | Severe acute respiratory syndrome coronavirus 2 (cause of COVID-19) |
| SCCS | self-controlled case series |
| SCRI | self-controlled risk interval |
| SD | standard deviation |
| SFN | Small fiber neuropathy |
| SIDIAP | Sistema d'Informació per el Desenvolupament de la Investigació en Atenció Primària [Information System for the Improvement of Research in Primary Care] |
| SOCV | single organ cutaneous vasculitis |
| SPEAC | Safety Platform for Emergency vACcines |
| TTS | thrombosis thrombocytopenia syndrome |
| UK | United Kingdom |
| VAC4EU | Vaccine Monitoring Collaboration for Europe |

## 3. INVESTIGATORS

### Principal Investigator(s) of the Protocol

| Name, degree(s) | Job Title | Affiliation |
|---|---|---|
| Cynthia de Luise, PhD, MPH | Senior Director, Safety Surveillance Research | Pfizer, Inc. |
| Daniel Weibel, PhD | Assistant Professor | University Medical Center Utrecht |
| Alejandro Arana, MD, MPH | Senior Director, Epidemiology | RTI Health Solutions |
| Miriam Sturkenboom, PhD | Professor | University Medical Center Utrecht |
| Xabier Garcia de Albeniz, MD, PhD | Director, Epidemiology | RTI Health Solutions |
| Estel Plana, MSc | Director, Biostatistics | RTI Health Solutions |
| Rachel Weinrib, MPH | Research Epidemiologist | RTI Health Solutions |

### Lead Country Investigator(s) of the Protocol

| Name, degree(s) | Job Title | Affiliation | Address |
|---|---|---|---|
| Jetty Overbeek, PhD | Head of Research | PHARMO Institute for Drug Outcomes Research | Van Deventerlaan 30-40<br>3528 AE Utrecht<br>The Netherlands |
| Anteneh Desalegn, PhD | Researcher | University of Oslo | PO 1068<br>Blindern<br>0316 Oslo, Norway |
| Carlo Giaquinto, MD | President | Fondazione Penta ETS | Corso Stati Uniti 4<br>35127 Padova<br>Italy |
| Antonio Gimeno-Miguel, MPH, PhD | Researcher | EpiChron Research Group. Instituto Aragonés de Ciencias de la Salud | Hospital Universitario Miguel Servet<br>Paseo Isabel la Católica 1-3<br>50009, Zaragoza, Spain |
| Debabrata Roy, PhD | Head of Epidemiology and Research | Drug Safety Research Unit (DSRU) | Drug Safety Research Unit<br>Bursledon Hall<br>Blundell Lane<br>Southampton, Hampshire<br>SO31 1AA<br>United Kingdom |

## List of other investigators by country

| Name, degree(s) | Title | Affiliation |
|---|---|---|
| Rosa Gini, PhD | Head Pharmacoepidemiology Unit | Agenzia regionale di sanità della Toscana |
| Francesco Lapi PhD | Director | Health Search Research |
| Thom Lysen, MD PhD | Senior Researcher | PHARMO Institute for Drug Outcomes Research |
| Jesse van den Berg, MD | Researcher | |
| Jordy Gaspersz, MSc | Researcher | |
| Linda Härmark, MPharm, MEpi, PhD, MBA | Director | Drug Safety Research Unit (DSRU) |
| Catherine Fry, PhD | Epidemiologist | |
| Samantha Lane, MSc, PgD, BSc | Senior Epidemiologist | |
| Taylor Aurelius, PhD | Epidemiologist | |
| Denise Morris, PhD | Epidemiologist | |
| Beatriz Poblador-Plou, MPH, PhD | Researcher | EpiChron Research Group. Instituto Aragonés de Ciencias de la Salud |
| Alejandro Santos-Meijías | Researcher | |
| Felipe Villalobos, MD, PhD | Senior Researcher | IDIAP-Jordi Gol |
| Carlo Alberto Bissacco, MSc | Statistician | |
| Meritxell Pallejá, MSc | Statistician | |
| Marc Far, MSc | Data Scientist | |
| Angela Lupattelli, PhD† | Professor | University of Oslo |
| Mahmoud Zidan, MSc | Researcher | |

†Deceased 23 January 2025

## 4. OTHER RESPONSIBLE PARTIES

| Responsible Party Name and Affiliation | Role in the study |
|---|---|
| Vaccine Monitoring Collaboration for Europe (VAC4EU) | Coordination of VAC4EU study framework and network across VAC4EU studies; contracting Scientific Advisory Board;<br>Support for:<br>• contract templates; negotiations, and contract amendments;<br>• archiving of study documents; support quality system oversight and implementation<br>Support and implementation of tools<br>Scientific review |
| Wan-Ting Huang, MD, National Taiwan University Children's Hospital, Taipei, Taiwan | Scientific Advisory Board member |
| Ian Douglas, PhD, London School of Hygiene and Tropical Medicine, United Kingdom | Scientific Advisory Board member |
| Elena Palà, PhD, Teamit Institute | Study Manager |
| Irene Pazos, PhD, Teamit Institute | Study Manager |
| Anna Brutau, PhD, Teamit Institute | Study Manager |
| Chiara Messina, MPH | Head of Program Operations, LOC |
| Luana Ferlito, PharmD, Penta Foundation | Clinical Project Manager, LOC |
| Margaret Haugh, PhD, MediCom Consult | Medical Writer |

## 5. MILESTONES

| Milestone | Planned date | Actual date | Comments |
|---|---|---|---|
| Date of independent institutional review board (IRB) approval of protocol | | 05 October 2021 | |
| Registration in the EU PAS register | 25 June 2021 | 25 June 2021 | |
| Start of data collection | 30 September 2021 | 30 September 2021 | |
| End of study data collection | 30 September 2024 | 31 March 2025 | |
| Study progress report [1] | 30 September 2021 | 27 September 2021 | |
| Interim report I | 31 March 2022 | 23 March 2022 | |
| Interim report 2 | 30 September 2022 | 15 September 2022 | |
| Interim report 3 | 31 March 2023 | 20 March 2023 | |
| Interim report 4 | 30 September 2023 | 15 September 2023 | |
| Interim report 5 | 31 March 2024 | 26 March 2024 | |
| Final study report | 20 December 2024 | 10 September 2025 | |

[1] Data were not provided in the progress report

## 6. RATIONALE AND BACKGROUND

The novel coronavirus, SARS-CoV-2, the cause of COVID-19, resulted in a global pandemic that was declared on March 11, 2020. The Pfizer-BioNTech COVID-19 vaccine, BNT162b, 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. This was automatically converted to a CMA in the United Kingdom on 01 January 2021. The nucleoside-modified mRNA in the original BNT162b2 and variant adapted BNT162b2 is formulated in lipid nanoparticles (LNPs), which enable delivery of the RNA into host cells to allow expression of the SARS-CoV-2 S antigen. Comirnaty does not contain the virus itself and cannot cause COVID-19. The vaccine elicits both neutralising antibody and cellular immune responses to the S antigen, that contributes to protection against SARS-CoV-2 infection.

The Pfizer-BioNTech COVID-19 vaccine is indicated for active immunisation to prevent COVID-19 caused by infection with the SARS-CoV-2 virus, in individuals 6 months of age and older. The primary vaccination schedule in children ≥6 months to ≤4 years consists of three doses, with the first two doses administered preferably 3 weeks apart and the third dose 8 weeks after the second, and a single dose in children ≥5 years.

Booster dose(s) of the original BNT162b2, bivalent BNT162b2 (original/Omi BA.1 or original/Omi BA.4/BA.5), BNT162b2 OMI XBB.1.5; BNT162b2 Monovalent OMI JN.1, or BNT162b2 Monovalent OMI KP.2 may be administered after the primary schedule, at timing dependent on individuals' age. Formulations, presentations, and posology in the approved populations may vary.

At the time of the 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 that included over 43,000 individuals aged ≥16 years. 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, for participants aged ≥16 years who had received two doses of the 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 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. 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 COVID-19 vaccine, rapid uptake was expected. Public health authorities identified priority populations for vaccination based on healthcare or essential worker status, comorbidities, and age. The vaccine was, therefore, initially provided to vulnerable groups at higher risk for SARS-CoV-2 infection and COVID-19 complications.[2] The initial authorisation was for adults and older adolescents (aged ≥16 years) only, both by the EMA (CMA) and the FDA (emergency use authorisation (EUA). However, the authorisation for the Pfizer-BioNTech COVID-19 vaccine expanded progressively from adults to adolescents, then to younger children and infants, with dose adjustments and schedules tailored for these age groups. The Pfizer-BioNTech COVID-19 vaccine 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 PV activities have been conducted, with periodic safety update reports (PSUR) submitted initially every 6 months and now annually. The Pharmacovigilance Risk Assessment Committee (PRAC) assessed various safety issues after the roll out of the vaccine (**Table 1**).

**Table 1. Summary of safety issues assessed by the Pharmacovigilance Risk Assessment Committee (PRAC)**

| Safety Issue | Earliest PRAC Discussion / Reporting Date | Notes |
|---|---|---|
| Allergic reactions and anaphylaxis | December 2020 – January 2021 | Addressed initially in risk management plan and early monitoring, product information updated and DHPC issued. |
| Local reactions (swelling, redness, pain) | December 2020 | Included in product information at first authorisation |
| Paraesthesia / hypoesthesia | December 2020 | Included early among neurological side effects. |
| Pregnancy and breastfeeding | Ongoing from December 2020 | Regularly reviewed with reassuring data on safety. |
| Myocarditis and pericarditis | July 2021 (initial); October 2021 (formal listing) | Rare but confirmed risk, especially in younger males post-second dose; product information and risk management plan updates made and DHPC issued. |
| Facial paralysis (Bell's palsy) | Early 2021 (case reports August 2021) | Recognised as rare side effect after review. |
| Lymphadenopathy | Early 2021 | Observed early after rollout, listed in safety profile. |
| Heavy menstrual bleeding | October 2022 | Added as adverse drug reaction in product information after thorough signal evaluation. |
| Erythema multiforme | Early 2022 | Included in product information after case reports raised concern. |
| Facial swelling (dermal fillers) | 2021 | Recognised and added in product information as side effect. |
| Glomerulonephritis | 2023 | Discussed as a safety signal with reported cases; ongoing surveillance and monitoring or PSUR; causality unconfirmed. |
| Hemophagocytic lymphohistiocytosis (HLH) | Ongoing through PSUR cycles (latest mid-2023 to 2024) | No new safety information identified; cumulative evidence to be reviewed in PSUR and the literature (ongoing). |
| Idiopathic inflammatory myopathies/myositis | From 2023 | Rising case reports reviewed; included as AESI (adverse event of special interest) and monitored in PASS studies and PSUR. |
| Small fiber neuropathy (SFN) | Under review in latest PSUR cycles | MAH requested to provide cumulative evidence in PSUR for ongoing review; causality assessment ongoing. |
| Postmenopausal haemorrhage | October 2023 | Monitoring closed December 2023. |

**Table 1. Summary of safety issues assessed by the Pharmacovigilance Risk Assessment Committee (PRAC)**

| Safety Issue | Earliest PRAC Discussion / Reporting Date | Notes |
|---|---|---|
| Amenorrhoea (absence of menstruation) | Under review, no causal link established | Continues to be monitored 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. |

*DHPC: Direct Healthcare Professional Communication*

Because of the relatively short prelicensure 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 programme in Europe and elsewhere. C4591021 is a post-authorisation safety study (PASS) that assessed the risk of 37 prespecified adverse events of special interest (AESI) in individuals of all ages in the general European population who received >1 dose of the Pfizer-BioNTech COVID-19 vaccine. This study is a category 3 commitment in the EU risk management plan and a post-marketing requirement to the FDA. Five interim study reports have been prepared for submission to the EMA and FDA every 6 months beginning in September 2021 through to March 2024. This document is the final C4591021 study report.

## 7. RESEARCH QUESTION AND OBJECTIVES

Research question: Is there an increased risk of select adverse events of special interest (AESIs) after being vaccinated with the Pfizer-BioNTech COVID-19 vaccine?

### 7.1. Objectives

#### 7.1.1. Primary study objective

- To determine whether an increased risk of prespecified AESIs 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.

#### 7.1.2. Secondary study objectives

- To estimate the incidence rates of prespecified AESIs 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 AESIs exists following the administration of at least one dose of the Pfizer-BioNTech COVID-19 vaccine compared 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 AESIs exists following the administration of at least one dose of the Pfizer-BioNTech COVID-19 vaccine compared with no COVID-19 vaccination, in pregnant women 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.

- 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.

## 8. AMENDMENTS AND UPDATES

Details of the changes made for the six protocol amendments can be found in the Standalone Appendix 2 (Protocol V8.0, 30 September 2025).

## 9. RESEARCH METHODS

Full details of the research methods used can be found in the protocol (Standalone Appendix 2) and are summarised here.

### 9.1. Study design

This post-authorisation active surveillance study of AESIs (**Table 2**) associated with the Pfizer-BioNTech COVID-19 vaccine used a retrospective matched cohort design involving multiple databases (Protocol Standalone Appendix 2). In addition, a self-controlled risk interval (SCRI) design was used for a subset of the AESIs studied. Sensitivity analyses were conducted using historical controls during 2018 and 2019 (prior to COVID-19) and during 2020 (COVID-19 period). Details of the design are described in the protocol (Standalone Appendix 2).

**Table 2. List of selected adverse events of special interest**

| Body system/ classification | Adverse event of special interest | Estimated risk window (days)* | Analytic approach |
|---|---|---|---|
| Autoimmune diseases | Guillain-Barré syndrome[a] | 42[3] | Cohort/SCRI |
| | Acute disseminated encephalomyelitis | 42[3] | Cohort/SCRI |
| | Narcolepsy[a] | 42[b] | Cohort/SCRI |
| | Acute aseptic arthritis | 42[c] | Cohort/SCRI |
| | Diabetes mellitus type I | 365 | Cohort |
| | Idiopathic thrombocytopenia[a] | 42[4] | Cohort/SCRI |
| | Thrombosis thrombocytopenia syndrome (TTS) [a] | 15[3] | Cohort/SCRI |
| | Myositis | 365 | Cohort |

## Table 2. List of selected adverse events of special interest

| Body system/ classification | Adverse event of special interest | Estimated risk window (days)* | Analytic approach |
|---|---|---|---|
| Cardiovascular system | Acute cardiovascular injury | 365[d]dd | Cohort |
| | Arrhythmia | 365 | Cohort |
| | Heart failure | 365 | Cohort |
| | Stress cardiomyopathy | 365 | Cohort |
| | Coronary artery disease | 365 | Cohort |
| | Myocarditis[a]<br>Pericarditis[a]<br>Myocarditis or pericarditis[a] | 21 after each dose<br>14 after each dose<br>7 after each dose | Cohort/SCRI |
| Circulatory system | Coagulation disorders: thromboembolism, haemorrhage | 28[3] | Cohort/SCRI |
| | Single organ cutaneous vasculitis | 28[e] | Cohort/SCRI |
| | Cerebral venous sinus thrombosis | 28 | Cohort/SCRI |
| Hepato-gastrointestinal and renal system | Acute liver injury | 365 | Cohort |
| | Acute kidney injury | 365 | Cohort |
| | Acute pancreatitis | 365 | Cohort |
| | Rhabdomyolysis | 365 | Cohort |
| | Glomerulonephritis | 180 | Cohort |
| Nerves and central nervous system | Generalised convulsions | 42[3] | Cohort/SCRI |
| | Meningoencephalitis | 42[3] | Cohort/SCRI |
| | Transverse myelitis[a] | 42[3] | Cohort/SCRI |
| | Bell's palsy | 42[3] | Cohort/SCRI |
| Respiratory system | Acute respiratory distress syndrome | 365 | Cohort |
| Skin and mucous membrane, bone and joints system | Erythema multiforme | 42[f] | Cohort |
| | Chilblain-like lesions | 42[e] | Cohort |
| Reproductive system | Secondary amenorrhoea | 183 | Cohort |
| | Hypermenorrhoea | 183 | Cohort |
| Other system | Anaphylaxis[a] | 1[3] | Cohort/SCRI |
| | Multisystem inflammatory syndrome | 42[g] | Cohort |
| | Death (any causes) | 365 | Cohort |
| | Subacute thyroiditis | 365[c] | Cohort |
| | Sudden death | 365 | Cohort |
| Pregnancy outcome, maternal | Gestational diabetes | After 20 weeks gestation | Sub-cohort |
| | Preeclampsia | After 20 weeks gestation | Sub-cohort |
| | Maternal death | Any time pregnancy | Sub-cohort |
| Pregnancy outcome, neonates. Define design taking trimester into account | Foetal growth restriction | Any time pregnancy | Sub-cohort |
| | Spontaneous abortions | At termination | Sub-cohort |
| | Stillbirth | At birth | Sub-cohort |
| | Preterm birth | At preterm birth | Sub-cohort |
| | Major congenital anomalies[a] | 1 year after birth | Sub-cohort |
| | Microcephaly | At birth | Sub-cohort |
| | Neonatal death | At birth | Sub-cohort |
| | Termination of pregnancy for foetal anomaly | At termination | Sub-cohort |

**Table 2. List of selected adverse events of special interest**

| Body system/ classification | Adverse event of special interest | Estimated risk window (days)* | Analytic approach |
|---|---|---|---|

**Notes:**
* 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).
a This AESI will undergo clinical validation.
b Published risk and control intervals for demyelinating diseases and cranial disorders were applied to TM and narcolepsy/cataplexy.
c Published risk and control intervals for autoimmune disorders were applied to similar autoimmune rheumatic conditions (i.e., fibromyalgia and autoimmune thyroiditis).
d Published risk and control intervals for myocarditis and pericarditis were applied to other cardiovascular conditions (i.e., heart failure and cardiogenic shock, stress cardiomyopathy, CAD, arrhythmia, AMI).
e Similar risk and control intervals were applied to all cardiovascular and haematological disorders characterised by damage to the blood vessels and/or arteries and clotting (i.e., microangiopathy, DVT, pulmonary embolus, limb ischaemia, haemorrhagic disease, DIC, chilblain-like lesions). The published risk and control intervals for KD were applied to vasculitis given that KD is a type of medium and small-vessel vasculitis.
f Published risk and control intervals for non-anaphylactic allergic reactions were applied to hypersensitivity disorders (i.e., erythema multiforme).
g As severe COVID-19 symptoms range from severe pneumonia, acute respiratory distress syndrome, and multisystem organ failure/MIS-A, a 1-42 day risk window was applied to capture the 14-day incubation period of the disease and 4-5 day period from exposure to symptom onset

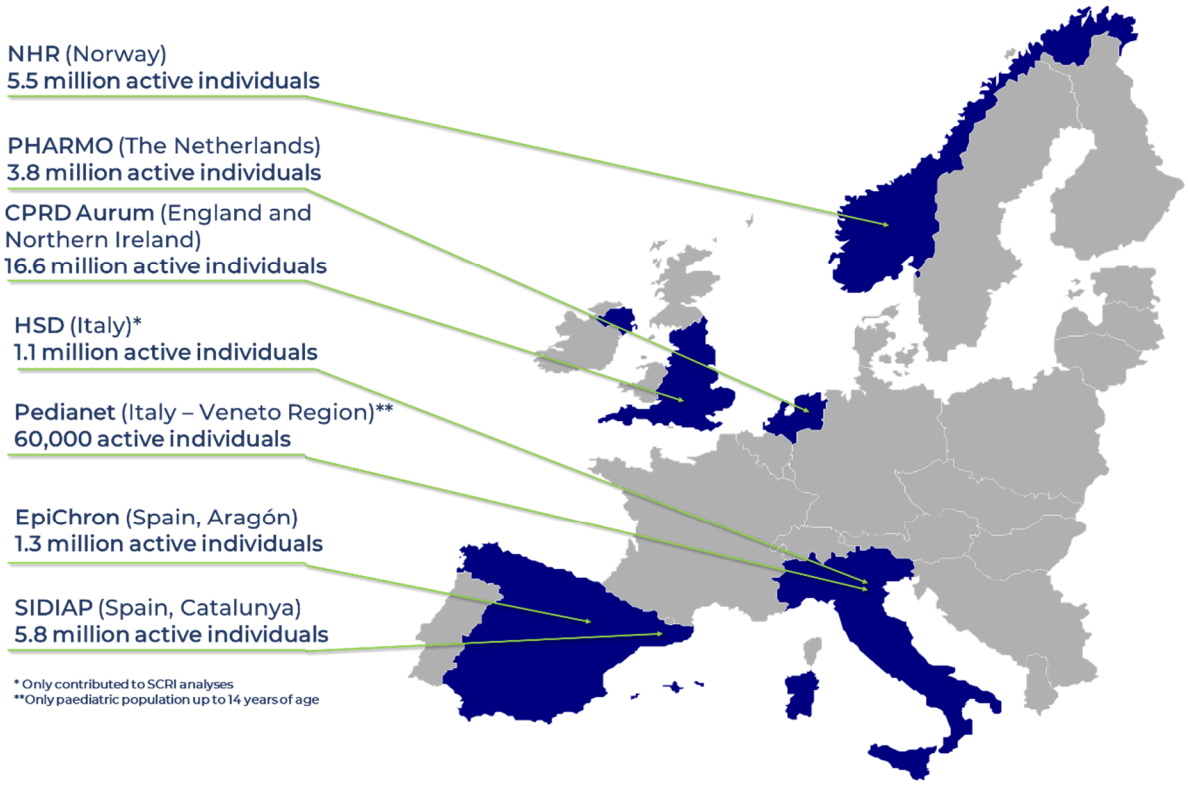
## 9.2. Setting

The study planned to use data from eight European electronic healthcare data sources in Italy, the Netherlands, Norway, Spain and part of the UK (England and Northern Ireland). However, one data source in Italy, Agenzia Regionale di Sanita' della Toscana (ARS Toscana), only contributed to the first and second interim reports due to national and regional re-assessment of regulations affecting their ability to provide public data for PASS studies. Therefore, this final report contains data from seven European electronic healthcare data sources.

### 9.2.1. Data sources

Seven electronic healthcare data sources from five European countries provided data for this final report (**Figure 1**):

**Figure 1. Location and number of active individuals in each data source**




HSD: Health Search Database; PHARMO: PHARMO Data Network; NHR: The Norwegian health registers; EpiChron: EpiChron Research Group on Chronic Diseases at the Aragon Health Sciences Institute; SIDIAP: Sistema d'Informació per el Desenvolupament de la Investigació en Atenció Primària [Information System for the Improvement of Research in Primary Care]; CPRD (Clinical Practice Research Datalink) Aurum.

### 9.2.2. 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 3**) and ended on the date of the latest data availability. The study period was two years for AESIs. The specific risk windows for acute and non-acute events have been described in the statistical analysis plan (SAP) (Standalone Appendix 4). Women who became pregnant during the two-year study period, were followed up for an additional year for the pregnancy outcomes.

**Table 3. 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<br>HSD: 01 January 2021–30 June 2023 |
| The Netherlands (PHARMO) | 08 January 2021 | GP data: 06 January 2021–30 June 2023<br>Hospital data: 6 January 2021–31 Dec 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<br>SIDIAP: 01 January 2021–30 June 2023 |
| England and Northern Ireland (CPRD Aurum) | 08 December 2020 | 08 December 2020–07 June 2023 |

### 9.3. Subjects

The source population for both the cohort and SCRI designs was all individuals registered in the healthcare data sources shown in **Figure 1**.

#### 9.3.1. Concurrent vaccinated and unvaccinated matched cohorts

The primary objective was assessed using a retrospective matched cohort design to estimate the incidence and risk of the selected AESIs (**Table 2**) in individuals after receipt of the first dose of the Pfizer-BioNTech COVID-19 vaccine (vaccinated cohort) compared with individuals who did not receive any COVID-19 vaccine (unvaccinated cohort). Details of the inclusion and exclusion criteria are provided in the protocol (Standalone Appendix 2).

#### 9.3.2. Sensitivity analyses in specific subgroups

Comparative analyses of the incidences of the specified AESIs occurring in the matched vaccinated and unvaccinated cohorts were also performed in the following subgroups:

- individuals diagnosed with previous COVID-19 infection (yes/no) any time prior to time zero;
- sex (male/female);
- age-specific groups (0-17, 18-29, 30-39, 40-49, 50-59, 60-64, 65-69, 70-79, 80+ years);
    - the 0–17-year age group were additionally divided into 0-1, 2-4, 5-11, 12-15, and 16-17 year groups, where feasible;

- analyses were also reported in the following subpopulations:
    - pregnant women;
    - individuals who were classified as immunocompromised;
    - individuals who were frail or had comorbidities.

The following sensitivity analyses were conducted in

- individuals who had no healthcare contact in the seven days prior to time zero
- individuals who had received 2 doses of Pfizer-BioNTech COVID-19 vaccine within 6 weeks.

#### 9.3.3. Self-controlled risk interval design

The SCRI design was performed in the overall vaccinated population. Details of the inclusion and exclusion criteria are provided in the protocol (Standalone Appendix 2).

### 9.4. Variables

#### 9.4.1. Exposure definition

Exposure definitions differed by data source and were based on recorded prescription, dispensing, or administration of the Pfizer-BioNTech COVID-19 vaccine as described in the protocol (Standalone Appendix 2). The main exposure of interest was the receipt of at least one dose of the Pfizer-BioNTech COVID-19 vaccine. Cohorts of individuals exposed to a third dose of the Pfizer-BioNTech COVID-19 vaccine were also analysed.

#### 9.4.2. Definition of outcomes

##### 9.4.2.1. Safety outcomes

Selected AESIs included in the study are listed in **Table 2**. The AESIs were identified in the data sources with algorithms based on codes for diagnoses, procedures, and treatments. Definitions, codes, and proposed algorithms for all AESI incorporated definitions were developed by the ACCESS (vACcine Covid-19 monitoring readinESS) project[5] and are described in more detail in the SAP (Standalone Appendix 4). Algorithms were tailored to the data source to take into consideration the nature of the records that identified the outcome, e.g., primary care, access to hospital care, and access to emergency care.[6]

##### 9.4.2.2. Outcome identification and validation

AESIs were identified based on patient profile review of electronic medical records by healthcare professionals. In addition, for selected outcomes listed in **Table 2**, manual review of patient charts conducted by clinicians blinded to COVID-19 vaccine exposure was performed using the levels of certainty in existing and RWE modified Brighton Collaboration definitions. Data collection forms are available in Standalone Appendix 5.

### 9.4.3. Covariate definition

The covariables that were assessed at time zero (for the cohort design) or the date of initial vaccine dose (for the SCRI design) to define patient populations of special interest or priority vaccination groups, to define subgroups of interest for secondary analyses, or to control for confounding, included age, sex and prior COVID-19 history (previous illness or positive test result for COVID-19). Further details can be found in the study protocol (Standalone Appendix 2).

## 9.5. Data sources and measurement

The main exposure of interest was the receipt of at least one dose of the Pfizer-BioNTech COVID-19 vaccine. Exposure to Pfizer-BioNTech COVID-19 vaccine was based on recorded prescription, dispensing, or administration data. Vaccine receipt and date of vaccination was obtained from all possible sources that captured COVID-19 vaccination, such as pharmacy dispensing records, general practice records, immunisation registers, vaccination records, medical records, or other secondary data sources. Further details can be found in the study protocol (Standalone Appendix 2).

## 9.6. Bias

This study was subject to biases related to both the study designs and use of secondary healthcare data. One study design-related bias for both the cohort and SCRI designs was uncertainty about the AESI-specific risk periods, which could lead to misclassification and attenuation of risk estimates. Further information about can be found in the study protocol (Standalone Appendix 2).

## 9.7. Study size

The study was conducted in a source population of 38.9 million individuals captured in the electronic healthcare data sources.

Appendix Table 1 shows the sample size calculations for AESIs with different assumptions for the risk ratios. For example, assuming a two-sided alpha of 0.95, power of 80%, and a ratio of 1 to 1 exposed to unexposed, to detect a risk ratio of 2 for Guillain-Barré syndrome, 22,340,153 exposed and 22,340,153 unexposed individuals would need to be included.

## 9.8. Data transformation

Detailed methodology for data transformations, particularly complex transformations (e.g., many raw variables used to derive an analytic variable), are documented in the SAP, which is dated, filed and maintained by the Sponsor (Standalone Appendix 4).

## 9.9. Statistical methods

### 9.9.1. Main summary measures

All individuals vaccinated with at least one dose of the Pfizer-BioNTech COVID-19 vaccine and satisfying the inclusion criteria during the study period were included and then matched to unvaccinated individuals. The matching variables were age, sex, prior COVID-19 diagnosis, geographical location, prior influenza vaccination, pregnancy status, immunocompromised status, presence of Centers for Disease Control and Prevention

(CDC) risk factors, and when available, socioeconomic status/education level. Further details about the matching variables can be found in the SAP (Standalone Appendix 4).

The main summary measures reported for the matched vaccinated and unvaccinated cohorts were:

- Attrition table for matched cohort design.
- The matching statistics (number of Pfizer-BioNTech vaccinated individuals excluded, included and matched by calendar time and age).
- Population description at time zero by exposure group.
- Prior AESI at time zero (exclusion criteria for the AESI-specific analysis).
- Cohort follow-up and reasons for censoring.
- Population description at time zero by cohort (age groups, sex, age groups by sex, influenza vaccination, COVID-19 infection, history of AESI – exclusion criteria with prior history within one year – documented for the previous 10 years).
- Quarterly Incidence rates of AESIs in unvaccinated historical controls and unvaccinated comparators

### 9.9.2. 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.

#### 9.9.2.1.Propensity score method

Originally it was planned to use the difference in the cumulative incidence of symptomatic SARS-CoV-2 infection at day 12 in the matched vaccinated and unvaccinated cohorts as a negative control, calculated using a 1-KM estimator, as has been done previously.[7] If the 12-day risk difference of symptomatic SARS-CoV-2 infection was ≤0.10%, the matching would

have been considered to be sufficient to achieve baseline exchangeability and if it was >0.10%, the matching would have been considered not sufficient to achieve baseline exchangeability. In the latter case, it was planned to use the inverse probability of treatment weighting (IPTW), a propensity score (PS) method, to adjust the estimates. PS methods are appropriate when there is a small number of events for each outcome, which is the case in this study. However, it was decided to use PS irrespective of the result from the negative control outcome. Full details about this method can be found in the SAP (Standalone Appendix 4).

### 9.9.3. Sensitivity analyses

The sensitivity analyses described in **Section 9.3.2** were performed. More details can be found in the protocol (Standalone Appendix 2).

### 9.9.4. Analyses for direct healthcare professional communication

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.

### 9.9.5. 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 (published on the Zenodo community page of the Safety Platform for Emergency vACcines (SPEAC) project).[8] 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.

Cases classified as Level 4 may meet a higher level of diagnostic certainty if additional data are collected as part of a follow-up investigation. Since this could happen in retrospective assessment, we considered cases classified as Level 4 of diagnostic certainty as potential cases.

To adapt to heterogeneity of real-world data, the VAC4EU Validation Task Force modified the levels of certainty, adding a level 4a (diagnosis made by specialist) and 4b (diagnosis made by GP).

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

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

The following PPVs were calculated for each validated AESI in the vaccinated and unvaccinated cohorts:

- **PPV strict** was defined as the number of cases in diagnostic certainty levels 1, 2 and 3 divided by the number of all cases evaluated regardless of level of certainty (levels 1, 2, 3, 4a, 4b, 5).

- **PPV broad** was defined as the number of cases in diagnostic certainty levels 1 to 4a divided by the number of all cases evaluated regardless of level of certainty (levels 1, 2, 3, 4a, 4b, 5).

More complete details can be found in the SAP (Standalone Appendix 4).

### 9.9.6. Missing values

Individuals with missing data for the matching variables and those with missing exposure status or any of the outcome data were not included in the analyses. In the analyses it was assumed that the absence of information for clinical events meant that the event did not occur.

### 9.9.7. Amendments to the statistical analysis plan

A summary of the amendments that were made to the SAP is provided in the SAP (Standalone Appendix 4).

## 9.10. Quality control

Rigorous quality control (QC) was used for throughout this study. Data transformation into the CDM was conducted by each subcontracted data expert and access partner (DEAP) from its associated database. Standard operating procedures or internal process guidance at each DEAP were used to guide the conduct of the study. These included rules for secure and confidential data storage, backup, and recovery; methods to maintain and archive project documents; QC procedures for programming; standards for writing analysis plans; and requirements for scientific review by senior staff. Details about the quality control used in each data sources can be found in the protocol (Standalone Appendix 2).

At University Medical Center Utrecht (UMCU), the scientific coordinating centre responsible for central data management and analysis and scientific coleader centre, all documents underwent QC review and senior scientific review. Data management and statistical analysis

followed standard operating procedures. All statistical analysis programmes were double-coded.

At RTI Health Solutions (RTI-HS), the scientific coleader centre, the study protocol underwent QC review, senior scientific review, and editorial review. Senior reviewers with expertise in the appropriate subject matter area provided advice on the design of research study approaches and the conduct of the study and reviewed results, reports, and other key study documents.

### 9.11. Protection of human subjects

#### Subject information and consent

Not applicable.

#### Independent Ethics Committee (IEC)/Institutional Review Board (IRB)

The final protocol, any amendments, and informed consent documentation were reviewed and approved by an Institutional Review Board (IRB) for each site participating in the study, in compliance with local requirements and policies (Standalone Appendix 3).

The final protocol, any amendments, and informed consent documentation were reviewed and approved by a local data protection agency for each site participating in the study.

#### Ethical conduct of the study

The study was conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and followed generally accepted research practices described in the *Guidelines for Good Pharmacoepidemiology Practices (GPP)*[9] and according to the *ENCePP Code of Conduct*.[10]

## 10. RESULTS

### 10.1. Participants

Six of the seven participating data sources contributed data for all analyses in this final report (**Section 9.2.1**). The remaining data source, HSD (IT), was not eligible to participate in the cohort study, due to misclassification of COVID-19 vaccination, which could have resulted in unvaccinated individuals being classified as vaccinated and vice-versa. However, since inclusion in the SCRI analyses was conditioned on exposure, HSD contributed to the SCRI analyses.

The study period for this final report started in each country with the first Pfizer-BioNTech COVID-19 vaccinations between 08 December 2020 in CPRD Aurum (England and Northern Ireland) and 08 January 2021 in PHARMO (The Netherlands) (**Table 3**). Data collection started on 31 May 2021 in Pedianet (Italy) because vaccination in children started later. The end dates for data extraction for this final report are summarised in **Table 3**.

#### 10.1.1. Main cohort

A total of 18,475,392 individuals received a first dose of Pfizer-BioNTech COVID-19 vaccine during the study period (**Table 4**). 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. By data source, the highest percentage excluded was in CPRD Aurum (58.14%), and the lowest percentage excluded was in NHR (10.36%). 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. The results for attrition, follow up and censoring, baseline characteristics and incident rates after first, second, and third dose Pfizer-BioNTech COVID-19 vaccination in the vaccinated cohorts before matching can be found in Standalone **Section 15**.

Of the 12,398,589 vaccinated individuals eligible for matching, 11,496,929 (92.73%) were matched to unvaccinated individuals. The median number of times unvaccinated individuals were matched with a vaccinated individual was 1, although some were matched up with up to 23 different vaccinated individuals in CPRD Aurum. A total of 26,696 of the 48,439 (55.11%) vaccinated, pregnant women could be matched to unvaccinated, pregnant women (**Table 4**).

Of the matched vaccinated individuals 30.30% were censored due to receipt of a non-Pfizer-BioNTech COVID-19 vaccine. In contrast, 67.85% of all the matched unvaccinated individuals were censored before end of follow-up because of receipt of a COVID-19 vaccine (Pfizer-BioNTech COVID-19 vaccine or another COVID-19 vaccine). Available follow-up times were much longer for the vaccinated cohorts than for the unvaccinated cohorts, when censoring of the pair was not considered. The median follow-up was very short in the unvaccinated cohorts in NHR (0.8 month) and EpiChron (1.0 month). As described in the SAP, both the matched vaccinated and unvaccinated individuals were censored for the comparative analyses when either the vaccinated or the unvaccinated individual was censored, which resulted in short follow-up times (**Table 5**).

AESIs in the year prior to time zero in the vaccinated and matched unvaccinated main cohorts by data source are summarised in Appendix Table 2. The occurrence of these AESIs were outcome-specific exclusion criteria, but as only a few individuals experienced AESI-specific events in the year prior to receiving their first Pfizer-BioNTech COVID-19 vaccine dose, any exclusions had very little impact on the size of the AESI-specific cohorts. Prior events were balanced between the vaccinated and unvaccinated cohorts, with absolute standardised differences (ASDs) of ≤0.1 for all events in all data sources. For the pregnancy sub-study that assessed pregnancy and neonatal AESIs, the gynaecological and obstetrics histories for previous pregnancies and for the current pregnancy in the matched vaccinated and unvaccinated pregnancy cohorts are shown in Appendix Table 2. These obstetrics histories were balanced between the vaccinated and unvaccinated cohorts with ASDs of ≤0.1, except for prior caesarean section that had an ASD of 0.11.

### 10.1.2. Historical controls

A total of 12,049,838 vaccinated individuals were matched to 23,818,759 historical controls in the pre-COVID-19 period (one control in 2018 and one control in 2019) (**Table 4**). The historical controls in 2018 and 2019 were combined in a single cohort, in principle, giving us a 1:2 ratio. However, in practice, some exposed individuals only had either a 2018 match, or a 2019 match, but not both. The decision was taken to include vaccinated individuals who were matched with at least one unvaccinated control, giving a mix of 1:1 and 1:2 matching.

This explains why the historical unvaccinated cohort does not have twice as many individuals as in the vaccinated cohort. The difference is equal to the number of individuals with a single match in 2018 or 2019 but not the other year.

In addition, 11,319,784 vaccinated individuals were matched 1:1 to 11,319,784 historical controls in the COVID-19 period from 01 January 2020 to 31 November 2020. Overall, there were 12,796,600 unique controls in the pre-COVID-19 period, and 8,265,670 individuals in the COVID-19 period. Most of the historical controls were matched once (51.19% for the pre-COVID-19 period and 73.16% for COVID-19 period) and they were rarely matched more than five times (3.72% pre-COVID-19 period and 0.55% COVID-19 period) (**Table 5**).

From the 7,746,458 vaccinated individuals included for the pre-COVID-19 period (2018 and 2019) analyses, 2,411,970 (31.14%) matched pairs were censored due to the vaccinated individual having received a non-Pfizer-BioNTech COVID-19 vaccine (**Table 5**). For the COVID-19 period comparison 3,345,144 (31.42%) of the 10,647,344 matched pairs included were censored for the same reason (**Table 5**).

**Table 4. Attrition table for the matched vaccinated and unvaccinated cohorts and sub-cohorts, historical matched cohorts and pregnancy cohort by data source and overall**

| | Pedianet | PHARMO | NHR | EpiChron | SIDIAP | CPRD Aurum | Total |
|---|---|---|---|---|---|---|---|
| **Received 1st dose, N*** | 12,046 | 1,595,383 | 4,002,649 | 924,273 | 3,772,034 | 8,169,007 | 18,475,392 |
| **Reason for exclusion, n (%)** | | | | | | | |
| <12 months continuous enrolment | 762 (6.33) | 6,138 (0.38) | 40,509 (1.01) | 16,280 (1.76) | 72,080 (1.91) | 1,700,685 (20.82) | 1,836,454 (9.94) |
| Prior vaccination with COVID-19 vaccine | 737 (6.12) | 226,279 (14.18) | 374,439 (9.35) | 121,481 (13.14) | 468,523 (12.42) | 3,048,890 (37.32) | 4,240,349 (22.95) |
| Total vaccinated included,[a] n (%) | 10,547 (87.56) | 1,362,966 (85.43) | 3,587,701 (89.57) | 786,512 (85.31) | 3,231,431 (85.67) | 3,419,432 (41.72) | 12,398,589 (67.11) |
| Pregnant women vaccinated, n (%) | 0 (0) | 3,106 (0.23) | 13,843 (0.39) | 3,216 (0.41) | 10,299 (0.32) | 17,975 (0.53) | 48,439 (0.39) |
| **Main matched cohort** | | | | | | | |
| Vaccinees matched, n (%) | 10,497 (99.53) | 1,222,612 (89.70) | 3,571,573 (99.55) | 674,523 (85.76) | 3,231,245 (99.99) | 2,786,479 (81.49) | 11,496,929 (92.73) |
| Served as control before vaccination, n (%) | 2,567 (24.45) | 318,153 (26.02) | 1,497,431 (41.93) | 208,863 (30.96) | 1,120,555 (34.68) | 608,434 (21.84) | 3,756,003 (32.67) |
| Unvaccinated matched, n | 10,497 | 1,222,612 | 3,571,573 | 674,523 | 3,231,245 | 2,786,479 | 11,496,929 (92.73) |
| Unique unvaccinated matched included, n (%) | 8,059 (76.77) | 900,371 (73.64) | 2,070,221 (57.96) | 425,759 (63.12) | 2,078,098 (64.31) | 2,105,846 (75.57) | 7,588,354 (66.00%) |
| Median number of times comparator selected for matching | | | | | | | |
| Median (Q1–Q3) | 1 (1–1) | 1 (1–2) | 1 (1–2) | 1 (1–2) | 1 (1–2) | 1 (1–1) | 1 (1-2) |
| Min, Max | 1, 6 | 1, 9 | 1, 14 | 1, 20 | 1, 13 | 1, 23 | 1, 23 |
| 1, n (%) | 6,125 (76.00) | 657,177 (72.99) | 1,183,706 (57.18) | 269,505 (63.30) | 1,320,852 (63.56) | 1,595,819 (75.78) | 5,033,184 (66.33) |
| 2, n (%) | 1,526 (18.94) | 182,443 (20.26) | 515,964 (24.92) | 98,444 (23.12) | 495,009 (23.82) | 383,425 (18.21) | 1,676,811 (22.10) |
| 3, n (%) | 337 (4.18) | 46,531 (5.17) | 220,302 (10.64) | 36,455 (8.56) | 173,763 (8.36) | 95,101 (4.52) | 572,489 (7.54) |
| 4, n (%) | 51 (0.63) | 11,043 (1.23) | 91,480 (4.42) | 13,350 (3.14) | 58,780 (2.83) | 23,280 (1.11) | 197,984 (2.61) |
| 5 or more, n (%) | 20 (0.25) | 3,177 (0.35) | 58,769 (2.84) | 8,005 (1.88) | 29,694 (1.43) | 8,221 (0.39) | 107,886 (1.42) |
| **Sub-cohorts, (n=matched pairs)** | | | | | | | |
| Immunocompromised individuals** | 3,057 | 243,375 | 747,853 | 44,125 | 655,839 | 433,634 | 2,127,883 |
| Frail or comorbidity*** | 8,535 | 765,074 | 2,570,052 | 471,091 | 2,177,654 | 2,138,484 | 8,130,890 |
| ≥1 healthcare contact within 7 days prior to 1st dose excluded | 9,063 | 1,072,347 | 2,733,610 | 499,879 | 2,253,835 | 2,308,240 | 8,876,974 |
| COVID-19 diagnosis or positive test | 1,051 | 40,842 | 71,696 | 52,428 | 544,889 | 218,665 | 929,571 |
| Pregnant women | NA | 913 | 11,928 | 974 | 10,204 | 2531 | 26,550 |
| **Matched historical cohorts** | | | | | | | |
| **Vaccinated matched with historical pre-COVID-19 (2028/2019) comparator** | | | | | | | |
| Vaccinees matched, n (%)[b] | 10,141 (96.15) | 1,308,313 (95.99) | 3,585,140 (99.93) | 718,240 (91.32) | 3,231,401 (100) | 3,196,603 (93.48) | 12,049,838 |

**Table 4. Attrition table for the matched vaccinated and unvaccinated cohorts and sub-cohorts, historical matched cohorts and pregnancy cohort by data source and overall**

| | Pedianet | PHARMO | NHR | EpiChron | SIDIAP | CPRD Aurum | Total |
|---|---|---|---|---|---|---|---|
| Served as control before vaccination, n (%) | 3,806 (37.53) | 729,135 (55.73) | 2,619,682 (73.07) | 436,666 (60.80) | 2,094,726 (64.82) | 1,372,747 (42.94) | 7,256,762 |
| Historical unvaccinated matched, n | 18,875 (100) | 2,581,036 (100) | 7,166,959 (100) | 1,410,834 (100) | 6,462,763 (100) | 6,178,292 (100) | 23,818,759 |
| Unique unvaccinated matched included, n (%) | 8,509 (45.08) | 1,548,832 (60.01) | 3,366,295 (46.97) | 719,791 (51.02) | 3,598,051 (55.67) | 3,555,122 (57.54) | 12,796,600 |
| Median number of times comparator selected for matching | | | | | | | |
| Median (Q1–Q3) | 1 (1–2) | 1 (1–2) | 2 (1–3) | 1 (1–2) | 1 (1–2) | 1 (1–2) | |
| Min, Max | 1, 36 | 1, 67 | 1, 38 | 1, 91 | 1, 13 | 1, 160 | |
| 1, n (%) | 4,655 (54.71) | 896,440 (57.88) | 1,412,745 (41.97) | 360,951 (50.15) | 1,840,775 (51.16) | 2,034,897 (57.24) | 6,550,463 (51.19) |
| 2, n (%) | 1,873 (22.01) | 410,235 (26.49) | 969,699 (28.81) | 193,810 (26.93) | 1,036,263 (28.80) | 905,807 (25.48) | 3,517,687 (27.49) |
| 3, n (%) | 766 (9.00) | 155,516 (10.04) | 520,674 (15.47) | 87,837 (12.20) | 459,254 (12.76) | 361,475 (10.17) | 1,585,522 (12.39) |
| 4, n (%) | 345 (4.05) | 56,257 (3.63) | 249,808 (7.42) | 39,238 (5.45) | 174,639 (4.85) | 147,226 (4.14) | 667,513 (5.22) |
| 5 or more, n (%) | 870 (10.22) | 30,384 (1.96) | 213,369 (6.34) | 37,955 (5.27) | 87,120 (2.42) | 105,717 (2.97) | 475,415 (3.72) |
| **Vaccinated matched with historical COVID-19 (2020) comparator** | | | | | | | |
| Vaccinees matched, n (%) | 6,716 (63.68) | 1,252,263 (91.88) | 3,514,894 (97.97) | 672,440 (85.50) | 3,105,356 (96.10) | 2,768,115 (80.95) | 11,319,784 |
| Served as control before vaccination, n (%) | 1,703 (25.36) | 530,318 (42.35) | 1,840,003 (52.35) | 310,358 (46.15) | 1,311,325 (42.23) | 1,008,368 (36.43) | 5,002,075 |
| Historical unvaccinated matched, n | 6,716 (100) | 1,252,263 (100) | 3,514,894 (100) | 672,440 (100) | 3,105,356 (100) | 2,768,115 (100) | 11,319,784 |
| Unique unvaccinated matched included, n (%) | 5,103 (75.98) | 995,506 (79.50) | 2,383,616 (67.81) | 492,059 (73.18) | 2,138,069 (68.85) | 2,251,317 (81.33) | 8,265,670 |
| Median number of times comparator selected for matching | | | | | | | |
| Median (Q1–Q3) | 1 (1–1) | 1 (1–1) | 1 (1–2) | 1 (1–2) | 1 (1–2) | 1 (1–1) | |
| Min, Max | 1, 9 | 1, 40 | 1, 120 | 1, 53 | 1, 659 | 1, 108 | |
| 1, n (%) | 3,925 (76.92) | 781,897 (78.54) | 1,561,080 (65.49) | 355,144 (72.18) | 1,522,919 (71.23) | 1,822,480 (80.95) | 6,047,445 (73.16) |
| 2, n (%) | 876 (17.17) | 177,508 (17.83) | 598,930 (25.13) | 104,577 (21.25) | 442,085 (20.68) | 358,926 (15.94) | 1,682,902 (20.36) |
| 3, n (%) | 215 (4.21) | 30,705 (3.08) | 170,180 (7.14) | 24,953 (5.07) | 113,384 (5.30) | 58,351 (2.59) | 397,788 (4.81) |
| 4, n (%) | 61 (1.20) | 4,597 (0.46) | 40,319 (1.69) | 5,456 (1.11) | 32,775 (1.53) | 8,889 (0.39) | 92,097 (1.11) |
| 5 or more, n (%) | 26 (0.51) | 799 (0.08) | 13,107 (0.55) | 1,929 (0.39) | 26,906 (1.26) | 2,671 (0.12) | 45,438 (0.55) |
| **Matched pregnancy cohort** | | | | | | | |
| Pregnant women in vaccinated cohort, n (%) | NA | 915 (0.07) | 12,062 (0.34) | 974 (0.14) | 10,212 (0.32) | 2,533 (0.09) | 26,696 |
| Vaccinated pregnant women matched, n (%) | NA | 915 (100.00) | 12,062 (100.00) | 974 (100.00) | 10,212 (100.00) | 2,533 (100.00) | 26,696 |

**Table 4. Attrition table for the matched vaccinated and unvaccinated cohorts and sub-cohorts, historical matched cohorts and pregnancy cohort by data source and overall**

| | Pedianet | PHARMO | NHR | EpiChron | SIDIAP | CPRD Aurum | Total |
|---|---|---|---|---|---|---|---|
| Served as control before vaccination, n (%) | NA | 66 (7.21) | 2,158 (17.89) | 132 (13.55) | 2,070 (20.27) | 116 (4.58) | 4,542 |
| Pregnant unvaccinated matched, n | NA | 915 (100) | 12,062 (100) | 974 (100) | 10,212 (100) | 2,533 (100) | 26,696 |
| Unique unvaccinated matched included, n (%) | NA | 831 (90.82) | 10,003 (82.93) | 839 (86.14) | 8,053 (78.86) | 2,406 (94.99) | 22,132 |
| Median number of times comparator selected for matching | NA | | | | | | |
| Median (Q1–Q3) | NA | 1 (1–1) | 1 (1–1) | 1 (1–1) | 1 (1–1) | 1 (1–1) | |
| Min, Max | NA | 1, 4 | 1, 6 | 1, 4 | 1, 6 | 1, 3 | |
| 1, n (%) | NA | 762 (91.70) | 8,274 (82.72) | 722 (86.05) | 6,286 (78.06) | 2,289 (95.14) | 18,333 (82.83) |
| 2, n (%) | NA | 56 (6.74) | 1,443 (14.43) | 101 (12.04) | 1,433 (17.79) | 107 (4.45) | 3,140 (14.19) |
| 3, n (%) | NA | 11 (1.32) | 249 (2.49) | 14 (1.67) | 282 (3.50) | 10 (0.42) | 566 (2.56) |
| 4, n (%) | NA | 2 (0.24) | 31 (0.31) | 2 (0.24) | 47 (0.58) | 0 | 82 (0.37) |
| 5 or more, n (%) | NA | 0 | 6 (0.06) | 0 | 5 (0.06) | 0 | 11 (0.05) |

[a] *Received ≥1 dose of the Pfizer-BioNTech COVID-19 vaccine, had ≥12 months continuous enrolment AND no prior COVID-19 vaccination, other than Pfizer-BioNTech COVID-19 vaccine*

[b] *matching 1:2, one control for each comparator year 2018 and 2018*

**Refer to **Table 3** for information on time periods for data;*

*** Identification of immunocompromised individuals is based on an algorithm including HIV or AIDS, immunodeficiency without HIV, cancer haematoma, organ transplantation, or corticosteroid, immunosuppressant, or HIV treatment in past 10 years.*

**** Identification of frail or individuals with comorbidities was based on an algorithm including myocardial infarction, congestive heart failure, cerebrovascular disease, coagulation deficiencies, sickle cell disease, cardiovascular disease, chronic liver disease, diabetes mellitus (types 1 and 2), diabetes with complications, lipid abnormalities, bladder incontinence, chronic kidney disease, ambulance transport, home hospital bed, home oxygen, rehabilitation care, wheelchair use, AIDS, sepsis, HIV, influenza or other respiratory infections, anaphylaxis, allergies, autoimmune disorders, immunocompromised, difficulty walking, weakness, obesity, arthritis, connective tissue disease, psychiatric illness, dementia, hemiplegia, vertigo, malignant tumour, chronic respiratory disease, skin ulcer, cancer screening, hypertension, peripheral vascular disease, liver disease, severe renal disease, metastatic solid tumour, paralysis, Parkinson, or treatments against cancer, or treatments with corticosteroids, immunostimulants, or immunosuppressants,*

**Table 5. Cohort follow-up and reasons for censoring for the matched vaccinated and unvaccinated cohorts by data source (not considering censoring of the pair)**

PART 1 (SEE PART 2 BELOW)

| | Pedianet | | PHARMO | | NHR | |
|---|---|---|---|---|---|---|
| | **Vaccinated** | **Unvaccinated** | **Vaccinated** | **Unvaccinated** | **Vaccinated** | **Unvaccinated** |
| **Main matched cohort, N** | 10,497 | 10,497 | 1,222,612 | 1,222,612 | 3,571,573 | 3,571,573 |
| Person-months of follow-up | | | | | | |
| Median (Q1, Q3) (months) | 11.9 (11.5, 12.4) | 11.4 (1.6, 12) | 15.4 (8.1, 18.1) | 10.2 (0.8, 18) | 17.9 (7.7, 20.2) | 0.8 (0.3, 3.4) |
| Min–max (months) | 0.1–22.3 | 0–22.3 | 0–24.1 | 0–24.2 | 0–24.5 | 0–24.5 |
| **Reasons for censoring, n (%)** | | | | | | |
| Non-Pfizer-BioNTech COVID-19 vaccine received | 16 (0.2) | NA | 512,861 (41.9) | NA | 985,182 (27.6) | NA |
| Unvaccinated received Pfizer or non-Pfizer COVID-19 vaccine | NA | 3,570 (34.0) | NA | 599,887 (49.1) | NA | 2,863,377 (80.2) |
| Death (any cause) | <5 (NR) | 0 | 8,851 (0.70) | 7,156 (0.60) | 63,826 (1.80) | 19,636 (0.50) |
| Exit from data source | 10,480 (99.80) | 6,927 (66) | 700,900 (57.30) | 615,569 (50.30) | 2,522,565 (70.60) | 688,560 (19.30) |
| Reached administrative end of follow up | 0 | 0 | 0 | 0 | 0 | 0 |
| **Matched pre-COVID-19 cohort, N** | 10,141 | 18,875 | 1,308,313 | 2,581,064 | NA | NA |
| Person-months of follow-up | | | | | NA | NA |
| Median (Q1, Q3) (months) | 12 (11.6, 12.4) | 12 (5.6, 22.3) | 15.30 (8.1, 18.1) | 11.7 (6.7, 18.7) | NA | NA |
| Min–max (months) | 0.40–22.3 | 0–24.1 | 0–24.2 | 0–24.1 | NA | NA |
| **Reasons for censoring, n (%)** | | | | | NA | NA |
| Non-Pfizer-BioNTech COVID-19 vaccine received | 16 (0.20) | NA | 545,188 (41.70) | NA | NA | NA |
| Unvaccinated received Pfizer or non-Pfizer COVID-19 vaccine | NA | 0 | NA | 0 | NA | NA |
| Death (any cause) | <5 (NR) | 0 | 9,849 (0.80) | 25,513 (1) | NA | NA |
| Exit from data source | 10,124 (99.80) | 0 | 753,276 (57.60) | 8,322 (0.30) | NA | NA |
| Reached administrative end of follow up | 0 | 18,875 (100) | 0 | 2,547,201 (98.70) | NA | NA |
| **Matched COVID-19 cohort, N** | 6,716 | 6,716 | 1,252,263 | 1,252,263 | 3,514,894 | 3,514,894 |
| Person-months of follow-up | | | | | | |
| Median (Q1, Q3) (months) | 11.8 (11.3, 12.0) | 11.6 (5.3, 11.9) | 15.6 (8.1, 18.1) | 6.8 (5.8, 8.3) | 17.9 (7.6, 20.2) | 6.6 (5.6, 8.5) |
| Min–max (months) | 0.1-22.3 | 1.1–12.1 | 0-24.1 | 0–12.1 | 0-24.1 | 0-12.1 |

**Table 5. Cohort follow-up and reasons for censoring for the matched vaccinated and unvaccinated cohorts by data source (not considering censoring of the pair)**

PART 1 (SEE PART 2 BELOW)

| | Pedianet | | PHARMO | | NHR | |
|---|---|---|---|---|---|---|
| | **Vaccinated** | **Unvaccinated** | **Vaccinated** | **Unvaccinated** | **Vaccinated** | **Unvaccinated** |
| **Reasons for censoring, n (%)** | | | | | | |
| Non-Pfizer-BioNTech COVID-19 vaccine received | 13 (0.2) | NA | 542,601 (43.3) | NA | 983,542 (28.0) | NA |
| Unvaccinated received Pfizer or non-Pfizer COVID-19 vaccine | NA | 0 | NA | 290 (<0.01) | NA | 11,222 (0.30) |
| Death (any cause) | <5 (NR) | 0 | 9,997 (0.8) | 6,842 (0.5) | 59,164 (1.7) | 545 (<0.01) |
| Exit from data source | 6,702 (99.8) | 0 | 699,665 (55.9) | 1,794 (0.1) | 2,472,188 (70.3) | 900 (<0.01) |
| Reached administrative end of follow up | 0 | 6,716 (100) | 0 | 1,243,337 (99.3) | 0 | 3,502,227 (99.6) |
| **Matched pregnancy cohort, N** | | | 915 (100) | 915 (100) | 12,062 (100) | 12,062 (100) |
| Person-months of follow-up | | | | | | |
| Median (Q1, Q3) (months) | NA | NA | 18.1 (17.2, 18.3) | 13.5 (2.5, 18) | 15.6 (11.9-17) | 2.9 (1.2-12) |
| Min–max (months) | NA | NA | 0.9-23.7 | 0-23.7 | 0.3-24.4 | 0-24.3 |
| **Reasons for censoring, n (%)** | | | | | | |
| Non-Pfizer-BioNTech COVID-19 vaccine received | NA | NA | 12 (1.3) | | 2,706 (22.4) | NA |
| Unvaccinated received Pfizer or non-Pfizer COVID-19 vaccine | NA | NA | NA | 403 (44.0) | NA | 8,746 (72.5) |
| Death (any cause) | NA | NA | 0 | 0 | <5 (NR) | <5 (NR) |
| Exit from data source | NA | NA | 903 (98.7) | 512 (56) | 9,355 (77.6) | 3,314 (27.5) |
| Reached administrative end of follow up | NA | NA | 0 | 0 | 0 | 0 |
| **Matched pregnancy pre-COVID-19 cohort, N** | NA | NA | 1,603 (100) | 2,385 (100) | NA | NA |
| Person-months of follow-up | NA | NA | | | NA | NA |
| Median (Q1, Q3) (months) | NA | NA | 18.0 (16.2-18.2) | 23.7 (18.1-30.1) | NA | NA |
| Min–max (months) | NA | NA | 0.6-23.7 | 2.8-36.2 | NA | NA |
| **Reasons for censoring, n (%)** | NA | NA | | | NA | NA |
| Non-Pfizer-BioNTech COVID-19 vaccine received | NA | NA | 18 (1.10) | | NA | NA |

**Table 5. Cohort follow-up and reasons for censoring for the matched vaccinated and unvaccinated cohorts by data source (not considering censoring of the pair)**

PART 1 (SEE PART 2 BELOW)

| | Pedianet | | PHARMO | | NHR | |
|---|---|---|---|---|---|---|
| | **Vaccinated** | **Unvaccinated** | **Vaccinated** | **Unvaccinated** | **Vaccinated** | **Unvaccinated** |
| Unvaccinated received Pfizer or non-Pfizer COVID-19 vaccine | NA | NA | | 0 | NA | NA |
| Death (any cause) | NA | NA | 0 | <5 (NR) | NA | NA |
| Exit from data source | NA | NA | 1,585 (98.9) | <5 (NR) | NA | NA |
| Reached administrative end of follow up | NA | NA | 0 | 2,380 (99.8) | NA | NA |
| **Matched pregnancy COVID-19 cohort, N** | NA | NA | 1,182 (100) | 1,182 (100) | 11,601 (100) | 11,601 (100) |
| Person-months of follow-up | NA | NA | | | | |
| Median (Q1, Q3) (months) | NA | NA | 18 (16.70-18.3) | 12.60 (11.70-17.9) | 15.80 (11.0-17.1) | 11.4 (10.0-13.2) |
| Min–max (months) | NA | NA | 1-23.7 | 3.50-24.1 | 0.30-24.1 | 0.90-24.2 |
| **Reasons for censoring, n (%)** | NA | NA | | | | |
| Non-Pfizer-BioNTech COVID-19 vaccine received | NA | NA | 9 (0.8) | | 2,796 (24.1) | |
| Unvaccinated received Pfizer or non-Pfizer COVID-19 vaccine | NA | NA | | 763 (64.6) | | 10,420 (89.8) |
| Death (any cause) | NA | NA | 0 | 0 (0) | <5 (NR) | 0 |
| Exit from data source[a] | NA | NA | 1,173 (99.2) | <5 (NR) | 8,804 (75.9) | 14 (0.1) |
| Reached administrative end of follow up | NA | NA | 0 | 417 (35.3) | 0 | 1,167 (10.1) |

**Table 5. Cohort follow-up and reasons for censoring for the matched vaccinated and unvaccinated main cohorts by data source (not considering censoring of the pair)**

PART 2 (SEE PART 1 ABOVE)

| | EpiChron | | SIDIAP | | CPRD Aurum | |
|---|---|---|---|---|---|---|
| | **Vaccinated** | **Unvaccinated** | **Vaccinated** | **Unvaccinated** | **Vaccinated** | **Unvaccinated** |
| **Main matched cohort, N** | 674,523 | 674,523 | 3,231,245 | 3,231,245 | 2,786,479 | 2,786,479 |
| Person-months of follow-up | | | | | | |
| Median (Q1, Q3) (months) | 17.2 (9.7, 19.0) | 1.0 (0.2, 12.6) | 12.6 (7.6, 18.1) | 1.0 (0.3, 12.0) | 16.5 (10.8, 19.7) | 3.1 (0.6, 14.3) |
| Min–max (months) | 0–24.5 | 0–24.5 | 0–24.4 | 0–24.4 | 0–25.1 | 0–24.9 |
| **Reasons for censoring, n (%)** | | | | | | |
| Non-Pfizer-BioNTech COVID-19 vaccine received | 193,930 (28.8) | NA | 1,361,279 (42.1) | NA | 429,893 (15.4) | NA |
| Unvaccinated received Pfizer or non-Pfizer COVID-19 vaccine | | 471,719 (69.90) | NA | 2,261,157 (70.0) | NA | 1,601,333 (57.5) |
| Death (any cause) | 13,012 (1.90) | 3,316 (0.50) | 53,853 (1.7) | 37,062 (1.1) | 20,780 (0.70) | 6,892 (0.20) |
| Exit from data source[a] | 467,581 (69.30) | 199,488 (29.60) | 33,355 (1.0) | 109,460 (3.4) | 2,335,806 (83.80) | 1,178,254 (42.30) |
| Reached administrative end of follow up | 0 | 0 | 1,782,758 (55.2) | 823,566 (25.5) | 0 | 0 |
| **Matched pre-COVID-19 cohort, N** | NA | NA | 3,231,401 | 6,462,763 | 3,196,603 (100.00) | 6,178,292 (100.00) |
| Person-months of follow-up | NA | NA | | | | |
| Median (Q1, Q3) (months) | NA | NA | 12.6 (7.6-18.1) | 11.8 (6.6-18.7) | 16.50 (10.90-19.70 ) | 11.90 (7-19.10 ) |
| Min–max (months) | NA | NA | 0–24.4 | 0–24.1 | 0-25.10 | 0-24.10 |
| **Reasons for censoring, n (%)** | | | | | | |
| Non-Pfizer-BioNTech COVID-19 vaccine received | NA | NA | 1,361,323 (42.1) | NA | 505,443 (15.80) | |
| Unvaccinated received Pfizer or non-Pfizer COVID-19 vaccine | NA | NA | NA | 0 | | 0 (0) |
| Death (any cause) | NA | NA | 53,867 (1.7) | 100,871 (1.6) | 27,644 (0.90) | 11,121 (0.20) |
| Exit from data source[a] | NA | NA | 33,358 (1.0) | 87,585 (1.4) | 2,663,516 (83.30) | 120,652 (2) |
| Reached administrative end of follow up | NA | NA | 1,782,853 (55.2) | 6,274,307 (97.1) | 0 (0) | 6,046,519 (97.90) |
| **Matched -COVID-19 cohort, N** | NA | NA | 3,105,356 | 3,105,356 | 2,768,115 | 2,768,115 |
| Person-months of follow-up | NA | NA | | | | |
| Median (Q1, Q3) (months) | NA | NA | 14.5 (7.5, 18.2) | 6.7 (5.6, 8.4) | 17.2 (11.3, 19.7) | 7.2 (5.9, 10.6) |
| Min–max (months) | NA | NA | 0-24.1 | 0-12.1 | 0-24.10 | 0-12.10 |

**Table 5. Cohort follow-up and reasons for censoring for the matched vaccinated and unvaccinated main cohorts by data source (not considering censoring of the pair)**

PART 2 (SEE PART 1 ABOVE)

| | EpiChron | | SIDIAP | | CPRD Aurum | |
|---|---|---|---|---|---|---|
| | **Vaccinated** | **Unvaccinated** | **Vaccinated** | **Unvaccinated** | **Vaccinated** | **Unvaccinated** |
| **Reasons for censoring, n (%)** | | | | | | |
| Non-Pfizer-BioNTech COVID-19 vaccine received | NA | NA | 1,353,395 (43.6) | NA | 465,593 (16.80) | |
| Unvaccinated received Pfizer or non-Pfizer COVID-19 vaccine | NA | NA | NA | 4,947 (0.2) | | 27,713 (1) |
| Death (any cause) | NA | NA | 50,896 (1.6) | 46,116 (1.5) | 22,022 (0.80) | 13,597 (0.50) |
| Exit from data source[a] | NA | NA | 32,680 (1.1) | 24,964 (0.8) | 2,280,500 (82.40) | 98,509 (3.60) |
| Reached administrative end of follow up | NA | NA | 1,668,385 (53.7) | 3,029,329 (97.6) | 0 (0) | 2,628,296 (94.90) |
| **Matched pregnancy cohort, N** | 974 (100) | 974 (100) | 10,212 (100) | 10,212 (100) | 2,533 (100) | 2,533 (100) |
| Person-months of follow-up | | | | | | |
| Median (Q1, Q3) (months) | 16.6 (13.8, 17.7) | 2.5 (1.1, 6.5) | 22.3 (13.0, 23.0) | 4.5 (1.4, 22.0) | 18.1 (9.9, 19.3) | 4.6 (1.6, 15.5) |
| Min–max (months) | 5.1-23.8 | 0-23.8 | 0.5-30.1 | 0-30.1 | 0.5-24.8 | 0-24.5 |
| **Reasons for censoring, n (%)** | | | | | | |
| Non-Pfizer-BioNTech COVID-19 vaccine received | 235 (24.1) | NA | 2,420 (23.7) | NA | 504 (19.9) | NA |
| Unvaccinated received Pfizer or non-Pfizer COVID-19 vaccine | NA | 763 (78.3) | NA | 6,257 (61.3) | NA | 1,658 (65.5) |
| Death (any cause) | 0 | 0 | <5 (NR) | <5 (NR) | 0 | <5 (NR) |
| Exit from data source[a] | 739 (75.9) | 211 (21.7) | 7,791 (76.3) | 3,953 (38.7) | 2,029 (80.1) | 873(34.5) |
| Reached administrative end of follow up | 0 | 0 | 0 | 0 | 0 | 0 |
| **Matched pregnancy pre-COVID-19 cohort, N** | NA | NA | 10,272 | 20,510 | 5,842 | 7,325 |
| Person-months of follow-up | NA | NA | | | | |
| Median (Q1, Q3) (months) | NA | NA | 22.3 (13.10-23.0) | 23.5 (16.9-28.9) | 16.8 (9-18.9) | 20.4 (18.4-30.5) |
| Min–max (months) | NA | NA | 0.5-30.1 | 0.2-36.2 | 0.8-24.6 | 0.5-36.2 |
| **Reasons for censoring, n (%)** | NA | NA | | | | |
| Non-Pfizer-BioNTech COVID-19 vaccine received | NA | NA | 2,426 (23.6) | | 1,182 (20.2) | |

**Table 5. Cohort follow-up and reasons for censoring for the matched vaccinated and unvaccinated main cohorts by data source (not considering censoring of the pair)**

PART 2 (SEE PART 1 ABOVE)

| | EpiChron | | SIDIAP | | CPRD Aurum | |
|---|---|---|---|---|---|---|
| | **Vaccinated** | **Unvaccinated** | **Vaccinated** | **Unvaccinated** | **Vaccinated** | **Unvaccinated** |
| Unvaccinated received Pfizer or non-Pfizer COVID-19 vaccine | NA | NA | | 17 (0.1) | | 63 (0.9) |
| Death (any cause) | NA | NA | <5 (NR) | 5 (<0.01) | <5 (NR) | <5 (NR) |
| Exit from data source[a] | NA | NA | 7,845 (76.4) | 377 (1.8) | 4,659 (79.8) | 639 (8.7) |
| Reached administrative end of follow up | NA | NA | 0 | 20,111 (98.1) | 0 | 6,619 (90.4) |
| **Matched pregnancy COVID-19 cohort, N** | NA | NA | 10,009 | 10,009 | 3,865 | 3,865 |
| Person-months of follow-up | NA | NA | | | | |
| Median (Q1, Q3) (months) | NA | NA | 22.3 (13.2-23.0) | 11.6 (10.2-13.8) | 17.0 (9.1-19.0) | 11.7 (9.4-12.7) |
| Min–max (months) | NA | NA | 0.5-30.0 | 0.4-24.0 | 0.9-24.1 | 0.2-24.1 |
| **Reasons for censoring, n (%)** | NA | NA | | | | |
| Non-Pfizer-BioNTech COVID-19 vaccine received | NA | NA | 2,367 (23.6) | | 806 (20.9) | |
| Unvaccinated received Pfizer or non-Pfizer COVID-19 vaccine | NA | NA | NA | 8,284 (82.8) | | 3,027 (78.3) |
| Death (any cause) | NA | NA | <5 (NR) | <5 (NR) | 0 | 0 |
| Exit from data source[a] | NA | NA | 7,641 (76.3) | 118 (1.20) | 3,059 (79.1) | 332 (8.6) |
| Reached administrative end of follow up | NA | NA | 0 | 1,606 (16.0) | 0 | 506 (13.1) |

[a]Administrative end of follow-up or death (except SIDIAP); NA not applicable; NR: not reportable (due to masking)

### 10.1.3. SCRI population

Individuals included the SCRI analyses comprised those with an event in the post-vaccination risk or control period for the specific AESI, who had been vaccinated, and had at least one day of follow-up in both the risk and control periods. Most outcomes were infrequent and the main reason for non-inclusion in the SCRI analyses was because the AESI occurred outside of the risk or control periods, particularly the AESIs with shorter risk windows (Appendix Table 3).

## 10.2. Descriptive data

### 10.2.1. Patterns of Pfizer-BioNTech COVID-19 vaccine use in all vaccinated individuals

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. This was highest in the two Spanish data sources >90%, and lower in Pedianet (85.4%), PHARMO (76.2%), NHR, (76.7%) and CPRD Aurum (89.4%). In the majority of individuals who received a second dose, it was received within 6 weeks (60.8%), but, again with variation between data sources. In Pedianet 97.3% received their second dose within 6 weeks (median 3.14 weeks), in PHARMO, this was 84.7% (median 5 weeks), in NHR this was 70.3% (median 6 weeks), in SIDIAP this was 92.7% (median 3 weeks), in EpiChron this was 91.5% (median 3 weeks) and in CPRD Aurum this was only 6.1% (median: 10.7 weeks). Overall, 34.8% of those with a first dose, also had a third dose and the median delay between dose 2 and 3 was 21.4 weeks in Pedianet, 26 weeks in PHARMO, 26 weeks in NHR, 31 weeks in SIDIAP, 29.7 weeks in EpiChron and 27 weeks in CPRD Aurum. Only 9% of those with a first dose also received a fourth dose of Pfizer-BioNTech during the follow-up period and 0.1% a fifth dose. The delay between the third and fourth doses was > 40 weeks in all data sources, except in CPRD Aurum where it was 25.7 weeks.

### 10.2.2. Main matched vaccinated and unvaccinated cohorts

The baseline characteristics, comorbidities and comedications in the matched vaccinated and unvaccinated cohorts of are summarised in **Table 6**, Appendix Table 4 and Appendix Table 5, respectively.

The median age of the matched vaccinated and unvaccinated cohorts was lowest in Pedianet (10 years) and highest in PHARMO (48 years). The first dose of Pfizer-BioNTech COVID-19 vaccine was most frequently received in the second quarter of 2021 in all data sources, except in the paediatric data source, Pedianet. Young children were included the vaccination programmes later and therefore the first dose was more frequently received in Q1 2022 in Pedianet. The absolute standardised difference (ASD) for age was 0.26 in Pedianet, due to tight age range. In the two Spanish data sources, vaccinated individuals had a higher primary care utilisation than unvaccinated individuals, with an ASD in EpiChron of 0.26, in SIDIAP 0.20. In PHARMO primary care utilisation was slightly higher in vaccinated individuals compared to unvaccinated. In NHR and Pedianet, primary care utilisation was balanced between vaccinated and unvaccinated individuals. Hospitalisations remain balanced between vaccinated and unvaccinated individuals in all data sources. The most frequent comorbidities in the 10 years prior to time zero were cardiovascular, chronic respiratory disease, and connective tissue disease, followed by hypertension and immunocompromising conditions. The Charlson Comorbidity Index Score showed that >80% of the included individuals had a score of 0 or 1. The individuals were about equally

distributed between scores 0, 1, or ≥1 condition in the CDC risk score, except in EpiChron where more than 50% had zero conditions. Antibiotics as well as NSAIDs and analgesics, were most frequently used in the year prior to time zero followed by psychotropics. Vaccination with other vaccines in the year prior to time zero was high in Pedianet, especially for polio, pneumococcal and varicella vaccines. In other data sources, where the population was older, influenza vaccination was most frequent in the year prior to time zero. Baseline comorbidities and comedications were well balanced between the vaccinated and unvaccinated cohorts with all ASDs being ≤0.1, except in the Pedianet cohorts, where HPV vaccination was higher in the vaccinated cohort (13.78%) than in the unvaccinated cohort (9.86%), with an ASD of 0.12.

**Table 6. Baseline demographics, lifestyle variables and healthcare resource utilisation with absolute standardised differences (ASDs) for the matched vaccinated and unvaccinated cohorts by data source**

Part 1: (SEE PART 2 BELOW)

| | Pedianet | | | PHARMO | | | NHR | | |
|---|---|---|---|---|---|---|---|---|---|
| | **Vaccinated** | **Unvaccinated** | **ASD** | **Vaccinated** | **Unvaccinated** | **ASD** | **Vaccinated** | **Unvaccinated** | **ASD** |
| **Total, N** | 10,497 | 10,497 | | 1,222,612 | 1,222,612 | | 3,571,573 | 3,571,573 | |
| **Demographics** | | | | | | | | | |
| Age (years) | | | 0.07 | | | <0.01 | | | <0.01 |
| Mean (SD) | 9.40 (2.48) | 9.22 (2.44) | | 47.70 (21.65) | 47.67 (21.64) | | 46.94 (21.06) | 46.88 (21.06) | |
| Median (Q1, Q3) | 10 (7, 12) | 10 (7, 11) | | 48 (29, 68) | 48 (29, 68) | | 47 (29, 64) | 47 (29, 64) | |
| Age groups (years), n (%) | | | 0.26 | | | 0.06 | | | 0.10 |
| 0-1 | 0 (0) | 0 (0) | | 6 (< 0.01) | 6 (< 0.01) | | 5 (< 0.01) | <5 (NR) | |
| 2-4 | 17 (0.16) | 269 (2.56) | | 104 (0.01) | 303 (0.02) | | 6 (< 0.01) | 214 (0.01) | |
| 5-11 | 7,733 (73.67) | 8,237 (78.47) | | 12,028 (0.98) | 16,471 (1.35) | | 10,273 (0.29) | 37,252 (1.04) | |
| 12-15 | 2,747 (26.17) | 1,991 (18.97) | | 69,883 (5.72) | 66,072 (5.40) | | 209,731 (5.87) | 194,275 (5.44) | |
| 16-17 | 0 | 0 | | 42,388 (3.47) | 41,817 (3.42) | | 119,254 (3.34) | 119,712 (3.35) | |
| 18-29 | 0 | 0 | | 183,550 (15.01) | 183,392 (15) | | 576,162 (16.13) | 563,398 (15.77) | |
| 30-39 | 0 | 0 | | 167,187 (13.67) | 167,256 (13.68) | | 487,407 (13.65) | 489,822 (13.71) | |
| 40-49 | 0 | 0 | | 167,952 (13.74) | 167,905 (13.73) | | 514,522 (14.41) | 514,006 (14.39) | |
| 50-59 | 0 | 0 | | 199,258 (16.30) | 194,879 (15.94) | | 548,876 (15.37) | 549,715 (15.39) | |
| 60-64 | 0 | 0 | | 12,984 (1.06) | 19,553 (1.60) | | 242,706 (6.80) | 248,745 (6.96) | |
| 65-69 | 0 | 0 | | 99,372 (8.13) | 97,787 (8.00) | | 240,209 (6.73) | 235,242 (6.59) | |
| 70-79 | 0 | 0 | | 188,140 (15.39) | 189,721 (15.52) | | 409,877 (11.48) | 409,654 (11.47) | |
| 80+ | 0 | 0 | | 79,760 (6.52) | 77,450 (6.33) | | 212,545 (5.95) | 209,534 (5.87) | |
| Female, n (%) | 5,153 (49.09) | 5,153 (49.09) | <0.01 | 623,879 (51.03) | 623,879 (51.03) | <0.01 | 1,771,150 (49.59) | 1,771,150 (49.59) | <0.01 |
| Females aged 15 to 55 years, n (%) | 0 | 0 | <0.01 | 344,937 (28.21) | 344,836 (28.20) | <0.01 | 1,016,437 (28.46) | 1,013,560 (28.38) | <0.01 |
| **Pregnancy status, n (%)** | | | <0.01 | | | <0.01 | | | <0.01 |
| First trimester | 0 | 0 | | 297 (32.49) | 286 (31.29) | | 3,863 (32.35) | 3,562 (29.57) | |
| Second trimester | 0 | 0 | | 358 (39.17) | 310 (33.92) | | 4,310 (36.09) | 3,523 (29.24) | |
| Third trimester | 0 | 0 | | 256 (28.01) | 308 (33.70) | | 3,757 (31.46) | 4,724 (39.21) | |
| Unknown | 0 | 0 | | <5 (NR) | 10 (1.09) | | 12 (0.10) | 239 (1.98) | |
| **Date of vaccination or matching, n (%)** | | | <0.01 | | | <0.01 | | | <0.01 |
| 1 Oct–31 Dec 2020 | 0 (< 0.01) | 0 (< 0.01) | | <5 (NR) | <5 (NR) | | 10,461 (0.29) | 10,461 (0.29) | |
| 1 Jan–31 March 2021 | <5 (NR) | <5 (NR) | | 128,010 (10.47) | 128,010 (10.47) | | 498,323 (13.95) | 498,323 (13.95) | |
| 1 Apr–30 Jun 2021 | 197 (1.88) | 197 (1.88) | | 615,260 (50.32) | 615,260 (50.32) | | 1,675,622 (46.92) | 1,675,622 (46.92) | |
| 1 Jul–30 Sep 2021 | 1,665 (15.86) | 1,665 (15.86) | | 362,482 (29.65) | 362,482 (29.65) | | 1,233,990 (34.55) | 1,233,990 (34.55) | |
| 1 Oct–31 Dec 2021 | 3,315 (31.58) | 3,315 (31.58) | | 61,579 (5.04) | 61,579 (5.04) | | 109,804 (3.07) | 109,804 (3.07) | |
| 1 Jan–31 Mar 2022 | 5,114 (48.72) | 5,114 (48.72) | | 39,462 (3.23) | 39,462 (3.23) | | 34,057 (0.95) | 34,057 (0.95) | |

**Table 6. Baseline demographics, lifestyle variables and healthcare resource utilisation with absolute standardised differences (ASDs) for the matched vaccinated and unvaccinated cohorts by data source**

Part 1: (SEE PART 2 BELOW)

| | Pedianet | | | PHARMO | | | NHR | | |
|---|---|---|---|---|---|---|---|---|---|
| | **Vaccinated** | **Unvaccinated** | **ASD** | **Vaccinated** | **Unvaccinated** | **ASD** | **Vaccinated** | **Unvaccinated** | **ASD** |
| 1 Apr–30 Jun 2022 | 137 (1.31) | 137 (1.31) | | 4,273 (0.35) | 4,273 (0.35) | | 6,265 (0.18) | 6,265 (0.18) | |
| 1 Jul–30 Sep 2022 | 54 (0.51) | 54 (0.51) | | 3,425 (0.28) | 3,425 (0.28) | | 1,960 (0.05) | 1,960 (0.05) | |
| 1 Oct–31 Dec 2022 | 14 (0.13) | 14 (0.13) | | 8,118 (0.66) | 8,118 (0.66) | | 1,091 (0.03) | 1,091 (0.03) | |
| **Personal lifestyle characteristics** | | | | | | | | | |
| **Smoking status** | | | NA | | | 0.12 | | | NA |
| Never | NA | NA | | 31,547 (2.58) | 25,578 (2.09) | | NA | NA | |
| Former | NA | NA | | 56,834 (4.65) | 53,437 (4.37) | | NA | NA | |
| Current | NA | NA | | 101,982 (8.34) | 82,870 (6.78) | | NA | NA | |
| Never or former | NA | NA | | 130,632 (10.68) | 98,751 (8.08) | | NA | NA | |
| Unknown | NA | NA | | 901,617 (73.75) | 961,976 (78.68) | | NA | NA | |
| **BMI, n (%)*** | | | 0.04 | | | 0.12 | | | <0.01 |
| Unknown | 2,794 (26.62) | 2,967 (28.27) | | 899,949 (73.61) | 961,207 (78.62) | | 3,571,573 (100) | 3,571,573 (100) | |
| Underweight (BMI <20kg/m$^2$) | 6,091 (58.03) | 6,012 (57.27) | | 8,757 (0.72) | 8,225 (0.67) | | 0 (0) | 0 (0) | |
| Normal weight (BMI 20 to <25kg/m$^2$) | 1,296 (12.35) | 1,222 (11.64) | | 75,498 (6.18) | 60,904 (4.98) | | 0 (0) | 0 (0) | |
| Overweight (BMI 25 to <30kg/m$^2$) | 265 (2.52) | 246 (2.34) | | 138,796 (11.35) | 109,565 (8.96) | | 0 (0) | 0 (0) | |
| Obese (BMI ≥30kg/m$^2$) | 51 (0.49) | 50 (0.48) | | 99,612 (8.15) | 82,711 (6.77) | | 0 (0) | 0 (0) | |
| Obesity diagnosis or obesity surgery | 578 (5.51) | 514 (4.90) | 0.03 | 30,728 (2.51) | 29,569 (2.42) | 0.01 | 143,578 (4.02) | 121,344 (3.40) | 0.03 |
| **Healthcare utilisation** | | | | | | | | | |
| Hospitalisations, n (%) | | | 0.01 | | | NA | | | <0.01 |
| 0 | 10,112 (96.33) | 10,118 (96.39) | | NA | NA | | 3,208,303 (89.83) | 3,210,358 (89.89) | |
| 1 | 297 (2.83) | 281 (2.68) | | NA | NA | | 257,861 (7.22) | 258,492 (7.24) | |
| 2+ | 88 (0.84) | 98 (0.93) | | NA | NA | | 105,409 (2.95) | 102,723 (2.88) | |
| Emergency department visits, n (%) | | | 0.01 | | | NA | | | NA |
| 0 | 9,262 (88.23) | 9,281 (88.42) | | NA | NA | | NA | NA | |
| 1 | 976 (9.30) | 967 (9.21) | | NA | NA | | NA | NA | |
| 2+ | 259 (2.47) | 249 (2.37) | | NA | NA | | NA | NA | |
| Primary care utilisation, n (%) | | | 0.04 | | | 0.35 | | | 0.08 |
| 0 | 1,294 (12.33) | 1,428 (13.60) | | 382,935 (31.32) | 591,521 (48.38) | | 507,495 (14.21) | 608,405 (17.03) | |

**Table 6. Baseline demographics, lifestyle variables and healthcare resource utilisation with absolute standardised differences (ASDs) for the matched vaccinated and unvaccinated cohorts by data source**

Part 1: (SEE PART 2 BELOW)

| | Pedianet | | | PHARMO | | | NHR | | |
|---|---|---|---|---|---|---|---|---|---|
| | **Vaccinated** | **Unvaccinated** | **ASD** | **Vaccinated** | **Unvaccinated** | **ASD** | **Vaccinated** | **Unvaccinated** | **ASD** |
| 1 | 1,744 (16.61) | 1,722 (16.40) | | 166,906 (13.65) | 124,819 (10.21) | | 366,151 (10.25) | 379,229 (10.62) | |
| 2+ | 7,459 (71.06) | 7,347 (69.99) | | 672,771 (55.03) | 506,272 (41.41) | | 2,697,927 (75.54) | 2,583,939 (72.35) | |
| Cancer screening, n (%) | | | NA | | | NA | | | NA |
| 0 | NA | NA | | NA | NA | | NA | NA | |
| 1 | NA | NA | | NA | NA | | NA | NA | |
| 2+ | NA | NA | | NA | NA | | NA | NA | |
| COVID-19 tests, n (%) | | | 0.09 | | | NA | | | <0.01 |
| 0 | 2,967 (28.27) | 3,338 (31.80) | | NA | NA | | 3,500,660 (98.01) | 3,500,413 (98.01) | |
| 1-2 | 6,489 (61.82) | 6,272 (59.75) | | NA | NA | | 70,911 (1.99) | 71,159 (1.99) | |
| 3-4 | 956 (9.11) | 813 (7.75) | | NA | NA | | <5 (NR) | <5 (NR) | |
| 5+ | 85 (0.81) | 74 (0.70) | | NA | NA | | 0 (0) | 0 (0) | |

ASD: absolute standardised difference; BMI: body mass index; NR: not reportable; NA: not available
* No child-specific BMI algorithm was applied.

**Table 6. Baseline demographics, lifestyle variables and healthcare resource utilisation with absolute standardised differences (ASDs) for the matched vaccinated and unvaccinated cohorts by data source**

Part 2: (SEE PART 1 ABOVE)

| | EpiChron | | | SIDIAP | | | CPRD Aurum | | |
|---|---|---|---|---|---|---|---|---|---|
| | **Vaccinated** | **Unvaccinated** | **ASD** | **Vaccinated** | **Unvaccinated** | **ASD** | **Vaccinated** | **Unvaccinated** | **ASD** |
| **Total, N** | 674,523 | 674,523 | | 3,231,245 | 3,231,245 | | 2,786,479 | 2,786,479 | |
| **Demographics** | | | | | | | | | |
| Age (years) | | | <0.01 | | | <0.01 | | | 0 |
| Mean (SD) | 46.70 (23.09) | 46.61 (23.06) | | 46.09 (23.19) | 46.03 (23.18) | | 35.21 (20.42) | 35.14 (20.45) | |
| Median (Q1, Q3) | 46 (29, 67) | 46 (29, 67) | | 45 (28, 60) | 45 (28, 61) | | 31 (19, 47) | 31 (19, 47) | |
| Age groups (years), n (%) | | | 0.06 | | | 0.07 | | | 0.09 |
| 0-1 | 0 (0) | 0 (0) | | <5 (NR) | <5 (NR) | | <5 (NR) | <5 (NR) | |
| 2-4 | 0 (0) | 1,154 (0.17) | | 13 (< 0.01) | 6,286 (0.19) | | 121 (<0.01) | 4,419 (0.16) | |
| 5-11 | 49,157 (7.29) | 49,845 (7.39) | | 191,419 (5.92) | 206,978 (6.41) | | 123,192 (4.42) | 162,615 (5.84) | |
| 12-15 | 33,028 (4.90) | 32,281 (4.79) | | 199,206 (6.16) | 184,050 (5.70) | | 309,531 (11.11) | 280,760 (10.08) | |
| 16-17 | 15,607 (2.31) | 15,103 (2.24) | | 99,475 (3.08) | 91,218 (2.82) | | 165,370 (5.93) | 164,510 (5.90) | |
| 18-29 | 72,110 (10.69) | 71,776 (10.64) | | 358,900 (11.11) | 361,126 (11.18) | | [731896-731899] ([26.27-26.27]) | [719464-719467] ([25.82-25.82]) | |
| 30-39 | 81,104 (12.02) | 81,619 (12.10) | | 415,476 (12.86) | 417,230 (12.91) | | 581,571 (20.87) | 577,395 (20.72) | |
| 40-49 | 129,245 (19.16) | 129,541 (19.20) | | 623,021 (19.28) | 624,642 (19.33) | | 242,404 (8.70) | 244,338 (8.77) | |
| 50-59 | 108,428 (16.07) | 106,859 (15.84) | | 526,198 (16.28) | 517,508 (16.02) | | 207,998 (7.46) | 209,565 (7.52) | |
| 60-64 | 10,529 (1.56) | 10,997 (1.63) | | 42,063 (1.30) | 46,403 (1.44) | | 85,135 (3.06) | 87,867 (3.15) | |
| 65-69 | 27,293 (4.05) | 29,665 (4.40) | | 45,876 (1.42) | 51,538 (1.59) | | 71,552 (2.57) | 72,281 (2.59) | |
| 70-79 | 86,261 (12.79) | 86,148 (12.77) | | 407,788 (12.62) | 411,645 (12.74) | | 148,864 (5.34) | 150,065 (5.39) | |
| 80+ | 61,761 (9.16) | 59,535 (8.83) | | 321,808 (9.96) | 312,617 (9.67) | | 118,841 (4.26) | 113,196 (4.06) | |
| Female, n (%) | 348,758 (51.70) | 348,758 (51.70) | 0 | 1,677,695 (51.92) | 1,677,695 (51.92) | 0 | 1,420,960 (50.99) | 1,420,960 (50.99) | 0 |
| Females aged 15 to 55 years, n (%) | 185,542 (27.51) | 185,543 (27.51) | 0 | 930,462 (28.80) | 929,648 (28.77) | 0 | 970,961 (34.85) | 968,792 (34.77) | 0 |
| **Pregnancy status, n (%)** | | | <0.01 | | | 0.01 | | | 0.01 |
| First trimester | 263 (26.95) | 265 (27.18) | | 3,516 (34.44) | 3,278 (32.11) | | [931-934] ([36.77-36.89]) | 709 (28.00) | |
| Second trimester | 418 (42.83) | 386 (39.59) | | 3,781 (37.04) | 3,428 (33.58) | | 875 (34.56) | 832 (32.86) | |
| Third trimester | 294 (30.12) | 318 (32.62) | | 2,896 (28.37) | 3,371 (33.02) | | 722 (28.52) | 967 (38.19) | |
| Unknown | <5 (NR) | 6 (0.62) | | 15 (0.15) | 132 (1.29) | | <5 (NR) | 24 (0.95) | |

**Table 6. Baseline demographics, lifestyle variables and healthcare resource utilisation with absolute standardised differences (ASDs) for the matched vaccinated and unvaccinated cohorts by data source**

Part 2: (SEE PART 1 ABOVE)

| | EpiChron | | | SIDIAP | | | CPRD Aurum | | |
|---|---|---|---|---|---|---|---|---|---|
| | **Vaccinated** | **Unvaccinated** | **ASD** | **Vaccinated** | **Unvaccinated** | **ASD** | **Vaccinated** | **Unvaccinated** | **ASD** |
| **Date of vaccination or matching, n (%)** | | | 0 | | | 0 | | | 0 |
| 1 Oct–31 Dec 2020 | 1,918 (0.28) | 1,918 (0.28) | | 4,972 (0.15) | 4,972 (0.15) | | 95,443 (3.43) | 95,443 (3.43) | |
| 1 Jan–31 March 2021 | 89,982 (13.34) | 89,982 (13.34) | | 428,778 (13.27) | 428,778 (13.27) | | 845,679 (30.35) | 845,679 (30.35) | |
| 1 Apr–30 Jun 2021 | 325,968 (48.33) | 325,968 (48.33) | | 1,642,173 (50.82) | 1,642,173 (50.82) | | 888,909 (31.90) | 888,909 (31.90) | |
| 1 Jul–30 Sep 2021 | 193,460 (28.68) | 193,460 (28.68) | | 876,188 (27.12) | 876,188 (27.12) | | 382,858 (13.74) | 382,858 (13.74) | |
| 1 Oct–31 Dec 2021 | 37,816 (5.61) | 37,816 (5.61) | | 171,527 (5.31) | 171,527 (5.31) | | 335,469 (12.04) | 335,469 (12.04) | |
| 1 Jan–31 Mar 2022 | 22,750 (3.37) | 22,750 (3.37) | | 92,435 (2.86) | 92,435 (2.86) | | 94,329 (3.39) | 94,329 (3.39) | |
| 1 Apr–30 Jun 2022 | 1,677 (0.25) | 1,677 (0.25) | | 8,310 (0.26) | 8,310 (0.26) | | 109,343 (3.92) | 109,343 (3.92) | |
| 1 Jul–30 Sep 2022 | 673 (0.10) | 673 (0.10) | | 4,223 (0.13) | 4,223 (0.13) | | 25,777 (0.93) | 25,777 (0.93) | |
| 1 Oct–31 Dec 2022 | 279 (0.04) | 279 (0.04) | | 2,639 (0.08) | 2,639 (0.08) | | 8,672 (0.31) | 8,672 (0.31) | |
| **Personal lifestyle characteristics** | | | | | | | | | |
| **Smoking status** | | | 0.03 | | | 0.01 | | | 0.03 |
| Never | 12,051 (1.79) | 10,138 (1.50) | | 0 (0) | 0 (0) | | 0 (0) | 0 (0) | |
| Former | 0 (0) | 0 (0) | | 65,814 (2.04) | 64,245 (1.99) | | 0 (0) | 0 (0) | |
| Current | 38,169 (5.66) | 36,051 (5.34) | | 222,565 (6.89) | 226,159 (7) | | 741,974 (26.63) | 772,750 (27.73) | |
| Never or former | 0 (0) | 0 (0) | | 0 (0) | 0 (0) | | 0 (0) | 0 (0) | |
| Unknown | 624,303 (92.55) | 628,334 (93.15) | | 2,942,866 (91.08) | 2,940,841 (91.01) | | 2,044,505 (73.37) | 2,013,729 (72.27) | |
| **BMI, n (%)*** | | | 0.04 | | | 0.01 | | | 0.10 |
| Unknown | 542,412 (80.41) | 551,018 (81.69) | | 2,494,896 (77.21) | 2,505,059 (77.53) | | 1,545,883 (55.48) | 1,674,175 (60.08) | |
| Underweight (BMI <20kg/m$^2$) | 28,882 (4.28) | 26,521 (3.93) | | 175,259 (5.42) | 173,116 (5.36) | | 153,360 (5.50) | 150,943 (5.42) | |
| Normal weight (BMI 20 to <25kg/m$^2$) | 39,473 (5.85) | 34,834 (5.16) | | 179,580 (5.56) | 176,398 (5.46) | | 410,749 (14.74) | 365,014 (13.10) | |
| Overweight (BMI 25 to <30kg/m$^2$) | 36,551 (5.42) | 34,723 (5.15) | | 216,433 (6.70) | 213,960 (6.62) | | 361,396 (12.97) | 319,310 (11.46) | |
| Obese (BMI ≥30kg/m$^2$) | 27,205 (4.03) | 27,427 (4.07) | | 165,077 (5.11) | 162,712 (5.04) | | 315,091 (11.31) | 277,037 (9.94) | |
| Obesity diagnosis or obesity surgery | 38,036 (5.64) | 38,840 (5.76) | <0.01 | 487,939 (15.10) | 492,328 (15.24) | <0.01 | 140,139 (5.03) | 132,714 (4.76) | 0.01 |
| **Healthcare utilisation** | | | | | | | | | |
| Hospitalisations, n (%) | | | 0.01 | | | 0.01 | | | 0.01 |
| 0 | 629,314 (93.30) | 630,565 (93.48) | | 2,982,787 (92.31) | 2,981,326 (92.27) | | 2,745,520 (98.53) | 2,743,696 (98.46) | |
| 1 | 36,668 (5.44) | 34,832 (5.16) | | 194,512 (6.02) | 192,004 (5.94) | | 33,097 (1.19) | 33,619 (1.21) | |
| 2+ | 8,541 (1.27) | 9,126 (1.35) | | 53,946 (1.67) | 57,915 (1.79) | | 7,862 (0.28) | 9,164 (0.33) | |

**Table 6. Baseline demographics, lifestyle variables and healthcare resource utilisation with absolute standardised differences (ASDs) for the matched vaccinated and unvaccinated cohorts by data source**

Part 2: (SEE PART 1 ABOVE)

| | EpiChron | | | SIDIAP | | | CPRD Aurum | | |
|---|---|---|---|---|---|---|---|---|---|
| | **Vaccinated** | **Unvaccinated** | **ASD** | **Vaccinated** | **Unvaccinated** | **ASD** | **Vaccinated** | **Unvaccinated** | **ASD** |
| Emergency department visits, n (%) | | | 0.03 | | | NA | | | 0.02 |
| 0 | 552,432 (81.90) | 558,305 (82.77) | | NA | NA | | 2,493,512 (89.49) | 2,503,778 (89.85) | |
| 1 | 84,814 (12.57) | 79,072 (11.72) | | NA | NA | | 221,212 (7.94) | 207,731 (7.45) | |
| 2+ | 37,277 (5.53) | 37,146 (5.51) | | NA | NA | | 71,755 (2.58) | 74,970 (2.69) | |
| Primary care utilisation, n (%) | | | 0.26 | | | 0.20 | | | 0.16 |
| 0 | 86,183 (12.78) | 151,435 (22.45) | | 416,183 (12.88) | 650,167 (20.12) | | 878,359 (31.52) | 1,088,125 (39.05) | |
| 1 | 52,914 (7.84) | 50,378 (7.47) | | 241,525 (7.47) | 234,419 (7.25) | | 400,922 (14.39) | 371,706 (13.34) | |
| 2+ | 535,426 (79.38) | 472,710 (70.08) | | 2,573,537 (79.65) | 2,346,659 (72.62) | | 1,507,198 (54.09) | 1,326,648 (47.61) | |
| Cancer screening, n (%) | | | NA | | | NA | | | 0.04 |
| 0 | NA | NA | | NA | NA | | 2,531,721 (90.86) | 2,565,181 (92.06) | |
| 1 | NA | NA | | NA | NA | | 213,579 (7.66) | 186,854 (6.71) | |
| 2+ | NA | NA | | NA | NA | | 41,179 (1.48) | 34,444 (1.24) | |
| COVID-19 tests, n (%) | | | 0.09 | | | 0.01 | | | 0.18 |
| 0 | 484,678 (71.85) | 510,572 (75.69) | | 2,240,432 (69.34) | 2,253,608 (69.74) | | 1,752,681 (62.90) | 1,977,740 (70.98) | |
| 1-2 | 189,845 (28.15) | 163,951 (24.31) | | 731,283 (22.63) | 722,192 (22.35) | | 807,830 (28.99) | 651,788 (23.39) | |
| 3-4 | 0 (0) | 0 (0) | | 171,282 (5.30) | 168,530 (5.22) | | 145,590 (5.22) | 109,904 (3.94) | |
| 5+ | 0 (0) | 0 (0) | | 88,248 (2.73) | 86,915(2.69) | | 80,378 (2.88) | 47,047 (1.69) | |

ASD: absolute standardised difference; NR: not reportable; Vac: vaccinated cohort; Unvac: unvaccinated cohort; NA: not available
* No child-specific BMI algorithm was applied

### 10.2.3. Historical control cohort

Demographic characteristics of the matched vaccinated and historical control cohorts are listed in **Standalone Section 15**.

### 10.2.4. SCRI

Demographic characteristics of the cases included in the SCRI study cohorts are listed in **Standalone Section 15**.

### 10.2.5. Matched vaccinated and unvaccinated pregnancy cohorts

For the matched pregnancy analysis cohort, baseline characteristics, pregnancy history, comorbidities and comedications are summarised in Appendix Table 6, Appendix Table 7, Appendix Table 8 and Appendix Table 9, respectively. No pregnancies were observed in Pedianet as this is a paediatric data source. Pregnant women were mostly vaccinated in Q3 2021 except in CPRD Aurum in Q2 2021 with similar numbers in their first, second and third trimesters.

The median age of the matched vaccinated and unvaccinated pregnancy cohorts was between 31 and 34 years. Smoking status and BMI during pregnancy were not well recorded in the available healthcare records and were mostly unknown. In PHARMO, vaccinated pregnant women had more primary care visits than the matched unvaccinated pregnant women in the year prior to time zero (ASD: 0.28). In the other data sources, primary care utilisation was balanced between the vaccinated and unvaccinated cohorts. The number of hospitalisations in the year prior to time zero was balanced between the matched vaccinated and unvaccinated pregnancy cohorts in all data sources. Trimester of pregnancy was not balanced in any of the data sources, with more women in their second trimester in the vaccinated cohort compared with the unvaccinated cohort. Few women had a history of pregnancy complications in prior pregnancies, with a balanced between the matched vaccinated and unvaccinated cohorts, although the absolute rates of spontaneous abortion and prior caesarean section was highly variable between data sources. There were fewer than 2% of multiple pregnancies. History of caesarean sections was highest in EpiChron, NHR and CPRD Aurum. The data for gravidity seem to suggest that most pregnancies were first pregnancies, except for CPRD Aurum, which may be due to misclassification.

The rates of comorbidities were very low, and distributions were balanced between the cohorts (Appendix Table 8). Cardiovascular and chronic respiratory diseases were the most frequent comorbidities, followed by history of allergies, connective tissue disease and immunocompromising conditions. This latter result could be due to the use of steroids, which are indicated for foetal lung maturation during pregnancies at risk of premature delivery. Antibiotics, NSAIDs and analgesics, were most frequently used in the year prior to time zero followed by psychotropics. The frequencies of comorbidities and medication use were balanced between vaccinated and unvaccinated pregnant women in all data sources.

Use of other vaccinations was relatively high in the Spanish data sources, CPRD Aurum and NHR. In PHARMO only influenza vaccines could be assessed. There was significant heterogeneity between data sources, probably based on maternal immunisation practices. Comedications and vaccines were balanced between vaccinated and unvaccinated pregnant women.

### 10.3. Outcome data

A total of 37 AESIs (sudden death could not be assessed accurately) with varying risk windows were assessed in this study (**Table 2**).

### 10.4. Main outcomes

An overview of the number of events, PY and incidence rates in the matched vaccinated and unvaccinated cohorts, as well propensity score adjusted HRs and RDs by data source for all 20 of the selected AESIs are summarised in **Table 7**. A summary of these data for the other AESIs can be found in Appendix Table 10.

**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**

| | Vaccinated | | | Unvaccinated | | | | |
|---|---|---|---|---|---|---|---|---|
| **Adverse event of special interest** | **Events (n)** | **PY** | **Incidence rate (95% CI)** | **Events (n)** | **PY** | **Incidence rate (95% CI)** | **Adjusted HR[a]** | **Adjusted RD[a]** |
| **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) |

**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**

| | Vaccinated | | | Unvaccinated | | | | |
|---|---|---|---|---|---|---|---|---|
| **Adverse event of special interest** | **Events (n)** | **PY** | **Incidence rate (95% CI)** | **Events (n)** | **PY** | **Incidence rate (95% CI)** | **Adjusted HR[a]** | **Adjusted RD[a]** |
| **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) |
| 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 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**

| | Vaccinated | | | Unvaccinated | | | | |
|---|---|---|---|---|---|---|---|---|
| **Adverse event of special interest** | **Events (n)** | **PY** | **Incidence rate (95% CI)** | **Events (n)** | **PY** | **Incidence rate (95% CI)** | **Adjusted HR[a]** | **Adjusted RD[a]** |
| 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** | | | | | | | | |
| **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) |

**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**

| | Vaccinated | | | Unvaccinated | | | | |
|---|---|---|---|---|---|---|---|---|
| **Adverse event of special interest** | **Events (n)** | **PY** | **Incidence rate (95% CI)** | **Events (n)** | **PY** | **Incidence rate (95% CI)** | **Adjusted HR[a]** | **Adjusted RD[a]** |
| 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[b]** | | | | | | | | |
| Pedianet | 0 | 28.70 | 0 (0, 3.67) | 0 | 28.70 | NE | NE | NR (NR, NR) |
| PHARMO | <5 | NR | 0.01 (0, 0.05) | <5 | NR | 0.01 (0, 0.06) | 0.87 (0.05, 13.97) | NR (NR, 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) |

**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**

| | Vaccinated | | | Unvaccinated | | | | |
|---|---|---|---|---|---|---|---|---|
| **Adverse event of special interest** | **Events (n)** | **PY** | **Incidence rate (95% CI)** | **Events (n)** | **PY** | **Incidence rate (95% CI)** | **Adjusted HR[a]** | **Adjusted RD[a]** |
| 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) |

NA: not available; NE: not estimated; NR: not reportable due to obligation to mask number of events when less than 5.
[a] see **Section 9.9.2.1**; [b] as the risk window for anaphylaxis was one day, the prevalence was calculated per 10,000 persons and prevalence ratios are provided.

### 10.4.1. Outcomes that are identified risks in risk management plan or discussed by the PRAC

In this report, AESIs were pre-classified as identified risks in the Pfizer-BioNTech COVID-19 vaccine risk management plan (RMP) (anaphylaxis and myocarditis/pericarditis), followed by those that were discussed as safety signals by the Pharmacovigilance Risk Assessment Committee (PRAC)[11] as well as cardiovascular and circulatory AESI and death. Together we call these core AESI, they are followed by other AESI, that were also identified by the Safety Platform for Emergency Vaccines (SPEAC). The results for the pregnancy outcomes are described in the last section of the main results. Identified risks in Pfizer-BioNTech risk management plan.

The identified risks in the RMP are anaphylaxis, myocarditis and pericarditis. Incidence rates were not established for anaphylaxis because the risk window was one day. Instead, prevalence rates and prevalence ratios (PR) are provided. The rates of myocarditis, pericarditis and myocarditis or pericarditis by quarter from Q1 2018 to Q4 2022 by data source showed a peak incidence each winter in EpiChron and SIDIAP (**Figure 3**).

#### 10.4.1.1.1. Anaphylaxis

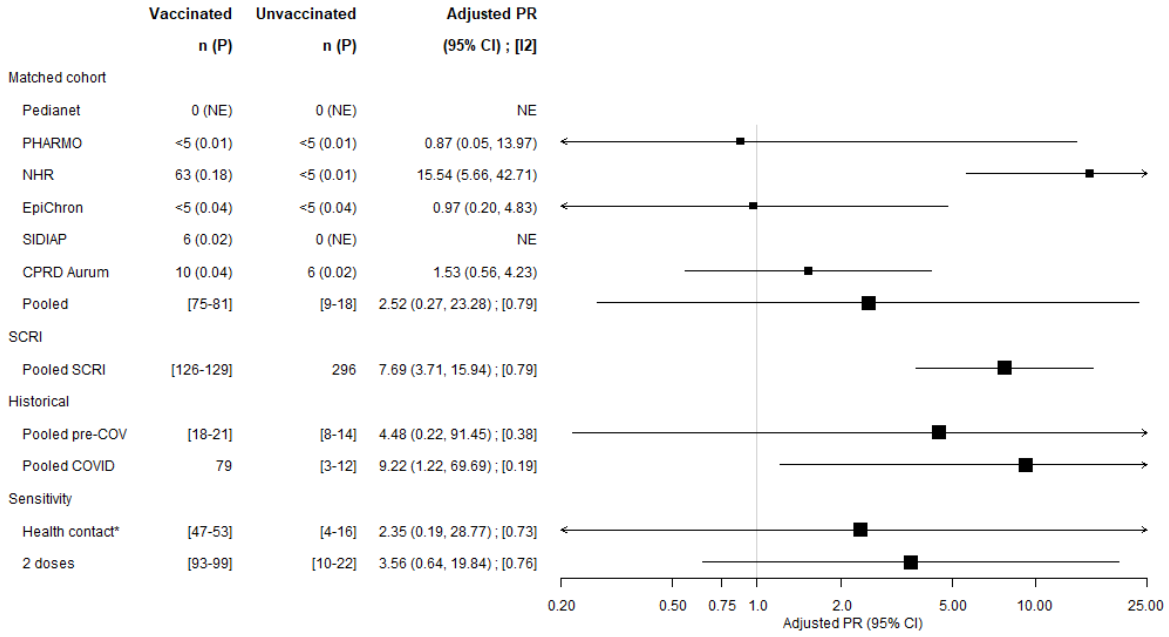
Prevalence rates of anaphylaxis were very low but were highest in the vaccinated cohort in NHR (0.18/10,000 PY) (**Table 7**).

The propensity score adjusted PRs for anaphylaxis in the primary analysis were elevated in NHR and CPRD Aurum but with wide 95% CIs (**Table 7**). 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 2**). 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**): 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) 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 2. 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

### 10.4.1.1.2. 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 3**. 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).

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 4**). 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 4**). 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. 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 4**). 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. 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 3. 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**

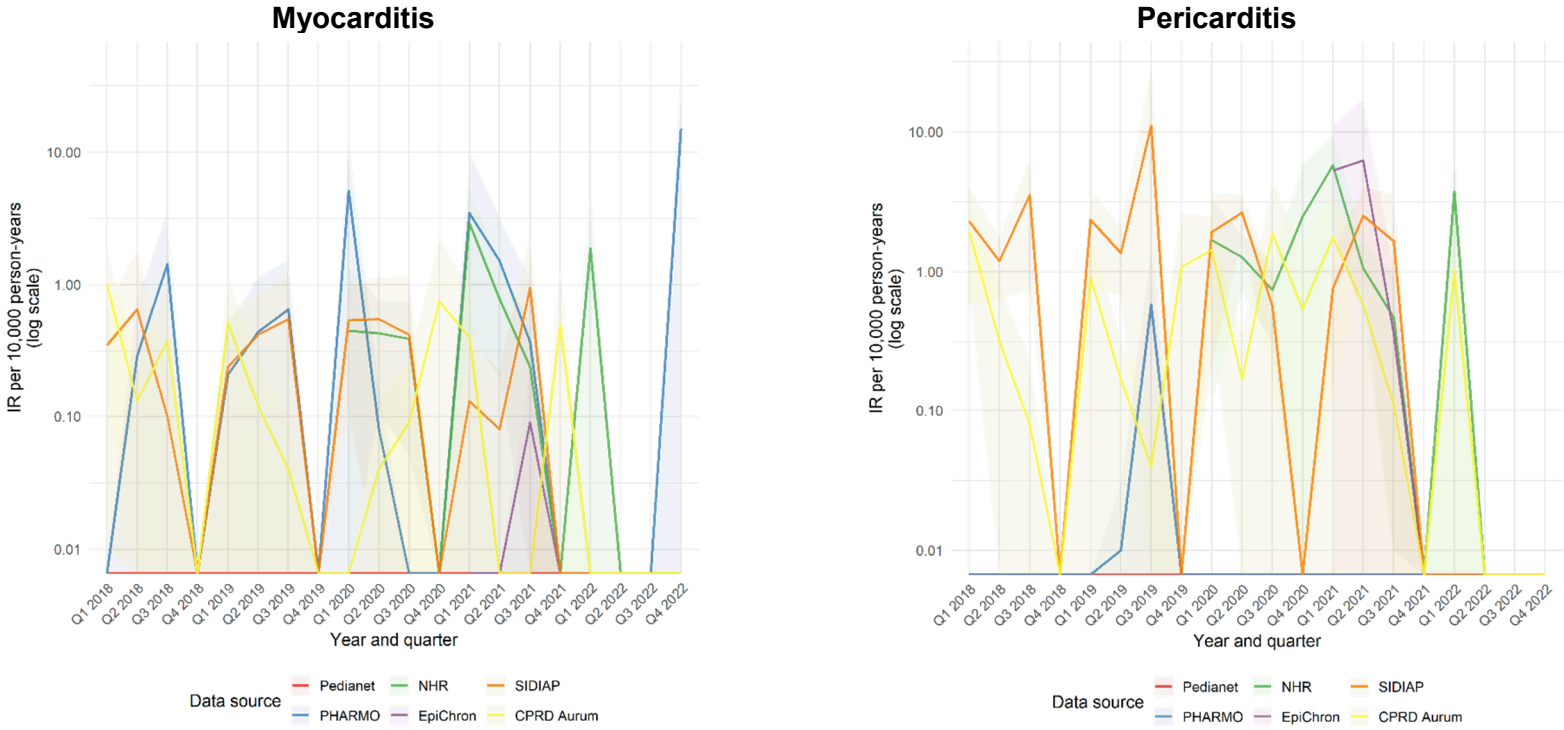


**Figure 3. Incidence rates by quarter from Q1 2018 to Q4 2022 for myocarditis, pericarditis and myocarditis, and pericarditis in unvaccinated individuals, standardised to the age in the data source specific population in 2020, by data sources**

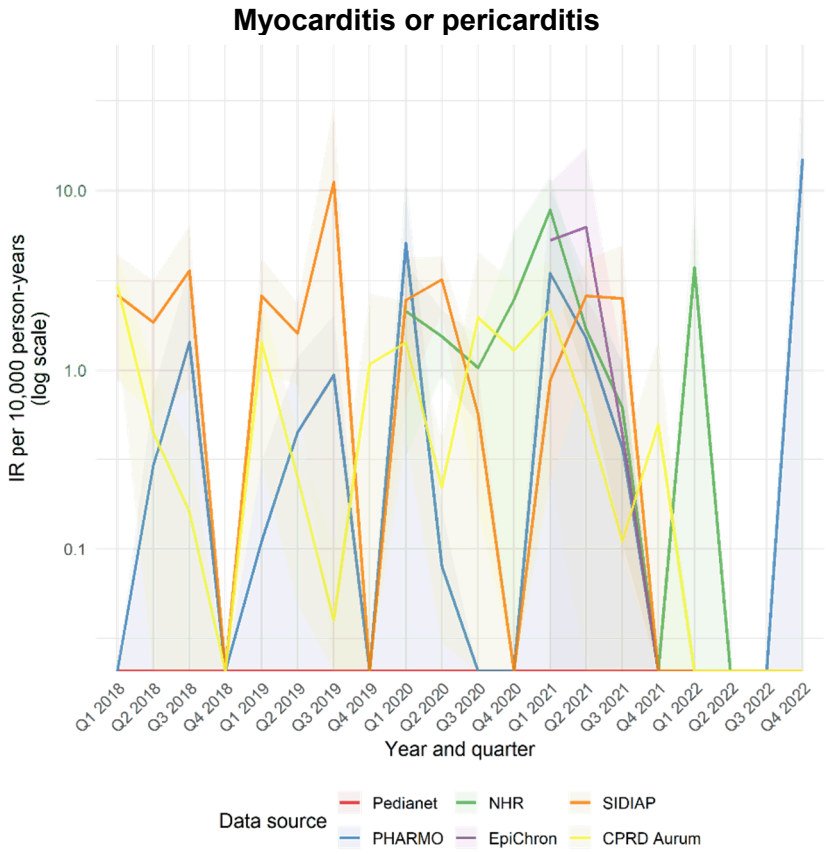


**Figure 4. Pooled analyses for myocarditis, pericarditis, and myocarditis or pericarditis (21 days) in the main cohort, historical cohorts and sensitivity analyses**

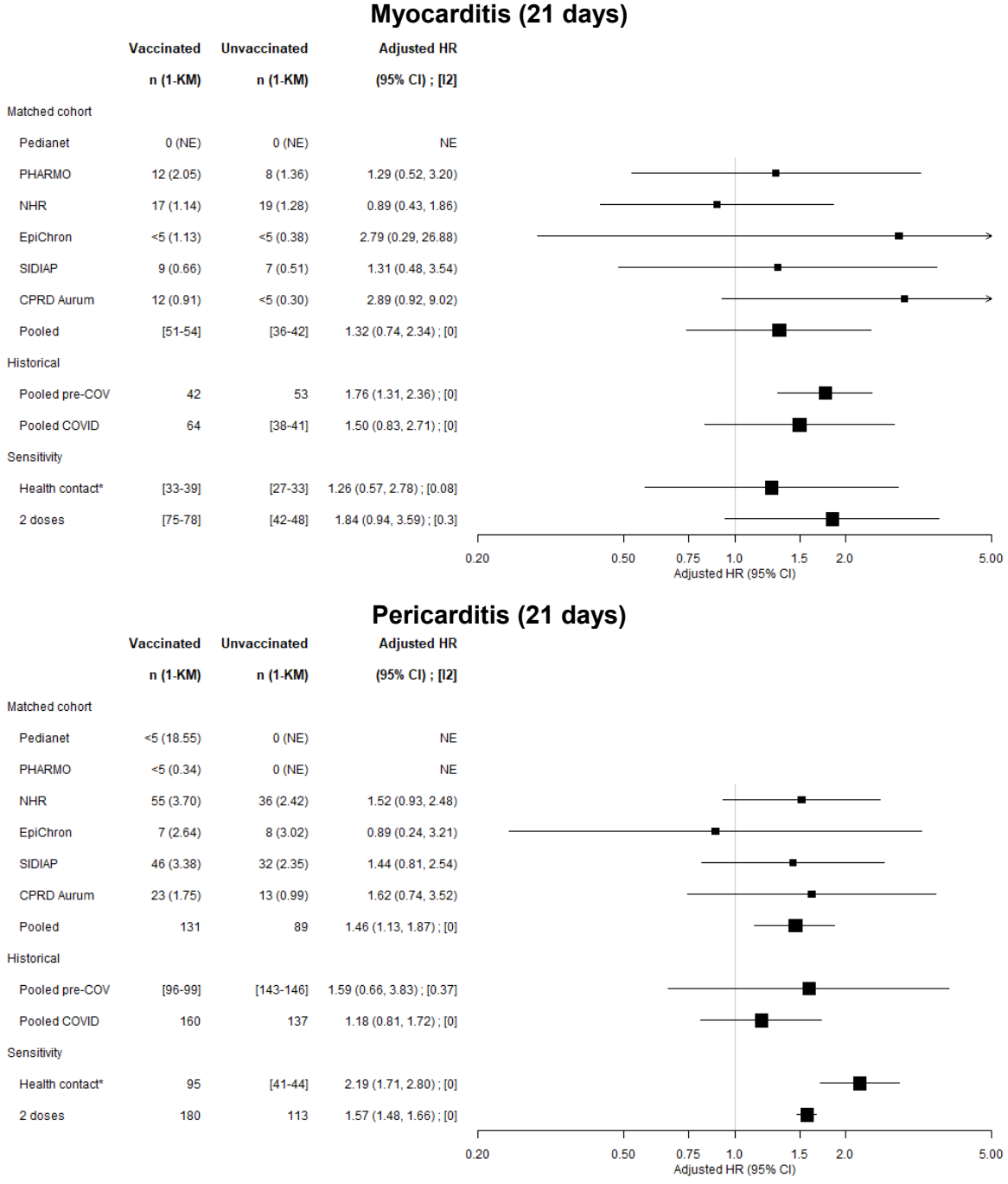
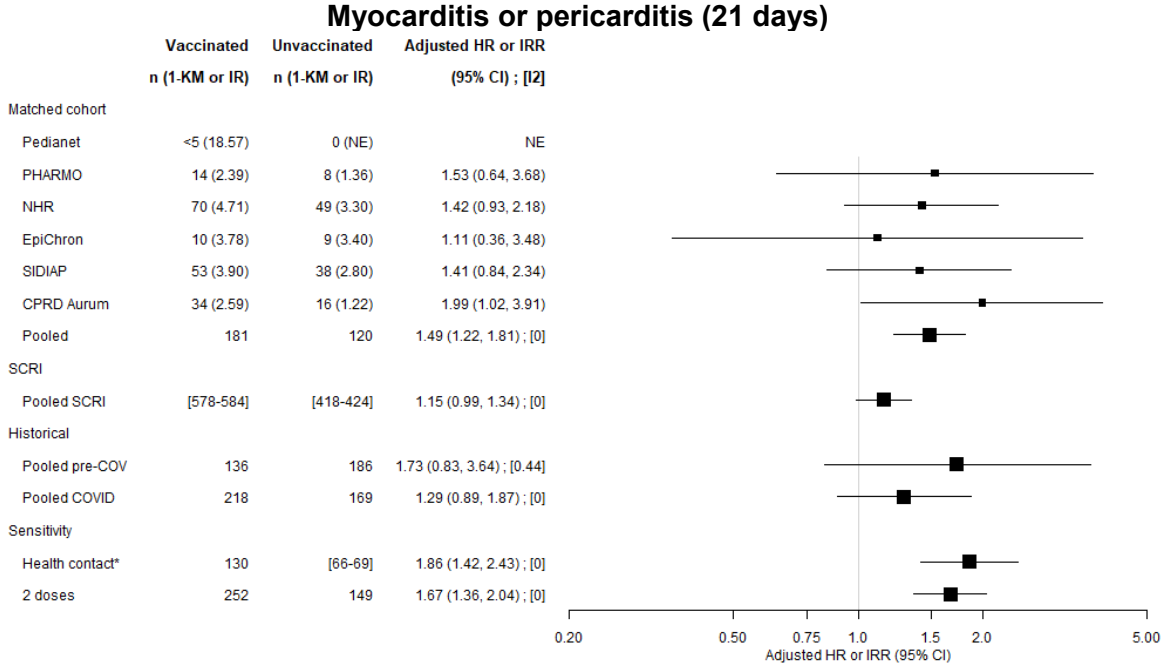


**Figure 4. Pooled analyses for myocarditis, pericarditis, and myocarditis or pericarditis (21 days) in the main cohort, historical cohorts and sensitivity analyses**




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

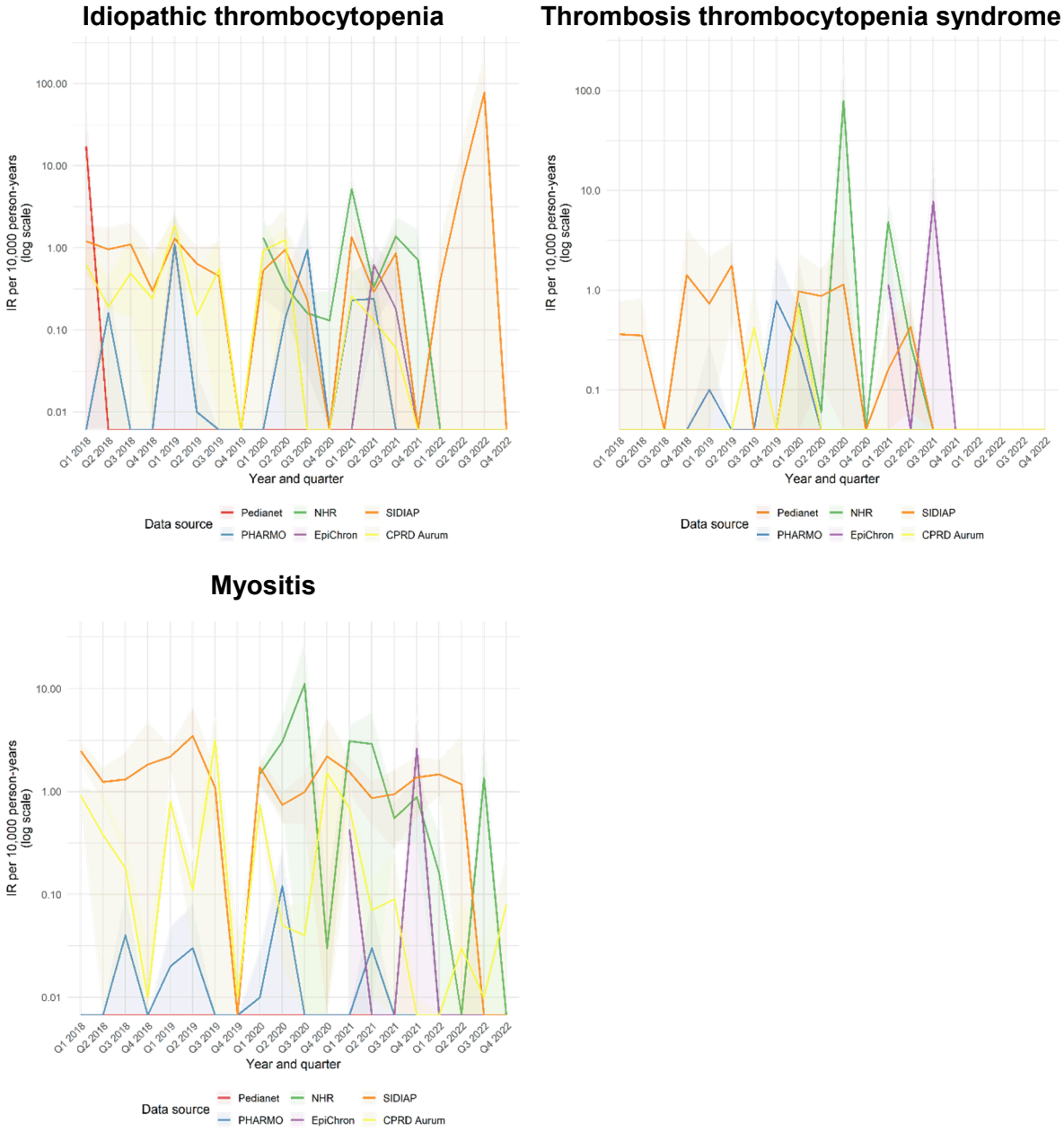
### 10.4.1.2. AESIs identified as signals and assessed by the PRAC

#### 10.4.1.2.1. Autoimmune diseases

The AESIs in this category are idiopathic thrombocytopenia (ITP), thrombosis thrombocytopenia syndrome (TTS) and myositis.

The incidence rates for idiopathic thrombocytopenia, thrombosis thrombocytopenia syndrome and myositis in unvaccinated comparator cohorts for 2018, 2019, 2020 and in unvaccinated comparators after 2020, standardised to data source specific populations in 2020 by data sources, are shown in **Figure 5**. The incidence rates of each of these conditions were very low, and show evidence of seasonal variation, with lowering in the summer for ITP and TTS. This can be explained since viral infections are an important risk factor, this is also demonstrated during the COVID-19 period. Myositis demonstrated a smaller seasonal effect.

**Figure 5. Age-standardised incidence rates for autoimmune disease AESIs in unvaccinated individuals, standardised to the data source specific population in 2020, by data sources**




### 10.4.1.2.2. Idiopathic thrombocytopenia

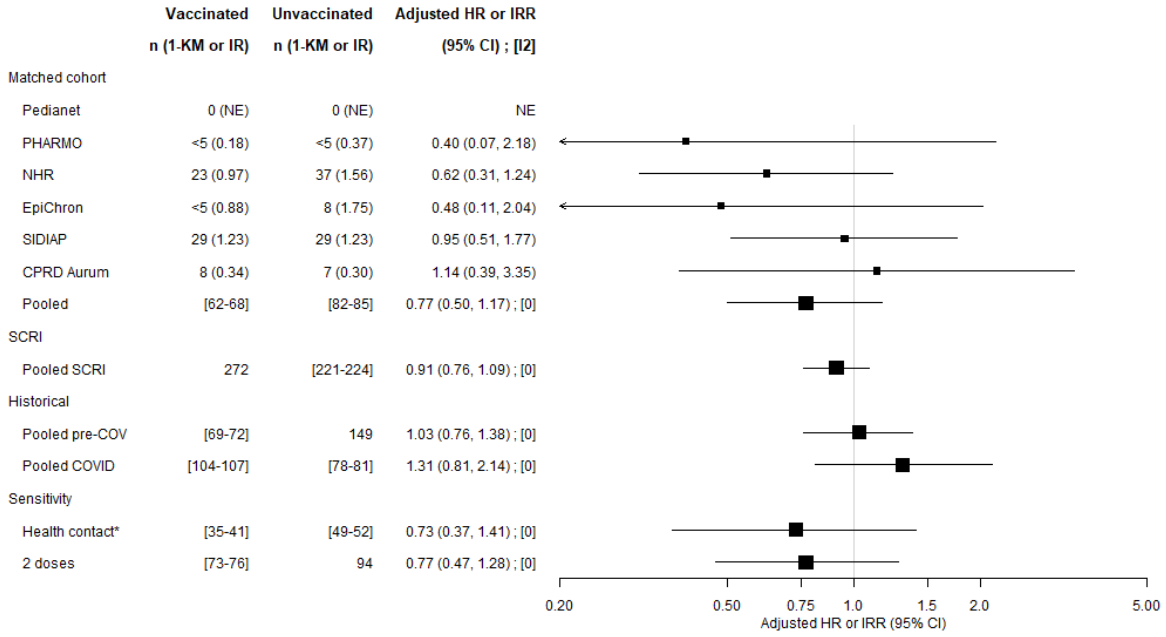
ITP events within a 42-day-risk window were identified in all data sources, except in Pedianet (**Table 7**). These events were very rare with fewer events in PHARMO and CPRD Aurum (GP-based data sources) than in EpiChron, NHR, and SIDIAP, which had access to hospital data. The adjusted pooled HRs for idiopathic thrombocytopenia within 42 days of time zero in the main matched cohort consistently showed no elevated risk and the pooled

adjusted hazard ratio was below 1. The cumulative risk curves showed no differences between the vaccinated and unvaccinated cohorts (Appendix Figure 8).

The pooled adjusted HR was higher than 1 in the comparison with the matched COVID-19 (2020) period historical cohort. In contrast, the comparison with the pre-COVID-19 2018 and 2019 historical cohorts no increased risk was observed. The results of the analyses restricted to those without healthcare contact 7 days prior to time zero or those who received a second dose of Pfizer-BioNTech COVID-19 vaccine according to the recommendations at that time, showed that the pooled adjusted HRs were consistent with the main results, with an absence of association. Sub-cohort analyses could not be conducted in Pedianet, PHARMO or EpiChron due to the absence or low number of events. The analyses in the other data sources showed a consistent absence of an association for the different sub-cohorts (Appendix Figure 9). No estimates could be obtained in the sub-cohort of pregnant women.

The IRR for the pooled SCRI analyses that was conducted in the vaccinated population after all doses was consistent with those in the main analysis, showing no elevated risk for ITP following vaccination with the Pfizer-BioNTech COVID-19 vaccine (**Figure 6**). This was consistent across subgroups and stratified analyses.

**Figure 6. Pooled analyses for idiopathic thrombocytopenia in the overall, SCRI, historical cohorts and sensitivity analyses**




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

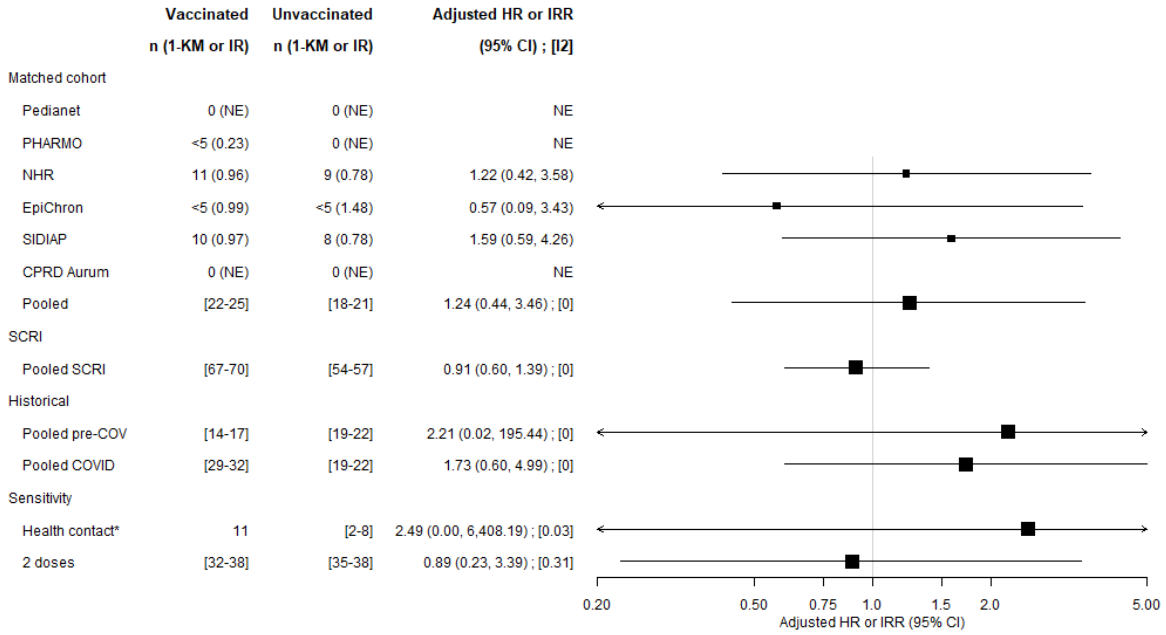
### 10.4.1.2.3. Thrombosis thrombocytopenia syndrome

TTS was identified within 15 days after baseline. Although this event was not directly discussed as a safety issue for the Pfizer-BioNTech COVID-19 vaccine, it is a special form of ITP that was discussed extensively by the PRAC for adenovirus-based COVID-19 vaccines.

Cumulative incidence curves for TTS in the main matched cohort showed no difference between vaccinated and unvaccinated within the 15 days (Appendix Figure 10).

The main matched analysis did not show an association with TTS and the pooled adjusted HR had wide confidence intervals. Sensitivity analyses showed that use of historical controls and restriction to those without healthcare contact within 7 days of time zero increased the pooled HR, but confidence intervals were very wide. The SCRI and 2-dose cohort analysis, both showed no association (**Figure 7**). An isolated finding was observed for the SCRI analysis in males 70-79 with a pooled IRR of 2.10, 95% CI: 2.03-2.16, based on results in SIDIAP (IRR= 2.09, 95% CI 0.56-7.80) and NHR IRR=2.10, 95% CI: 0.65-6.85) (*Post hoc* pooling analysis).

**Figure 7. Pooled analyses for thrombosis thrombocytopenia syndrome in the overall, SCRI, historical cohorts and sensitivity analyses**




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

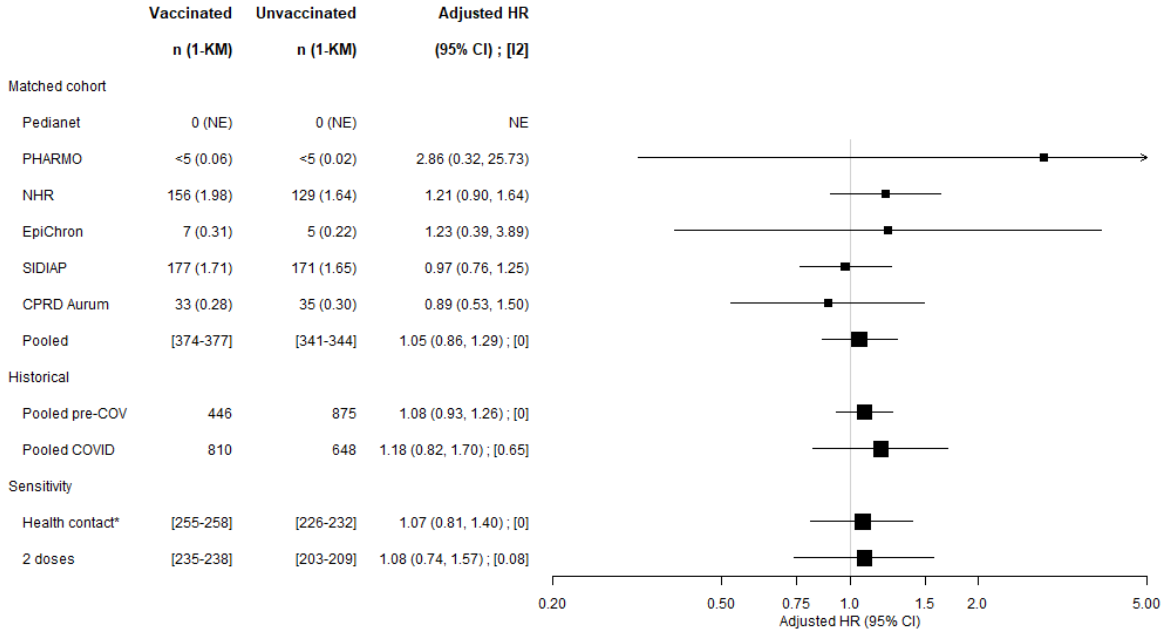
### 10.4.1.2.4. Myositis

The cumulative incidence for myositis within 365 days is presented in Appendix Figure 12. No differences were observed, except in NHR where survival curves diverged at the end of follow-up. As shown in **Figure 8**, the main matched analysis did not show an association with myositis, the pooled adjusted HR (1.05, 95% CI: 0.86-1.29) had narrow confidence intervals.

Sensitivity analyses showed that comparison with historical controls and restriction to those without healthcare contact within 7 days of time zero only increased the pooled HR slightly. The 2-dose cohort analyses showed no association (HR 1.08, 0.74-1.57) (**Figure 8**).

Subgroup analyses of the cohort showed some variability in estimates, but no clear patterns or important elevations of risk (Appendix Figure 12). The pooled direct effect of the vaccine on myositis was HR=1.02, 95% CI: 0.76- 1.39 (*Post-hoc* analysis).

**Figure 8. Pooled analyses for myositis in the overall, historical cohorts and sensitivity analyses**



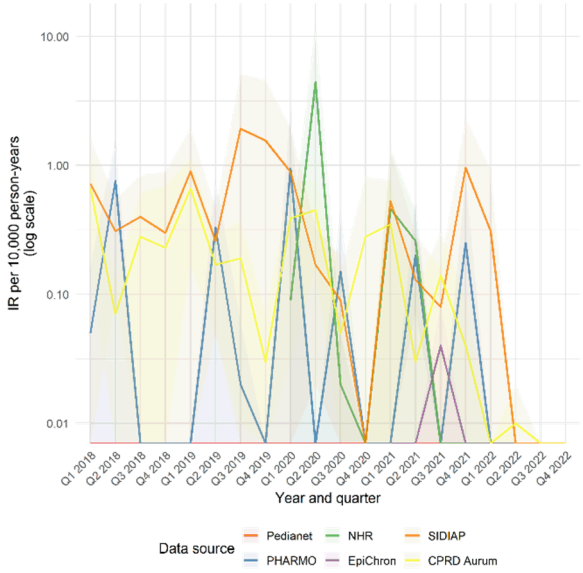

NE: not estimable; *no healthcare contact in 7 days prior to time zero; two doses within 6 weeks

### 10.4.1.2.5. Skin and mucous membranes bones and joints

The only AESI in this class that was discussed by the PRAC was erythema multiforme.

**Figure 9** shows that the incidence rate of erythema multiforme in unvaccinated individuals is very low and seems to have small spikes, corresponding with seasons, with wide confidence intervals. The rates were lower from Q3 2020 to Q1 2021.

**Figure 9. Incidence rates by quarter from Q1 2018 to Q4 2022 for erythema multiforme in unvaccinated individuals, standardised to the data source specific population in 2020, by data sources**

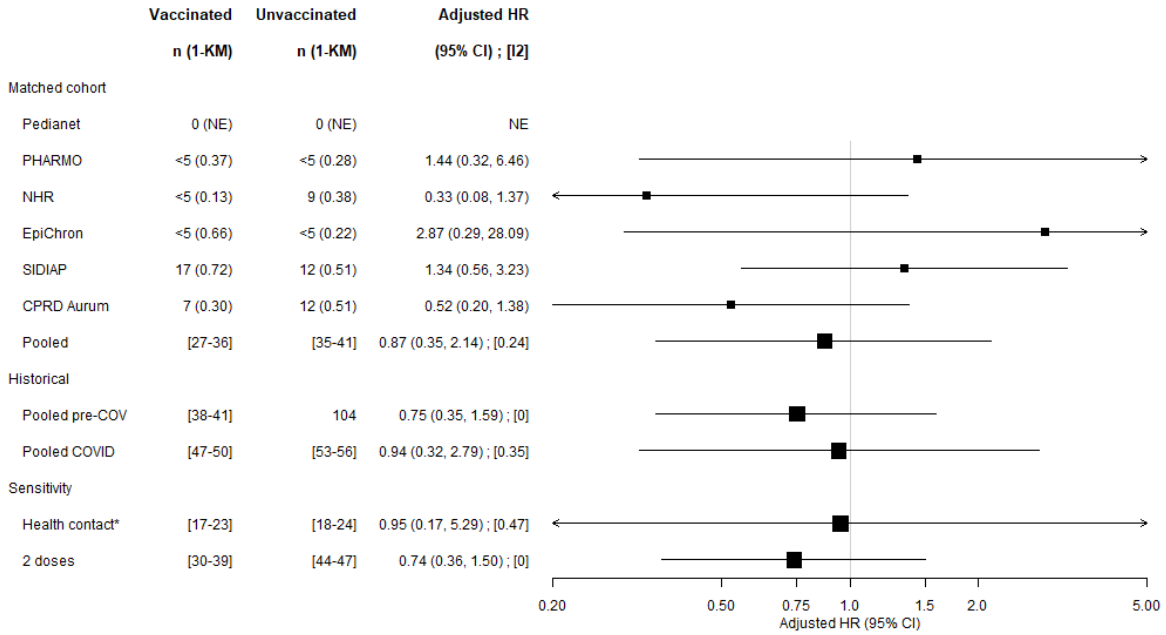



Erythema multiforme events within 42 days following time zero were consistently very low, with no events in Pedianet and <5 events in both cohorts in PHARMO and EpiChron and in the vaccinated cohort in NHR (**Table 7**). The cumulative incidence curves showed in CPRD Aurum and SIDIAP showed a steady increase in events during the 42 days risk window with no differences between the vaccinated and unvaccinated cohorts (Appendix Figure 14).

The adjusted HRs for erythema multiforme in the main matched cohort analysis were elevated in PHARMO, EpiChron and SIDIAP, with very wide 95% CIs due to low number of events (**Table 7**). The highest adjusted HR was in EpiChron and the lowest in NHR. The pooled HR was below 1 (**Figure 10**). The pooled HRs for both historical cohorts were consistently below 1 similar to the pooled HR. The $I^2$ showed that there was little or moderate heterogeneity between the results across the data sources although there was large within-data source variance.

The pooled HRs for the sensitivity analyses in the main cohort analysis restricted to those without recent healthcare contact and those with at least 2 doses of Pfizer-BioNTech COVID-19 vaccine were consistent with the overall results showing no evidence of an association. The comparisons of the adjusted HRs in the stratified analyses for age and gender, showed some variation across different strata, but overall were consistent with absence of an association (Appendix Figure 15). No estimate could be calculated for pregnant women.

**Figure 10. Pooled analyses for erythema multiforme in the overall, historical cohorts and sensitivity analyses**



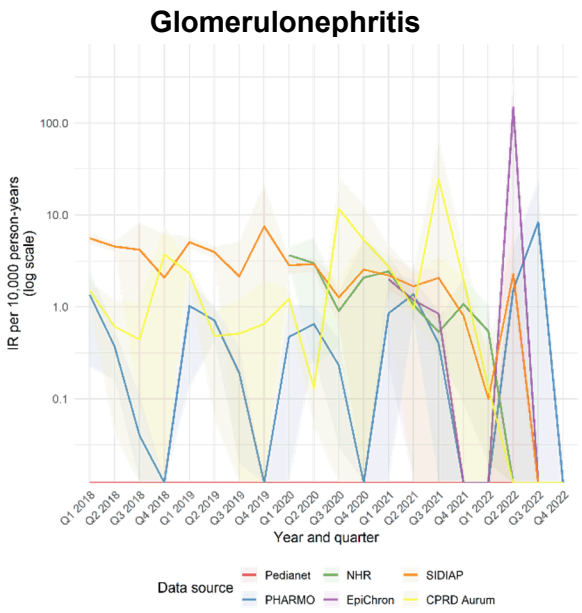

NE: not estimable; *no healthcare contact in 7 days prior to time zero; two doses within 6 weeks

### 10.4.1.2.6. Hepato-gastrointestinal and renal system

*Glomerulonephritis* is the only AESI in the hepato-gastrointestinal and renal system class that was discussed by the PRAC.

The age-standardised incidence rates for glomerulonephritis in unvaccinated comparator cohorts for 2018, 2019, 2020 and in unvaccinated comparators after 2020, standardised to data source specific populations in 2020 are shown by data sources in **Figure 11**. Rates vary by season, since infections are an important risk factor, and are highest in GP-based data sources.

**Figure 11. Age-standardised Incidence rates for glomerulonephritis in unvaccinated individuals, standardised to the data source specific population in 2020, by data source**

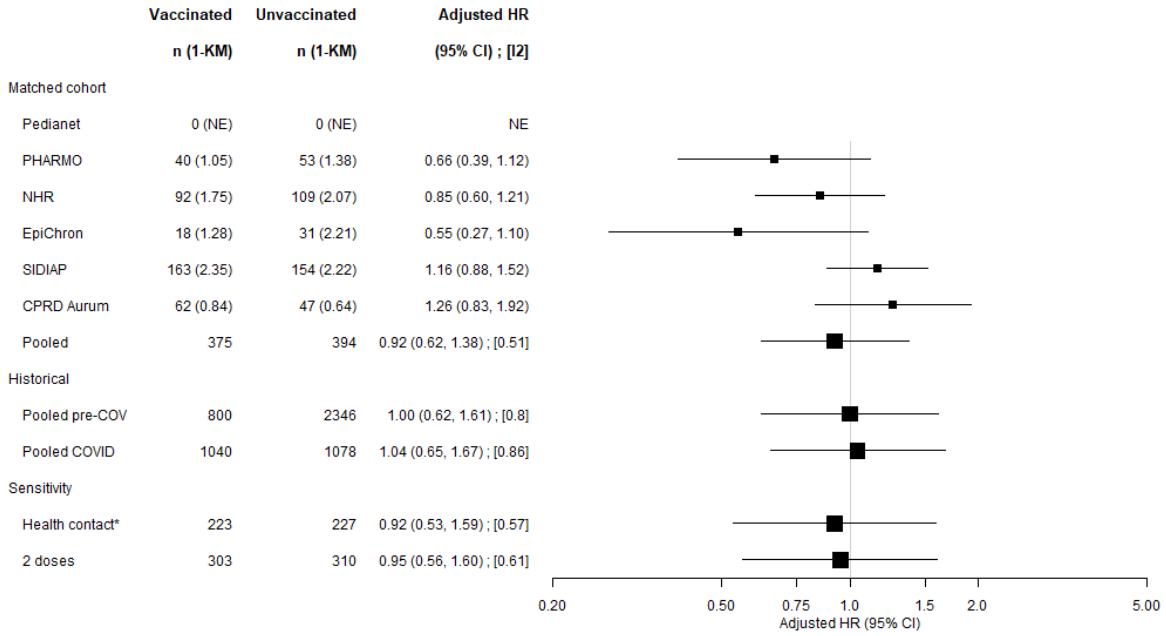



For the main matched cohort analysis, the adjusted pooled HR showed an absence of an association (all HRs below 1) except for SIDIAP and CPRD Aurum where the adjusted HRs were above 1 but the 95% CIs included 1.

The cumulative incidence curves showed no differences between the vaccinated and unvaccinated cohorts over the 180-day risk window (Appendix Figure 16). The adjusted pooled HR was consistent with no increased risk of glomerulonephritis within 180 days of time zero, with moderate heterogeneity between data sources ($I^2$=0.51) (**Figure 12**). The results of the sensitivity analyses consistently showed no association. Comparisons of the HRs in the sub-cohorts and stratified analyses for age and gender in the other data sources showed some age and gender variation, which was inconsistent across data sources (Appendix Figure 17).

In SIDIAP there were <5 events in the pregnant vaccinated and unvaccinated cohorts and the adjusted HR was 2.27 (95% CI: 0.21-25.08) (*Post hoc* pooling analysis) but with a very wide 95% CI; no events were identified in the other data sources for this sub-group.

**Figure 12. Pooled analyses for glomerulonephritis in the overall and historical cohorts and sensitivity analyses**

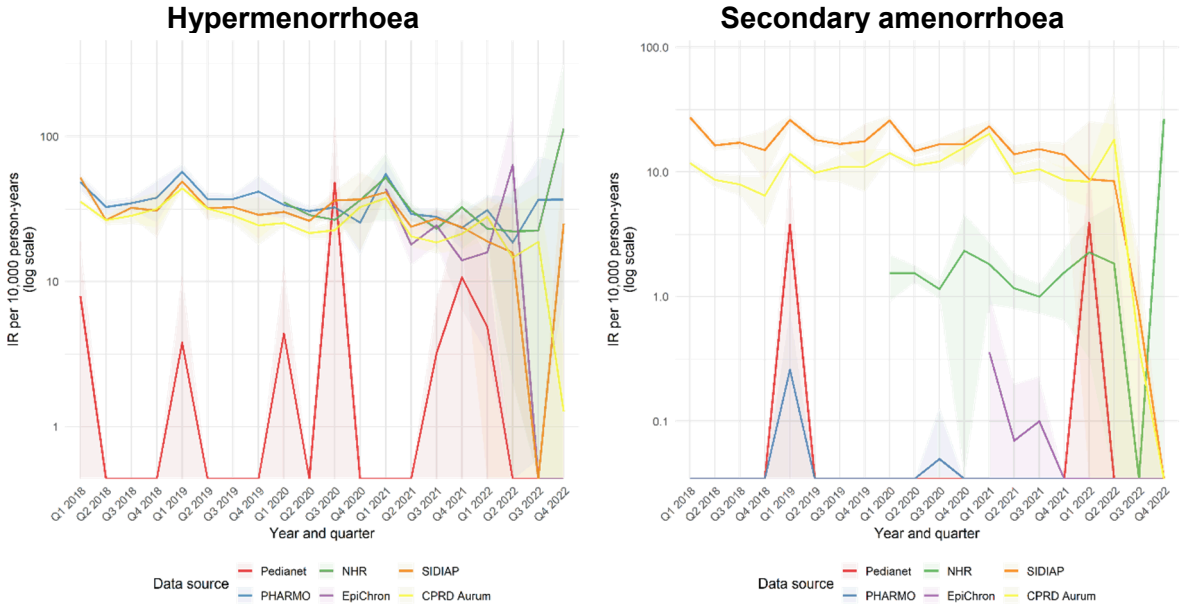



NE: not estimable; *no healthcare contact in 7 days prior to time zero; two doses within 6 weeks

### 10.4.1.2.7. Reproductive system (hypermenorrhoea and secondary amenorrhoea)

Figure 13 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 13. Age-standardised incidence rates for hypermenorrhoea and secondary amenorrhoea in unvaccinated individuals, standardised to the data source specific population in 2020, by data sources**

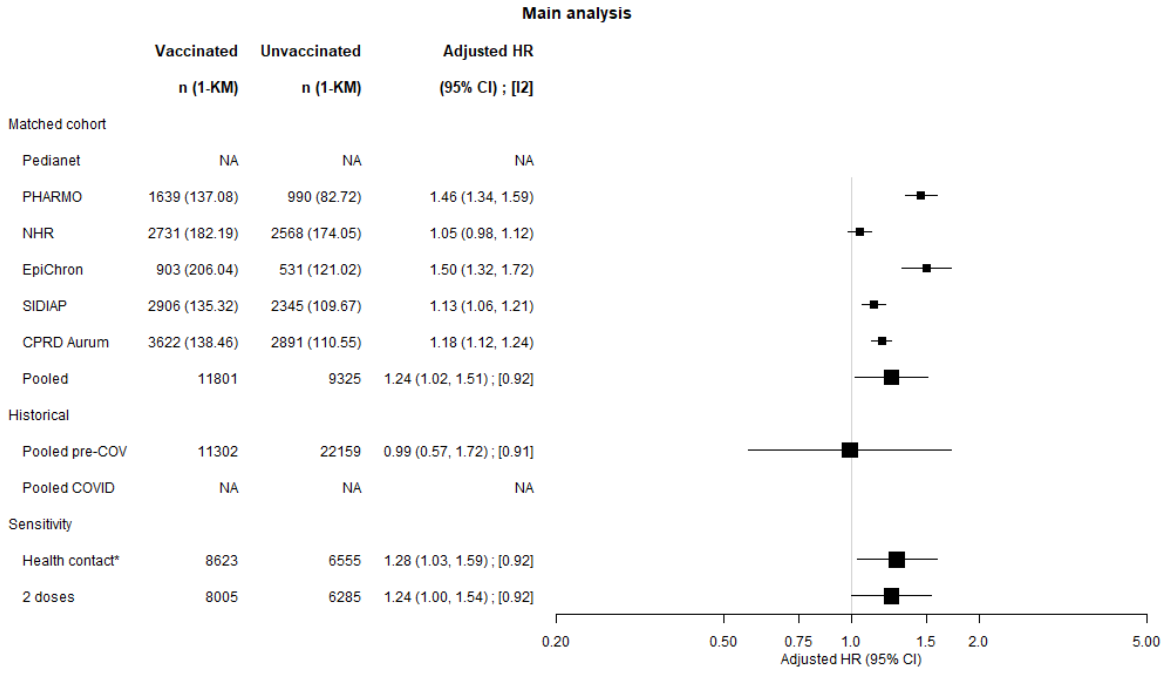



The cumulative risk curves during follow-up in the main matched cohort of women generally showed a higher risk for hypermenorrhoea but not for secondary amenorrhoea, except in CPRD Aurum (Appendix Figure 18, Appendix Figure 19).

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 14**). 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).

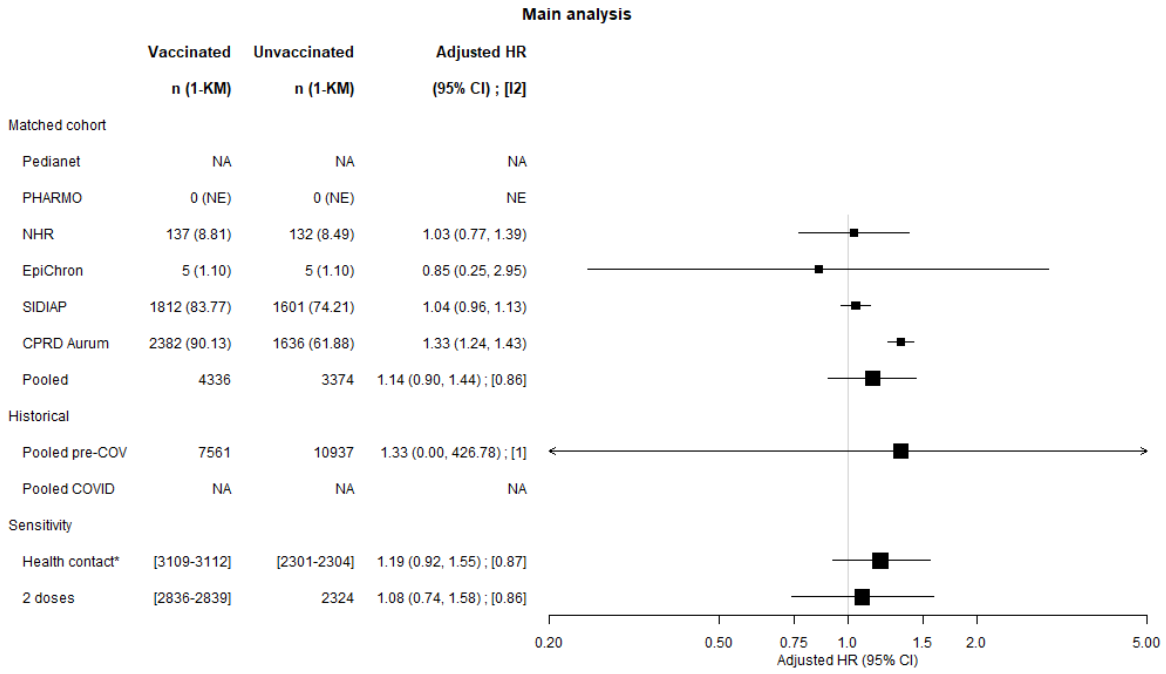
The adjusted HRs for *secondary* amenorrhoea within 183 days of time zero were around 1 in NHR and SIDIAP and elevated in CPRD Aurum (HR=1.33, 95% CI: 1.24-1.43). Pedianet data cannot assessed since it only includes children up till 14 years of age. The pooled analysis in the main matched cohort analysis and the sensitivity analyses showed the HRs for secondary amenorrhoea were only very slightly elevated (**Figure 15**). 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). 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 14. Pooled analyses for hypermenorrhoea in 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

**Figure 15. Pooled analyses for secondary amenorrhoea in in the overall cohort, historical cohorts and sensitivity analyses**

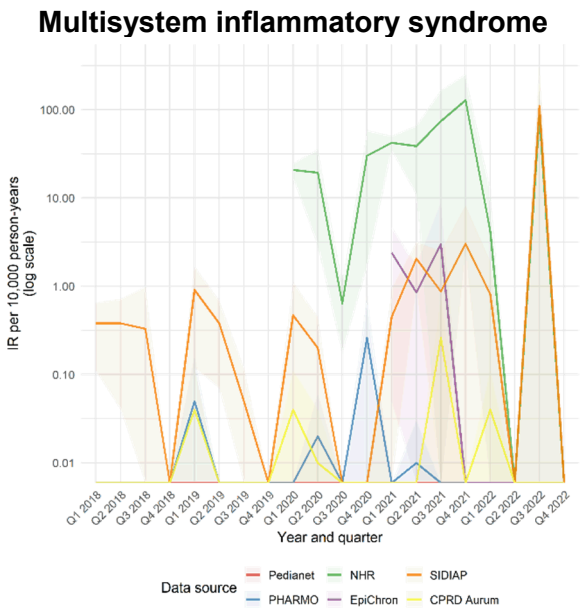



NE: not estimable; *no healthcare contact in 7 days prior to time zero; two doses within 6 weeks

### 10.4.1.2.8. Other AESIs: multisystem inflammatory syndrome

Figure 16 shows the age-standardised incidence rates of multisystem inflammatory syndrome in COVID-19 unvaccinated individuals. The higher incidence in 2021 could be explained by the introduction of the ICD-10 for this event at that time. The disease incidence shows a seasonal pattern with reductions in Q4, except during the COVID-19 period.

**Figure 16. Age-standardised incidence rates for multisystem inflammatory syndrome in unvaccinated individuals, standardised to the data source specific population in 2020, by data source**



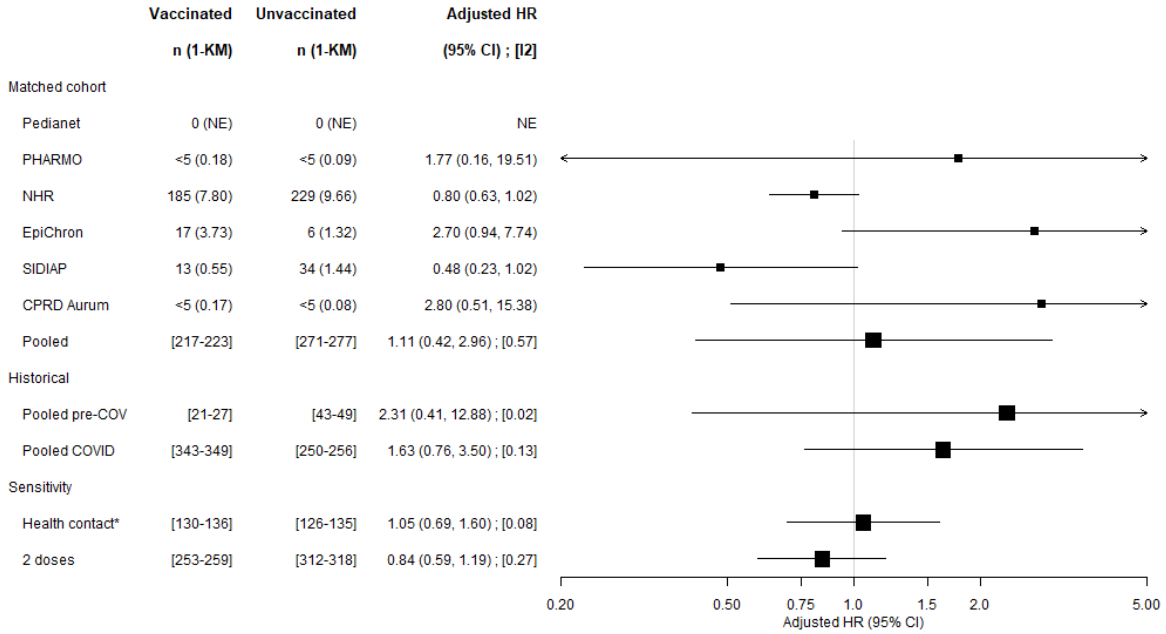

Multisystem inflammatory syndrome within 42 days after time zero in the matched cohort analysis varied considerably across data sources, with the highest rates in NHR. Cumulative incidences were comparable between the vaccinated and unvaccinated cohorts (Appendix Figure 22).

The adjusted HRs for multisystem inflammatory syndrome within 42 days of time zero in the main matched cohort were elevated in PHARMO, EpiChron, SIDIAP, and CPRD Aurum. The pooled analysis for multisystem inflammatory syndrome showed heterogeneity of the results within and between the data sources with a high $I^2$ (**Figure 17**). The comparisons with concurrent unvaccinated cohorts varied, with elevated risks in EpiChron, CPRD Aurum and PHARMO, but reduced risk in NHR. The pooled adjusted HR in the main analysis showed no increased risk but should be interpreted with caution due to substantial heterogeneity.

Comparisons with the historical unvaccinated cohorts showed an elevation of risk, which can be explained by the fact that the code of MIS was introduced in 2021. Sensitivity analyses amongst those without healthcare contact within 7 days of time zero and those with at least 2 doses of the Pfizer-BioNTech COVID-19 vaccine were consistent with the pooled HR from the main analysis, showing no association. Sub-group and stratified analyses could not be done in Pedianet, PHARMO or CPRD Aurum because there were no or too few cases.

The HRs in the sub-cohort and stratified analyses for age and gender consistently showed an absence of an association in NHR and SIDIAP (Appendix Figure 23). In contrast, in EpiChron, the HR estimates were mostly >1, but with wide 95% CIs. No estimate of association could be calculated in the pregnancy cohort.

**Figure 17. Pooled analyses for multisystem inflammatory syndrome 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

### 10.4.1.3. Events prespecified and discussed in literature

#### 10.4.1.3.1. Cardiovascular system

Figure 18 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.

The incidence rate of stress cardiomyopathy in unvaccinated individuals was very low and showed seasonality with lowest peaks during Q4, rates were slightly lower during the COVID-19 pandemic period.

The incidence rates of CAD in unvaccinated individuals did not show seasonality. The highest rates were observed in NHR, probably because of the diagnostic settings that were used for data captured. The rates decreased in 2021.

**Figure 18. Age-standardised incidence rates for cardiovascular AESIs in unvaccinated individuals, standardised to the data source specific population in 2020, by data source**

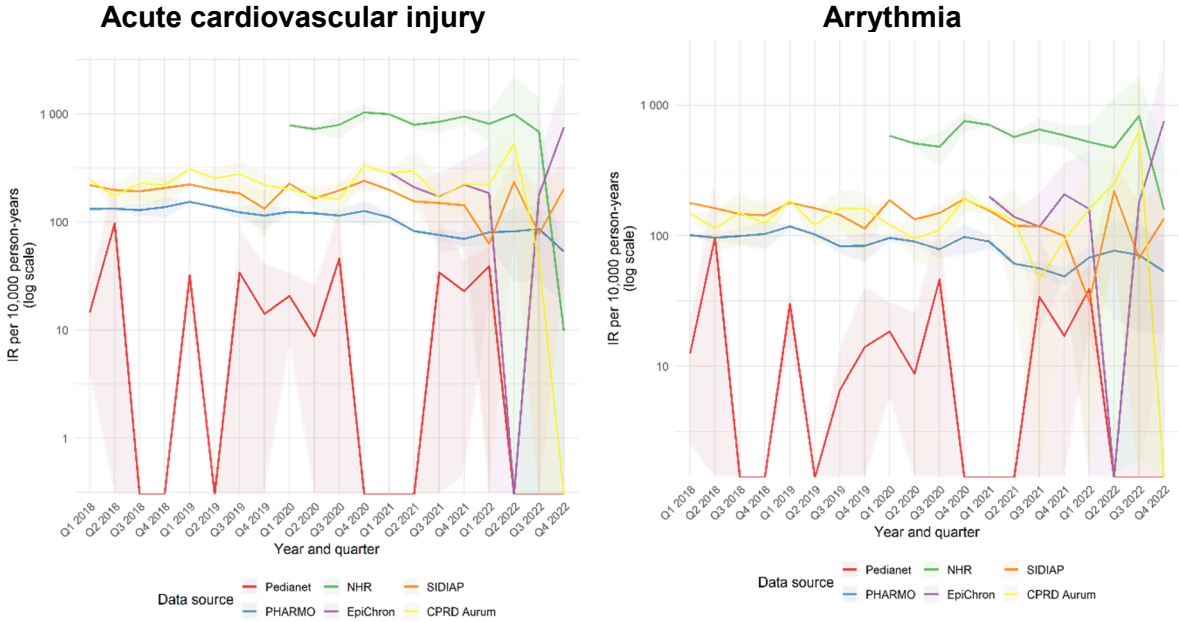
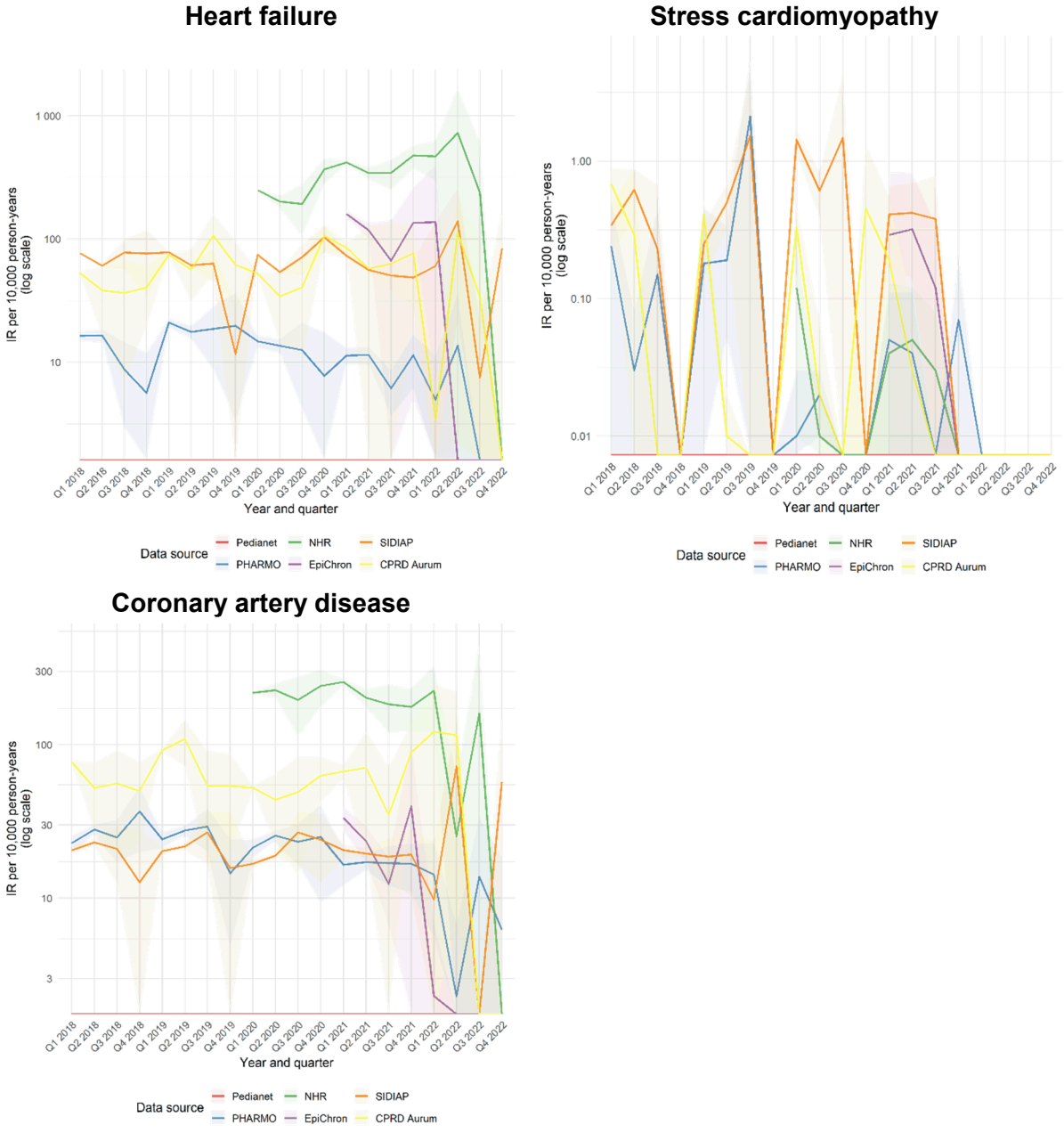


**Figure 18. Age-standardised incidence rates for cardiovascular AESIs in unvaccinated individuals, standardised to the data source specific population in 2020, by data source**



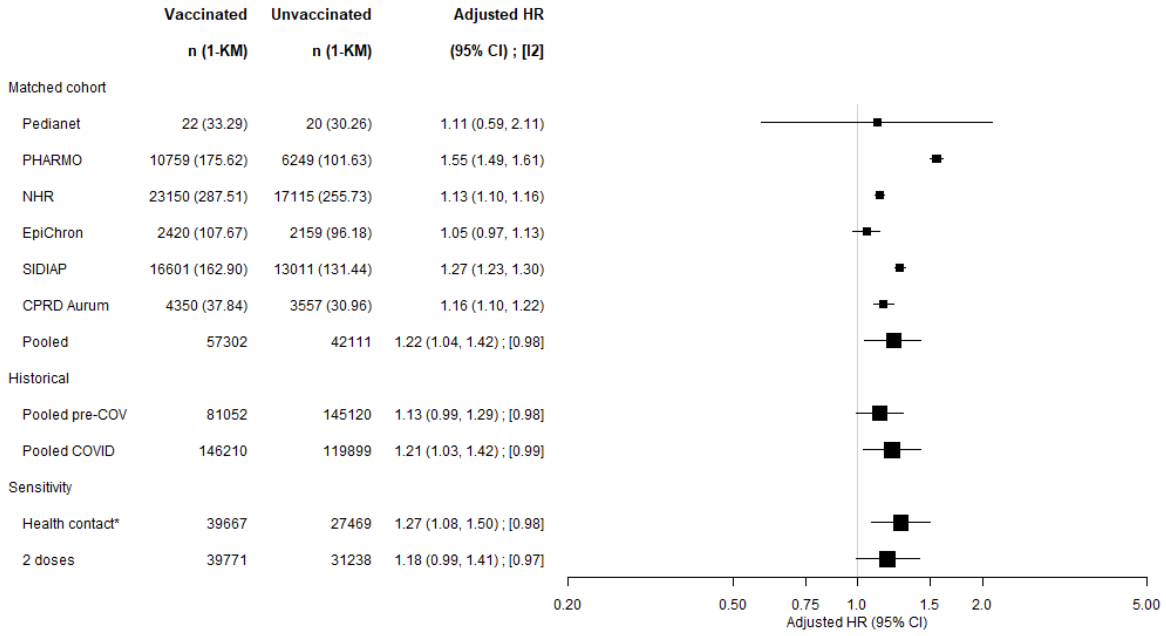

### 10.4.1.3.1.1. Acute cardiovascular injury (ACI)

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).

Data source-specific adjusted HRs were consistently elevated, except in EpiChron (**Figure 19**). 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 19. 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

### 10.4.1.3.1.2. Arrhythmia

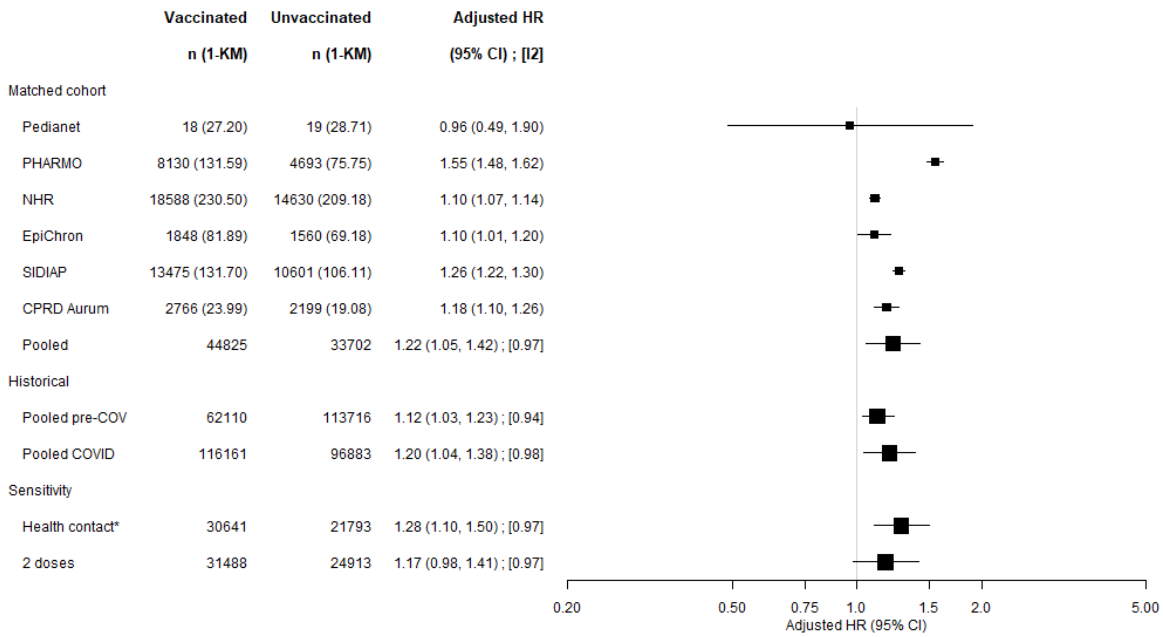
The cumulative incidence of arrhythmia within 365 days in the main cohort showed that after 2 months the curves of vaccinated diverged from unvaccinated, with higher risks in vaccinated (Appendix Figure 26).

The adjusted HRs for arrhythmia within 365 days after time zero were slightly elevated in all data sources except Pedianet. The pooled adjusted HR showed large heterogeneity between data sources ($I^2$=0.97) (**Figure 20**).

High $I^2$ values were also observed for the sensitivity analyses. The pooled results should therefore be interpreted with caution. Comparisons with pre-COVID-19 controls showed that the HR lowered, possibly indicating that during the COVID-19 period, less healthcare was sought, which is consistent with the age- standardised rates in unvaccinated.

Sub-cohort and stratified analyses were interpretable in all data sources except in Pedianet due to the low event counts (Appendix Figure 27). In PHARMO there was a slightly higher risk in females than in males. The younger adults from 18 to 49 years seemed to have slightly higher adjusted HR than children and the older age groups. The adjusted HR in the sub-cohort analyses for immunocompromised individuals and those that were frail or who had comorbidities were elevated in PHARMO, NHR, and SIDIAP. Elevated adjusted HRs for arrhythmia were observed for pregnant women in PHARMO, CPRD and EpiChron, but with high imprecision (**Standalone section 15**).

**Figure 20. Pooled analyses for arrhythmia 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.

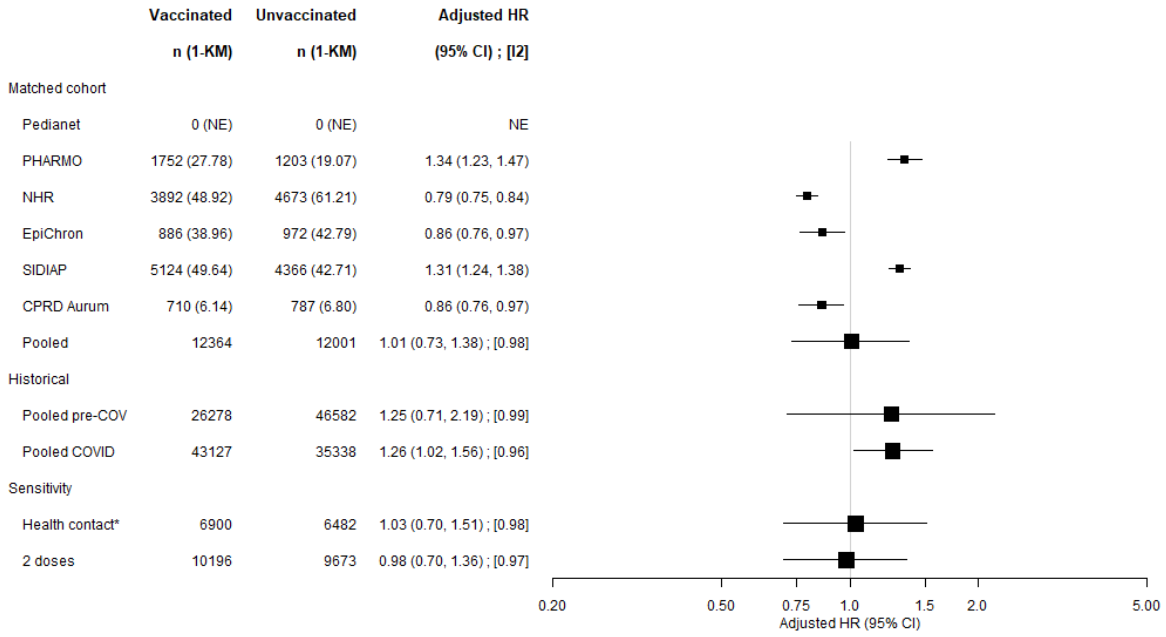
### 10.4.1.3.1.3. Heart failure

The adjusted HRs for heart failure varied between data sources. Elevated adjusted HRs were observed for PHARMO and SIDIAP in contrast to NHR, EpiChron and CPRD Aurum in which the adjusted HRs were below 1. The cumulative incidence rates showed inconsistent results and divergence of incidences after the first 2 months, in most data sources. (Appendix Figure 28).

The pooled HR analysis for the main matched cohort analysis showed high heterogeneity across data sources ($I^2$ = 0.98) with no elevation. (**Figure 21**). Heterogeneity was high also for the sensitivity analyses. The pooled HR for the COVID-19 period historical comparison was increased and slightly higher than the HR from the pre-COVID period The other sensitivity analyses were consistent with the pooled main matched cohort result showing absence of association.

Sub-cohort and stratified analyses for heart failure were conducted in all data sources, except Pedianet due to the absence of events (Appendix Figure 29). The age stratified analyses suggest a higher but imprecise risk for younger adults around 18-29 and 30-39 years of age in all data sources. The pooled immunocompromised and frail/comorbidity sub-cohort analyses show consistent elevated HRs compared with the pooled main matched HRs in PHARMO and SIDIAP, but not in NHR and EpiChron. Only very few heart failure events were identified in the pregnancy sub-cohorts.

**Figure 21. Pooled analyses for heart failure in the overall cohort, and historical cohorts and sensitivity analyses**




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

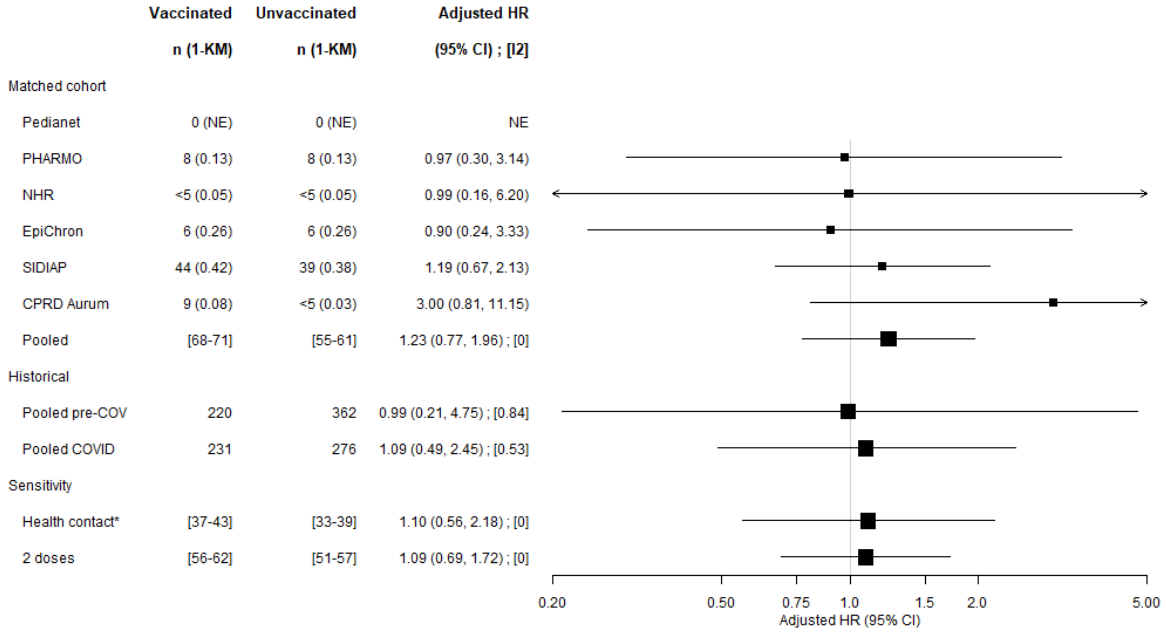
### 10.4.1.3.1.4. Stress cardiomyopathy

The cumulative incidence rates for stress cardiomyopathy within 365 days were comparable between the vaccinated and unvaccinated cohorts (Appendix Figure 30).

**Figure 22** summarises the results for the pooled analysis and sensitivity analysis for stress cardiomyopathy. There was no evidence of heterogeneity between data sources and the pooled HR estimate showed a slight elevation (HR=1.23, 95% CI: 0.77-1.96), mostly driven by CPRD Aurum, that only had a few cases. In each of the sensitivity analyses, this elevation was lowered, showing absence of elevation.

Sub-cohort analyses could not be done in Pedianet and NHR due to lack of or low number of events (Appendix Figure 31). The HRs for the stratified analyses were imprecise, with a high HR for individuals with prior COVID-19 in SIDIAP. No estimates were available for pregnant women.

**Figure 22. Pooled analyses for stress cardiomyopathy 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

### 10.4.1.3.1.5. Coronary artery disease (CAD)

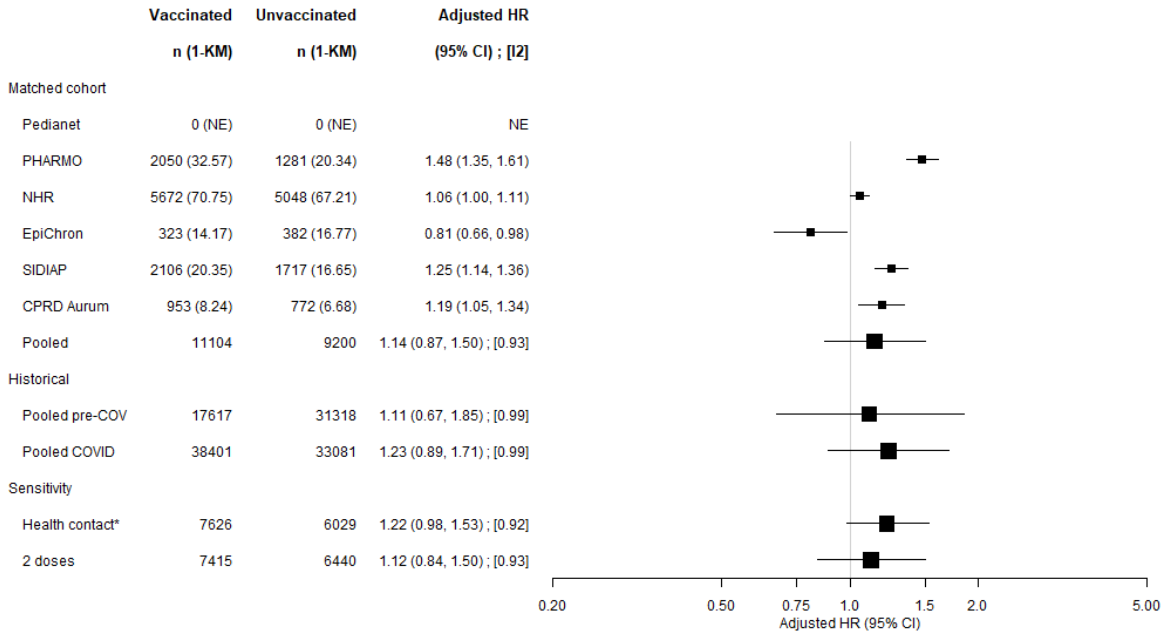
The cumulative incidence rates of CAD during the 365 days are presented in (Appendix Figure 32), showing a divergence of incidences after the first month, except in NHR

The results from PHARMO, SIDIAP, and CPRD Aurum show slightly elevated adjusted HRs for coronary artery disease within 365 days after time zero, but in EpiChron the adjusted HR was below 1 (**Figure 23**). The adjusted pooled HR of coronary artery disease showed no association (adjusted HR =1.14, 95% CI 0.87-1.50) but showed substantial heterogeneity between-data sources. The HR of the historical comparator cohort of the pre-COVID period from the years 2018 and 2019 showed no elevation of risk, whereas the pooled HR of the

2020 COVID period showed a slightly higher adjusted HR, pointing to an effect of lockdown. The pooled HRs for the people without healthcare contact in the 7 days before time zero, and those who had at least 2 vaccine doses showed no material change compared with the results from the main analysis (**Figure 23**).

The sub-cohort and stratified analyses for coronary artery disease showed no consistent differences between age and sex across the data sources (Appendix Figure 33). The immunocompromised and frail/comorbidities sub-cohorts presented consistent pooled adjusted HRs compared with the pooled main matched cohort adjusted HR. No increased risk was identified in individuals with previous COVID-19 nor in the pregnant cohort in all data sources, except in SIDIAP and PHARMO where vaccination in persons with previous COVID-19 showed an elevated adjusted HR.

**Figure 23. Pooled analyses for coronary artery disease in the overall cohort, historical cohorts and sensitivity analyses**



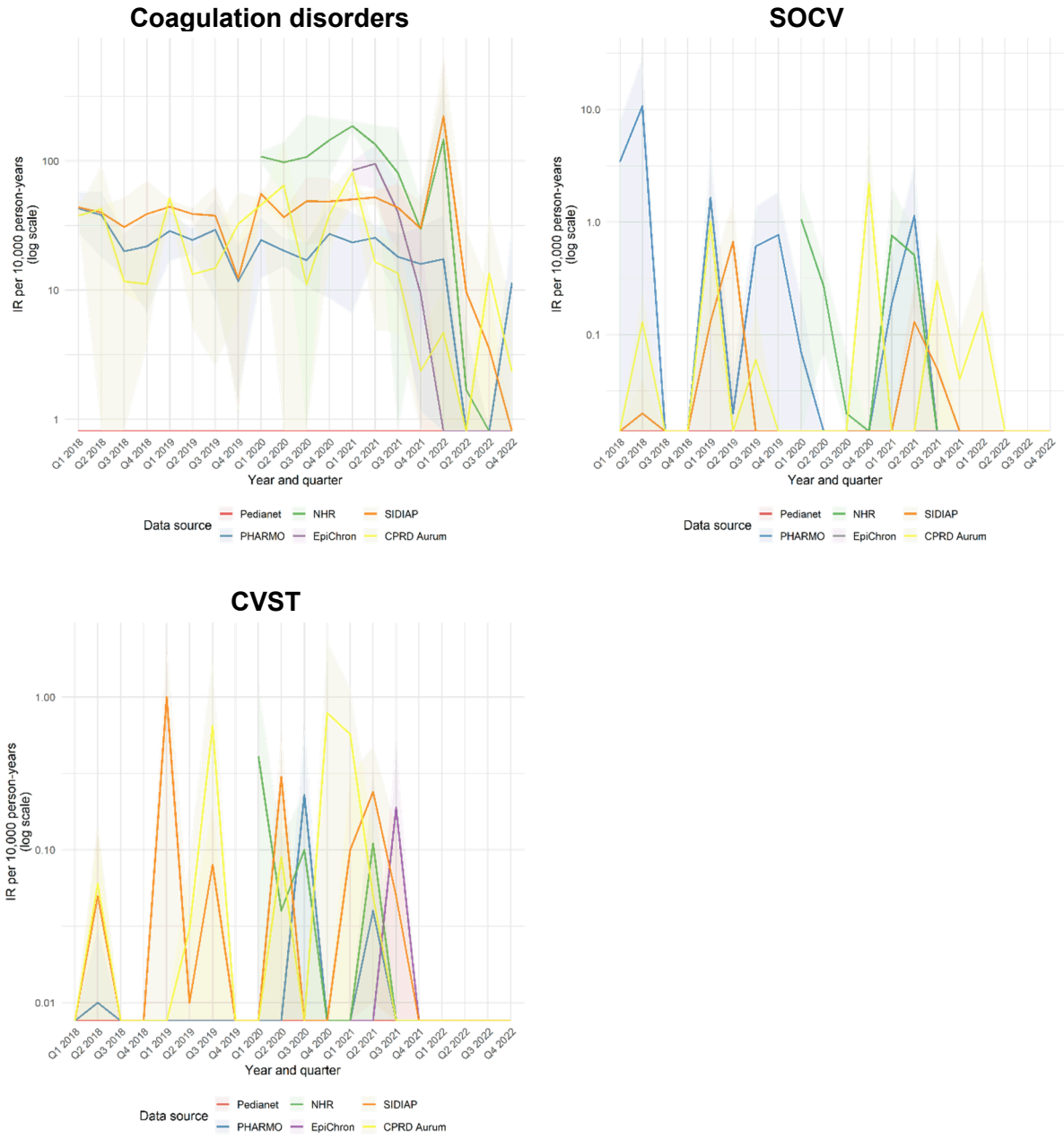

NE: not estimable; *no healthcare contact in 7 days prior to time zero; two doses within 6 weeks

### 10.4.1.3.2. Circulatory system

**Figure 24** shows the age- standardised incidence rates of events in the circulatory system AESIs, in unvaccinated individuals. The incidence of AESI related to the circulatory system was rare (coagulation disorders including thromboembolism and haemorrhage) or very rare (single organ cutaneous vasculitis (SOCV), cerebral venous sinus thrombosis (CVST)).

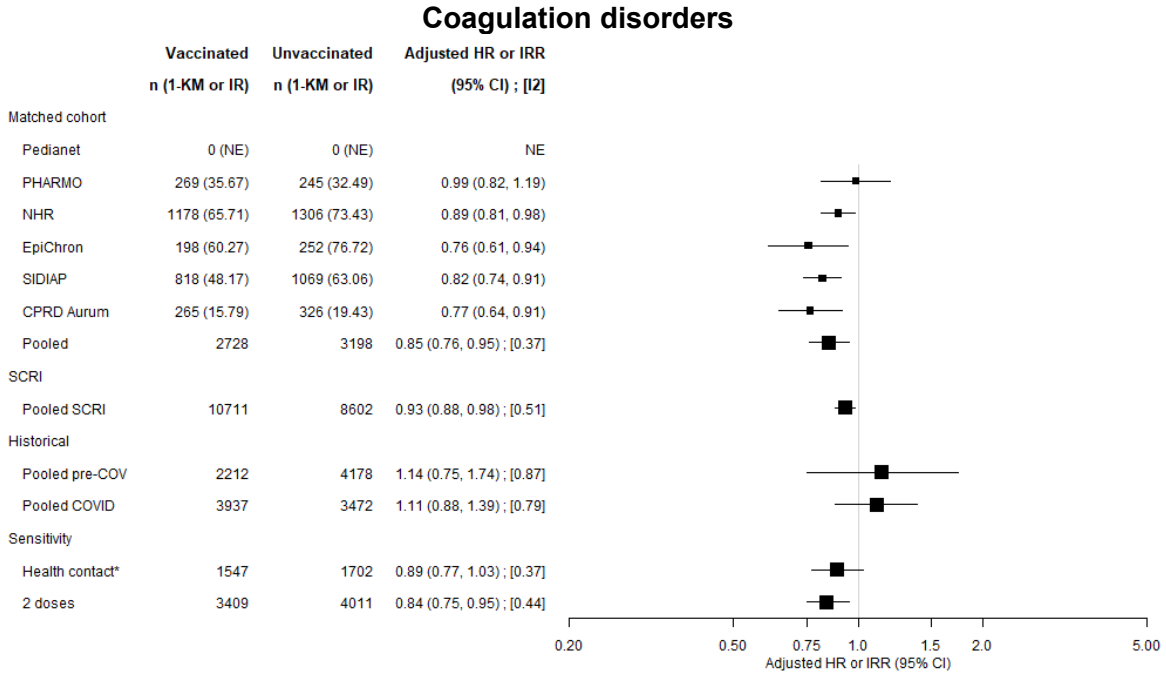
The incidence rates of coagulation disorders in unvaccinated individuals were relatively stable with an increase in NHR in 2021 and a drop in 2022, which may be explained by the reduction in unvaccinated individuals. The incidence rates of SOCV showed that the disease is very rare, and the occurrence was spiky without clear or consistent temporal pattern. CVST is also very rare, and peaks in summer months in all data sources, infections of the head and neck (otitis, sinusitis, meningitis) are an important acquired risk factor.

**Figure 24. Age-standardised incidence rates for circulatory systems AESIs in unvaccinated individuals, standardised to the data source specific population in 2020, by data sources**




The cumulative risk curves for coagulation disorders showed lower risks in the vaccinated cohorts compared with the unvaccinated cohorts (Appendix figure 34). No meaningful cumulative risk curves could be produced for SOCV or CVST due to the low number of events in all data sources. The pooled adjusted HR for coagulation disorders was 0.85, 95% CI: 0.76-0.95 (**Figure 25**). The adjusted HRs in the sensitivity analyses were compatible with the main analysis. The HRs in the stratified analyses and in subgroups did not show a consistent pattern (Appendix Figure 35).

**Figure 25. Pooled analyses for circulatory system AESIs 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

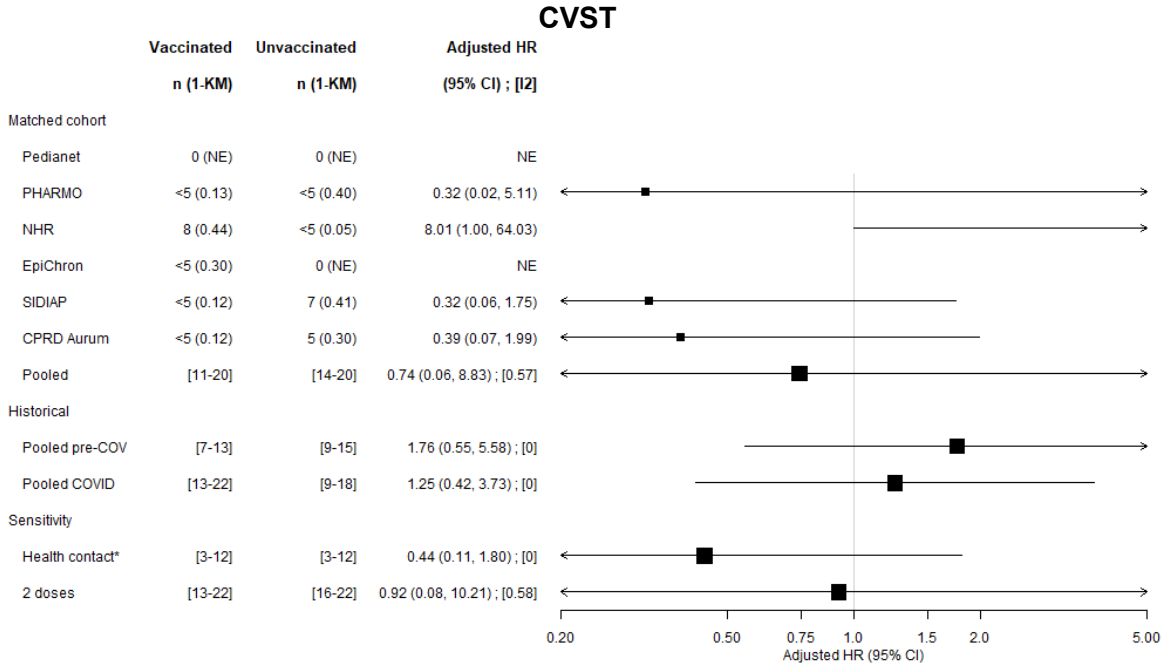
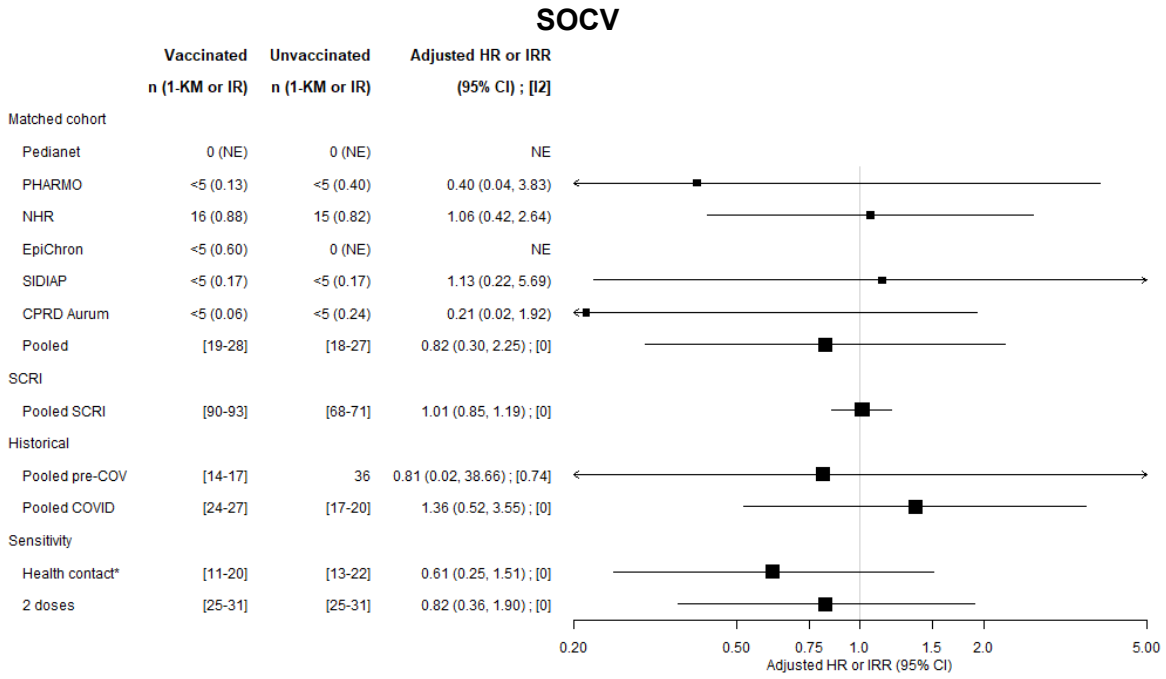


**Figure 25. Pooled analyses for circulatory system AESIs in the overall and historical cohorts and sensitivity analyses**




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

The adjusted HRs for CVST varied across data sources but were all very imprecise. Pooled adjusted HR was 0.74, 95% CI: 0.06-8.83. Sensitivity analyses showed that in general the $HRs_{adj}$ were below 1 (**Figure 25**). The adjusted HR for the comparison with COVID-19 period historical cohort was 1.25, 95% CI: 0.42-3.73. The pooled adjusted HR for CVST was higher in immunocompromised individuals: HR=4.00, 95% CI: 0.45-35.78, but had wide confidence intervals (*Post-hoc* pooling analysis).

The adjusted HRs for SOCV were not elevated in the main cohort analysis nor in the SCRI.

#### 10.4.1.3.3. Death (any cause)

**Figure 26. Age-standardised incidence rates for any-cause death in unvaccinated individuals, standardised to the data source specific population in 2020, by data sources**

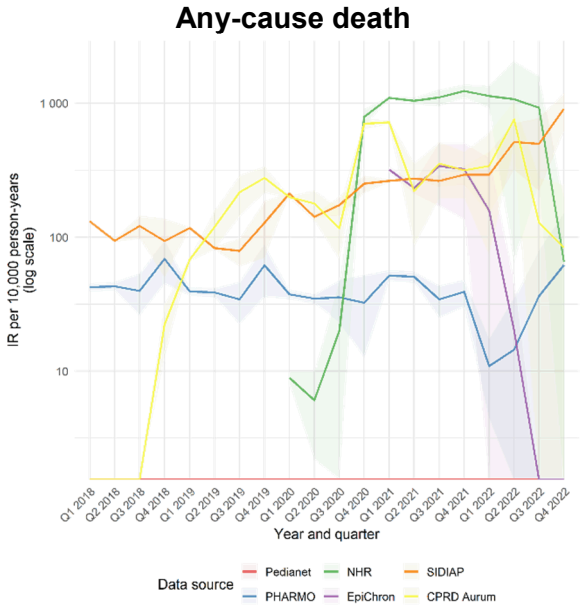



**Figure 26** shows the age- standardised incidence of all-cause death in unvaccinated individuals. The rates were lowest in Pedianet (children only) and PHARMO (incompleteness of date of death). Data were not available for NHR or EpiChron until 2020/2021, and in most data sources the rate of death increased in 2021.

The rates and risks of death were consistently lower in the vaccinated cohorts than in the unvaccinated cohorts. The cumulative incidence of death increased rapidly in the unvaccinated cohorts and were consistently higher for unvaccinated in all data sources (Appendix Figure 36).

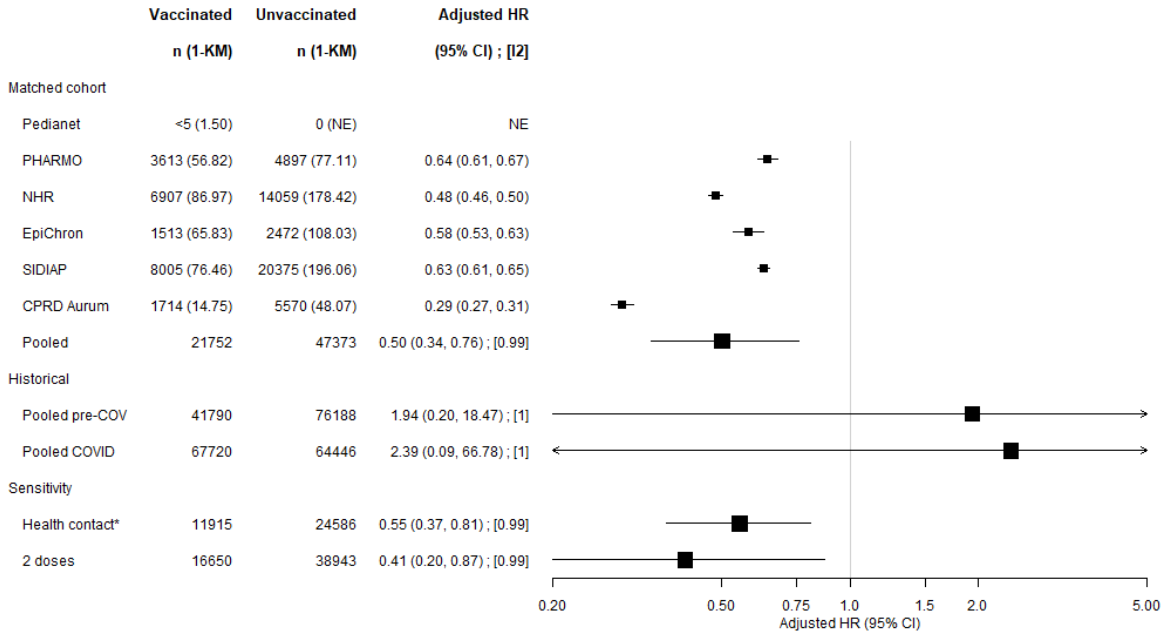
The pooled HR analyses for all-cause death showed heterogeneity between data sources ($I^2$=0.99) (**Figure 27**), although all HRs were consistently below 1, with narrow confidence intervals. The pooled adjusted results for analyses with historical controls were restricted to SIDIAP, PHARMO and CPRD because the EpiChron and NHR had limitations in their data for death in historical cohorts. The comparisons with historical controls in SIDIAP and CPRD showed higher risks, but this is likely to be due to confounding by COVID-19, since concurrent controls showed a reduction of risk (*Post-hoc* analyses).

Sensitivity analyses for individuals without healthcare contact within 7 days of time zero and at least two doses also showed a consistent protective effect for all-cause death. Due to the absence of events in Pedianet, sub-cohort and stratified analyses could not be conducted.

In PHARMO the HR for all-cause death were consistently reduced in all strata, except in younger age groups (Appendix Figure 37). In NHR a similar pattern was observed, while in SIDIAP the HRs did not show any particular pattern. In several DEAPs no protective effect

on all-cause death could be observed in the youngest age groups for the main analysis, but confidence intervals were wide (PHARMO, NHR, CPRD Aurum).

**Figure 27. Pooled analyses for death (any cause) 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

### 10.4.1.4. Other pre-specified AESIs neither identified as signals nor discussed by the PRAC

A summary of the incidence rates, adjusted HRs, and RDs for the 19 AESI that were pre-specified in the protocol but are not identified risks in RMP nor discussed by the PRAC can be found in Appendix Table 10. Below the results of the pooled analyses for these AESIs are summarised for the main comparisons and the sensitivity analyses by body system class. Incidence rates and cumulative incidence curves as well as forest plots on subgroup analyses can be found in **Standalone Section 15**.

#### 10.4.1.4.1. Autoimmune diseases

**Figure 28** shows the quarterly incidence rates of autoimmune AESIs in unvaccinated individuals for the period 2018-2022. These include Guillain Barré syndrome, acute disseminated encephalomyelitis, narcolepsy, and acute aseptic arthritis. These autoimmune AESIs were very rare, in the range of 1 case per 100,000 person years and showed seasonal patterns of occurrence. Acute aseptic arthritis incidence appears as 1 per 10,000 person years because it was defined with a very sensitive list of codes that include false positives as there are no specific codes for acute aseptic arthritis in the different dictionaries. Incidence of type 1 diabetes ranged between 1 and 10 per 10,000 person years and was relatively stable although it dropped in Q4 2020, coinciding with the pandemic lock down, in NHR and PHARMO.

**Figure 28. Incidence rates by quarter from Q1 2018 to Q4 2022 for autoimmune AESIs in unvaccinated individuals standardised to the data source specific population in 2020, by data source**

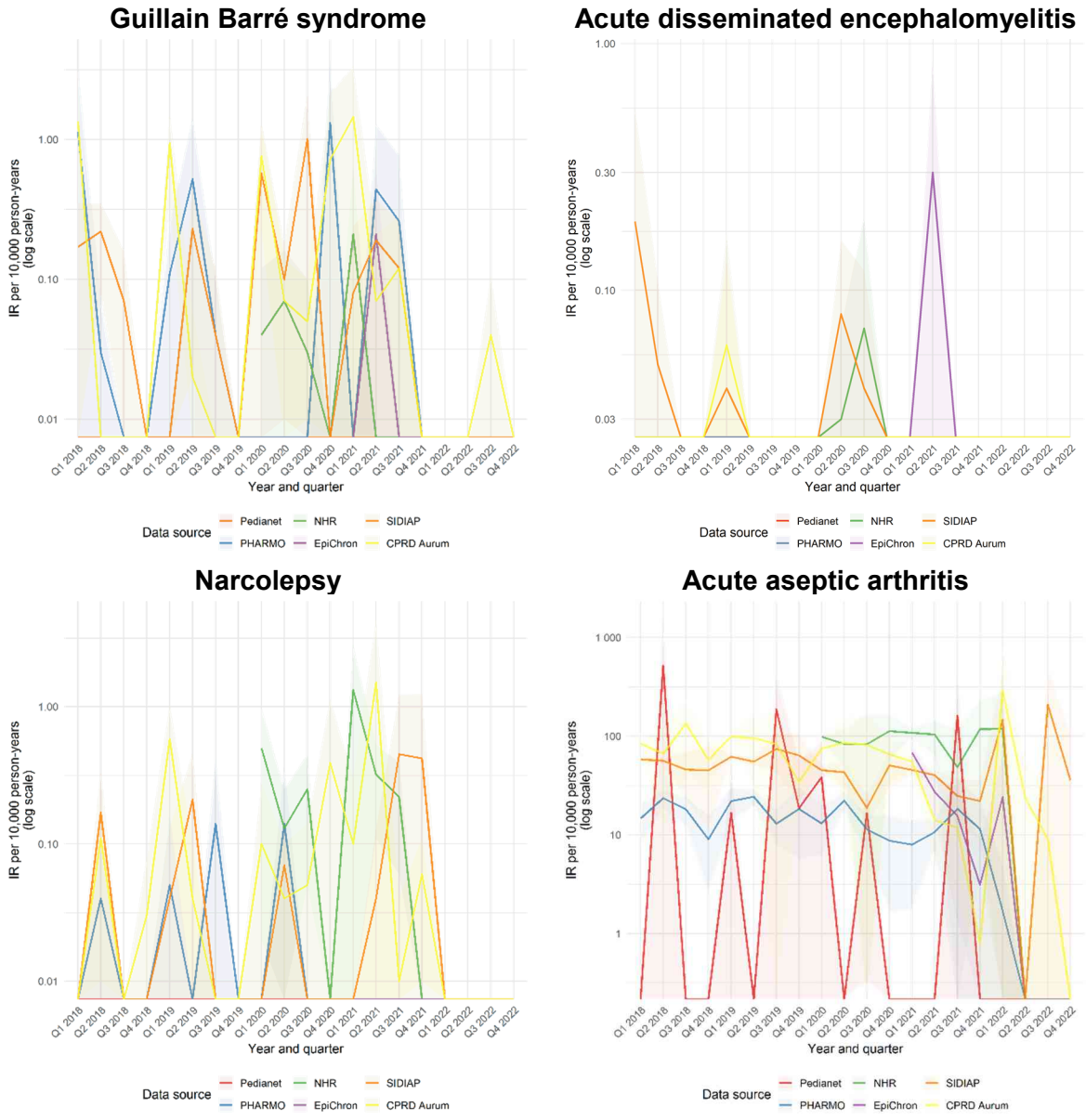
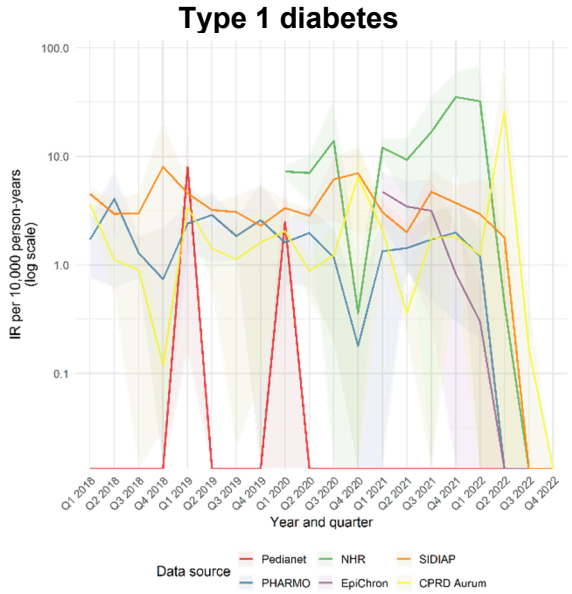


**Figure 28. Incidence rates by quarter from Q1 2018 to Q4 2022 for autoimmune AESIs in unvaccinated individuals standardised to the data source specific population in 2020, by data source**




Although not measured in every data source, autoimmune-related AESIs (Guillain-Barré syndrome, acute disseminated encephalomyelitis (ADEM), narcolepsy, acute aseptic, arthritis, type 1 diabetes mellitus) did not show an increased risk following vaccination with Pfizer-BioNTech COVID-19 vaccine. The pooled adjusted HR in the main matched analysis for GBS was 1.05, (95% CI: 0.27-4.13); for ADEM a pooled HR could not be computed; for narcolepsy the pooled adjusted HR was 0.54 (95% CI: 0.09-3.31); for acute aseptic arthritis the pooled adjusted HR was 1.13 (95% CI: 0.99-1.30); and for diabetes mellitus 1 the pooled adjusted HR was 1.05, 95% CI: 0.89-1.24 (Appendix Figures 38 to 42). Age specific analyses showed an isolated finding of a pooled adjusted HR of 2.24 (95% CI: 1.05–4.77) in females aged 16–17 for type 1 diabetes mellitus (*Post hoc* pooling analyses).

The results from the SCRI analyses were consistent with the absence of risk, which is important because these analyses control for within-person residual confounding that may exist in the cohort analyses. The pooled IRRs from the SCRI analyses, which were performed in the all-vaccinated cohort that included all doses of the Pfizer-BioNTech COVID-19 vaccine, were: GBS IRR 0.91 (95% CI: 0.67-1.25), IRR ADEM 1.39 (95% CI: 0.01-317.66), IRR narcolepsy 0.76 (95% CI: 0.38-1.53), and acute aseptic arthritis IRR 0.99 (95% CI: 0.88-1.11).

The pooled HR using the pre-COVID-19 period historical comparison frequently showed a lowering of the HR, which could be due to higher healthcare-seeking behaviour and therefore increased opportunity for diagnosis in that period, whereas comparison with the COVID-19 period lockdown historical cohort often showed an elevation of the HR (Appendix Figures 38 to 42). Sensitivity analyses excluding persons with healthcare contact in the 7 days before time zero or restricting the analyses to those with 2 doses of the vaccine within 6 weeks and analysing dose 2 risk window as well, showed no marked changes with respect to the results for the main analysis.

#### 10.4.1.4.2. Hepato-gastrointestinal and renal system

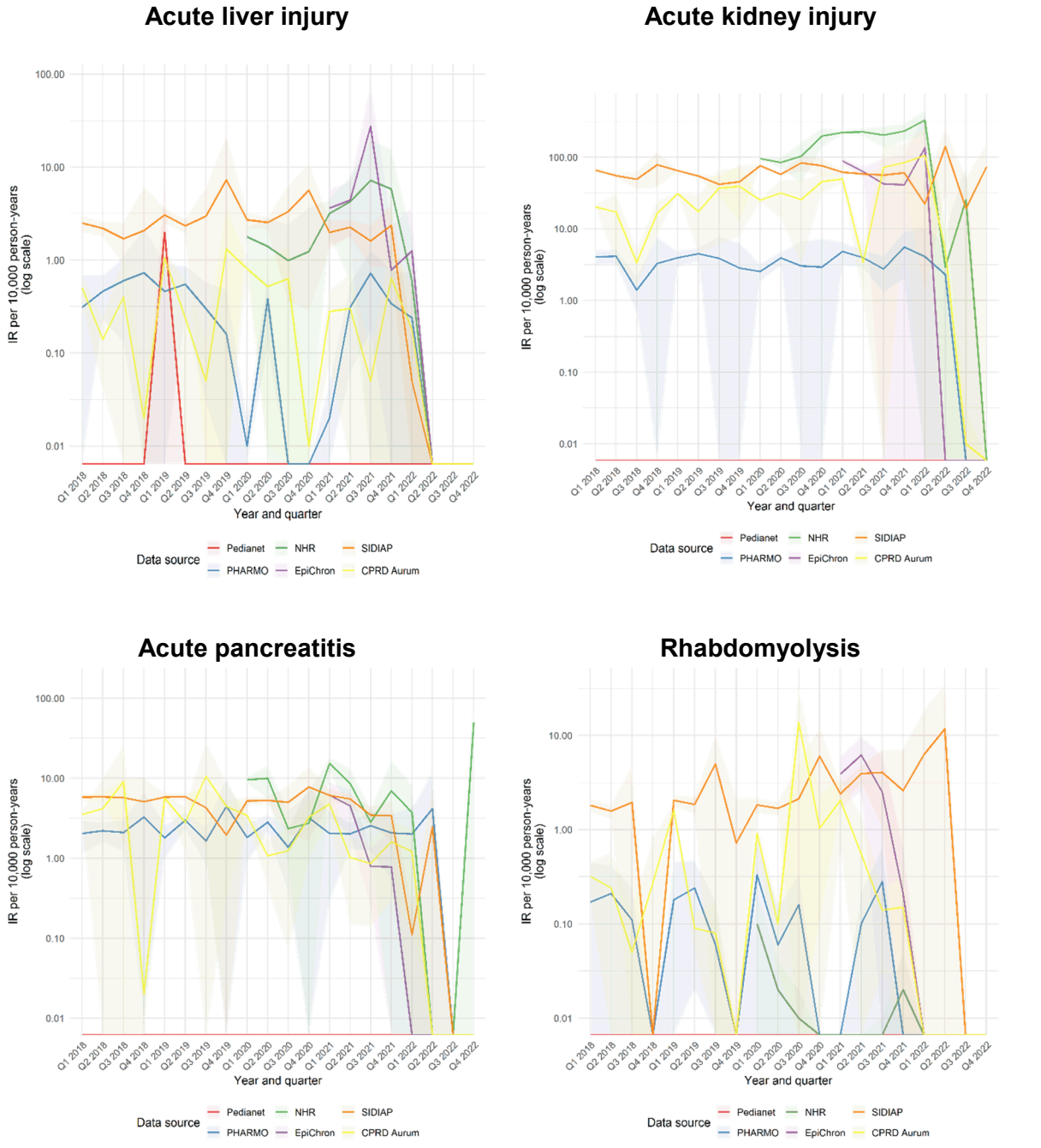
**Figure 29** shows the incidence rates (2018-2022) of acute liver injury, acute kidney injury, acute pancreatitis and rhabdomyolysis in unvaccinated individuals. The incidence of acute liver injury was low and lower in PHARMO and CPRD than in data sources with hospitalisation data. Rates of acute kidney injury events were stable over calendar time with lower rates in PHARMO than in other data sources. Acute pancreatitis was also rare, with more homogeneous rates between data sources and small seasonal patterns, whereas rhabdomyolysis was very rare with seasonal variations in all data sources. Towards the end of the observation period, the rates decreased since only a few remain unvaccinated.

The adjusted HRs for acute liver injury, acute kidney injury, acute pancreatitis, and rhabdomyolysis varied across data sources (Appendix Figures 43 to 46). For acute liver injury the HR in CPRD Aurum showed an association which was not found in other data sources HR=2.20, (95% CI: 1.23-3.91).

The pooled adjusted HRs for the main matched cohort analysis were: 1.07 (95% CI: 0.69-1.66) for acute liver injury; 0.92 (95% CI: 0.74-1.16) for acute kidney injury; 1.05 (95% CI: 0.88-1.25) for acute pancreatitis; and 0.77 (95% CI: 0.59-1.01) for rhabdomyolysis.

The sensitivity analyses excluding healthcare contact within 7 days before time zero r or limiting to those with 2 doses of the vaccine within 6 weeks, showed consistency with the main comparison. The results showed an increase in HRs when comparing with historical controls in the COVID-19 period in 2020, when there was lockdown, which points to lower opportunity for diagnosis in that period.

**Figure 29. Incidence rates by quarter from Q1 2018 to Q4 2022 for hepato-gastrointestinal and renal system AESIs in unvaccinated individuals standardised to the data source specific population in 2020, by data sources**




### 10.4.1.4.3. Nerves and central nervous system

**Figure 30** 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 30. 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**

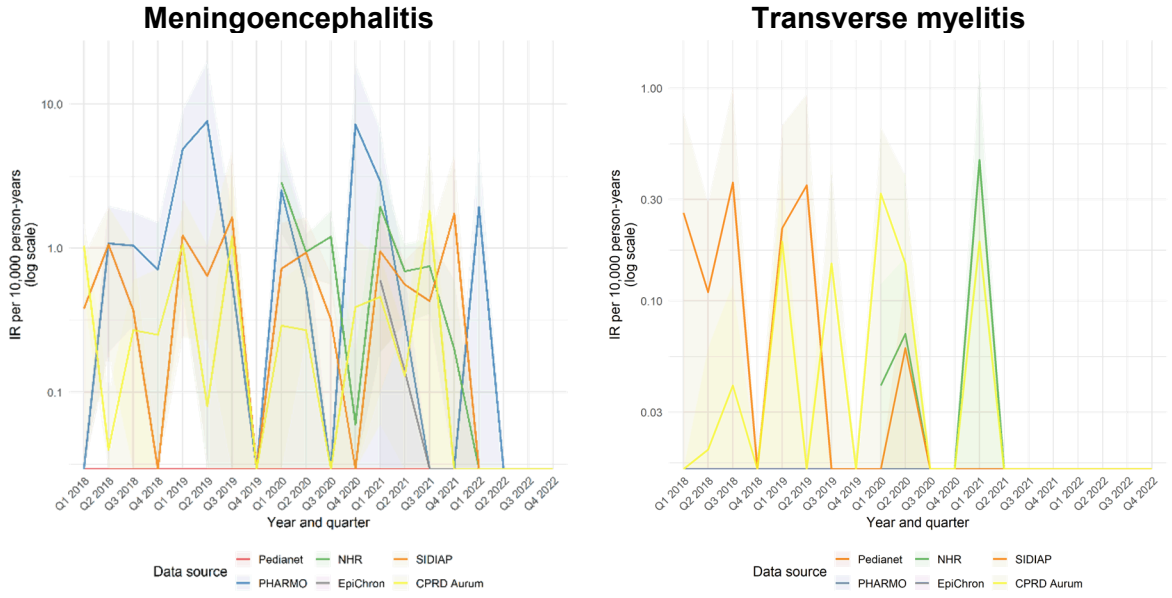
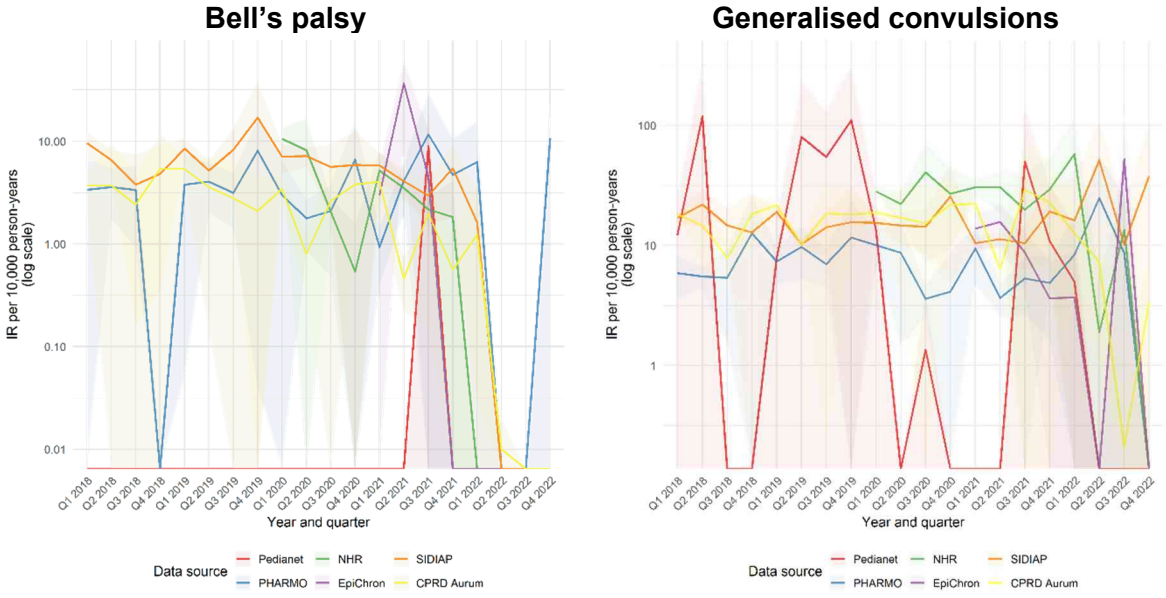


**Figure 30. Incidence rates by quarter from Q1 2018 to Q4 2022 for nerves and central nervous system AESIs in unvaccinated individuals standardised to the data source specific population in 2020, by data source**

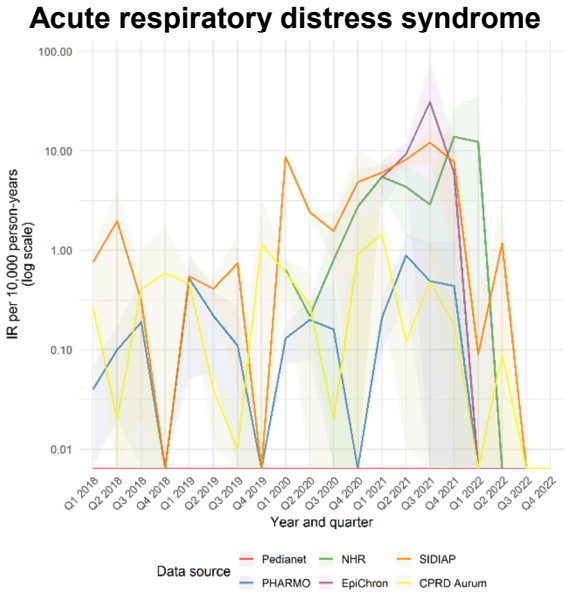



### 10.4.1.4.4. Respiratory system

**Figure 31** shows that the incidence rates from Q1 2018 to Q4 2022 for acute respiratory distress syndrome in unvaccinated individuals was very low but showed a seasonal pattern and increased during the COVID-19 period.

The pooled adjusted HR for ARDS was 0.27 (95% CI: 0.11-0.63) (Appendix Figure 51). Although the adjusted HRs were heterogeneous across data sources, they were compatible with the pooled adjusted HR. The HRs in the sensitivity analyses were consistent with those for the matched cohorts, the exception being that HRs for the historical controls were higher, accompanied by wide 95% CIs.

**Figure 31. Incidence rates by quarter from Q1 2018 to Q4 2022 for respiratory system AESIs in unvaccinated individuals standardised to the data source specific population in 2020, by data sources**



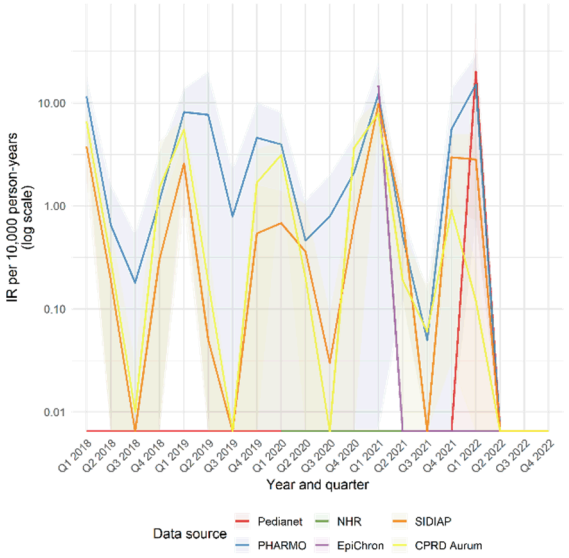

### 10.4.1.4.5. Skin and mucous membrane bone and joints

**Figure 32** shows the incidence rate (2018-2022) of chilblain like lesions in unvaccinated individuals, which shows a clear seasonality with higher rates in the winter period.

The pooled adjusted HR for chilblain-like lesions was 0.81 (95% CI: 0.45-1.44) (Appendix Figure 52). The pooled results and sensitivity analyses were consistent, except when historical controls in the COVID-19 period were compared, which increased the HR to 2.74 (95% CI: 0.65-11.65).

**Figure 32. Incidence rates by quarter from Q1 2018 to Q4 2022 for skin and mucous membrane bone and joints AESIs in unvaccinated individuals standardised to the data source specific population in 2020, by data sources**

**Chilblain-like lesions**




### 10.4.1.4.6. Other AESI: 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 33** shows that the incidence of subacute thyroiditis from Q1 2018 to Q4 2022 was very low with slight seasonal variation.

**Figure 34** 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). 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 33. 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**

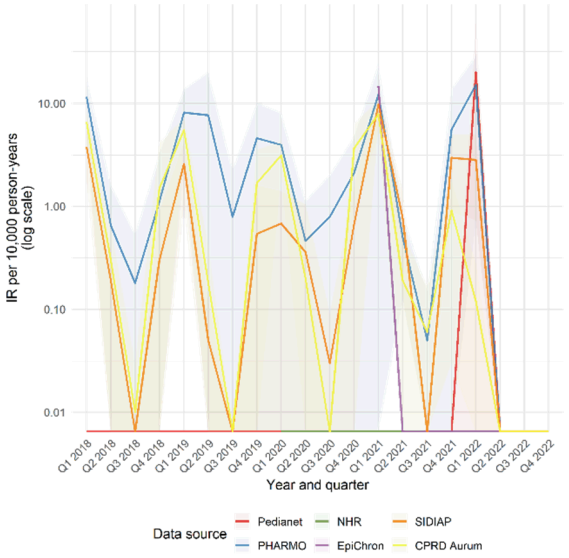
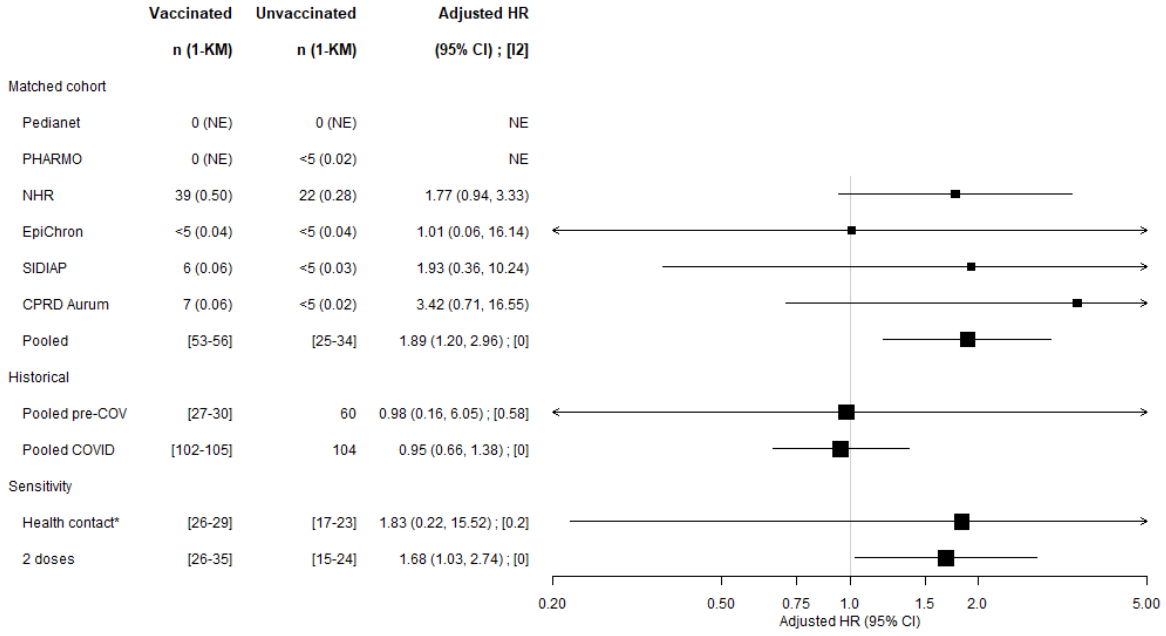



**Figure 34. Pooled analyses for subacute thyroiditis in the overall and historical cohorts and sensitivity analyses**




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

### 10.4.2. 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 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).

#### 10.4.2.1. 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). The comparison with historical controls showed no elevation of the HR (Appendix Figure 54).

The prevalence of preeclampsia varied highly between data sources with the lowest prevalence in CPRD Aurum (Appendix Table 11). 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).

#### 10.4.2.2. Neonatal pregnancy outcomes

The prevalence of foetal growth restriction (FGR) varied across the different data sources (Appendix Table 11). 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). 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% (Appendix Table 11). 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). 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). 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).

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), 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). The prevalence rate ratios showed a lowering of prevalence in NHR and an elevation in SIDIAP, with wide 95% CIs (Appendix Figure 60). 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).

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) (Appendix Table 11). 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 (Appendix Table 11).

### 10.5. Other analyses

#### 10.5.1. Validation results

A partial validation assessment of nine AESIs was performed in PEDIANET, EpiChron, NHR, PHARMO, SIDIAP, and CPRD Aurum (Appendix Table 12). In these six data sources the number of validated cases for each AESI among vaccinated and unvaccinated individuals was low. Due to the need to mask numbers when less than five events were identified, the total number of validated cases and the levels of certainty across the data sources cannot be presented with granularity. The ability to reach a high level of certainty depends on the type of data that the validators could use to validate. Pedianet, PHARMO, and CPRD Aurum used medical record data from GPs, which were manually reviewed. Validators could not access patients' hospital files directly and relied on discharge letters from specialists or copies and transcripts of results that were reported to the GPs. In PHARMO and PEDIANET no PPVs could be reported for any of the nine AESIs.

The PPV values for the strict and broad AESI definitions in the matched vaccinated and unvaccinated cohorts are summarised in **Table 8**. In CPRD Aurum and SIDIAP, many cases were classified as having a level of certainty of 4a (i.e., diagnosis made by specialist but no further information available to reach a higher level of diagnostic certainty). Using a broader definition (inclusion of specialist diagnosis as true case) resulted in an improvement of the PPV. In NHR, SIDIAP, and EpiChron, clinical data from in-hospital information or charts was available for validation, in these data sources level 1-3 could be easier achieved, because the proper source data to validate were available. PPV levels for anaphylaxis were low, PPV values for myocarditis were high in NHR and EpiChron, but lower in SIDIAP and CPRD

Aurum. PPV values for pericarditis were lower than for myocarditis. The PPV for major congenital anomalies differed between the vaccinated and unvaccinated cohorts in NHR.

**Table 8. Overview of PPV values (%) for validated AESIs, by vaccination status and data sources, for strict (level 1-3) and broad (Level 1-4a) Brighton Collaboration levels of diagnostic certainty classifications**

| | | NHR | | EpiChron | | SIDIAP | | CPRD Aurum | |
|---|---|---|---|---|---|---|---|---|---|
| | | Vaccinated | Unvaccinated | Vaccinated | Unvaccinated | Vaccinated | Unvaccinated | Vaccinated | Unvaccinated |
| Anaphylaxis | n | 32 | <5 | <5 | 0 | 0 | 0 | 10 | <5 |
| | Strict | 22 (11–39) | 100 (21–100) | 0 (0–56) | | | | 0 (0–28) | 0 (0–56) |
| | Broad | 59 (42–74) | 100 (21–100) | 0 (0–56) | | | | 70 (4–89) | 0 (0–56) |
| Myocarditis | n | 8 | 0 | <5 | <5 | 7 | 5 | 12 | <5 |
| | Strict | 75 (41–93) | | 67 (21–94) | 0 (0–79) | 29 (8–64) | 0 (0–43) | 17 (5–45) | NE |
| | Broad | 75 (41–93) | | 67 (21–94) | 0 (0–79) | 29 (8–64) | 0 (0–43) | 50 (25–75) | NE |
| Pericarditis | n | 26 | 20 | 8 | 18 | 39 | 67 | 20 | 0 |
| | Strict | 46 (29–65) | 70 (48–85) | 38 (14–69) | 50 (29–71) | 38 (25–54) | 52 (40–64) | 0 (0–16) | |
| | Broad | 85 (66–94) | 90 (70–97) | 62 (31–86) | 50 (29–71) | 41 (27–57) | 52 (40–64) | 55 (34–74) | |
| ITP | n | 12 | 12 | <5 | 18 | 26 | 18 | <5 | 0 |
| | Strict | 83 (55–95) | 92 (65–99) | 33 (6–79) | 33 (16–56) | 62 (43–78) | 56 (34–75) | 25 (5–70) | |
| | Broad | 83 (55–95) | 92 (65–99) | 33 (6–79) | 33 (16–56) | 62 (43–78) | 72 (49–88) | 100 (51–100) | |
| TTS | n | <5 | 0 | <5 | <5 | 5 | <5 | 0 | 0 |
| | Strict | 33 (6–79) | | 50 (9–91) | 100 (21–100) | 40 (12–77) | 0 (0–66) | | |
| | Broad | 33 (6–79) | | 50 (9–91) | 100 (21–100) | 40 (12–77) | 0 (0–66) | | |
| GBS | n | <5 | <5 | 0 | <5 | 9 | 5 | <5 | <5 |
| | Strict | 0 (0–56) | NR | | NR | 0 (0–30) | 0 (0–43) | 0 (0–49) | 0 (0–79) |
| | Broad | 67 (21–94) | NR | | NR | 56 (27–81) | 0 (0–43) | 50 (15–85) | 100 (21–100) |
| Transverse myelitis | n | <5 | <5 | <5 | 0 | <5 | 0 | <5 | <5 |
| | Strict | NR | NR | 0 (0–66) | | 0 (0–66) | | 100 (21–100) | 0 (0-79) |
| | Broad | NR | NR | 0 (0–66) | | 0 (0–66) | | 100 (21–100) | 100 (21-100) |
| Narcolepsy | n | 9 | 19 | 0 | 0 | <5 | 6 | <5 | <5 |
| | Strict | 33 (12–65) | 79 (57–91) | | | 0 (0–66) | 0 (0–39) | 0 (0–79) | 0 (0–39) |
| | Broad | 56 (27–81) | 100 (83–100) | | | 0 (0–66) | 17 (3–56) | 100 (21–100) | 17 (3–56) |
| Major Congenital anomalies | n | 14 | 10 | 0 | 0 | 0 | 0 | <5 | 0 |
| | Strict | 29 (12–55) | 90 (60–98) | | | | | 100 (21–100) | |
| | broad | 100 (78–100) | 100 (72–100) | | | | | 100 (21–100) | |

NE: not estimable; NR: not reportable due to masking when <5 events were identified

### 10.5.2. Direct Healthcare Professional Communication

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 35**). 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 three data sources that captured this information (**Table 9**).

**Figure 35. 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**

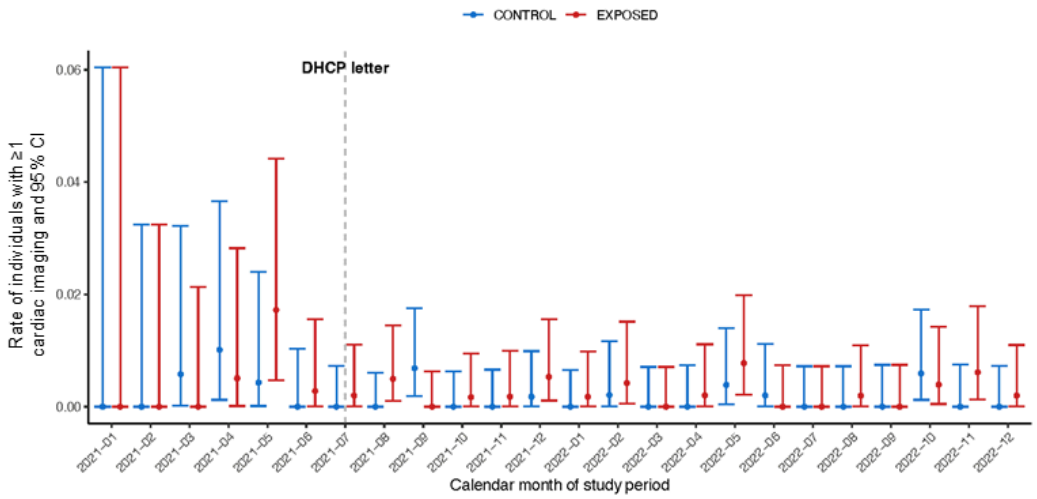
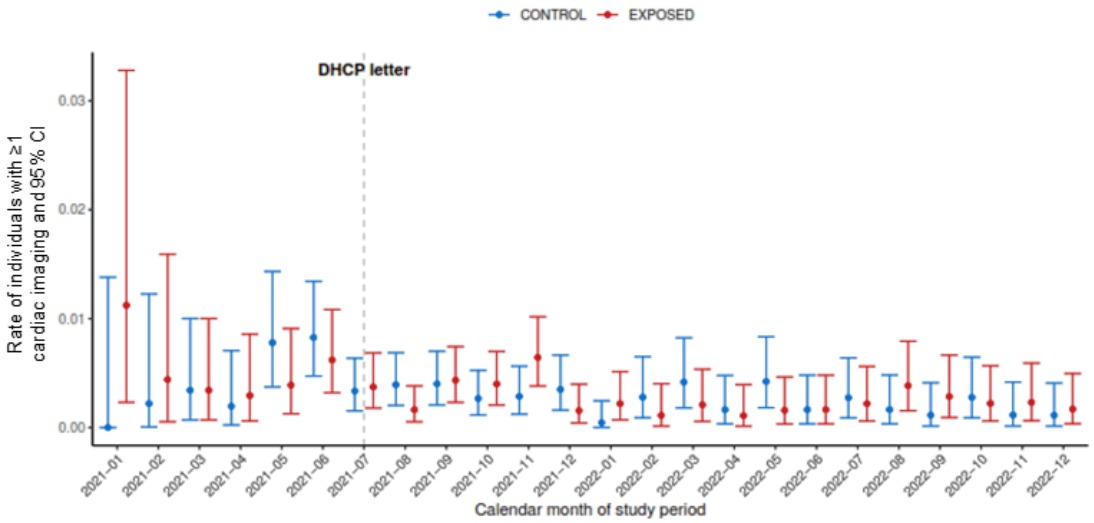


**Figure 35. Evolution of rates of individuals undergoing at least one cardiac imaging event before and after the issue of the Direct Healthcare Professional Communication (DHPC)**

**SIDIAP**




**CPRD Aurum**

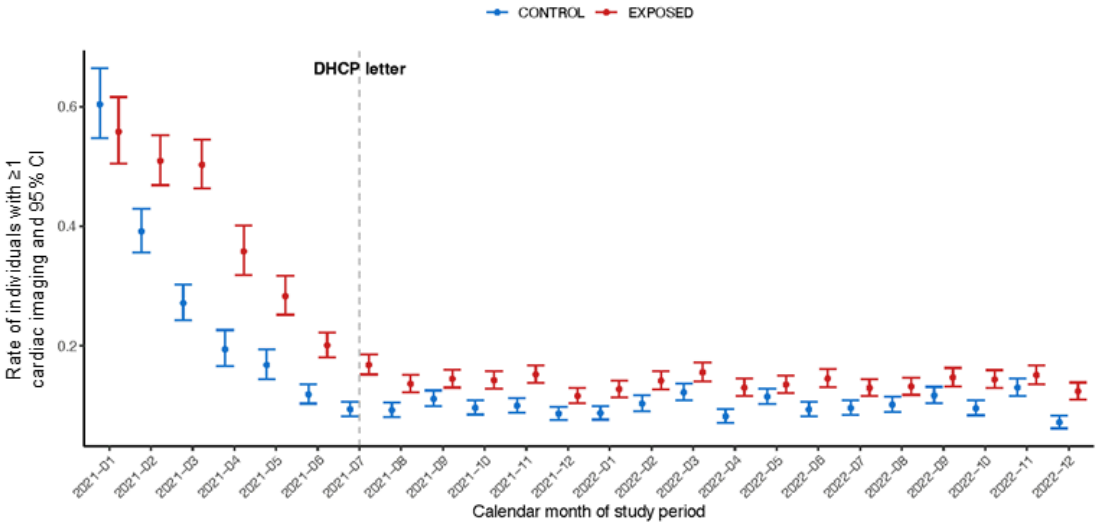


**Table 9. Rate ratios for matched vaccinated and unvaccinated individuals undergoing ≥1 cardiac imaging procedure comparing after with before the direct healthcare professional communication (DHPC) issuance by data source**

| | 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) |

### 10.6. Adverse events / adverse reactions

No adverse events (AEs), other than those reported in aggregated data in this report, were observed during study.

This study involves a combination of existing structured data and unstructured data, which were converted to structured form during the implementation of the protocol solely by a computer using automated algorithmic methods, such as natural language processing.

In these data sources, it is not possible to link, (i.e., identify a potential association between) a particular product and medical event for any individual. Thus, the minimum criteria for reporting an AE (i.e., identifiable patient, identifiable reporter, a suspect product, and event) cannot be met.

## 11. DISCUSSION

### 11.1. Statistical interpretation

In alignment with guidance from the American Statistical Association, and the International Committee of Medical Journal Editors, the C4591021 PASS research consortium did not rely on statistical significance as the primary basis for interpreting study results.[13, 14] Rather than adopting a binary framework based on statistical significance, we applied a more nuanced approach that considered the magnitude and precision of effect estimates, as well as potential sources of bias. This methodology was deemed more appropriate for evaluating observational data, as it avoids attributing findings solely to chance when conventional significance thresholds are not met.

For AESIs, random-effects meta-analyses were conducted when data were available from at least two data sources. This method was used to generate a pooled estimate, representing a weighted average of the individual effect estimates, and to evaluate heterogeneity across data sources. The random-effects model was selected to account for between-study variability in the estimation process and in the construction of 95% confidence intervals. However, it is important to note that while this approach incorporates heterogeneity into the analysis, it does not resolve it and should not replace a thorough investigation of its sources.[15] In the presence of heterogeneity, random-effects models tend to assign relatively greater weight to smaller studies. Heterogeneity was assessed using the $I^2$ statistic. Thresholds for the interpretation of the $I^2$ statistic can be misleading, since the importance of inconsistency depends on several factors, but we used the following classification as recommended by the Cochrane Collaboration: 0% to 40%: might not be important; 30% to 60%: may represent moderate heterogeneity; 50% to 90%: may represent substantial heterogeneity; 75% to 100%: considerable heterogeneity.[16]

### 11.2. Key results

This final report is based on healthcare data from seven population-based sources across five 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 data cut-off dates varied by data source: Pedianet (31 December 2022), PHARMO (30 June 2023 for GP data and 31 December 2022 for hospital data), SIDIAP (30 June 2023), EpiChron (31 July 2023), NHR (31 December 2022), and CPRD Aurum (07 June 2023) (**Table 3**). The observation period encompassed the timeframe during which individuals could receive up to five 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.

#### 11.2.1. Descriptive results

##### 11.2.1.1. Cohort attrition

During the study period, 12,398,589 individuals received a first dose of the Pfizer-BioNTech COVID-19 vaccine, with at least one year of lookback and no prior COVID-19 vaccination. In CPRD 20.82% have been excluded because less of 12 months of continuous enrolment in the data source. This is likely because patients have been registered with a GP for less than 12 months due to having moved and changed GP or being classed as temporary residents (e.g. students or those away from home for a short period). It may be that case that in the setting of a mass vaccination programme people who had moved and not changed to their local GP id so on mass in order to receive the covid vaccine. Of these, 84.9% received a second dose, with uptake ranging between 76.2% in PHARMO to over 90% in the Spanish data sources. Among second-dose recipients, 60.8% received it within six weeks, with wide variations, ranging from 97.3% in Pedianet (median: 3.14 weeks) to 6.1% in CPRD Aurum (median: 10.7 weeks). Third doses were given to 34.8% of first-dose recipients, with median intervals between second and third doses ranging from 21.4 to 31 weeks. A fourth dose was administered to 9%, and 0.1% received a fifth dose. The interval between third and fourth doses exceeded 40 weeks in all sources except CPRD Aurum (25.7 weeks). In the UK, extended intervals between the earlier doses were due to recommendation from the Joint Committee on Vaccination and Immunisation (JCVI) to delay the second dose to 12 weeks to maximise first-dose coverage during the Alpha variant surge.[17]

A total of 48,439 pregnant women received a first dose of the Pfizer-BioNTech COVID-19 vaccine during pregnancy, had one year of lookback and had not received any other COVID-19 vaccine before. Among these, 55.11% could be matched with unvaccinated, pregnant women for the pregnancy and neonatal outcomes.

Among the total vaccinated population, 92.73% (11,496,929) were matched with unvaccinated individuals. Censoring occurred in 30.30% of vaccinated matches due to receipt of a non-Pfizer vaccine, and in 67.85% of unvaccinated matches due to subsequent COVID-19 vaccination. The median follow-up was short in unvaccinated cohorts and ranged from 0.8 months in NHR to 1.0 month in EpiChron. To reduce bias, both members of a

matched pair were censored when either was censored. For analyses of those who received two doses within six weeks and those who had no healthcare contact in the seven days prior to time zero, pairs were excluded if only one met the criteria. SCRI analyses included individuals with AESIs in post-vaccination risk or control windows and compared the risk for AESIs in each window. Sensitivity analyses matched 12,049,838 vaccinated individuals to 23,818,759 historical unvaccinated controls from 2018–2019 (1:2 matching, with one control from 2018 and another from 2019), and 11,319,784 vaccinated individuals to 11,319,784 unvaccinated controls from 01 January to 30 November 2020 (1:1 matching).

#### 11.2.1.2. Demographics and comorbidities

The matched cohorts differed in age, healthcare use, and vaccination timing across data sources. Median age ranged from 10 years in Pedianet to 48 years in PHARMO. Most first doses were administered in Q2 2021, except in Pedianet, a paediatric data source, where first dose administration peaked in Q1 2022 because child vaccination began later. In Spain, vaccinated individuals had higher primary care use than unvaccinated individuals (ASD: 0.26 in EpiChron, 0.20 in SIDIAP), while this use was balanced in the other data sources. Hospitalisation rates were similar across all cohorts. Over 80% had a Charlson score of 0 or 1, and common comorbidities included cardiovascular, respiratory, and connective tissue diseases. Medication use was highest for antibiotics, NSAIDs, and psychotropics. Vaccination history reflected age, with childhood vaccines common in Pedianet and influenza vaccines in older age groups. Baseline characteristics were well balanced (ASDs ≤0.1), except for HPV vaccination in Pedianet (13.78% vs. 9.86%, ASD: 0.12).

#### 11.2.1.3. 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 01/01/2020. 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 1, 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 (very rare adverse events were defined as those occurring in<1 in 10,000 individuals, and rare ≥1 in 10,000 and <1 in 1,000 individuals);

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[18];

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 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 further examine subgroups of interest. A summary of the core findings for the main comparisons with adjusted hazard ratios (HRs) pooled across data sources and the results from the SCRI analyses are provided in **Table 10**. Together these results answer the primary study objective.

### 11.2.2. Outcomes identified as risks in risk management plan

#### 11.2.2.1. Myocarditis and pericarditis

Results show increased risks for myocarditis and pericarditis, with varying results across risk windows, sensitivity analyses, and subgroup analyses (**Table 10**).

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.

#### 11.2.2.2. Anaphylaxis

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.

## Table 10. 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 |
| 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) |

## Table 10. 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) |
| 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) |

ND: not done; Sudden death could not be accurately assessed.

### 11.2.3. Risks discussed by PRAC

#### 11.2.3.1. Idiopathic thrombocytopenia

Idiopathic thrombocytopenia was discussed in March 2021 by the PRAC (**Table 1**) and several case series were published.[27-29] This PASS study found no association between the Pfizer-BioNTech COVID-19 vaccine and idiopathic thrombocytopenia (ITP) in the main analysis, SCRI study, or sensitivity analyses. An increased HR was observed in the comparisons with the 2020 historical controls, probably due to reduced healthcare utilisation during that period, which is also reflected in lower ITP incidence in NHR and SIDIAP in Q2–Q3 2020 in unvaccinated individuals. The broad PPV for ITP was 83% in vaccinated and 92% in unvaccinated in NHR, 33% in EpiChron, for both vaccinated and unvaccinated, moderate (62% and 72%, respectively) in SIDIAP, and 100% for vaccinated in CPRD Aurum, with either no PPV for unvaccinated or overlapping confidence intervals between vaccinated and unvaccinated individuals. In NHR, where misclassification was minimal, the adjusted hazard ratio was 0.62 (95% CI: 0.31–1.24), lower than in other sources.

#### 11.2.3.2. Thrombotic thrombocytopenia syndrome

Thrombotic thrombocytopenia syndrome (TTS) was discussed by the PRAC in relation to COVID-19 vaccines with an adenovirus platform, not for the Pfizer-BioNTech COVID-19 vaccine.[11] The Pfizer-BioNTech COVID-19 vaccine was shown to have a lower risk of TTS than vaccines with an adenovirus platform in prior studies, and across different studies.[30] Only a few cases of TTS following vaccination were identified. TTS was not associated with an elevated risk in the matched cohort or in the SCRI analysis. The broad PPV for TTS was ≤50% in vaccinated individuals with wide confidence intervals due to a very low number of events. The low PPV will lead to an attenuation of the HRs and IRRs.

#### 11.2.3.3. Glomerulonephritis and erythema multiforme

Glomerulonephritis and erythema multiforme were discussed in 2023 by PRAC and resulted in a request for routine pharmacovigilance and monitoring of periodic safety update reports (PSURs) for glomerulonephritis and a change in product information for erythema multiforme. For both AESIs case series have been published.[31, 32] The results from this study showed no association between Pfizer-BioNTech COVID-19 vaccine and these two AESIs, in the main analyses or in the sensitivity analyses. The events were not validated; therefore, the direction of bias cannot be predicted.

#### 11.2.3.4. Multisystem inflammatory syndrome

The PRAC discussed MIS in October 2021 based on case series from EudraVigilance and the literature. Although MIS is similar to conditions like Kawasaki disease and toxic shock syndrome, the exact cause is believed to be a delayed immune response to SARS-CoV-2. Multisystem inflammatory syndrome (MIS), a rare but serious condition affecting multiple organs, emerged shortly after the onset of COVID-19 and was formally coded in ICD-10 CM as M35.81 in 2021 for both children (MIS-C) and adults (MIS-A). Due to the timing of this formal classification, historical controls could not be used to assess pre-COVID incidence. This PASS study found no association between MIS and the Pfizer-BioNTech COVID-19 vaccine, with a pooled adjusted hazard ratio of 1.02 (95% CI: 0.35–3.00) in both adults and children, confirmed across sensitivity analyses. Validation was not conducted for this event therefore the direction of bias cannot be predicted.

#### 11.2.3.5. Hypermenorrhoea and secondary amenorrhoea

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.

#### 11.2.3.6. Myositis

PRAC reviewed myositis as a safety signal for the Pfizer-BioNTech COVID-19 vaccine, based on 156 reports of idiopathic inflammatory myopathies from January to December 2023, including cases with no alternative explanation and some with recurrence after re-exposure.[37] This study found no association between the vaccine and myositis. Although the risk appeared higher in PHARMO data, the estimates were imprecise. Myositis was not validated; therefore, the direction of bias cannot be predicted.

Several other events were discussed by PRAC, but these were not pre-specified in this study and were not requested to be added to the label, as they are monitored through routine pharmacovigilance.

### 11.2.4. Other prespecified AESIs discussed elsewhere

#### 11.2.4.1. Death

In January 2021, Norway reported 23 deaths among individuals who were frail or had comorbidities within six days of receiving the Pfizer-BioNTech COVID-19 vaccine, raising concerns about vulnerability to side effects. However, WHO's Global Advisory Committee on Vaccine Safety (GACVS) found no evidence of a causal link, noting the deaths aligned with expected mortality in this population.[38] This study found a strong protective effect of the vaccine on all-cause mortality, which was highest in CPRD Aurum, with a pooled risk reduction of 50%. The effect was consistent across immunocompromised individuals, those who were frail or had comorbidities, and both sexes. A positive effect was not shown in children aged 5–11 due to the low number of events in the vaccinated and unvaccinated cohorts and lack of power. When individuals with prior COVID-19 were excluded, the adjusted HR remained protective at 0.53 (95% CI: 0.36–0.78). These events were not validated; therefore, the direction of bias cannot be predicted.

#### 11.2.4.2. Cardiovascular events

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**). 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.

### 11.2.5. Other AESI

The 17 other pre-specified AESIs which were studied, are briefly discussed here.

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).

For type 1 diabetes mellitus (DM-1), isolated post-vaccination cases have been reported, though a large Hong Kong study found no association.[43] This PASS study also found no association between the vaccine and DM-1, except for an isolated finding of an elevated in females aged 16–17.

While case reports and pharmacovigilance data suggest a possible link between the Pfizer-BioNTech COVID-19 vaccine and autoimmune hepatitis (AIH)-like liver injury, a large, self-controlled case series (SCCS) study in Hong Kong found no increased risk of acute liver injury.[44-46] This PASS which, focused on acute liver injury which is broader than AIH alone, we did not observe a consistent increase in risk. However, the HR was elevated in CPRD Aurum (adjusted HR: 2.20; 95% CI: 1.23–3.91). Rare instances of acute kidney injury have been reported post-vaccination, but a large cohort study showed higher risk after SARS-CoV-2 infection than vaccination.[47, 48] This PASS found no association between the Pfizer-BioNTech COVID-19 vaccine and acute kidney injury (with high heterogeneity), including in the direct effect analyses. Several case reports on acute pancreatitis following Pfizer-BioNTech COVID-19 vaccination have been published.[49] To the best of the MAH's knowledge no comparative study has been conducted. In this study no association between

Pfizer-BioNTech COVID-19 vaccination and acute pancreatitis was observed, in the main analyses, the direct effect or the sensitivity analyses. There have been a few reported cases suggesting an association between the Pfizer-BioNTech COVID-19 vaccine and rhabdomyolysis, but this AESI is very rare.[50-52] To the best of the MAH's knowledge no comparative studies have been conducted at present. In this study no association between the Pfizer-BioNTech COVID-19 vaccine and rhabdomyolysis was found. The HR for the direct effect was also below 1.

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. 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. 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.

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.

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]

Acute respiratory distress syndrome (ARDS) has been reported to be strongly associated with severe COVID-19 but not with the Pfizer-BioNTech COVID-19 vaccine. In this PASS a strong protective effect was observed in the vaccinated cohorts compare with the unvaccinated cohorts, except in the youngest age groups, 5-11 and 12-17 years of age where power was limited. As expected, the protective direct effect of vaccination was weaker when individuals who had previously had COVID-19 previously were removed, as these individuals already had built immunity.

Chilblain-like lesions (also known as pernio-like lesions or 'COVID toes') have been reported as a rare side effect following Pfizer-BioNTech COVID-19 vaccination, even without recorded SARS-CoV-2 infection.[64, 65] The suspected mechanism involves a strong immune response, particularly type I interferon signalling. However, this study found no association between the vaccine and these lesions in any pooled, sensitivity, nor subgroup analyses.

Single organ cutaneous vasculitis (SOCV) has been reported after Pfizer-BioNTech COVID-19 vaccination, typically presenting as purpuric, itchy skin lesions confirmed by dermatological and histopathological exams.[66] The condition is believed to be immune-mediated. This PASS found no overall association between the vaccine and SOCV. However, in immunocompromised individuals, the adjusted hazard ratio was elevated at 1.66 (95% CI: 0.54–5.05) based on NHR data, with wide confidence intervals indicating uncertainty.

#### 11.2.5.1. Pregnancy and maternal Outcomes

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] 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.

#### 11.2.5.2. Direct Healthcare Professional Communication

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.[69] 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. The impact of this risk minimisation measure was evaluated by assessing if the frequency of any cardiac imaging test after the issue of the DHPC had increased compared with the period before the DHPC

in vaccinated and unvaccinated individuals. Although it was expected that incidence rates of imaging would increase after the DHPC, it was observed that incidence rates of recorded cardiac imaging were higher before the issuance of the DHPC letter, i.e., assessed in the period from 01 January 2021 to 30 June 2021, than after, i.e., assessed in the period from 01 August 2021 to 31 December 2022, in both vaccinated and unvaccinated individuals. This unexpected finding may be explained by several factors:

- Pre-existing heightened clinical vigilance: Before the DHPC issue date (19 July 2021), there was already 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 and because of the study from Israel.[70] Healthcare providers might have been proactively ordering cardiac imaging based on initial reports or studies, causing elevated imaging rates before official communications.

- Public and media attention prior to DHPC: Media coverage and patient awareness of concerns about myocarditis and pericarditis in relation to vaccines might have prompted more individuals to seek medical evaluation and physicians to order diagnostic tests even before the formal communication about safety was disseminated. EMA started safety assessments on myocarditis events after the Pfizer-BioNTech COVID-19 vaccine 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.

- 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 might have led to more targeted and judicious use of cardiac imaging, avoiding unnecessary tests following the official advice.

- 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 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.[71]

- 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 myocarditis might already have occurred.

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

### 11.3. Limitations

#### 11.3.1. Measurement errors in data sources

#### 11.3.2. 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.

#### 11.3.3. 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.[73] 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.

### 11.3.4. 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.

### 11.3.5. 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.

### 11.3.6. 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.

### 11.3.7. 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.

### 11.3.8. 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.

## 11.4. 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.

### 11.5. 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.

## 12. OTHER INFORMATION

Not applicable.

## 13. CONCLUSIONS

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 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.

## 14. REFERENCES

1. Pfizer-BioNTech. Fact sheet for healthcare providers administering vaccine (vaccination providers) emergency use authorization (EUA) of the Pfizer-BioNTech COVID-19 vaccine to prevent coronavirus disease 2019 (COVID-19). 2022. Available at: https://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=&ved=2ahUKEwiPm-LkzsL9AhXoQaQEHTvuB_QQFnoECBMQAQ&url=https%3A%2F%2Flabeling.pfizer.com%2FShowLabeling.aspx%3Fid%3D14471%26format%3Dpdf&usg=AOvVaw2E4D3Ukykhj7IiDTmq53If. Accessed: 4 March 2023,

2. ECDC. Overview of COVID-19 vaccination strategies and vaccine deployment plans in the EU/EEA and the UK. Stockholm: European Centre for Disease Prevention and Control; 2 December 2020. Available at: https://www.ecdc.europa.eu/sites/default/files/documents/Overview-of-EU_EEA-UK-vaccination-deployment-plans.pdf. Accessed: 17 December 2020.

3. Yih WK, Lee GM, Lieu TA, Ball R, Kulldorff M, Rett M, et al. Surveillance for adverse events following receipt of pandemic 2009 H1N1 vaccine in the Post-Licensure Rapid Immunization Safety Monitoring (PRISM) System, 2009-2010. Am J Epidemiol. 2012;175(11):1120–8.

4. Liu CH, Yeh YC, Huang WT, Chie WC, Chan KA. Assessment of pre-specified adverse events following varicella vaccine: A population-based self-controlled risk interval study. Vaccine. 2020;38(11):2495–502.

5. Duran C, Riera J, Mohammadi S, Fortuny J, Ehrenstein V, Rebordosa C, et al. COVID-19 Vaccine Monitoring Project (CVM)-electronic health record data sources codelist. 2023. Available at: https://zenodo.org/records/8199481. Accessed: 31 July 2025,

6. Gini R, Dodd CN, Bollaerts K, Bartolini C, Roberto G, Huerta-Alvarez C, et al. Quantifying outcome misclassification in multi-database studies: the case study of pertussis in the ADVANCE project. Vaccine. 2020;38 Suppl 2:B56–B64.

7. Dagan N, Barda N, Kepten E, Miron O, Perchik S, Katz MA, et al. BNT162b2 mRNA COVID-19 vaccine in a nationwide mass vaccination setting. N Engl J Med. 2021;384(15):1412–23.

8. SPEAC: Safety Platform for Emergency vAccines. 2023. Available at: https://zenodo.org/communities/speac_project/?page=1&size=20. Accessed: 5 June 2023,

9. International Society for Pharmacoepidemiology. Guidelines for good pharmacoepidemiology practices (GPP). Revision 3. June, 2015. Available at: https://www.pharmacoepi.org/resources/policies/guidelines-08027/. Accessed: 26 September 2022,

10. ENCePP. The ENCePP code of conduct for scientific independence and transparency in the conduct of pharmacoepidemiological and pharmacovigilance studies (Revision 4). 15 March 2018. Available at: http://www.encepp.eu/code_of_conduct/. Accessed: 17 January 2020.

11. Caplanusi I, Szmigiel A, van der Elst M, Schougaard Christiansen ML, Thirstrup S, Zaccaria C, et al. The role of the European Medicines Agency in the safety monitoring of COVID-19 vaccines and future directions in enhancing vaccine safety globally. Drug Saf. 2024;47(5):405–18.

12. Information available upon request.

13. Wasserstein RL, Lazar NA. The ASA statement on p-Values: Context, process, and purpose. The American Statistician. 2016;70(2):129–33.

14. ICMJE. Recommendations for the conduct, reporting, editing, and publication of scholarly work in medical journals. April 2025, 2025. Available at: https://www.icmje.org/recommendations/. Accessed: 30 July 2025,

15. Deeks J, Higgins J, Altman D, Cochrane Statistical Methods Group. Chapter 10: Analysing data and undertaking meta-analyses. In: Higgins J, Thomas J, Chandler J, Cumpston M, Li T, Page M, et al., editors. Cochrane Handbook for Systematic Reviews of Interventions version 64 (updated August 2023); 2023.

16. Deeks J, Higgins J, Altman D, McKenzie J, Veroniki A. Section 10.10.2 Identifying and measuring heterogeneity. 2024. Available at: https://www.cochrane.org/authors/handbooks-and-manuals/handbook/current/chapter-10#section-10-10-2. Accessed: 22 Aaugust 2025,

17. Imai N, Rawson T, Knock ES, Sonabend R, Elmaci Y, Perez-Guzman PN, et al. Quantifying the effect of delaying the second COVID-19 vaccine dose in England: a mathematical modelling study. Lancet Public Health. 2023;8(3):e174–e83.

18. Saine ME, Carbonari DM, Newcomb CW, Gallagher AM, Blak BT, Roy JA, et al. Concordance of hospitalizations between Clinical Practice Research Datalink and linked Hospital Episode Statistics among patients treated with oral antidiabetic therapies. Pharmacoepidemiol Drug Saf. 2019;28(10):1328–35.

19. Bots SH, Riera-Arnau J, Belitser SV, Messina D, Aragón M, Alsina E, et al. Myocarditis and pericarditis associated with SARS-CoV-2 vaccines: A population-based descriptive cohort and a nested self-controlled risk interval study using electronic health care data from four European countries. Front Pharmacol. 2022;13:1038043.

20. Karlstad Ø, Hovi P, Husby A, Härkänen T, Selmer RM, Pihlström N, et al. SARS-CoV-2 vaccination and myocarditis in a Nordic cohort study of 23 million residents. JAMA Cardiol. 2022;7(6):600–12.

21. Morciano C, Spila Alegiani S, Menniti Ippolito F, Belleudi V, Trifirò G, Zanoni G, et al. Post-marketing active surveillance of Guillain Barré Syndrome following COVID-19 vaccination in persons aged ⩾12 years in Italy: A multi-database self-controlled case series study. PLoS One. 2024;19(1):e0290879.

22. Stowe J, Miller E, Andrews N, Whitaker HJ. Risk of myocarditis and pericarditis after a COVID-19 mRNA vaccine booster and after COVID-19 in those with and without prior SARS-CoV-2 infection: A self-controlled case series analysis in England. PLoS Med. 2023;20(6):e1004245.

23. Kitano T, Salmon DA, Dudley MZ, Saldanha IJ, Thompson DA, Engineer L. Age- and sex-stratified risks of myocarditis and pericarditis attributable to COVID-19 vaccination: a systematic review and meta-analysis. Epidemiol Rev. 2025;47(1):1–11.

24. Rothman KJ, Greenland S. Validity and generalizability in epidemiologic studies. In: Wiley StatsRef: Statistics Reference Online. Available at: https://onlinelibrary.wiley.com/doi/abs/10.1002/9781118445112.stat05223.

25. Shimabukuro T, Nair N. Allergic reactions including anaphylaxis after receipt of the first dose of Pfizer-BioNTech COVID-19 vaccine. Jama. 2021;325(8):780–1.

26. Centres for Disease Control and Prevention. Allergic reactions including anaphylaxis after receipt of the first dose of Pfizer-BioNTech COVID-19 vaccine - United States, December 14-23, 2020. MMWR Morb Mortal Wkly Rep. 2021;70(2):46–51.

27. Moulis G, Crickx E, Thomas L, Massy N, Mahévas M, Valnet-Rabier MB, et al. De novo and relapsed immune thrombocytopenia after COVID-19 vaccines: results of French safety monitoring. Blood. 2022;139(16):2561–5.

28. Ghosh AK, Bhushan S, Lopez LDR, Sampat D, Salah Z, Hatoum CA. BNT162b2 COVID-19 Vaccine induced immune thrombocytopenic purpura. Case Rep Med. 2022;2022:5603919.

29. Akiyama H, Kakiuchi S, Rikitake J, Matsuba H, Sekinada D, Kozuki Y, et al. Immune thrombocytopenia associated with Pfizer-BioNTech's BNT162b2 mRNA COVID-19 vaccine. IDCases. 2021;25:e01245.

30. Li X, Burn E, Duarte-Salles T, Yin C, Reich C, Delmestri A, et al. Comparative risk of thrombosis with thrombocytopenia syndrome or thromboembolic events associated with different covid-19 vaccines: international network cohort study from five European countries and the US. BMJ. 2022;379:e071594.

31. Fornara L, Musetti C, Guglielmetti G, Cantaluppi V. MO208: De Novo glomerulonephritides following BNT162B2 COVID-19 vaccine: A case series. Nephrology Dialysis Transplantation. 2022;37(Supplement_3).

32. Saleh W, Alharbi H, Cha S. Increased prevalence of erythema multiforme in patients with COVID-19 infection or vaccination. Sci Rep. 2024;14(1):2801.

33. European Medicines Agencies. Meeting highlights from the Pharmacovigilance Risk Assessment Committee (PRAC) 24 - 27 October 2022. 2022. Available at: https://www.ema.europa.eu/en/news/meeting-highlights-pharmacovigilance-risk-assessment-committee-prac-24-27-october-2022. Accessed: 30 July 2025,

34. European Medicines Agencies. Signal assessment report on heavy menstrual bleeding with tozinameran / Comirnaty (COVID-19 mRNA vaccine). EPITT no: 19783, Procedure no: SDA 053.1. 2022. Available at: https://www.ema.europa.eu/en/documents/prac-recommendation/signal-assessment-report-heavy-menstrual-bleeding-tozinameran-comirnaty-covid-19-mrna-vaccine_en.pdf. Accessed: 30 July 2025,

35. Smaardijk VR, Jajou R, Kant A, van Hunsel FPAM. Menstrual disorders following COVID-19 vaccination: a review using a systematic search. Frontiers in Drug Safety and Regulation. 2024;Volume 4 - 2024.

36. European Medicines Agencies. Meeting highlights from the Pharmacovigilance Risk Assessment Committee (PRAC) 7-10 June 2022. 2022. Available at: https://www.ema.europa.eu/en/news/meeting-highlights-pharmacovigilance-risk-assessment-committee-prac-7-10-june-2022. Accessed: 2 August 2025,

37. European Medicines Agencies. COMIRNATY : Periodic safety update report assessment. 19 June 2023 to 18 December 2023. 2024. Available at: https://www.ema.europa.eu/en/documents/covid-19-vaccine-safety-update/comirnaty-periodic-safety-update-report-assessment-19-june-2023-18-december-2023_en.pdf. Accessed: 2 August 2025,

38. World Health Organization (WHO). GACVS COVID-19 Vaccine Safety subcommittee meeting to review reports of deaths of very frail elderly individuals vaccinated with Pfizer BioNTech COVID-19 vaccine, BNT162b2. 2021. Accessed: 2 August 2025,

39. Law B. Second update - Priority list of adverse events of special interest: COVID-19. Zenodo. 2021. Accessed: 2 August 2025,

40. Paknahad MH, Yancheshmeh FB, Soleimani A. Cardiovascular complications of COVID-19 vaccines: A review of case-report and case-series studies. Heart Lung. 2023;59:173–80.

41. Xu Y, Li H, Santosa A, Wettermark B, Fall T, Björk J, et al. Cardiovascular events following coronavirus disease 2019 vaccination in adults: a nationwide Swedish study. Eur Heart J. 2025;46(2):147–57.

42. Ippolito S, Gallo D, Rossini A, Patera B, Lanzo N, Fazzino GFM, et al. SARS-CoV-2 vaccine-associated subacute thyroiditis: insights from a systematic review. J Endocrinol Invest. 2022;45(6):1189–200.

43. Mochizuki S, Miura J, Ucida K, Kubota R, Fujikawa H, Takagi S, et al. Type 1 diabetes mellitus following COVID-19 vaccination: a report of two cases and review of literature. Diabetol Int. 2024;15(3):577–82.

44. Cheah M, Girgis S, Bain VG. Acute hepatitis following mRNA BNT162b2 COVID-19 vaccination. Canadian Liver Journal. 2022;5(4):535–9.

45. Pinazo-Bandera JM, Hernández-Albújar A, García-Salguero AI, Arranz-Salas I, Andrade RJ, Robles-Díaz M. Acute hepatitis with autoimmune features after COVID-19 vaccine: coincidence or vaccine-induced phenomenon? Gastroenterol Rep (Oxf). 2022;10:goac014.

46. Efe C, Kulkarni AV, Terziroli Beretta-Piccoli B, Magro B, Stättermayer A, Cengiz M, et al. Liver injury after SARS-CoV-2 vaccination: Features of immune-mediated hepatitis, role of corticosteroid therapy and outcome. Hepatology. 2022;76(6):1576–86.

47. Annicchiarico Petruzzelli L, Minale B, Serio V, De Luca A, Marino Marsilia G, Campione S, et al. Pediatric Minimal Change Disease and AKI following the Pfizer-BioNTech COVID-19 Vaccine: causal or incidental correlation? G Ital Nefrol. 2022;39(6).

48. Luo H, Li X, Ren Q, Zhou Y, Chen G, Zhao B, et al. Acute kidney injury after COVID-19 vaccines: a real-world study. Ren Fail. 2022;44(1):958–65.

49. Hussain A, Augustine SW, Pyakurel S, Vempalli H, Dabbara R, O'Dare R A, et al. Acute pancreatitis induced by COVID-19 vaccine: A systematic review. Cureus. 2024;16(3):e55426.

50. Banamah TA, Bogari AA, Neyazi A, Kotbi E, Almaghraby H, Atwah F. Severe Rhabdomyolysis Complicated With Acute Kidney Injury Required Renal Replacement Therapy After Pfizer COVID-19 Vaccine Cureus. 2022;14(5):e25199.

51. Nassar M, Chung H, Dhayaparan Y, Nyein A, Acevedo BJ, Chicos C, et al. COVID-19 vaccine induced rhabdomyolysis: Case report with literature review. Diabetes Metab Syndr. 2021;15(4):102170.

52. Ruijters VJ, van der Meulen MFG, van Es MA, Smit T, Hoogendijk JE. Rhabdomyolysis after COVID-19 Comirnaty vaccination: A case report. Case Rep Neurol. 2022;14(3):429–32.

53. Nabizadeh F, Noori M, Rahmani S, Hosseini H. Acute disseminated encephalomyelitis (ADEM) following COVID-19 vaccination: A systematic review. J Clin Neurosci. 2023;111:57–70.

54. Shahsavarinia K, Mahmoodpoor A, Sadeghi-Ghyassi F, Nedayi A, Razzaghi A, Zehi Saadat M, et al. Bell's Palsy and COVID-19 Vaccination: A Systematic Review. Med J Islam Repub Iran. 2022;36:85.

55. Wan EYF, Ng VWS, Chang RS, Yan VKC, Chui CSL, Wong CKH, et al. Association between the risk of seizure and COVID-19 vaccinations: A self-controlled case-series study. Epilepsia. 2022;63(12):3100–10.

56. Shemer A, Pras E, Einan-Lifshitz A, Dubinsky-Pertzov B, Hecht I. Association of COVID-19 Vaccination and Facial Nerve Palsy: A Case-Control Study. JAMA Otolaryngol Head Neck Surg. 2021;147(8):739–43.

57. Dutch Pharmocovigilance Service (bijwerkingen centrumlarb). Overview of Bell's palsy associated with COVID-19 vaccines. 2022. Available at: https://www.lareb.nl/media/dy2cc2b3/signals_2022_covid-19-vaccines-and-bell-s-palsy.pdf. Accessed: 2 August 2025,

58. de Gregorio C, Colarusso L, Calcaterra G, Bassareo PP, Ieni A, Mazzeo AT, et al. Cerebral Venous Sinus Thrombosis following COVID-19 Vaccination: Analysis of 552 Worldwide Cases. Vaccines (Basel). 2022;10(2).

59. Walton M, Tomkies R, Teunissen T, Lumley T, Hanlon T. Thrombotic events following the BNT162b2 mRNA COVID-19 vaccine (Pfizer-BioNTech) in Aotearoa New Zealand: A self-controlled case series study. Thrombosis Research. 2023;222:102–8.

60. Censi S, Bisaccia G, Gallina S, Tomassini V, Uncini A. Guillain-Barré syndrome and COVID-19 vaccination: a systematic review and meta-analysis. J Neurol. 2024;271(3):1063–71.

61. Nguyen S, Bastien E, Chretien B, Sassier M, Defer G, Nehme A, et al. Transverse Myelitis Following SARS-CoV-2 Vaccination: A Pharmacoepidemiological Study in the World Health Organization's Database. Ann Neurol. 2022;92(6):1080–9.

62. Dutch Pharmocovigilance Service (bijwerkingen centrumlarb). Overview of transverse myelitis after COVID-19 vaccination. 2023. Available at: https://www.lareb.nl/Knowledge/FilePreview?id=42797&p=33550. Accessed: 2 August 2025,

63. Mahamid A, Bornstein RJ, Amir H. Pfizer/BioNTech SARS-CoV-2 vaccine as a potential trigger for the development of narcolepsy: a case report. J Clin Sleep Med. 2022;18(10):2503–6.

64. Russo R, Cozzani E, Micalizzi C, Parodi A. Chilblain-like Lesions after COVID-19 Vaccination: A Case Series. Acta Derm Venereol. 2022;102:adv00711.

65. Shaikh TG, Waseem S, Ahmed SH, Qadir NA, Piccolo V. SARS-CoV-2 vaccination and chilblain-like lesions: What do we know so far? Dermatol Pract Concept. 2022;12(4):e2022170.

66. Colia R, Rotondo C, Corrado A, Cantatore FP. Cutaneous vasculitis after severe acute respiratory syndrome coronavirus 2 vaccine. Rheumatol Adv Pract. 2021;5(3):rkab050.

67. Ding C, Liu Y, Pang W, Zhang D, Wang K, Chen Y. Associations of COVID-19 vaccination during pregnancy with adverse neonatal and maternal outcomes: A systematic review and meta-analysis. Front Public Health. 2023;11:1044031.

68. Marchand G, Patil AS, Masoud AT, Ware K, King A, Ruther S, et al. Systematic review and meta-analysis of COVID-19 maternal and neonatal clinical features and pregnancy outcomes up to June 3, 2021. AJOG Glob Rep. 2022;2(1):100049.

69. European Medicines Agencies. Meeting highlights from the Pharmacovigilance Risk Assessment Committee (PRAC) 5-8 July 2021. 2021. Available at: https://www.ema.europa.eu/en/news/meeting-highlights-pharmacovigilance-risk-assessment-committee-prac-5-8-july-2021. Accessed: 28 August 2025,

70. Barda N, Dagan N, Ben-Shlomo Y, Kepten E, Waxman J, Ohana R, et al. Safety of the BNT162b2 mRNA COVID-19 vaccine in a nationwide setting. N Engl J Med. 2021;385(12):1078–90.

71. ECDC. Overview of the implementation of COVID-19 vaccination strategies and deployment plans in the EU/EEA. 8 September 2022. 2022. Available at: https://www.ecdc.europa.eu/sites/default/files/documents/Overview-vaccination-strategies-COVID-19-8-September-2022.pdf. Accessed: 4 August 2024,

72. Gallagher AM, Dedman D, Padmanabhan S, Leufkens HGM, de Vries F. The accuracy of date of death recording in the Clinical Practice Research Datalink GOLD database in England compared with the Office for National Statistics death registrations. Pharmacoepidemiology and Drug Safety. 2019;28(5):563–9.

73. Durán CE, Messina D, Gini R, Riefolo F, Aragón M, Belitser S, et al. Rapid safety assessment of SARS-CoV-2 Vaccines in EU Member States using electronic health care data sources (COVID Vaccine Monitor-CVM study): Final study report for WP3 (electronic health record data) (1.2). Zenodo. . 2023. Available at: https://doi.org/10.5281/zenodo.8280175. Accessed: 15 September 2023,

74. JA A, T E, RD F. The rise of mRNA COVID-19 vaccine-associated myocarditis and its implications on the future use of this new vaccine platform. Cureus. 2022;14(6):e25631.

75. Massari M, Spila Alegiani S, Morciano C, Spuri M, Marchione P, Felicetti P, et al. Postmarketing active surveillance of myocarditis and pericarditis following vaccination with COVID-19 mRNA vaccines in persons aged 12 to 39 years in Italy: A multi-database, self-controlled case series study. PLoS Med. 2022;19(7):e1004056.

76. de Vries E, Denig P, Monster TBM, Mol PGM. Mixed impact of direct healthcare professional communications when considering proximal outcomes and the targeted population: A systematic review. Pharmacoepidemiol Drug Saf. 2025;34(3):e70135.

77. Wei JJ, Lin EX, Shi JD, Yang K, Hu ZL, Zeng XT, et al. Meta-analysis with zero-event studies: a comparative study with application to COVID-19 data. Mil Med Res. 2021;8(1):41.

## 15. LIST OF SOURCE TABLES AND FIGURES

Standalone document.

# Document Approval Record

| | |
|---|---|
| **Document Name:** | C4591021 Final Non-Interventional Study Report |
| **Document Title:** | C4591021 |

| Signed By: | Date(GMT) | Signing Capacity |
|---|---|---|
| Younus, Muhammad | 15-Sep-2025 12:05:11 | Final Approval |
| De Bernardi, Barbara | 15-Sep-2025 13:59:41 | EUQPPV Approval |