NON-INTERVENTIONAL (NI) STUDY
INTERIM REPORT 5

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 interim study report	V1.0
Date	12 March 2024
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)
Marketing Authorization Holder (MAH)	BioNTech Manufacturing GmbH
Joint PASS	No
Research question and objectives	The research question addressed by this study is: Is there an increased risk of select adverse events of special interest (AESI) after being vaccinated with the Pfizer-BioNTech COVID-19 vaccine?

	Objectives ***Primary study objective*** To determine whether an increased risk of prespecified AESI exists following the administration of at least one dose of the Pfizer-BioNTech COVID-19 vaccine using two approaches: (a) a cohort design comparing risk in vaccinated and unvaccinated individuals and (b) a self-controlled risk interval (SCRI) design. ***Secondary study objectives*** • To estimate the incidence rates of prespecified AESI among individuals who receive at least one dose of the Pfizer-BioNTech COVID-19 vaccine using a cohort study design. • To describe the incidence rates and determine whether an increased risk of prespecified AESI exists following the administration of at least one dose of the Pfizer-BioNTech COVID-19 vaccine compared with a matched comparator group with no COVID-19 vaccination within subcohorts of interest (i.e., individuals who are immunocompromised, individuals who are frail and have comorbidities, individuals diagnosed with previous COVID-19 infection, and age-specific groups) in Europe using a cohort study design and/or a SCRI design. • To determine whether an increased risk of prespecified AESI exists following the administration of at least one dose of the Pfizer-BioNTech COVID-19 vaccine compared with no COVID-19 vaccination, in pregnant people and their neonates using a cohort study design. To characterise utilisation patterns of Pfizer-BioNTech COVID-19 vaccine among individuals within Europe, including estimating the proportion of individuals

	receiving the vaccine; two-dose vaccine completion rate and distribution of time gaps between the first and second doses; and demographics and clinical characteristics of recipients, overall and among subcohorts of interest, such as individuals who are immunocompromised, elderly, or have specific comorbidities.
Country(-ies) of study	The Netherlands (NL), Norway (NO), Italy (IT), Spain (ES), United Kingdom (UK)
Author	4.1(b) [redacted] University Medical Center Utrecht AND 4.1(b) [redacted] RTI Health Solutions On behalf of the Vaccine Monitoring Collaboration for Europe (VAC4EU) Consortium research team

Marketing Authorization Holder(s)

Marketing Authorization Holder(s)	BioNTech Manufacturing GmbH An der Goldgrube 12 55131 Mainz Germany
MAH contact person	4.1(b) [redacted]

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Not applicable.

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Not applicable.

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Not applicable.

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1. ABSTRACT (STAND-ALONE DOCUMENT)

2. LIST OF ABBREVIATIONS

Abbreviation	Definition
ACCESS project	vACcine Covid-19 monitoring readinESS
AESI	Adverse event of special interest
ARS Toscana	Agenzia Regionale di Sanita' della Toscana (a research institute of the Tuscany region of Italy)
ATC	Anatomical Therapeutic Chemical (classification system)
BDU	User database at EpiChron
BIFAP	Base de Datos para la Investigación Farmacoepidemiológica en Atención Primària (a data resource for pharmacoepidemiology in Spain)
CDM	Common data model
CHESS	COVID-19 Hospitalisation in England Surveillance System (UK)
CI	Confidence interval
COVID-19	Coronavirus disease 2019
CPRD Aurum	Clinical Practice Research Datalink Aurum
DAP	Database access provider
DRE	Digital Research Environment (NL)
DSRU	Drug Safety Research Unit (UK)
DTP	Diphtheria, tetanus, and pertussis vaccine
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EpiChron	EpiChron Research Group on Chronic Diseases at the Aragon Health Sciences Institute (Spain)
ES	Spain
ETL	Extraction, transformation, and loading (a process for putting data into a common data model)
EU PAS Register	European Union electronic register of post-authorisation studies
EU	European Union
FDA	Food and Drug Administration

Abbreviation	Definition
GP	General practitioner
GPP	Good Pharmacoepidemiology Practices
GVP	Good Pharmacovigilance Practices
HSD	Health Search Database (Italy)
ICD	International Classification of Diseases
ICD-9-CM	International Classification of Diseases, 9th Revision, Clinical Modification
ICD-10	International Classification of Diseases, 10th Revision
ICNARC	Intensive Care National Audit and Research Centre
ICPC	International Classification of Primary Care
IR	Incidence rate
ISPE	International Society for Pharmacoepidemiology
IT	Italy
KM	Kaplan-Meier
MAH	Marketing authorisation holder
MBRN	Medical Birth Registry of Norway
mRNA	Messenger RNA
MSIS	Norwegian Surveillance System for Communicable Diseases
NHS	National Health Service (UK)
NIPH	Norwegian Institute of Health
NL	Netherlands
NO	Norway
NPR	National Patient Register (Norway)
ONS	Office for National Statistics
PASS	Post-authorisation safety study
PHARMO	PHARMO Institute for Drug Outcomes Research or PHARMO Data Network (Netherlands)
PHE	Public Health England
PMR	postmarketing requirement
PS	Propensity score
QC	Quality control

Abbreviation	Definition
RTI-HS	RTI Health Solutions
SAP	Statistical analysis plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2 (cause of COVID-19 disease)
SCRI	Self-controlled risk interval (study design)
SIDIAP	Sistema d'Informació per el Desenvolupament de la Investigació en Atenció Primària [Information System for the Improvement of Research in Primary Care] (Spain)
SQL	Structured Query Language
SSB	Statistics Norway
SGSS	Second Generation Surveillance System
SYSVAK	National, electronic immunisation register
TMS	Task management system
UK	United Kingdom
UMCU	University Medical Center Utrecht
USA	United States of America
VAC4EU	Vaccine monitoring Collaboration for Europe
VV	Varicella zoster virus
WHO	World Health Organization

3. INVESTIGATORS

Principal Investigator(s) of the Protocol

Name, degree(s)	Job Title	Affiliation
4.1(b)	4.1(b)	Pfizer, Inc.
Daniel Weibel, PhD	Assistant Professor	University Medical Center Utrecht
Alejandro Arana, MD, MPH	Senior Director, Epidemiology	RTI Health Solutions
4.1(b)	4.1(b)	University Medical Center Utrecht
4.1(b)	4.1(b)	RTI Health Solutions
4.1(b)	4.1(b)	RTI Health Solutions
4.1(b)	4.1(b)	RTI Health Solutions
4.1(b)	4.1(b)	RTI Health Solutions
4.1(b)	4.1(b)	RTI Health Solutions

Lead Country Investigator(s) of the Protocol

Name, degree(s)	Title	Affiliation
Rosa Gini, PhD	Head Pharmacoepidemiology Unit	Agenzia regionale di sanità della Toscana
Francesco Lapi PhD	Director	Health Search Research
4.1(b)	4.1(b)	PHARMO Institute for Drug Outcomes Research
Jetty Overbeek, PhD	Head of PHARMO Research	
4.1(b)	4.1(b)	
4.1(b)	4.1(b)	
4.1(b)	4.1(b)	
Carlo Giaquinto, MD	President	Fondazione Penta ETS

Name, degree(s)	Title	Affiliation
Saad Shakir, MB ChB, LRCP&S, FRCP, FFPM, FISPE, MRCGP	Director	Drug Safety Research Unit (DSRU)
4.1(b)	4.1(b)	
4.1(b)	4.1(b)	
4.1(b)	4.1(b)	
4.1(b)	4.1(b)	
4.1(b)	4.1(b)	
Antonio Gimeno-Miguel, MPH, PhD	Researcher	EpiChron Research Group. Instituto Aragonés de Ciencias de la Salud
4.1(b)	4.1(b)	
Felipe Villalobos, MD, PhD	Researcher	IDIAP-Jordi Gol
4.1(b)	4.1(b)	
4.1(b)	4.1(b)	
4.1(b)	4.1(b)	
Angela Lupattelli, PhD	Professor	University of Oslo
4.1(b)	4.1(b)	
4.1(b)	4.1(b)	
4.1(b)	4.1(b)	

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 SAB; Support for: • contract templates; negotiations, and contract amendments; • archiving of study documents; support quality system oversight and implementation Support and implementation of tools (e.g., DRE, TMS, ETL specifications; CDM, Catalogue); Scientific review
4.1(b) [redacted], National Taiwan University Children's Hospital, Taipei, Taiwan	Scientific Advisory Board member
4.1(b) [redacted] London School of Hygiene and Tropical Medicine, United Kingdom	Scientific Advisory Board member
4.1(b) [redacted], BioNTech Manufacturing GmbH	MAH contact person
4.1(b) [redacted], Teamit Institute S.L	Programme Manager
4.1(b) [redacted], Teamit Institute S.L	Study Manager
4.1(b) [redacted], 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	31 March 2024		
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	12 March 2024	
Final study report[2]	20 December 2024		

1 Data were not provided in the progress report
2 Pending approval from EMA

6. RATIONALE AND BACKGROUND

The novel coronavirus, SARS-CoV-2, the cause of COVID-19, has resulted in a global pandemic. The Pfizer-BioNTech COVID-19 vaccine, tozinameran (Comirnaty®) a novel mRNA-based vaccine, has been authorised for use in several countries, including those in the European Union (EU), for the prevention of COVID-19. 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 will be needed in European countries.

The safety of the Pfizer-BioNTech COVID-19 vaccine has been investigated in clinical studies conducted in the United States, Europe, Turkey, South Africa, and South America and included over 43,000 patients aged 16 years and older. The overall safety profile of the vaccine was found to be favourable in the trial setting. Reported adverse reactions from unblinded data (i.e., from the overall trial population) on participants aged 16 years and older who received two doses of Pfizer-BioNTech COVID-19 vaccine 21 days apart after 2 months of follow-up included pain at the injection site (84.1%), fatigue (62.9%), headache (55.1%), muscle pain (38.3%), chills (31.9%), joint pain (23.6%), fever (14.2%), injection site swelling (10.5%), injection site redness (9.5%), nausea (1.1%), malaise (0.5%), and lymphadenopathy (0.3%). The safety database revealed an imbalance of cases of Bell's palsy (four in the vaccine group and none in the placebo group).[1] Severe allergic reactions have been reported following receipt of the Pfizer-BioNTech COVID-19 vaccine in mass vaccination campaigns outside clinical trials in various countries. Additional safety events may become evident with more widespread use in the general population.

Public health authorities identified priority populations for vaccination based on health care or essential worker status, comorbidities, and age and therefore the vaccine was initially provided to vulnerable groups at higher risk for COVID-19 infection and COVID-19 complications.[2] As recommendations for vaccination were updated over time, the characteristics of vaccine recipients varied over time.

This non-interventional study was designated as a Post-Authorization Safety Study (PASS) and is a commitment to EMA and a postmarketing requirement to the Food and Drug Administration.

7. RESEARCH QUESTION AND OBJECTIVES

Research question: Is there an increased risk of select adverse events of special interest (AESI) 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 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.

7.1.2. Secondary study objectives

- To estimate the incidence rates of prespecified AESI among individuals who receive at least one dose of the Pfizer-BioNTech COVID-19 vaccine using a cohort study design.

- To describe the incidence rates and determine whether an increased risk of prespecified AESI exists following the administration of at least one dose of the Pfizer-BioNTech COVID-19 vaccine compared with no COVID-19 vaccination within sub-cohorts of interest (i.e., individuals who are immunocompromised, individuals who are frail and have comorbidities, individuals diagnosed with previous COVID-19 infection, and age-specific groups) in Europe using a cohort study design and/or a SCRI design.

- To determine whether an increased risk of prespecified AESI exists following the administration of at least one dose of the Pfizer-BioNTech COVID-19 vaccine compared with no COVID-19 vaccination, in pregnant people and their neonates using a cohort study design.

- To characterise utilisation patterns of Pfizer-BioNTech COVID-19 vaccine among individuals within Europe, including estimating the proportion of individuals receiving the vaccine; two-dose vaccine completion rate and distribution of time gaps between the first and second doses; and demographics and clinical characteristics of recipients, overall and among 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

A summary of the protocol amendments is provided in Table 1 below.

Table 1. Amendments to the protocol

Amendment number	Date	Section of protocol changed	Summary of amendment/update	Reason
4	18 October 2023	4. Abstract and 6. Milestones	Extended final study report timeline to 20 December 2024	Moved 3 months forward to avoid overlap with the production of study 1038 (Natural history of myocarditis) final report and 1052 (safety of the bivalent PFE vaccine) first interim report. These 3 studies share resources and avoiding overlap will impact positively in the quality of the report.

Table 1. Amendments to the protocol

Amendment number	Date	Section of protocol changed	Summary of amendment/update	Reason
4	18 October 2023	9.3.2.1 Safety Outcomes	New AESIs added to Table 2: myositis, hypermenorrhoea, glomerulonephritis and cerebral venous sinus thrombosis	Request from European Medicines Agency (EMA) and to align AESIs with Pfizer-BioNTech COVID-19 bivalent study C4591052
4	18 October 2023	9.3.2.1 Safety Outcomes	VAED changed to severe COVID-19 defined as either COVID-19 hospitalisation or death	Updated to provide clarity
4	18 October 2023	9.3.2.1 Safety Outcomes Table 2	Risk windows modified to remove 1	Updated for accuracy and clarity
4	18 October 2023	9.3.3 Covariate Definitions	The covariates, race and/or ethnicity, residency in a long-term care facility, healthcare work or essential worker status, skilled nursing facility, nursing home, or extended care facility stay, wheelchair use, home hospital bed, home oxygen, rehabilitation care were removed	These covariates are not available in any of the study data sources
4	18 October 2023	9.3.3 Covariate Definitions	The covariate, CDC at-risk groups was added	This covariate is employed as a matching variable
4	18 October 2023	9.3.3 Covariate Definitions	Paragraph on at-risk medical conditions for developing severe COVID-19 was added to define the covariate, CDC at-risk groups	This covariate was added to the list of covariates and is employed as a matching variable
4	18 October 2023	9.5 Study Size	VAED in study size calculations changed to severe COVID-19	Updated for consistency with AESI definitions in Table 2
4	18 October 2023	9.7.1 Cohort design and 9.7.2 Comparison with historical comparators	Sections; Comparison with historical comparators, and Time trends in AESI in pre-pandemic, post-pandemic, and post-vaccination periods have been further developed and clarified Section on age-standardised outcome measures removed from the Cohort design section	Updated to provide clarity
4	18 October 2023	9.7.4	Stratification by age of reporting of cardiac MRI and	Request from European Medicines Agency (EMA)

Table 1. Amendments to the protocol

Amendment number	Date	Section of protocol changed	Summary of amendment/update	Reason
			echocardiogram by age added Discussion of the interpretation of results and conclusions on effectiveness of DHCP letter added	
3	11 April 2023	General	Administrative, formatting, and typographical corrections have been made	Updated to provide clarity and to be consistent with remainder of protocol
3	11 April 2023	3 Responsible parties	Updated degree(s) and added Other Responsible Parties Contributing to the Protocol	Added missing degree information and missing Other Responsible Parties
3	11 April 2023	7 Rationale and background 8.2 Objectives 9.2 Setting 9.7 Data analysis	Add new secondary objective: To describe the rate of cardiac imaging use among vaccinated and unvaccinated individuals each calendar month of the study period, before and after distribution of the DHPC letter	Request from EMA
3	11 April 2023	9.4.1 Exposure definitionerr 9.5 CPRD	Update sources of data for CPRD	Some COVID-19 specific databases linked to CPRD were identified as not necessary to obtain study variables based on recent experience in the study
3	11 April 2023	9.3.2.1 Safety outcomes	New AESI added: secondary amenorrhoea	Request from European Medicines Agency (EMA)
3	11 April 2023	9.3.2.1 Safety outcomes	COVID-19 disease removed as a safety outcome	COVID-19 disease is not an AESI and COVID-19 testing is not systematically performed in the healthcare systems of the study data sources
3	11 April 2023	9.3.2.1 Safety outcomes	Table 1, AESI 'Thrombocytopenia with venous thromboembolism' was removed and the AESI 'Heparin-induced thrombocytopenia (HIT)-like event' was renamed 'Thrombosis thrombocytopenia syndrome (TTS)'	These three events are equivalent and have the same definition, but TTS is the preferred name
3	11 April 2023	9.3.2.2 Outcome identification	Add description of the validation process for HSD	This was previously combined with the description for Pedianet

Table 1. Amendments to the protocol

Amendment number	Date	Section of protocol changed	Summary of amendment/update	Reason
		and validation, by data source		
3	11 April 2023	9.3.2.3 Cardiac imaging	Cardiac imaging defined	Needed for the added secondary objective.
3	11 April 2023	9.4.3 Covariate definition	Covariate definition will be updated to the following age groups: 0-1, 2-4, 5-11, 12-15, 16-17,18-29, 30-39, 40-49, 50-59, 60-64, 65-69, 70-79, and 80+ years.	These categories were chosen to align with age groups as authorized and prioritized during vaccine rollout indications of the vaccine in children younger than 16 years old
3	11 April 2023	9.4 Data sources	Re-ordered data sources to be consistent with order in other studies	Consistency
3	11 April 2023	9.4.4 PHARMO	Update sources of data for PHARMO	Outpatient Pharmacy Database will not be used
2	31 March 2022	6 Milestones	Added study end date of 31 December 2023	To clarify that the last date of data available will be 31 December 2023, which differs from the end of data collection date that takes into account lag times
2	31 March 2022	9.1.1.1 Matching process	Added that one individual will be randomly selected if multiple individuals match a vaccinated individual	To clarify how multiple matches will be handled
2	31 March 2022	9.2.2.1 Cohort and SCRI designs	Removed the exclusion criterion, 'Have contact with the healthcare system in the 7 days before time zero'	Request from EMA
2	31 March 2022	9.2.3 Sensitivity analysis	Added a sensitivity analysis excluding individuals who have had contact with the healthcare system in the 7 days before time zero	Request from EMA to remove from main analysis and add as a sensitivity analysis
2	31 March 2022	9.2.5 Study period	Added 2018-2019 as a historical period	To assess time trends in health seeking behaviour
2	31 March 2022	9.3.2.1 Safety outcomes	Added an additional risk window of 1-21 days for myocarditis and pericarditis	Request from EMA
2	31 March 2022	9.3.2.1 Safety outcomes	Added thrombocytopenia with venous thromboembolism	This outcome is an important AESI to include in the study

Table 1. Amendments to the protocol

Amendment number	Date	Section of protocol changed	Summary of amendment/update	Reason
2	31 March 2022	9.3.2.1 Safety outcomes	Modified risk intervals and preferred study design for various outcomes	To align with the latest version of the SAP
2	31 March 2022	9.3.3 Covariate definitions	Combined the age category of 18-19 years with the adult age category, yielding a category 18-29 years	To align with the latest version of the SAP
2	31 March 2022	9.3.3 Covariate definitions	Removed 'batch of vaccine received' from the list of covariates	This variable will not be informative for the planned analyses because only the effect of the vaccine as a whole, and not by batches, is being investigated
2	31 March 2022	9.7.1.5 Age-standardised outcome measures	Added quarterly calculation of crude and age-standardised incidence rates of AESIs in a historical period of 2018-2019 and during the post-vaccination follow-up period; rates in these periods will be compared	To include a calculation of background rates of AESIs in each data source
2	31 March 2022	10.4 Ethical conduct of the study	Removed Good Epidemiological Practice guidelines issued by the International Epidemiological Association	Guidelines no longer available
2	31 March 2022	11 Management and reporting of adverse events / adverse reactions	Updated name of training	To reflect current training name
2	31 March 2022	General	Minor administrative, formatting, and typographical changes have been made	Updated to provide clarity and be consistent with remainder of protocol
1	16 Decemb er 2021	3 Responsible Parties	Updated Pfizer principal investigator	New principal investigator for study
1	16 Decemb er 2021	6 Milestones	Updated end of data collection date	Incorrect date in initial protocol
1	16 Decemb er 2021	9.1.1.1 Matching process	Updated figure Figure 1	The "V" to symbolise time of vaccination was moved to be consistent with the timeline in the figure. Also the label "patient" was changed to

Table 1. Amendments to the protocol

Amendment number	Date	Section of protocol changed	Summary of amendment/update	Reason
				"person" in the figure to align with the description that appears below the figure
1	16 December 2021	9.3.1.1 Cohort design	Inclusion of addition sensitivity analysis to assess AESIs after 2nd and 3rd doses	Request from Center for Biologics Evaluation and Research (CBER) to include dose stratification
1	16 December 2021	9.3.2 Outcome definitions	Inclusion of myocarditis/pericarditis as outcome	Request from EMA/CBER to include myocarditis and pericarditis as an outcome separate from the cardiovascular composite endpoint
1	16 December 2021	9.3.3 Covariate definitions	Additional stratification of age group 0-19 years	In anticipation of future indications of the vaccine in children younger than 16 years old
1	16 December 2021	9.5 Study size	Update of the sample size calculation to the matching ratio 1:1	The matching ratio was changed from 1:4 to 1:1, and the sample size section was inadvertently not updated
1	16 December 2021	General	Minor administrative, formatting, and typographical changes have been made	Updated to provide clarity and be consistent with remainder of protocol
1	16 December 2021	9.1.1.1 Matching process	The following matching criterion was added: Socioeconomic status/education level (as available, exact matching)	Such a criterion was used in an observational study with the same objective and design as the current one
1	16 December 2021	9.1.1.1 Matching process	Matching without replacement has been changed to matching with replacement.	To address the anticipated limited number of unvaccinated individuals in certain intervals of the study period
1	16 December 2021	9.2.1.1 Cohort design	Changed inclusion criterion from "No history of vaccination with a non–Pfizer-BioNTech COVID-19 vaccine before time zero" to "No history of vaccination with a COVID-19 vaccine before time zero"	Inclusion criterion was incorrect.
1	16 December 2021	9.2.2.1 Cohort and SCRI designs	Added the following two inclusion criteria: Having contact with the healthcare system within 7 days before time zero (as an indicator of a health event not	New evidence has been published recommending these two inclusion criteria

Table 1. Amendments to the protocol

Amendment number	Date	Section of protocol changed	Summary of amendment/update	Reason
			related to subsequent vaccination that could reduce the probability of receiving the vaccine) Having a diagnosis of the specific AESI under study within 1 year before time zero (to distinguish the recording of previous events from true new events) and at any time before time zero for diabetes type 1.	
1	16 December 2021	9.9 Limitations of the research methods	Added an additional paragraph on the limitations of the matching process	To add the fact that the resulting matching process produces estimates that are the average causal effect in vaccinated. If further adjustment via inverse probability weighting is applied, because the weights are estimated and applied to the matched population, the estimated effect will still be the causal effect in a population that has the distribution of matching variables of the vaccinated.

Following final assessment of the fourth interim report by PRAC, anosmia, ageusia and severe COVID-19 have been removed from the list of AESIs reported in this fifth interim report because they are no longer considered as an important potential risk after exposure to the Pfizer-BioNTech COVID-19 vaccine. These changes will be included in the next protocol and SAP amendments.

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 safety events of interest associated with the Pfizer-BioNTech COVID-19 vaccine used a retrospective cohort design involving multiple databases (Table 2).

In addition to the cohort analysis, for a subset of the study endpoints (see Table 2), the SCRI design was also used to assess risk. The SCRI design was used to sequentially monitor the occurrence of AESIs while controlling for time-invariant confounders (such as sex, race, chronic illness, and health state).

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
Cardiovascular system	Acute cardiovascular injury	365[d]	Cohort
	Arrhythmia	365	Cohort
	Heart failure	365	Cohort
	Stress cardiomyopathy	365	Cohort
	Coronary artery disease	365	Cohort
	Myocarditis[a] Pericarditis[a] Myocarditis and pericarditis[a]	21 after each dose 14 after each dose 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	365	Cohort
Nerves and central nervous system	Generalised convulsion	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

Table 2. List of selected adverse events of special interest

Body system/ classification	Adverse event of special interest	Estimated risk window (days)*	Analytic Approach
	Sudden death	365	Cohort
Pregnancy outcome, maternal	Gestational diabetes	Any time pregnancy	Subcohort
	Preeclampsia	After 20 weeks gestation	Subcohort
	Maternal death	Any time pregnancy	Subcohort
Pregnancy outcome, neonates. Define design taking trimester into account	Foetal growth restriction	Any time pregnancy	Subcohort
	Spontaneous abortions	At termination	Subcohort
	Stillbirth	At birth	Subcohort
	Preterm birth	At preterm birth	Subcohort
	Major congenital anomalies[a]	1 year after birth	Subcohort
	Microcephaly	At birth	Subcohort
	Neonatal death	At birth	Subcohort
	Termination of pregnancy for foetal anomaly	At termination	Subcohort

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 (ie, fibromyalgia and autoimmune thyroiditis).
d Published risk and control intervals for myocarditis and pericarditis were applied to other cardiovascular conditions (ie, 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 (ie, microangiopathy, DVT, pulmonary embolus, limb ischaemia, haemorrhagic disease, DIC, chilblain-like lesions). The published risk and control intervals for KD were applied to vasculitides 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).

9.1.1. Retrospective cohort design

A retrospective cohort design was used to estimate the incidence of AESI after receipt of the vaccine. Incidence rates of prespecified AESIs among individuals who receive at least one dose of the Pfizer-BioNTech COVID 19 vaccine were calculated.

The primary objective was addressed in comparative analyses of these incidences with those the AESI incidences occurring in an unvaccinated matched comparator group.

In this retrospective cohort design, time zero was defined as the time at which the exposure status was assigned, when inclusion and exclusion criteria were applied and when study outcomes started to be counted.[5-8] Time zero in the *exposed* groups (i.e., vaccine recipients) was the day the first vaccination dose was received. Time zero in the *unexposed* group was the day when they had not received a Pfizer-BioNTech COVID-19 vaccine dose. This day was chosen by calendar matching to the time zero of the corresponding exposed

group; at each calendar day when an individual was vaccinated, those individuals who were not vaccinated that same day (time zero) or before were assigned to the unexposed group, and they were matched to the vaccinated individuals by age, sex, geographical region, previous identified COVID-19 infection, previous influenza vaccination at time zero, pregnancy, immunocompromised, CDC risk criteria and socioeconomic status/education level. Matched pair were censored if the vaccinated individual received a non-Pfizer-BioNTech COVID-19 vaccine or if the unvaccinated individual received any COVID-19 vaccine.

Despite matching for potentially relevant confounders, residual confounding can remain. Symptomatic SARS-CoV-2 infection was used as a negative control outcome, under the assumption that confounders for symptomatic SARS-CoV-2 were equally relevant for developing adverse clinical conditions. We, therefore, used 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 (Section 9.9.3) to check baseline exchangeability.

9.1.2. Self-controlled risk interval design

As an additional and complementary approach for a subset of study outcomes that were acute and meet other necessary assumptions, a SCRI design will be used in the final analysis. These assumptions will include that the outcome has an acute onset and short latency and has relatively well-known risk intervals; the design is less suited to study outcomes that affect the probability of exposure, but this potential bias was reduced by the use of a post-vaccination control interval.

Vaccine exposure is known to be challenging to measure, particularly in a pandemic setting where vaccines may be administered outside the usual health care system. Often, this results in under-ascertainment of exposure and the inclusion of exposed persons in the unexposed cohort. This under ascertainment of exposure could result in a bias towards the null if the vaccine does increase the risk of an event. As the SCRI design includes only people with known vaccine exposure, it is not subject to this bias.

The SCRI design will compare the risk of each outcome during a prespecified period following each dose during which there is a hypothetical increased risk of the outcome (‘risk interval’) with a self-matched control interval, used to assess the baseline risk of the outcome.

The SCRI design will be performed in the overall vaccinated population, including among vaccinated individuals not included in the retrospective cohort analysis because a matching comparator was not found. This design will serve as a sensitivity analysis and will enable the evaluation of the exclusion of unmatched pairs from the analysis.

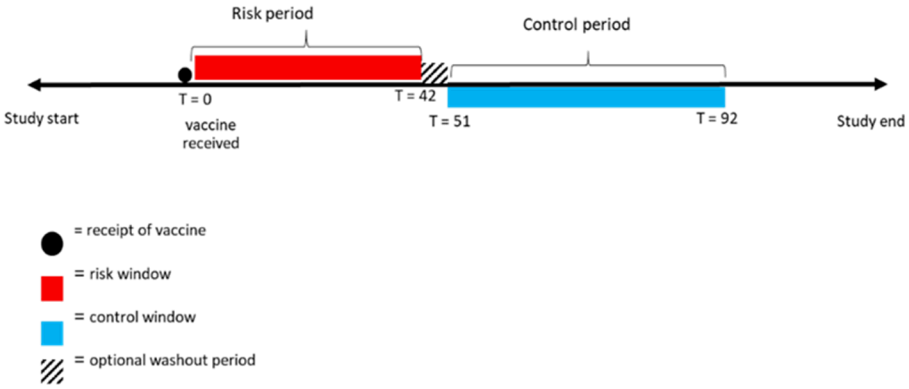
The AESIs for which a SCRI analysis is a valid approach and their risk windows are indicated in Table 2.

A prespecified post-vaccination control interval will be used for each outcome. This approach will minimise bias because of outcomes affecting the probability of exposure (e.g., the outcome is a contraindication for exposure or delayed exposure). For individuals who

received more than one dose of the vaccine, the risk interval will be extended beyond each dose.

For outcomes with short risk intervals, for each dose, the control interval occurred temporally close to the risk interval associated with that dose and before the next dose was given. For outcomes with risk intervals longer than the gap between doses, the control interval for each dose occurred after the risk interval of the second dose (Figure 1).

Figure 1. Self-controlled risk interval design



T = time measured in days.
Note: Example with a risk period of 42 days and a control period of 42 days.

9.2. Setting

The study planned to use data from eight European electronic health care databases in Italy, the Netherlands, Norway, Spain and the UK.

9.2.1. Data sources

The following European electronic health care databases and two-letter country codes were planned to be used as data sources (Figure 2):

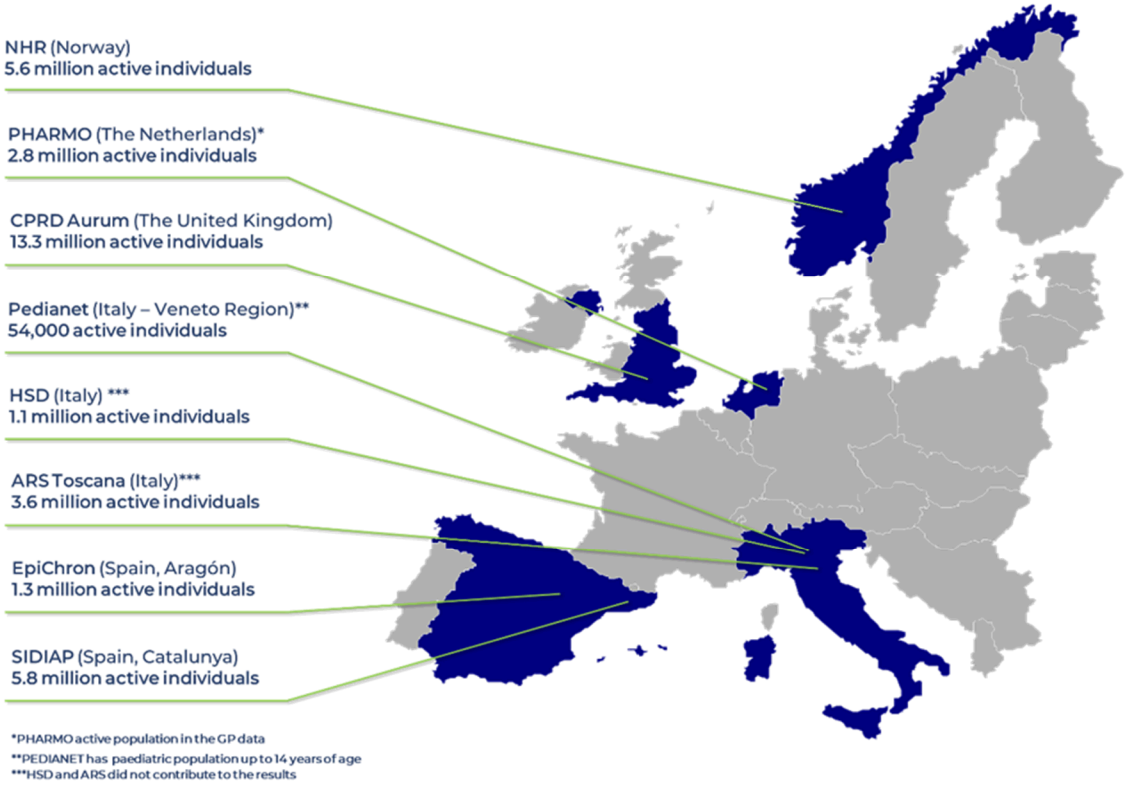
- ARS Toscana (Agenzia Regionale di Sanita' della Toscana) [a research institute of the Tuscany region of Italy] (IT)][1]
- Pedianet (IT)
- Health Search Database (HSD) (IT)[2]

[1] Due to an ongoing review of the data protection law and the secondary use of the Tuscany administrative data, the research team at ARS Toscana have to suspend research temporarily.

[2] Due to concerns about the accuracy of the vaccination status of 'unvaccinated' individuals no data from HSD have been included in this report

- PHARMO (PHARMO Data Network) (NL)
- NHR (The Norwegian health registers) (NO)
- EpiChron (EpiChron Research Group on Chronic Diseases at the Aragon Health Sciences Institute) (ES)
- SIDIAP (Sistema d'Informació per el Desenvolupament de la Investigació en Atenció Primària) [Information System for the Improvement of Research in Primary Care] (ES)
- CPRD (Clinical Practice Research Datalink) Aurum (UK)

Figure 2. Map showing location and number of active individuals in each data source



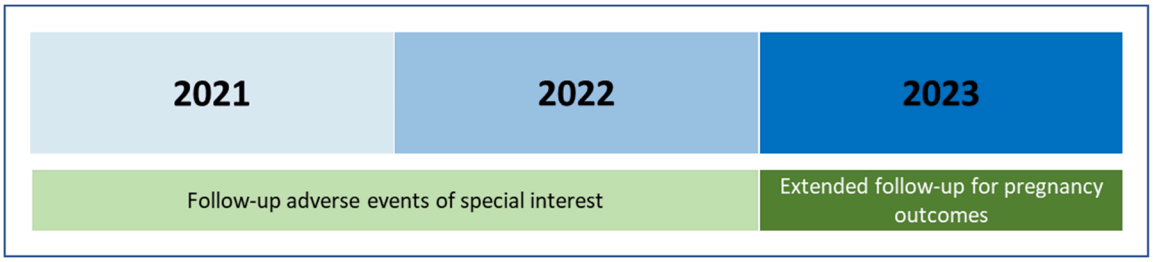
9.2.2. Study period and follow-up

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 will end on the date of the latest data availability. Follow-up will last for two years for AESIs. Differences in follow-up for acute and non-acute events are described in the statistical analysis plan (SAP) (Standalone Appendix 4). Pregnancy outcomes will be followed up for an additional year in women who become pregnant during the two years of follow-up; the results will be reported in the final report (Figure 3).

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)	31 May 2021	31 May 2021 – 31 Dec 2022
The Netherlands (PHARMO)	06 January 2021	GP data: 6 January 2021 – 30 June 2023 Hospital data: 6 January 2021 – 31 Dec 2022
Norway (NHR)	27 December 2020	1 January 2021 – 31 December 2022
Spain (EpiChron, SIDIAP)	27 December 2020	EpiChron: 27 December 2020 – 31 Jul 2023 SIDIAP: 01 January 2021 – 30 Jun 2023
UK (CPRD Aurum)	08 December 2020	08 December 2020 – 21 March 2022

Figure 3. Study period and follow-up



9.3. Subjects

The source population for both cohort and SCRI designs was all individuals registered in the health care data sources listed in Section 9.2.1.

9.3.1. Inclusion criteria

9.3.1.1. Cohort design

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

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

At any time, vaccinated individuals may differ from the remaining population in characteristics that may determine their risk of AESI. Measured baseline differences were adjusted for in the analyses (Section 9.9.3).

For the study of pregnancy outcomes, the cohort was restricted to pregnant women. Details of the differences from the main cohort approach are described in the SAP (Standalone Appendix 4).

9.3.1.2. Self-controlled risk interval design

For analyses of outcomes assessed with the SCRI design, the criteria below will have to be met. Note that the study population for each outcome-specific analysis will therefore be different.

- Have received at least one dose of the Pfizer-BioNTech COVID-19 vaccine.
- Have experienced an event during the risk or control interval.
- Have full accrual of data used to define the event in the risk and control intervals combined, taking into account the data lag and timing of data extraction.

9.3.1.3. Exclusion criteria for cohort and self-controlled risk interval designs

- Have had contact with the health care system in the seven days before time zero (as an indicator of a health event not related to subsequent vaccination that could reduce the probability of receiving the vaccine). It is planned to assess this exclusion criterion in a sensitivity analysis.[9]
- Have had a diagnosis of the specific AESI under study within 1 year before time zero (to distinguish the recording of previous events from true new events) and at any time before time zero for diabetes type 1.

Individuals having any specified contraindication to vaccination or being part of a group not recommended for vaccination in the jurisdiction of the study will be analysed separately in the final report.

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 Section 9.5. 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.

9.4.1.1. Cohort design

The vaccination categories for the different exposure groups were defined as follows:

1. Receipt of at least one dose of the Pfizer-BioNTech COVID-19 vaccine, followed or not by a second dose or booster of the Pfizer-BioNTech COVID-19 vaccine.

Individuals were censored if and when they received a non–Pfizer-BioNTech COVID-19 vaccine during follow-up.

2. The vaccination category for the matched unexposed group was defined as not receiving a COVID-19 vaccine of any brand during the study period. Individuals were censored when they received a dose of any COVID-19 vaccine during follow-up.

The following sensitivity analyses were implemented for the cohort design:

1. A vaccination category consisting of the receipt of two vaccination doses, per the recommended primary vaccination schedule was studied (i.e., receipt of a first dose of the Pfizer-BioNTech COVID-19 vaccine, followed by a second dose by week 4 after the first dose in the absence of an adverse event, and having never received a non–Pfizer-BioNTech COVID-19 vaccine). For this specific sensitivity analysis, but not for the main analysis, individuals were censored if they did not receive the second dose of the Pfizer-BioNTech COVID-19 vaccine by week 6 after the first dose in the absence of an adverse event or if they received a non–Pfizer-BioNTech COVID-19 vaccine during follow-up. The operationalisation of these exposure strategies is described in Section 9.5.

2. The risks for AESIs following a second or subsequent dose were estimated as follows:

    - Risk of AESIs following a second dose of the Pfizer-BioNTech COVID-19 vaccine. In this sensitivity analysis, the study population were individuals who received a second dose of the Pfizer-BioNTech COVID-19 vaccine, and follow-up started on the day the second dose was received. The risk of AESIs were estimated using the same estimators used in the main analysis.

    - The risk of AESIs following subsequent doses of the Pfizer-BioNTech COVID-19 vaccine were estimated in a similar way. In these sensitivity analyses, the study population was individuals who received a subsequent dose of the Pfizer-BioNTech COVID-19 vaccine, and follow-up started the day the subsequent dose was received. The risks of AESIs were estimated using the same estimators used in the main analysis (i.e., incidence rates (IRs), hazard rations (HRs), risk differences (RDs).

Individuals who received a first dose (population studied in the main analysis) may be different from the individuals who received a second dose and they may also be different from the individuals receiving subsequent doses (populations studied in this sensitivity analysis). These differences could be due to both the national vaccination policies concerning dosing recommendations (i.e., a third dose was indicated for specific at-risk individuals) and the fact that individuals who received subsequent doses were survivors who had not suffered any serious adverse reactions (e.g., an anaphylactic reaction to a first dose) that would have contraindicated the continuation of the vaccination schedule. We were only able to identify that a third dose was given without being able to distinguish if it was the third dose in a 2+1 vaccination primary schedule or a booster dose.

9.4.1.2. Self-controlled risk interval design

As per the protocol and SAP, the results from the SCRI study are not reported in this interim report. For the SCRI design, for each dose, person-time in the risk interval will be considered as 'exposed', while person-time in the control interval will be considered 'unexposed'. Risk intervals are specific to the outcome of interest and will be defined to reflect the length of post-vaccine exposure that an incident post-vaccine event was expected to occur. The risk windows for events after vaccination were not well known for COVID-19 vaccines when the study protocol and SAP were drafted, so these were defined based on prior post-marketing studies of other vaccines (where applicable), clinical trial data (where applicable), and passive post-marketing surveillance activities (as they became available). An acute event, while time-limited in duration, does not necessarily have a defined risk window if there is no known time-limited window after vaccine exposure that the acute event would be expected to occur post-vaccination.

Outcome-specific control intervals will also be defined. For outcomes with short risk intervals, the control interval occurs relatively close in time to the risk interval for each dose. For outcomes with long risk intervals, among individuals receiving two or more doses, the control interval for both the first and second doses occurs after the risk interval of the second or subsequent dose and do not overlap with the risk interval of the following dose. A sensitivity analysis will be performed, where the exposed group of vaccinees will be restricted to those who were vaccinated as per the recommended schedule, (i.e., two doses of the Pfizer-BioNTech COVID-19 vaccine per the Pfizer-BioNTech recommended dosing schedule).[3]

9.4.2. Definition of outcomes

9.4.2.1. Safety outcomes

Outcomes were defined homogeneously across the data sources to the fullest extent possible. Selected AESIs currently included in the study are listed in Table 2 and were based on those proposed by the ACCESS project (vACcine COVID-19 monitoring readinESS), which was funded by the EMA to ensure that a European infrastructure is in place to effectively monitor COVID-19 vaccines in the real world, once the vaccines are authorised- in the EU (http://www.encepp.eu/encepp/viewResource.htm?id=37274.). Additional outcomes were added following discussions and requests from EMA: Thrombotic thrombocytopenia syndrome (TTS) and myocarditis and pericarditis, with 1 to 7, 1 to 14 and 1 to 21-day risk windows individually and as a combined event.

Outcomes were identified in EHR databases with algorithms based on codes for diagnoses, procedures, and treatments. Definitions, codes, and proposed algorithms for all AESI incorporated definitions developed by the ACCESS project

[3] This refers to the original 2-dose schedule.

(https://zenodo.org/communities/vac4eu/?page=1&size=20) and are described in more detail in the SAP (Standalone Appendix 4).

a. Outcome identification and validation, by data source

AESIs were identified based on patient profile review of electronic medical records by health care professionals. In addition, for selected outcomes listed in Table 2 and others (if considered necessary in a future evaluation of results), manual review of patient charts conducted by clinicians blinded to COVID-19 vaccine exposure will be performed starting in 2023, when possible, and the results will be included in the final report. Confirmation of an event diagnosis will be classified using the levels of certainty in existing Brighton Collaboration definitions and those currently being developed.

Standard algorithms for each outcome definition were applied to participant data sources, based on the results of the ACCESS project. 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.[10] Multiple algorithms for the same outcome were included in the analysis, to assess the potential impact of differential misclassification.

Pedianet (IT): A validation mechanism, including individual linkage with the electronic regional immunisation registry, will be in place. The validation process will include review by clinicians of the individual EHRs, which contain information from primary care reports.

PHARMO (NL): In the Netherlands, for the validation study, information on selected endpoints from patient medical records were abstracted by local medical professionals employed at PHARMO, provided that medical chart review was approved by the ethics committee and other local and/or national governing bodies.

NHR (NO): In Norway, the validation process was based on the manual review of hospital charts for a subsample of individuals with the AESI, compared with registered diagnoses in the Patient Registry of Norway.

EpiChron (ES): In Aragon (Spain), the proposed validation process was based on a review of the individuals' electronic medical records by clinicians from the research team who are blinded to COVID-19 vaccination status. These records included information from primary care reports, hospital discharge reports (including hospital emergency rooms), and results of diagnostic tests and laboratory tests.

SIDIAP (ES): In Catalonia (Spain), the validation process was part of the data quality control. Validation was based on a review of the electronic medical record information (ECAP) by members of the SIDIAP research group who were blinded to COVID-19 vaccination status.

CPRD Aurum (UK): In the United Kingdom (UK), validation was conducted by a review of electronic medical record information for selected endpoints by clinicians who were blinded to COVID-19 vaccination status.

9.4.3. Covariate definition

The following variables 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. The AESIs may have different sets of risk factors, and outcome-specific analyses therefore could contain different covariate sets. Potential covariates could include the following information, as available in each data source:

- Demographics
    - Age at time zero (used to define subgroups for secondary analyses)
    - Age in categories, in line with published background incidence rates from ACCESS (0-17, 18-29, 30-39, 40-49, 50-59, 60-64, 65-69, 70-79, 80+ years)
        - The age group 0-17 years was further categorised, when feasible, as follows: 0-1, 2-4, 5-11, 12-15, 16-17
    - Sex
    - Pregnancy status and pregnancy trimester at time zero
    - Geographic region, as appropriate in each country
    - Socioeconomic status, as available in each country (including housing, employment, and income, if available)
    - Date of vaccination (categorised in trimesters)
- COVID-19 history, as available in each data source (used to define subgroups of interest)
    - Previous diagnosis of COVID-19
    - Positive test result for COVID-19
- Personal lifestyle characteristics
    - Smoking status (if available)
    - Body mass index (if available)
- Comorbidities
    - History of anaphylaxis
    - History of allergies

- Diabetes mellitus (types 1 and 2)
- Hypertension
- Cardiovascular disease
- Cerebrovascular disease
- Chronic respiratory disease
- Chronic kidney disease
- Chronic liver disease
- Cancer
- Autoimmune disorders
- Influenza infection or other respiratory infections
- Charlson Comorbidity Index (reported as individual items and as a composite score)
- CDC at risk groups

- Immunocompromising conditions (used to define subgroups for secondary analyses)
  - Immunodeficiencies
  - Immunosuppressant medication use
  - Human immunodeficiency virus and other immunosuppressing conditions
- Comedication use during the year before time zero (prescriptions or dispensing, no over-the-counter medication use). For this report, comedication use was assessed for ten years prior to time zero, but this will be corrected in the next interim report.
  - Analgesics
  - Antibiotics
  - Antiviral medications
  - Corticosteroids
  - Non-steroidal anti-inflammatory drugs
  - Psychotropics

    - Statins
    - Novel oral anticoagulants
    - Warfarin
- Health care utilisation in the year before time zero and in the 2 weeks before time zero
    - Number of hospitalisations
    - Number of emergency department visits
    - Primary care utilisation
    - Cancer screening
    - Other preventive health services, as appropriate
    - COVID-19 tests
- Other vaccinations
    - Influenza
    - Pneumococcal
    - DTP (diphtheria, tetanus, and pertussis)
    - TPV (polio)
    - TV (MMR) (measles, mumps and rubella)
    - Hib (Haemophilus influenzae type b)
    - HB (hepatitis B virus)
    - VV (varicella zoster virus)
    - HZ (herpes-zoster virus)
    - HPV (human papillomavirus)
    - Meningococcal
    - Rotavirus
- Surrogates of frailty

- Paralysis
- Parkinson's disease
- Skin ulcer
- Weakness
- Stroke/brain injury
- Ambulance transport
- Dementia
- Difficulty walking
- Psychiatric illness
- Sepsis
- Heart failure
- Podiatric care
- Bladder incontinence
- Diabetes complications
- Arthritis
- Coagulation deficiencies
- Vertigo
- Lipid abnormalities.

The CDC at risk groups will be defined based on at-risk medical conditions for developing severe COVID-19 and will be reported as baseline characteristics for vaccinated and non-vaccinated individuals. These will be defined based on scientific evidence available on the US Centers for Disease Control and Prevention website and the UK National Health Services digital website.[11, 12] Those websites are updated regularly and provide a classification based on levels of evidence.

At-risk medical conditions that are considered as at higher risk to develop severe COVID-19 are summarised in Table 4. Medicinal products that can be considered as proxies for these conditions are also listed. At-risk Subgroups will be identified using medical codes and associated dates for at-risk medical conditions characterising at-risk groups for developing severe COVID-19 as well as prescription and/or dispensing records for drug exposures which may be used as proxies for their identification. At-risk subgroups will be created for

each of the at-risk medical conditions listed in Table 4. Multimorbidity, i;e., individuals in more than one at-risk subgroup will be included in each subgroup.

Table 4. Comorbidities and related medicinal products with evidence of being at high risk for developing severe COVID-19

At-risk medical conditions identified by diagnosis codes	Medicinal product proxy(ies) (ATC code)
Cancer (with chemo/immuno/radiotherapy, cancer treatment, immunosuppressant; targeted cancer treatment (such as protein kinase inhibitors or PARP inhibitors); blood or bone marrow cancer (such as leukaemia, lymphoma, myeloma)	Alkylating agents (L01A) Antimetabolites (L01B) Plant alkaloids and other natural products (L01C) Cytotoxic antibiotics and related substances (L01D) Other antineoplastic agents (L01X) Hormones and related agents (L02A) Hormone antagonists and related agents (L02B) Immunostimulants (L03) Immunosuppressants (L04)
Type 1& 2 Diabetes	Blood glucose lowering drugs A10A & A10B
Obesity (BMI > 30)	Peripherally acting anti-obesity products (A08AB) Centrally acting anti-obesity products (A08AA)
Cardiovascular disease/ Serious heart conditions including heart failure, coronary artery disease, cardiomyopathies	Antiarrhythmics, class I and III (C01B) Cardiac stimulants excl. Cardiac glycosides (C01C) Vasodilators used in cardiac diseases (C01D) Other cardiac preparations (C01E) Antithrombotic agents (B01A)
Chronic lung disease including COPD, asthma, bronchiectasis, interstitial lung disease, cystic fibrosis, tuberculosis.	Drugs for obstructive airway diseases (R03) Lung surfactants (R07AA) Respiratory stimulants (R07AB)
Chronic kidney disease	Erythropoietin (B03XA01)
HIV	Protease inhibitors (J05AE) Combinations to treat HIV (J05AR) NRTI (J05AF) NNRTI (J05AG)
Immunosuppression	Immunosuppressants (L04A) Corticosteroids (H02)
Sickle cell disease	Hydroxyurea (L01XX05) Other haematologic agents (B06AX)
Hypertension	anti-hypertensive drugs (C02, C03, C07, C08, C09)

9.5. Data sources and measurement

Exposure was based on recorded prescription, dispensing, or administration data for the Pfizer-BioNTech COVID-19 vaccine. Vaccine receipt and date of vaccination was obtained from all possible sources that capture COVID-19 vaccination, such as pharmacy dispensing records, general practice records, immunisation registers, vaccination records, medical records, or other secondary data sources. Depending on the data source, vaccines were identified via nationally-used product codes and included batch numbers, where possible. The main exposure of interest was the receipt of at least one dose of the Pfizer-BioNTech

COVID-19 vaccine. The source of exposure was as described below for the six data sources that contributed to this interim report.

Pedianet (IT): Information on COVID-19 vaccine included date of immunisation, type of vaccine, vaccine batch number, and dose. Information on COVID-19 immunisation was retrieved via a direct linkage with the regional immunization registry. The family care physicians synchronise the data every trimester.

PHARMO (NL): Information on vaccination, obtained from PHARMO's General Practitioner (GP) database, included Anatomical Therapeutic Chemical (ATC) code, brand, batch, and date of application.

NHR (NO): All vaccinations, including COVID-19 vaccinations, are subject to notification to SYSVAK and are registered without obtaining patient consent. The following data were registered: individual personal identifier, vaccine name and ATC code, vaccine batch number, date of vaccination, and the centre where the vaccine was administered.

EpiChron (ES): The Aragon Health System (Aragon, Spain) implemented a specific vaccination register embedded in the electronic health record (EHR) system. The COVID-19 vaccination was systematically registered in this register by health care professionals. This register collected all the relevant information regarding the vaccination process, such as patient's identifier; date of administration and due date for next dose, when applicable; centre of administration; injection site; name of the vaccine; brand (laboratory); batch number; dose; and vaccination criteria (risk group to which the patient belongs). There was also a free-text section in which health professionals included their observations (e.g., presence or not of an allergic reaction).

SIDIAP (ES): For all 8 million individuals of the Catalan Institute of Health–Primary Care teams, SIDIAP has information available on the administration of COVID-19 vaccines to individuals linked to a unique and anonymous identifier. The information is originated from the electronic medical records. For each patient, SIDIAP has date and centre of administration, dose, brand, reasons for vaccination (e.g., risk group), and other information related to vaccination.

CPRD Aurum (UK): Information on COVID-19 vaccination in the CPRD Aurum data source included the brand of COVID-19 vaccine administered, the date that the vaccine was administered to the patient, and the date that the record of vaccination was entered in the primary care medical record. In the UK, the majority of COVID-19 vaccines were administered at local immunisation centres or pharmacies in the community. Details of the vaccination were systematically entered by healthcare professionals into a national database at the time of administration, which was linked with primary care health records via the patient's NHS number. This information is now available to researchers as anonymised primary healthcare records via CPRD Aurum.

9.6. Bias

This study is subject to limitations related to both the study design and use of secondary health care data. A data-related limitation of this study is the reliance on the accuracy of codes and algorithms to identify outcomes. Outcomes and their dates of occurrence were validated, but the extent of validation may be limited because medical records were used for

validation, and these could be incomplete. Exposure identification could be based on pharmacy dispensing records, general practice records, immunisation registers, medical records, or other secondary data sources. The ability to identify specific COVID-19 vaccine products and dates of vaccination in these data sources is detailed in Section 9.5. It is possible that vaccination of individuals outside the health care system was not recorded in secondary EHR databases, thereby leading to potential bias because of exposure misclassification for the cohort study. It is also possible that some AESIs are the result of immunisation errors occurring during the administration of the Pfizer-BioNTech COVID-19 vaccine. This information was not collected regularly and could not be taken into account with the current protocol.

A study design-related limitation of both the cohort and SCRI designs is that any uncertainty regarding risk periods will lead to misclassification and attenuation of risk estimates. A limitation of the cohort design is the potential for residual or unmeasured confounding, as it is unlikely that the data sources will have information on all potential confounders. To address potential confounding, the SCRI, which automatically adjusts for time-invariant confounders, was used as a secondary approach. However, the SCRI is not well suited to study outcomes with gradual onset, long latency, or risk periods that are not well known. It also may be subject to bias for outcomes that affect the probability of exposure. The SCRI design was complementary to the cohort design for prespecified AESI with defined risk intervals.

In addition, in Italy, the COVID-19 vaccination campaign started in December 2020 with each of the 20 regions having adopted different vaccination strategies involving hubs and/or general practices. The primary care setting was actively involved in the vaccination campaign only at the beginning of April 2021, and only certain age categories and/or types of vaccines were available for direct administration by GPs. Thus, for the period between January and March 2021, Italian GPs have likely recorded vaccine injections according to three main pathways: a) some regions automatically informed GPs regarding their patients' COVID-19 vaccination status; b) GPs referred patients to a specific hub to register their vaccination status there; and c) patients autonomously reported their vaccination to their GPs. For the first six months of 2021, HSD expects to find complete data for certain age categories, while in the first three months and for some other age categories, they will only find incomplete data for some regions. In HSD, after preliminary evaluation of data completeness, the study design (e.g., self-controlled or cohort design) will be chosen for the specific objectives.

The matching procedure in the cohort analysis produced a study population (i.e., a set of matched pairs) with a distribution of matching variables representative of the vaccinated individuals by matching unvaccinated individuals to vaccinated individuals based on a prespecified set of baseline variables. Therefore, the cohort analysis estimated the average causal effect in the vaccinated population i.e., in a population that had the distribution of matching variables of the vaccinated. When further adjustment via inverse probability weighting was applied, the estimated effect remained the causal effect in a population that had the distribution of matching variables with the vaccinated cohort because the weights were estimated and applied to the matched population. The average causal effect in the treated and untreated populations differed only if any baseline variable modified the effect, in addition to random variation. This will have to be considered when comparing effect estimates with other studies.

The main analysis for both the cohort and SCRI analysis pooled together the population used to estimate the effect of a first dose of the Pfizer-BioNTech COVID-19 vaccine and the population used to estimate the effect of subsequent doses of the same vaccine. This pooling was done to gain statistical precision, under the assumption that the effect of a first or second dose in both populations is homogeneous. If this assumption is inaccurate, e.g., because receiving a first dose sensitises the immune system to react against a second dose, the estimates of the main analysis will be biased.

9.7. Study Size

The study is conducted in a source population of 38.9 million individuals captured in the electronic health care data sources.

Table 5 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.

Table 5. Number of individuals needed to detect different risk ratios for selected adverse events of special interestfor a range of background rates

			Sample size[a]	
AESI	**Background rate during risk window**	**Risk ratio**	**Exposed**	**Unexposed**
Anaphylaxis	1/40,000	5	25,164,513	25,164,513
Anaphylaxis	1/40,000	7	15,147,759	15,147,759
Anaphylaxis	1/40,000	10	9,341,969	9,341,969
Anaphylaxis	1/40,000	50	1,081,289	1,081,289
Guillain-Barré syndrome	1/100,000	2	22,340,153	22,340,153
Guillain-Barré syndrome	1/100,000	3	7,725,193	7,725,193
Guillain-Barré syndrome	1/100,000	5	2,997,860	2,997,860
Guillain-Barré syndrome	1/100,000	10	1,112,913	1,112,913

AESI = adverse event of special interest; Severe COVID-19 defined as COVID-19-related hospitalisation or death.
a Assuming a two-sided alpha = 0.95, power of 80%, and a ratio of 1:1 exposed to unexposed.
Background incidence rate (IR) taking into account the risk window (source: https://doi.org/10.1093/infdis/jiab628):
Anaphylaxis 1/40,000; (1/40,000)/365 * risk window (risk window 2 days) = <0.010000137
Guillain-Barré syndrome 1/100,000; (1/100,000)/365 * risk window (risk window 42 days) = <0.01000115

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 statistical analysis plan (SAP), which is dated, filed and maintained by the sponsor (Standalone Appendix 4).

9.9. Statistical methods

9.9.1. Main summary measures

In this Interim Report (IR) #5, all individuals vaccinated with at least a first dose of the Pfizer-BioNTech COVID-19 vaccine and satisfying the inclusion criteria during the time periods below were included. The main summary measures reported for the unmatched vaccinated cohort were:

- Attrition table for the Pfizer-BioNTech COVID-19 vaccinated cohort.
- Counts and proportions of administered Pfizer-BioNTech COVID-19 vaccine doses patterns by age groups and sex. This table was repeated for immunocompromised, elderly and individuals who have specific comorbidities.
- Population description at the time of first and third dose.
- Prior AESI (outcome-specific exclusion criteria) at time zero.
- Cohort follow-up duration and censoring reasons.

For the matched cohort design, matched on a subset of variables:

- Age: age of vaccinated individuals categorised into 2-year age groups (exact matching);
- Sex: male, female (exact matching);
- Previous COVID-19 diagnosis at time 0 (exact matching);
- Place of residence: at the level of neighbourhood, small town or at GP practice level (exact matching);
- At least one influenza vaccine in the last five years (yes/no) (not recorded is considered as not vaccinated) (exact matching);
- Pregnancy status yes, no (exact matching):
    - Among pregnant women, matching will take a ‘greedy matching’ approach, in which a matched will be first sought by last menstrual period (LMP) within 7 days of each other; if no matches are found, the period will be extended to 30 days;

- Immunocompromised yes, no (exact matching)*:*
    - At least one of the following in the last 10 years: *immunodeficiencies, immunosuppressant medication use, human immunodeficiency virus and other immunosuppressing conditions*
- Number of pre-existing conditions considered by the Centers for Disease Control and Prevention (CDC) as risk factors:
    - Cancer, type 1& 2 diabetes, obesity (BMI > 30), cardiovascular disease/ serious heart conditions (heart failure, coronary artery disease, cardiomyopathies), chronic lung disease including COPD, asthma, chronic kidney disease, HIV, immunosuppression, sickle cell disease, hypertension
    - CDC at risk group 0 = none of the conditions above
    - CDC at risk group 1 = 1 of the conditions above
    - CDC at risk group 2 ≥ 1 of the conditions above
- Socioeconomic status/education level (as available, exact matching)

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 patients excluded, included and matched by calendar 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).

9.9.2. Main statistical methods

- The IR of all AESIs by different time windows after dose 1.
- The IR of all AESIs within the risk windows after dose 1, dose 2, and dose 3.
- The number of cases, and risk estimates (IR, Kaplan-Meier (KM) for all AESI (identified electronically) in each matched exposure group, overall and by subgroups.

- The crude cumulative incidence (1- KM) curves for each AESI by exposure group taking risk windows in consideration.

- Cumulative incidence curves (1 - KM) for the negative control outcome, starting from the day of administration of the first dose of vaccine.

9.9.3. Baseline exchangeability and negative control outcome

Despite matching for potentially relevant confounders, baseline exchangeability may not be achieved and residual confounding may remain. An observational study of the effectiveness of the Pfizer-BioNTech COVID-19 vaccine used the cumulative incidence of symptomatic SARS-CoV-2 infections at day 12 as a negative control, and a difference of approximately 0.06% was considered as proof of non-relevant residual confounding.[13] Similarly, symptomatic SARS-CoV-2 infection was used as a negative control outcome, under the assumption that confounders for symptomatic SARS-CoV-2 were equally relevant for developing adverse clinical conditions. More details are available in the statistical analysis plan.

We, therefore, used 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 (Figure 4). It was established a priori that, if the 12-day risk difference of symptomatic SARS-CoV-2 infection was ≤0.10%, the matching would be considered to be sufficient to achieve baseline exchangeability and if it was >0.1%, the matching would be considered not sufficient to achieve baseline exchangeability. In the latter case, inverse probability of treatment weighting (IPTW), a form of propensity score (PS) method, would be used to adjust the estimates using PS methods. PS methods are appropriate when there is a small number of events for each outcome, which is the case in this study.

The PS was defined as the probability of receiving the Pfizer-BioNTech COVID-19 vaccine at baseline in the matched population, conditional on the matching variables and on any baseline variables with an ASD ≥0.1. This probability was estimated using a logistic regression model including all the matching variables, all variables with an ASD ≥0.1, prior history for each AESI and age (i.e., 0-5, 6-11, 12-17, 18-29, 30-39, 40-49, 50-59, 60-64, 65-69, 70-79, ≥80 years), as independent variables. Geographic region was excluded from the model to avoid complete separation between groups. The analyses did not use any specific statistical technique for handling missing values and the only restriction was not including any variables with more than 30% of missing values.

One single PS model was estimated in the eligible population without selection on the outcome, and used to adjust all outcome estimators. Variables highly correlated with exposure (i.e., OR<0.1 or OR>10 and prevalence >2%) were excluded from the model in order to avoid complete separation of the curves of the PS.

The stabilised weights were calculated as:

$$W^{baseline} = 0.5 * \left(\frac{A}{PS} + \frac{1-A}{1-PS}\right)$$

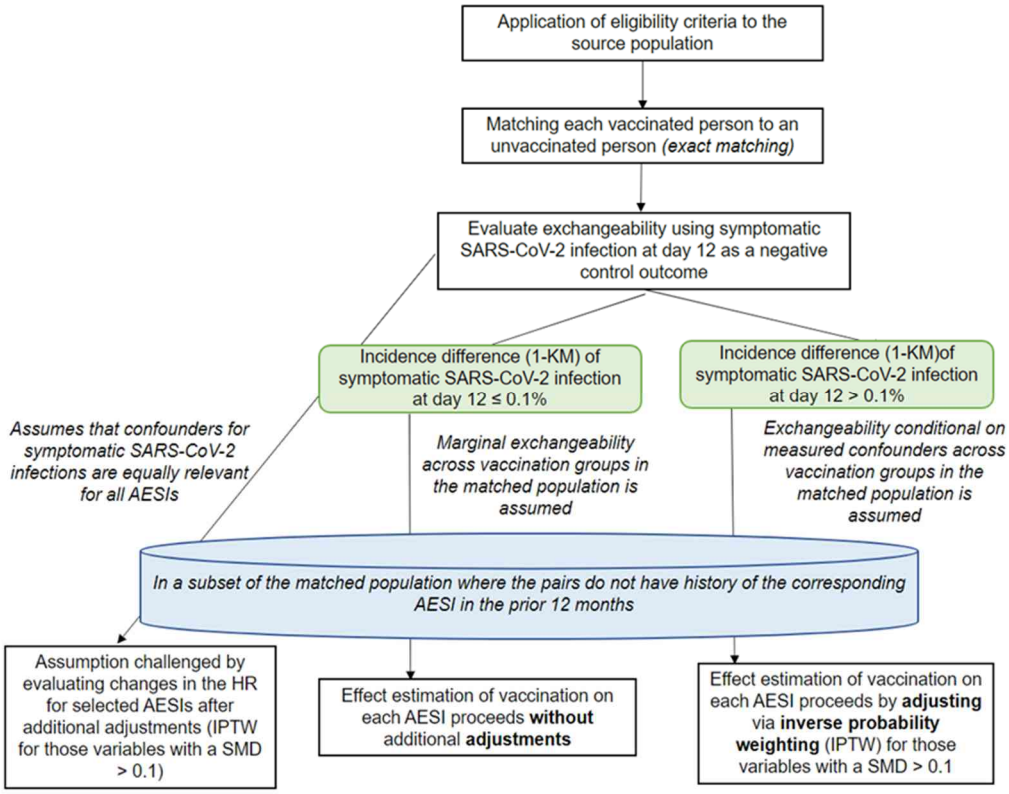
Where PS is the propensity score and A is the vaccination status at baseline (vaccinated: A=1, unvaccinated: A=0), i.e., the weight for the vaccinated cohort was 0.5/PS and for the unvaccinated cohort it was 0.5/(1-PS). Since, by design, the marginal probability of being exposed is ½, the weights were stabilized by multiplying by 0.5.

The distribution of the weights was assessed using min, max, P1, P99, median, mean, and standard deviation. We described the distribution of assessed weights and truncated the weights at the 1st and 99th percentile of the distribution of weights in each group to avoid undue influence of extreme weights.

Adjusted HRs and 95% CIs were estimated via weighted Cox proportional hazard regression model with robust estimation of the variance. Adjusted cumulative incidence (1-KM) differences were obtained by subtracting 1-KM, weighted using the IPTW, estimated at the end of the risk window for each AESI.

In this report, regardless of the result of the 12-day risk difference to achieve baseline exchangeability we calculated PS adjusted estimates which are reported here.

Figure 4. Overview of proposed analytical approach to assess baseline exchangeability in the retrospective matched cohort study



9.9.4. Missing values

Patients 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. We assumed that the absence of information on clinical events meant that the event did not occur.

9.9.5. Sensitivity analyses

The sensitivity analyses described in Section 9.4.1.1 above were tested and, for completeness, the tables are included in on-line supplementary data available on request. These will be further refined and reported in subsequent reports.

9.9.6. Amendments to the statistical analysis plan

A summary of the amendments that have been made to the SAP is provided in Table 6.

Table 6. Summary of amendments to the statistical analysis plan

Amendment number	Date	Section of SAP changed	Summary of amendment/update	Reason
3	March 2024	2.1	Update list of outcomes to exclude 'severe COVID-19 disease'	Request by EMA because vaccine-associated enhanced disease/vaccine-associated enhanced respiratory disease (VAED/VAERD) is longer considered as an important potential risk
3	March 2024	2.1	Update list of outcomes to include 'cerebral venous sinus thrombosis' and 'glomerulonephritis'	Request by EMA
3	March 2024	7.2.8	Updated section on description of cardiac imaging use before and after the issue of the direct healthcare professional communication letter to be consistent with changes to protocol V5.0, section 9.3.2.1	Request by EMA

Table 6. Summary of amendments to the statistical analysis plan

Amendment number	Date	Section of SAP changed	Summary of amendment/update	Reason
2	28 Jun 2023	2	Updated introduction	To describe new objective i.e., assessment of the effectiveness of the direct healthcare professional communication (DHPC) letter
2	28 Jun 2023	2.1	Update list of outcomes to include myositis, secondary amenorrhoea and hypermenorrhoea to be consistent with changes to protocol V5.0, section 9.3.2.1	Request by EMA
2	28 Jun 2023	2.2.6.3	Removed 'verified' from AESIs in Table 3	
2	28 Jun 2023	2.4.2	Added new secondary objective described in protocol V5.0, section 8.2: to assess the effectiveness of the direct healthcare professional communication (DHPC) letter by describing the rate of cardiac imaging use for vaccinated and unvaccinated individuals each calendar month of the study period, before and after distribution of the DHPC letter	Included in European risk management plan as an additional risk minimization measure
2	28 Jun 2023	5.2.1	Added myocarditis/pericarditis to Table 6	
2	28 Jun 2023	5.3	Added cardiac imaging as additional endpoint	Inclusion of endpoints for new objective described above related to DHPC

Table 6. Summary of amendments to the statistical analysis plan

Amendment number	Date	Section of SAP changed	Summary of amendment/update	Reason
2	28 Jun 2023	5.4.1	Demographic variables removed from list: • race/ethnicity • residency in long-term care facility • healthcare worker or essential worker status	DAPs have confirmed these variables are not available.
2	28 Jun 2023	5.4.4	Added additional conditions to the CDC at risk-groups	
2	28 Jun 2023	5.4.7	Healthcare use variable deleted • skilled nursing facility	DAPs confirmed variable not available
2	28Jun 2023	5.4.12	Added additional respiratory conditions in Table 8	
2	28 Jun 2023	7.2.5	Added section in Final Report	Include analysis of new objective related to DHPC
2	28 Jun 2023	7.2.8	Added section on Description of cardiac imaging use before and after the issue of the direct healthcare professional communication letter	Analysis of new objective related to DHPC
2	28 Jun 2023	2.2.5 4.1 7.2.5 7.2.7	Updated sections • Comparison with historical controls, • Study period • Analysis. Final Report • Comparison with historical comparators.	The comparison with historical periods will be made via the matched historical comparators analysis
2	28 Jun 2023	5.4.1 Demographics	Protocol V4.0, section 9.3.3: age categories have been modified;	To be consistent with the change in age categories that has been communicated to regulatory authorities via an administrative change letter

Table 6. Summary of amendments to the statistical analysis plan

Amendment number	Date	Section of SAP changed	Summary of amendment/update	Reason
1	15-Apr-2022	2.1 Study Design; 5.2.1 Identification and validation of outcome in each data source; 8.3 Events	Renamed the AESI, 'HIT-like event' to 'thrombotic thrombocytopenia syndrome (TTS)' and deleted 'thrombocytopenia, venous thromboembolism' from the list of AESIs	These three names refer to the same event, so there was a duplication in the list. The current name in common use for the syndrome potentially associated with COVID-19 vaccination has been selected
1	15-Apr-2022	7.2.6.8 Subgroup analyses; 7.2.8.2 Measures of association	Revised age categorisations	To align with vaccine authorization schedule and distribution rollout
1	15-Apr-2022	7.2.1 Analysis timelines	Added study end date of 31 December 2023 and changed end of data collection to 31 March 2024	To clarify that the last date of data available will be 31 December 2023, which differs from the end of data collection date that takes into account lag times.
1	15-Apr-2022	7.2.6.10 Sensitivity Analyses; 7.2.4 Interim Reports 2-5	Added a sensitivity analysis for the cohort design excluding individuals who have had contact with the healthcare system in the seven days before time zero	Request from EMA to remove from main analysis and add as a sensitivity analysis
1	15-Apr-2022	2.2.2.4.1. Matching process	Added the variable 'Immunocompromised (yes/no) – exact matching' to the list of matching variables	To align with the latest version of the study protocol
1	15-Apr-2022	2.2.2.2 Exclusion criteria; 2.2.6.2. Exclusion criteria	Removed exclusion criteria, 'have had been in contact with the healthcare system in the 7 days before time 0'	Request from EMA

Table 6. Summary of amendments to the statistical analysis plan

Amendment number	Date	Section of SAP changed	Summary of amendment/update	Reason
1	15-Apr-2022	2.2.2.1 Inclusion criteria	Removed inclusion criterion, 'live in an area where COVID-19 vaccination is under way at baseline'	The criterion is implicit and will be met by every participant given the data sources used for the study
1	15-Apr-2022	2.1 Study design	Added an additional risk window of 1-21 days for myocarditis and pericarditis	Request from EMA
1	15-Apr-2022	2.1 Study design	Modified risk intervals and preferred study design for various outcomes	For clarity and to align with the latest version of the protocol
1	15-Apr 2022	7.2.7 Comparison with historical comparators	Added an analysis to describe time trends in AESI during the pre-pandemic, post-pandemic, and post-vaccination periods	Request from CBER

The changes to the statistical analysis documented in the amended protocols and described in the amended SAPs have been implemented:

9.10. Quality control

Rigorous quality control (QC) has been used for all deliverables. Data transformation into the CDM was conducted by each subcontracted research partner from its associated database, using the processes described below. Standard operating procedures or internal process guidance at each research centre 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.

At UMCU, as 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), as the project coordinating centre and 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.

9.10.1. Pedianet

Pedianet data processing included QC steps to verify the correspondence between a diagnostic code and its open-text descriptor, conducted through manual validation of clinical histories, in addition to standardised procedures in SQL and Microsoft Access to extract data from database. Quality control checks of patient general data were conducted through the detection of outlier values and validation rules; grouping of diseases; and regular monitoring of aggregate clinical and drug data. All transformations in the data were logged in R scripts. To ensure code reliability, double programming in R and Stata or Python was used for all scripts. The study is being conducted according to the *Guidelines for Good Pharmacoepidemiology Practices (GPP)*[14] and the *ENCePP Code of Conduct*.[15]

9.10.2. PHARMO (NL)

PHARMO adhered to high standards throughout the research process based on robust methodologies, transparency, and scientific independence, in accordance with the *ENCePP Guide on Methodological Standards in Pharmacoepidemiology*[16] and the *ENCePP Code of Conduct*.[15] PHARMO is ISO 9001:2015 certified. Standard operating procedures, work instructions, and checklists were used to guide the conduct of this study. These procedures and documents include internal quality audits, rules for secure and confidential data storage, methods to maintain and archive project documents, rules and procedures for execution and QC of SAS programming, standards for writing protocols and reports, and requirements for senior scientific review of key study documents.

9.10.3. NHR (University of Oslo) (NO)

The University of Oslo had centralised information security policies in place to preserve the confidentiality, integrity and availability of the organisation's systems and data. All data are stored and analyzed within the TSD platform, a service for sensitive data at the University of Oslo (https://www.uio.no/english/services/it/research/sensitive-data/). Only authorized researchers can access and handle the data within TSD. A two-step authentication process is in place to access TSD. The study was conducted according to the *Guidelines for Good Pharmacoepidemiology Practices (GPP)*[16] and the *ENCePP Code of Conduct*.[15] Data quality is a high priority at the Norwegian Health Registries; updated data are released regularly for research purposes after centralized quality control. The University of Oslo has rules for secure and confidential data storage and analysis, as well as rules for data cleaning, linkage, and programming.

9.10.4. EpiChron (ES)

The EpiChron Cohort is built from the BIGAN platform which integrates a technical infrastructure and a data lake gathering individual patient data from the regional health service information systems. The completion of the hospital CMBD register and the drug dispensation database, is systematic, uniform, and normative, in compliance with legal requirements. Specific on-line training and chart documentation on the use of EHR software was regularly provided to physicians and nurses in Aragon. The BIGAN platform includes several processes to control and improve the quality of its data, mainly in the extraction, transformation, and loading (ETL) processes of capture and persistence in the data lake. Among these mechanisms, there are validation rules (for example, for dates and time intervals) or cross-checks with master tables, requiring that certain coded data exist in a standardised dictionary. Analysis of the distribution of variables is also carried out

periodically, in search of 'outliers' that identify errors in the data capture or transformation processes. As a rule, records that do not validate QA procedures are kept in a 'holding area to be reviewed and discarded or reprocessed. The resulting databases are pseudonymised to encrypt individual-level identification codes, protecting individuals' privacy and complying with data protection laws, and they are stored on a central computer server, with restricted access by members of the research group, using a double-entry password. The research group was a multidisciplinary qualified team including public health specialists, epidemiologists, clinicians, pharmacists, statisticians, and data managers, who were all trained in data management and patient data protection.

9.10.5. SIDIAP (ES)

Data quality processes were implemented at each phase of the data flow cycle. Quality control checks were performed at the extraction and uploading steps. The elements present were described by geographical areas, registering physician, time and the distribution function of values to assess data completeness. Correctness was assessed by validity checks on outliers, out of range values, formatting errors and logical date incompatibilities. Completeness and correctness measures were used to inform decisions on the required transformations to improve data quality (e.g., harmonisation, normalisation, and clean-up) and the fitness of the data for the purpose of this specific research project.

9.10.6. CPRD Aurum (UK)

The DSRU has information security policies in place to preserve the confidentiality, integrity and availability of the organisation's systems and data. These include ensuring that the premises provide suitable physical and environmental security, all equipment is secure and protected against malicious software, the network can be accessed only by authorised staff, telecommunication lines to the premises are protected from interception by being routed overhead or underground, and personnel receive training regarding security awareness. The study will be conducted according to the International Society for Pharmacoepidemiology *Guidelines for Good Pharmacoepidemiology Practices (GPP)*[16] and according to the *ENCePP Code of Conduct*.[15] Data quality is a high priority at the DSRU and is assured through a number of methods based on staff training, validated systems, error prevention, data monitoring, data cleaning, and documentation, including the following:

- Staff training on data processing standard operating procedures
- Data management plan for every research study outlining the legal basis for data collection, data flows, data access rights, data retention periods, etc.
- Routine data cleaning to screen for errors, missing values, and extreme values and diagnose their cause
- System process logs to document staff access, etc.

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 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)*[16] and according to the *ENCePP Code of Conduct*.[15]

10. RESULTS

10.1. Participating data sources

Six of the eight data sources contributed data for this interim report (Section 9.2.1):

- Pedianet (IT)
- PHARMO (NL)
- NHR (NO)
- EpiChron (ES)
- SIDIAP (ES)
- CPRD Arum (UK).

The study period for this fifth interim report started in each country with the first Pfizer-BioNTech COVID-19 vaccinations between 27 December 2020 in EpiChron (Spain) and 6 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 interim report are summarised in Table 3.

Pedianet is an Italian paediatric general practice research database that includes children until the age of 14, after which they are transferred to general practitioners. The vaccination campaign for children in Italy started on 31 May 2021, which is reflected by the different calendar time of first vaccination. AESIs are based on diagnoses in the paediatricians' record, which may include information from hospitalisation, when it is reported back to them, but this may not be complete, which is why Pedianet could not contribute data for all AESIs.

The data in this interim report from PHARMO were extracted from GP records up to 30 June 2023 and hospital records up to 31 December 2022. Data on pregnancy status were not available from PHARMO for this interim report. The International Classification of Primary

Care (ICPC) coding system is used in the PHARMO databases. This is not as granular as International Classification of Diseases (ICD) coding, and therefore identification of AESIs was supplemented with free-text searching. The identification algorithms for free text searches were based on commonly used, internally developed algorithms at PHARMO tailored to this study. These algorithms enable additional cases to be classified and thus will improve sensitivity of AESI identification. The algorithms were not formally validated for this study. Substantial efforts were made to improve the ETL script for the events, which has led to increases in rates, and rates that are more aligned with other data sources.

The NHR data source provided GP data from the Norway Control and Payment of Primary Health Care Refunds (KUHR) and hospital data from the Norwegian Patient Registry up to 31 December 2022 for this report. The KUHR GP data source is at max 4 digits for ICPC2 codes because more details digits are not used in the KUHR GP data source. This can lead to a less specific identification of events resulting in higher event and incident numbers from Norway.

The EpiChron data sources included diagnostic codes from general practitioners and from hospital discharge records up to 31 July 2023 for this interim report.

The SIDIAP data source included diagnostic codes from general practitioners and from hospital discharge records up to 30 June 2023 in this interim report #5. However, because of differences in lag times in different data bases within SIDAP and delays in notifications about hospitalisations data for the end of the follow-up period, may be incomplete.

The CPRD Aurum data source included diagnostic codes from general practitioners up to 21 March 2022 for this interim report.

All the matching criteria were used except pregnancy in PHARMO, CPRD and Pedianet, socio-economic indicator in CPRD, and influenza vaccination in NHR and the balance between the matched vaccinated and unvaccinated cohorts was verified. We have also included data for those who received a third and fourth (booster) dose of the Pfizer-BioNTech COVID-19 vaccine, which was implemented in many countries in the fall of 2022. In addition, PS adjusted risk estimates were included. Pregnancy data were not available for this interim report.

Two data sources, ARS and HSD from Italy, could not contribute data to this interim report:

- Data from ARS were reported in the first and second interim reports, but due to an ongoing review of the data protection law and the secondary use of the Tuscany administrative data, the research team at ARS have to suspend research temporarily.

- Data on COVID-19 vaccination were missing for a high percentage of individuals in HSD (Italian GP databases) and it was, therefore, not considered to be fit-for-purpose. In Italy, GPs were involved in the COVID-19 vaccination campaign in March 2021 only for their patients aged 80 or older. There was no automated system to collect data on patients' vaccination status, and recording this information depended entirely on the efforts of the GPs. Since it is mandatory for Italian GPs to collect vaccine-related information for their own electronic dossiers, the accuracy of vaccine

registration is expected to improve over the coming months. However, we cannot exclude the possibility that recording of vaccine brand may be selective. We will monitor vaccine uptake data in HSD to assess whether data are fit-for-purpose.

10.1.1. Vaccinated cohort

From among the 17,677,132 individuals who received ≥1 dose of the Pfizer-BioNTech COVID-19 vaccine, application of the inclusion criteria of being enrolled at least 12 months in the database and not having received a prior non-Pfizer COVID-19 vaccination yielded a total of 12,613,349 (71.35%) eligible individuals (Table 7). These individuals were from Italy (Pedianet 10,547 (0.08% of the total eligible population); the Netherlands (PHARMO 1,091,265 (8.65%)), Norway (NHR 3,587,702 (28.44%)), Spain (EpiChron 735,237 (5.83%) and SIDIAP 3,089,610 (24.50%)) and the UK (CPRD Aurum 4,098,988 (32.50%). The main reason for exclusion was the receipt of a COVID-19 vaccine other than Pfizer-BioNTech; the highest exclusion rate was in CPRD Aurum (47.26%) and the lowest in NHR (10.37%). A total of 26,980 pregnant women who had received at least one dose of the Pfizer-BioNTech COVID-19 vaccine were included.

Table 7. Attrition table for the Pfizer-BioNTech COVID-19 vaccinated cohort (before matching) by data source*

	Pedianet n (%)	NHR n (%)	PHARMO n (%)	EpiChron n (%)	SIDIAP n (%)	CPRD Aurum n (%)
Received a first dose of Pfizer-BioNTech COVID-19 vaccine	12,046 (100)	4,002,649 (100)	1,230,629 (100)	887,188 (100)	3,772,034 (100)	7,772,586 (100)
Had ≥12 months continuous enrolment[a] AND received a Pfizer-BioNTech vaccine	11,284 (93.67)	3,962,140 (98.99)	1,222,172 (99.31)	871,425 (98.22)	3,699,954 (98.09)	6,764,107 (87.03)
Received no prior COVID-19 vaccination, other than Pfizer-BioNTech vaccine, AND had ≥12 months continuous enrolment AND received a Pfizer-BioNTech vaccine	10,547 (87.56)	3,587,702 (89.63)	1,091,265 (88.68)	735,237 (82.87)	3,089,610 (81.91)	4,098,988 (52.74)
Total Pfizer-BioNTech COVID-19 vaccinated cohort[b]	10,547 (87.56)	3,587,702 (89.63)	1,091,265 (88.68)	735,237 (82.87)	3,089,610 (81.91)	4,098,988 (52.74)
Pregnant women vaccinated with 1st dose Pfizer-BioNTech vaccinated included**	0	13,708 (0.34)	0	3,225 (0.36)	10,047 (0.27)	0

a ≥12 months continuous enrolment before t0 (time of vaccination) or lifetime enrolment if age <12 months
b ≥12 months continuous enrolment AND no prior COVID-19 vaccination
*Refer to Table 3 for information on time periods for data; ** Pedianet only has data for a paediatric population, and pregnancy data for PHARMO and CPRD Aurum will be available for the final report and pregnancy outcomes will be reported

10.1.1.1. Number and timing of doses in the vaccinated cohort before matching

The number of Pfizer-BioNTech COVID 19 vaccine doses and the timing of vaccination (in weeks) by data source are summarized in Table 8. Overall as a total of all data sources, 10,665,306 persons received a second dose (84.6%). The interval between the first and second doses was longer than 6 weeks for 16.6% of these individuals in all data sources except CPRD Aurum. In CPRD Aurum 81.27% were vaccinated with the second dose outside the 6-week window. This 6-week interval is based on the recommended 4-week scheme, with an additional 2-week security margin, except in the UK, where the recommendation was for a 3-month interval. The number of individuals who received a second dose within 6 weeks after the 1st dose varied from 53.9% in NHR to 90.0% in EpiChron. In the paediatric data source, Pedianet, 83.1% of the children received their second dose within six weeks, at the time of database lock.

At the time of database lock (Table 3), a total of 4,642,445 individuals received a third dose of the Pfizer-BioNTech COVID 19 vaccine, which is 36.8% of the individuals included who had received the 1st dose. The interval between doses 2 and 3 varied between data sources with medians that ranged from 21 weeks (Pedianet) to 31 weeks (SIDIAP). The current EMA guidelines recommend 28 days between 2nd and 3rd dose for individuals older than 5 years and at least 3 months for the booster dose (i.e., Comirnaty 30 micrograms) after primary vaccination for individuals older than 12 years.[17] In Spain (EpiChron and SIDIAP) individuals aged 18 years and older were recommended to receive a first booster (i.e., third dose) five months after the last dose of the complete vaccination schedule. In the Netherlands (PHARMO) individuals older than 11 years were recommended to receive repeated vaccinations after at least 3 months after the last vaccination. In Italy (Pedianet) and Norway (NHR) specific recommendations are for at special risk population only.

A total of 1,021,555 individuals received a fourth dose (8.1%) and 7,801 (0.1%) a fifth dose at the time of database lock.

Table 8. Pfizer-BioNTech COVID‑19 vaccine doses received (n, %) and timing (in weeks) by data source*

	Pedianet	NHR	PHARMO	EpiChron	SIDIAP	CPRD Aurum
Total first dose COVID-19 vaccine received, N	10,547 (100)	3,587,702 (100)	1,091,265 (100)	735,237 (100)	3,089,610 (100)	4,098,988 (100)
Second dose COVID-19 vaccine received						
Within 6 weeks (completion rate) after 1st dose, n (%)	8,762 (83.08)	1,935,334 (53.94)	722,638 (66.22)	657,921 (89.48)	2,601,256 (84.19)	229,496 (5.60)
>6 weeks after 1st dose, n (%)	247 (2.34)	816,101 (22.75)	123,462 (11.31)	27,749 (3.77)	211,158 (6.83)	3,331,182 (81.27)
Total second dose received, n (%)	9,009 (85.42)	2,751,435 (76.69)	846,100 (77.53)	685,670 (93.26)	2,812,414 (91.03)	3,560,678 (86.87)
Interval between first and second dose COVID-19 vaccine (weeks)						
Median (Q1, Q3) (weeks)	3.14 (3.00, 3.86)	6.00 (5.86, 7.29)	5.00 (5.00, 5.14)	3.00 (3.00, 3.00)	3.00 (3.00,3.29)	10.57 (8.43, 11.29)
Minimum, maximum (weeks)	[2.29-45.86]	[2.14-93.86]	[2.14-106.71]	[2.29-111.14]	[2.14-107]	[2.14-64.43]
< 2 weeks, n (%)	0	0	0	0	0	0
2-4 weeks, n (%)	7,975 (88.52)	530,109 (19.27)	133,231 (15.75)	654,635 (95.47)	2,566,260 (91.25)	130,728 (3.67)
5-6 weeks, n (%)	787 (8.74)	1,405,225 (51.07)	589,407 (69.66)	3,286 (0.48)	34,996 (1.24)	98,768 (2.77)
7-8 weeks, n (%)	25 (0.28)	414,419 (15.06)	10,032 (1.19)	1,317 (0.19)	80,327 (2.86)	833,971 (23.42)
9-12 weeks, n (%)	9 (0.10)	278,706 (10.13)	8,359 (0.99)	1,605 (0.23)	54,794 (1.95)	2,028,717 (56.98)
13-18 weeks, n (%)	24 (0.27)	37,409 (1.36)	7,315 (0.86)	2,113 (0.31)	23,125 (0.82)	275,106 (7.73)
>18 weeks, n (%)	189 (2.10)	85,567 (3.11)	97,756 (11.55)	22,714 (3.31)	52,912 (1.88)	193,388 (5.43)
Third dose COVID-19 vaccine received	1,230 (11.66)	1,782,452 (49.68)	222,344 (20.37)	237,270 (32.27)	489,483 (15.84)	1,909,666 (46.59)
Interval between second and third dose COVID-19 vaccine (weeks)						
Median (Q1, Q3) (weeks)	21.43 (19.14, 24.86)	26.14 (21.86, 29.14)	26.14 (22.86, 33.86)	29.86 (27.43, 35.00)	31 (27.43, 43.14)	27.29 (24.43, 29.29)
Minimum, maximum (weeks)	[14.14-55.57]	[13-99]	[13-108]	[19.43-129.43]	[13-123.43]	[13-62]

Table 8. Pfizer-BioNTech COVID‑19 vaccine doses received (n, %) and timing (in weeks) by data source*

	Pedianet	NHR	PHARMO	EpiChron	SIDIAP	CPRD Aurum
<12 weeks, n (%)	0	0	0	0	0	0
12-24 weeks, n (%)	925 (75.20)	718,926 (40.33)	97,687 (43.94)	12,506 (5.27)	19,005 (3.88)	498,500 (26.10)
25-37 weeks, n (%)	277 (22.52)	915,451 (51.36)	83,918 (37.74)	173,256 (73.02)	320,713 (65.52)	1,344,468 (70.40)
38-50 weeks, n (%)	24 (1.95)	128,686 (7.22)	28,293 (12.72)	24,114 (10.16)	75,538 (15.43)	66,135 (3.46)
>50 weeks, n (%)	4 (0.33)	19,389 (1.09)	12,446 (5.60)	27,394 (11.55)	74,227 (15.16)	563 (0.03)
Fourth dose COVID-19 vaccine received	16 (0.15)	641,085 (17.87)	27,488 (2.52)	67,799 (9.22)	256,834 (8.31)	28,333 (0.69)
Interval between third and fourth dose COVID-19 vaccine (weeks)						
Median (Q1, Q3) (weeks)	41.43 (40.61, 44.25)	40.71 (37.57, 44.71)	40.57 (25.00, 43.57)	49.00 (47.14, 51.43)	49.86 (47.71, 52.57)	16.00 (14.14, 18.43)
Minimum, maximum (weeks)	[32.57-45.86]	[13-78.57]	[13-84.29]	[19.43-87.29]	[13-90]	[13-37.14]
<12 weeks, n (%)	0	0	0	0	0	0
12-24 weeks, n (%)	0	18,672 (2.91)	6,832 (24.85)	652 (0.96)	2,225 (0.87)	28,181 (99.46)
25-37 weeks, n (%)	2 (12.50)	156,815 (24.46)	3,982 (14.49)	2,408 (3.55)	6,361 (2.48)	152 (0.54)
38-50 weeks, n (%)	14 (87.50)	428,152 (66.79)	15,273 (55.56)	44,965 (66.32)	148,333 (57.75)	0
>50 weeks, n (%)	0	37,446 (5.84)	1,401 (5.10)	19,774 (29.17)	99,915 (38.90)	0
Fifth dose COVID-19 vaccine received	0	5,259 (0.15)	2,248 (0.21)	60 (0.01)	234 (0.01)	0
Interval between third and fourth dose COVID-19 vaccine (weeks)						
Median (Q1, Q3) (weeks)	NA	32.00 (23.14, 38.14)	25.00 (18.43, 28.14)	28.07 (22.82, 31.21)	26.86 (22.00, 29.82)	NA
Minimum, maximum (weeks)	NA	[13-56.14]	[13-50.43]	[19.86-49.14]	[13.29-54]	NA
<12 weeks, n (%)	0	0	0	0	0	0
12-24 weeks, n (%)	0	1,489 (28.31)	1,085 (48.27)	22 (36.67)	91 (38.89)	0
25-37 weeks, n (%)	0	2,394 (45.52)	1,089 (48.44)	37 (61.67)	123 (52.56)	0

Table 8. Pfizer-BioNTech COVID‑19 vaccine doses received (n, %) and timing (in weeks) by data source*

	Pedianet	NHR	PHARMO	EpiChron	SIDIAP	CPRD Aurum
38-50 weeks, n (%)	0	1,370 (26.05)	74 (3.29)	1 (1.67)	17 (7.26)	0
>50 weeks, n (%)	0	6 (0.11)	0	0	3 (1.28)	0

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

10.1.1.2. Baseline characteristics of vaccinated cohort (before matching)

The baseline characteristics of those who received at least one dose and three doses of the Pfizer-BioNTech COVID-19 vaccine in the vaccinated cohort are summarised in Table 9. The median age of the vaccinated cohort at first dose ranged from 36 years in CPRD Aurum to 49 years in PHARMO and EpiChron. The median age at first dose in Pedianet, that contains data for children only, was 10 years. The percentage of females among those who received a 1st dose varied from 49.10% in Pedianet to 52.70% in CPRD Aurum (Table 9).

A maximum (i.e., with masking of numbers under five) of 162 children under 5 years of age received a first dose of the Pfizer-BioNTech COVID-19 vaccine.

A total of 9,234 pregnant women received their first dose during their first trimester of pregnancy and 9,763 during their second trimester.

Most individuals received their first dose in the second quarter of 2021, except in CPRD Aurum, where it was the first quarter 2021, and Pedianet where the first dose was mainly received in the last quarter of 2021 and the first quarter of 2022, since paediatric vaccination began in Italy on 31 May 2021. The third dose was most frequently received in the fourth quarter of 2021, except in PHARMO where it was received in the first quarter 2022.

The median age of individuals who received a third dose ranged from 36 years in PHARMO to 74 years in SIDIAP. The percentages of females among those who received a third dose ranged from 49.43% in Pedianet to 56.75% in SIDIAP.

Information on long-term care facility residency and healthcare or essential worker status was not available in the databases. Only limited Information on personal lifestyle variables was available: smoking status was only available in PHARMO, EpiChron, and SIDIAP, but not for all individuals, and although BMI was available in Pedianet, PHARMO, EpiChron, and SIDIAP the level of missing data was high. Available data for personal lifestyle variables showed that between 5-10% of those who received dose 1 and dose 3 were current smokers in EpiChron and SIDIAP and between 1-5% in PHARMO. BMI data indicated overweight and obesity of below 5% of dose 1 and 3 vaccinated in PHARMO, around 5% in EpiChron, and between 10-20% in SIDIAP. In SIDIAP 14.95% of those who received dose 1 and 21.04% of those who received dose 3 had been diagnosed as obese. In the other data sources the percentages were below 8% for both doses. Between 61.72% in PHARMO and 81.39% in EpiChron of those vaccinated had used primary care at least twice in the year prior to their 1st dose. In the year prior to vaccination, between 0.84% in Pedianet and 2.96% in NHR of those who had received a first dose had been hospitalised at least two times.

Table 9. PART 1: Baseline demographics, lifestyle variables and healthcare utilisation at the time of the first and third Pfizer-BioNTech COVID-19 vaccine doses in the Pfizer-BioNTech vaccinated cohort, by data source*

(SEE PART 2 BELOW)

	Pedianet		NHR		PHARMO	
Baseline characteristics	**1st dose**	**3rd dose**	**1st dose**	**3rd dose**	**1st dose**	**3rd dose**
Total, n (%)	10,547	1,230	3,587,702	1,782,452	1,091,265	222,344
Demographics						
Age (years)						
Mean (SD)	9.40 (2.48)	12.76 (0.66)	46.95 (21.06)	58.04 (18.89)	48.66 (21.74)	42.30 (20.09)
Median (Q1, Q3)	10 (7, 12)	13 (12, 13)	47 (29, 64)	61 (46, 73)	49 (30, 69)	36 (27,56)
Age groups (years), n (%)						
0-1	0	0	5 (<0.01)	0	<5	0
2-4	17 (0.16)	0	6 (<0.01)	0	78 (0.01)	0
5-11	7,757 (73.55)	0	10,287 (0.29)	16 (<0.01)	10,086 (0.92)	11 (<0.01)
12-15	2,773 (26.29)	1,230 (100)	209,840 (5.85)	290 (0.02)	62,493 (5.73)	3,584 (1.61)
16-17	NA	NA	119,437 (3.33)	1,053 (0.06)	36,286 (3.33)	3,795 (1.71)
18-29	NA	NA	578,954 (16.14)	196,287 (11.01)	150,513 (13.79)	60,957 (27.42)
30-39	NA	NA	490,131 (13.66)	141,347 (7.93)	141,492 (12.97)	59,349 (26.69)
40-49	NA	NA	516,944 (14.41)	204,150 (11.45)	147,143 (13.48)	27,489 (12.36)
50-59	NA	NA	551,359 (15.37)	303,446 (17.02)	185,075 (16.96)	20,250 (9.11)
60-64	NA	NA	244,051 (6.80)	160,737 (9.02)	15,071 (1.38)	4,733 (2.13)
65-69	NA	NA	241,396 (6.73)	205,416 (11.52)	90,180 (8.26)	7,663 (3.45)
70-79	NA	NA	411,663 (11.47)	372,108 (20.88)	177,166 (16.23)	20,303 (9.13)
80+	NA	NA	213,629 (5.95)	197,602 (11.09)	75,680 (6.94)	14,210 (6.39)
Female, n (%)	5,179 (49.10)	608 (49.43)	1,780,147 (49.62)	928,599 (52.10)	557,320 (51.07)	115,032 (51.74)
Females aged 14 to 50 years, n (%)	0	0	884,364 (49.68)	302,171 (32.54)	256,091 (45.95)	77,731 (67.57)
Pregnancy status, n (%)						

Table 9. PART 1: Baseline demographics, lifestyle variables and healthcare utilisation at the time of the first and third Pfizer-BioNTech COVID-19 vaccine doses in the Pfizer-BioNTech vaccinated cohort, by data source*

(SEE PART 2 BELOW)

	Pedianet		NHR		PHARMO	
Baseline characteristics	**1st dose**	**3rd dose**	**1st dose**	**3rd dose**	**1st dose**	**3rd dose**
First trimester	0	0	4,871 (35.57)	1,721 (28.13)	NA	NA
Second trimester	0	0	4,654 (33.98)	3,148 (51.46)	NA	NA
Third trimester	0	0	4,171 (30.45)	1,248 (20.40)	NA	NA
Date of vaccination, n (%)						
1 Oct–31 Dec 2020	0	0	10,495 (0.29)	0	7 (<0.01)	0
1 Jan–31 Mar 2021	<5	0	499,803 (13.93)	0	117,235 (10.74)	0
1 Apr–30 Jun 2021	198 (1.88)	0	1,681,233 (46.86)	47 (<0.01)	548,206 (50.24)	113 (0.05)
1 Jul–30 Sep 2021	1,679 (15.92)	0	1,240,266 (34.57)	13,090 (0.73)	312,169 (28.61)	289 (0.13)
1 Oct–31 Dec 2021	3,326 (31.54)	<5	111,749 (3.11)	1,167,113 (65.48)	58,228 (5.34)	47,491 (21.36)
1 Jan–31 Mar 2022	5,133 (48.67)	1,087 (88.37)	34,715 (0.97)	548,321 (30.76)	38,966 (3.57)	138,306 (62.20)
1 Apr–30 Jun 2022	139 (1.32)	92 (7.48)	6,317 (0.18)	25,152 (1.41)	4,248 (0.39)	12,424 (5.59)
1 Jul–30 Sep 2022	57 (0.54)	29 (2.36)	2,000 (0.06)	17,591 (0.99)	3,413 (0.31)	6,905 (3.11)
1 Oct–31 Dec 2022	14 (0.13)	19 (1.54)	1,124 (0.03)	11,138 (0.62)	8,263 (0.76)	15,372 (6.91)
Personal lifestyle characteristics						
Smoking status, n (%)						
Current	NA	NA	NA	NA	46,496 (4.26)	7,310 (3.29)
Former	NA	NA	NA	NA	96,172 (8.81)	11,538 (5.19)
Never	NA	NA	NA	NA	150,747 (13.81)	23,952 (10.77)
Never or former	NA	NA	NA	NA	0	0
Unknown	NA	NA	NA	NA	797,850 (73.11)	179,544 (80.75)
Body Mass Index, n (%)**						
Underweight (BMI < 20 kg/m2)	6,121 (58.04)	571 (46.42)	NA	NA	1,792 (0.16)	416 (0.19)

Table 9. PART 1: Baseline demographics, lifestyle variables and healthcare utilisation at the time of the first and third Pfizer-BioNTech COVID-19 vaccine doses in the Pfizer-BioNTech vaccinated cohort, by data source*

(SEE PART 2 BELOW)

	Pedianet		NHR		PHARMO	
Baseline characteristics	**1st dose**	**3rd dose**	**1st dose**	**3rd dose**	**1st dose**	**3rd dose**
Normal weight (BMI 20 to < 25 kg/m2)	1,306 (12.38)	278 (22.60)	NA	NA	16,620 (1.52)	3,749 (1.69)
Overweight (BMI 25 to < 30 kg/m2)	267 (2.53)	67 (5.45)	NA	NA	32,051 (2.94)	6,784 (3.05)
Obese (BMI ≥ 30 kg/m2)	51 (0.48)	20 (1.63)	NA	NA	22,843 (2.09)	5,031 (2.26)
BMI missing	2,802 (26.57)	294 (23.90)	NA	NA	1,017,959 (93.28)	206,364 (92.81)
Obesity diagnosis or obesity surgery	581 (5.51)	90 (7.32)	121,186 (3.38)	75,473 (4.23)	13,743 (1.26)	2,966 (1.33)
Healthcare utilisation						
Number of hospitalisations, n (%)						
0	10,159 (96.32)	1,184 (96.26)	3,221,921 (89.80)	1,554,994 (87.24)	NA	NA
1	299 (2.83)	39 (3.17)	259,653 (7.24)	152,648 (8.56)	NA	NA
2+	89 (0.84)	7 (0.57)	106,128 (2.96)	74,810 (4.20)	NA	NA
Number of emergency department visits, n (%)						
0	9,304 (88.21)	1,073 (87.24)	NA	NA	NA	NA
1	984 (9.33)	122 (9.92)	NA	NA	NA	NA
2+	259 (2.46)	35 (2.85)	NA	NA	NA	NA
Skilled nursing facility, nursing home, extended care facility, n (%)						
0	NA	NA	NA	NA	NA	NA
1	NA	NA	NA	NA	NA	NA
2+	NA	NA	NA	NA	N!a	NA
Primary care utilisation, n visits (%)						

Table 9. PART 1: Baseline demographics, lifestyle variables and healthcare utilisation at the time of the first and third Pfizer-BioNTech COVID-19 vaccine doses in the Pfizer-BioNTech vaccinated cohort, by data source*

(SEE PART 2 BELOW)

	Pedianet		NHR		PHARMO	
Baseline characteristics	**1st dose**	**3rd dose**	**1st dose**	**3rd dose**	**1st dose**	**3rd dose**
0	1,296 (12.29)	136 (11.06)	509,272 (14.19)	226,088 (12.68)	259,808 (23.81)	53,716 (24.16)
1	1,746 (16.55)	201 (16.34)	367,341 (10.24)	147,512 (8.28)	157,964 (14.48)	32,927 (14.81)
2+	7,505 (71.16)	893 (72.60)	2,711,089 (75.57)	1,408,852 (79.04)	673,493 (61.72)	135,701 (61.03)
Cancer screening, n (%)						
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	2,964 (28.10)	173 (14.07)	NA	NA	NA	NA
1-2	6,521 (61.83)	836 (67.97)	NA	NA	NA	NA
3-4	976 (9.25)	203 (16.50)	NA	NA	NA	NA
5+	86 (0.82)	18 (1.46)	NA	NA	NA	NA

*Refer to Table 3 for information on time periods for data; ** Child-specific BMI algorithm is pending validation; ***NHR only records positive COVID-19 test results so the number of tests performed is not available
NA: not applicable

Table 9. PART 2: Baseline demographics, lifestyle variables and healthcare utilisation at the time of the first and third Pfizer-BioNTech COVID-19 vaccine doses in the Pfizer-BioNTech vaccinated cohort, by data source

(SEE PART 1 ABOVE)

	EpiChron		SIDIAP		CPRD Aurum	
Baseline characteristics	**1st dose**	**3rd dose**	**1st dose**	**3rd dose**	**1st dose**	**3rd dose**
Total, n (%)	735,237	237,270	3,089,610	489,483	4,098,988	1,909,666
Demographics						
Age (years)						
Mean (SD)	50.56 (21.68)	59.99 (19.75)	45.06 (22.62)	63.34 (23.06)	42.36 (22.63)	54.73 (21.73)
Median (Q1, Q3)	49 (35, 70)	58 (46.00, 76)	45 (27, 58)	74 (44, 81)	36 (24, 61)	56 (35, 74)
Age groups (years), n (%)						
0-1	0	0	<5	0	<5	0
2-4	0	0	33 (<0.01)	<5	8 (<0.01)	0
5-11	2,651 (0.36)	0	190,872 (6.18)	255 (0.05)	7,539 (0.18)	<5
12-15	36,900 (5.02)	920 (0.39)	197,402 (6.39)	2,680 (0.55)	337,861 (8.24)	882 (0.05)
16-17	17,685 (2.41)	1,856 (0.78)	98,269 (3.18)	3,651 (0.75)	194,075 (4.73)	17,805 (0.93)
18-29	81,355 (11.07)	14,038 (5.92)	349,245 (11.30)	54,134 (11.06)	938,760 (22.90)	282,772 (14.81)
30-39	93,222 (12.68)	20,799 (8.77)	402,647 (13.03)	41,382 (8.45)	856,638 (20.90)	328,394 (17.20)
40-49	144,299 (19.63)	39,676 (16.72)	610,817 (19.77)	50,159 (10.25)	354,007 (8.64)	186,534 (9.77)
50-59	125,143 (17.02)	48,013 (20.24)	516,261 (16.71)	42,287 (8.64)	338,352 (8.25)	224,484 (11.76)
60-64	13,581 (1.85)	5,182 (2.18)	40,503 (1.31)	7,156 (1.46)	168,489 (4.11)	123,983 (6.49)
65-69	33,854 (4.60)	12,781 (5.39)	43,728 (1.42)	4,961 (1.01)	168,959 (4.12)	127,872 (6.70)
70-79	104,985 (14.28)	48,424 (20.41)	387,065 (12.53)	128,235 (26.20)	373,129 (9.10)	311,740 (16.32)
80+	81,562 (11.09)	45,581 (19.21)	252,766 (8.18)	154,579 (31.58)	361,168 (8.81)	305,198 (15.98)
Female, n (%)	383,543 (52.17)	125,765 (53.01)	1,604,257 (51.92)	277,783 (56.75)	2,159,983 (52.70)	1,068,133 (55.93)
Females aged 14 to 50 years, n (%)	179,872 (46.90)	41,722 (33.17)	780,629 (48.66)	81,714 (29.42)	1,272,611 (58.92)	467,770 (43.79)
Pregnancy status, n (%)						

Table 9. PART 2: Baseline demographics, lifestyle variables and healthcare utilisation at the time of the first and third Pfizer-BioNTech COVID-19 vaccine doses in the Pfizer-BioNTech vaccinated cohort, by data source

(SEE PART 1 ABOVE)

	EpiChron		SIDIAP		CPRD Aurum	
Baseline characteristics	**1st dose**	**3rd dose**	**1st dose**	**3rd dose**	**1st dose**	**3rd dose**
First trimester	921 (28.60)	83 (22.68)	3,442 (34.31)	334 (34.90)	NA	NA
Second trimester	1,383 (42.95)	175 (47.81)	3,726 (37.14)	364 (38.04)	NA	NA
Third trimester	916 (28.45)	108 (29.51)	2,864 (28.55))	259 (27.06)	NA	NA
Date of vaccination, n (%)						
1 Oct–31 Dec 2020	2,297 (0.31)	0	3,401 (0.11)	0	192,811 (4.70)	0
1 Jan–31 Mar 2021	106,096 (14.43)	0	365,417 (11.83)	0	1,591,029 (38.82)	0
1 Apr–30 Jun 2021	379,460 (51.61)	0	1,588,038 (51.40)	8 (<0.01)	1,223,197 (29.84)	42 (<0.01)
1 Jul–30 Sep 2021	224,287 (30.51)	11,418 (4.81)	855,425 (27.69)	20,952 (4.28)	512,769 (12.51)	138,511 (7.25)
1 Oct–31 Dec 2021	16,365 (2.23)	101,746 (42.88)	168,924 (5.47)	273,618 (55.90)	447,894 (10.93)	1,538,451 (80.56)
1 Jan–31 Mar 2022	4,726 (0.64)	81,254 (34.25)	91,825 (2.97)	43,745 (8.94)	131,288 (3.20)	232,662 (12.18)
1 Apr–30 Jun 2022	604 (0.08)	11,614 (4.89)	8,177 (0.26)	64,122 (13.10)	NA	NA
1 Jul–30 Sep 2022	437 (0.06)	12,228 (5.15)	4,142 (0.13)	49,251 (10.06)	NA	NA
1 Oct–31 Dec 2022	586 (0.08)	12,953 (5.46)	2,526 (0.08)	26,343 (5.38)	NA	NA
Personal lifestyle characteristics						
Smoking status, n (%)						
Current	49,706 (6.76)	16,164 (6.81)	268,594 (8.69)	27,891 (5.70)	NA	NA
Former	0	0	89,577 (2.90)	19,790 (4.04)	NA	NA
Never	0	0	1,025,000 (33.18)	243,772 (49.80)	NA	NA
Never or former	135,119 (18.38)	55,506 (23.39)	0	0	NA	NA
Unknown	550,412 (74.86)	165,600 (69.79)	1,706,439 (55.23)	198,030 (40.46)	NA	NA
Body Mass Index, n (%)						

Table 9. PART 2: Baseline demographics, lifestyle variables and healthcare utilisation at the time of the first and third Pfizer-BioNTech COVID-19 vaccine doses in the Pfizer-BioNTech vaccinated cohort, by data source

(SEE PART 1 ABOVE)

	EpiChron		SIDIAP		CPRD Aurum	
Baseline characteristics	**1st dose**	**3rd dose**	**1st dose**	**3rd dose**	**1st dose**	**3rd dose**
Underweight (BMI < 20 kg/m2)	18,529 (2.52)	2,288 (0.96)	242,023 (7.83)	10,554 (2.16)	NA	NA
Normal weight (BMI 20 to < 25 kg/m2)	44,307 (6.03)	11,245 (4.74)	378,352 (12.25)	69,809 (14.26)	NA	NA
Overweight (BMI 25 to < 30 kg/m2)	44,365 (6.03)	16,789 (7.08)	469,428 (15.19)	121,042 (24.73)	NA	NA
Obese (BMI ≥ 30 kg/m2)	33,299 (4.53)	14,200 (5.98)	350,983 (11.36)	87,386 (17.85)	NA	NA
BMI missing	594,737 (80.89)	192,748 (81.24)	1,648,824 (53.37)	200,692 (41)	NA	NA
Obesity diagnosis or obesity surgery	47,873 (6.51)	17,665 (7.45)	461,774 (14.95)	102,999 (21.04)	177,831 (4.34)	113,375 (5.94)
Healthcare utilisation						
Number of hospitalisations, n (%)						
0	675,629 (91.89)	213,464 (89.97)	2,868,988 (92.86)	425,078 (86.84)	4,020,290 (98.08)	1,861,773 (97.49)
1	47,532 (6.46)	18,130 (7.64)	176,813 (5.72)	46,656 (9.53)	60,831 (1.48)	36,642 (1.92)
2+	12,076 (1.64)	5,676 (2.39)	43,809 (1.42)	17,749 (3.63)	17,867 (0.44)	11,251 (0.59)
Number of emergency department visits, n (%)						
0	594,158 (80.81)	188,645 (79.51)	NA	NA	3,648,640 (89.01)	1,678,366 (87.89)
1	95,611 (13)	32,562 (13.72)	NA	NA	306,897 (7.49)	154,567 (8.09)
2+	45,468 (6.18)	16,063 (6.77)	NA	NA	143,451 (3.50)	76,733 (4.02)
Skilled nursing facility, nursing home, extended care facility, n (%)						
0	NA	NA	NA	NA	4,094,595 (99.89)	1,907,419 (99.88)
1	NA	NA	NA	NA	3,071 (0.07)	1,630 (0.09)
2+	NA	NA	NA	NA	1,322 (0.03)	617 (0.03)

Table 9. PART 2: Baseline demographics, lifestyle variables and healthcare utilisation at the time of the first and third Pfizer-BioNTech COVID-19 vaccine doses in the Pfizer-BioNTech vaccinated cohort, by data source

(SEE PART 1 ABOVE)

	EpiChron		SIDIAP		CPRD Aurum	
Baseline characteristics	**1st dose**	**3rd dose**	**1st dose**	**3rd dose**	**1st dose**	**3rd dose**
Primary care utilisation, n visits (%)						
0	84,598 (11.51)	16,016 (6.75)	400,364 (12.96)	21,726 (4.44)	NA	NA
1	52,260 (7.11)	13,792 (5.81)	235,349 (7.62)	15,840 (3.24)	NA	NA
2+	598,379 (81.39)	207,462 (87.44)	2,453,897 (79.42)	451,917 (92.33)	NA	NA
Cancer screening, n (%)						
0	NA	NA	NA	NA	3,601,937 (87.87)	1,440,630 (75.44)
1	NA	NA	NA	NA	287,783 (7.02)	206,013 (10.79)
2+	NA	NA	NA	NA	209,268 (5.11)	263,023 (13.77)
COVID-19 tests, n (%)						
0	518,190 (70.48)	132,574 (55.87)	1,368,977 (44.31)	170,171 (34.77)	2,697,394 (65.81)	1,084,754 (56.80)
1-2	217,047 (29.52)	104,696 (44.13)	1,209,464 (39.15)	181,381 (37.06)	1,095,722 (26.73)	563,293 (29.50)
3-4	0	0	346,542 (11.22)	71,857 (14.68)	188,843 (4.61)	138,670 (7.26)
5+	0	0	164,627 (5.33)	66,074 (13.50)	117,029 (2.86)	122,949 (6.44)

*Refer to Table 3 for information on time periods for data
NA: not applicable

10.1.2. Matched cohorts

The attrition data for the matched vaccinated and unvaccinated cohorts are summarised by data source in Table 10. From a total of 12,613,349 vaccinated individuals included, 12,400,847 (98.32%) could be matched with an unvaccinated individual at time zero (Table 10). Unvaccinated individuals were eligible to be matched until they received any COVID-19 vaccine. Although each unvaccinated individual could be matched several times, the median number of times was one in each of the data sources.

Table 10. Attrition table for the matched cohort by data source*

	Pedianet	NHR	PHARMO	EpiChron	SIDIAP	CPRD Aurum
Vaccinated cohort						
Received a Pfizer-BioNTech vaccine, n (%)	12,046 (100)	4,002,649 (100)	1,230,629 (100)	887,188 (100)	3,772,034 (100)	7,772,586 (100)
Total vaccinated included, n (%)[a]	10,547 (87.56)	3,587,702 (89.63)	1,091,265 (88.68)	735,237 (82.87)	3,089,610 (81.91)	4,098,988 (52.74)
Pregnant women vaccinated, n (%)	0	13,708 (0.34)	NA	3,225 (0.36)	10,047 (0.27)	NA
Matched cohort						
Vaccinees matched, n (%)	10,500 (87.17)	3,584,238 (89.55)	992,144 (80.62)	627,972 (70.78)	3,087,124 (81.84)	4,098,869 (52.73)
Served as control before vaccination, n (%)	3,061 (29.15)	2,474,628 (69.04)	380,302 (38.33)	298,505 (47.53)	1,657,254 (53.68)	1,347,172 (32.87)
Unvaccinated, n	10,500	3,584,238	992,144	627,972	3,087,124	4,098,869
Unique unvaccinated matched included, n (%)	8,022 (76.40)	2,082,345 (58.10)	706,102 (71.17)	394,137 (62.76)	1,962,666 (63.58)	3,059,568 (74.64)
Mean number of times a comparator selected for matching	1.31	1.72	1.41	1.59	1.57	1.34
Median (Q1–Q3)	1 (1.00–1.00)	1 (1.00–2.00)	1 (1.00–2.00)	1 (1.00–2.00)	1 (1.00–2.00)	1 (1.00–2.00)
Min, Max	1 (6)	1 (15)	1 (10)	1 (23)	1 (15)	1 (12)
1, n (%)	6,084 (75.84)	1,187,374 (57.02)	496,100 (70.26)	248,034 (62.93)	1,233,234 (62.83)	2,268,076 (55.33)
2, n (%)	1,506 (18.77)	524,128 (25.17)	152,871 (21.65)	91,510 (23.22)	470,593 (23.98)	599,347 (14.62)
3, n (%)	342 (4.26)	223,978 (10.76)	42,753 (6.05)	34,322 (8.71)	170,468 (8.69)	148,607 (3.63)
4, n (%)	75 (0.93)	90,669 (4.35)	10,845 (1.54)	12,519 (3.18)	57,842 (2.95)	34,048 (0.83)
5 or more, n (%)	15 (0.19)	56,196 (2.70)	3,533 (0.50)	7,752 (1.97)	30,529 (1.56)	9,490 (0.23)

a ≥12 months continuous enrolment AND no prior COVID-19 vaccination, other than Pfizer-BioNTech vaccine
*Refer to Table 3 for information on time periods for data;

The median months of follow up from first dose until censoring ranged from 0.9 months in NHR to 11.3 months in Pedianet. The follow-up time was short in all data sources, but was similar for vaccinated and unvaccinated cohorts since the censoring date was the same for both (Table 11).

A total of 6,217,296 (50.14%) matched unvaccinated individuals were censored because of receipt of a COVID-19 vaccine (Pfizer-BioNTech COVID-19 vaccine or a non-Pfizer-BioNTech COVID-19 vaccine) (Table 11). The percentages of individuals censored for exiting the data sources or end of data availability ranged from 0.4% in the vaccinated cohort in EpiChron to 36.7% in unvaccinated cohort in CPRD Aurum.

Table 11. Cohort follow-up and reasons for censoring by vaccination status (matched cohort design), by data source

	Pedianet		NHR		PHARMO	
	Vac	Unvac	Vac	Unvac	Vac	Unvac
Total, N	10,500	10,500	3,584,238	3,584,238	992,144	992,144
Person-months of follow-up						
Median (Q1, Q3) (months)	11.30 (1.90, 11.90)	11.30 (1.90, 11.90)	0.90 (0.40, 2.60)	0.90 (0.40, 2.50)	5.90 (0.60, 16.40)	5.60 (0.70, 15.10)
Min, max (months)	0.10, 22.10	0, 22.10	0, 24.30	0, 24.30	0, 29.70	0, 29.70
Reasons for censoring, n (%)						
Non-Pfizer-BioNTech vaccine received	8 (0.10)	322 (3.10)	288,041 (8)	322,446 (9)	165,165 (16.60)	87,027 (8.80)
Unvaccinated received Pfizer or non-Pfizer COVID-19 vaccine	NA	3,086 (29.40)	NA	2,426,459 (67.70)	NA	422,533 (42.60)
Exit from data source[a]	738 (7.00)	665 (6.30)	551,997 (15.40)	552,043 (15.40)	126,410 (12.70)	195,907 (19.70)

	EpiChron		SIDIAP		CPRD Aurum	
	Vac	Unvac	Vac	Unvac	Vac	Unvac
Total, N	627,972	627,972	3,087,124	3,087,124	4,098,869	4,098,869
Person-months of follow-up						
Median (Q1, Q3) (months)	1 (0.30, 7.60)	1 (0.30, 7.60)	1.20 (0.30, 7.10)	1.20 (0.30, 7.10)	2.20 (0.60, 6.70)	2.10 (0.60, 6.50)
Min, max (months)	0, 31.20	0, 31.20	0.10, 30.0	0.10, 30.0	0, 15.40	0, 15.40
Reasons for censoring, n (%)						
Non-Pfizer-BioNTech vaccine received	38,763 (6.20)	79,088 (12.60)	267,231 (8.70)	568,186 (18.40)	166,538 (4.10)	1,102,616 (26.90)
Unvaccinated received Pfizer or non-Pfizer COVID-19 vaccine	NA	368,991 (58.80)	NA	1,655,969 (53.60)	NA	1,340,258 (32.70)
Exit from data source[a]	2,488 (0.40)	3,212 (0.50)	0	0	1,505,360 (36.70)	1,499,323 (36.60)

a Administrative end of follow-up or death; NA not applicable

10.1.2.1. Baseline characteristics

The prevalence of the baseline characteristics in the vaccinated and unvaccinated cohorts, and their absolute standardised differences (ASDs) for each data source are summarised in Table 12. The median age at first dose in the vaccinated and unvaccinated cohorts ranged from 36 years in CPRD Aurum to 49 years in PHARMO. The median age at first dose in Pedianet, was 10 years. The percentage of females (in both cohorts since they were matched on sex) who had received a 1st dose from 49.08% in Pedianet to 52.70% in CPRD Aurum (Table 12). Most first doses of the Pfizer-BioNTech COVID-19 vaccine were administered in the second quarter of 2021, except in CPRD Aurum in the first quarter of 2021 and in the paediatric population in Pedianet and in CPRD Aurum when this was in the first quarter of 2022, due to the later starting date for paediatric vaccination.

Pregnancy information at time zero was collected in NHR, EpiChron and SIDIAP. Pregnant women were more frequently vaccinated in the second trimester in EpiChron and SIDIAP and in the first trimester in NHR. Information on long-term care facility residency and healthcare worker or essential worker status could not be identified in the data sources.

Smoking status was missing for Pedianet, NHR and CPRD Aurum. Among those with data, around 4% were current smokers in PHARMO and between 5 and 9% in EpiChron and SIDIAP, respectively. BMI data were missing for about 27% of individuals in Pedianet, 53% of individuals in SIDIAP, about 80% of individuals in EpiChron and about 95% of individuals in PHARMO; BMI data were not available in NHR. The percentages of individuals with an obesity diagnosis or obesity surgery were similar between the vaccinated and unvaccinated cohorts.

More unvaccinated individuals had no primary care visits, with 37% of unvaccinated individuals compared with 25% of vaccinated individuals in PHARMO, 23% of unvaccinated individuals versus 13% of vaccinated individuals in EpiChron, and 13% of unvaccinated individuals versus 18% of vaccinated individuals in SIDIAP. Also, more unvaccinated individuals did not have any COVID-19 tests, with the most notable differences in SIDIAP (52% of unvaccinated individuals compared with 44% of vaccinated individuals) and CPRD Aurum (74% of unvaccinated individuals versus 66% of vaccinated individuals). Other healthcare utilisation outcomes, such as hospitalisation, were similar between vaccinated and unvaccinated individuals across data sources.

Table 12. Part 1: Baseline demographics, lifestyle variables and health resources utilisation for vaccinated and unvaccinated cohorts with absolute standardised difference (ASD) by data source

(SEE PART 2 BELOW)

	Pedianet			NHR			PHARMO		
	Vac	**Unvac**	**ASD**	**Vac**	**Unvac**	**ASD**	**Vac**	**Unvac**	**ASD**
Total, N	10,500	10,500		3,584,238	3,584,238		992,144	992,144	
Demographics									
Age (years)			0.09			0.004			0.002
Mean (SD)	9.40 (2.48)	9.17 (2.46)		46.94 (21.05)	46.87 (21.05)		48.31 (21.64)	48.26 (21.63)	
Median (Q1, Q3)	10 (7.00, 12.00)	10 (7.00, 11.00)		47 (29.00, 64.00)	47 (29.00, 64.00)		49 (30.00, 68.00)	49 (30.00, 68.00)	
Age groups (years), n (%)			0.301			0.105			0.071
0-1	0	0		5	<5		<5	<5	
2-4	17 (0.16)	357 (3.40)		6	260 (0.01)		73 (0.01)	271 (0.03)	
5-11	7,733 (73.65)	8,205 (78.14)		10,273 (0.29)	41,151 (1.15)		9,446 (0.95)	14,299 (1.44)	
12-15	2,750 (26.19)	1,938 (18.46)		209,744 (5.85)	193,192 (5.39)		58,519 (5.90)	54,215 (5.46)	
16-17	NA	NA		119,332 (3.33)	119,234 (3.33)		33,644 (3.39)	34,065 (3.43)	
18-29	NA	NA		578,529 (16.14)	563,690 (15.73)		138,134 (13.92)	137,071 (13.82)	
30-39	NA	NA		489,811 (13.67)	492,387 (13.74)		129,445 (13.05)	129,077 (13.01)	
40-49	NA	NA		516,547 (14.41)	516,082 (14.40)		133,389 (13.44)	133,575 (13.46)	
50-59	NA	NA		550,997 (15.37)	551,472 (15.39)		170,375 (17.17)	166,430 (16.77)	
60-64	NA	NA		243,827 (6.80)	250,854 (7)		12,585 (1.27)	18,546 (1.87)	
65-69	NA	NA		241,138 (6.73)	235,984 (6.58)		82,555 (8.32)	81,295 (8.19)	
70-79	NA	NA		411,192 (11.47)	410,834 (11.46)		160,688 (16.20)	162,199 (16.35)	
80+	NA	NA		212,837 (5.94)	209,096 (5.83)		63,289 (6.38)	61,099 (6.16)	
Female, n (%)	5,153 (49.08)	5,153 (49.08)	0	1,778,272 (49.61)	1,778,272 (49.61)	0	506,601 (51.06)	506,601 (51.06)	0
Females aged 14 to 50 years, n (%)	0	0		883,609 (49.69)	879,819 (49.48)		233,578 (46.11)	233,234 (46.04)	
Pregnancy status, n (%)						0			

Table 12. Part 1: Baseline demographics, lifestyle variables and health resources utilisation for vaccinated and unvaccinated cohorts with absolute standardised difference (ASD) by data source

(SEE PART 2 BELOW)

	Pedianet			NHR			PHARMO		
	Vac	**Unvac**	**ASD**	**Vac**	**Unvac**	**ASD**	**Vac**	**Unvac**	**ASD**
First trimester	NA	NA		4,787 (35.46)	3,463 (26.05)		NA	NA	
Second trimester	NA	NA		4,605 (34.11)	4,209 (26.05)		NA	NA	
Third trimester	NA	NA		4,108 (30.43)	5,624 (42.30)		NA	NA	
Date of vaccination or matching, n (%)			0			0			0
1 Oct–31 Dec 2020	0	0		10,467 (0.29)	10,467 (0.29)		6	6	
1 Jan–31 March 2021	<5	<5		499,170 (13.93)	499,170 (13.93)		105,029 (10.59)	105,029 (10.59)	
1 Apr–30 Jun 2021	197 (1.88)	197 (1.88)		1,680,167 (46.88)	1,680,167 (46.88)		504,483 (50.85)	504,483 (50.85)	
1 Jul–30 Sep 2021	1,667 (15.88)	1,667 (15.88)		1,239,193 (34.57)	1,239,193 (34.57)		287,879 (29.02)	287,879 (29.02)	
1 Oct–31 Dec 2021	3,315 (31.57)	3,315 (31.57)		111,312 (3.11)	111,312 (3.11)		49,299 (4.97)	49,299 (4.97)	
1 Jan–31 Mar 2022	5,115 (48.71)	5,115 (48.71)		34,530 (0.96)	34,530 (0.96)		32,788 (3.30)	32,788 (3.30)	
1 Apr–30 Jun 2022	137 (1.30)	137 (1.30)		6,306 (0.18)	6,306 (0.18)		3,463 (0.35)	3,463 (0.35)	
1 Jul–30 Sep 2022	54 (0.51)	54 (0.51)		1,980 (0.06)	1,980 (0.06)		2,650 (0.27)	2,650 (0.27)	
1 Oct–31 Dec 2022	14 (0.13)	14 (0.13)		1,113 (0.03)	1,113 (0.03)		6,181 (0.62)	6,181 (0.62)	
Personal lifestyle characteristics									
Smoking status									0.123
Current	NA	NA		NA	NA		41,307 (4.16)	40,572 (4.09)	
Former	NA	NA		NA	NA		85,675 (8.64)	66,740 (6.73)	
Never	NA	NA		NA	NA		134,784 (13.59)	105,582 (10.64)	
Never or former	NA	NA		NA	NA		0	0	
Unknown	NA	NA		NA	NA		730,378 (73.62)	779,250 (78.54)	
BMI, n (%)*			0.041						0.054

Table 12. Part 1: Baseline demographics, lifestyle variables and health resources utilisation for vaccinated and unvaccinated cohorts with absolute standardised difference (ASD) by data source

(SEE PART 2 BELOW)

	Pedianet			NHR			PHARMO		
	Vac	**Unvac**	**ASD**	**Vac**	**Unvac**	**ASD**	**Vac**	**Unvac**	**ASD**
Underweight (BMI <20kg/m^2)	6,093 (58.03)	6,029 (57.42)		NA	NA		1,593 (0.16)	1,549 (0.16)	
Normal weight (BMI 20 to <25kg/m^2)	1,296 (12.34)	1,229 (11.70)		NA	NA		14,902 (1.50)	11,944 (1.20)	
Overweight (BMI 25 to <30kg/m^2)	265 (2.52)	234 (2.23)		NA	NA		28,814 (2.90)	22,556 (2.27)	
Obese (BMI ≥30kg/m^2)	51 (0.49)	47 (0.45)		NA	NA		20,496 (2.07)	17,281 (1.74)	
BMI missing	2,795 (26.62)	2,961 (28.20)		3,584,238 (100)	3,584,238 (100)		926,339 (93.37)	938,814 (94.62)	
Obesity diagnosis or obesity surgery	578 (5.50)	524 (4.99)		121,103 (3.38)	103,663 (2.89)		11,413 (1.15)	12,144 (1.22)	
Healthcare utilisation									
Number of hospitalisations, n (%)			0.006			0.002			
0	10,114 (96.32)	10,122 (96.40)		3,219,179 (89.81)	3,219,132 (89.81)		NA	NA	
1	297 (2.83)	294 (2.80)		259,206 (7.23)	260,313 (7.26)		NA	NA	
2+	89 (0.85)	84 (0.80)		105,853 (2.95)	104,793 (2.92)		NA	NA	
Number of emergency department visits, n (%)			0.017						
0	9,265 (88.24)	9,312 (88.69)		NA	NA		NA	NA	
1	976 (9.30)	952 (9.07)		NA	NA		NA	NA	
2+	259 (2.47)	236 (2.25)		NA	NA		NA	NA	
Skilled nursing facility, nursing home, or extended care facility stay, n (%)									
0	NA	NA		NA	NA		NA	NA	
1	NA	NA		NA	NA		0	NA	
2+	NA	NA		NA	NA		0	NA	

Table 12. Part 1: Baseline demographics, lifestyle variables and health resources utilisation for vaccinated and unvaccinated cohorts with absolute standardised difference (ASD) by data source

(SEE PART 2 BELOW)

	Pedianet			NHR			PHARMO		
	Vac	**Unvac**	**ASD**	**Vac**	**Unvac**	**ASD**	**Vac**	**Unvac**	**ASD**
Primary care utilisation, n (%)			0.035			0.097			0.272
0	1,294 (12.32)	1,403 (13.36)		508,912 (14.20)	632,646 (17.65)		244,890 (24.68)	368,551 (37.15)	
1	1,745 (16.62)	1,787 (17.02)		367,102 (10.24)	374,005 (10.43)		146,021 (14.72)	121,939 (12.29)	
2+	7,461 (71.06)	7,310 (69.62)		2,708,224 (75.56)	2,577,587 (71.91)		601,233 (60.60)	501,654 (50.56)	
Cancer screening, n (%)									
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 (%)			0.085			0.001			
0	2,958 (28.17)	3,319 (31.61)		3,508,985 (97.90)	3,508,681 (97.89)		NA	NA	
1-2	6,489 (61.80)	6,291 (59.91)		75,251 (2.10)	75,555 (2.11)		NA	NA	
3-5	967 (9.21)	826 (7.87)		<5	<5		NA	NA	
5+	86 (0.82)	64 (0.61)		0	0		NA	NA	

ASD: absolute standardised difference; NR: not reportable; Vac: vaccinated cohort; Unvac: unvaccinated cohort; NA: not available
* Child-specific BMI algorithm is pending validation

Table 12. Part 2: Baseline demographics, lifestyle variables and health resources utilisation for vaccinated and unvaccinated cohorts with absolute standardised difference (ASD) by data source

(SEE PART 1 ABOVE)

	EpiChron			SIDIAP			CRPD Aurum		
	Vac	**Unvac**	**ASD**	**Vac**	**Unvac**	**ASD**	**Vac**	**Unvac**	**ASD**
Total, N	627,972	627,972		3,087,124	3,087,124		4,098,869	4,098,869	
Demographics									
Age (years)			0.005			0.004			0.003
Mean (SD)	49.60 (21.31)	49.49 (21.27)		45.05 (22.61)	44.96 (22.58)		42.36 (22.63)	42.30 (22.65)	
Median (Q1, Q3)	48(34.00,69.00)	48(34.00,68.00)		45(27.00,58.00)	45(27.00,58.00)		36(24.00,61.00)	36(24.00,61.00)	
Age groups (years), n (%)			0.065			0.085			0.137
0-1	0	0		<5	<5		<5	<5	
2-4	0	0		33 (<0.01)	8,053 (0.26)		8 (<0.01)	168 (<0.01)	
5-11	2,359 (0.38)	5,169 (0.82)		190,826 (6.18)	207,210 (6.71)		7,539 (0.18)	55,274 (1.35)	
12-15	32,535 (5.18)	30,985 (4.93)		197,309 (6.39)	181,315 (5.87)		337,854 (8.24)	308,831 (7.53)	
16-17	15,602 (2.48)	14,860 (2.37)		98,219 (3.18)	88,587 (2.87)		194,067 (4.73)	191,220 (4.67)	
18-29	72,157 (11.49)	71,887 (11.45)		348,959 (11.30)	351,451 (11.38)		938,744 (22.90)	924,479 (22.55)	
30-39	81,333 (12.95)	81,879 (13.04)		402,401 (13.03)	404,437 (13.10)		856,627 (20.90)	850,910 (20.76)	
40-49	129,303 (20.59)	129,898 (20.69)		610,549 (19.78)	612,716 (19.85)		353,997 (8.64)	356,638 (8.70)	
50-59	108,495 (17.28)	106,539 (16.97)		516,017 (16.72)	504,880 (16.35)		338,341 (8.25)	340,973 (8.32)	
60-64	10,537 (1.68)	11,046 (1.76)		40,440 (1.31)	45,703 (1.48)		168,483 (4.11)	173,654 (4.24)	
65-69	27,290 (4.35)	29,954 (4.77)		43,663 (1.41)	50,501 (1.64)		168,955 (4.12)	170,790 (4.17)	
70-79	86,404 (13.76)	86,409 (13.76)		386,748 (12.53)	392,338 (12.71)		373,119 (9.10)	376,369 (9.18)	
80+	61,957 (9.87)	59,346 (9.45)		251,958 (8.16)	239,931 (7.77)		361,132 (8.81)	349,561 (8.53)	
Female, n (%)	325,995 (51.91)	325,995 (51.91)	0	1,602,861 (51.92)	1,602,861 (51.92)	0	2,159,944 (52.70)	2,159,944 (52.70)	0
Females aged 14 to 50 years, n (%)	157,179 (48.22)	157,386 (48.28)		780,072 (48.67)	778,035 (48.54)		1,272,597 (58.92)	1,268,839 (58.74)	
Pregnancy status, n (%)			0			0			0

Table 12. Part 2: Baseline demographics, lifestyle variables and health resources utilisation for vaccinated and unvaccinated cohorts with absolute standardised difference (ASD) by data source

(SEE PART 1 ABOVE)

	EpiChron			SIDIAP			CRPD Aurum		
	Vac	**Unvac**	**ASD**	**Vac**	**Unvac**	**ASD**	**Vac**	**Unvac**	**ASD**
First trimester	388 (29.57)	352 (0.22)		3,366 (34.38)	2,984 (30.74)		NA	NA	
Second trimester	553 (42.15)	494 (37.60)		3,636 (37.13)	3,302 (34.02)		NA	NA	
Third trimester	371 (28.28)	468 (35.62)		2,790 (28.49)	3,421 (35.24)		NA	NA	
Date of vaccination or matching, n (%)			0			0			2.085
1 Oct–31 Dec 2020	1,914 (0.30)	1,914 (0.30)		3,390 (0.11)	3,390 (0.11)		192,806 (4.70)	192,806 (4.70)	
1 Jan–31 March 2021	90,082 (14.34)	90,082 (14.34)		365,000 (11.82)	365,000 (11.82)		1,590,992 (38.82)	1,590,992 (38.82)	
1 Apr–30 Jun 2021	326,134 (51.93)	326,134 (51.93)		1,587,152 (51.41)	1,587,152 (51.41)		1,223,173 (29.84)	1,223,173 (29.84)	
1 Jul–30 Sep 2021	193,267 (30.78)	193,267 (30.78)		854,613 (27.68)	854,613 (27.68)		512,743 (12.51)	512,743 (12.51)	
1 Oct–31 Dec 2021	11,741 (1.87)	11,741 (1.87)		168,650 (5.46)	168,650 (5.46)		447,871 (10.93)	447,871 (10.93)	
1 Jan–31 Mar 2022	3,525 (0.56)	3,525 (0.56)		91,786 (2.97)	91,786 (2.97)		131,284 (3.20)	131,284 (3.20)	
1 Apr–30 Jun 2022	448 (0.07)	448 (0.07)		8,168 (0.26)	8,168 (0.26)		0	0	
1 Jul–30 Sep 2022	304 (0.05)	304 (0.05)		4,134 (0.13)	4,134 (0.13)		0	0	
1 Oct–31 Dec 2022	297 (0.05)	297 (0.05)		2,505 (0.08)	2,505 (0.08)		0	0	
Personal lifestyle characteristics									
Smoking status			0.042			0.032			
Current	42,056 (6.70)	39,551 (6.30)		268,452 (8.70)	284,305 (9.21)		NA	NA	
Former	0	0		89,495 (2.90)	81,470 (2.64)		NA	NA	
Never	0	0		1,023,895 (33.17)	991,306 (32.11)		NA	NA	
Never or former	111,199 (17.71)	102,607 (16.34)		0	0		NA	NA	
Unknown	474,717 (75.60)	485,814 (77.36)		1,705,282 (55.24)	1,730,043 (56.04)		4,098,869 (100)	4,098,869 (100)	
BMI, n (%)			0.042			0.019			

Table 12. Part 2: Baseline demographics, lifestyle variables and health resources utilisation for vaccinated and unvaccinated cohorts with absolute standardised difference (ASD) by data source

(SEE PART 1 ABOVE)

	EpiChron			SIDIAP			CRPD Aurum		
	Vac	**Unvac**	**ASD**	**Vac**	**Unvac**	**ASD**	**Vac**	**Unvac**	**ASD**
Underweight (BMI <20kg/m^2)	16,234 (2.59)	13,922 (2.22)		241,878 (7.84)	245,048 (7.94)		NA	NA	
Normal weight (BMI 20 to <25kg/m^2)	37,463 (5.97)	33,214 (5.29)		377,833 (12.24)	363,715 (11.78)		NA	NA	
Overweight (BMI 25 to <30kg/m^2)	36,338 (5.79)	34,490 (5.49)		468,918 (15.19)	457,009 (14.80)		NA	NA	
Obese (BMI ≥30kg/m^2)	26,959 (4.29)	26,879 (4.28)		350,764 (11.36)	354,932 (11.50)		NA	NA	
BMI missing	510,978 (81.37)	519,467 (82.72)		1,647,731 (53.37)	1,666,420 (53.98)		4,098,869 (100)	4,098,869 (100)	
Obesity diagnosis or obesity surgery	38,148 (6.07)	38,588 (6.14)		461,540 (14.95)	465,994 (15.09)		177,827 (4.34)	183,067 (4.47)	
Healthcare utilisation									
Number of hospitalisations, n (%)			0.014			0.006			0.016
0	583,439 (92.91)	584,736 (93.11)		2,866,870 (92.87)	2,862,986 (92.74)		4,020,179 (98.08)	4,012,630 (97.90)	
1	36,079 (5.75)	34,283 (5.46)		176,526 (5.72)	178,480 (5.78)		60,824 (1.48)	64,253 (1.57)	
2+	8,454 (1.35)	8,953 (1.43)		43,728 (1.42)	45,658 (1.48)		17,866 (0.44)	21,986 (0.54)	
Number of emergency department visits, n (%)			0.025						0.021
0	514,931 (82)	520,123 (82.83)		NA	NA		3,648,548 (89.01)	3,656,162 (89.20)	
1	78,097 (12.44)	73,002 (11.63)		NA	NA		306,880 (7.49)	288,678 (7.04)	
2+	34,944 (5.56)	34,847 (5.55)		NA	NA		143,441 (3.50)	154,029 (3.76)	
Skilled nursing facility, nursing home, or extended care facility stay, n (%)									0.006
0	NA	NA		NA	NA		4,094,478 (99.89)	4,093,713 (99.87)	
1	NA	NA		NA	NA		3,070 (0.07)	3,733 (0.09)	
2+	NA	NA		NA	NA		1,321 (0.03)	1,423 (0.03)	

Table 12. Part 2: Baseline demographics, lifestyle variables and health resources utilisation for vaccinated and unvaccinated cohorts with absolute standardised difference (ASD) by data source

(SEE PART 1 ABOVE)

	EpiChron			SIDIAP			CRPD Aurum		
	Vac	**Unvac**	**ASD**	**Vac**	**Unvac**	**ASD**	**Vac**	**Unvac**	**ASD**
Primary care utilisation, n (%)			0.264			0.153			0
0	80,867 (12.88)	143,472 (22.85)		400,309 (12.97)	570,263 (18.47)		NA	NA	
1	47,953 (7.64)	45,942 (7.32)		235,283 (7.62)	232,983 (7.55)		NA	NA	
2+	499,152 (79.49)	438,558 (69.84)		2,451,532 (79.41)	2,283,878 (73.98)		NA	NA	
Cancer screening, n (%)									0.041
0	NA	NA		NA	NA		3,601,837 (87.87)	3,655,938 (89.19)	
1	NA	NA		NA	NA		287,776 (7.02)	257,800 (6.29)	
2+	NA	NA		NA	NA		209,256 (5.11)	185,131 (4.52)	
COVID-19 tests, n (%)			0.089			0.175			0.185
0	459,117 (73.11)	483,174 (76.94)		1,368,338 (44.32)	1,606,662 (52.04)		2,697,349 (65.81)	3,032,105 (73.97)	
1-2	168,855 (26.89)	144,798 (23.06)		1,208,357 (39.14)	1,099,113 (35.60)		1,095,676 (26.73)	864,685 (21.10)	
3-5	0	0		346,123 (11.21)	282,407 (9.15)		188,833 (4.61)	137,063 (3.34)	
5+	0	0		164,306 (5.32)	98,942 (3.20)		117,011 (2.85)	65,016 (1.59)	

ASD: absolute standardised difference; NR: not reportable; Vac: vaccinated cohort; Unvac: unvaccinated cohort; NA: not available

10.1.2.2. Baseline comorbidities

The prevalence of baseline comorbidities in the 10 years prior to time zero in the vaccinated and unvaccinated cohorts with absolute standardised differences (ASDs) are summarised by data source in Table 13. About 7 to 12% of individuals had a history of either a positive COVID-19 test or a COVID-19 diagnosis. Both NHR and PHARMO reported <2.1%, which is likely to be underestimated due to registration practices in Norway and The Netherlands. History of anaphylaxis was rare, as expected. Cardiovascular disease, hypertension, allergies and chronic respiratory disease were the most prevalent comorbidities.

Although the prevalence rates of the baseline comorbidities varied between data sources, the comparison between the vaccinated and unvaccinated cohorts showed a good balance since the ASDs were small for each of the variables (Table 13).

Table 13. Part 1: Baseline comorbidities at time zero (past 10 years) by exposure group (matched cohort design) by data source

(SEE PART 2 BELOW)

	Pedianet			NHR			PHARMO		
	Vac	**Unvac**	**ASD**	**Vac**	**Unvac**	**ASD**	**Vac**	**Unvac**	**ASD**
Total, n (%)	10,500 (100)	10,500 (100)		3,584,238 (100)	3,584,238 (100)		992,144 (100)	992,144 (100)	
COVID-19 history, n (%)									
Previous diagnosis of COVID-19	0	0		5,224 (0.15)	4,830 (0.13)	0.003	17,340 (1.75)	17,344 (1.75)	0
Positive test result for COVID-19	1,054 (10.04)	1,054 (10.04)	0	75,253 (2.10)	75,557 (2.11)	0.001	0	0	
Comorbidities, n (%)									
History of anaphylaxis	81 (0.77)	83 (0.79)	0.002	56,354 (1.57)	55,829 (1.56)	0.001	6,081 (0.61)	5,994 (0.60)	0.001
History of allergies	1,709 (16.28)	1,720 (16.38)	0.003	79,798 (2.23)	78,642 (2.19)	0.002	20,685 (2.08)	18,542 (1.87)	0.016
Diabetes mellitus (types 1 and 2)	28 (0.27)	37 (0.35)	0.015	266,517 (7.44)	244,053 (6.81)	0.024	59,496 (6)	61,841 (6.23)	0.01
Hypertension	<5	9 (0.09)	0.024	761,684 (21.25)	751,950 (20.98)	0.007	70,035 (7.06)	71,509 (7.21)	0.006
Cardiovascular disease	442 (4.21)	399 (3.80)	0.021	1,570,275 (43.81)	1,567,711 (43.74)	0.001	324,586 (32.72)	320,397 (32.29)	0.009
Chronic respiratory disease	6,177 (58.83)	6,241 (59.44)	0.012	821,902 (22.93)	810,372 (22.61)	0.008	122,414 (12.34)	121,610 (12.26)	0.002
Chronic kidney disease	<5	<5	0.008	7,331 (0.20)	5,630 (0.16)	0.011	16,098 (1.62)	14,148 (1.43)	0.016
Chronic liver disease	<5	<5	0	26,774 (0.75)	33,426 (0.93)	0.02	932 (0.09)	1,605 (0.16)	0.019
Cancer	67 (0.64)	61 (0.58)	0.007	268,230 (7.48)	248,275 (6.93)	0.022	56,854 (5.73)	61,063 (6.15)	0.018
Autoimmune disorders	250 (2.38)	221 (2.10)	0.019	707,068 (19.73)	677,030 (18.89)	0.021	47,287 (4.77)	45,795 (4.62)	0.007
Influenza infection or other respiratory infections	6,233 (59.36)	6,252 (59.54)	0.004	758,790 (21.17)	731,272 (20.40)	0.019	41,354 (4.17)	39,177 (3.95)	0.011
Charlson Comorbidity Index Score, n (%)			0.009			0.028			0.055
0 or 1	10,329 (98.37)	10,329 (98.37)		2,881,286 (80.39)	2,920,591 (81.48)		924,198 (93.15)	914,735 (92.20)	
2	147 (1.40)	151 (1.44)		317,963 (8.87)	300,744 (8.39)		37,566 (3.79)	36,910 (3.72)	
3	24 (0.23)	20 (0.19)		384,989 (10.74)	362,903 (10.12)		30,380 (3.06)	40,499 (4.08)	

Table 13. Part 1: Baseline comorbidities at time zero (past 10 years) by exposure group (matched cohort design) by data source

(SEE PART 2 BELOW)

	Pedianet			NHR			PHARMO		
	Vac	**Unvac**	**ASD**	**Vac**	**Unvac**	**ASD**	**Vac**	**Unvac**	**ASD**
Myocardial infarct	8 (0.08)	<5 (0.04)	0.016	76,688 (2.14)	74,243 (2.07)	0.005	14,152 (1.43)	15,903 (1.60)	0.014
Congestive heart failure	<5	<5	0	90,226 (2.52)	89,534 (2.50)	0.001	8,042 (0.81)	11,482 (1.16)	0.035
Cerebrovascular disease	79 (0.75)	73 (0.70)	0.007	153,658 (4.29)	147,079 (4.10)	0.009	15,949 (1.61)	18,208 (1.84)	0.018
Peripheral vascular disease	51 (0.49)	48 (0.46)	0.004	226,202 (6.31)	215,936 (6.02)	0.012	31,272 (3.15)	29,502 (2.97)	0.01
Mild to moderate kidney disease	<5	<5	0.008	5,458 (0.15)	3,638 (0.10)	0.014	3,330 (0.34)	5,642 (0.57)	0.035
Severe kidney disease	<5	0	0.014	19,073 (0.53)	18,359 (0.51)	0.003	2,969 (0.30)	5,072 (0.51)	0.033
Mild liver disease	<5	0	0.02	7,191 (0.20)	8,621 (0.24)	0.009	259 (0.03)	421 (0.04)	0.009
Moderate or severe liver disease	0	0		11,738 (0.33)	11,898 (0.33)	0.001	454 (0.05)	492 (0.05)	0.002
Malignant tumour	51 (0.49)	47 (0.45)	0.006	239,356 (6.68)	219,230 (6.12)	0.023	30,122 (3.04)	36,018 (3.63)	0.033
Metastasic solid tumour	0	0		25,195 (0.70)	22,349 (0.62)	0.01	4,034 (0.41)	9,413 (0.95)	0.066
HIV/AIDS	6 (0.06)	<5 (0.02)	0.02	7,267 (0.20)	7,911 (0.22)	0.004	955 (0.10)	954 (0.10)	0
Diabetes with complications	0	0		32,248 (0.90)	25,704 (0.72)	0.02	3,561 (0.36)	4,585 (0.46)	0.016
Diabetes no complications	7 (0.07)	9 (0.09)	0.007	112,700 (3.14)	94,455 (2.64)	0.03	3,185 (0.32)	3,667 (0.37)	0.008
Dementia	0	0		40,021 (1.12)	27,409 (0.76)	0.036	6,095 (0.61)	9,078 (0.91)	0.035
Skin ulcer	<5	<5	0	31,827 (0.89)	34,724 (0.97)	0.008	2,123 (0.21)	2,490 (0.25)	0.008
Hemiplegia	10 (0.10)	10 (0.10)	0	11 (<0.01)	7 (<0.01)	0.001	1,648 (0.17)	2,702 (0.27)	0.023
Connective tissue disease	151 (1.44)	154 (1.47)	0.002	266,555 (7.44)	253,955 (7.09)	0.014	9,210 (0.93)	7,746 (0.78)	0.016
CDC at-risk groups, n (%) [a]			0.008			0.014			0.001
Group 0 (no conditions)	3,443 (32.79)	3,443 (32.79)		1,285,288 (35.86)	1,285,288 (35.86)		531,509 (53.57)	531,509 (53.57)	
Group 1 (1 condition)	3,839 (36.56)	3,804 (36.23)		912,928 (25.47)	932,388 (26.01)		228,126 (22.99)	228,604 (23.04)	

Table 13. Part 1: Baseline comorbidities at time zero (past 10 years) by exposure group (matched cohort design) by data source

(SEE PART 2 BELOW)

	Pedianet			NHR			PHARMO		
	Vac	**Unvac**	**ASD**	**Vac**	**Unvac**	**ASD**	**Vac**	**Unvac**	**ASD**
Group 2 (>1 condition)	3,218 (30.65)	3,253 (30.98)		1,386,022 (38.67)	1,366,562 (38.13)		232,509 (23.44)	232,031 (23.39)	
Immunocompromising conditions, n (%)	3,056 (29.10)	3,056 (29.10)	0	752,857 (21)	752,857 (21)	0	130,937 (13.20)	130,937 (13.20)	0
Surrogates of frailty, n (%)									
Wheelchair use	NA	NA		NA	NA		NA	NA	
Home hospital bed	NA	NA		NA	NA		NA	NA	
Paralysis	6 (0.06)	<5	0.02	7,339 (0.20)	7,072 (0.20)	0.002	2,984 (0.30)	3,906 (0.39)	0.016
Parkinson's disease	NA	NA		13,183 (0.37)	11,029 (0.31)	0.01	2,267 (0.23)	2,438 (0.25)	0.004
Weakness	0	<5 (0.01)	0.014	685,153 (19.12)	671,155 (18.73)	0.01	60,221 (6.07)	51,482 (5.19)	0.038
Stroke/brain injury	77 (0.73)	73 (0.70)	0.005	153,658 (4.29)	147,079 (4.10)	0.009	15,902 (1.60)	18,164 (1.83)	0.018
Ambulance transport	NA	NA		NA	NA		NA	NA	
Difficulty walking	61 (0.58)	61 (0.58)	0	NA	NA		862 (0.09)	1,345 (0.14)	0.015
Home oxygen	NA	NA		NA	NA		NA	NA	
Rehabilitation care	NA	NA		NA	NA		NA	NA	
Psychiatric illness	351 (3.34)	312 (2.97)	0.021	580,456 (16.19)	629,441 (17.56)	0.036	41,846 (4.22)	42,011 (4.23)	0.001
Sepsis	<5	<5	0.019	96,661 (2.70)	93,084 (2.60)	0.006	11,799 (1.19)	10,940 (1.10)	0.008
Podiatric care	NA	NA		NA	NA		NA	NA	
Bladder incontinence	202 (1.92)	197 (1.88)	0.003	158,193 (4.41)	150,323 (4.19)	0.011	13,576 (1.37)	12,171 (1.23)	0.013
Arthritis	376 (3.58)	332 (3.16)	0.023	865,330 (24.14)	842,663 (23.51)	0.015	65,869 (6.64)	55,680 (5.61)	0.043
Coagulation deficiencies	82 (0.78)	72 (0.69)	0.011	22,935 (0.64)	22,339 (0.62)	0.002	2,441 (0.25)	2,645 (0.27)	0.004
Vertigo	59 (0.56)	38 (0.36)	0.029	496,447 (13.85)	488,261 (13.62)	0.007	51,708 (5.21)	42,179 (4.25)	0.045
Lipid abnormalities	0	<5	0.024	314,205 (8.77)	301,407 (8.41)	0.013	22,837 (2.30)	18,656 (1.88)	0.029

Table 13. Part 1: Baseline comorbidities at time zero (past 10 years) by exposure group (matched cohort design) by data source

(SEE PART 2 BELOW)

	Pedianet			NHR			PHARMO		
	Vac	**Unvac**	**ASD**	**Vac**	**Unvac**	**ASD**	**Vac**	**Unvac**	**ASD**

ASD: absolute standardised difference; NR: not reportable; Vac: vaccinated cohort; Unvac: unvaccinated cohort; NA not available
a CDC at-risk groups conditions: cancer, type 1 and 2 diabetes, obesity (BMI > 30), cardiovascular disease/ serious heart conditions (heart failure, coronary artery disease, cardiomyopathies), chronic lung disease including COPD, asthma, chronic kidney disease, HIV, immunosuppression, sickle cell disease, hypertension.

Table 13. Part 2: Baseline comorbidities at time zero (past 10 years) by exposure group (matched cohort design) by data source

(SEE PART 1 ABOVE)

	EpiChron			SIDIAP			CPRD Aurum		
	Vac	**Unvac**	**ASD**	**Vac**	**Unvac**	**ASD**	**Vac**	**Unvac**	**ASD**
Total, n (%)	627,972 (100)	627,972 (100)		3,087,124 (100)	3,087,124 (100)		4,098,869 (100)	4,098,869 (100)	
COVID-19 history, n (%)									
Previous diagnosis of COVID-19	3,309 (0.53)	3,759 (0.60)	0.01	378,481 (12.26)	375,307 (12.16)	0.003	378,053 (9.22)	378,042 (9.22)	0
Positive test result for COVID-19	45,030 (7.17)	45,036 (7.17)	0	326,332 (10.57)	337,630 (10.94)	0.012	<5	<5	0
Comorbidities, n (%)									
History of anaphylaxis	3,205 (0.51)	2,951 (0.47)	0.006	18,611 (0.60)	16,441 (0.53)	0.009	4,096 (0.10)	4,914 (0.12)	0.006
History of allergies	154,899 (24.67)	140,957 (22.45)	0.052	443,433 (14.36)	436,753 (14.15)	0.006	499,265 (12.18)	469,116 (11.45)	0.023
Diabetes mellitus (types 1 and 2)	55,982 (8.91)	59,047 (9.40)	0.017	248,941 (8.06)	259,530 (8.41)	0.012	429,936 (10.49)	423,633 (10.34)	0.005
Hypertension	102,476 (16.32)	104,635 (16.66)	0.009	419,615 (13.59)	418,422 (13.55)	0.001	736,474 (17.97)	742,289 (18.11)	0.004
Cardiovascular disease	235,599 (37.52)	228,910 (36.45)	0.022	980,910 (31.77)	966,456 (31.31)	0.01	444,043 (10.83)	431,504 (10.53)	0.01
Chronic respiratory disease	80,287 (12.79)	80,245 (12.78)	0	813,274 (26.34)	813,291 (26.34)	0	700,099 (17.08)	708,414 (17.28)	0.005
Chronic kidney disease	23,300 (3.71)	22,957 (3.66)	0.003	121,257 (3.93)	118,967 (3.85)	0.004	197,480 (4.82)	193,589 (4.72)	0.004
Chronic liver disease	2,360 (0.38)	2,633 (0.42)	0.007	83,897 (2.72)	89,892 (2.91)	0.012	13,968 (0.34)	14,738 (0.36)	0.003
Cancer	25,095 (4.00)	25,424 (4.05)	0.003	111,646 (3.62)	111,274 (3.60)	0.001	197,963 (4.83)	180,981 (4.42)	0.02
Autoimmune disorders	45,253 (7.21)	44,214 (7.04)	0.006	190,360 (6.17)	190,000 (6.15)	0	321,187 (7.84)	286,480 (6.99)	0.032
Influenza infection or other respiratory infections	104,944 (16.71)	98,177 (15.63)	0.029	888,500 (28.78)	862,667 (27.94)	0.019	353,730 (8.63)	338,293 (8.25)	0.014
Charlson Comorbidity Index Score, n (%)			0.006			0.007			0.026
0 or 1	531,266 (84.60)	529,970 (84.39)		2,581,358 (83.62)	2,573,413 (83.36)		3,097,537 (75.57)	3,102,884 (75.70)	
2	53,994 (8.60)	54,836 (8.73)		264,974 (8.58)	270,201 (8.75)		387,927 (9.46)	360,935 (8.81)	

Table 13. Part 2: Baseline comorbidities at time zero (past 10 years) by exposure group (matched cohort design) by data source

(SEE PART 1 ABOVE)

	EpiChron			SIDIAP			CPRD Aurum		
	Vac	**Unvac**	**ASD**	**Vac**	**Unvac**	**ASD**	**Vac**	**Unvac**	**ASD**
3	42,712 (6.80)	43,166 (6.87)		240,792 (7.80)	243,510 (7.89)		613,405 (14.97)	635,050 (15.49)	
Myocardial infarct	6,103 (0.97)	6,620 (1.05)	0.008	28,799 (0.93)	29,788 (0.96)	0.003	45,711 (1.12)	44,880 (1.09)	0.002
Congestive heart failure	13,908 (2.21)	14,519 (2.31)	0.007	57,982 (1.88)	58,306 (1.89)	0.001	49,858 (1.22)	52,404 (1.28)	0.006
Cerebrovascular disease	12,804 (2.04)	12,247 (1.95)	0.006	68,564 (2.22)	66,319 (2.15)	0.005	94,586 (2.31)	96,753 (2.36)	0.004
Peripheral vascular disease	10,568 (1.68)	10,641 (1.69)	0.001	85,509 (2.77)	85,461 (2.77)	0	22,847 (0.56)	23,560 (0.57)	0.002
Mild to moderate kidney disease	23,437 (3.73)	23,105 (3.68)	0.003	120,597 (3.91)	118,244 (3.83)	0.004	172,322 (4.20)	168,248 (4.10)	0.005
Severe kidney disease	859 (0.14)	922 (0.15)	0.003	4,712 (0.15)	3,589 (0.12)	0.01	15,294 (0.37)	15,834 (0.39)	0.002
Mild liver disease	2,141 (0.34)	2,224 (0.35)	0.002	19,569 (0.63)	20,642 (0.67)	0.004	48,447 (1.18)	42,907 (1.05)	0.013
Moderate or severe liver disease	561 (0.09)	703 (0.11)	0.007	1,679 (0.05)	2,001 (0.06)	0.004	43,382 (1.06)	59,407 (1.45)	0.035
Malignant tumour	21,897 (3.49)	22,245 (3.54)	0.003	87,396 (2.83)	88,875 (2.88)	0.003	197,632 (4.82)	180,712 (4.41)	0.02
Metastasic solid tumour	1,896 (0.30)	2,272 (0.36)	0.01	9,006 (0.29)	10,391 (0.34)	0.008	2,961 (0.07)	2,639 (0.06)	0.003
HIV/AIDS	291 (0.05)	434 (0.07)	0.009	0	0		161 (<0.01)	197 (<0.01)	0.001
Diabetes with complications	4,958 (0.79)	5,253 (0.84)	0.005	48,558 (1.57)	50,045 (1.62)	0.004	153,916 (3.76)	154,302 (3.76)	0
Diabetes no complications	9,085 (1.45)	9,866 (1.57)	0.01	45,505 (1.47)	47,076 (1.52)	0.004	250,334 (6.11)	232,885 (5.68)	0.018
Dementia	7,377 (1.17)	5,693 (0.91)	0.026	42,641 (1.38)	35,072 (1.14)	0.022	51,271 (1.25)	65,337 (1.59)	0.029
Skin ulcer	2,754 (0.44)	2,940 (0.47)	0.004	15,239 (0.49)	15,655 (0.51)	0.002	44,610 (1.09)	41,430 (1.01)	0.008
Hemiplegia	2,363 (0.38)	2,241 (0.36)	0.003	14,439 (0.47)	12,604 (0.41)	0.009	2,498 (0.06)	2,411 (0.06)	0.001
Connective tissue disease	83,354 (13.27)	74,220 (11.82)	0.044	207,031 (6.71)	202,750 (6.57)	0.006	111,929 (2.73)	98,789 (2.41)	0.02
CDC at-risk groups, n (%) [a]			0.002			0.001			0

Table 13. Part 2: Baseline comorbidities at time zero (past 10 years) by exposure group (matched cohort design) by data source

(SEE PART 1 ABOVE)

	EpiChron			SIDIAP			CPRD Aurum		
	Vac	**Unvac**	**ASD**	**Vac**	**Unvac**	**ASD**	**Vac**	**Unvac**	**ASD**
Group 0 (no conditions)	299,702 (47.73)	299,702 (47.73)		1,347,940 (43.66)	1,347,940 (43.66)		2,164,699 (52.81)	2,164,699 (52.81)	
Group 1 (1 condition)	116,320 (18.52)	116,789 (18.60)		692,041 (22.42)	690,984 (22.38)		1,060,268 (25.87)	1,060,002 (25.86)	
Group 2 (>1 condition)	211,950 (33.75)	211,481 (33.68)		1,047,143 (33.92)	1,048,200 (33.95)		873,902 (21.32)	874,168 (21.33)	
Immunocompromising conditions, n (%)	37,581 (5.98)	37,581 (5.98)	0	615,371 (19.93)	615,371 (19.93)	0	26,800 (0.65)	26,800 (0.65)	0
Surrogates of frailty, n (%)									
Wheelchair use	NA	NA		NA	NA		876 (0.02)	1,302 (0.03)	0.006
Home hospital bed	NA	NA		NA	NA		0	6 (<0.01)	0.002
Paralysis	3,356 (0.53)	3,152 (0.50)	0.005	16,280 (0.53)	14,232 (0.46)	0.009	6,195 (0.15)	6,456 (0.16)	0.002
Parkinson’s disease	2,923 (0.47)	2,483 (0.40)	0.011	10,461 (0.34)	9,374 (0.30)	0.006	10,854 (0.26)	12,266 (0.30)	0.006
Weakness	5,622 (0.90)	5,747 (0.92)	0.002	204,925 (6.64)	209,865 (6.80)	0.006	112,879 (2.75)	100,789 (2.46)	0.019
Stroke/brain injury	8,601 (1.37)	8,504 (1.35)	0.001	68,209 (2.21)	65,957 (2.14)	0.005	96,639 (2.36)	99,120 (2.42)	0.004
Ambulance transport	NA	NA		NA	NA		1,073 (0.03)	1,319 (0.03)	0.004
Difficulty walking	1,670 (0.27)	1,534 (0.24)	0.004	30,347 (0.98)	28,257 (0.92)	0.007	26,674 (0.65)	30,690 (0.75)	0.012
Home oxygen	NA	NA		NA	NA		612 (0.01)	777 (0.02)	0.003
Rehabilitation care	NA	NA		NA	NA		3,305 (0.08)	2,658 (0.06)	0.006
Psychiatric illness	164,147 (26.14)	156,167 (24.87)	0.029	833,439 (27)	847,693 (27.46)	0.01	540,468 (13.19)	501,776 (12.24)	0.028
Sepsis	3,513 (0.56)	3,502 (0.56)	0	18,246 (0.59)	18,388 (0.60)	0.001	28,483 (0.69)	31,794 (0.78)	0.009
Podiatric care	NA	NA		NA	NA		38,065 (0.93)	36,323 (0.89)	0.004
Bladder incontinence	32,304 (5.14)	29,815 (4.75)	0.018	149,846 (4.85)	139,438 (4.52)	0.016	89,488 (2.18)	90,426 (2.21)	0.002
Arthritis	232,249 (36.98)	215,220 (34.27)	0.057	787,715 (25.52)	782,386 (25.34)	0.004	592,694 (14.46)	554,027 (13.52)	0.027

Table 13. Part 2: Baseline comorbidities at time zero (past 10 years) by exposure group (matched cohort design) by data source

(SEE PART 1 ABOVE)

	EpiChron			SIDIAP			CPRD Aurum		
	Vac	**Unvac**	**ASD**	**Vac**	**Unvac**	**ASD**	**Vac**	**Unvac**	**ASD**
Coagulation deficiencies	15,009 (2.39)	14,935 (2.38)	0.001	10,622 (0.34)	10,240 (0.33)	0.002	15,938 (0.39)	13,852 (0.34)	0.008
Vertigo	9,522 (1.52)	9,226 (1.47)	0.004	399,542 (12.94)	393,198 (12.74)	0.006	425,173 (10.37)	391,336 (9.55)	0.028
Lipid abnormalities	34,119 (5.43)	33,759 (5.38)	0.003	267,836 (8.68)	264,658 (8.57)	0.004	69,963 (1.71)	65,840 (1.61)	0.008

ASD: absolute standardised difference; NR: not reportable; Vac: vaccinated cohort; Unvac: unvaccinated cohort; NA not available
a CDC at-risk groups conditions: cancer, type 1 and 2 diabetes, obesity (BMI > 30), cardiovascular disease/ serious heart conditions (heart failure, coronary artery disease, cardiomyopathies), chronic lung disease including COPD, asthma, chronic kidney disease, HIV, immunosuppression, sickle cell disease, hypertension.

10.1.2.3. Baseline comedications

Comedication use for 1 year prior to time zero is summarised (with ASDs) in the vaccinated and unvaccinated cohorts by data source in Table 14. We observed higher use of antibiotics, non-steroidal anti-inflammatory drugs (NSAIDs), and psychotropics in NHR, EpiChron and SIDIAP compared with PHARMO, where the results are based on GP prescriptions only. Data for most vaccines were not available in PHARMO as these data are not provided by GPs. The ASDs for the comparison of prevalence of comedication variables show no imbalance between the vaccinated and unvaccinated cohorts.

Table 14. Part 1: Baseline comedications at time zero by exposure group (matched cohort design) by data source

(SEE PART 2 BELOW)

	Pedianet			NHR			PHARMO		
	Vac	**Unvac**	**ASD**	**Vac**	**Unvac**	**ASD**	**Vac**	**Unvac**	**ASD**
Total, n (%)	10,500 (100)	10,500 (100)		3,584,238 (100)	3,584,238 (100)		992,144 (100)	992,144 (100)	
Comedications, n (%)									
Analgesics	19 (0.18)	25 (0.24)	0.012	793,145 (22.13)	767,156 (21.40)	0.018	59,272 (5.97)	53,827 (5.43)	0.024
Antibiotics	1,050 (10)	1,173 (11.17)	0.038	610,097 (17.02)	587,087 (16.38)	0.017	86,788 (8.75)	75,590 (7.62)	0.041
Antiviral medications	25 (0.24)	29 (0.28)	0.008	46,181 (1.29)	44,012 (1.23)	0.005	2,491 (0.25)	2,292 (0.23)	0.004
Corticosteroids	329 (3.13)	362 (3.45)	0.018	178,331 (4.98)	170,758 (4.76)	0.01	26,755 (2.70)	24,647 (2.48)	0.013
Non-steroidal anti-inflammatory drugs	113 (1.08)	160 (1.52)	0.04	654,868 (18.27)	618,214 (17.25)	0.027	58,192 (5.87)	49,088 (4.95)	0.041
Psychotropics	61 (0.58)	73 (0.70)	0.014	511,711 (14.28)	524,431 (14.63)	0.01	46,850 (4.72)	42,808 (4.31)	0.02
Statins	0	0		515,691 (14.39)	478,758 (13.36)	0.03	99,722 (10.05)	80,924 (8.16)	0.066
Novel oral anticoagulants	<5	5 (0.05)	0.023	436,567 (12.18)	418,277 (11.67)	0.016	76,799 (7.74)	64,574 (6.51)	0.048
Warfarin	<5	<5	0.008	25,112 (0.70)	23,825 (0.66)	0.004	<5	<5	0.001
Immunosuppressant medications	336 (3.20)	367 (3.50)	0.016	221,595 (6.18)	204,472 (5.70)	0.02	34,235 (3.45)	30,766 (3.10)	0.02
Other vaccines, n (%)									
Influenza	3,843 (36.60)	3,907 (37.21)	0.013	NA	NA		712 (0.07)	1,090 (0.11)	0.013
Pneumococcal	5,275 (50.24)	5,246 (49.96)	0.006	300,445 (8.38)	280,018 (7.81)	0.021	NA	NA	
DTP (diphtheria, tetanus, and pertussis)	2,696 (25.68)	2,491 (23.72)	0.045	68,326 (1.91)	72,708 (2.03)	0.009	NA	NA	
TPV (polio)	8,684 (82.70)	8,505 (81)	0.044	127,540 (3.56)	130,561 (3.64)	0.005	NA	NA	
TV (MMR) (measles, mumps and rubella)	7 (0.07)	9 (0.09)	0.007	NA	NA		NA	NA	
Hib (Haemophilus influenzae type b)	4,609 (43.90)	4,729 (45.04)	0.023	25,319 (0.71)	31,347 (0.87)	0.019	NA	NA	
HepB (hepatitis B virus)	54 (0.51)	172 (1.64)	0.109	382,001 (10.66)	335,808 (9.37)	0.043	NA	NA	
VZV (varicella-zoster virus)	8,311 (79.15)	7,935 (75.57)	0.086	5,068 (0.14)	4,283 (0.12)	0.006	NA	NA	
HPV (human papillomavirus)	98 (0.93)	53 (0.50)	0.051	443,426 (12.37)	401,980 (11.22)	0.036	NA	NA	

Table 14. Part 1: Baseline comedications at time zero by exposure group (matched cohort design) by data source

(SEE PART 2 BELOW)

	Pedianet			NHR			PHARMO		
	Vac	**Unvac**	**ASD**	**Vac**	**Unvac**	**ASD**	**Vac**	**Unvac**	**ASD**
Meningitis	5,523 (52.60)	5,261 (50.10)	0.05	267,482 (7.46)	212,928 (5.94)	0.061	NA	NA	
Rotavirus	496 (4.72)	495 (4.71)	0	2,013 (0.06)	2,036 (0.06)	0	NA	NA	

ASD: absolute standardised difference, NR: not reportable; Vac: vaccinated cohort; Unvac: unvaccinated cohort

Table 14. Part 2: Baseline comedications at time zero by exposure group (matched cohort design) by data source (SEE PART 1 ABOVE)

	EpiChron			SIDIAP			CPRD Aurum		
	Vac	**Unvac**	**ASD**	**Vac**	**Unvac**	**ASD**	**Vac**	**Unvac**	**ASD**
Total, n (%)	627,972 (100)	627,972 (100)		3,087,124 (100)	3,087,124 (100)		4,098,869 (100)	4,098,869 (100)	
Comedications, n (%)									
Analgesics	185,986 (29.62)	172,280 (27.43)	0.048	753,688 (24.41)	745,272 (24.14)	0.006	529,937 (12.93)	517,062 (12.61)	0.009
Antibiotics	118,641 (18.89)	105,391 (16.78)	0.055	459,540 (14.89)	444,042 (14.38)	0.014	553,564 (13.51)	499,256 (12.18)	0.04
Antiviral medications	3,997 (0.64)	3,751 (0.60)	0.005	18,546 (0.60)	16,842 (0.55)	0.007	36,632 (0.89)	31,372 (0.77)	0.014
Corticosteroids	23,984 (3.82)	24,300 (3.87)	0.003	110,059 (3.57)	110,583 (3.58)	0.001	NA	NA	
Non-steroidal anti-inflammatory drugs	164,579 (26.21)	143,204 (22.80)	0.079	565,245 (18.31)	548,693 (17.77)	0.014	231,241 (5.64)	202,597 (4.94)	0.031)
Psychotropics	136,657 (21.76)	122,193 (19.46)	0.057	470,100 (15.23)	439,520 (14.24)	0.028	206,312 (5.03)	202,810 (4.95)	0.004
Statins	117,606 (18.73)	111,322 (17.73)	0.026	348,087 (11.28)	328,745 (10.65)	0.02	605,446 (14.77)	560,929 (13.68)	0.031
Novel oral anticoagulants	57,079 (9.09)	55,689 (8.87)	0.008	214,285 (6.94)	208,275 (6.75)	0.008	253,412 (6.18)	245,216 (5.98)	0.008
Warfarin	216 (0.03)	203 (0.03)	0.001	4,108 (0.13)	4,206 (0.14)	0.001	NA	NA	
Immunosuppressant medications	25,587 (4.07)	25,863 (4.12)	0.002	117,775 (3.82)	117,833 (3.82)	0	NA	NA	
Other vaccines, n (%)									
Influenza	179,815 (28.63)	179,815 (28.63)	0	820,081 (26.56)	820,081 (26.56)	0	1,730,281 (42.21)	1,730,281 (42.21)	0
Pneumococcal	32,710 (5.21)	27,925 (4.45)	0.036	291,231 (9.43)	283,469 (9.18)	0.009	NA	NA	
DTP (diphtheria, tetanus, and pertussis)	140,418 (22.36)	122,617 (19.53)	0.07	384,332 (12.45)	381,256 (12.35)	0.003	1,352,988 (33.01)	1,151,025 (28.08)	0.107
TPV (polio)	1,136 (0.18)	1,489 (0.24)	0.012	115,598 (3.74)	120,137 (3.89)	0.008	1,205,327 (29.41)	1,007,190 (24.57)	0.109
TV (MMR) (measles, mumps and rubella)	24,970 (3.98)	20,196 (3.22)	0.041	252,531 (8.18)	269,560 (8.73)	0.02	325,690 (7.95)	323,350 (7.89)	0.002

Table 14. Part 2: Baseline comedications at time zero by exposure group (matched cohort design) by data source (SEE PART 1 ABOVE)

	EpiChron			SIDIAP			CPRD Aurum		
	Vac	Unvac	ASD	Vac	Unvac	ASD	Vac	Unvac	ASD
Hib (Haemophilus influenzae type b)	702 (0.11)	664 (0.11)	0.002	105,405 (3.41)	105,779 (3.43)	0.001	34,413 (0.84)	46,015 (1.12)	0.029
HepB (hepatitis B virus)	6,606 (1.05)	5,822 (0.93)	0.013	107,762 (3.49)	110,447 (3.58)	0.005	156,815 (3.83)	118,806 (2.90)	0.051
VZV (varicella-zoster virus)	10,553 (1.68)	8,831 (1.41)	0.022	<5	<5	0.001	4,671 (0.11)	4,427 (0.11)	0.002
HPV (human papillomavirus)	34,816 (5.54)	27,623 (4.40)	0.053	23 (<0.01)	16 (<0.01)	0.001	324,287 (7.91)	251,301 (6.13)	0.07
Meningitis	63,163 (10.06)	49,606 (7.90)	0.076	459,496 (14.88)	423,655 (13.72)	0.033	597,739 (14.58)	465,682 (11.36)	0.096
Rotavirus	20 (<0.01)	14 (<0.01)	0.002	28,157 (0.91)	20,275 (0.66)	0.029	2,592 (0.06)	2,724 (0.07)	0.001

ASD: absolute standardised difference, NR: not reportable; Vac: vaccinated cohort; Unvac: unvaccinated cohort

10.1.2.4. Censoring due to prior events of special interest

Prior AESIs (outcome-specific exclusion criteria) in the year prior to receiving their first Pfizer-BioNTech COVID-19 vaccine dose the Pfizer-BioNTech vaccinated cohort and the matched unvaccinated cohort by data source are summarized in Table 15. As only low numbers of individuals experienced AESI-specific events in the year prior to receiving their first Pfizer-BioNTech COVID-19 vaccine dose, the AESI-specific exclusion criteria of having experienced that specific AESI prior to the first dose of Pfizer-BioNTech COVID-19 vaccine had very little impact on the analyses (Table 15).

Table 15. Part 1: Prior adverse events of special interest (AESIs) within one year of time zero (outcome-specific exclusion criteria) by exposure group by data source

(SEE PART 2 BELOW)

	Pedianet			NHR			PHARMO		
	Vac	**Unvac**	**ASD**	**Vac**	**Unvac**	**ASD**	**Vac**	**Unvac**	**ASD**
Total, n (%)	10,500 (100)	10,500 (100)		3,584,238 (100)	3,584,238 (100)		992,144 (100)	992,144 (100)	
Autoimmune diseases, n (%)									
Guillain-Barré syndrome	<5 (0.02)	6 (0.06)	0.020	148 (<0.01)	118 (<0.01)	0.001	10 (<0.01)	10 (<0.01)	<0.001
Acute disseminated encephalomyelitis	NA	NA		28 (<0.01)	26 (<0.01)	<0.001	<5	0	0.001
Narcolepsy	0	0	<0.001	369 (0.01)	476 (0.01)	0.003	<5	<5	0.001
Acute aseptic arthritis	44 (0.42)	38 (0.36)	0.009	28,323 (0.79)	27,223 (0.76)	0.004	511 (0.05)	484 (0.05)	0.001
Diabetes mellitus type 1	14 (0.13)	18 (0.17)	0.010	49,714 (1.39)	39,943 (1.11)	0.025	1,642 (0.17)	1,596 (0.16)	0.001
(Idiopathic) thrombocytopenia	0	0	<0.001	659 (0.02)	658 (0.02)	<0.001	19 (<0.01)	33 (<0.01)	0.003
Thrombotic thrombocytopenia syndrome (TTS)	NA	NA		174 (<0.01)	179 (<0.01)	<0.001	12 (<0.01)	29 (<0.01)	0.004
Myositis	NA	NA		880 (0.02)	843 (0.02)	0.001	5 (<0.01)	17 (<0.01)	0.004
Cardiovascular system, n (%)									
Acute cardiovascular injury[a]	31 (0.30)	19 (0.18)	0.023	238,308 (6.65)	229,449 (6.40)	0.010	11,203 (1.13)	11,124 (1.12)	0.001
Arrhythmia	22 (0.21)	18 (0.17)	0.009	166,532 (4.65)	161,814 (4.51)	0.006	8,890 (0.90)	8,813 (0.89)	0.001
Heart failure	NA	NA		40,065 (1.12)	40,848 (1.14)	0.002	1,383 (0.14)	1,678 (0.17)	0.008
Stress cardiomyopathy	NA	NA		18 (<0.01)	29 (<0.01)	0.001	7 (<0.01)	6 (<0.01)	<0.001
Coronary artery disease	NA	NA		70,122 (1.96)	65,757 (1.83)	0.009	2,225 (0.22)	2,131 (0.21)	0.002
Myocarditis	6 (0.06)	0	0.034	387 (0.01)	440 (0.01)	0.001	11 (<0.01)	14 (<0.01)	0.001
Pericarditis	<5	0	0.020	1,001 (0.03)	948 (0.03)	0.001	25 (<0.01)	33 (<0.01)	0.001
Circulatory system, n (%)									
Coagulation disorders: thromboembolism, haemorrhage	6 (0.06)	<5 (0.03)	0.014	29,837 (0.83)	29,476 (0.82)	0.001	1,142 (0.12)	1,323 (0.13)	0.005
Single organ cutaneous vasculitis	NA	NA		337 (0.01)	368 (0.01)	0.001	<5	10 (<0.01)	0.003
Cerebral venous sinus thrombosis	0	0	<0.001	130 (<0.01)	127 (<0.01)	<0.001	8 (<0.01)	12 (<0.01)	0.001

Table 15. Part 1: Prior adverse events of special interest (AESIs) within one year of time zero (outcome-specific exclusion criteria) by exposure group by data source

(SEE PART 2 BELOW)

	Pedianet			NHR			PHARMO		
	Vac	**Unvac**	**ASD**	**Vac**	**Unvac**	**ASD**	**Vac**	**Unvac**	**ASD**
Hepato-gastrointestinal and renal system, n (%)									
Acute liver injury	0	0	<0.001	514 (0.01)	543 (0.02)	0.001	8 (<0.01)	14 (<0.01)	0.002
Acute kidney injury	0	0	<0.001	10,005 (0.28)	10,693 (0.30)	0.004	461 (0.05)	705 (0.07)	0.010
Acute pancreatitis	NA	NA		2,446 (0.07)	2,498 (0.07)	0.001	176 (0.02)	209 (0.02)	0.002
Rhabdomyolysis	NA	NA		9 (<0.01)	<5	0.002	10	7 (<0.01)	0.001
Glomerulonephritis	0	0	<0.001						
Nerves and central nervous system, n (%)									
Generalised convulsion	23 (0.22)	36 (0.34)	0.023	24,681 (0.69)	21,548 (0.60)	0.011	311 (0.03)	426 (0.04)	0.006
Meningoencephalitis	0	0	<0.001	1,018 (0.03)	811 (0.02)	0.004	30	33 (<0.01)	0.001
Transverse myelitis	<5	0	0.014	42 (<0.01)	25 (<0.01)	0.002	0	<5	0.001
Bell's palsy	<5	0	0.014	2,710 (0.08)	2,796 (0.08)	0.001	160 (0.02)	165 (0.02)	<0.001
Respiratory system									
Acute respiratory distress syndrome	NA	NA		183 (0.01)	191 (0.01)	<0.001	5 (<0.01)	8 (<0.01)	0.001
Skin and mucous membrane, bone, and joints system, n (%)									
Erythema multiforme	<5 (0.01)	<5 (0.01)	<0.001	141 (<0.01)	145 (<0.01)	<0.001	<5	<5	<0.001
Chilblain-like lesions	<5 (0.03)	<5 (0.01)	0.014	8 (<0.01)	6 (<0.01)	<0.001	119 (0.01)	91 (0.01)	0.003
Reproductive system, n (%)									
Secondary amenorrhoea	<5	0	0.014	1,127 (0.03)	1,046 (0.03)	0.001	<5	<5	0.001
Hypermenorrhoea	14 (0.13)	7 (0.07)	0.021	NA	NA		22 (<0.01)	25 (<0.01)	0.001
Other systems, n (%)									
Anaphylaxis	13 (0.12)	14 (0.13)	0.003	1,612 (0.04)	1,591 (0.04)	<0.001	23 (<0.01)	31 (<0.01)	0.002
Multisystem inflammatory syndrome	NA	NA		2,205 (0.06)	2,270 (0.06)	0.001	12 (<0.01)	12 (<0.01)	<0.001
Subacute thyroiditis	NA	NA		162 (<0.01)	148 (<0.01)	0.001	0	0	<0.001

Table 15. Part 1: Prior adverse events of special interest (AESIs) within one year of time zero (outcome-specific exclusion criteria) by exposure group by data source

(SEE PART 2 BELOW)

	Pedianet			NHR			PHARMO		
	Vac	Unvac	ASD	Vac	Unvac	ASD	Vac	Unvac	ASD

ASD: absolute standardised difference; NR: not reportable; Vac: vaccinated cohort; Unvac: unvaccinated cohort
a including microangiopathy ASD: Absolute standardised difference

Table 15. Part 2: Prior adverse events of special interest (AESIs) within one year of time zero (outcome-specific exclusion criteria) by exposure group by data source

(SEE PART 1 ABOVE)

	EpiChron			SIDIAP			CPRD Aurum		
	Vac	**Unvac**	**ASD**	**Vac**	**Unvac**	**ASD**	**Vac**	**Unvac**	**ASD**
Total, n (%)	627,972 (100)	627,972 (100)		3,087,124 (100)	3,087,124 (100)		4,098,869 (100)	4,098,869 (100)	
Autoimmune diseases, n (%)									
Guillain-Barré syndrome	16 (0.01)	24 (<0.01)	0.002	135 (<0.01)	150 (<0.01)	0.001	319 (0.01)	310 (0.01)	<0.001
Acute disseminated encephalomyelitis	0	<5	0.002	9 (<0.01)	6 (<0.01)	0.001	<5	<5	<0.001
Narcolepsy	9 (<0.01)	<5	0.002	48 (<0.01)	43 (<0.01)	<0.001	126 (<0.01)	114 (<0.01)	0.001
Acute aseptic arthritis	3,731 (0.59)	3,486 (0.56)	0.005	15,008 (0.49)	14,687 (0.48)	0.002	21,549 (0.53)	19,035 (0.46)	0.009
Diabetes mellitus type 1	4,064 (0.65)	4,356 (0.69)	0.006	7,742 (0.25)	8,003 (0.26)	0.002	493 (0.01)	318 (0.01)	0.004
(Idiopathic) thrombocytopenia	34 (0.01)	51 (0.01)	0.003	276 (0.01)	306 (0.01)	0.001	419 (0.01)	384 (0.01)	0.001
Thrombotic thrombocytopenia syndrome (TTS)	28 (<0.01)	43 (0.01)	0.003	192 (0.01)	218 (0.01)	0.001	28 (<0.01)	32 (<0.01)	<0.001
Myositis	29 (<0.01)	32 (0.01)	0.001	408 (0.01)	411 (0.01)	<0.001	298 (0.01)	290 (0.01)	<0.001
Cardiovascular system, n (%)									
Acute cardiovascular injury[a]	14,421 (2.30)	14,771 (2.35)	0.004	60,950 (1.97)	61,356 (1.99)	0.001	79,955 (1.95)	75,119 (1.83)	0.009
Arrhythmia	11,310 (1.80)	11,440 (1.82)	0.002	49,121 (1.59)	49,372 (1.60)	0.001	43,962 (1.07)	40,982 (1)	0.007
Heart failure	4,249 (0.68)	4,607 (0.73)	0.007	14,705 (0.48)	15,328 (0.50)	0.003	16,250 (0.40)	16,956 (0.41)	0.003
Stress cardiomyopathy	32 (0.01)	25 (<0.01)	0.002	193 (0.01)	224 (0.01)	0.001	146 (<0.01)	112 (<0.01)	0.001
Coronary artery disease	1,617 (0.26)	1,801 (0.29)	0.006	7,071 (0.23)	7,532 (0.24)	0.003	23,133 (0.56)	20,962 (0.51)	0.007
Myocarditis	27 (<0.01)	22 (<.010)	0.001	124 (<0.01)	123 (<0.01)	<0.001	231 (0.01)	189 (<0.01)	0.001
Pericarditis	120 (0.02)	111 (0.02)	0.001	746 (0.02)	803 (0.03)	0.001	534 (0.01)	518 (0.01)	<0.001
Circulatory system, n (%)									
Coagulation disorders: thromboembolism, haemorrhage	4,073 (0.65)	4,364 (0.69)	0.006	12,416 (0.40)	13,394 (0.43)	0.005	13,520 (0.33)	13,647 (0.33)	0.001
Single organ cutaneous vasculitis	6 (<0.01)	5 (<0.01)	0.001	50 (<0.01)	62 (<0.01)	0.001	64 (<0.01)	40 (<0.01)	0.002
Cerebral venous sinus thrombosis	8 (<0.01)	7 (<0.01)	<0.001	34 (<0.01)	45 (<0.01)	0.001	92 (<0.01)	97 (<0.01)	<0.001

Table 15. Part 2: Prior adverse events of special interest (AESIs) within one year of time zero (outcome-specific exclusion criteria) by exposure group by data source

(SEE PART 1 ABOVE)

	EpiChron			SIDIAP			CPRD Aurum		
	Vac	**Unvac**	**ASD**	**Vac**	**Unvac**	**ASD**	**Vac**	**Unvac**	**ASD**
Hepato-gastrointestinal and renal system, n (%)									
Acute liver injury	178 (0.03)	208 (0.03)	0.003	449 (0.01)	545 (0.02)	0.002	264 (0.01)	246 (0.01)	0.001
Acute kidney injury	2,052 (0.33)	2,421 (0.39)	0.010	13,290 (0.43)	14,267 (0.46)	0.005	9,235 (0.23)	9,817 (0.24)	0.003
Acute pancreatitis	453 (0.07)	508 (0.08)	0.003	2,011 (0.07)	2,202 (0.07)	0.002	1,301 (0.03)	1,148 (0.03)	0.002
Rhabdomyolysis	127 (0.02)	162 (0.03)	0.004	527 (0.02)	580 (0.02)	0.001	199 (<0.01)	345 (0.01)	0.004
Glomerulonephritis	68 (0.01)	75 (0.01)	0.001	568 (0.02)	494 (0.02)	0.002	575 (0.01)	523 (0.01)	0.001
Nerves and central nervous system, n (%)									
Generalised convulsion	1,123 (0.18)	965 (0.15)	0.006	4,355 (0.14)	4,191 (0.14)	0.001	9,459 (0.23)	9,225 (0.23)	0.001
Meningoencephalitis	45 (0.01)	52 (0.01)	0.001	176 (0.01)	170 (0.01)	<0.001	178 (<0.01)	180 (<0.01)	<0.001
Transverse myelitis	<5	0	0.003	16 (<0.01)	10 (<0.01)	0.001	86 (<0.01)	79 (<0.01)	<0.001
Bell's palsy	375 (0.06)	473 (0.08)	0.006	2,561 (0.08)	2,671 (0.09)	0.001	1,599 (0.04)	1,525 (0.04)	0.001
Respiratory system, n (%)									
Acute respiratory distress syndrome	108 (0.02)	186 (0.03)	0.008	1,055 (0.03)	1,508 (0.05)	0.007	130 (<0.01)	153 (<0.01)	0.001
Skin and mucous membrane, bone, and joints system, n (%)									
Erythema multiforme	29 (<0.01)	26 (<0.01)	0.001	140 (<0.01)	141 (<0.01)	<0.001	202 (<0.01)	165 (<0.01)	0.001
Chilblain-like lesions	282 (0.04)	242 (0.04)	0.003	1,782 (0.06)	1,713 (0.06)	0.001	1,768 (0.04)	1,222 (0.03)	0.007
Reproductive system, n (%)									
Secondary amenorrhoea	1,041 (0.17)	962 (0.15)	0.003	7,630 (0.25)	8,366 (0.27)	0.005	14,781 (0.36)	11,548 (0.28)	0.014
Hypermenorrhoea	3,208 (0.51)	2,915 (0.46)	0.007	12,311 (0.40)	12,579 (0.41)	0.001	NA	NA	
Other systems, n (%)									
Anaphylaxis	314 (0.05)	372 (0.06)	0.004	451 (0.01)	457 (0.01)	<0.001	558 (0.01)	664 (0.02)	0.002
Multisystem inflammatory syndrome	104 (0.02)	146 (0.02)	0.005	55 (<0.01)	62 (<0.01)	0.001	0	8 (<0.01)	0.002
Subacute thyroiditis	<5	<5	0.001	11 (<0.01)	10 (<0.01)	<0.001	30 (<0.01)	24 (<0.01)	0.001

Table 15. Part 2: Prior adverse events of special interest (AESIs) within one year of time zero (outcome-specific exclusion criteria) by exposure group by data source

(SEE PART 1 ABOVE)

	EpiChron			SIDIAP			CPRD Aurum		
	Vac	Unvac	ASD	Vac	Unvac	ASD	Vac	Unvac	ASD

ASD: absolute standardised difference; NR: not reportable; Vac: vaccinated cohort; Unvac: unvaccinated cohort
a including microangiopathy ASD: Absolute standardised difference

10.1.2.5. Outcome data in the unmatched vaccinated cohort

Incidence rates (95% CI) for AESIs among individuals who receive a first dose of the Pfizer-BioNTech COVID-19 vaccine (before matching) in the pre-specified time windows defined in Table 2 by data source were calculated (available in an online repository and accessible on request).

Incidence rates (95% CI) for AESIs in Pfizer-BioNTech vaccinated population after a first, second, or third dose (before matching by data source) are provided in Tables 15.9.1-7 (available in an online repository and accessible on request).

10.2. Main results

The main results for this interim report #5 are those for the following two secondary analyses:

- Estimated incidence rates of prespecified AESI among individuals who receive at least one dose of the Pfizer-BioNTech COVID19 vaccine compared with individuals in a matched comparator unvaccinated cohort using a cohort study design.

- Description of incidence rates and assessment of a potential increased risk of prespecified AESI 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 in Europe using a cohort study design.

In this fifth interim report, regardless of the results from the negative control, baseline imbalances were adjusted using IPTW to challenge the assumption that confounders for symptomatic SARS-CoV-2 infections are equally relevant for all AESIs (SAP section 2.2.2.6, SAP Figure 6). Individuals following each vaccination category under study may have different characteristics that may determine their risk for any AESI. To account for such potential confounding, PS methods were used to estimate the adjusted risk ratios and 95% CIs. PS represent the probability of being vaccinated at any calendar time given a set of baseline covariates.

The results are summarized for each data source, per AESI, in the following tables and figures. The data for COVID-19 disease in the first 12 days after vaccination were used for the negative control (see Section 10.2.1 below).

10.2.1. Results from negative control

To assess baseline exchangeability, the incidences of COVID-19 in the first 12 days after vaccination in the vaccinated and unvaccinated cohorts were compared. In NHR, PHARMO, EpiChron and SIDIAP the differences between the incidences were less than 1 per 1000 cases, which was the a-priori set threshold for baseline exchangeability (Figure 5). In Pedianet, the difference between the incidences of COVID-19 disease in the first 12 days was 2 per 1000 cases (see Figure 5). Cumulative incidence curves for vaccinated and unvaccinated cohorts increase similarly in the first 12 days after time zero. In Pedianet the background incidence of COVID-19 disease in the first 12 days was higher (350 per 10,000 individuals) than those in the other data sources (around 40 per 10,000 individuals) but this is not suggestive of confounding. Although we considered that the matching process achieved the required balance between the cohorts, the analyses were performed in the

matched cohorts with additional control for confounding to evaluate the effect of the PS adjustment.

Figure 5. Cumulative incidence of COVID-19 disease in the first 12 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source

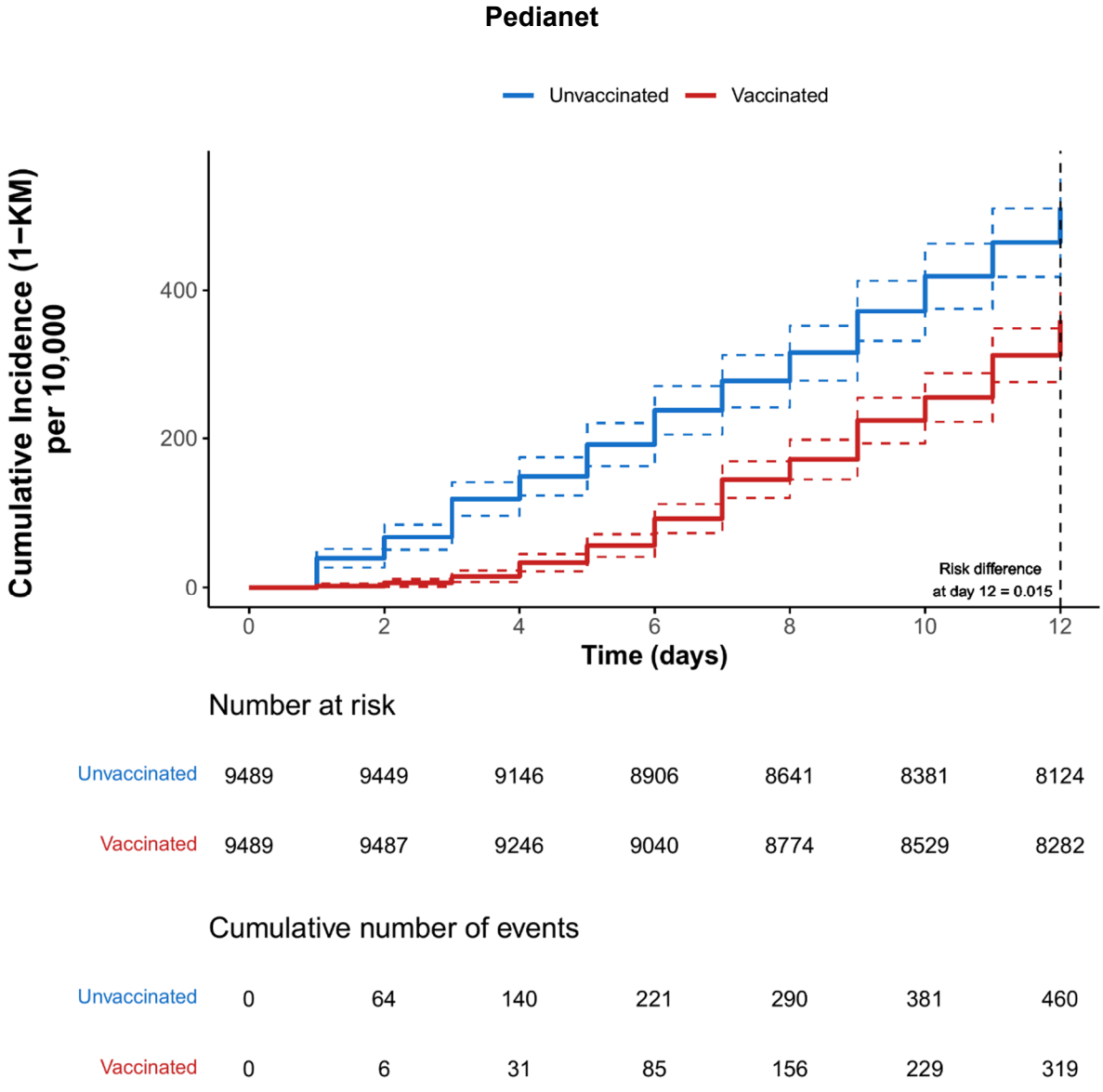
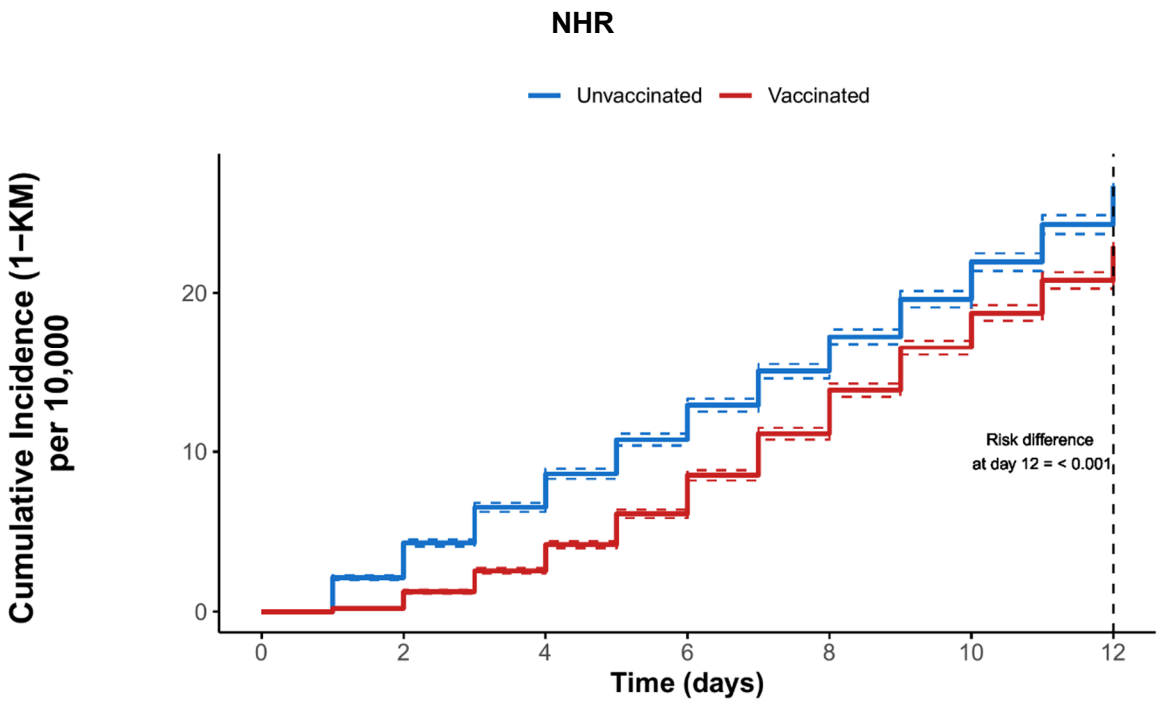


Figure 5. Cumulative incidence of COVID-19 disease in the first 12 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source



Number at risk

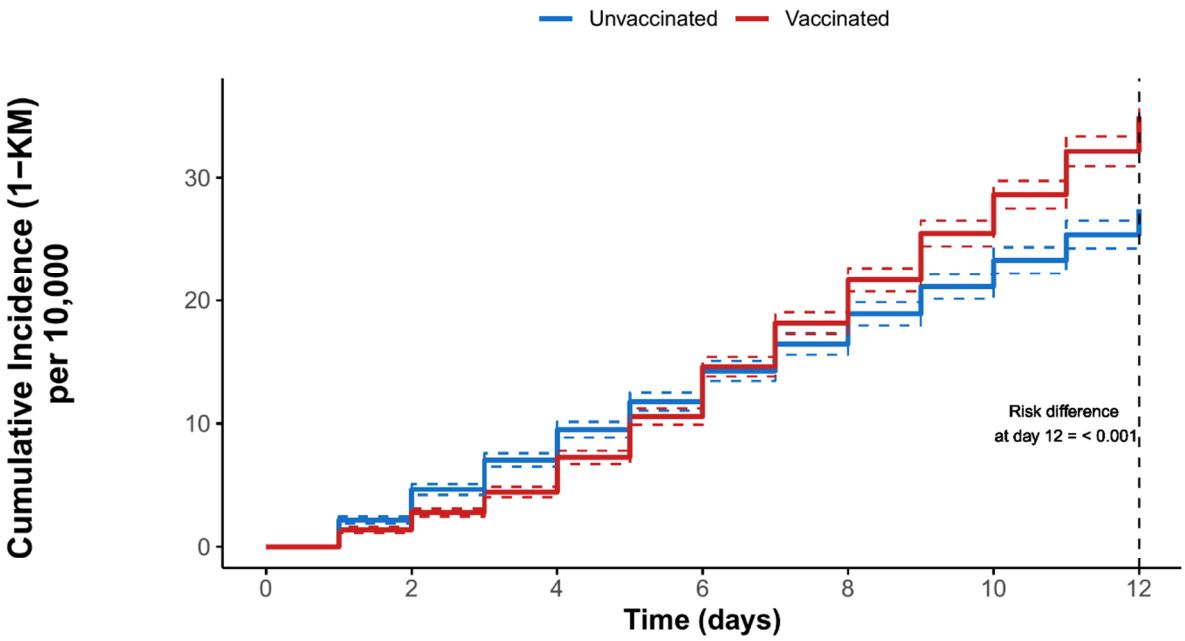
Unvaccinated	3508584	3507638	3295769	3098509	2913615	2742298	2585164
Vaccinated	3508584	3508511	3297737	3101100	2916421	2745238	2588719

Cumulative number of events

Unvaccinated	0	1507	2957	4308	5591	6904	8163
Vaccinated	0	434	1420	2786	4364	5732	6840

Figure 5. Cumulative incidence of COVID-19 disease in the first 12 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source

PHARMO



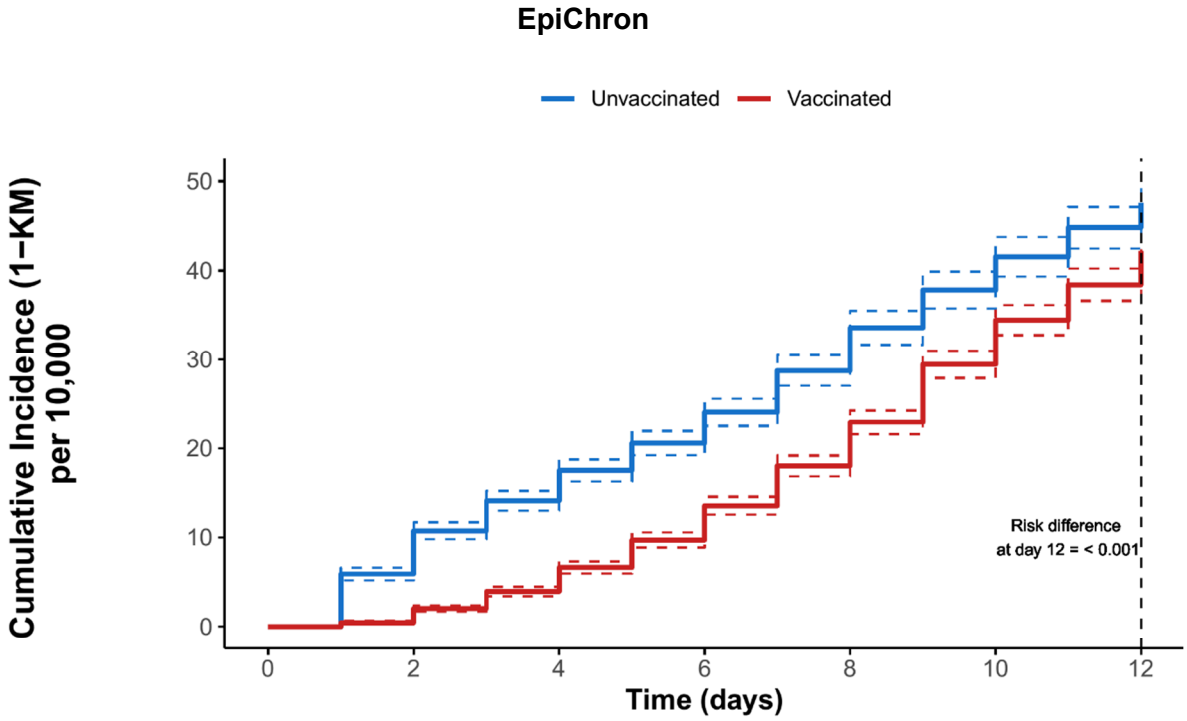
Number at risk

Unvaccinated	975023	974626	916411	873156	839376	811701	788896
Vaccinated	975023	971484	913828	870803	837135	809554	786895

Cumulative number of events

Unvaccinated	0	453	905	1326	1719	2079	2410
Vaccinated	0	269	684	1332	1931	2499	3004

Figure 5. Cumulative incidence of COVID-19 disease in the first 12 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source



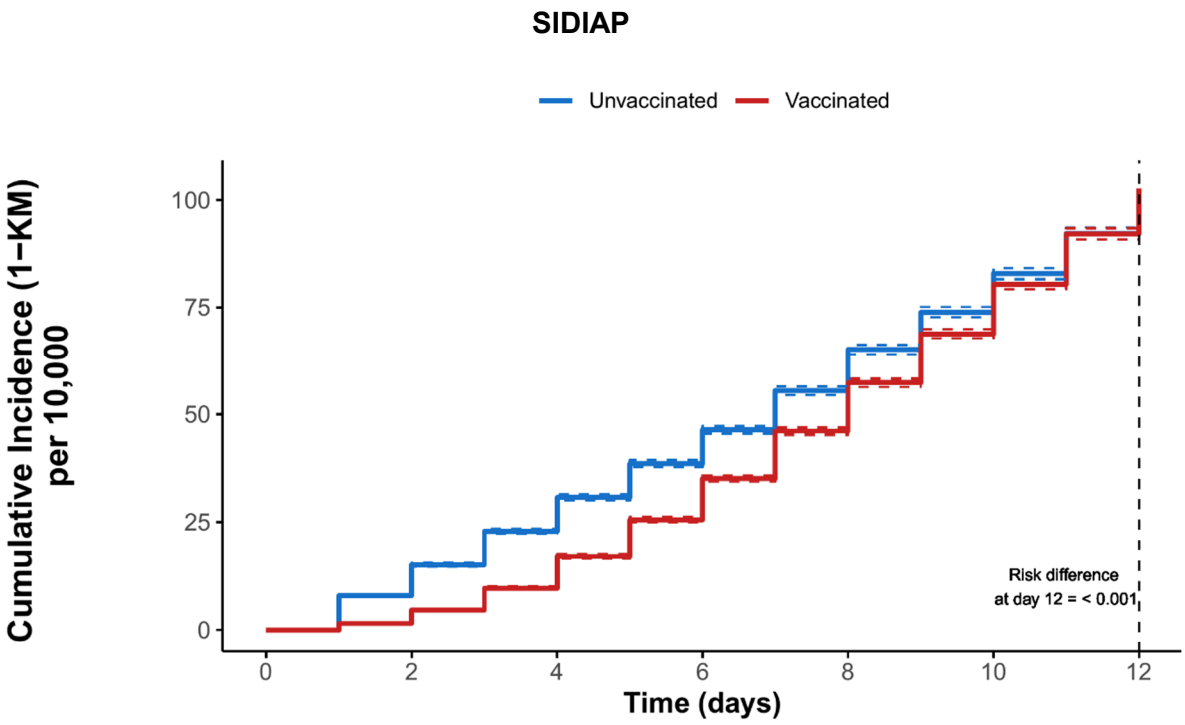
Number at risk

Unvaccinated	583059	582681	515473	498598	449278	384326	371571
Vaccinated	583059	583032	516128	499328	450096	385175	372407

Cumulative number of events

Unvaccinated	0	627	982	1311	1756	2071	2299
Vaccinated	0	118	360	709	1145	1603	1896

Figure 5. Cumulative incidence of COVID-19 disease in the first 12 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source



Number at risk

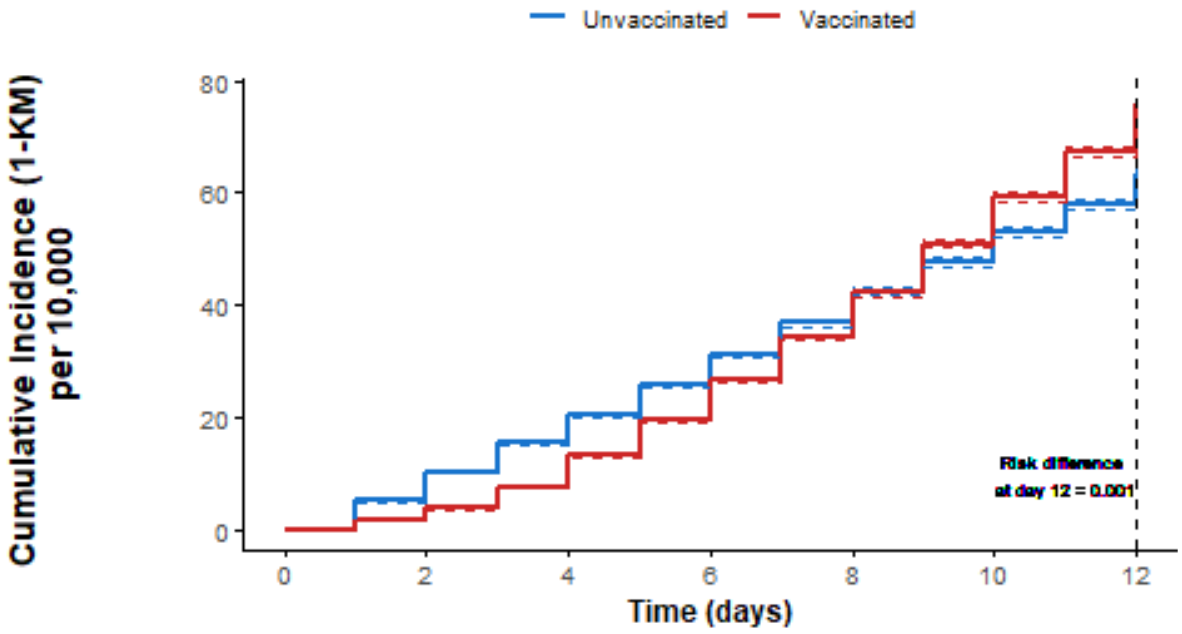
Unvaccinated	2693090	2690954	2418389	2260615	2087119	1921348	182944
Vaccinated	2693090	2692691	2421941	2264276	2090279	1924073	183163

Cumulative number of events

Unvaccinated	0	4071	7928	11548	15569	19067	22467
Vaccinated	0	1228	4313	8471	13231	17789	21954

Figure 5. Cumulative incidence of COVID-19 disease in the first 12 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source

CPRD Aurum



Number at risk

Unvaccinated	722033	3718422	3532926	3382526	3237635	3095112	298056
Vaccinated	722033	3720878	3538119	3388120	3242954	3099779	298447

Cumulative number of events

Unvaccinated	0	3866	7479	11154	14847	18176	21300
Vaccinated	0	1396	4734	9400	14532	19907	24851

10.2.2. Incidence rates and hazard ratios for AESIs

The overall results for each AESI by data source are summarised in Table 16. More complete results can be found in Standalone Annex 2. More complete results for AESIs of specific interest are provided in Section 10.2.3.

Table 16. Summary of number of events, person-years (PY), and incidence rates for each AESI in the vaccinated and unvaccinated cohorts and the adjusted hazard ratio (HR) and rate difference (RD) by data source

	Vaccinated			Unvaccinated			Adjusted HR[a]	Adjusted RD[a]
Adverse event of special interest	**Events (n)**	**PY**	**Incidence rate (95% CI)**	**Events (n)**	**PY**	**Incidence rate (95% CI)**		
Autoimmune diseases								
Guillain-Barre syndrome								
Pedianet	0	1,036	0 (0, NC)	0	1,036	0 (0, NC)	0	0
NHR	7	257,572	0.27 (0.11, 0.56)	5	257,243	0.19 (0.07, 0.55)	1.40 (0.43, 4.58)	0.01
PHARMO	0	87,418	0 (0, 0.42)	<5	NR	0.23 (0.03, 1.62)	NA	-0.02
EpiChron	0	43,902	0 (0, 0.84)	<5	NR	0.46 (0.06, 3.24)	NA	-0.07
SIDIAP	7	230,053	0.30 (0.12, 0.63)	9	230,053	0.39 (0.16, 0.96)	0.76 (0.24, 2.43)	-0.01
CPRD Aurum	14	349,149	0.40 (0.22, 0.67)	14	347,825	0.40 (0.22, 0.75)	0.98 (0.43, 2.25)	-0.01
Acute disseminated encephalomyelitis								
Pedianet	NA	NA	NA	NA	NA	NA	NA	NA
NHR	<5	NR	0.12 (0.02, 0.34)	0	257,259	0 (0, NC)	NA	0.02
PHARMO	0	87,420	0 (0, NC)	0	87,590	0 (0, NC)	NA	0
EpiChron	0	43,906	0 (0, 0.84)	<5	NR	0.46 (0.06, 3.24)	NA	-0.06
SIDIAP	<5	NR	0.04 (0, 0.24)	0	230,072	0 (0, NC)	NA	0
CPRD Aurum	0	349,188	0 (0, 0.11)	0	347,863	0 (0, NC)	NA	0
Narcolepsy								
Pedianet	0	1,037	0 (0, NC)	0	1,037	0 (0, NC)	NA	0
NHR	21	257,522	0.82 (0.50, 1.25)	11	257,194	0.43 (0.21, 0.85)	1.89 (0.86, 4.17)	0.04
PHARMO	0	87,420	0 (0, NC)	0	87,590	0 (0, NC)	NA	0
EpiChron	0	43,905	0 (0, NC)	0	43,859	0 (0, NC)	NA	0
SIDIAP	<5	NR	0.09 (0.01, 0.31)	8	230,066	0.35 (0.17, 0.70)	0.24 (0.06, 0.96)	-0.03
CPRD Aurum	7	349,166	0.20 (0.08, 0.41)	8	347,841	0.23 (0.12, 0.46)	0.94 (0.34, 2.60)	0
Acute aseptic arthritis								
Pedianet	<5	NR	38.91 (10.60, 99.61)	5	1,029	48.61 (20.23, 116.77)	0.79 (0.21, 2.94)	-1.28
NHR	1,360	254,051	53.53 (50.72, 56.46)	1,285	253,740	50.64 (47, 54.57)	1.05 (0.96, 1.15)	0.27
PHARMO	39	87,336	4.47 (3.18, 6.10)	51	87,506	5.83 (4.16, 8.17)	0.72 (0.45, 1.15)	-0.18
EpiChron	306	43,445	70.43 (62.76, 78.79)	274	43,403	63.13 (53.22, 74.88)	1.05 (0.86, 1.29)	0.38
SIDIAP	1,000	228,262	43.81 (41.14, 46.61)	1,007	228,259	44.12 (40.45, 48.12)	0.95 (0.85, 1.05)	-0.18
CPRD Aurum	1,121	346,656	32.34 (30.47, 34.29)	886	345,371	25.65 (23.73, 27.73)	1.23 (1.11, 1.35)	0.74
Diabetes mellitus type 1								
Pedianet	0	6,974	0 (0, NC)	0	6,998	0 (0, NC)	0	0
NHR	476	836,725	5.69 (5.19, 6.22)	385	825,721	4.66 (4.01, 5.43)	1.21 (1.02, 1.45)	0.63
PHARMO	65	479,264	1.36 (1.05, 1.73)	61	473,634	1.29 (0.94, 1.76)	1.04 (0.70, 1.55)	0.07
EpiChron	52	206,385	2.52 (1.88, 3.30)	72	205,385	3.51 (2.39, 5.15)	0.71 (0.45, 1.13)	-1.12
SIDIAP	369	999,903	3.69 (3.32, 4.09)	385	999,919	3.85 (3.29, 4.51)	0.92 (0.76, 1.11)	-0.15
CPRD Aurum	245	1,284,669	1.91 (1.68, 2.16)	204	1,254,734	1.63 (1.37, 1.93)	1.20 (0.97, 1.48)	0.34
(Idiopathic) thrombocytopenia								

Table 16. Summary of number of events, person-years (PY), and incidence rates for each AESI in the vaccinated and unvaccinated cohorts and the adjusted hazard ratio (HR) and rate difference (RD) by data source

	Vaccinated			Unvaccinated			Adjusted HR[a]	Adjusted RD[a]
Adverse event of special interest	**Events (n)**	**PY**	**Incidence rate (95% CI)**	**Events (n)**	**PY**	**Incidence rate (95% CI)**		
Pedianet	0	1,037	0 (0, NC)	0	1,037	0 (0, NC)	0	0
NHR	25	257,490	0.97 (0.63, 1.43)	40	257,161	1.56 (1, 2.41)	0.62 (0.36, 1.09)	-0.07
PHARMO	<5	NR	0.23 (0.03, 0.83)	<5	NR	0.34 (0.11, 1.06)	0.60 (0.10, 3.57)	-0.02
EpiChron	<5	NR	0.46 (0.06, 1.65)	9	43,853	2.05 (0.79, 5.30)	0.23 (0.04, 1.23)	-0.23
SIDIAP	22	230,030	0.96 (0.60, 1.45)	27	230,029	1.17 (0.71, 1.93)	0.77 (0.40, 1.47)	-0.03
CPRD Aurum	26	349,128	0.74 (0.49, 1.09)	18	347,805	0.52 (0.31, 0.86)	1.40 (0.74, 2.67)	0.03
Thrombotic thrombocytopenia syndrome								
Pedianet	NA	NA	NA	NA	NA	NA	NA	NA
NHR	6	123,793	0.48 (0.18, 1.05)	7	123,744	0.57 (0.24, 1.31)	0.85 (0.27, 2.71)	0
PHARMO	0	35,681	0 (0, 1.03)	<5	NR	0.28 (0.04, 1.98)	NA	-0.01
EpiChron	<5	NR	0.99 (0.12, 3.57)	<5	NR	0.49 (0.07, 3.51)	1.72 (0.15, 19.10)	0.01
SIDIAP	<5	NR	0.39 (0.11, 0.99)	6	103,019	0.58 (0.26, 1.30)	0.63 (0.18, 2.25)	-0.01
CPRD Aurum	<5	NR	0.07 (0, 0.37)	<5	NR	0.13 (0.03, 0.54)	0.55 (0.05, 6.09)	0
Myositis								
Pedianet	NA	NA	NA	NA	NA	NA	NA	NA
NHR	153	854,133	1.79 (1.52, 2.10)	134	842,594	1.59 (1.22, 2.07)	1.12 (0.83, 1.52)	0.32
PHARMO	5	480,853	0.10 (0.03, 0.24)	6	475,212	0.13 (0.03, 0.54)	0.74 (0.13, 4.38)	-0.09
EpiChron	9	208,240	0.43 (0.20, 0.82)	<5	NR	0.19 (0.04, 0.91)	1.87 (0.34, 10.19)	0.05
SIDIAP	181	1,004,091	1.80 (1.55, 2.09)	187	1,004,106	1.86 (1.51, 2.30)	0.88 (0.68, 1.14)	-0.27
CPRD Aurum	50	1,284,805	0.39 (0.29, 0.51)	52	1,254,861	0.41 (0.29, 0.59)	0.91 (0.58, 1.42)	0.12
Cardiovascular system								
Acute cardiovascular injury including microangiopathy								
Pedianet	28	6,951	40.28 (26.77, 58.22)	20	6,977	28.67 (17.07, 48.16)	1.38 (0.73, 2.61)	10.12
NHR	20,167	772,035	261.22 (257.63, 264.85)	19,669	764,487	257.28 (251.86, 262.82)	1.01 (0.99, 1.04)	2.20
PHARMO	5,626	469,832	119.74 (116.64, 122.92)	3,766	465,082	80.97 (77.64, 84.46)	1.38 (1.31, 1.45)	33.31
EpiChron	3,446	201,712	170.84 (165.18, 176.64)	2,870	201,406	142.50 (134.71, 150.74)	1.10 (1.03, 1.18)	18.26
SIDIAP	11,569	979,663	118.09 (115.95, 120.26)	11,132	980,277	113.56 (110.25, 116.97)	0.99 (0.96, 1.03)	3.01
CPRD Aurum	10,041	1,258,613	79.78 (78.23, 81.35)	7,796	1,232,960	63.23 (61.38, 65.14)	1.23 (1.18, 1.27)	27.28
Arrhythmia								
Pedianet	25	6,959	35.92 (23.25, 53.03)	14	6,987	20.04 (11.44, 35.08)	1.75 (0.88, 3.49)	13.68
NHR	17,200	793,320	216.81 (213.58, 220.08)	16,543	784,864	210.78 (205.87, 215.80)	1.03 (1, 1.05)	5.25
PHARMO	4,696	471,867	99.52 (96.69, 102.41)	3,158	466,955	67.63 (64.58, 70.83)	1.36 (1.29, 1.44)	26.84
EpiChron	2,840	203,033	139.88 (134.78, 145.12)	2,305	202,602	113.77 (106.79, 121.21)	1.12 (1.04, 1.21)	16.77
SIDIAP	9,527	984,283	96.79 (94.86, 98.75)	9,146	984,781	92.87 (89.88, 95.97)	0.99 (0.96, 1.03)	2.84
CPRD Aurum	6,337	1,269,791	49.91 (48.68, 51.15)	4,735	1,242,440	38.11 (36.66, 39.62)	1.27 (1.21, 1.33)	21.25
Heart failure								

Table 16. Summary of number of events, person-years (PY), and incidence rates for each AESI in the vaccinated and unvaccinated cohorts and the adjusted hazard ratio (HR) and rate difference (RD) by data source

	Vaccinated			Unvaccinated			Adjusted HR[a]	Adjusted RD[a]
Adverse event of special interest	**Events (n)**	**PY**	**Incidence rate (95% CI)**	**Events (n)**	**PY**	**Incidence rate (95% CI)**		
Pedianet	NA	NA	NA	NA	NA	NA	NA	NA
NHR	3,885	838,216	46.35 (44.90, 47.83)	4,930	827,927	59.55 (56.84, 62.38)	0.77 (0.73, 0.82)	-13.33
PHARMO	780	479,288	16.27 (15.15, 17.46)	593	473,758	12.52 (11.20, 13.99)	1.29 (1.13, 1.47)	4.01
EpiChron	983	206,512	47.60 (44.67, 50.67)	1,035	205,745	50.30 (45.61, 55.49)	0.90 (0.80, 1.01)	-4.60
SIDIAP	2,569	998,769	25.72 (24.74, 26.74)	2,739	998,818	27.42 (25.73, 29.22)	0.89 (0.82, 0.96)	-1.19
CPRD Aurum	2,462	1,278,995	19.25 (18.50, 20.03)	2,299	1,250,241	18.39 (17.37, 19.47)	1.02 (0.95, 1.09)	5.23
Stress cardiomyopathy								
Pedianet	NA	NA	NA	NA	NA	NA	NA	NA
NHR	7	854,493	0.08 (0.03, 0.17)	10	842,940	0.12 (0.04, 0.37)	0.69 (0.18, 2.67)	0.02
PHARMO	6	480,858	0.12 (0.05, 0.27)	<5	NR	0.08 (0.03, 0.28)	1.49 (0.33, 6.69)	0
EpiChron	6	208,241	0.29 (0.11, 0.63)	6	207,207	0.29 (0.09, 0.90)	0.85 (0.21, 3.47)	-0.05
SIDIAP	35	1,004,330	0.35 (0.24, 0.48)	21	1,004,339	0.21 (0.11, 0.39)	1.51 (0.75, 3.04)	0.14
CPRD Aurum	14	1,284,916	0.11 (0.06, 0.18)	11	1,254,967	0.09 (0.04, 0.18)	1.30 (0.53, 3.20)	0.06
Coronary artery disease								
Pedianet	NA	NA	NA	NA	NA	NA	NA	NA
NHR	5,593	831,346	67.28 (65.52, 69.06)	5,541	820,893	67.50 (64.71, 70.41)	0.99 (0.94, 1.04)	0.43
PHARMO	893	478,964	18.64 (17.44, 19.91)	579	473,477	12.23 (10.99, 13.60)	1.49 (1.31, 1.69)	6.17
EpiChron	379	207,469	18.27 (16.47, 20.20)	371	206,465	17.97 (15.33, 21.06)	0.97 (0.80, 1.17)	0.57
SIDIAP	1,542	1,001,458	15.40 (14.64, 16.19)	1,464	1,001,552	14.62 (13.44, 15.90)	1 (0.91, 1.10)	0.52
CPRD Aurum	2,651	1,277,998	20.74 (19.96, 21.55)	1,804	1,249,224	14.44 (13.58, 15.36)	1.40 (1.30, 1.50)	7.83
Myocarditis (7 days)								
Pedianet	0	197	0 (0, NC)	0	197	0 (0, NC)	0	0
NHR	6	64,453	0.93 (0.34, 2.03)	9	64,442	1.40 (0.73, 2.68)	0.67 (0.24, 1.88)	-0.01
PHARMO	<5	NR	0.56 (0.01, 3.11)	0	17,936	0 (0, NC)	0	0.01
EpiChron	<5	NR	0.91 (0.02, 5.08)	0	10,976	0 (0, NC)	0	0.02
SIDIAP	0	54,205	0 (0, NC)	<5	NR	0.55 (0.18, 1.72)	NA	-0.01
CPRD Aurum	10	74,891	1.34 (0.64, 2.46)	<5	74,845	0.13 (0.02, 0.95)	9.70 (1.24, 75.97)**	0.02
Myocarditis (14 days)								
Pedianet	0	380	0 (0, NC)	0	380	0 (0, NC)	0	0
NHR	13	117,067	1.11 (0.59, 1.90)	12	117,024	1.03 (0.56, 1.89)	1.09 (0.48, 2.46)	0.01
PHARMO	<5	NR	0.60 (0.07, 2.15)	<5	NR	0.59 (0.08, 4.22)	0.81 (0.07, 8.92)	-0.01
EpiChron	<5	NR	1.04 (0.13, 3.77)	<5	NR	0.52 (0.07, 3.70)	1.84 (0.17, 20.30)	0.02
SIDIAP	6	97,369	0.62 (0.23, 1.34)	5	97,369	0.51 (0.21, 1.23)	1.09 (0.33, 3.62)	0.01
CPRD Aurum	14	140,114	1 (0.55, 1.68)	8	139,949	0.57 (0.26, 1.24)	1.74 (0.68, 4.44)	0.01
Myocarditis (21 days)								
Pedianet	0	553	0 (0, NC)	0	553	0 (0, NC)	0	0
NHR	16	160,598	1 (0.57, 1.62)	17	160,505	1.06 (0.62, 1.80)	0.94 (0.46, 1.94)	0

Table 16. Summary of number of events, person-years (PY), and incidence rates for each AESI in the vaccinated and unvaccinated cohorts and the adjusted hazard ratio (HR) and rate difference (RD) by data source

	Vaccinated			Unvaccinated			Adjusted HR[a]	Adjusted RD[a]
Adverse event of special interest	**Events (n)**	**PY**	**Incidence rate (95% CI)**	**Events (n)**	**PY**	**Incidence rate (95% CI)**		
PHARMO	<5	NR	0.62 (0.13, 1.82)	<5	NR	0.42 (0.06, 2.95)	1.23 (0.13, 11.84)	0.01
EpiChron	<5	NR	1.53 (0.42, 3.92)	<5	NR	0.38 (0.05, 2.72)	3.64 (0.41, 32.53)	0.07
SIDIAP	8	134,968	0.59 (0.26, 1.17)	7	134,968	0.52 (0.22, 1.20)	1.05 (0.35, 3.16)	0
CPRD Aurum	18	198,641	0.91 (0.54, 1.43)	8	198,282	0.40 (0.19, 0.88)	2.30 (0.94, 5.66)	0.03
Pericarditis (7 days)								
Pedianet	<5	NR	50.83 (1.29, 283.23)	0	197	0 (0, NC)	0	0.95
NHR	16	64,433	2.48 (1.42, 4.03)	24	64,422	3.73 (2.35, 5.91)	0.66 (0.34, 1.30)	-0.02
PHARMO	0	17,887	0 (0, NC)	<5	NR	0.56 (0.08, 3.96)	NA	-0.01
EpiChron	<5	NR	3.64 (0.99, 9.33)	5	10,973	4.56 (1.62, 12.85)	0.83 (0.20, 3.45)	-0.01
SIDIAP	19	54,182	3.51 (2.11, 5.48)	18	54,182	3.32 (1.67, 6.61)	0.96 (0.42, 2.17)	0
CPRD Aurum	12	74,880	1.60 (0.83, 2.80)	11	74,834	1.47 (0.77, 2.79)	1.10 (0.47, 2.58)	0
Pericarditis (14 days)								
Pedianet	<5	NR	26.28 (0.67, 146.40)	0	381	0 (0, NC)	0	0.95
NHR	36	117,030	3.08 (2.15, 4.26)	39	116,988	3.33 (2.24, 4.97)	0.92 (0.55, 1.54)	0
PHARMO	<5	NR	0.30 (0.01, 1.66)	<5	NR	0.30 (0.04, 2.11)	1.44 (0.09, 22.95)	0.01
EpiChron	6	19,166	3.13 (1.15, 6.81)	7	19,160	3.65 (1.44, 9.25)	0.84 (0.25, 2.87)	-0.02
SIDIAP	36	97,329	3.70 (2.59, 5.12)	34	97,329	3.49 (1.97, 6.18)	0.95 (0.49, 1.83)	-0.01
CPRD Aurum	22	140,094	1.57 (0.98, 2.38)	16	139,928	1.14 (0.68, 1.92)	1.36 (0.71, 2.61)	0.02
Pericarditis (21 days)								
Pedianet	<5	NR	18.06 (0.46, 100.64)	0	554	0 (0, NC)	0	0.95
NHR	55	160,548	3.43 (2.58, 4.46)	50	160,456	3.12 (2.14, 4.54)	1.10 (0.69, 1.73)	0.03
PHARMO	<5	NR	0.21 (0.01, 1.16)	<5	NR	0.21 (0.03, 1.47)	1.44 (0.09, 22.95)	0.01
EpiChron	6	26,098	2.30 (0.84, 5)	8	26,084	3.07 (1.23, 7.67)	0.74 (0.22, 2.49)	-0.05
SIDIAP	43	134,911	3.19 (2.31, 4.29)	38	134,912	2.82 (1.66, 4.77)	1.02 (0.56, 1.88)	0.01
CPRD Aurum	38	198,611	1.91 (1.35, 2.63)	24	198,253	1.21 (0.79, 1.86)	1.49 (0.87, 2.54)	0.04
Myocarditis or pericarditis (7 days)								
Pedianet	<5	NR	50.86 (1.29, 283.39)	0	197	0 (0, NC)	0	0.95
NHR	21	64,421	3.26 (2.02, 4.98)	32	64,410	4.97 (3.37, 7.32)	0.65 (0.37, 1.17)	-0.03
PHARMO	<5	NR	0.56 (0.01, 3.12)	<5	NR	0.56 (0.08, 3.96)	1.10 (0.07, 17.58)	0
EpiChron	5	10,974	4.56 (1.48, 10.63)	5	10,973	4.56 (1.62, 12.85)	1.02 (0.26, 3.93)	0.01
SIDIAP	18	54,178	3.32 (1.97, 5.25)	20	54,178	3.69 (1.96, 6.97)	0.81 (0.37, 1.75)	-0.01
CPRD Aurum	22	74,873	2.94 (1.84, 4.45)	12	74,827	1.60 (0.87, 2.95)	1.80 (0.86, 3.76)	0.02
Myocarditis or pericarditis (14 days)								
Pedianet	<5	NR	26.29 (0.67, 146.48)	0	380	0 (0, NC)	0	0.95
NHR	48	117,008	4.10 (3.02, 5.44)	49	116,965	4.19 (2.98, 5.90)	0.98 (0.63, 1.52)	0.01
PHARMO	<5	NR	0.89 (0.18, 2.61)	<5	NR	0.89 (0.21, 3.84)	0.98 (0.15, 6.58)	0
EpiChron	8	19,165	4.17 (1.80, 8.22)	8	19,159	4.18 (1.79, 9.76)	0.97 (0.33, 2.89)	0
SIDIAP	39	97,322	4.01 (2.85, 5.48)	38	97,322	3.90 (2.32, 6.57)	0.92 (0.50, 1.68)	-0.01

Table 16. Summary of number of events, person-years (PY), and incidence rates for each AESI in the vaccinated and unvaccinated cohorts and the adjusted hazard ratio (HR) and rate difference (RD) by data source

	Vaccinated			Unvaccinated			Adjusted HR[a]	Adjusted RD[a]
Adverse event of special interest	**Events (n)**	**PY**	**Incidence rate (95% CI)**	**Events (n)**	**PY**	**Incidence rate (95% CI)**		
CPRD Aurum	36	140,080	2.57 (1.80, 3.56)	24	139,915	1.72 (1.11, 2.64)	1.49 (0.87, 2.53)	0.03
Myocarditis or pericarditis (21 days)								
Pedianet	<5	NR	18.07 (0.46, 100.70)	0	553	0 (0, NC)	0	0.95
NHR	68	160,517	4.24 (3.29, 5.37)	64	160,424	3.99 (2.90, 5.48)	1.06 (0.71, 1.58)	0.03
PHARMO	<5	NR	0.83 (0.23, 2.13)	<5	NR	0.62 (0.14, 2.68)	1.29 (0.21, 7.90)	0.01
EpiChron	10	26,097	3.83 (1.84, 7.05)	9	26,083	3.45 (1.48, 8.02)	1.07 (0.38, 3.03)	0.02
SIDIAP	48	134,902	3.56 (2.62, 4.72)	44	134,902	3.26 (2.04, 5.23)	0.99 (0.57, 1.72)	0.01
CPRD Aurum	56	198,592	2.82 (2.13, 3.66)	32	198,235	1.61 (1.11, 2.35)	1.68 (1.06, 2.66)	0.07
Circulatory system								
Coagulation disorders: thromboembolism								
Pedianet	0	719	0 (0, 51.32)	<5	NR	13.91 (1.96, 98.77)	NA	-0.95
NHR	1,278	194,519	65.70 (62.15, 69.40)	1,359	194,372	69.92 (65.31, 74.86)	0.94 (0.86, 1.02)	-0.29
PHARMO	94	61,625	15.25 (12.33, 18.67)	88	61,748	14.25 (11.08, 18.34)	1.03 (0.75, 1.42)	0.03
EpiChron	222	32,012	69.35 (60.53, 79.10)	242	31,991	75.65 (63.66, 89.89)	0.88 (0.71, 1.09)	-0.71
SIDIAP	624	167,788	37.19 (34.33, 40.23)	861	167,776	51.32 (46.93, 56.12)	0.67 (0.60, 0.76)	-1.28
CPRD Aurum	643	250,854	25.63 (23.69, 27.69)	849	250,239	33.93 (31.45, 36.60)	0.74 (0.66, 0.82)	-0.70
Single organ cutaneous vasculitis								
Pedianet								
NHR	13	197,648	0.66 (0.35, 1.12)	7	197,491	0.35 (0.15, 0.82)	1.85 (0.68, 5.02)	0.02
PHARMO	0	61,781	0 (0, NC)	<5	NR	0.16 (0.02, 1.15)	NA	-0.01
EpiChron	<5	NR	0.31 (0.01, 1.72)	0	32,389	0 (0, NC)	0	0.03
SIDIAP	5	169,107	0.30 (0.10, 0.69)	<5	NR	0.06 (0.01, 0.42)	4.67 (0.54, 39.99)	0.02
CPRD Aurum	5	252,286	0.20 (0.06, 0.46)	7	251,664	0.28 (0.11, 0.70)	0.72 (0.20, 2.58)	-0.01
Cerebral venous sinus thrombosis								
Pedianet	0	719	0 (0, NC)	0	719	0 (0, NC)	0	0
NHR	7	197,673	0.35 (0.14, 0.73)	11	197,515	0.56 (0.28, 1.11)	0.63 (0.23, 1.74)	-0.01
PHARMO	<5	NR	0.16 (0, 0.90)	0	61,904	0 (0, NC)	0	0.01
EpiChron	<5	NR	0.31 (0.01, 1.72)	<5	NR	0.31 (0.04, 2.19)	0.90 (0.06, 14.09)	0.01
SIDIAP	<5	NR	0.12 (0.01, 0.43)	<5	NR	0.18 (0.06, 0.55)	0.68 (0.11, 4.20)	0
CPRD Aurum	5	252,280	0.20 (0.06, 0.46)	11	251,658	0.44 (0.23, 0.83)	0.43 (0.14, 1.27)	-0.02
Hepato-gastrointestinal and renal system								
Acute liver injury								
Pedianet	0	6,991	0 (0, NC)	0	7,014	0 (0, NC)	0	0
NHR	125	854,201	1.46 (1.22, 1.74)	167	842,663	1.98 (1.53, 2.57)	0.73 (0.54, 1)	-0.53
PHARMO	12	480,849	0.25 (0.13, 0.44)	7	475,208	0.15 (0.06, 0.34)	1.76 (0.65, 4.79)	0.09
EpiChron	68	208,124	3.27 (2.54, 4.14)	69	207,101	3.33 (2.23, 4.98)	0.91 (0.56, 1.46)	-0.11
SIDIAP	119	1,004,116	1.19 (0.98, 1.42)	160	1,004,106	1.59 (1.25, 2.03)	0.64 (0.47, 0.88)	-0.49

Table 16. Summary of number of events, person-years (PY), and incidence rates for each AESI in the vaccinated and unvaccinated cohorts and the adjusted hazard ratio (HR) and rate difference (RD) by data source

	Vaccinated			Unvaccinated			Adjusted HR[a]	Adjusted RD[a]
Adverse event of special interest	**Events (n)**	**PY**	**Incidence rate (95% CI)**	**Events (n)**	**PY**	**Incidence rate (95% CI)**		
CPRD Aurum	68	1,284,804	0.53 (0.41, 0.67)	70	1,254,863	0.56 (0.42, 0.75)	0.92 (0.63, 1.34)	0.07
Acute kidney injury								
Pedianet	0	6,991	0 (0, NC)	0	7,014	0 (0, NC)	0	0
NHR	2,480	849,109	29.21 (28.07, 30.38)	3,577	838,010	42.68 (40.29, 45.22)	0.68 (0.63, 0.73)	-14.55
PHARMO	340	480,188	7.08 (6.35, 7.87)	297	474,581	6.26 (5.36, 7.30)	1.11 (0.92, 1.34)	1.04
EpiChron	701	207,210	33.83 (31.37, 36.43)	703	206,336	34.07 (30.19, 38.45)	0.92 (0.80, 1.06)	-1.09
SIDIAP	3,069	997,291	30.77 (29.69, 31.88)	3,452	997,268	34.61 (32.82, 36.51)	0.82 (0.77, 0.87)	-3.83
CPRD Aurum	1,765	1,280,435	13.78 (13.15, 14.44)	1,977	1,251,085	15.80 (14.89, 16.77)	0.84 (0.78, 0.90)	-0.45
Acute pancreatitis								
Pedianet	NA	NA	NA	NA	NA	NA	NA	NA
NHR	474	853,262	5.56 (5.07, 6.08)	533	841,748	6.33 (5.53, 7.25)	0.87 (0.74, 1.03)	-0.63
PHARMO	86	480,661	1.79 (1.43, 2.21)	74	475,027	1.56 (1.13, 2.14)	1.08 (0.73, 1.58)	0.26
EpiChron	105	207,993	5.05 (4.13, 6.11)	84	206,971	4.06 (2.93, 5.62)	1.14 (0.78, 1.66)	0.68
SIDIAP	455	1,003,340	4.53 (4.13, 4.97)	513	1,003,342	5.11 (4.49, 5.83)	0.82 (0.70, 0.96)	-0.72
CPRD Aurum	271	1,284,267	2.11 (1.87, 2.38)	260	1,254,360	2.07 (1.77, 2.42)	0.99 (0.81, 1.21)	0.07
Rhabdomyolysis								
Pedianet	NA	NA	NA	NA	NA	NA	NA	NA
NHR	5	854,499	0.06 (0.02, 0.14)	7	842,942	0.08 (0.02, 0.38)	0.71 (0.12, 4.05)	-0.01
PHARMO	7	480,852	0.15 (0.06, 0.30)	<5	NR	0.06 (0.02, 0.20)	2.20 (0.56, 8.63)	0.07
EpiChron	47	208,172	2.26 (1.66, 3)	51	207,135	2.46 (1.34, 4.52)	0.86 (0.44, 1.68)	0.02
SIDIAP	135	1,004,110	1.34 (1.13, 1.59)	215	1,004,093	2.14 (1.71, 2.68)	0.60 (0.46, 0.80)	-0.68
CPRD Aurum	63	1,284,795	0.49 (0.38, 0.63)	82	1,254,853	0.65 (0.49, 0.87)	0.74 (0.51, 1.08)	-0.04
Glomerulonephritis								
Pedianet	0	6,991	0 (0, NC)	0	7,014	0 (0, NC)	0	0
NHR	NA	NA	NA	NA	NA	NA	NA	NA
PHARMO	NA	NA	NA	NA	NA	NA	NA	NA
EpiChron	12	208,226	0.58 (0.30, 1.01)	18	207,187	0.87 (0.40, 1.88)	0.59 (0.22, 1.55)	-0.28
SIDIAP	105	1,004,201	1.05 (0.86, 1.27)	73	1,004,208	0.73 (0.53, 1)	1.29 (0.88, 1.87)	0.29
CPRD Aurum	137	1,284,652	1.07 (0.90, 1.26)	150	1,254,718	1.20 (0.96, 1.48)	0.88 (0.67, 1.16)	-0.23
Nerves and central nervous system								
Generalised convulsion								
Pedianet	0	1,031	0 (0, NC)	<5	NR	19.40 (4.85, 77.53)	NA	-2.46
NHR	696	254,063	27.39 (25.40, 29.51)	688	253,745	27.11 (24.50, 30.01)	1.01 (0.89, 1.14)	0.05
PHARMO	38	87,350	4.35 (3.08, 5.97)	27	87,521	3.08 (2.06, 4.62)	1.37 (0.82, 2.31)	0.14
EpiChron	94	43,751	21.49 (17.36, 26.29)	73	43,707	16.70 (12.52, 22.28)	1.17 (0.83, 1.66)	0.59
SIDIAP	325	229,410	14.17 (12.67, 15.79)	348	229,408	15.17 (13.18, 17.45)	0.85 (0.71, 1.02)	-0.22
CPRD Aurum	628	347,581	18.07 (16.68, 19.54)	633	346,267	18.28 (16.73, 19.97)	0.97 (0.86, 1.09)	-0.03
Meningoencephalitis								

Table 16. Summary of number of events, person-years (PY), and incidence rates for each AESI in the vaccinated and unvaccinated cohorts and the adjusted hazard ratio (HR) and rate difference (RD) by data source

	Vaccinated			Unvaccinated			Adjusted HR[a]	Adjusted RD[a]
Adverse event of special interest	**Events (n)**	**PY**	**Incidence rate (95% CI)**	**Events (n)**	**PY**	**Incidence rate (95% CI)**		
Pedianet	0	1,037	0 (0, NC)	0	1,037	0 (0, NC)	0	0
NHR	46	257,455	1.79 (1.31, 2.38)	43	257,127	1.67 (1.14, 2.46)	1.07 (0.68, 1.69)	0.02
PHARMO	<5	NR	0.34 (0.07, 1)	6	87,584	0.69 (0.27, 1.73)	0.49 (0.11, 2.14)	-0.04
EpiChron	<5	NR	0.91 (0.25, 2.33)	<5	NR	0.23 (0.03, 1.62)	3.29 (0.37, 29.20)	0.09
SIDIAP	12	230,048	0.52 (0.27, 0.91)	17	230,048	0.74 (0.35, 1.57)	0.69 (0.27, 1.79)	-0.03
CPRD Aurum	9	349,160	0.26 (0.12, 0.49)	22	347,835	0.63 (0.35, 1.14)	0.40 (0.16, 0.96)	-0.05
Transverse myelitis								
Pedianet	0	1,036	0 (0, NC)	0	1,037	0 (0, NC)	0	0
NHR	<5	NR	0.08 (0.01, 0.28)	<5	NR	0.08 (0.01, 0.55)	0.99 (0.09, 10.88)	0
PHARMO	0	87,420	0 (0, NC)	0	87,590	0 (0, NC)	0	0
EpiChron	<5	NR	0.46 (0.06, 1.65)	0	43,860	0 (0, NC)	0	0.05
SIDIAP	<5	NR	0.13 (0.03, 0.38)	<5	NR	0.09 (0.01, 0.62)	1.18 (0.12, 11.36)	0
CPRD Aurum	6	349,174	0.17 (0.06, 0.37)	6	347,849	0.17 (0.08, 0.38)	0.91 (0.29, 2.87)	0
Bell's palsy								
Pedianet	0	1,036	0 (0, NC)	0	1,037	0 (0, NC)	0	0
NHR	166	257,184	6.45 (5.51, 7.51)	144	256,858	5.61 (4.49, 7.01)	1.15 (0.88, 1.50)	0.11
PHARMO	10	87,393	1.14 (0.55, 2.10)	14	87,563	1.60 (0.91, 2.80)	0.65 (0.28, 1.51)	-0.08
EpiChron	31	43,848	7.07 (4.80, 10.04)	34	43,803	7.76 (3.30, 18.25)	0.84 (0.34, 2.09)	-0.22
SIDIAP	167	229,708	7.27 (6.21, 8.46)	167	229,708	7.27 (5.96, 8.88)	0.96 (0.75, 1.24)	-0.01
CPRD Aurum	114	348,927	3.27 (2.70, 3.92)	116	347,605	3.34 (2.72, 4.09)	0.99 (0.75, 1.29)	-0.01
Respiratory system								
Acute respiratory distress syndrome								
Pedianet	NA	NA	NA	NA	NA	NA	NA	NA
NHR	56	854,397	0.66 (0.50, 0.85)	284	842,801	3.37 (2.76, 4.11)	0.19 (0.14, 0.27)	-3.27
PHARMO	<5	NR	0.04 (0.01, 0.15)	6	475,213	0.13 (0.05, 0.32)	0.30 (0.06, 1.63)	-0.12
EpiChron	26	208,169	1.25 (0.82, 1.83)	147	207,106	7.10 (5.55, 9.08)	0.16 (0.10, 0.25)	-6.22
SIDIAP	82	1,003,633	0.82 (0.65, 1.01)	579	1,003,438	5.77 (5.09, 6.54)	0.13 (0.10, 0.17)	-4.63
CPRD Aurum	18	1,284,870	0.14 (0.08, 0.22)	56	1,254,915	0.45 (0.31, 0.64)	0.31 (0.17, 0.55)	-0.29
Skin and musous membrane bone and joints								
Erythema multiforme								
Pedianet	0	1,036	0 (0, NC)	0	1,037	0 (0, NC)	NA	0
NHR	<5	NR	0.12 (0.02, 0.34)	7	257,242	0.27 (0.12, 0.63)	0.43 (0.10, 1.74)	-0.01
PHARMO	0	87,419	0 (0, NC)	0	87,590	0 (0, NC)	NA	0
EpiChron	<5	NR	0.68 (0.14, 2)	<5	NR	0.23 (0.03, 1.62)	3.18 (0.32, 31.35)	0.03
SIDIAP	10	230,051	0.43 (0.21, 0.80)	11	230,051	0.48 (0.24, 0.95)	0.82 (0.35, 1.96)	-0.02
CPRD Aurum	7	349,155	0.20 (0.08, 0.41)	11	347,830	0.32 (0.15, 0.66)	0.55 (0.18, 1.65)	-0.02
Chilblain-like lesions								

Table 16. Summary of number of events, person-years (PY), and incidence rates for each AESI in the vaccinated and unvaccinated cohorts and the adjusted hazard ratio (HR) and rate difference (RD) by data source

	Vaccinated			Unvaccinated			Adjusted HR[a]	Adjusted RD[a]
Adverse event of special interest	**Events (n)**	**PY**	**Incidence rate (95% CI)**	**Events (n)**	**PY**	**Incidence rate (95% CI)**		
Pedianet	<5	NR	19.30 (2.34, 69.73)	0	1,037	0 (0, NC)	NA	2.22
NHR	0	257,590	0 (0, NC)	0	257,262	0 (0, NC)	NA	0
PHARMO	5	87,403	0.57 (0.19, 1.34)	<5	NR	0.34 (0.11, 1.06)	1.51 (0.36, 6.38)	0.01
EpiChron	5	43,871	1.14 (0.37, 2.66)	13	43,824	2.97 (1.65, 5.32)	0.36 (0.12, 1.05)	-0.23
SIDIAP	59	229,814	2.57 (1.95, 3.31)	89	229,812	3.87 (2.94, 5.09)	0.65 (0.45, 0.94)	-0.15
CPRD Aurum	121	348,931	3.47 (2.88, 4.14)	98	347,607	2.82 (2.29, 3.48)	1.18 (0.89, 1.55)	0.06
Reproductive system								
Secondary amenorrhoea								
Pedianet	<5	NR	2.57 (0.07, 14.33)	0	3,902	0 (0, NC)	NA	1.11
NHR	136	141,726	9.60 (8.05, 11.35)	147	139,920	10.51 (8.34, 13.24)	0.91 (0.69, 1.21)	-0.55
PHARMO	<5	NR	0.13 (0, 0.73)	<5	NR	0.13 (0.02, 0.94)	0.77 (0.05, 11.99)	0
EpiChron	270	38,227	70.63 (62.46, 79.58)	141	38,189	36.92 (29.89, 45.61)	1.71 (1.34, 2.18)	14.62
SIDIAP	1,663	176,273	94.34 (89.86, 98.99)	1,582	175,905	89.93 (84.11, 96.16)	0.99 (0.91, 1.07)	0.08
CPRD Aurum	4,484	986,853	45.44 (44.12, 46.79)	3,326	974,615	34.13 (32.70, 35.61)	1.25 (1.18, 1.31)	3.24
Hypermenorrhea								
Pedianet	<5	NR	5.15 (0.62, 18.62)	<5	NR	7.70 (1.79, 33.20)	0.62 (0.08, 4.66)	-0.87
NHR	NA	NA	NA	NA	NA	NA	NA	NA
PHARMO	6	76,532	0.78 (0.29, 1.71)	5	75,683	0.66 (0.23, 1.86)	1.18 (0.31, 4.47)	0.04
EpiChron	858	37,157	230.91 (215.72, 246.89)	535	37,166	143.95 (128.81, 160.87)	1.40 (1.23, 1.60)	33.57
SIDIAP	2,502	175,111	142.88 (137.34, 148.59)	2,285	174,773	130.74 (123.61, 138.29)	1.02 (0.95, 1.09)	2.94
CPRD Aurum	NA	NA	NA	NA	NA	NA	NA	NA
Other								
Anaphylaxis*								
Pedianet	0	NA	0 (0, NC)	0	NA	0 (0, NC)	NA	NA
NHR	64	NA	0.18 (0.14, 0.23)	<5	NA	0.01 (0, 0.02)	31.95 (7.82, 130.52)	NA
PHARMO	<5	NA	0.01 (0, NC)	0	NA	0 (0, NC)	NA	NA
EpiChron	<5	NA	0.05 (0.02, 0.14)	<5	NA	0.02 (0, 0.11)	3.01 (0.31, 29.00)	NA
SIDIAP	5	NA	0.02 (0.01, 0.04)	<5	NA	0.01 (0, 0.03)	1.62 (0.39, 6.78)	NA
CPRD Aurum	<5	NA	0.03 (0.02, 0.05)	8	NA	0.02 (0.01, 0.04)	1.40 (0.58, 3.40)	NA
Multisystem inflammatory syndrome								
Pedianet	NA	NA	NA	NA	NA	NA	NA	NA
NHR	183	257,260	7.11 (6.12, 8.22)	233	256,935	9.07 (7.57, 10.86)	0.78 (0.62, 0.98)	-0.21
PHARMO	<5	NR	0.11 (0, 0.64)	<5	NR	0.11 (0.02, 0.81)	1.20 (0.08, 19.01)	0.01
EpiChron	17	43,889	3.87 (2.26, 6.20)	9	43,843	2.05 (0.94, 4.50)	1.84 (0.74, 4.61)	0.27
SIDIAP	8	230,064	0.35 (0.15, 0.69)	7	230,064	0.30 (0.13, 0.70)	1.19 (0.40, 3.58)	0.01
CPRD Aurum	<5	NR	0.09 (0.02, 0.25)	<5	NR	0.03 (0, 0.20)	3.36 (0.35, 32.30)	0.01
Death (any causes)								

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	Vaccinated			Unvaccinated			Adjusted HR[a]	Adjusted RD[a]
Adverse event of special interest	**Events (n)**	**PY**	**Incidence rate (95% CI)**	**Events (n)**	**PY**	**Incidence rate (95% CI)**		
Pedianet	<5	NR	1.43 (0.04, 7.97)	0	7,014	0 (0, NC)	NA	1.38
NHR	6,855	854,504	80.22 (78.33, 82.14)	14,385	842,949	170.65 (165.72, 175.72)	0.47 (0.45, 0.48)	-83.15
PHARMO	2,079	480,866	43.23 (41.40, 45.13)	2,855	475,224	60.08 (56.98, 63.34)	0.66 (0.62, 0.71)	-11.55
EpiChron	1,531	208,255	73.52 (69.88, 77.29)	2,494	207,218	120.36 (112.60, 128.65)	0.58 (0.54, 0.63)	-40.13
SIDIAP	NA	NA	NA	NA	NA	NA	NA	NA
CPRD Aurum	5,062	1,284,949	39.39 (38.32, 40.50)	15,617	1,254,994	124.44 (121.70, 127.24)	0.29 (0.28, 0.30)	-78.73
Subacute thyroiditis								
Pedianet	NA	NA	NA	NA	NA	NA	NA	NA
NHR	39	854,417	0.46 (0.32, 0.62)	22	842,870	0.26 (0.15, 0.45)	1.75 (0.93, 3.30)	0.15
PHARMO	0	480,866	0 (0, NC)	0	475,224	0 (0, NC)	0	0
EpiChron	<5	NR	0.10 (0.01, 0.35)	<5	NR	0.10 (0.01, 0.69)	0.92 (0.08, 10.11)	0.02
SIDIAP	5	1,004,405	0.05 (0.02, 0.12)	<5	NR	0.02 (0, 0.08)	2.14 (0.41, 11.09)	0.03
CPRD Aurum	12	1,284,929	0.09 (0.05, 0.16)	<5	NR	0.03 (0.01, 0.08)	2.98 (0.96, 9.25)	0.06
Sudden death								
Pedianet	NA	NA	NA	NA	NA	NA	NA	NA
NHR	93	854,481	1.09 (0.88, 1.33)	190	842,924	2.25 (1.78, 2.86)	0.48 (0.35, 0.65)	-1.28
PHARMO	<5	NR	0.04 (0.01, 0.15)	<5	NR	0.06 (0.01, 0.27)	0.75 (0.10, 5.51)	-0.04
EpiChron	0	208,255	0 (0, NC)	0	207,218	0 (0, NC)	0	0
SIDIAP	NA	NA	NA	NA	NA	NA	NA	NA
CPRD Aurum	6	1,284,948	0.05 (0.02, 0.10)	9	1,254,993	0.07 (0.03, 0.19)	0.65 (0.18, 2.33)	-0.01

NA: not available; NC: not calculable; NR: not reportable due to obligation to mask number of events when less than 5.
a see Section 9.3.33; * as risk window is one day, the prevalence was calculated per 10,000 persons; **Outlier, to be confirmed for final report.

10.2.3. Detailed results for 11 AESIs of specific interest

Detailed results are given for the following 11 AESIs either at the request of EMA and for the recently added AESIs.

10.2.3.1. Acute cardiovascular injury

Acute cardiovascular injury is a composite event consisting of microangiopathy, heart failure, stress cardiomyopathy, coronary artery disease, and arrhythmia. Acute cardiovascular injury was observed in both the vaccinated and unvaccinated cohorts in all data sources. The incidence rates in the vaccinated cohorts ranged from 40.28 per 10,000 person-years (95% CI: 26.77, 58.22) in Pedianet to 261.22 per 10,000 person-years (95% CI: 257.63, 264.85) in NHR and in the unvaccinated cohorts these ranged from 28.67 per 10,000 person-years (95% CI 17.07, 48.16) in Pedianet to 257.28 per 10,000 person-years (95% CI: 251.86, 262.82) in NHR.

The incidence of acute cardiovascular injury was higher in the older age groups in all data sources, in both the vaccinated and non-vaccinated cohorts during the 365-day risk interval. The matched HRs were 1.41 (95% CI: 0.74, 2.66) in Pedianet, 1.02 (95% CI: 0.99, 1.04) in NHR, 1.48 (95% CI: 1.41, 1.55) in PHARMO, 1.20 (95% CI: 1.12, 1.28) in EpiChron, 1.04 (95% CI: 1.00, 1.08) in SIDIAP, and 1.26 (95% CI: 1.21, 1.30) in CPRD Aurum. The adjusted HRs were 1.38 (95% CI: 0.73, 2.61) in Pedianet, 1.01 (95% CI: 0.99, 1.04) in NHR, 1.38 (95% CI: 1.31, 1.45) in PHARMO, 1.10 (95% CI: 1.03, 1.18) in EpiChron, 0.99 (95% CI: 0.96, 1.03) in SIDIAP, and 1.23 (95% CI: 1.18, 1.27) in CPRD Aurum. The matched and adjusted HR and CIs were >1 in PHARMO, EpiChron, and CPRD Aurum. The HRs for acute cardiovascular injury were primarily driven by arrhythmia.

Table 17. Risk estimates (95% CI) per 10,000 person-years (PY) for acute cardiovascular injury among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source (risk window: 365 days after dose 1)

	Vaccinated				Unvaccinated			
Data source	**Events (n)**	**Cumulative incidence (95% CI)**	**Person-years (PY)**	**Incidence rate (95% CI)**	**Events (n)**	**Cumulative incidence (95% CI)**	**Person-years (PY)**	**Incidence rate (95% CI)**
Pedianet	28	39.55 (24.84, 54.24)	6,951	40.28 (26.77, 58.22)	20	28.67 (13.85, 43.46)	6,977	28.67 (17.07, 48.16)
NHR	20,167	237.70 (234.04, 241.35)	772,035	261.22 (257.63, 264.85)	19,669	234.23 (228.47, 239.99)	764,487	257.28 (251.86, 262.82)
PHARMO	5,626	116.87 (113.70, 120.04)	469,832	119.74 (116.64, 122.92)	3,766	76.98 (73.65, 80.31)	465,082	80.97 (77.64, 84.46)
EpiChron	3,446	157.44 (151.89, 162.98)	201,712	170.84 (165.18, 176.64)	2,870	126.57 (118.91, 134.21)	201,406	142.50 (134.71, 150.74)
SIDIAP	11,569	107.47 (105.35, 109.60)	979,663	118.09 (115.95, 120.26)	11,132	99.88 (96.67, 103.08)	980,277	113.56 (110.25, 116.97)
CPRD Aurum	10,041	95.83 (92.89, 98.77)	1,258,613	79.78 (78.23, 81.35)	7,796	66.95 (63.62, 70.28)	1,232,960	63.23 (61.38, 65.14)

Note: Estimation of confidence intervals differs between vaccinated and unvaccinated, since the unvaccinated estimate is a generalised estimating equation (GEE) estimates (to account for individuals who were matched to more than one vaccinated individual). When NA (not-assessable) is listed for the 1-KM it means that there is no estimate for the duration of follow-up specified as risk interval, meaning that there was not any patient who reached the end of the risk window. The vaccinated and unvaccinated cohorts were matched on age, sex, geographical region, prior identified COVID-19 infection, prior influenza vaccination, pregnancy, immunocompromised and number of pre-existing conditions considered by the Centers for Disease Control and Prevention (CDC) as risk criteria (0, 1, 2, 3, 4+).

Figure 6. Cumulative incidence of acute cardiovascular injury among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source (risk window: 365 days after dose 1)

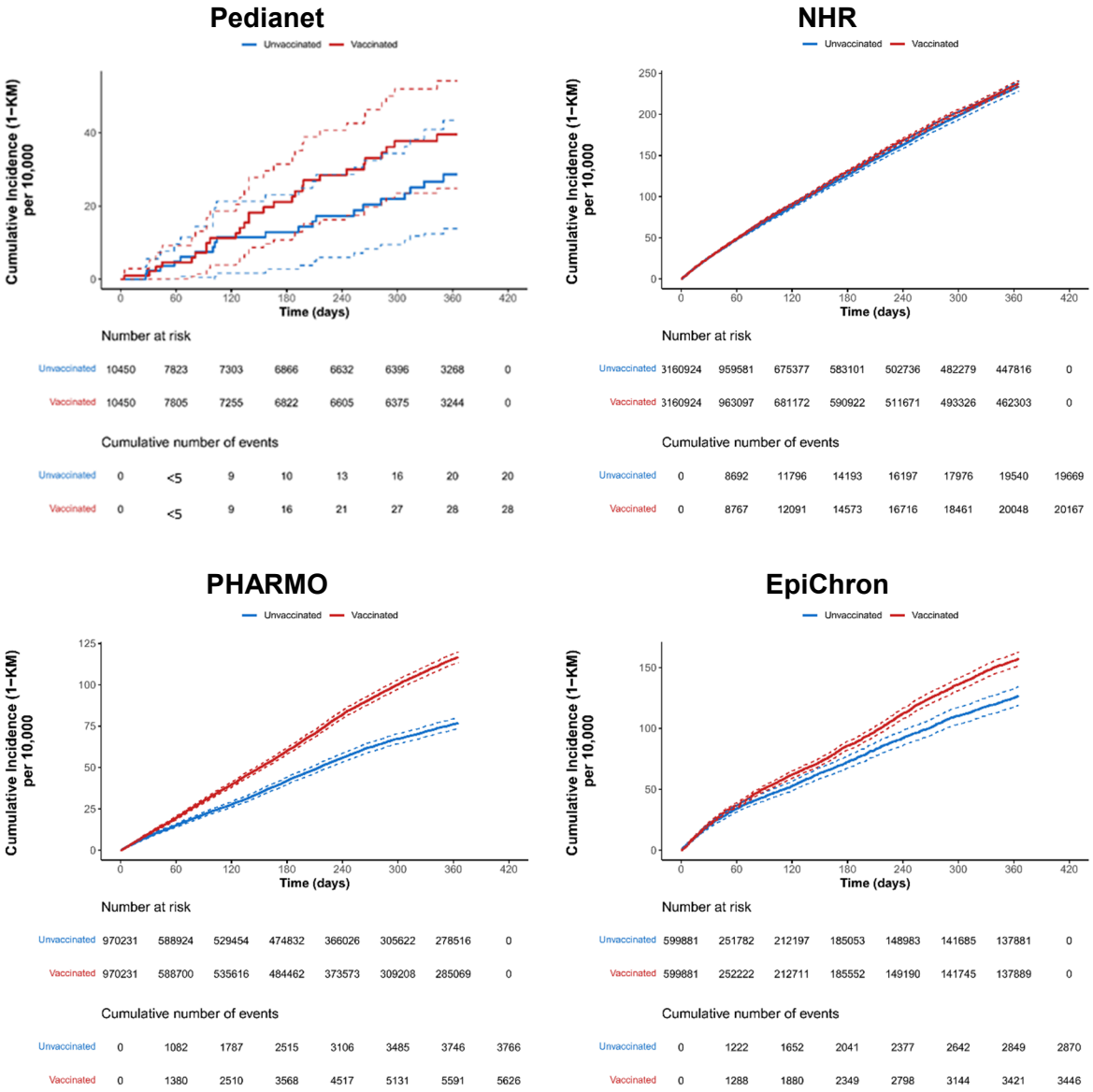
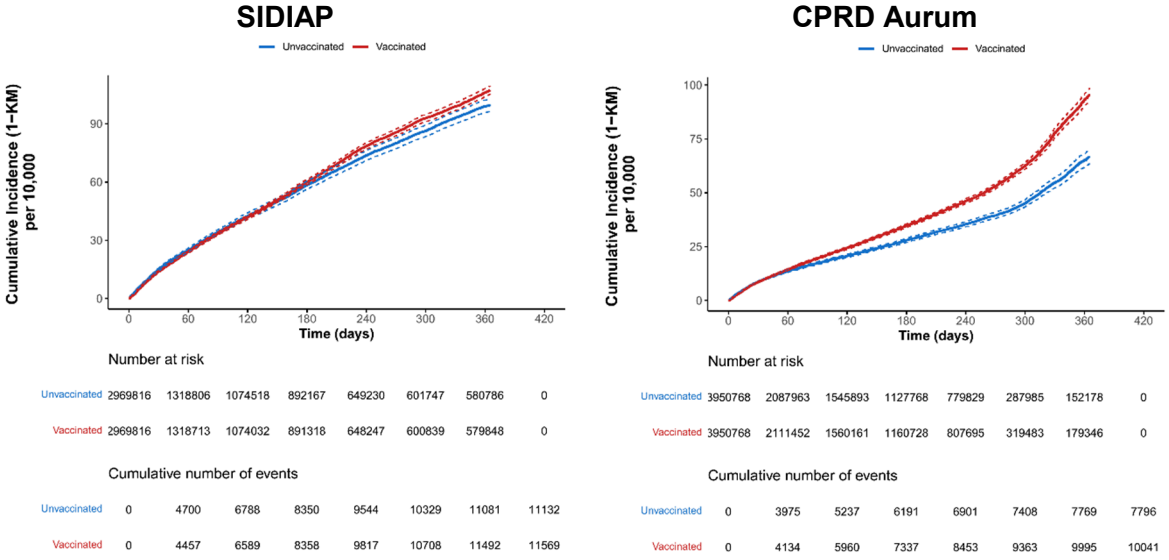
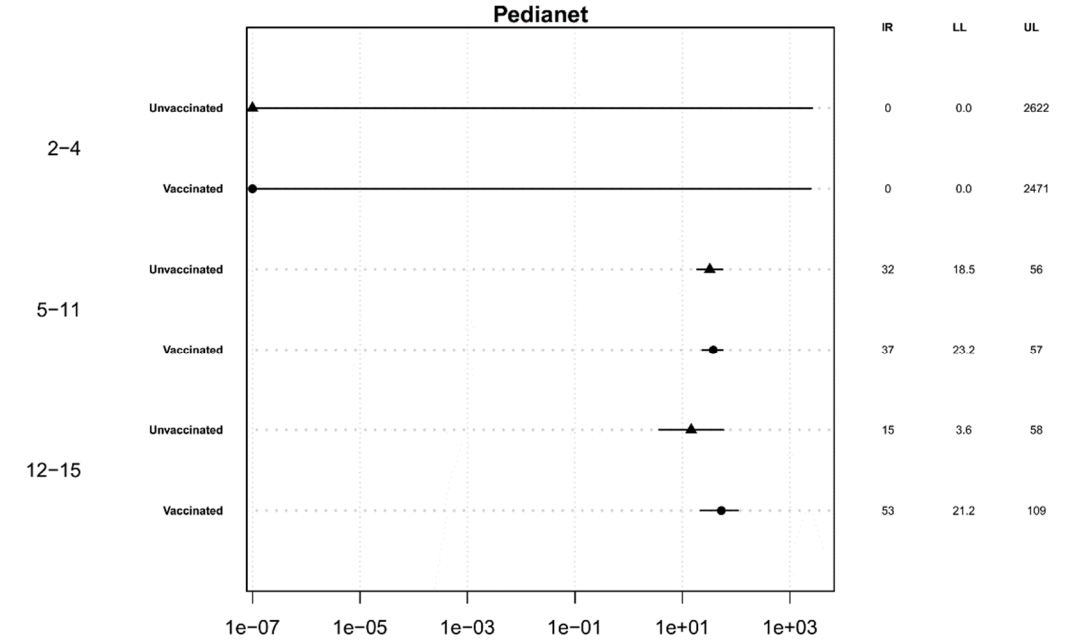


Figure 6. Cumulative incidence of acute cardiovascular injury among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source (risk window: 365 days after dose 1)



Cumulative incidence curves (1 – Kaplan–Meier risk) starting from the day of administration of the first dose of vaccine up to 365 days. Dotted lines represent 95% confidence intervals. The number at risk at each time point and the cumulative number of events during the 365-day risk window are also shown for each time point. The numerical data correspond to the days indicated by the tick marks on the x-axis.

Figure 7. Forest plot showing incidence rates and 95% confidence intervals for acute cardiovascular injury among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source and by age groups (risk window: 365 days after dose 1)



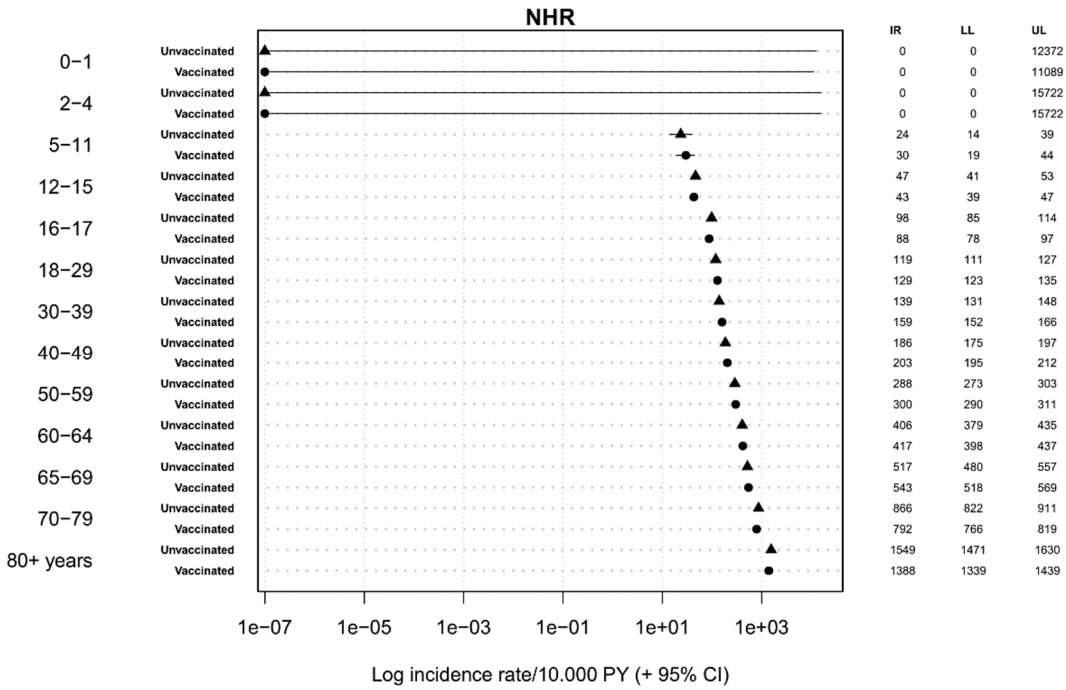
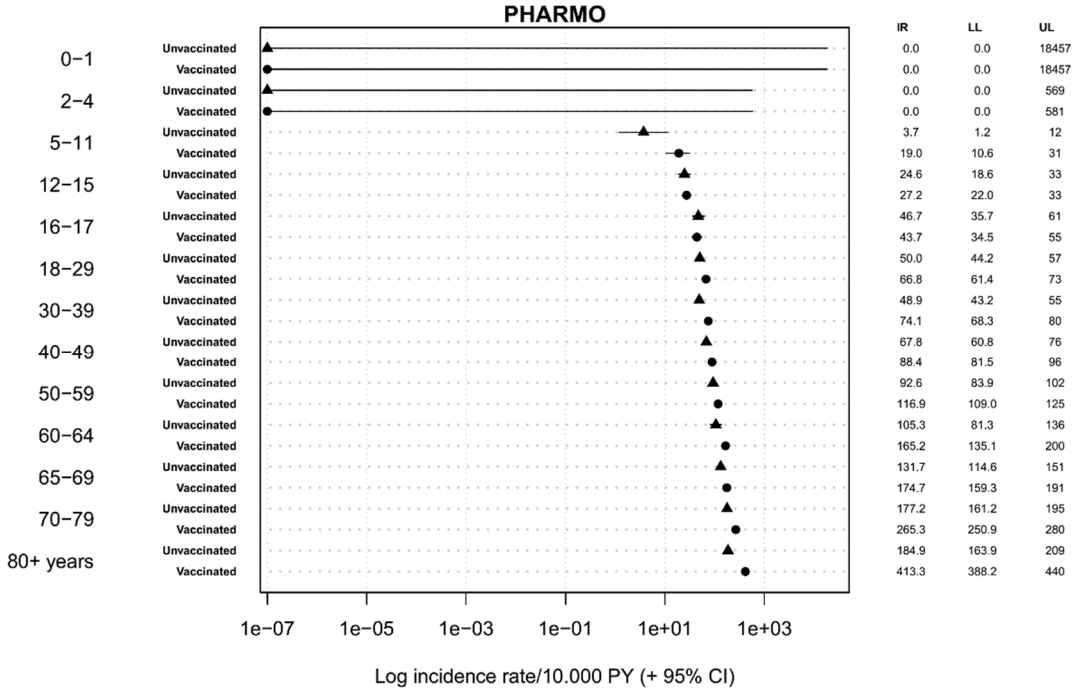


Figure 7. Forest plot showing incidence rates and 95% confidence intervals for acute cardiovascular injury among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source and by age groups (risk window: 365 days after dose 1)



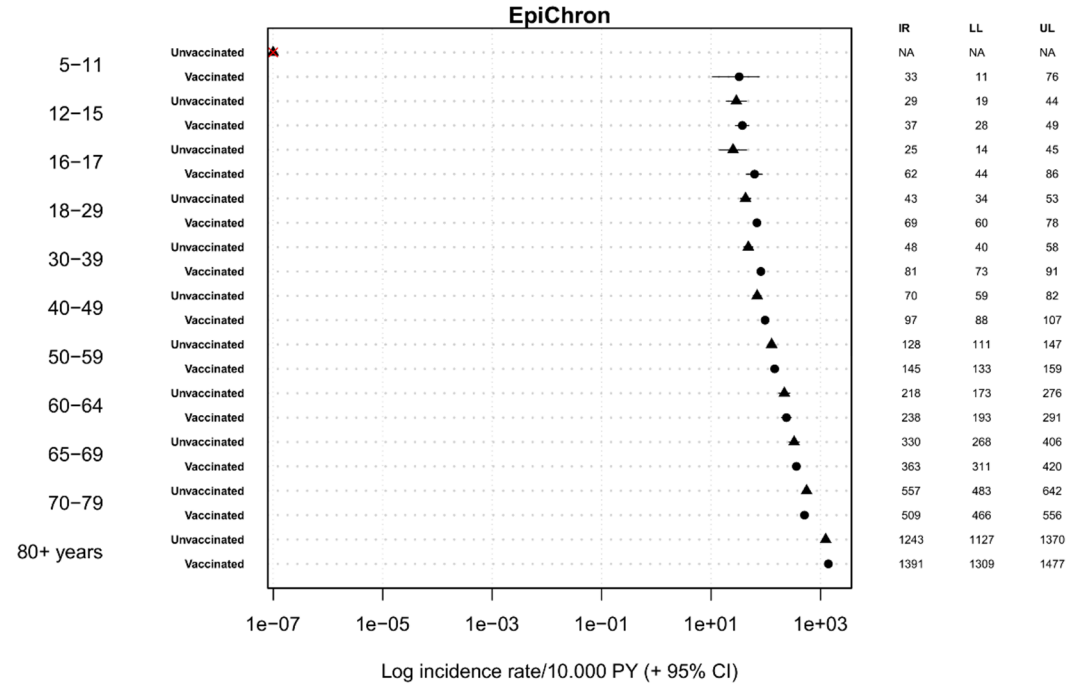


Figure 7. Forest plot showing incidence rates and 95% confidence intervals for acute cardiovascular injury among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source and by age groups (risk window: 365 days after dose 1)

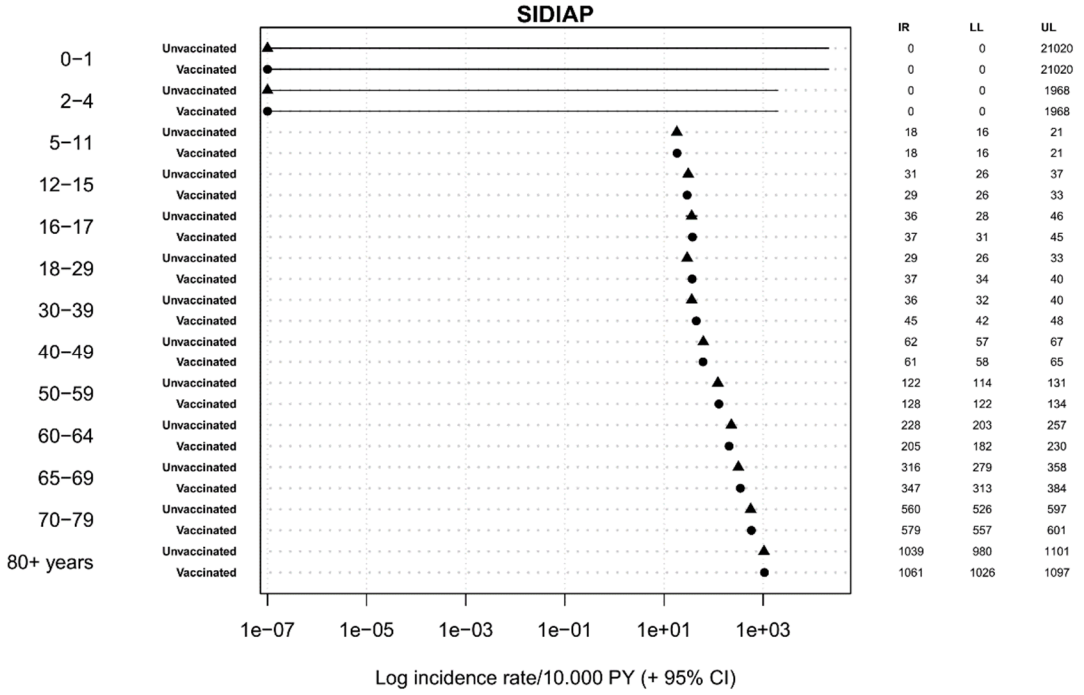


Figure 7. Forest plot showing incidence rates and 95% confidence intervals for acute cardiovascular injury among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source and by age groups (risk window: 365 days after dose 1)

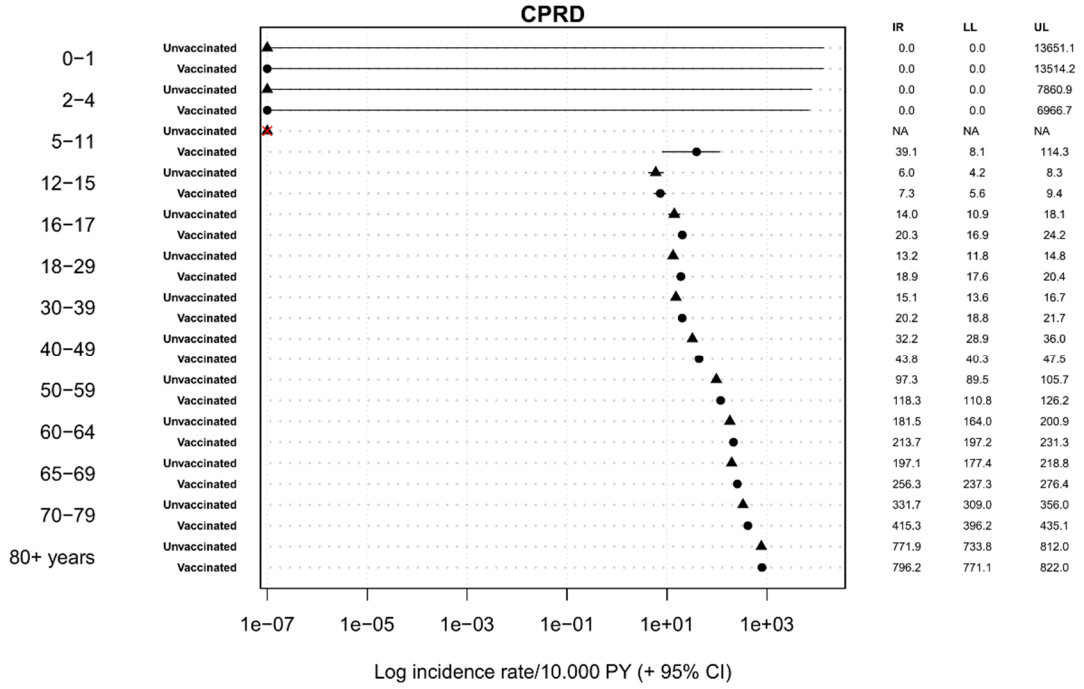


Table 18. Matched and adjusted hazard ratios (HRs) and matched and adjusted risk differences (RDs) per 10,000 person-years and their 95% CIs for acute cardiovascular injury among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source (risk window: 365 days after dose 1)

	Matched HR (95% CI)	Adjusted HR (95% CI)	Matched RD	Adjusted RD
Pedianet	1.41 (0.74, 2.66)	1.38 (0.73, 2.61)	10.88	10.12
NHR	1.02 (0.99, 1.04)	1.01 (0.99, 1.04)	3.47	2.20
PHARMO	1.48 (1.41, 1.55)	1.38 (1.31, 1.45)	39.89	33.31
EpiChron	1.20 (1.12, 1.28)	1.10 (1.03, 1.18)	30.87	18.26
SIDIAP	1.04 (1.00, 1.08)	0.99 (0.96, 1.03)	7.60	3.01
CPRD Aurum	1.26 (1.21, 1.30)	1.23 (1.18, 1.27)	28.88	27.28

NA: not assessable due to zero cases in the vaccinated or unvaccinated cohorts for HR or in both cohorts for RD

10.2.3.2. Arrhythmia

Arrhythmia was observed in the vaccinated and unvaccinated cohorts in all data sources. The incidence rates ranged from 35.92 per 10,000 person-years (95% CI: 23.25, 53.03) in Pedianet (children only) to 216.81 per 10,000 person-years (95% CI: 213.58, 220.08) in NHR in the vaccinated cohorts and from 20.04 per 10,000 person-years (95% CI: 11.44, 35.08) in Pedianet to 210.78 per 10,000 person-years (95% CI: 205.87, 215.80) in NHR in the unvaccinated cohorts. The cumulative incidences during the 365-day risk window ranged from 35.53 per 10,000 individuals (95% CI: 21.56, 49.48) in Pedianet to 199.30 per 10,000 person-years (95% CI: 195.98, 202.62) in NHR in the vaccinated cohorts and from 21.13 per 10,000 person-years (95% CI 9.15, 33.10) in Pedianet to 193.12 per 10,000 person-years (95% CI: 187.85, 198.38) in NHR in the unvaccinated cohorts.

The incidence rates were higher in the older age groups. The matched HRs were 1.79 (95% CI: 0.91, 3.55) in Pedianet, 1.03 (95% CI: 1, 1.06) in NHR, 1.47 (95% CI: 1.39, 1.55) in PHARMO, 1.23 (95% CI: 1.14, 1.32) in EpiChron, 1.04 (95% CI: 1, 1.08) in SIDIAP, and 1.31 (95% CI: 1.25, 1.37) in CPRD Aurum. The adjusted HRs were 1.75 (95% CI: 0.88, 3.49) in Pedianet, 1.03 (95% CI: 1, 1.05) in NHR, 1.36 (95% CI: 1.29, 1.44) in PHARMO, 1.12 (95% CI: 1.04, 1.21) in EpiChron, 0.99 (95% CI: 0.96, 1.03) in SIDIAP, and 1.27 (95% CI: 1.21, 1.33) in CPRD Aurum. In NHR, PHARMO, EpiChron, and CPRD Aurum the adjusted HRs and CIs were above 1.

Table 19. Risk estimates (95% CI) per 10,000 person-years (PY) for arrhythmia among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source (risk window: 365 days after dose 1)

	Vaccinated				Unvaccinated			
Data source	**Events (n)**	**Cumulative incidence (95% CI)**	**Person-years (PY)**	**Incidence rate (95% CI)**	**Events (n)**	**Cumulative incidence (95% CI)**	**Person-years (PY)**	**Incidence rate (95% CI)**
Pedianet	25	35.53 (21.56, 49.48)	6,959	35.92 (23.25, 53.03)	14	21.13 (9.15, 33.10)	6,987	20.04 (11.44, 35.08)
NHR	17,200	199.30 (195.98, 202.62)	793,320	216.81 (213.58, 220.08)	16,543	193.12 (187.85, 198.38)	784,864	210.78 (205.87, 215.80)
PHARMO	4,696	97.57 (94.67, 100.47)	471,867	99.52 (96.69, 102.41)	3,158	64.56 (61.49, 67.62)	466,955	67.63 (64.58, 70.83)
EpiChron	2,840	128.94 (123.93, 133.95)	203,033	139.88 (134.78, 145.12)	2,305	101.19 (94.34, 108.05)	202,602	113.77 (106.79, 121.21)
SIDIAP	9,527	88.46 (86.53, 90.39)	984,283	96.79 (94.86, 98.75)	9,146	81.49 (78.59, 84.39)	984,781	92.87 (89.88, 95.97)
CPRD Aurum	6,337	60.53 (58.21, 62.84)	1,269,791	49.91 (48.68, 51.15)	4,735	38.24 (35.76, 40.72)	1,242,440	38.11 (36.66, 39.62)

Note: Estimation of confidence intervals differs between vaccinated and unvaccinated, since the unvaccinated estimate is a generalised estimating equation (GEE*)* estimates (to account for individuals who were matched to more than one vaccinated individual). When NA (not-assessable) is listed for the 1-KM it means that there is no estimate for the duration of follow-up specified as risk interval, meaning that there was not any patient who reached the end of the risk window. The vaccinated and unvaccinated cohorts were matched on age, sex, geographical region, prior identified COVID-19 infection, prior influenza vaccination, pregnancy, immunocompromised and number of pre-existing conditions considered by the Centers for Disease Control and Prevention (CDC) as risk criteria (0, 1, 2, 3, 4+).

Figure 8. Cumulative incidence of arrhythmia among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source (risk window: 365 days after dose 1)

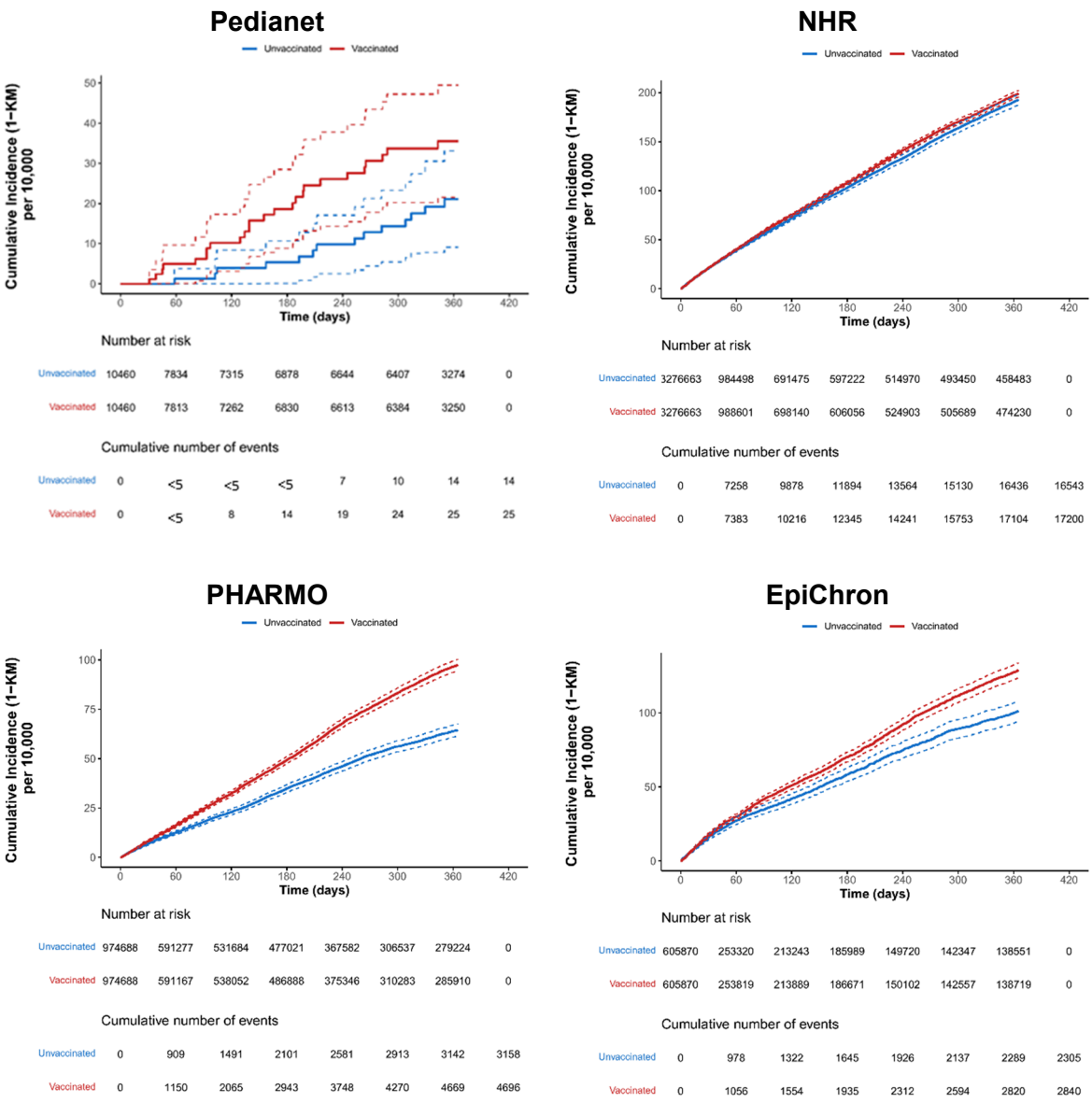
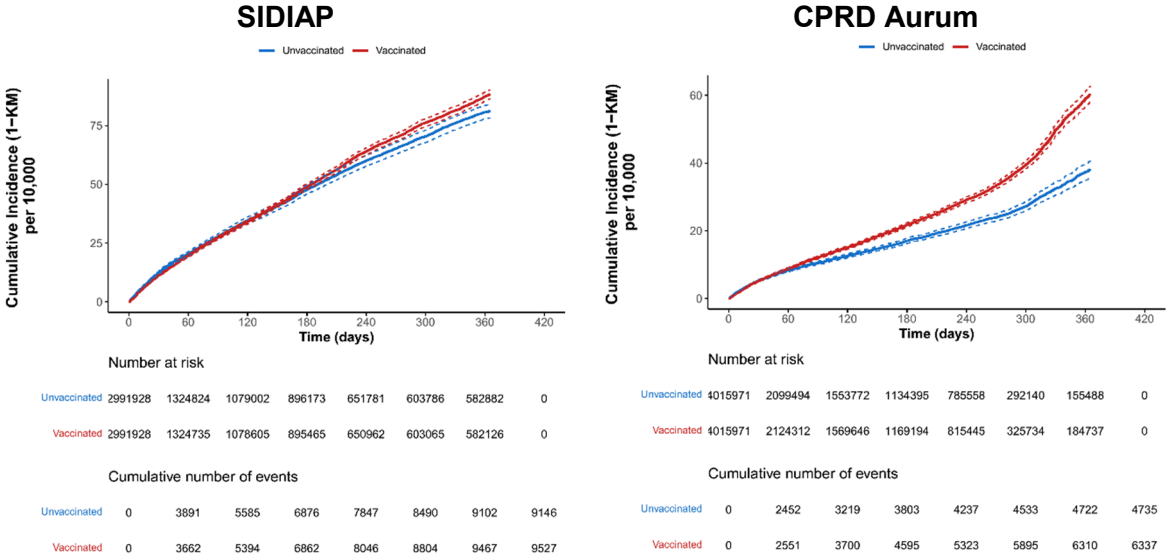
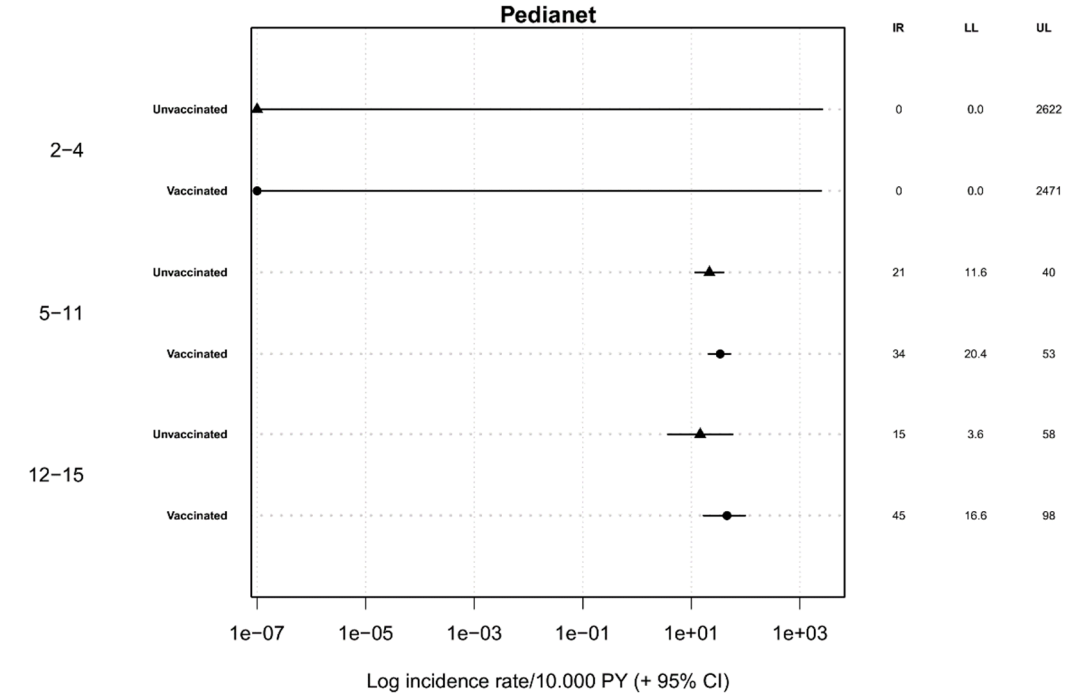


Figure 8. Cumulative incidence of arrhythmia among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source (risk window: 365 days after dose 1)



Cumulative incidence curves (1 – Kaplan–Meier risk) starting from the day of administration of the first dose of vaccine. Dotted lines represent 95% confidence intervals. The number at risk at each time point and the cumulative number of events during the 365-day risk window are also shown for each time point. The numerical data correspond to the days indicated by the tick marks on the x-axis.

Figure 9. Forest plot showing incidence rates and 95% confidence intervals for arrhythmia among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source and by age groups (risk window: 365 days after dose 1)



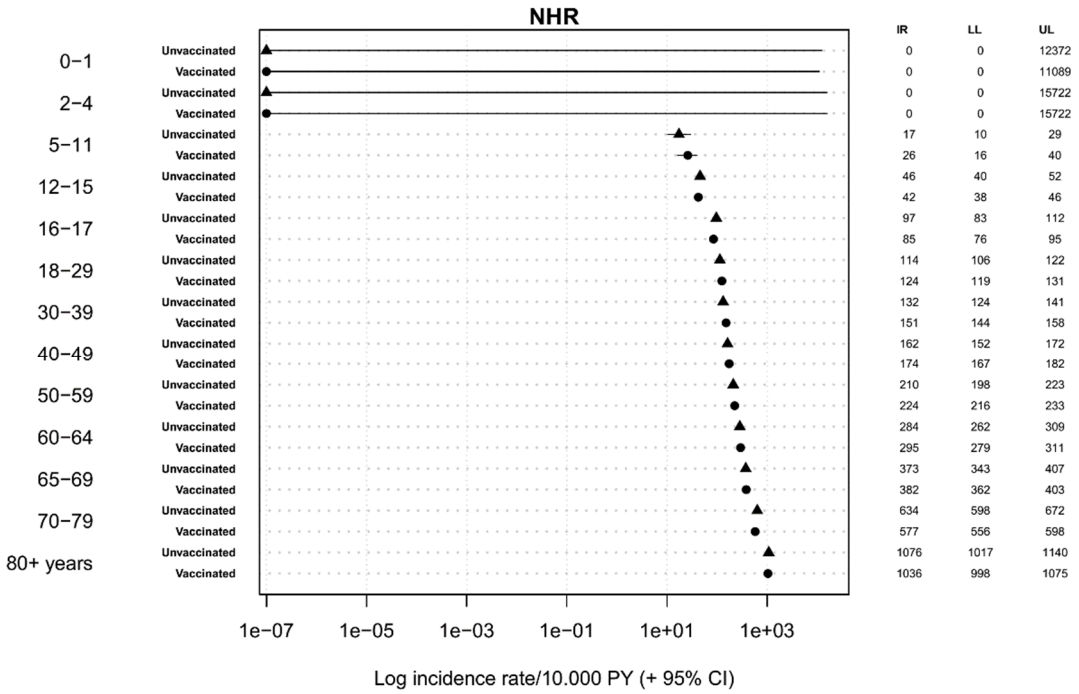
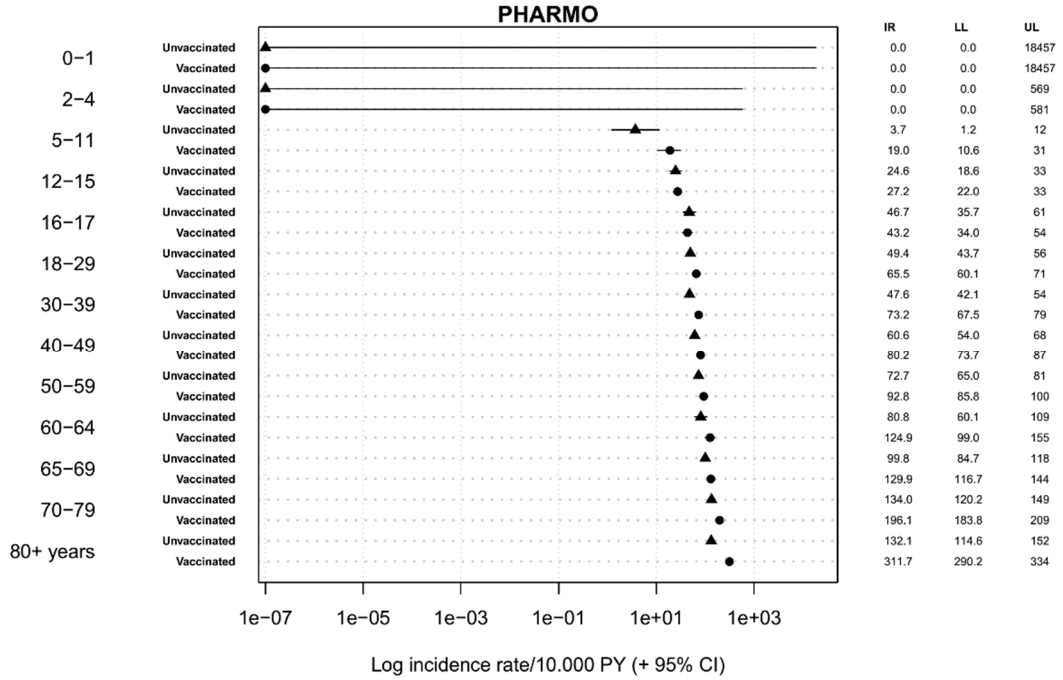


Figure 9. Forest plot showing incidence rates and 95% confidence intervals for arrhythmia among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source and by age groups (risk window: 365 days after dose 1)



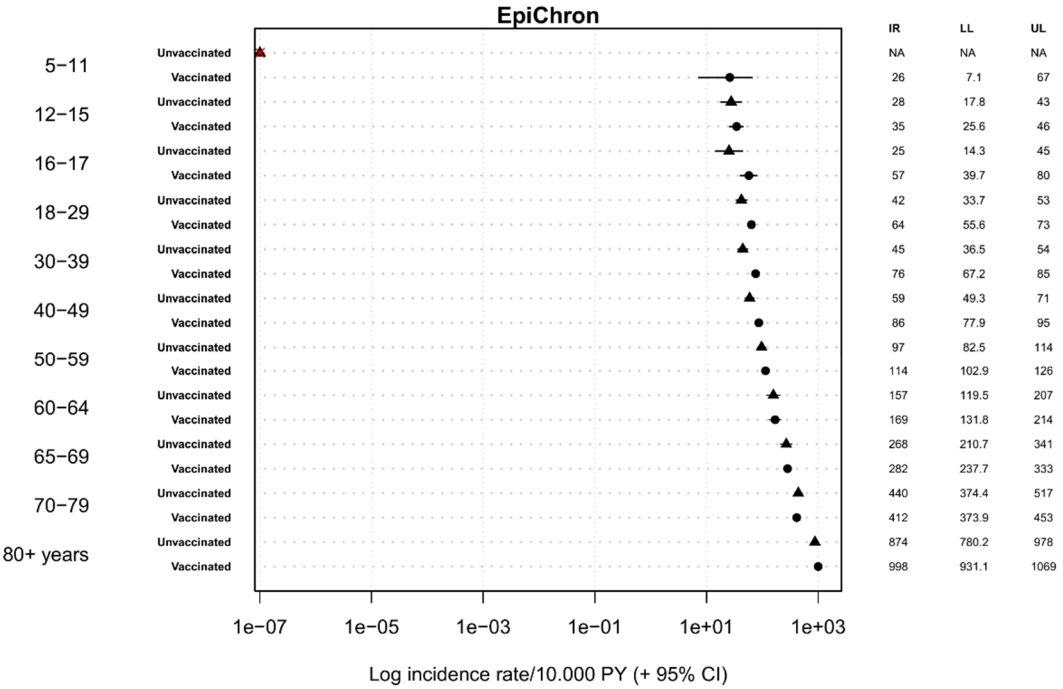


Figure 9. Forest plot showing incidence rates and 95% confidence intervals for arrhythmia among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source and by age groups (risk window: 365 days after dose 1)

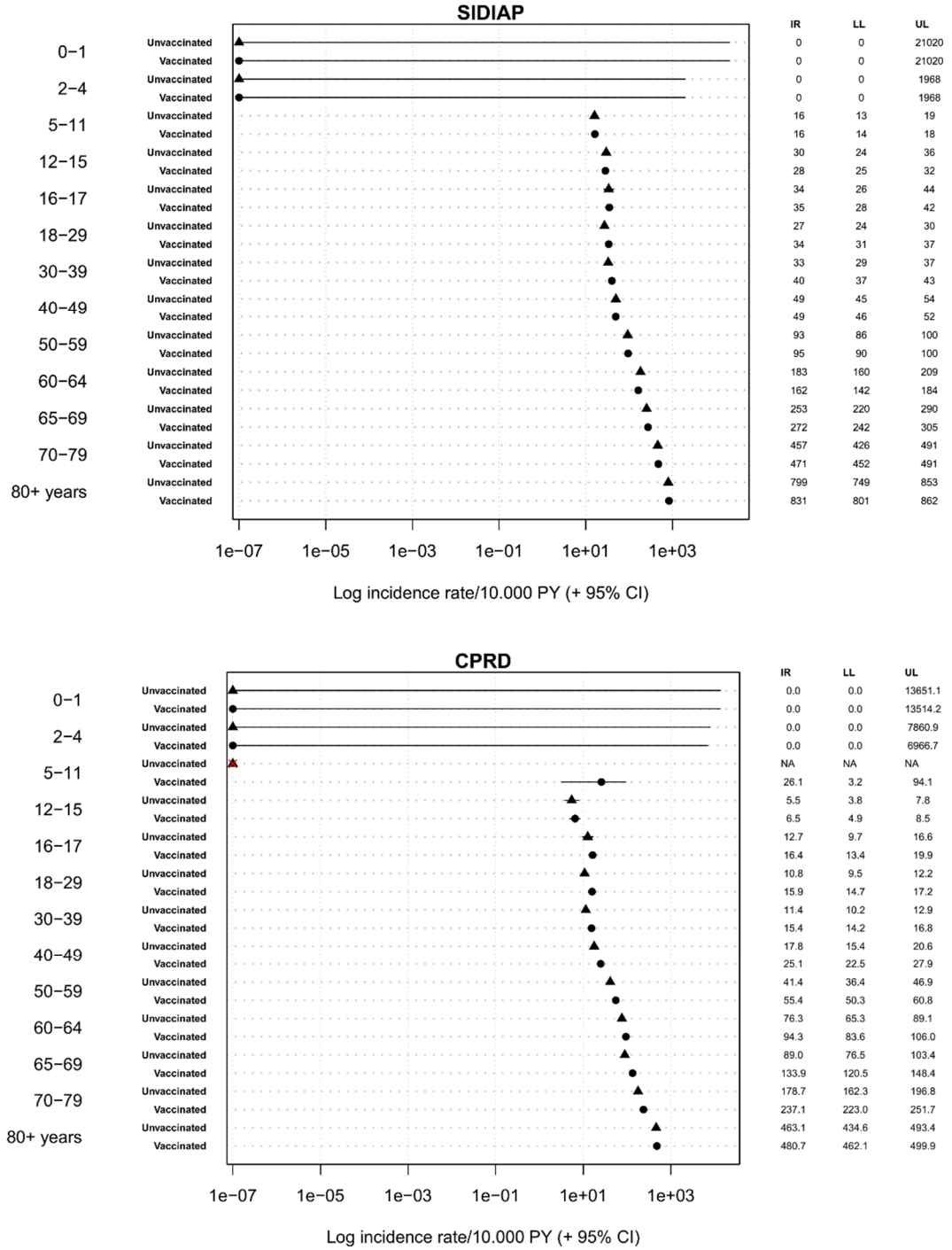


Table 20. Matched and adjusted hazard ratios (HRs) and matched and adjusted risk differences (RDs) per 10,000 person-years and their 95% CIs for arrhythmia among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source (risk window: 365 days after dose 1)

	Matched HR (95% CI)	Adjusted HR (95% CI)	Matched RD	Adjusted RD
Pedianet	1.79 (0.91, 3.55)	1.75 (0.88, 3.49)	14.40	13.68
NHR	1.03 (1.00, 1.06)	1.03 (1.00, 1.05)	6.18	5.25
PHARMO	1.47 (1.39, 1.55)	1.36 (1.29, 1.44)	33.01	26.84
EpiChron	1.23 (1.14, 1.32)	1.12 (1.04, 1.21)	27.75	16.77
SIDIAP	1.04 (1.00, 1.08)	0.99 (0.96, 1.03)	6.97	2.84
CPRD Aurum	1.31 (1.25, 1.37)	1.27 (1.21, 1.33)	22.28	21.25

10.2.3.3. Heart failure

Heart failure was observed in the vaccinated and unvaccinated cohorts in all data sources, except Pedianet. The incidence rates of heart failure ranged from 16.27 per 10,000 person-years (95% CI: 15.15, 17.46) in PHARMO to 47.60 per 10,000 person-years (95% CI: 44.67, 50.67) in EpiChron in the vaccinated cohorts and from 12.52 per 10,000 person-years (95% CI: 11.20, 13.99) in PHARMO to 59.55 per 10,000 person-years (95% CI: 56.84, 62.38) in NHR in the unvaccinated cohorts. The cumulative incidence of heart failure during the 365-day risk window showed differences between vaccinated and non-vaccinated in PHARMO and CPRD Aurum in the progression of follow-up time.

The incidence of heart failure was higher in the older age groups in all data sources. The matched HRs were 0.78 (95% CI: 0.74, 0.82) in NHR, 1.30 (95% CI: 1.14, 1.48) in PHARMO, 0.95 (95% CI: 0.84, 1.06) in EpiChron, 0.94 (95% CI: 0.87, 1.01) in SIDIAP, and 1.04 (95% CI: 0.97, 1.12) in CPRD Aurum. The adjusted HRs were 0.77 (95% CI: 0.73, 0.82) in NHR, 1.29 (95% CI: 1.13, 1.47) in PHARMO, 0.90 (95% CI: 0.80, 1.01) in EpiChron, 0.89 (95% CI: 0.82, 0.96) in SIDIAP, and 1.02 (95% CI: 0.95, 1.09) in CPRD Aurum. Differences were observed for the incidence of heart failure between the vaccinated and unvaccinated cohorts during the 365-day risk window in PHARMO.

Table 21. Risk estimates (95% CI) per 10,000 person-years (PY) for heart failure among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source (risk window: 365 days after dose 1)

	Vaccinated				Unvaccinated			
Data source	**Events (n)**	**Cumulative incidence (95% CI)**	**Person-years (PY)**	**Incidence rate (95% CI)**	**Events (n)**	**Cumulative incidence (95% CI)**	**Person-years (PY)**	**Incidence rate (95% CI)**
Pedianet	NA	NA	NA	NA	NA	NA	NA	NA
NHR	3,885	43.91 (42.36, 45.45)	838,216	46.35 (44.90, 47.83)	4,930	56.79 (53.75, 59.83)	827,927	59.55 (56.84, 62.38)
PHARMO	780	15.93 (14.76, 17.09)	479,288	16.27 (15.15, 17.46)	593	11.77 (10.42, 13.11)	473,758	12.52 (11.20, 13.99)
EpiChron	983	42.49 (39.65, 45.32)	206,512	47.60 (44.67, 50.67)	1,035	44.07 (39.20, 48.94)	205,745	50.30 (45.61, 55.49)
SIDIAP	2,569	23.53 (22.53, 24.53)	998,769	25.72 (24.74, 26.74)	2,739	23.54 (21.90, 25.19)	998,818	27.42 (25.73, 29.22)
CPRD Aurum	2,462	24.79 (23.26, 26.32)	1,278,995	19.25 (18.50, 20.03)	2,299	19.30 (17.36, 21.24)	1,250,241	18.39 (17.37, 19.47)

NA: Not available
Note: Estimation of confidence intervals differs between vaccinated and unvaccinated, since the unvaccinated estimate is a generalised estimating equation (GEE*)* estimates (to account for individuals who were matched to more than one vaccinated individual). When NA (not-assessable) is listed for the 1-KM it means that there is no estimate for the duration of follow-up specified as risk interval, meaning that there was not any patient who reached the end of the risk window. The vaccinated and unvaccinated cohorts were matched on age, sex, geographical region, prior identified COVID-19 infection, prior influenza vaccination, pregnancy, immunocompromised and number of pre-existing conditions considered by the Centers for Disease Control and Prevention (CDC) as risk criteria (0, 1, 2, 3, 4+).

Figure 10. Cumulative incidence of heart failure among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source (risk window: 365 days after dose 1)

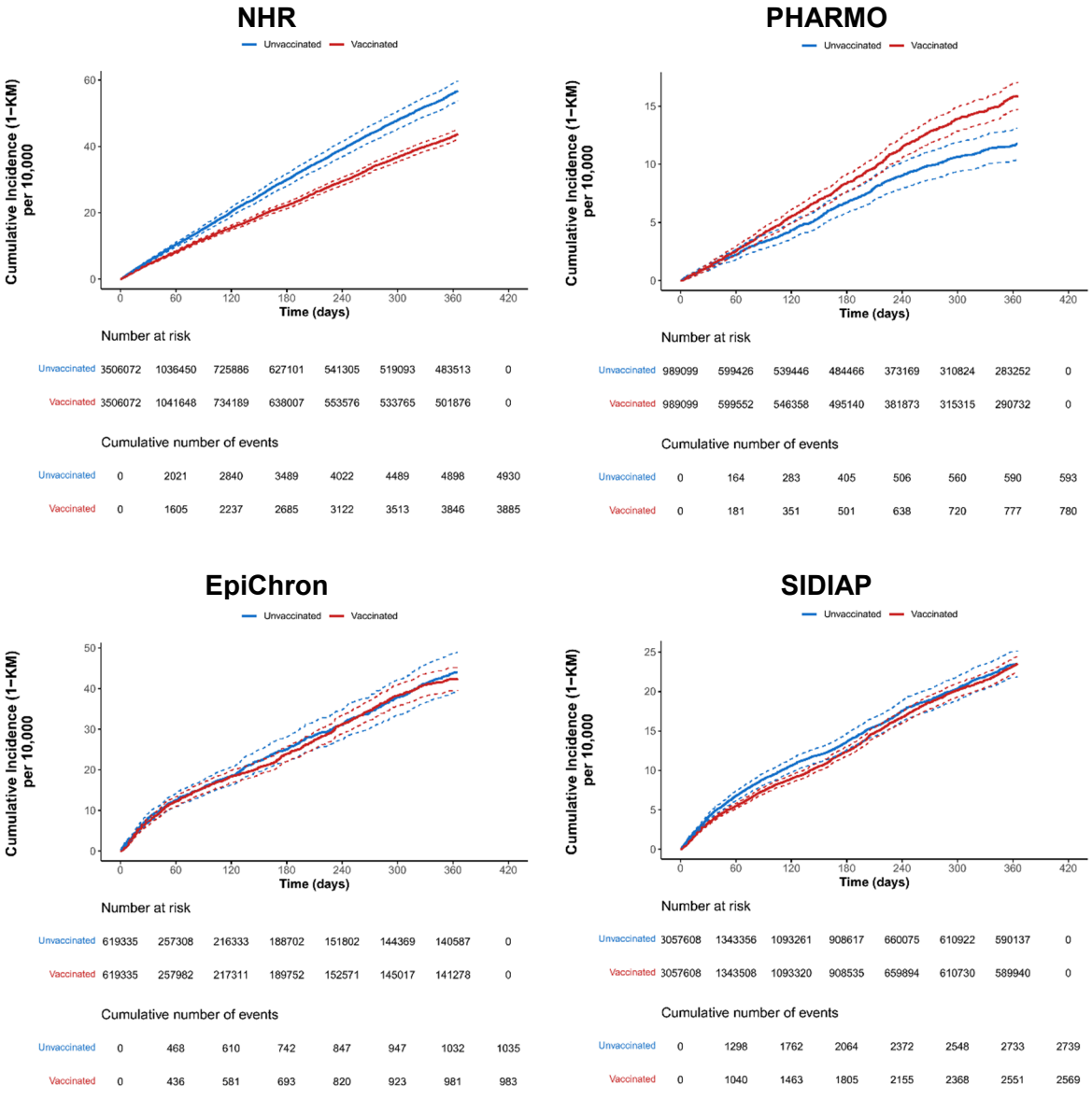
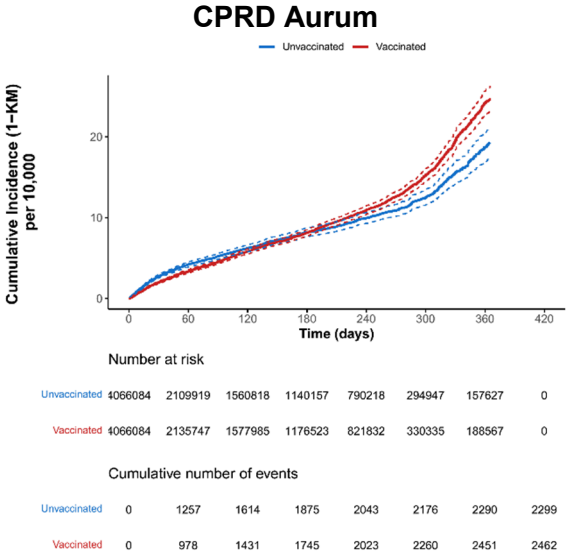
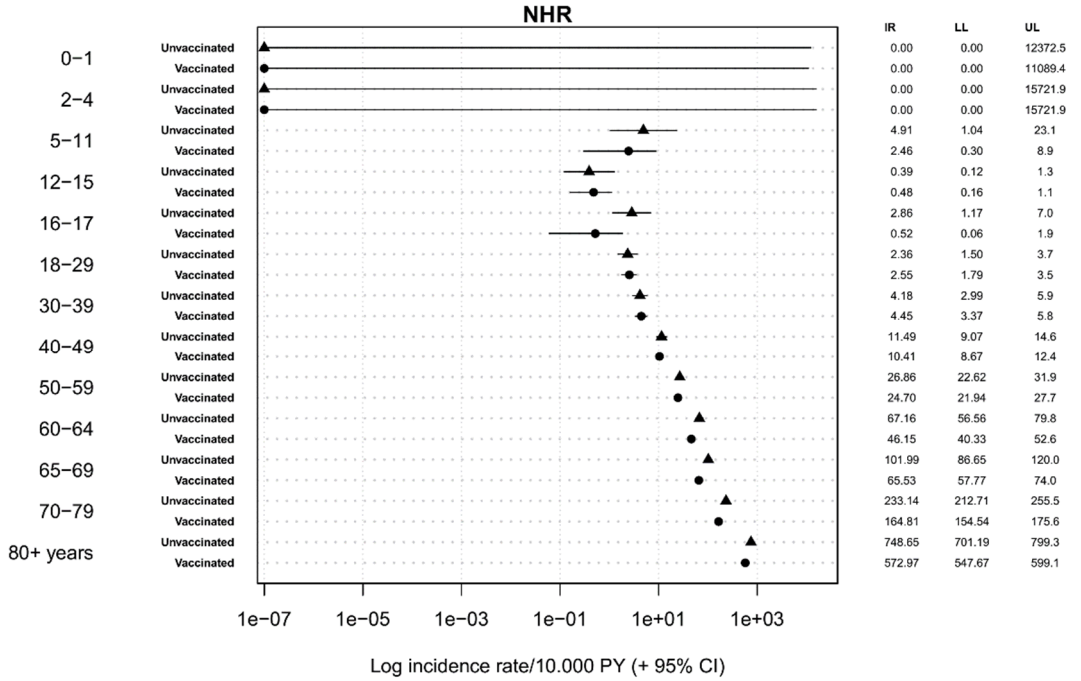


Figure 10. Cumulative incidence of heart failure among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source (risk window: 365 days after dose 1)



Cumulative incidence curves (1 – Kaplan–Meier risk) starting from the day of administration of the first dose of vaccine. Dotted lines represent 95% confidence intervals. The number at risk at each time point and the cumulative number of events during the 365-day risk window are also shown for each time point. The numerical data correspond to the days indicated by the tick marks on the x-axis.

Figure 11. Forest plot showing incidence rates and 95% confidence intervals for heart failure among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source and by age groups (risk window: 365 days after dose 1)



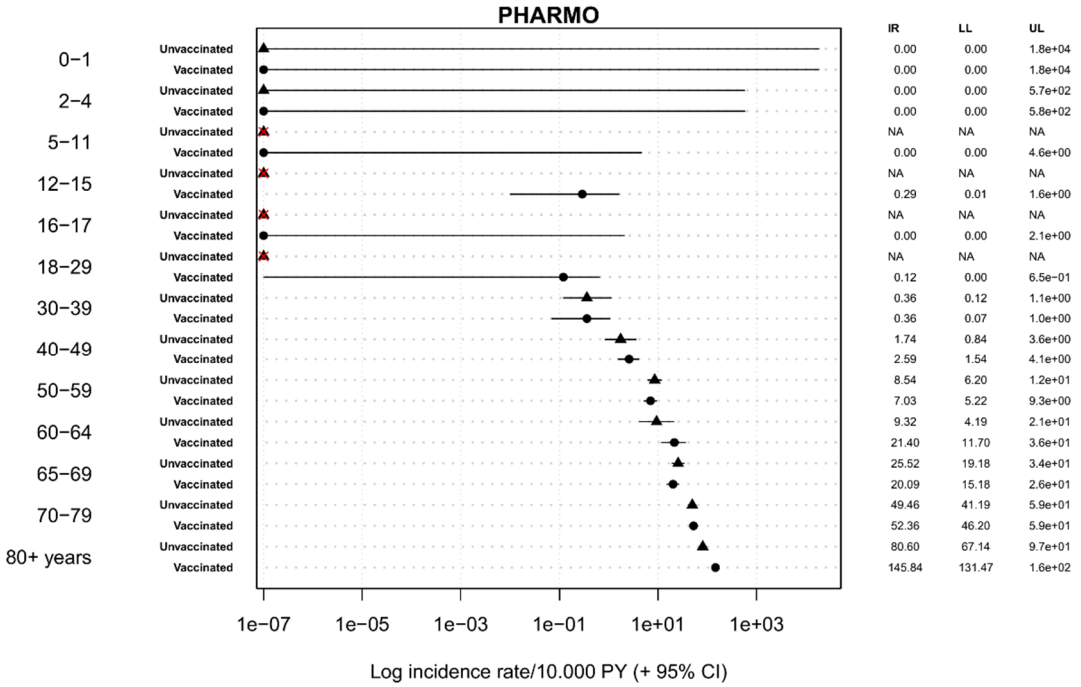
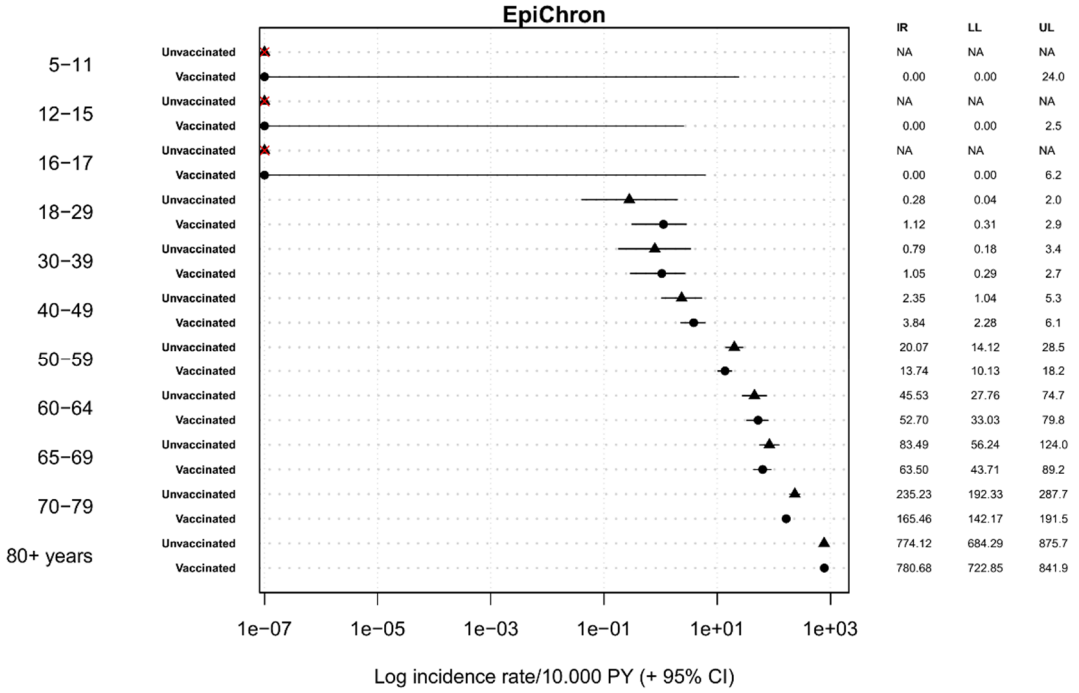


Figure 11. Forest plot showing incidence rates and 95% confidence intervals for heart failure among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source and by age groups (risk window: 365 days after dose 1)



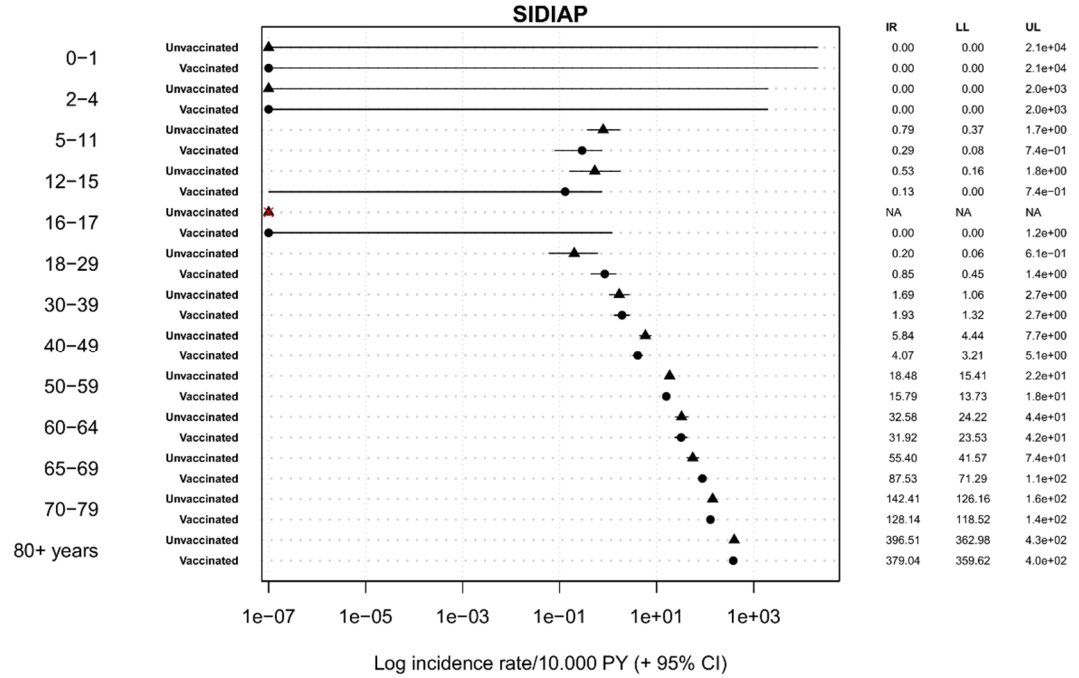


Figure 11. Forest plot showing incidence rates and 95% confidence intervals for heart failure among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source and by age groups (risk window: 365 days after dose 1)

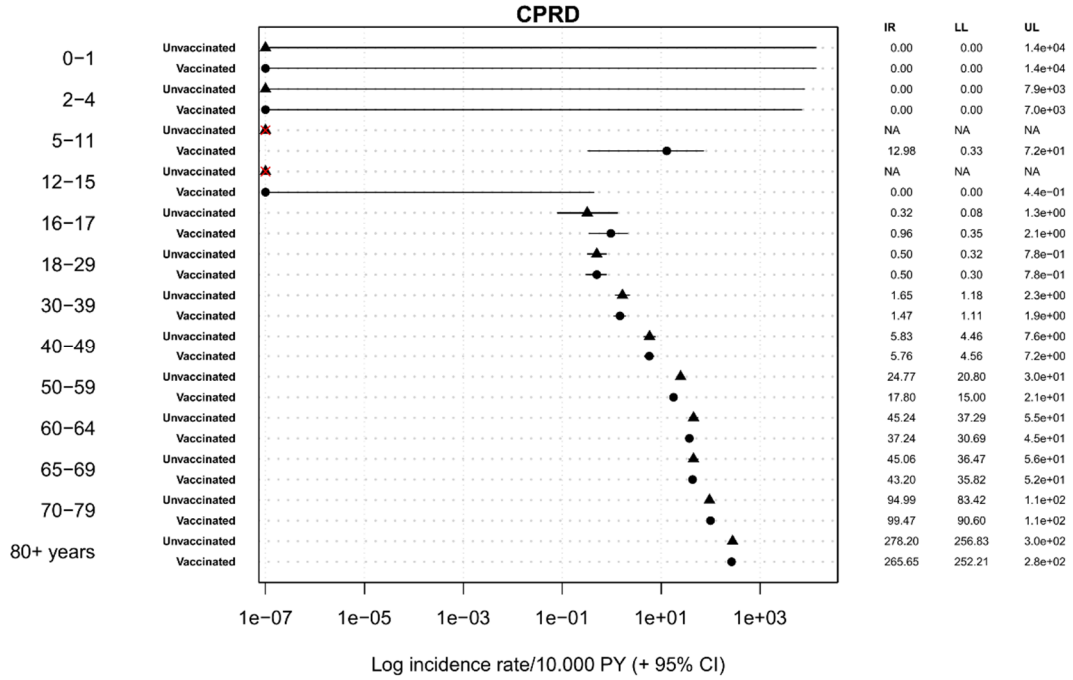


Table 22. Matched and adjusted hazard ratios (HRs) and matched and adjusted risk differences (RDs) per 10,000 person-years and their 95% CIs for heart failure among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source (risk window: 365 days after dose 1)

	Matched HR (95% CI)	Adjusted HR (95% CI)	Matched RD	Adjusted RD
Pedianet	NA	NA	NA	NA
NHR	0.78 (0.74, 0.82)	0.77 (0.73, 0.82)	-12.89	-13.33
PHARMO	1.30 (1.14, 1.48)	1.29 (1.13, 1.47)	4.16	4.01
EpiChron	0.95 (0.84, 1.06)	0.90 (0.80, 1.01)	-1.58	-4.60
SIDIAP	0.94 (0.87, 1.01)	0.89 (0.82, 0.96)	-0.01	-1.19
CPRD Aurum	1.04 (0.97, 1.12)	1.02 (0.95, 1.09)	5.49	5.23

NA: not assessable due to zero cases in the vaccinated or unvaccinated cohorts for HR or in both cohorts for RD

10.2.3.4. Stress cardiomyopathy

Stress cardiomyopathy was a rare event but could be identified in all data sources except Pedianet. The incidence rates for stress cardiomyopathy ranged from 0.08 per 10,000 person-years (95% CI: 0.03, 0.17) in NHR to 0.35 per 10,000 person-years (95% CI: 0.24, 0.48) in SIDIAP in the vaccinated cohorts and from 0.08 (0.03, 0.28) per 10,000 person-years (95% CI: 0.03, 0.28) in PHARMO to 0.29 per 10,000 person-years (95% CI: 0.09, 0.90) in EpiChron in the unvaccinated cohorts. The cumulative incidence during the 365-day risk window was less than 0.5 per 10,000 person-years in both cohorts in all three data sources.

The incidence of stress cardiomyopathy was higher in age groups over 40 years of age. The matched HRs for stress cardiomyopathy were 0.69 (95% CI: 0.18, 2.70) in NHR, 1.49 (95% CI: 0.35, 6.31) in PHARMO, 0.99 (95% CI: 0.25, 3.98) in EpiChron, 1.67 (95% CI: 0.82, 3.38) in SIDIAP, 1.25 (95% CI: 0.51, 3.07) in CPRD Aurum. The adjusted HRs were 0.69 (95% CI: 0.18, 2.67) in NHR, 1.49 (95% CI: 0.33, 6.69) in PHARMO, 0.85 (95% CI: 0.21, 3.47) in EpiChron, 1.51 (95% CI: 0.75, 3.04) in SIDIAP, 1.30 (95% CI: 0.53, 3.20) in CPRD Aurum. No differences were observed for the incidence of stress cardiomyopathy between the vaccinated and unvaccinated cohorts during the 365-day risk window.

Table 23. Risk estimates (95% CI) per 10,000 person-years (PY) for stress cardiomyopathy among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source (risk window: 365 days after dose 1)

	Vaccinated				Unvaccinated			
Data source	**Events (n)**	**Cumulative incidence (95% CI)**	**Person-years (PY)**	**Incidence rate (95% CI)**	**Events (n)**	**Cumulative incidence (95% CI)**	**Person-years (PY)**	**Incidence rate (95% CI)**
Pedianet	NA	NA	NA	NA	NA	NA	NA	NA
NHR	7	0.09 (0.02, 0.16)	854,493	0.08 (0.03, 0.17)	10	0.07 (0, 0.14)	842,940	0.12 (0.04, 0.37)
PHARMO	6	0.11 (0.02, 0.20)	480,858	0.12 (0.05, 0.27)	<5	0.10 (0, 0.23)	NR	0.08 (0.03, 0.28)
EpiChron	6	0.30 (0.06, 0.54)	208,241	0.29 (0.11, 0.63)	6	0.29 (0, 0.65)	207,207	0.29 (0.09, 0.90)
SIDIAP	35	0.33 (0.21, 0.45)	1,004,330	0.35 (0.24, 0.48)	21	0.18 (0.02, 0.33)	1,004,339	0.21 (0.11, 0.39)
CPRD Aurum	14	0.11 (0.04, 0.19)	1,284,916	0.11 (0.06, 0.18)	11	0.06 (0.01, 0.11)	1,254,967	0.09 (0.04, 0.18)

NA: Not available
Note: Estimation of confidence intervals differs between vaccinated and unvaccinated, since the unvaccinated estimate is a generalised estimating equation (GEE*)* estimates (to account for individuals who were matched to more than one vaccinated individual). When NA (not-assessable) is listed for the 1-KM it means that there is no estimate for the duration of follow-up specified as risk interval, meaning that there was not any patient who reached the end of the risk window. The vaccinated and unvaccinated cohorts were matched on age, sex, geographical region, prior identified COVID-19 infection, prior influenza vaccination, pregnancy, immunocompromised and number of pre-existing conditions considered by the Centers for Disease Control and Prevention (CDC) as risk criteria (0, 1, 2, 3, 4+).

Figure 12. Cumulative incidence of stress cardiomyopathy among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source (risk window: 365 days after dose 1)

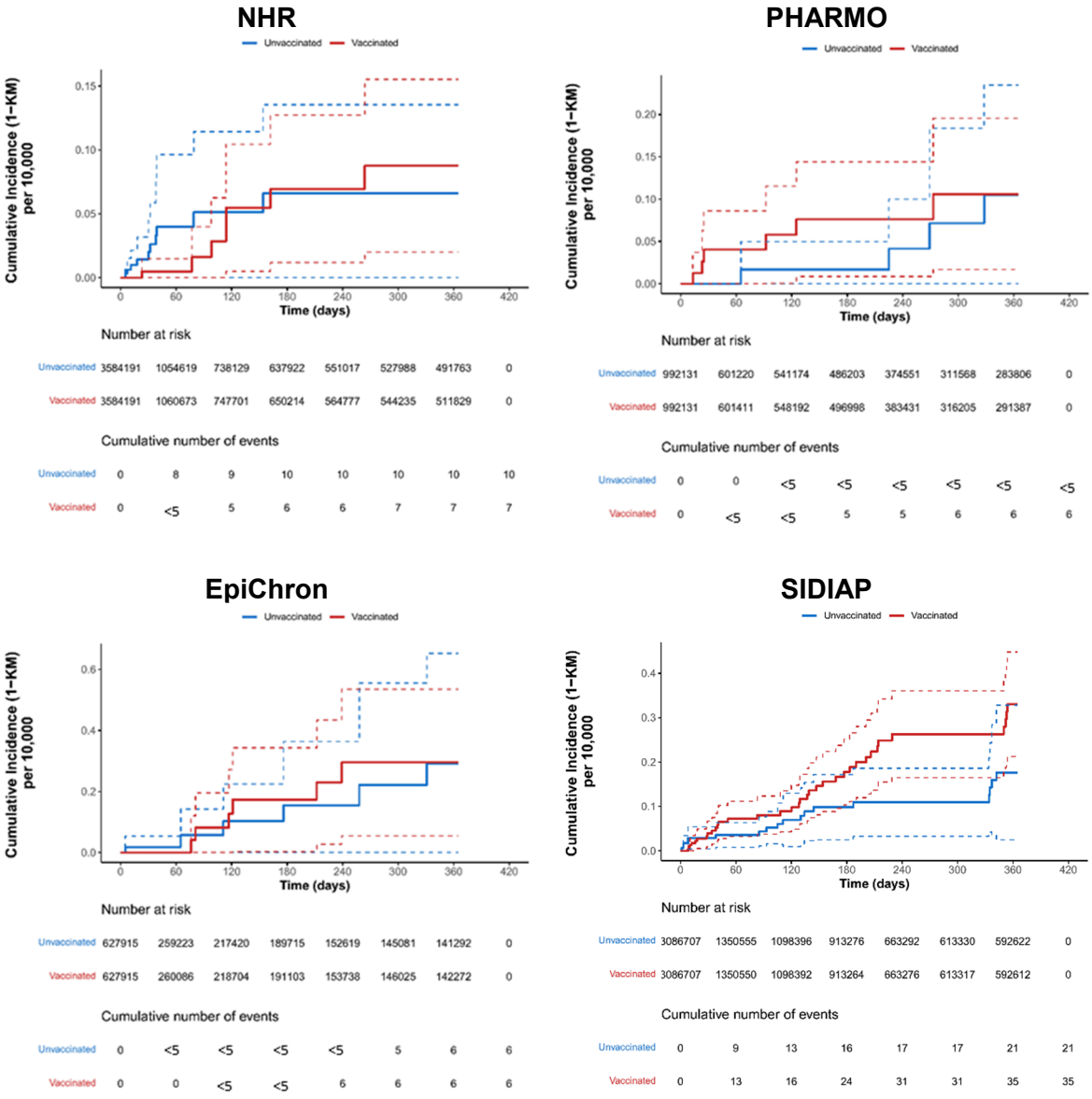
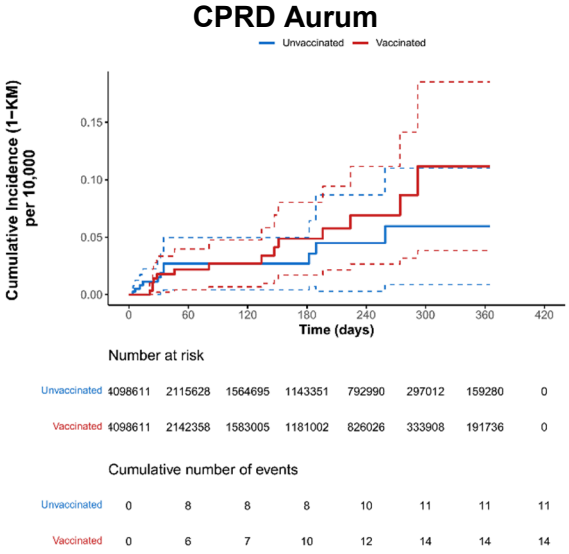


Figure 12. Cumulative incidence of stress cardiomyopathy among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source (risk window: 365 days after dose 1)



Cumulative incidence curves (1 – Kaplan–Meier risk) starting from the day of administration of the first dose of vaccine. Dotted lines represent 95% confidence intervals. The number at risk at each time point and the cumulative number of events during the 365-day risk window are also shown for each time point. The numerical data correspond to the days indicated by the tick marks on the x-axis.

Figure 13. Forest plot showing incidence rates and 95% confidence intervals for stress cardiomyopathy among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source and by age groups (risk window: 365 days after dose 1)

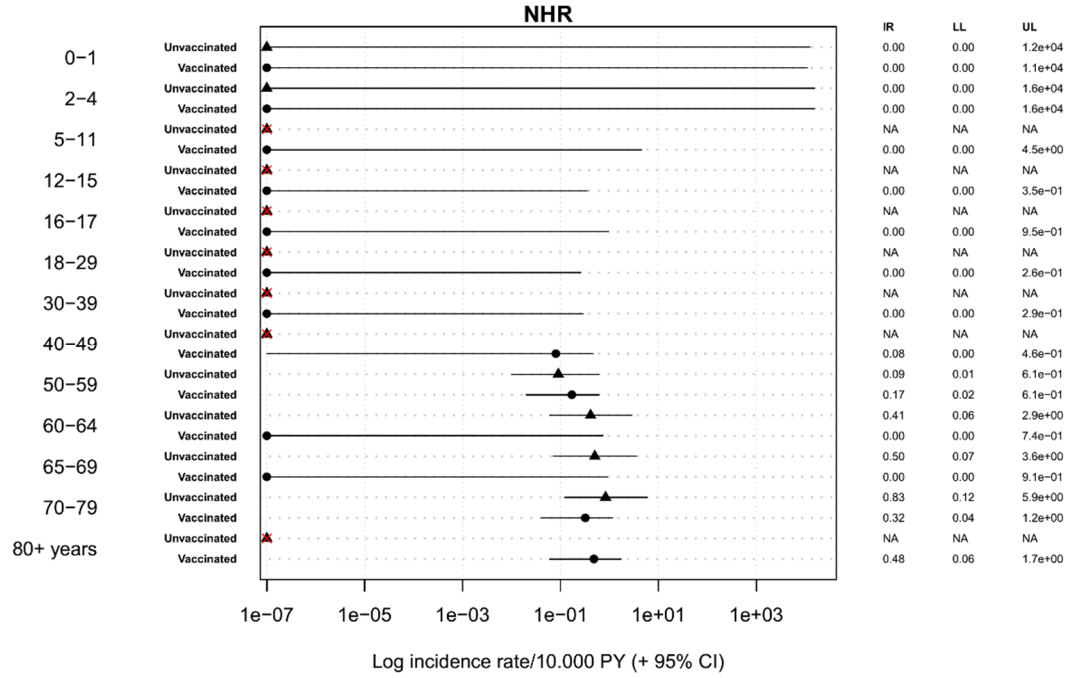
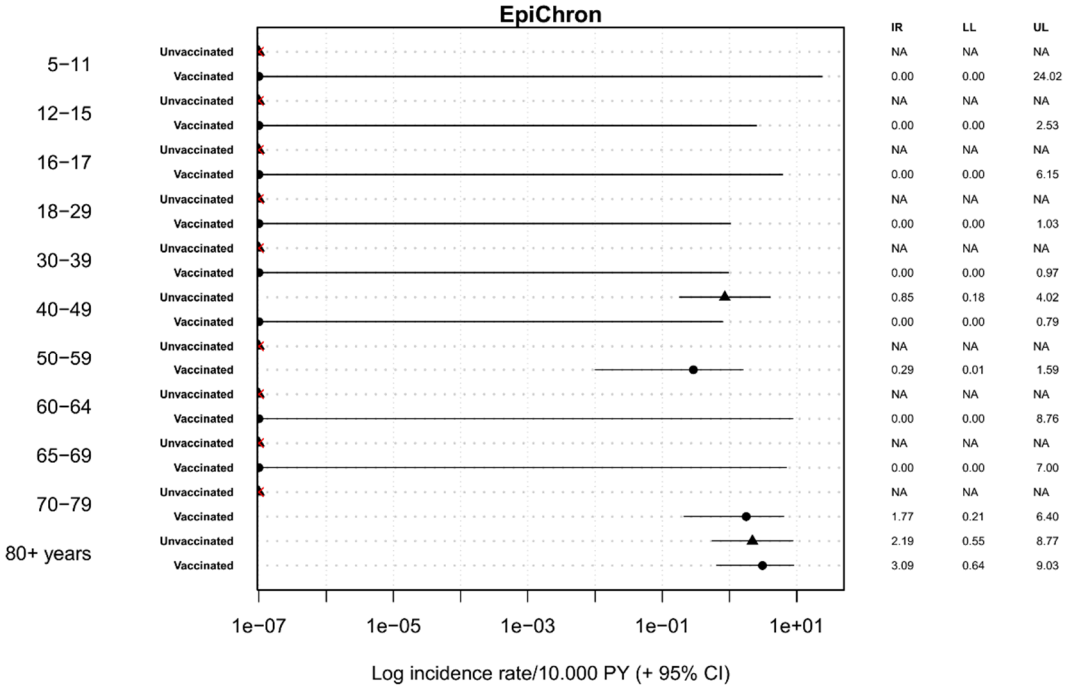


Figure 13. Forest plot showing incidence rates and 95% confidence intervals for stress cardiomyopathy among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source and by age groups (risk window: 365 days after dose 1)



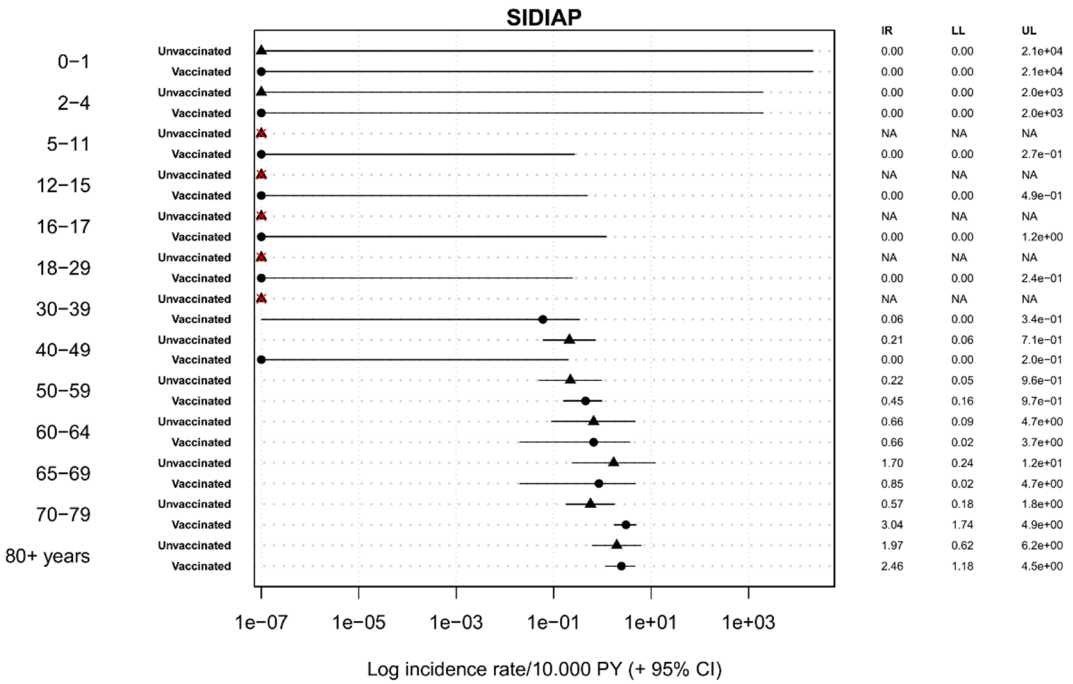


Figure 13. Forest plot showing incidence rates and 95% confidence intervals for stress cardiomyopathy among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source and by age groups (risk window: 365 days after dose 1)

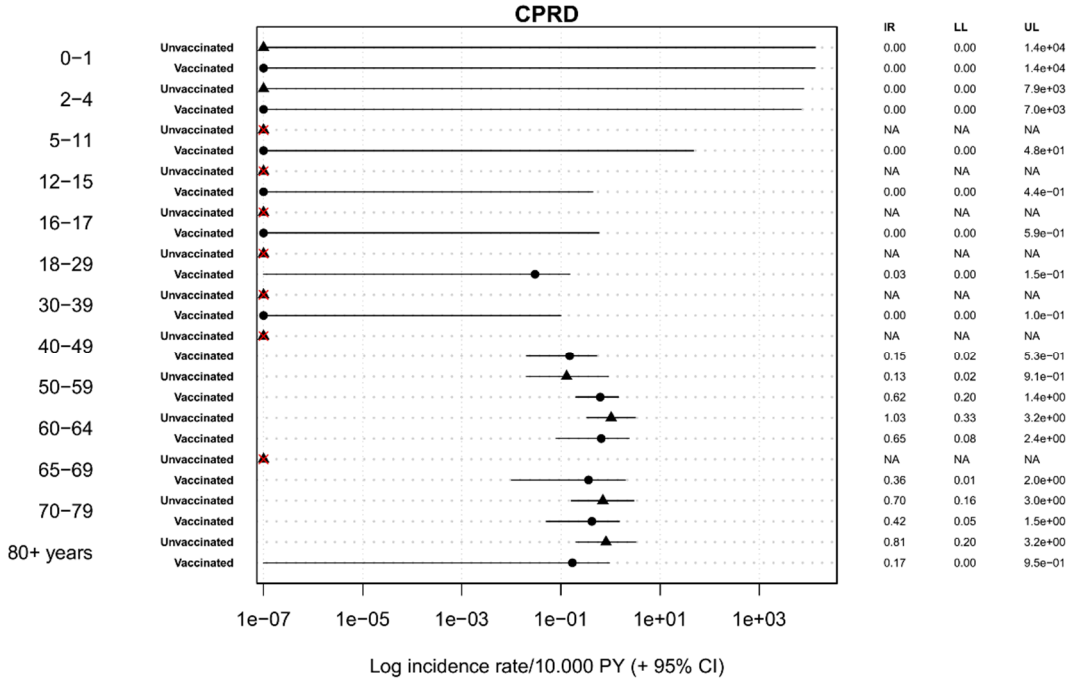


Table 24. Matched and adjusted hazard ratios (HRs) and matched and adjusted risk differences (RDs) per 10,000 person-years and their 95% CIs for stress cardiomyopathy among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source (risk window: 365 days after dose 1)

	Matched HR (95% CI)	Adjusted HR (95% CI)	Matched RD	Adjusted RD
Pedianet	NA	NA	NA	NA
NHR	0.69 (0.18, 2.70)	0.69 (0.18, 2.67)	0.02	0.02
PHARMO	1.49 (0.35, 6.31)	1.49 (0.33, 6.69)	0	0
EpiChron	0.99 (0.25, 3.98)	0.85 (0.21, 3.47)	0	-0.05
SIDIAP	1.67 (0.82, 3.38)	1.51 (0.75, 3.04)	0.15	0.14
CPRD Aurum	1.25 (0.51, 3.07)	1.30 (0.53, 3.20)	0.05	0.06

NA: not assessable due to zero cases in the vaccinated or unvaccinated cohorts for HR or in both cohorts for RD

10.2.3.5. Coronary artery disease

Coronary artery disease was observed in the vaccinated and unvaccinated cohorts in all data sources, except Pedianet. The incidence rates ranged from 15.40 per 10,000 person-years (95% CI: 14.64, 16.19) in SIDIAP to 67.28 per 10,000 person-years (95% CI: 65.52, 69.06) in NHR in the vaccinated cohorts and from 12.23 per 10,000 person-years (95% CI: 10.99, 13.60) in PHARMO to 67.50 per 10,000 person-years (95% CI: 64.71, 70.41) in NHR in the unvaccinated cohorts. The incidence of coronary artery disease was higher in higher age groups in all data sources in the vaccinated and unvaccinated cohorts.

The matched HRs of coronary artery disease were 1.00 (95% CI: 0.95, 1.05) in NHR, 1.53 (95% CI: 1.35, 1.73) in PHARMO, 1.02 (95% CI: 0.84, 1.23) in EpiChron, 1.05 (95% CI: 0.96, 1.16) in SIDIAP, 1.43 (95% CI: 1.33, 1.54) in CPRD Aurum. The adjusted HRs were 0.99 (95% CI: 0.94, 1.04) in NHR, 1.49 (95% CI: 1.31, 1.69) in PHARMO, 0.97 (95% CI: 0.80, 1.17) in EpiChron, 1.00 (95% CI: 0.91, 1.10) in SIDIAP, 1.40 (95% CI: 1.30, 1.50) in CPRD Aurum. In PHARMO and CPRD Aurum were HR above 1 and the lower limits of the 95% CI for the adjusted HRs were >1.

Table 25. Risk estimates (95% CI) per 10,000 person-years (PY) for coronary artery disease among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source (risk window: 365 days after dose 1)

	Vaccinated				Unvaccinated			
Data source	**Events (n)**	**Cumulative incidence (95% CI)**	**Person-years (PY)**	**Incidence rate (95% CI)**	**Events (n)**	**Cumulative incidence (95% CI)**	**Person-years (PY)**	**Incidence rate (95% CI)**
Pedianet	NA	NA	NA	NA	NA	NA	NA	NA
NHR	5,593	60.35 (58.55, 62.14)	831,346	67.28 (65.52, 69.06)	5,541	59.38 (56.38, 62.39)	820,893	67.50 (64.71, 70.41)
PHARMO	893	17.91 (16.69, 19.13)	478,964	18.64 (17.44, 19.91)	579	11.41 (10.15, 12.66)	473,477	12.23 (10.99, 13.60)
EpiChron	379	17.28 (15.43, 19.12)	207,469	18.27 (16.47, 20.20)	371	15.75 (13.16, 18.34)	206,465	17.97 (15.33, 21.06)
SIDIAP	1,542	14.23 (13.46, 15)	1,001,458	15.40 (14.64, 16.19)	1,464	13.01 (11.83, 14.19)	1,001,552	14.62 (13.44, 15.90)
CPRD Aurum	2,651	25.69 (24.16, 27.23)	1,277,998	20.74 (19.96, 21.55)	1,804	17.52 (15.70, 19.33)	1,249,224	14.44 (13.58, 15.36)

NA: Not available
Note: Estimation of confidence intervals differs between vaccinated and unvaccinated, since the unvaccinated estimate is a generalised estimating equation (GEE*)* estimates (to account for individuals who were matched to more than one vaccinated individual). When NA (not-assessable) is listed for the 1-KM it means that there is no estimate for the duration of follow-up specified as risk interval, meaning that there was not any patient who reached the end of the risk window. The vaccinated and unvaccinated cohorts were matched on age, sex, geographical region, prior identified COVID-19 infection, prior influenza vaccination, pregnancy, immunocompromised and number of pre-existing conditions considered by the Centers for Disease Control and Prevention (CDC) as risk criteria (0, 1, 2, 3, 4+).

Figure 14. Cumulative incidence of coronary artery disease among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source (risk window: 365 days after dose 1)

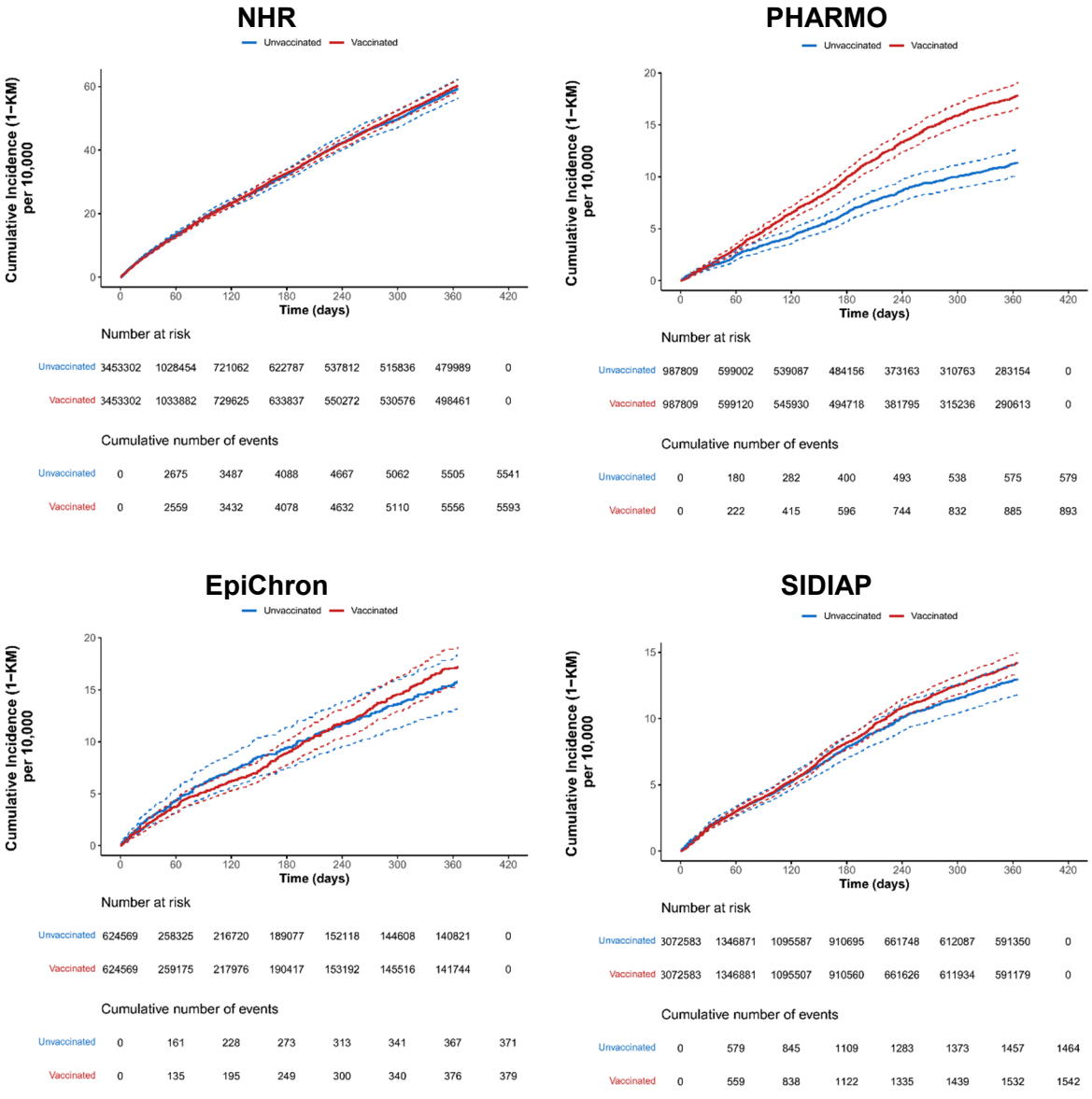
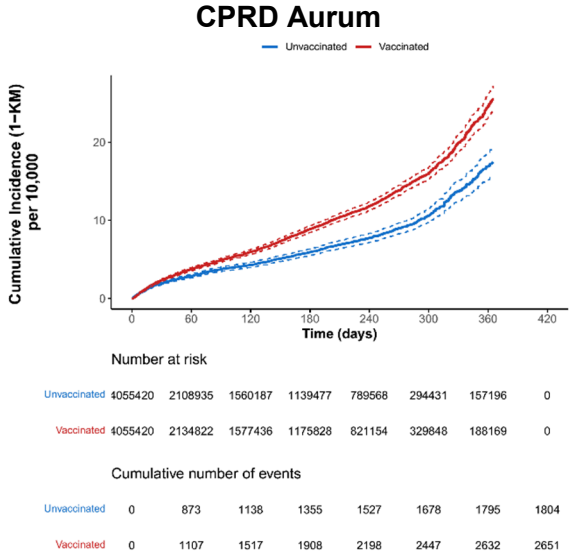
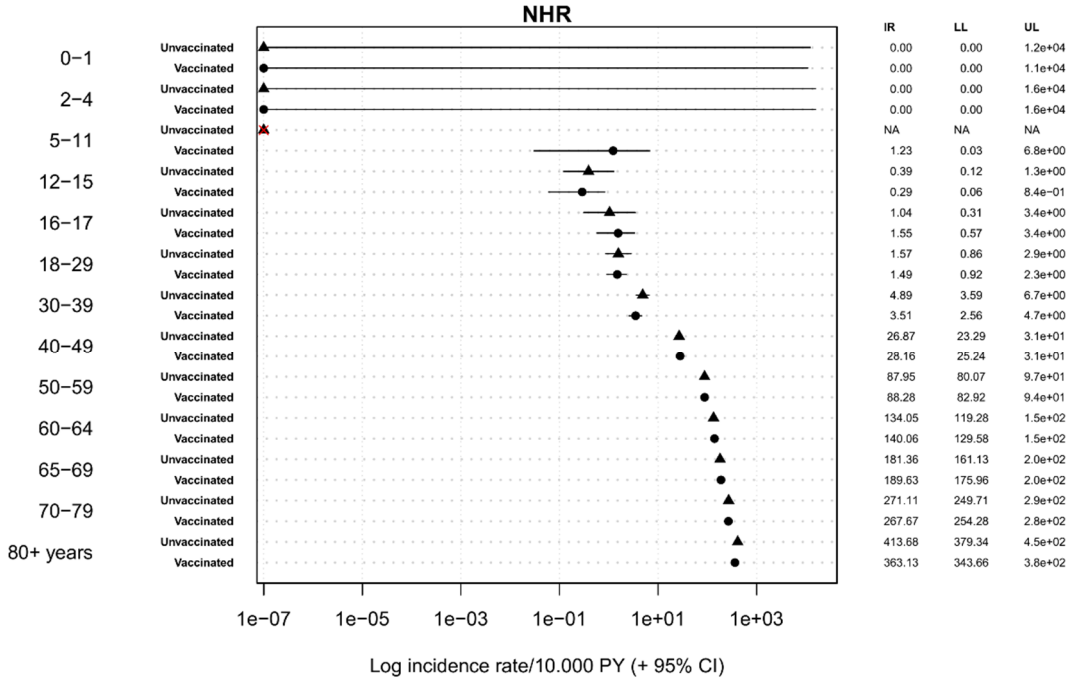


Figure 14. Cumulative incidence of coronary artery disease among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source (risk window: 365 days after dose 1)



Cumulative incidence curves (1 – Kaplan–Meier risk) starting from the day of administration of the first dose of vaccine. Dotted lines represent 95% confidence intervals. The number at risk at each time point and the cumulative number of events during the 365-day risk window are also shown for each time point. The numerical data correspond to the days indicated by the tick marks on the x-axis.

Figure 15. Forest plot showing incidence rates and 95% confidence intervals for coronary artery disease among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source and by age groups (risk window: 365 days after dose 1)



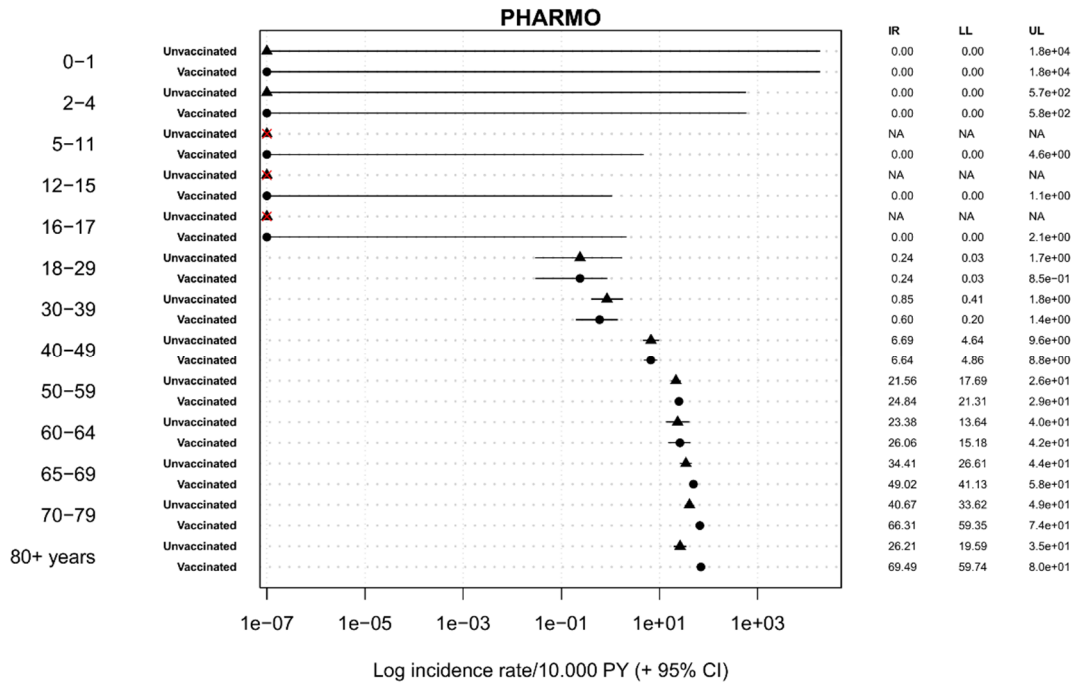


Figure 15. Forest plot showing incidence rates and 95% confidence intervals for coronary artery disease among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source and by age groups (risk window: 365 days after dose 1)

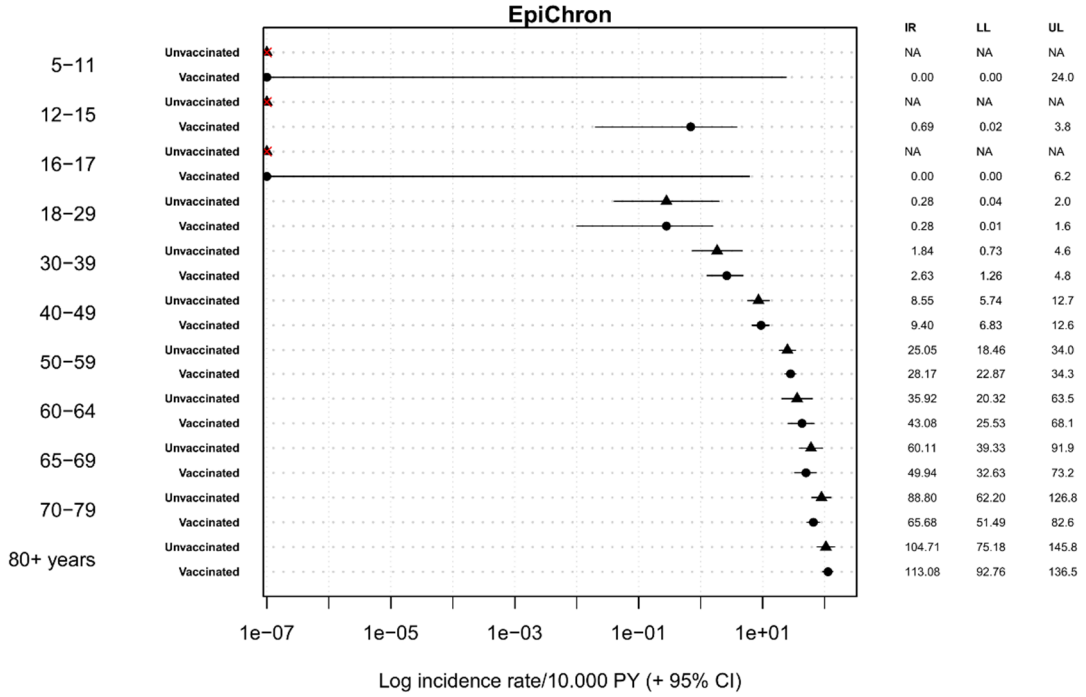
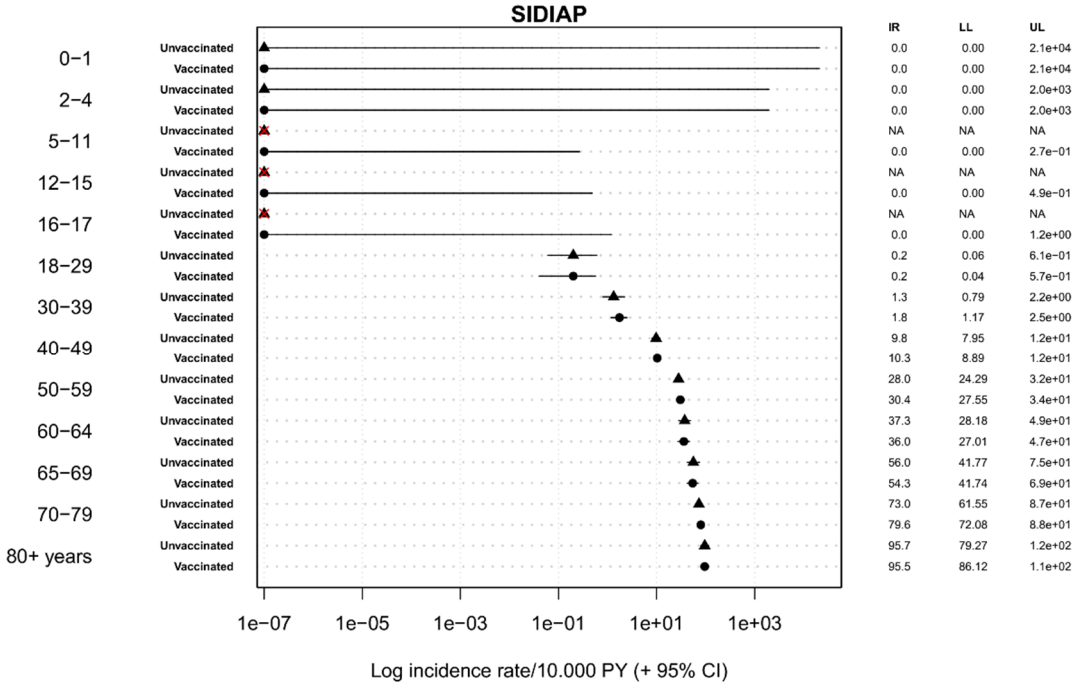


Figure 15. Forest plot showing incidence rates and 95% confidence intervals for coronary artery disease among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source and by age groups (risk window: 365 days after dose 1)



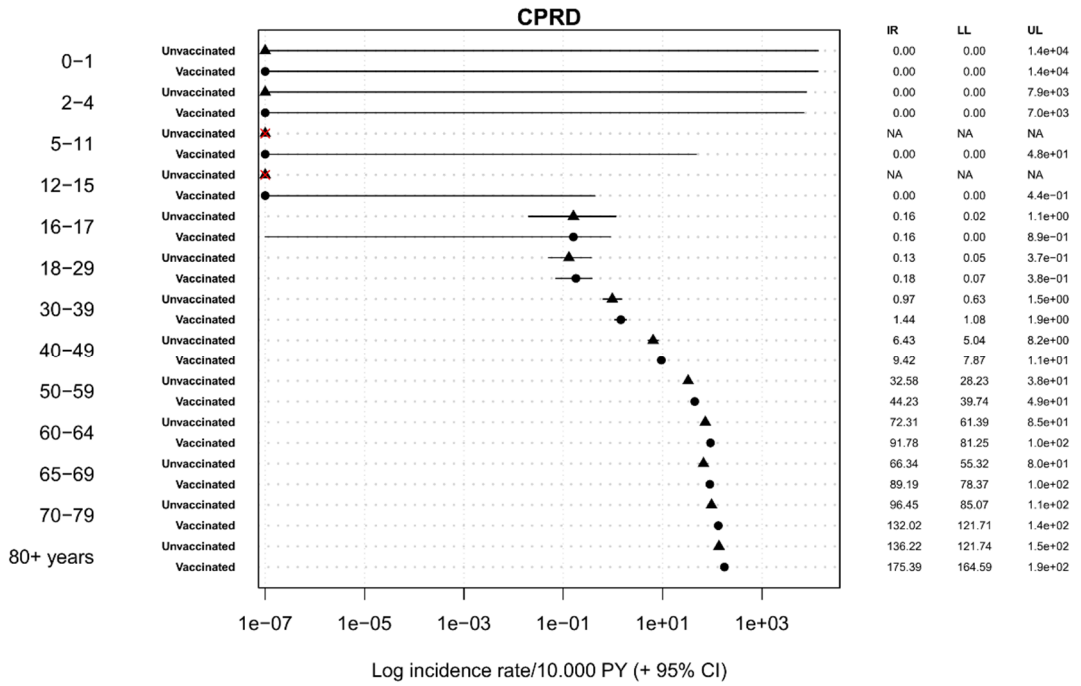


Table 26. Matched and adjusted hazard ratios (HRs) and matched and adjusted risk differences (RDs) per 10,000 person-years and their 95% CIs for coronary artery disease among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source (risk window: 365 days after dose 1)

	Matched HR (95% CI)	Adjusted HR (95% CI)	Matched RD	Adjusted RD
Pedianet	NA	NA	NA	NA
NHR	1.00 (0.95, 1.05)	0.99 (0.94, 1.04)	0.96	0.43
PHARMO	1.53 (1.35, 1.73)	1.49 (1.31, 1.69)	6.50	6.17
EpiChron	1.02 (0.84, 1.23)	0.97 (0.80, 1.17)	1.52	0.57
SIDIAP	1.05 (0.96, 1.16)	1.00 (0.91, 1.10)	1.22	0.52
CPRD Aurum	1.43 (1.33, 1.54)	1.40 (1.30, 1.50)	8.18	7.83

NA: not assessable due to zero cases in the vaccinated or unvaccinated cohorts for HR or in both cohorts for RD

10.2.3.6. Myocarditis (21-day risk window)

Myocarditis events were identified in all data sources. During the 21-day risk window after the start of follow-up, the incidence rates ranged from 0.83 per 10,000 person-years (95% CI: 0.23, 2.13) in PHARMO to 18.07 per 10,000 person-years (95% CI: 0.46, 100.70) in PEDIANET in the vaccinated cohorts and from 0.62 per 10,000 person-years in (95% CI: 0.14, 2.68) in PHARMO to 3.99 per 10,000 person-years (95% CI: 2.90, 5.48) in NHR in the unvaccinated cohorts. The cumulative incidence was below 1 per 10,000 individuals in both cohorts in each data source. There were no differences in the incidence of myocarditis in a 21-day risk window across age groups.

The matched HRs were 0.94 (95% CI: 0.46, 1.93) in NHR, 1.50 (95% CI: 0.16, 14.45) in PHARMO, 4.00 (95% CI: 0.45, 35.77) in EpiChron, 1.14 (95% CI: 0.38, 3.40) in SIDIAP, and 2.25 (95% CI: 0.91, 5.54) in CPRD Aurum. The adjusted HRs were 0.94 (95% CI: 0.46, 1.94) in NHR, 1.23 (95% CI: 0.13, 11.84) in PHARMO, 3.64 (95% CI: 0.41, 32.53) in EpiChron, 1.05 (95% CI: 0.35, 3.16) in SIDIAP, and 2.30 (95% CI: 0.94, 5.66) in CPRD Aurum. The lower limits of the CIs in the HRs for myocarditis assessed in a risk window of 21 days are below 1.

Table 27. Risk estimates (95% CI) per 10,000 person-years (PY) for myocarditis within 21 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source

	Vaccinated				Unvaccinated			
Data source	**Events (n)**	**Cumulative incidence (95% CI)**	**Person-years (PY)**	**Incidence rate (95% CI)**	**Events (n)**	**Cumulative incidence (95% CI)**	**Person-years (PY)**	**Incidence rate (95% CI)**
Pedianet	<5	0.98 (0, 2.89)	NR	18.07 (0.46, 100.70)	0	0 (0, NC)	553	0 (0, NC)
NHR	68	0.25 (0.19, 0.31)	160,517	4.24 (3.29, 5.37)	64	0.22 (0.15, 0.29)	160,424	3.99 (2.90, 5.48)
PHARMO	<5	0.05 (0, 0.10)	NR	0.83 (0.23, 2.13)	<5	0.03 (0, 0.09)	NR	0.62 (0.14, 2.68)
EpiChron	10	0.22 (0.08, 0.35)	26,097	3.83 (1.84, 7.05)	9	0.19 (0.03, 0.35)	26,083	3.45 (1.48, 8.02)
SIDIAP	48	0.21 (0.15, 0.26)	134,902	3.56 (2.62, 4.72)	44	0.18 (0.10, 0.27)	134,902	3.26 (2.04, 5.23)
CPRD Aurum	56	0.16 (0.12, 0.21)	198,592	2.82 (2.13, 3.66)	32	0.09 (0.06, 0.13)	198,235	1.61 (1.11, 2.35)

NA: Not available; NR: not reportable due to masking of numbers of events <5; NC: Not calculable
Note: Estimation of confidence intervals differs between vaccinated and unvaccinated, since the unvaccinated estimate is a generalised estimating equation (GEE*)* estimates (to account for individuals who were matched to more than one vaccinated individual). When NA (not-assessable) is listed for the 1-KM it means that there is no estimate for the duration of follow-up specified as risk interval, meaning that there was not any patient who reached the end of the risk window. The vaccinated and unvaccinated cohorts were matched on age, sex, geographical region, prior identified COVID-19 infection, prior influenza vaccination, pregnancy, immunocompromised and number of pre-existing conditions considered by the Centers for Disease Control and Prevention (CDC) as risk criteria (0, 1, 2, 3, 4+).

Figure 16. Cumulative incidence of myocarditis within 21 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source

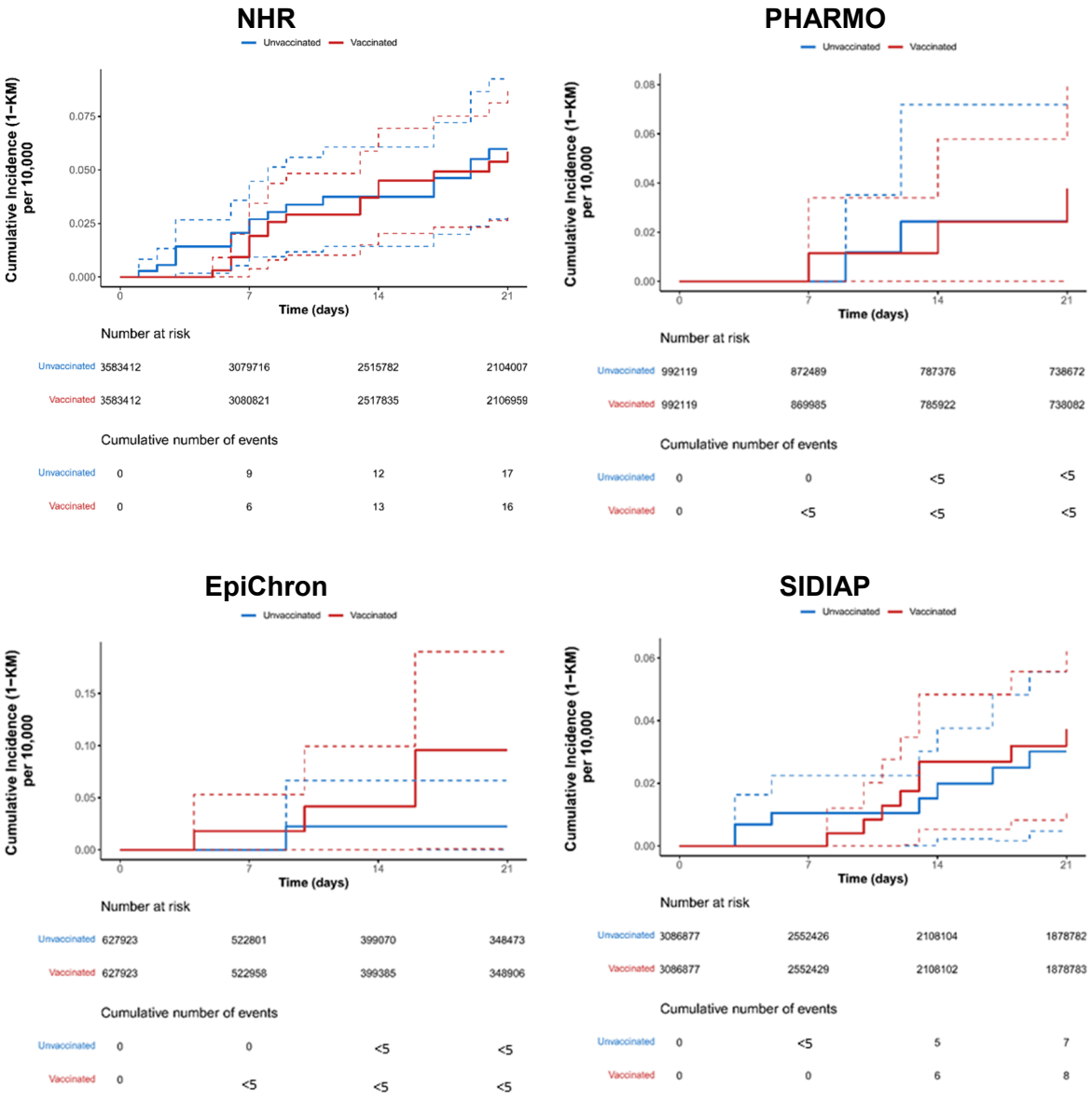
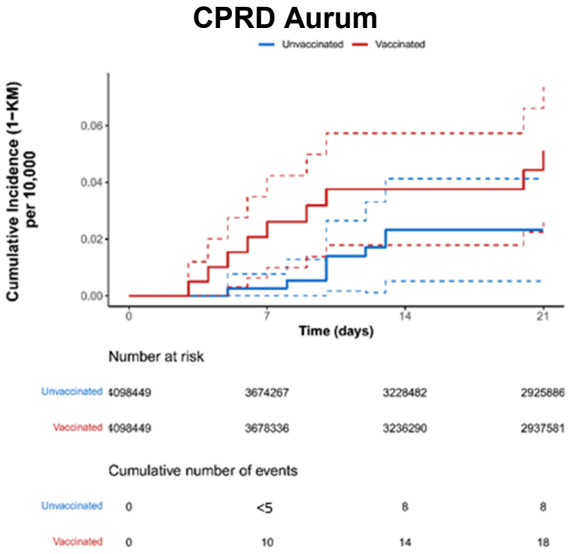
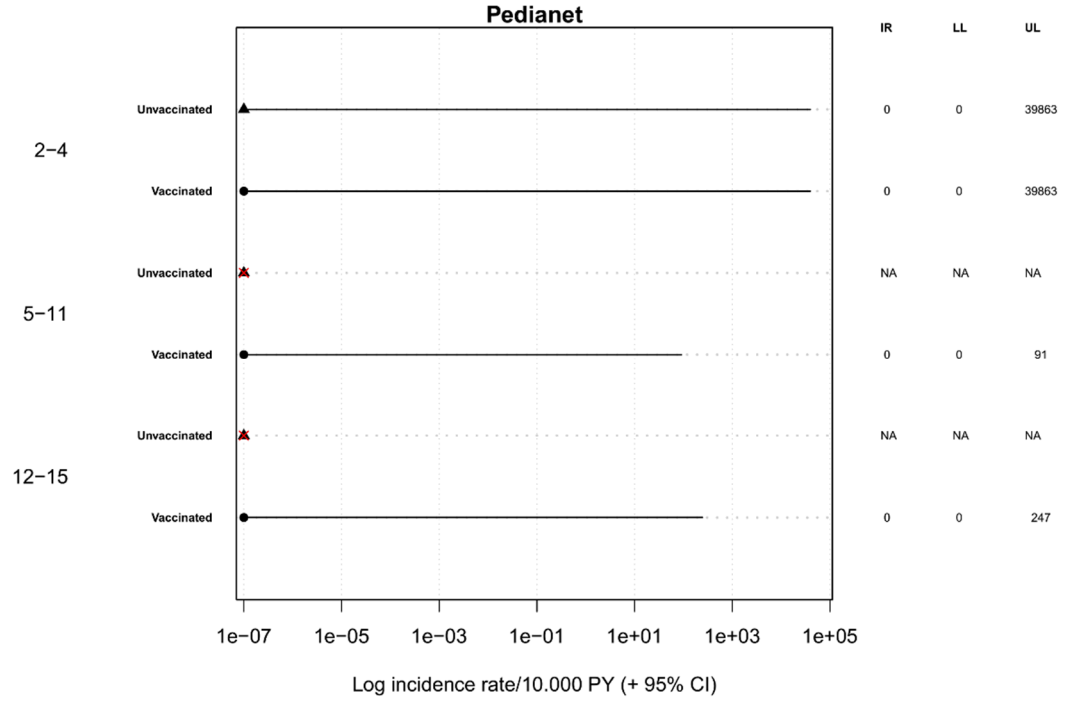


Figure 16. Cumulative incidence of myocarditis within 21 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source



Cumulative incidence curves (1 – Kaplan–Meier risk) starting from the day of administration of the first dose of vaccine. Dotted lines represent 95% confidence intervals. The number at risk at each time point and the cumulative number of events during the 21-day risk window are also shown for each time point. The numerical data correspond to the days indicated by the tick marks on the x-axis.

Figure 17. Forest plot showing incidence rates and 95% confidence intervals for myocarditis within 21 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source and by age groups



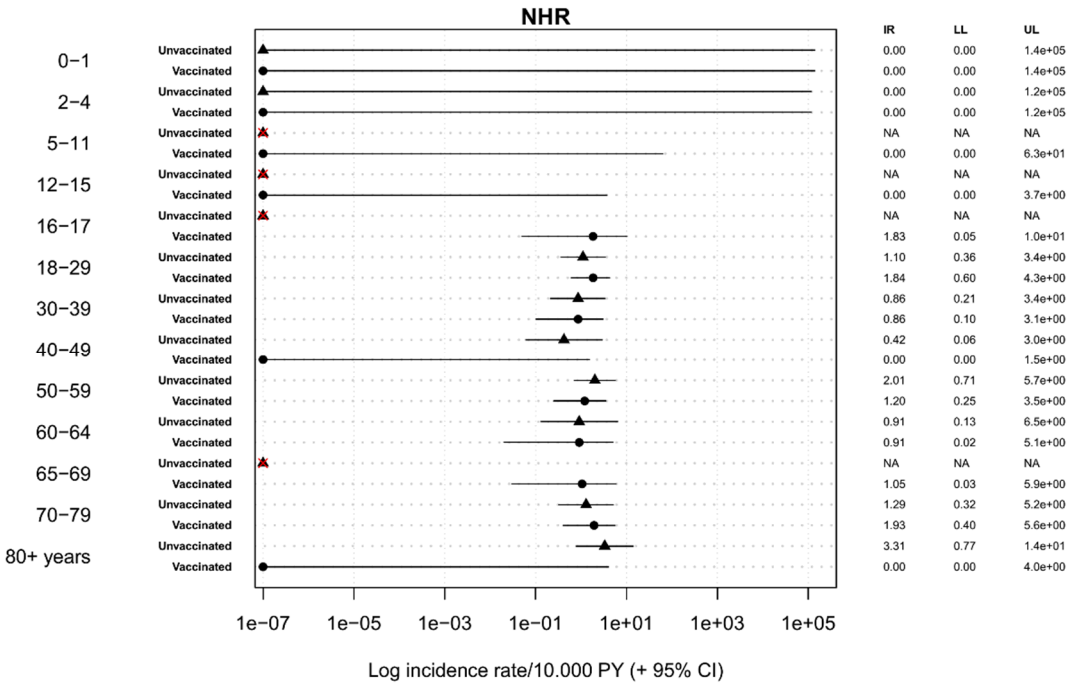
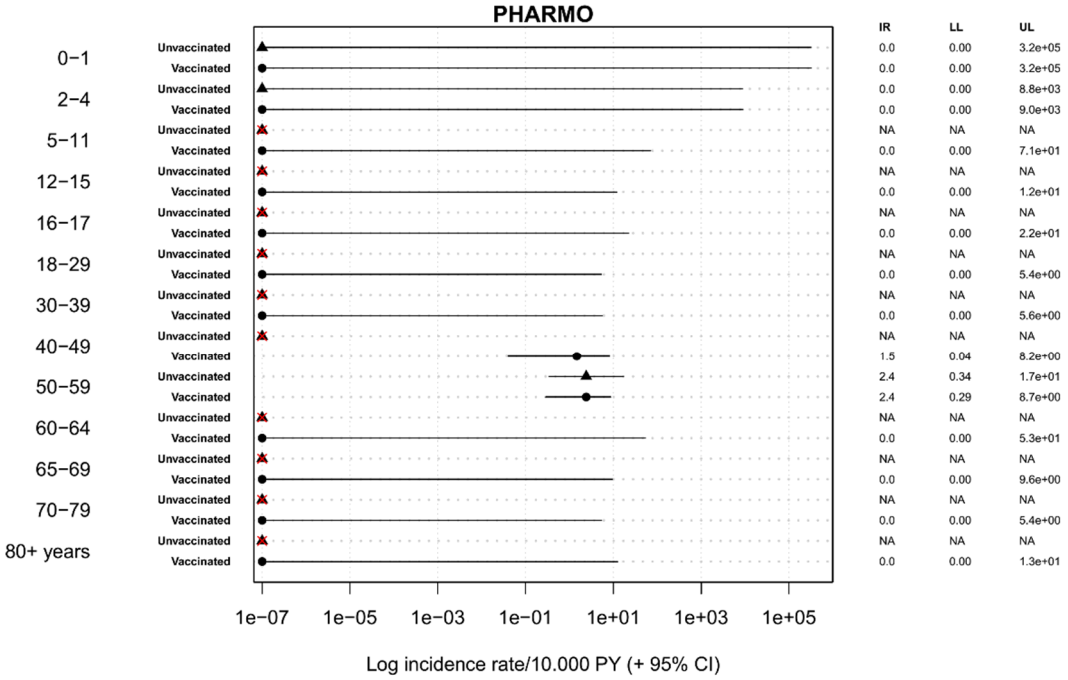


Figure 17. Forest plot showing incidence rates and 95% confidence intervals for myocarditis within 21 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source and by age groups



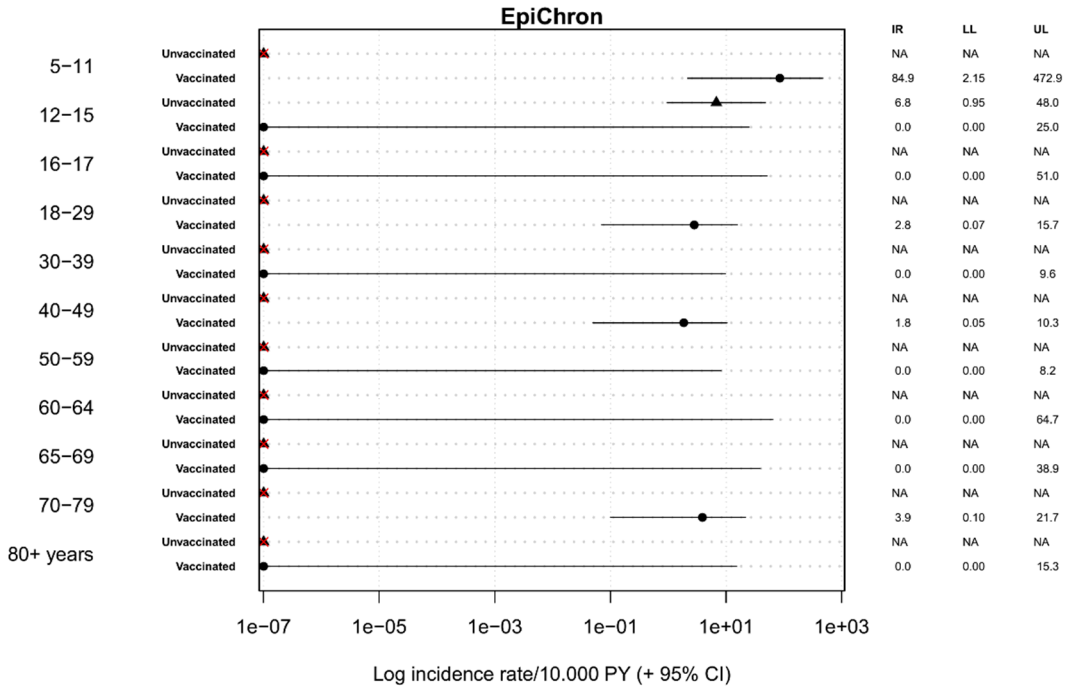


Figure 17. Forest plot showing incidence rates and 95% confidence intervals for myocarditis within 21 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source and by age groups

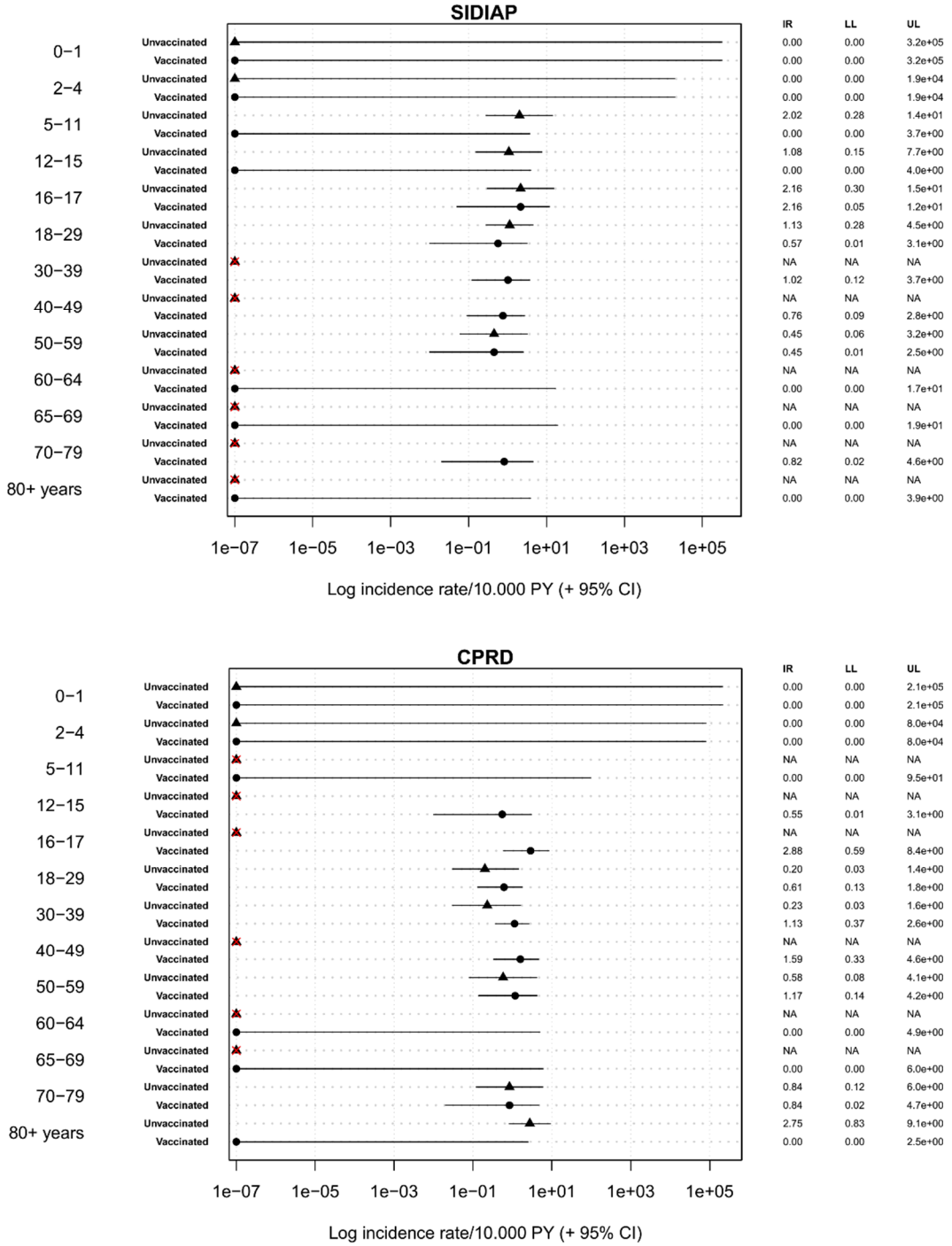


Table 28. Matched and adjusted hazard ratios (HRs) and matched and adjusted risk differences (RDs) per 10,000 person-years and their 95% CIs for myocarditis within 21 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source

	Matched HR (95% CI)	Adjusted HR (95% CI)	Matched RD	Adjusted RD
Pedianet	NA	NA	NA	NA
NHR	0.94 (0.46, 1.93)	0.94 (0.46, 1.94)	0	0
PHARMO	1.50 (0.16, 14.45)	1.23 (0.13, 11.84)	0.01	0.01
EpiChron	4.00 (0.45, 35.77)	3.64 (0.41, 32.53)	0.07	0.07
SIDIAP	1.14 (0.38, 3.40)	1.05 (0.35, 3.16)	0.01	0
CPRD Aurum	2.25 (0.91, 5.54)	2.30 (0.94, 5.66)	0.03	0.03

NA: not assessable due to zero cases in the vaccinated or unvaccinated cohorts for HR or in both cohorts for RD

10.2.3.7. Cerebral venous sinus thrombosis

Cerebral venous sinus thrombosis (CVST) was observed in both the vaccinated and unvaccinated cohorts in all data sources, except Pedianet. The incidence rates in the vaccinated cohorts ranged from 0.12 per 10,000 person-years (95% CI: 0.01, 0.43) in SIDIAP to 0.35 per 10,000 person-years (95% CI: 0.14, 0.73) in NHR and in the unvaccinated cohorts these ranged from 0.18 per 10,000 person-years (95% CI: 0.06, 0.55) in SIDIAP to 0.56 per 10,000 person-years (95% CI: 0.28, 1.11) in NHR.

There was no difference of the incidence of CVST observed between age groups in all data sources, in both the vaccinated and non-vaccinated cohorts, during the 28-day risk interval. The matched HRs were 0.64 (95% CI: 0.23, 1.75) in NHR, 1 (95% CI: 0.06, 15.96) in EpiChron, 0.67 (95% CI: 0.11, 3.99) in 0.45 (95% CI: 0.15, 1.35) in CPRD Aurum. The adjusted HRs were 10.63 (95% CI: 0.23, 1.74) in NHR, 0.90 (95% CI: 0.06, 14.09) in EpiChron, 0.68 (95% CI: 0.11, 4.20) in SIDIAP, 0.43 (95% CI: 0.14, 1.27) in CPRD Aurum. No differences between vaccinated and unvaccinated were observed for CVST.

Table 29. Risk estimates (95% CI) per 10,000 person-years (PY) for cerebral venous sinus thrombosis within 28 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source

	Vaccinated				Unvaccinated			
Data source	**Events (n)**	**Cumulative incidence (95% CI)**	**Person-years (PY)**	**Incidence rate (95% CI)**	**Events (n)**	**Cumulative incidence (95% CI)**	**Person-years (PY)**	**Incidence rate (95% CI)**
Pedianet	0	0 (0, NC)	719	0 (0, 51.28)	0	0 (0, 0)	719	0 (0, NC)
NHR	7	0.03 (0.01, 0.05)	197,673	0.35 (0.14, 0.73)	11	0.04 (0.01, 0.07)	197,515	0.56 (0.28, 1.11)
PHARMO	<5	0.01 (0, 0.03)	NR	0.16 (0, 0.90)	0	0 (0, 0)	61,904	
EpiChron	<5	0.03 (0, 0.09)	NR	0.31 (0.01, 1.72)	<5	0.02 (0, 0.05)	NR	0.31 (0.04, 2.19)
SIDIAP	<5	0.01 (0, 0.02)	NR	0.12 (0.01, 0.43)	<5	0.01 (0, 0.03)	NR	0.18 (0.06, 0.55)
CPRD Aurum	5	0.01 (0, 0.03)	252,280	0.20 (0.06, 0.46)	11	0.03 (0.01, 0.05)	251,658	0.44 (0.23, 0.83)

NA: Not available; NR: not reportable due to masking of events <5; NC: not calculable

Note: Estimation of confidence intervals differs between vaccinated and unvaccinated, since the unvaccinated estimate is a generalised estimating equation (GEE) estimates (to account for individuals who were matched to more than one vaccinated individual). When NA (not-assessable) is listed for the 1-KM it means that there is no estimate for the duration of follow-up specified as risk interval, meaning that there was not any patient who reached the end of the risk window. The vaccinated and unvaccinated cohorts were matched on age, sex, geographical region, prior identified COVID-19 infection, prior influenza vaccination, pregnancy, immunocompromised and number of pre-existing conditions considered by the Centers for Disease Control and Prevention (CDC) as risk criteria (0, 1, 2, 3, 4+).

Figure 18. Cumulative incidence of cerebral venous sinus thrombosis within 28 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source

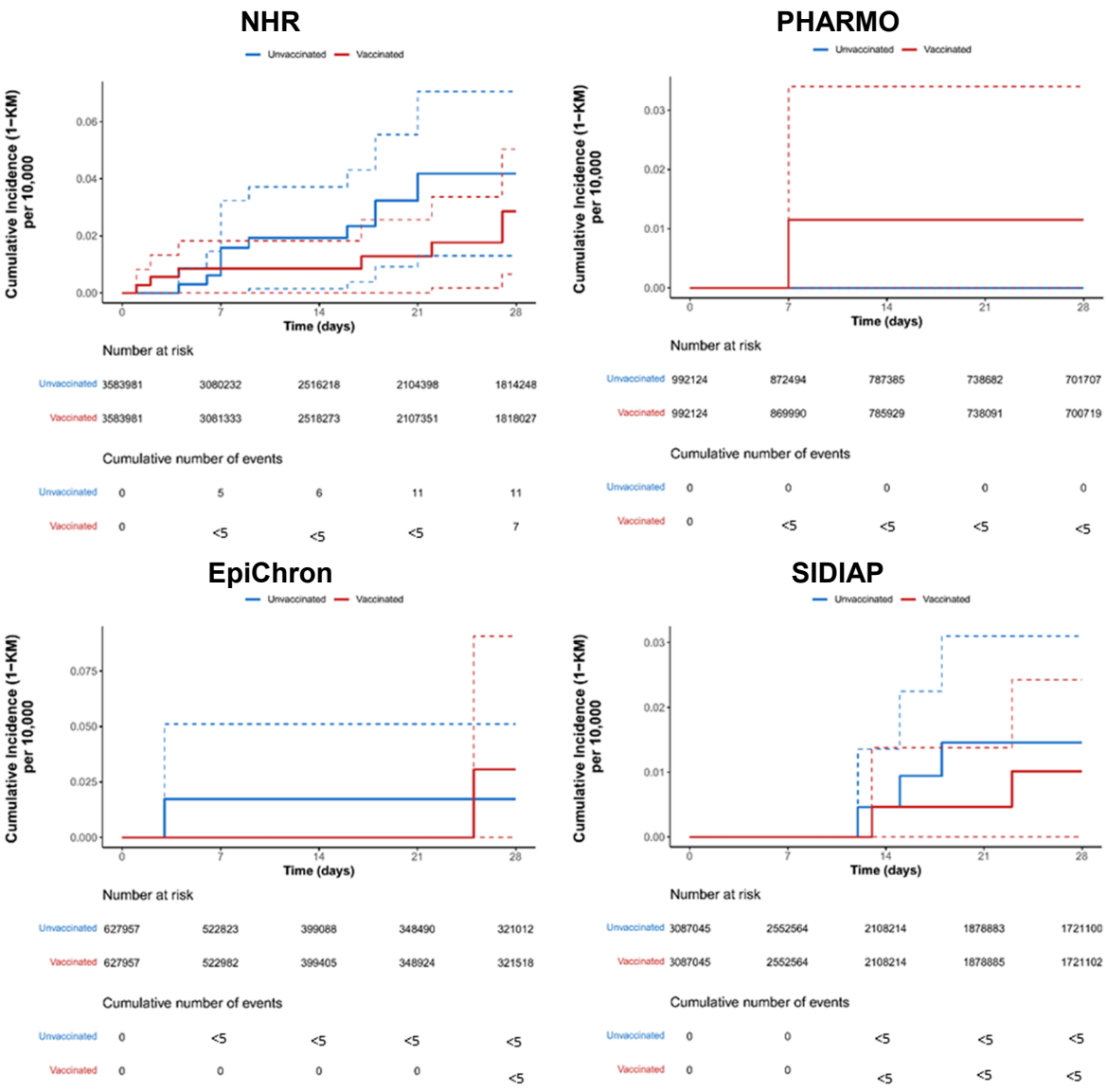
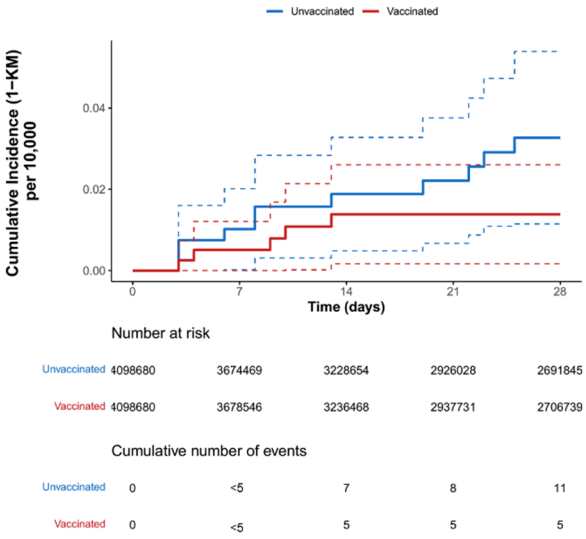


Figure 18. Cumulative incidence of cerebral venous sinus thrombosis within 28 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source

CPRD Aurum



Cumulative incidence curves (1 – Kaplan–Meier risk) starting from the day of administration of the first dose of vaccine. Dotted lines represent 95% confidence intervals. The number at risk at each time point and the cumulative number of events during the 365-day risk window are also shown for each time point. The numerical data correspond to the days indicated by the tick marks on the x-axis.

Figure 19. Forest plot showing incidence rates and 95% confidence intervals for cerebral venous sinus thrombosis within 28 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source and by age groups

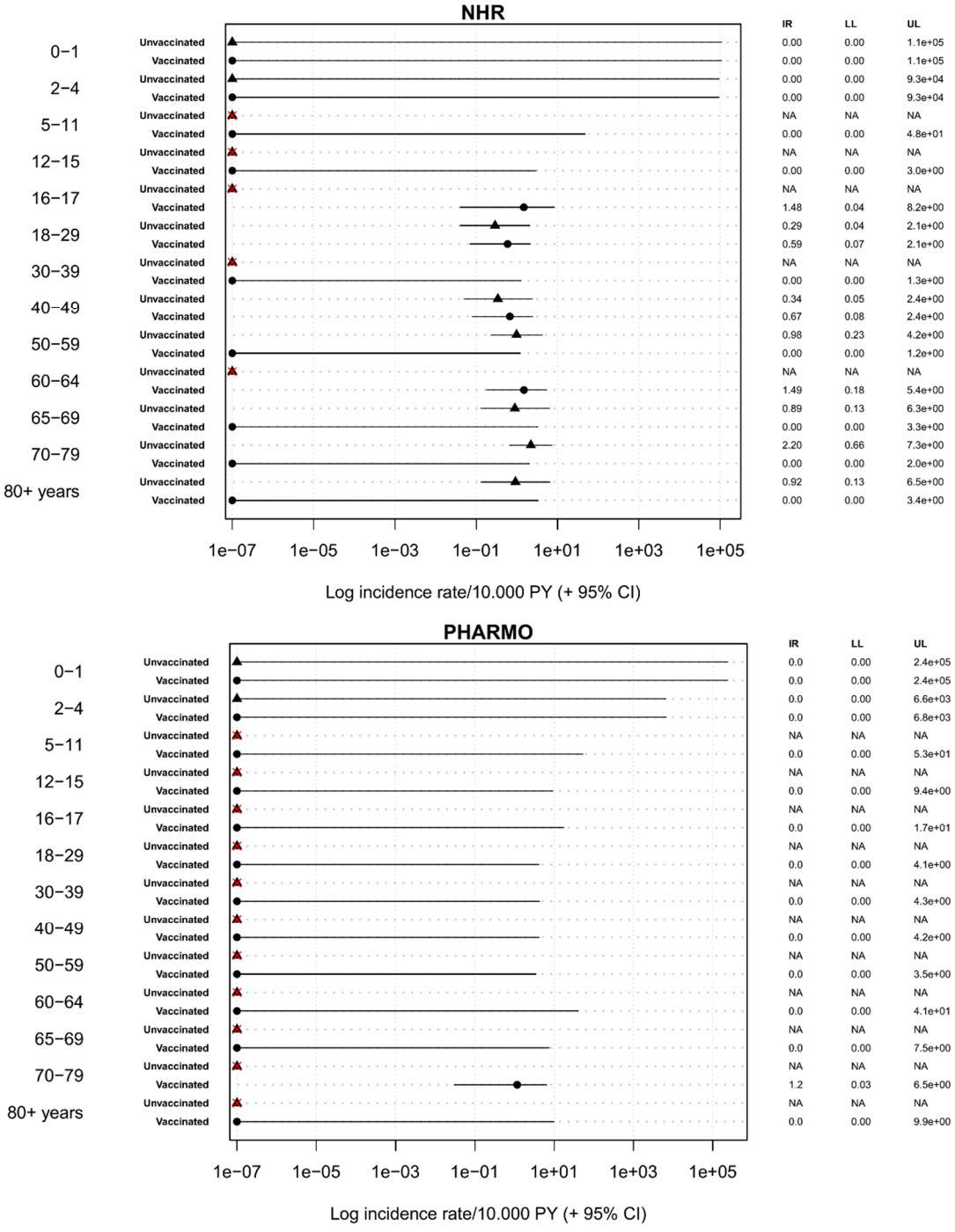


Figure 19. Forest plot showing incidence rates and 95% confidence intervals for cerebral venous sinus thrombosis within 28 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source and by age groups

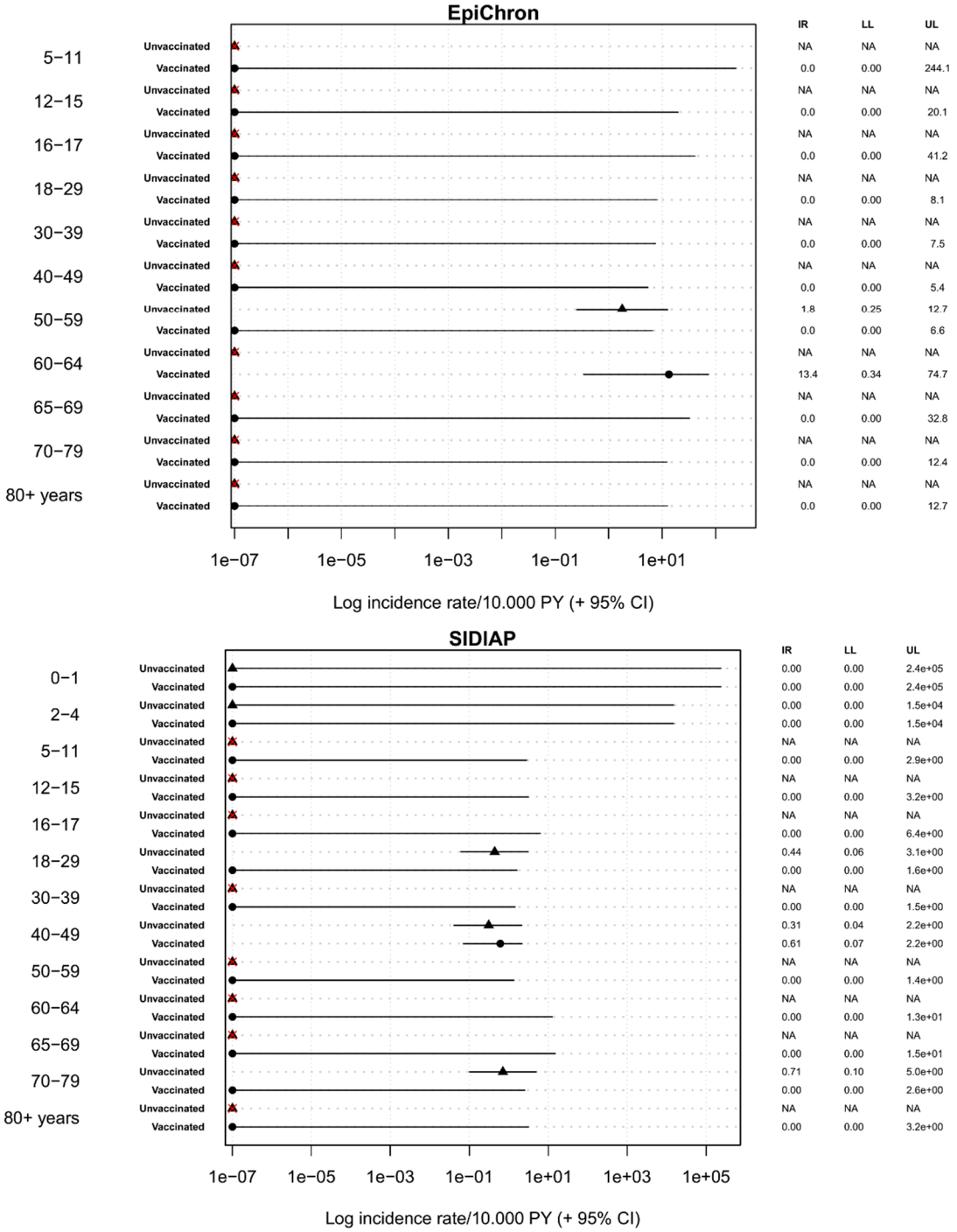


Figure 19. Forest plot showing incidence rates and 95% confidence intervals for cerebral venous sinus thrombosis within 28 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source and by age groups

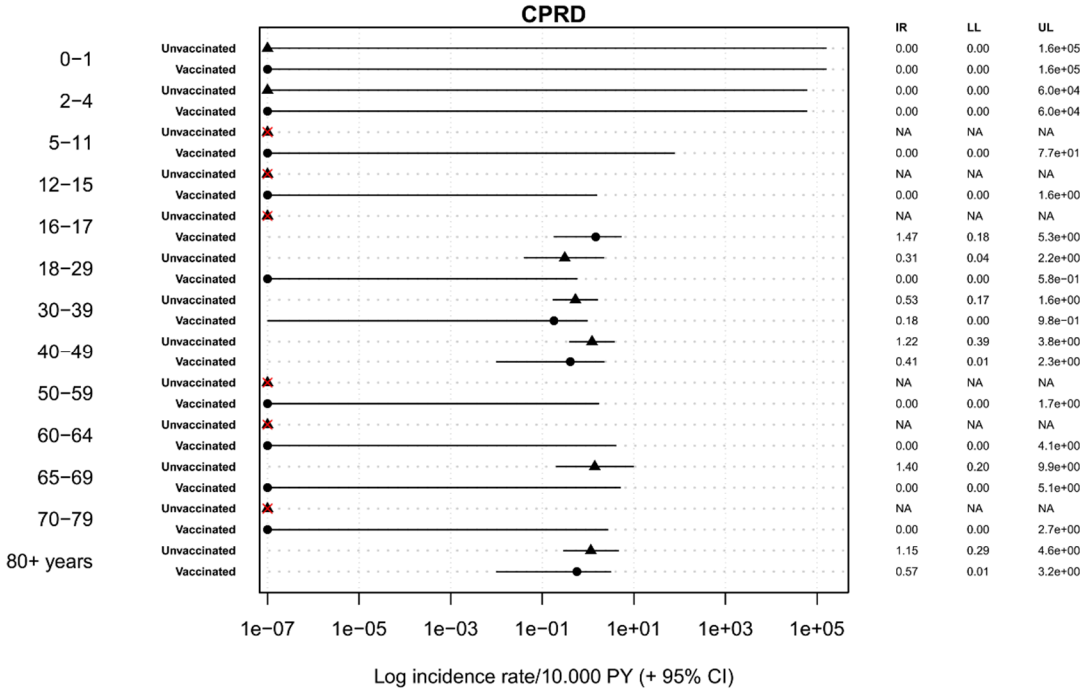


Table 30. Matched and adjusted hazard ratios (HRs) and matched and adjusted risk differences (RDs) per 10,000 person-years and their 95% CIs for cerebral venous sinus thrombosis within 28 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source

	Matched HR (95% CI)	Adjusted HR (95% CI)	Matched RD	Adjusted RD
Pedianet	NA	NA	NA	NA
NHR	0.64 (0.23, 1.75)	0.63 (0.23, 1.74)	-0.01	-0.01
PHARMO	NA	NA	0.01	0.01
EpiChron	1 (0.06, 15.96)	0.90 (0.06, 14.09)	0.01	0.01
SIDIAP	0.67 (0.11, 3.99)	0.68 (0.11, 4.20)	0	0
CPRD Aurum	0.45 (0.15, 1.35)	0.43 (0.14, 1.27)	-0.02	-0.02

NA: not assessable due to zero cases in the vaccinated or unvaccinated cohorts for HR or in both cohorts for RD

10.2.3.8. Glomerulonephritis

Glomerulonephritis events could be identified in all data sources, except NHR and PHARMO. Pedianet did not detect any events within the risk window. During the 21-day risk window after the start of follow-up, the incidence rates ranged from 0.58 per 10,000 person-years (95% CI: 0.30, 1.01) in EpiChron to 1.07 per 10,000 person-years (95% CI: 0.90, 1.26) in CPRD Aurum in the vaccinated cohorts and from 0.73 per 10,000 person-years in (95% CI: 0.53, 1.00) in SIDIAP to 1.20 per 10,000 person-years (95% CI: 0.96, 1.48) in CPRD Aurum in the unvaccinated cohorts. The cumulative incidence was around 1 per 10,000 individuals in both cohorts in each data source. The incidence of glomerulonephritis in a 365-day risk window is increasing with age.

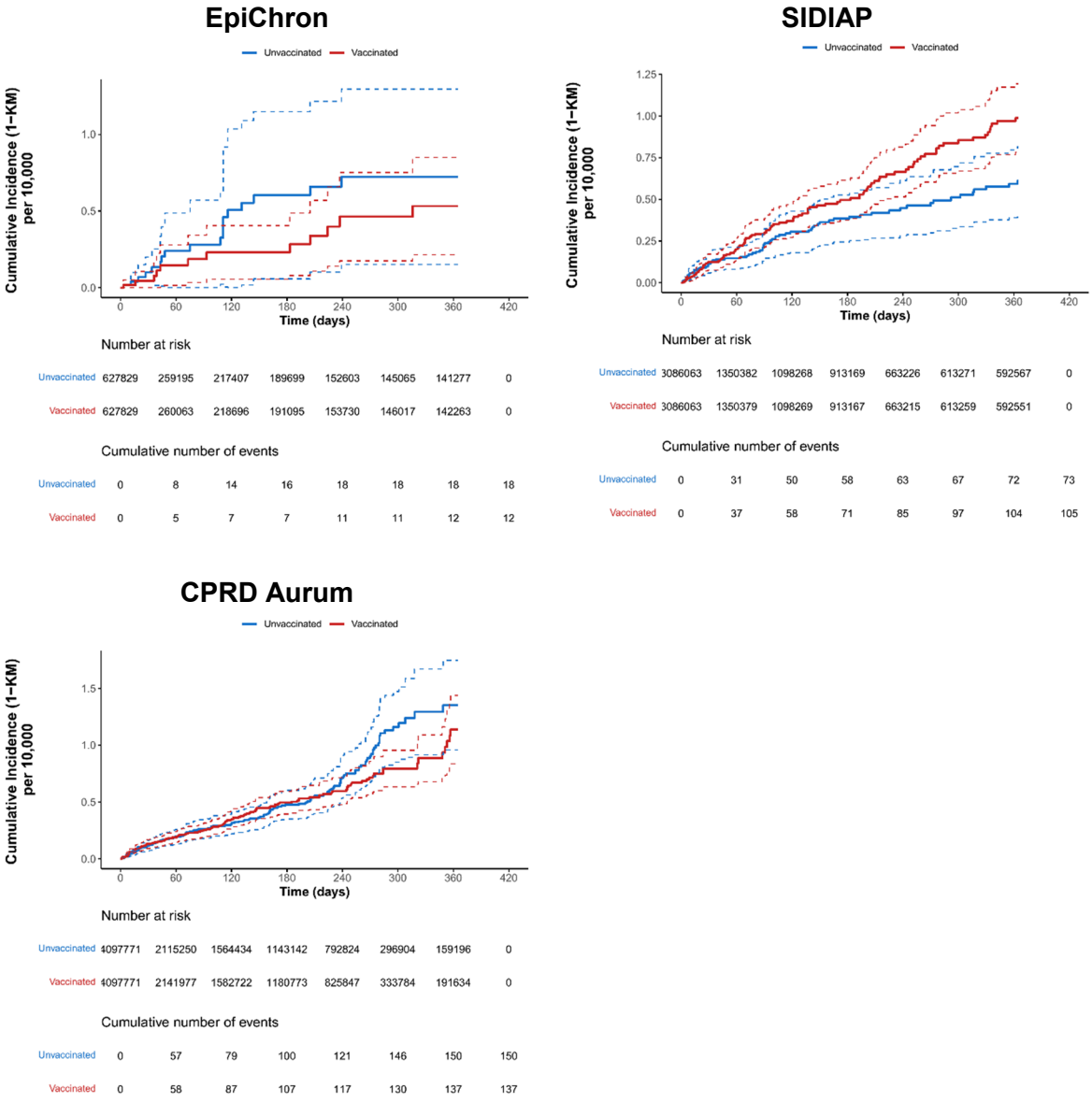
The matched HRs were 0.66 (95% CI: 0.26, 1.73) in EpiChron, 1.44 (95% CI: 0.99, 2.08) in SIDIAP, and 0.89 (95% CI: 0.68, 1.17) in CPRD Aurum. The adjusted HRs were 0.59 (95% CI: 0.22, 1.55) in EpiChron, 1.29 (95% CI: 0.88, 1.87) in SIDIAP, 0.88 (95% CI: 0.67, 1.16) in CPRD Aurum. The lower limits of the CIs in the HRs for glomerulonephritis assessed in a risk window of 365 days are below 1.

Table 31. Risk estimates (95% CI) per 10,000 person-years (PY) for 10.2.3.7. glomerulonephritis within 365 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source

	Vaccinated				Unvaccinated			
Data source	**Events (n)**	**Cumulative incidence (95% CI)**	**Person-years (PY)**	**Incidence rate (95% CI)**	**Events (n)**	**Cumulative incidence (95% CI)**	**Person-years (PY)**	**Incidence rate (95% CI)**
Pedianet	0	0 (0, NC)	6,991	0 (0, NC)	0	0 (0, NC)	7,014	0 (0, NC)
NHR	NA	NA	NA	NA	NA	NA	NA	NA
PHARMO	NA	NA	NA	NA	NA	NA	NA	NA
EpiChron	12	0.53 (0.21, 0.85)	208,226	0.58 (0.30, 1.01)	18	0.72 (0.15, 1.30)	207,187	0.87 (0.40, 1.88)
SIDIAP	105	0.99 (0.78, 1.19)	1,004,201	1.05 (0.86, 1.27)	73	0.61 (0.41, 0.82)	1,004,208	0.73 (0.53, 1.00)
CPRD Aurum	137	1.14 (0.84, 1.44)	1,284,652	1.07 (0.90, 1.26)	150	1.35 (0.96, 1.75)	1,254,718	1.20 (0.96, 1.48)

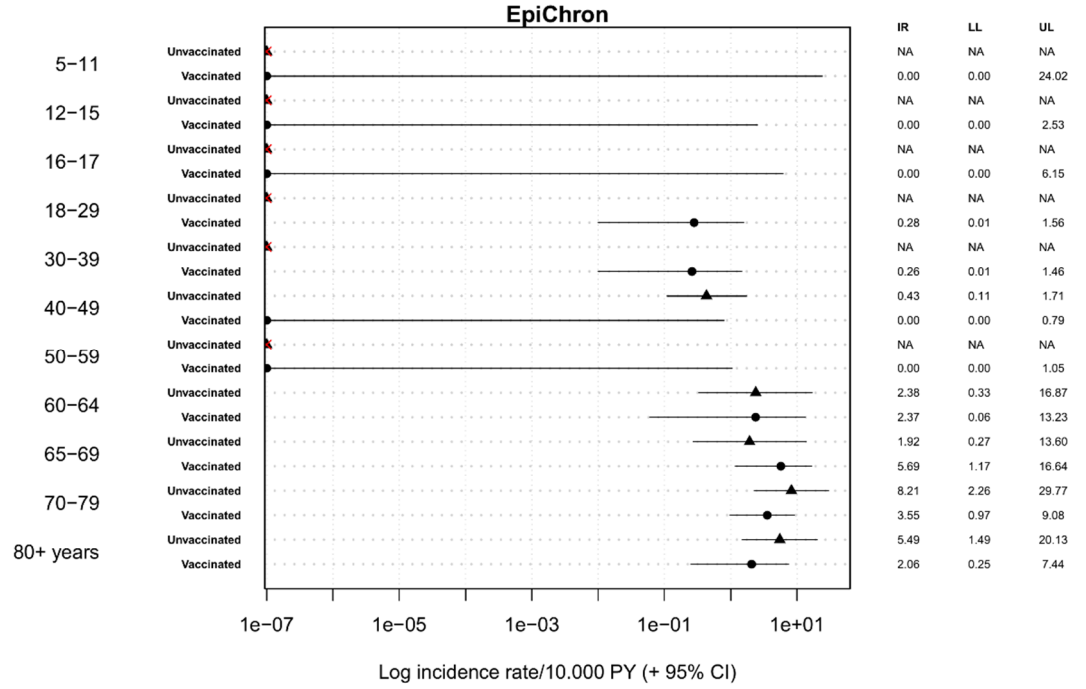
NA: Not available; NR: not reportable due to masking of numbers of events <5; NC: not calculable
Note: Estimation of confidence intervals differs between vaccinated and unvaccinated, since the unvaccinated estimate is a generalised estimating equation (GEE) estimates (to account for individuals who were matched to more than one vaccinated individual). When NA (not-assessable) is listed for the 1-KM it means that there is no estimate for the duration of follow-up specified as risk interval, meaning that there was not any patient who reached the end of the risk window. The vaccinated and unvaccinated cohorts were matched on age, sex, geographical region, prior identified COVID-19 infection, prior influenza vaccination, pregnancy, immunocompromised and number of pre-existing conditions considered by the Centers for Disease Control and Prevention (CDC) as risk criteria (0, 1, 2, 3, 4+).

Figure 20. Cumulative incidence of glomerulonephritis within 365 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source



Cumulative incidence curves (1 – Kaplan–Meier risk) starting from the day of administration of the first dose of vaccine. Dotted lines represent 95% confidence intervals. The number at risk at each time point and the cumulative number of events during the 21-day risk window are also shown for each time point. The numerical data correspond to the days indicated by the tick marks on the x-axis.

Figure 21. Forest plot showing incidence rates and 95% confidence intervals for glomerulonephritis within 365 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source and by age groups



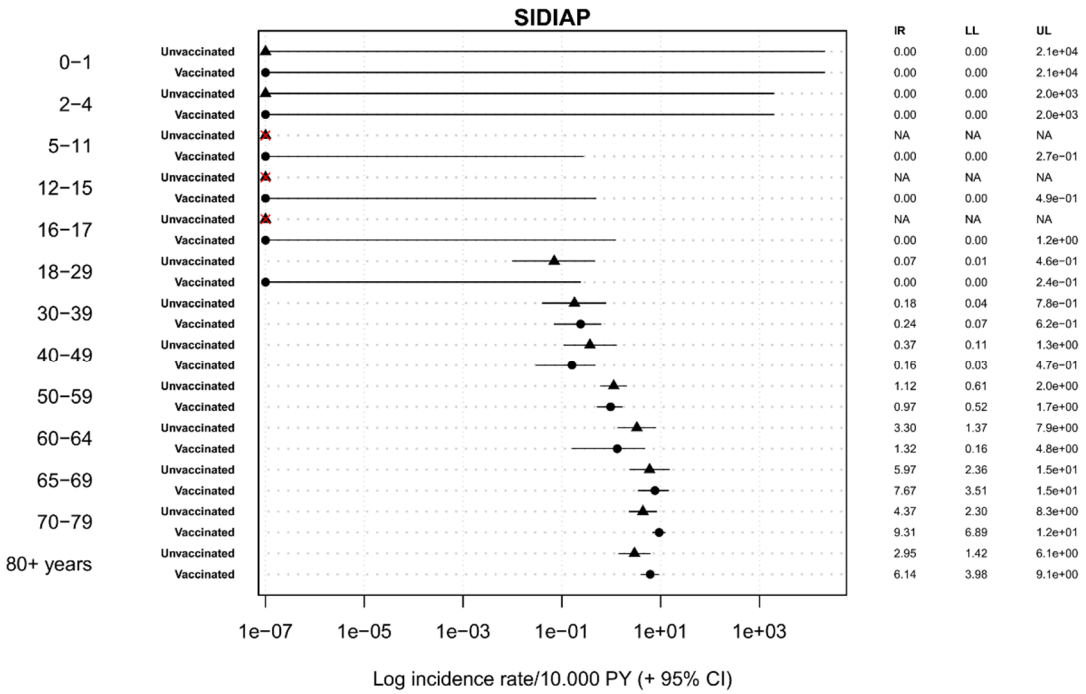


Figure 21. Forest plot showing incidence rates and 95% confidence intervals for glomerulonephritis within 365 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source and by age groups

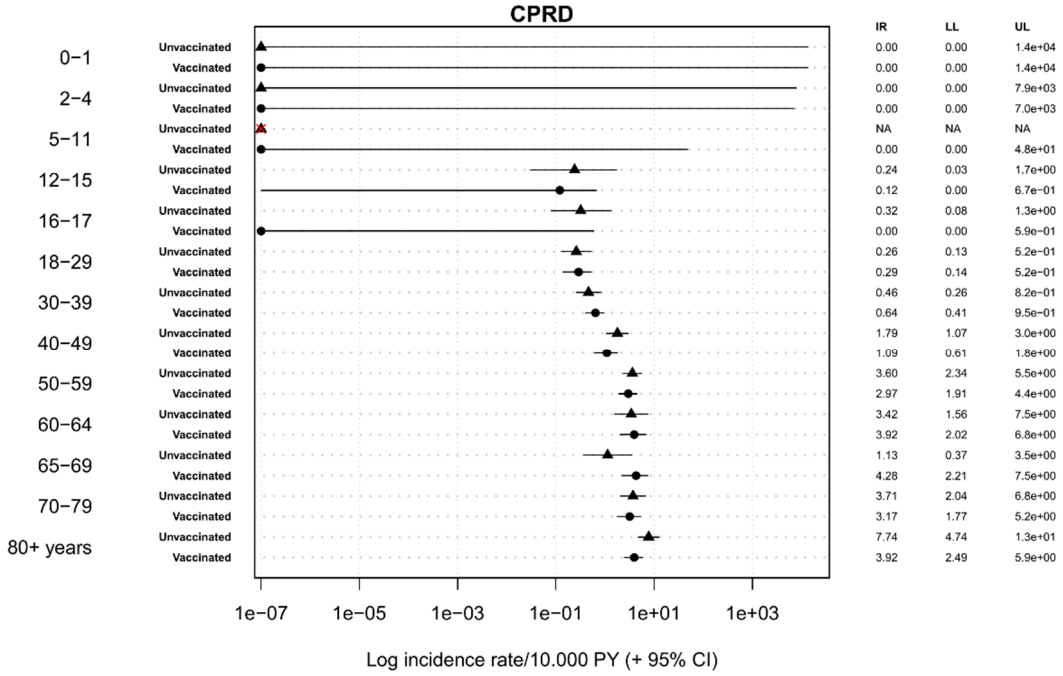


Table 32. Matched and adjusted hazard ratios (HRs) and matched and adjusted risk differences (RDs) per 10,000 person-years and their 95% CIs for glomerulonephritis within 365 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source

	Matched HR (95% CI)	Adjusted HR (95% CI)	Matched RD	Adjusted RD
Pedianet	NA	NA	NA	NA
NHR	NA	NA	NA	NA
PHARMO	NA	NA	NA	NA
EpiChron	0.66 (0.26, 1.73)	0.59 (0.22, 1.55)	-0.19	-0.28
SIDIAP	1.44 (0.99, 2.08)	1.29 (0.88, 1.87)	0.38	0.29
CPRD Aurum	0.89 (0.68, 1.17)	0.88 (0.67, 1.16)	-0.21	-0.23

NA: not assessable due to zero cases in the vaccinated or unvaccinated cohorts for HR or in both cohorts for RD

10.2.3.9. Bell's palsy

Bell's palsy events could be identified in all data sources, except in Pedianet, where no Bell's palsy events were identified within the risk window. The incidence rates ranged from 1.14 per 10,000 person-years (95% CI: 0.55, 2.10) in PHARMO to 7.27 per 10,000 person-years (95% CI: 6.21, 8.46) in SIDIAP in the vaccinated cohorts. In the unvaccinated cohorts these ranged from 1.60 per 10,000 person-years (95% CI: 0.91, 2.80) in PHARMO to 7.76 per 10,000 person-years (95% CI: 3.30, 18.25) in EpiChron. The cumulative incidence was below 1 per 10,000 individuals in both cohorts in all data sources except in the unvaccinated cohort in EpiChron where the cumulative incidence was 1.01 per 10,000 individuals (95% CI: 0.13, 1.89). The incidence was similar in the different age groups.

The matched HRs were 1.15 (95% CI: 0.88, 1.50) in NHR, 0.72 (95% CI: 0.31, 1.65) in PHARMO, 0.91 (95% CI: 0.36, 2.30) in EpiChron, 1.00 (95% CI: 0.78, 1.28) in SIDIAP, and 0.98 (95% CI: 0.75, 1.28) in CPRD Aurum. The adjusted HRs were 1.15 (95% CI: 0.88, 1.50) in NHR, 0.65 (95% CI: 0.28, 1.51) in PHARMO, 0.84 95% CI: (95% CI: 0.34, 2.09) in EpiChron, 0.96 (95% CI: 0.75, 1.24) in SIDIAP, and 0.99 (95% CI: 0.75, 1.29) in CPRD Aurum. The lower limits of the 95% CIs for the HRs were above 1 in the matched and adjusted results for Bells's palsy assessed within a risk window of 42 days.

Table 33. Risk estimates (95% CI) per 10,000 person-years (PY) for Bell's palsy within 42 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source

	Vaccinated				Unvaccinated			
Data source	**Events (n)**	**Cumulative incidence (95% CI)**	**Person-years (PY)**	**Incidence rate (95% CI)**	**Events (n)**	**Cumulative incidence (95% CI)**	**Person-years (PY)**	**Incidence rate (95% CI)**
Pedianet	0	0 (0, NC)	1,036	0 (0, NC)	0	0 (0, NC)	1,037	0 (0, NC)
NHR	166	0.74 (0.63, 0.86)	257,184	6.45 (5.51, 7.51)	144	0.63 (0.49, 0.78)	256,858	5.61 (4.49, 7.01)
PHARMO	10	0.12 (0.05, 0.20)	87,393	1.14 (0.55, 2.10)	14	0.19 (0.08, 0.30)	87,563	1.60 (0.91, 2.80)
EpiChron	31	0.86 (0.55, 1.17)	43,848	7.07 (4.80, 10.04)	34	1.01 (0.13, 1.89)	43,803	7.76 (3.30, 18.25)
SIDIAP	167	0.82 (0.69, 0.95)	229,708	7.27 (6.21, 8.46)	167	0.80 (0.64, 0.97)	229,708	7.27 (5.96, 8.88)
CPRD Aurum	114	0.37 (0.30, 0.44)	348,927	3.27 (2.70, 3.92)	116	0.38 (0.30, 0.46)	347,605	3.34 (2.72, 4.09)

NC: not calculable
Note: Estimation of confidence intervals differs between vaccinated and unvaccinated, since the unvaccinated estimate is a generalised estimating equation (GEE) estimates (to account for individuals who were matched to more than one vaccinated individual). When NA (not-assessable) is listed for the 1-KM it means that there is no estimate for the duration of follow-up specified as risk interval, meaning that there was not any patient who reached the end of the risk window. The vaccinated and unvaccinated cohorts were matched on age, sex, geographical region, prior identified COVID-19 infection, prior influenza vaccination, pregnancy, immunocompromised and number of pre-existing conditions considered by the Centers for Disease Control and Prevention (CDC) as risk criteria (0, 1, 2, 3, 4+).

Figure 22. Cumulative incidence of Bell's palsy within 42 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source

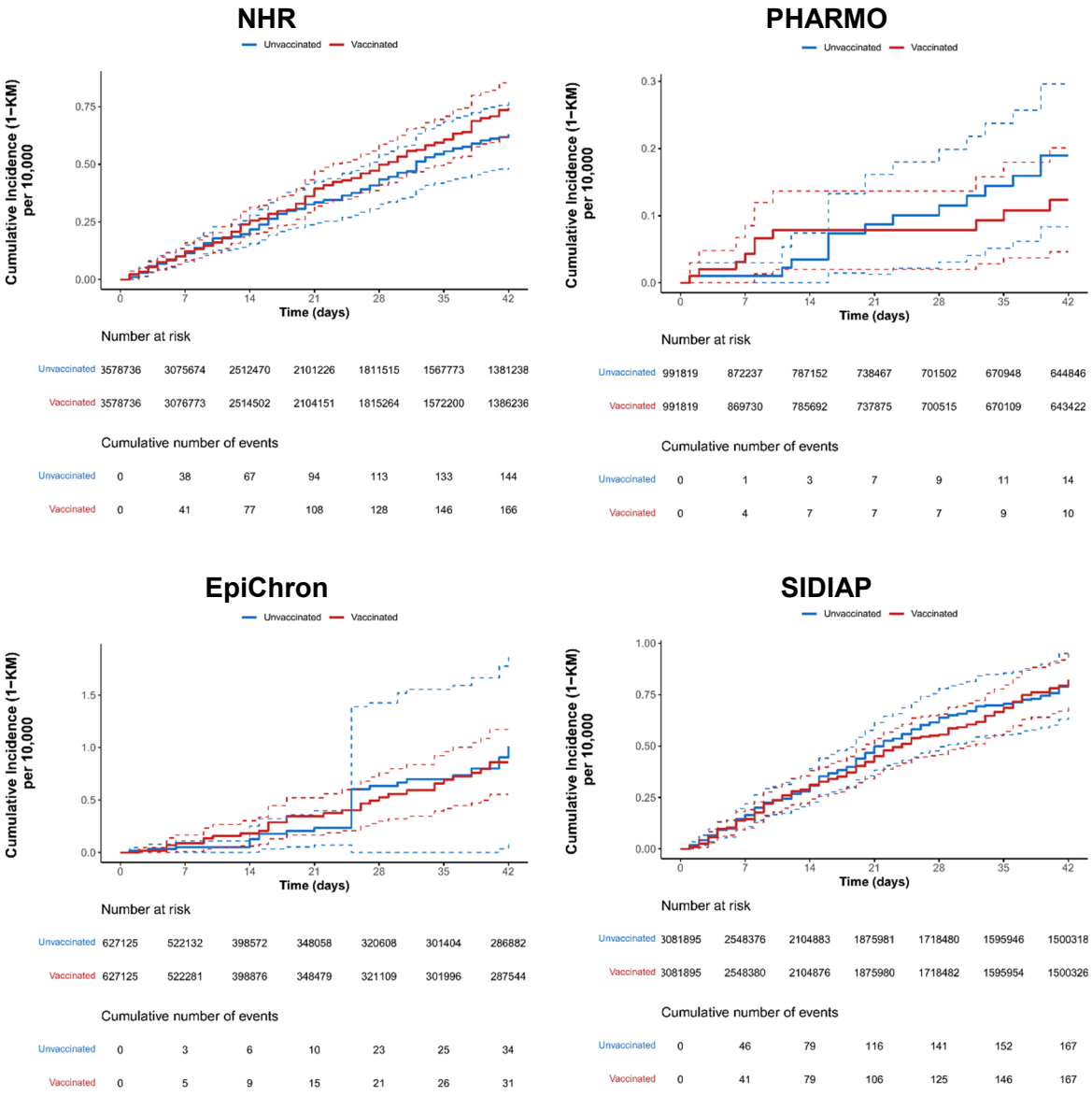
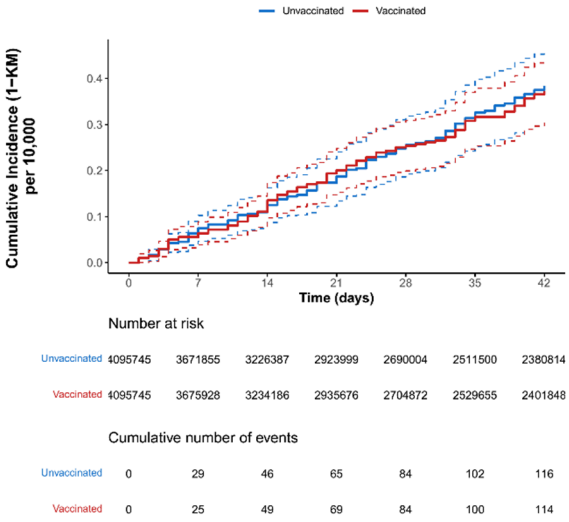


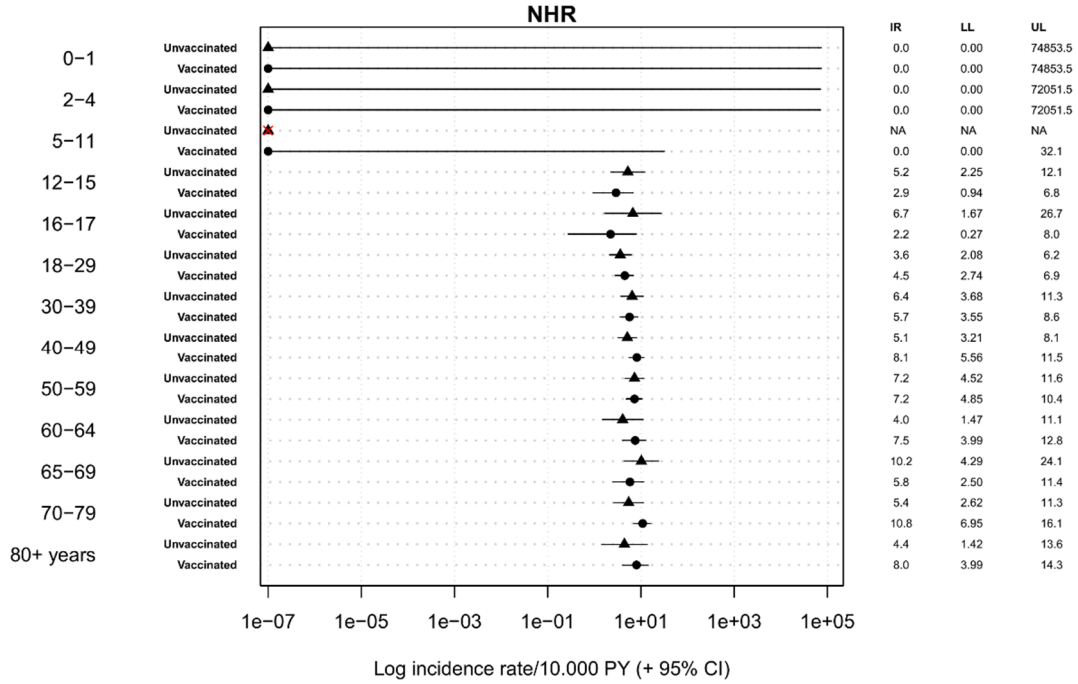
Figure 22. Cumulative incidence of Bell's palsy within 42 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source

CPRD Aurum



Cumulative incidence curves (1 – Kaplan–Meier risk) starting from the day of administration of the first dose of vaccine. Dotted lines represent 95% confidence intervals. The number at risk at each time point and the cumulative number of events during the 42-day risk interval are also shown for each time point. The numerical data correspond to the days indicated by the tick marks on the x-axis.

Figure 23. Forest plot showing incidence rates and 95% confidence intervals for Bell's palsy within 42 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source and by age groups



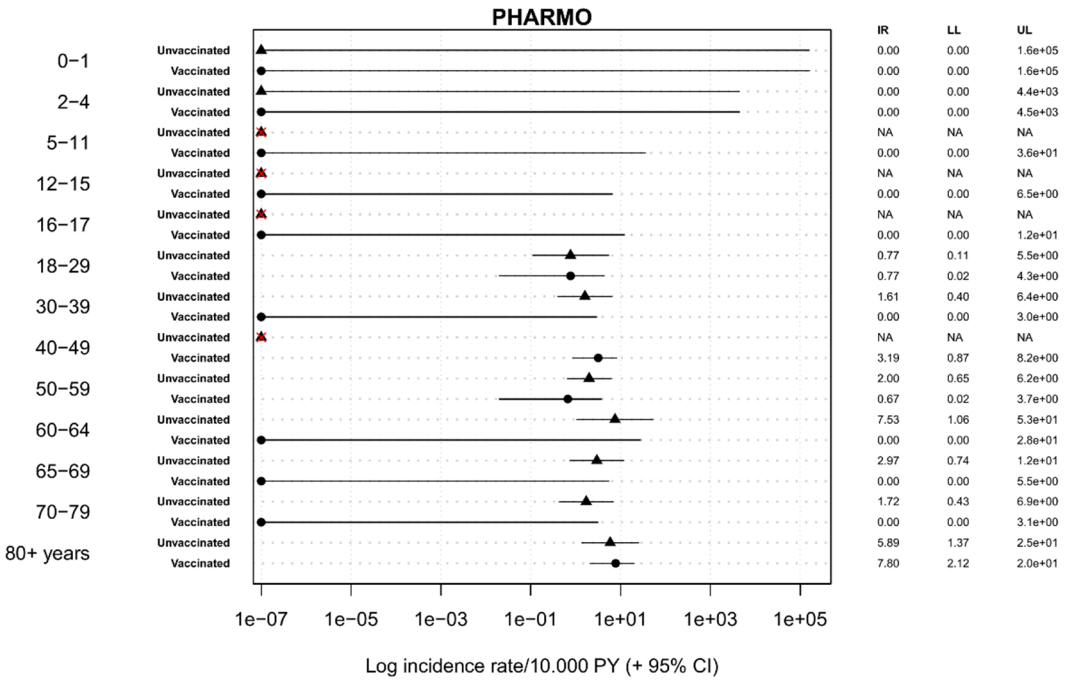
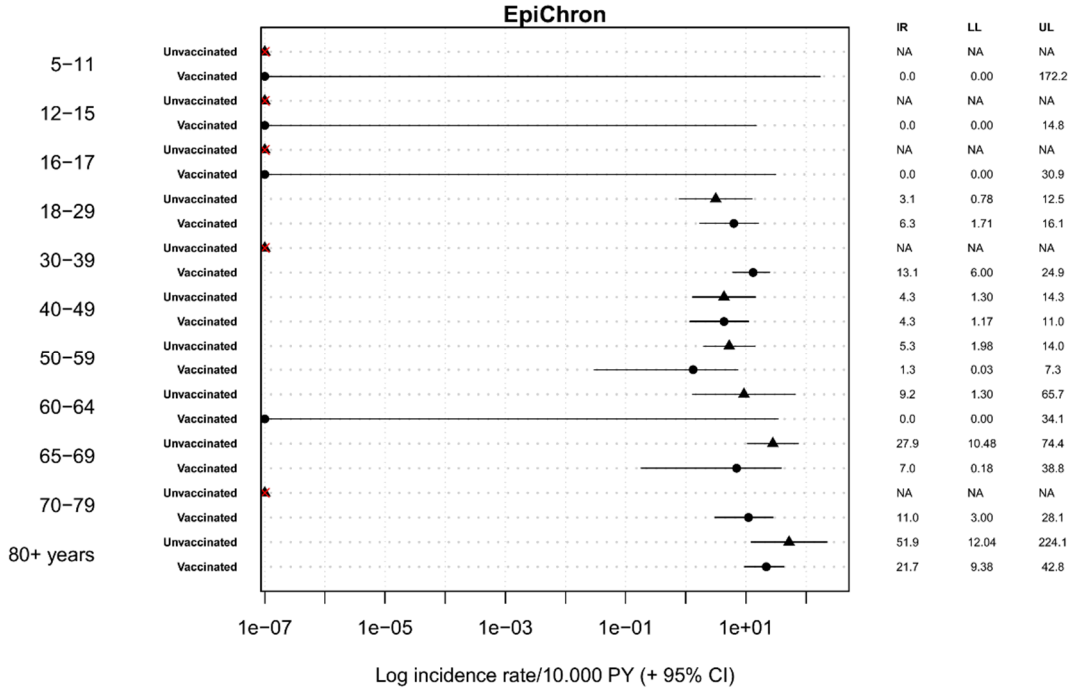


Figure 23. Forest plot showing incidence rates and 95% confidence intervals for Bell's palsy within 42 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source and by age groups



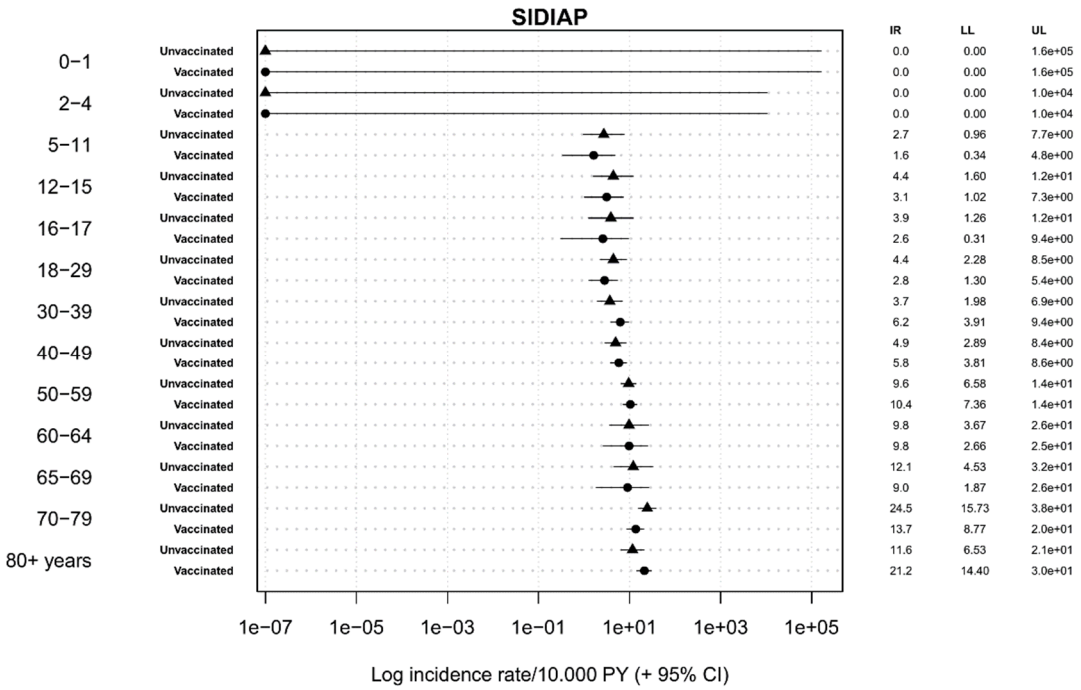


Figure 23. Forest plot showing incidence rates and 95% confidence intervals for Bell's palsy within 42 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source and by age groups

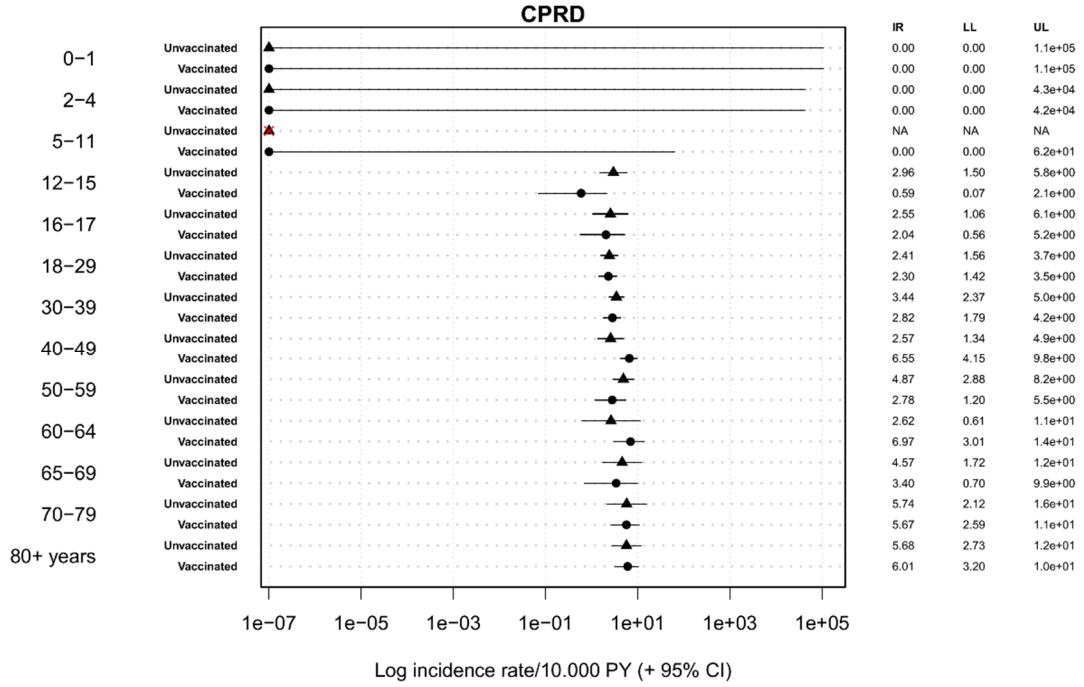


Table 34. Matched and adjusted hazard ratios (HRs) and matched and adjusted risk differences (RDs) per 10,000 person-years and their 95% CIs for Bell's Palsy within 42 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source

	Matched HR (95% CI)	Adjusted HR (95% CI)	Matched RD	Adjusted RD
Pedianet	NA	NA	0	0
NHR	1.15 (0.88, 1.50)	1.15 (0.88, 1.50)	0.11	0.11
PHARMO	0.72 (0.31, 1.65)	0.65 (0.28, 1.51)	-0.07	-0.08
EpiChron	0.91 (0.36, 2.30)	0.84 (0.34, 2.09)	-0.15	-0.22
SIDIAP	1.00 (0.78, 1.28)	0.96 (0.75, 1.24)	0.02	-0.01
CPRD Aurum	0.98 (0.75, 1.28)	0.99 (0.75, 1.29)	-0.01	-0.01

NA: not assessable due to zero cases in the vaccinated or unvaccinated cohorts for HR or in both cohorts for RD

10.2.3.10. Secondary amenorrhoea

Secondary amenorrhoea events were identified in all data sources, with a low number of events in Pedianet and PHARMO. In NHR, EpiChron, SIDIAP and CPRD Aurum, the incidence rates ranged from 9.60 per 10,000 person-years (95% CI: 8.05, 11.35) in NHR to 117.52 per 10,000 person-years (95% CI: 114.02, 121.10) in CPRD Aurum in the vaccinated cohorts. In the unvaccinated cohorts in NHR, EpiChron, SIDIAP and CPRD Aurum these ranged from 5.24 per 10,000 person-years (95% CI: 3.88, 6.60) in NHR to 44.50 per 10,000 person-years (95% CI: 42.47, 46.53) in CPRD Aurum. The cumulative incidence varied between 4.71 per 10,000 individuals (95% CI: 3.82, 5.59) in NHR and 56.19 per 10,000 individuals (95% CI: 54.44, 57.93) in CPRD Aurum in the vaccinated cohorts and between 5.24 per 10,000 individuals (95% CI: 3.88, 6.60) in NHR and 44.50 per 10,000 individuals (95% CI: 42.47, 46.53) in CPRD Aurum in the unvaccinated cohorts. The cumulative incidence curves of vaccinated and unvaccinated diverged in EpiChron and CPRD Aurum during follow up.

The matched HRs were in 0.91 (95% CI: 0.69, 1.22) in NHR, 0.99 (95% CI: 0.06, 15.60) in PHARMO, 1.91 (95% CI: 1.50, 2.43) in EpiChron, 1.05 (95% CI: 0.97, 1.14) in SIDIAP, and 1.32 (95% CI: 1.25, 1.39) in CPRD Aurum. The adjusted HRs were 0.91 (95% CI: 0.69, 1.21) in NHR, 0.77 (95% CI: 0.05, 11.99) in PHARMO, 1.71 (95% CI: 1.34, 2.18) in EpiChron, 0.99 (95% CI: 0.91, 1.07) in SIDIAP, and 1.24 (95% CI: 1.17, 1.30) in CPRD Aurum. Differences were observed in the incidence of secondary amenorrhoea between the vaccinated and unvaccinated cohorts in EpiChron and CPRD Aurum.

Table 35. Risk estimates (95% CI) per 10,000 person-years (PY) for secondary amenorrhoea within 183 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source

	Vaccinated				Unvaccinated			
Data source	**Events (n)**	**Cumulative incidence (95% CI)**	**Person-years (PY)**	**Incidence rate (95% CI)**	**Events (n)**	**Cumulative incidence (95% CI)**	**Person-years (PY)**	**Incidence rate (95% CI)**
Pedianet	<5	1.23 (0, 3.65)	NR	2.57 (0.07, 14.33)	0	0 (0, NC)	3,902	0 (0, NC)
NHR	136	4.71 (3.82, 5.59)	141,726	9.60 (8.05, 11.35)	147	5.24 (3.88, 6.60)	139,920	10.51 (8.34, 13.24)
PHARMO	<5	0.07 (0, 0.21)	NR	0.13 (0, 0.73)	<5	0.06 (0, 0.17)	NR	0.13 (0.02, 0.94)
EpiChron	270	34.82 (30.59, 39.05)	38,227	70.63 (62.46, 79.58)	141	17.68 (13.81, 21.55)	38,189	36.92 (29.89, 45.61)
SIDIAP	1,663	47.15 (44.82, 49.49)	176,273	94.34 (89.86, 98.99)	1,582	44.39 (41.32, 47.46)	175,905	89.93 (84.11, 96.16)
CPRD Aurum	4,257	56.19 (54.44, 57.93)	362,239	117.52 (114.02, 121.10)	3,174	44.50 (42.47, 46.53)	356,406	89.06 (85.25, 93.04)

NR: not reportable due to masking of numbers of events <5; NC: not calculable
Note: Estimation of confidence intervals differs between vaccinated and unvaccinated, since the unvaccinated estimate is a generalised estimating equation (GEE) estimates (to account for individuals who were matched to more than one vaccinated individual). When NA (not-assessable) is listed for the 1-KM it means that there is no estimate for the duration of follow-up specified as risk interval, meaning that there was not any patient who reached the end of the risk window. The vaccinated and unvaccinated cohorts were matched on age, sex, geographical region, prior identified COVID-19 infection, prior influenza vaccination, pregnancy, immunocompromised and number of pre-existing conditions considered by the Centers for Disease Control and Prevention (CDC) as risk criteria (0, 1, 2, 3, 4+).

Figure 24. Cumulative incidence of secondary amenorrhoea within 183 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source

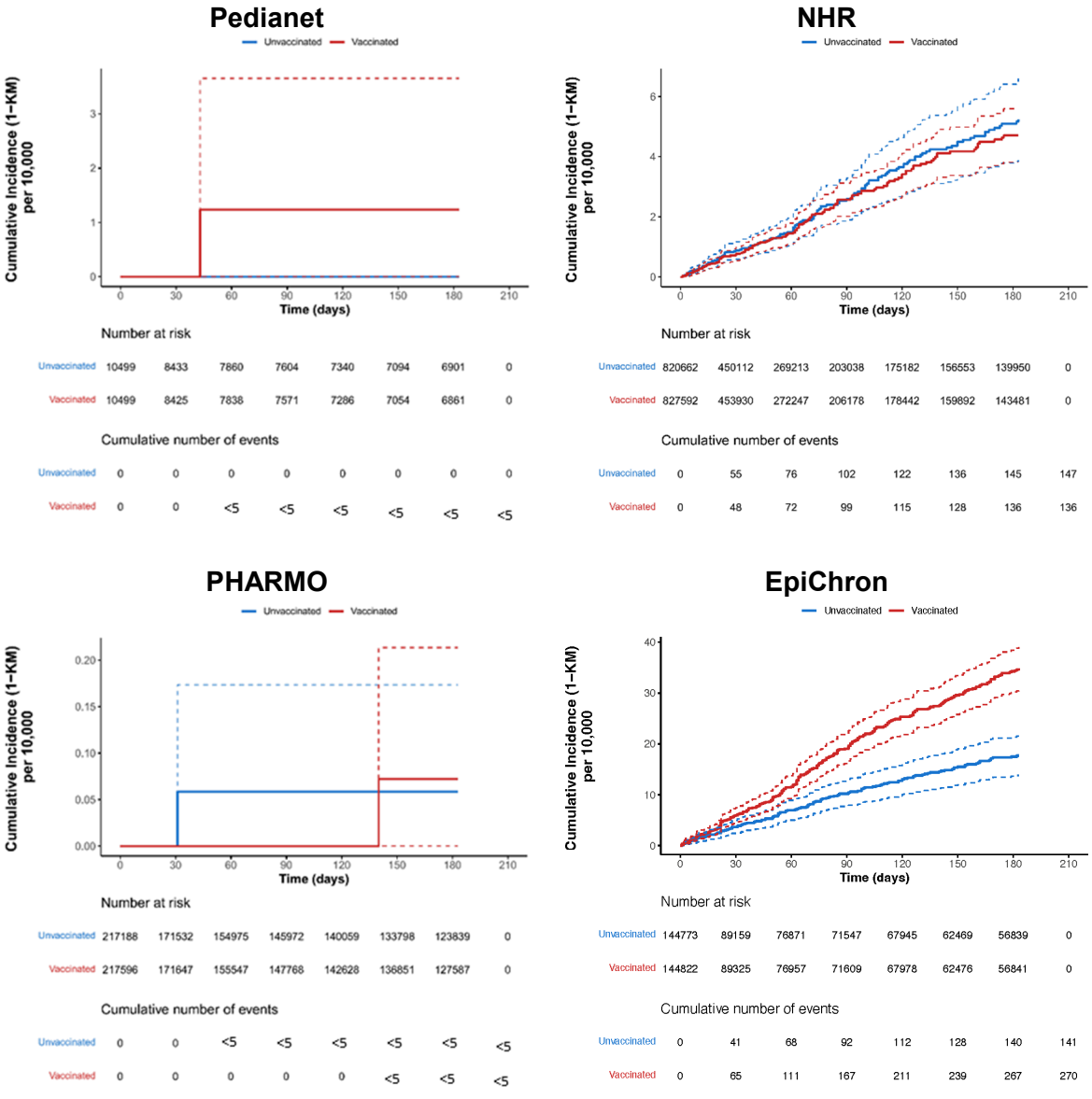
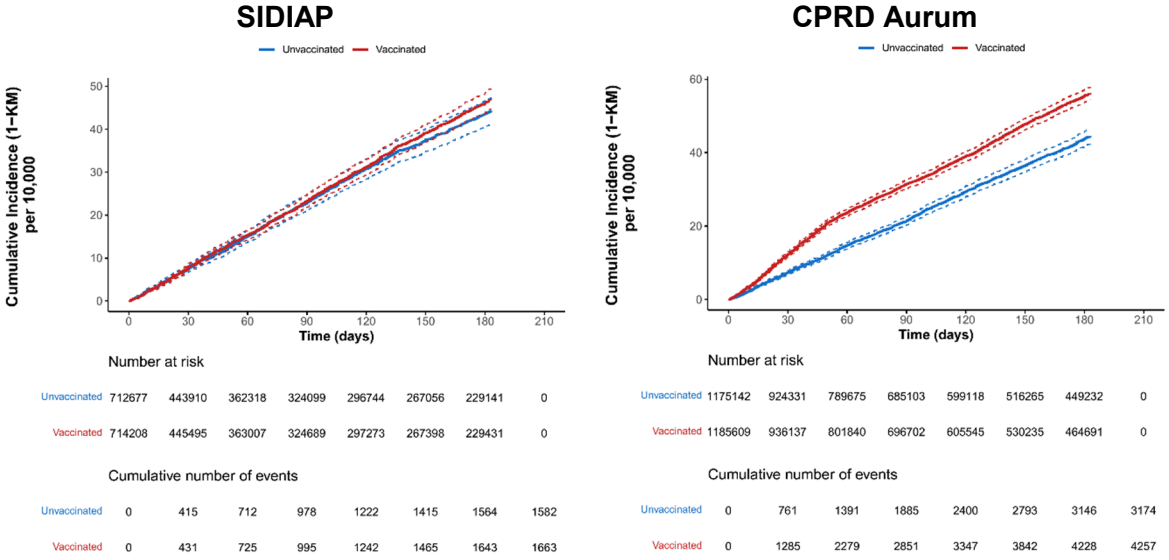


Figure 24. Cumulative incidence of secondary amenorrhoea within 183 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source



Cumulative incidence curves (1 – Kaplan–Meier risk) starting from the day of administration of the first dose of vaccine. Dotted lines represent 95% confidence intervals. The number at risk at each time point and the cumulative number of events during the 183-day risk window are also shown for each time point. The numerical data correspond to the days indicated by the tick marks on the x-axis.

Figure 25. Forest plot showing incidence rates and 95% confidence intervals for secondary amenorrhoea within 183 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source and by age groups

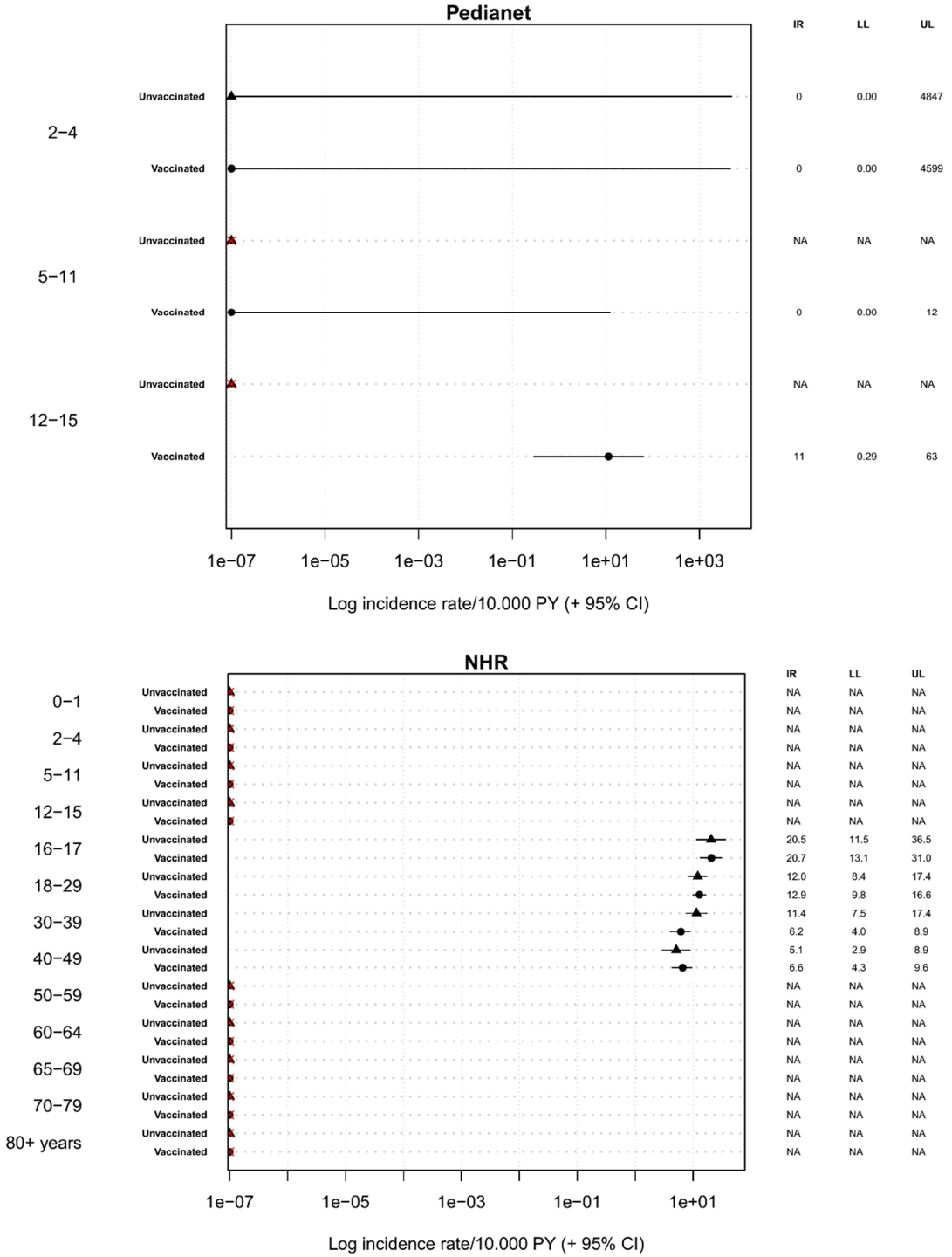
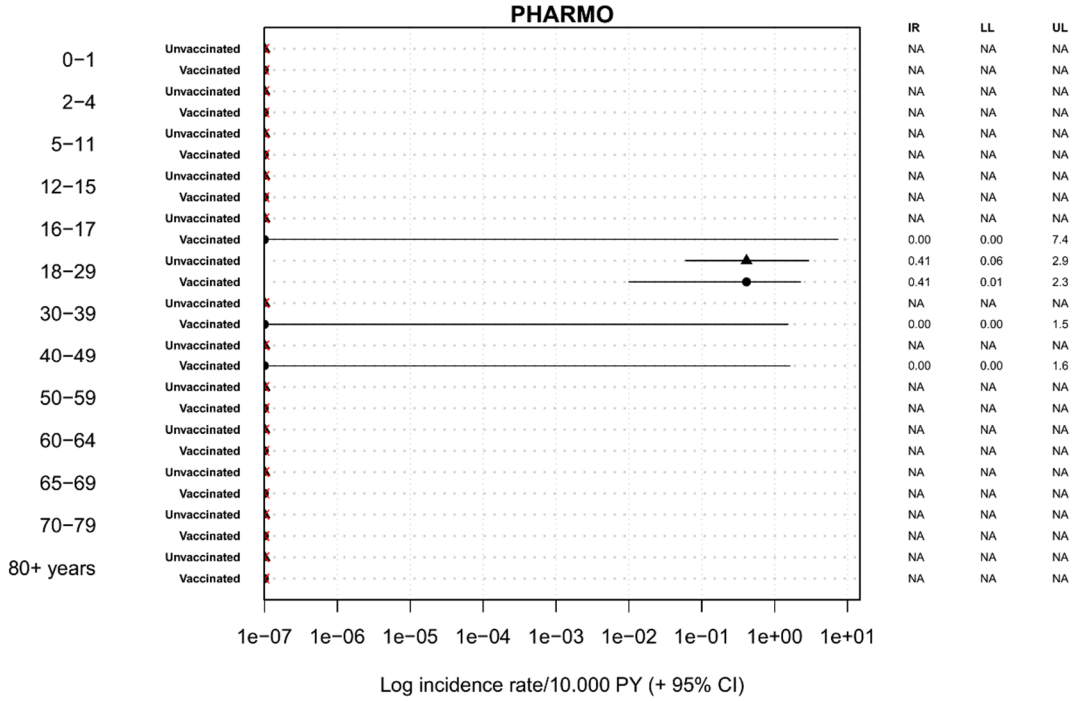


Figure 25. Forest plot showing incidence rates and 95% confidence intervals for secondary amenorrhoea within 183 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source and by age groups



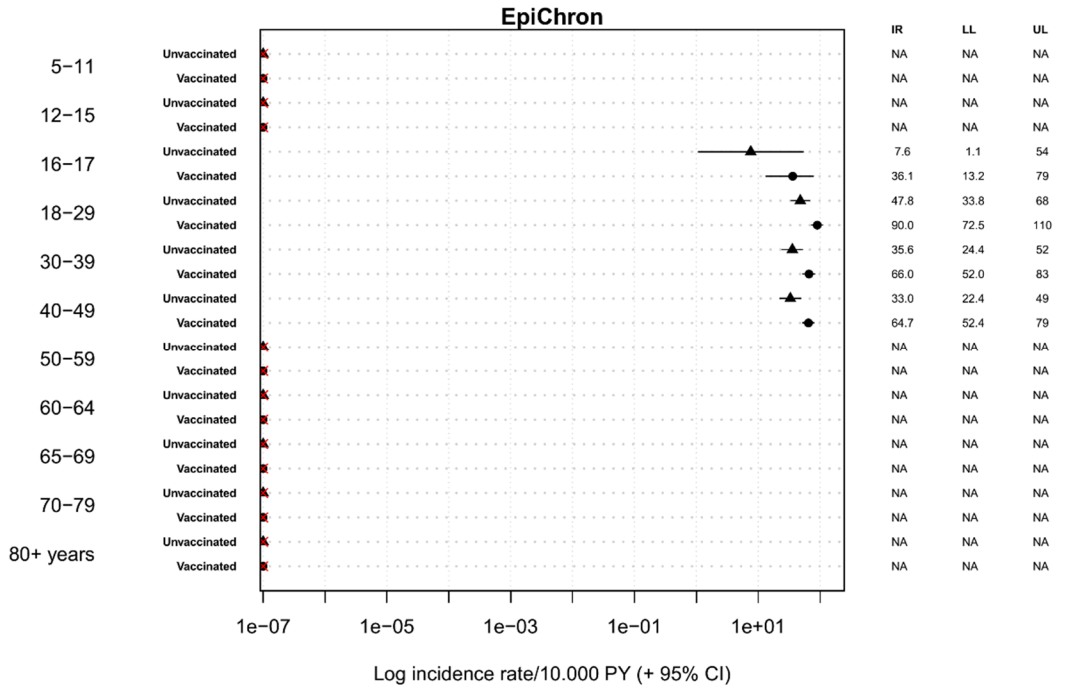


Figure 25. Forest plot showing incidence rates and 95% confidence intervals for secondary amenorrhoea within 183 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source and by age groups

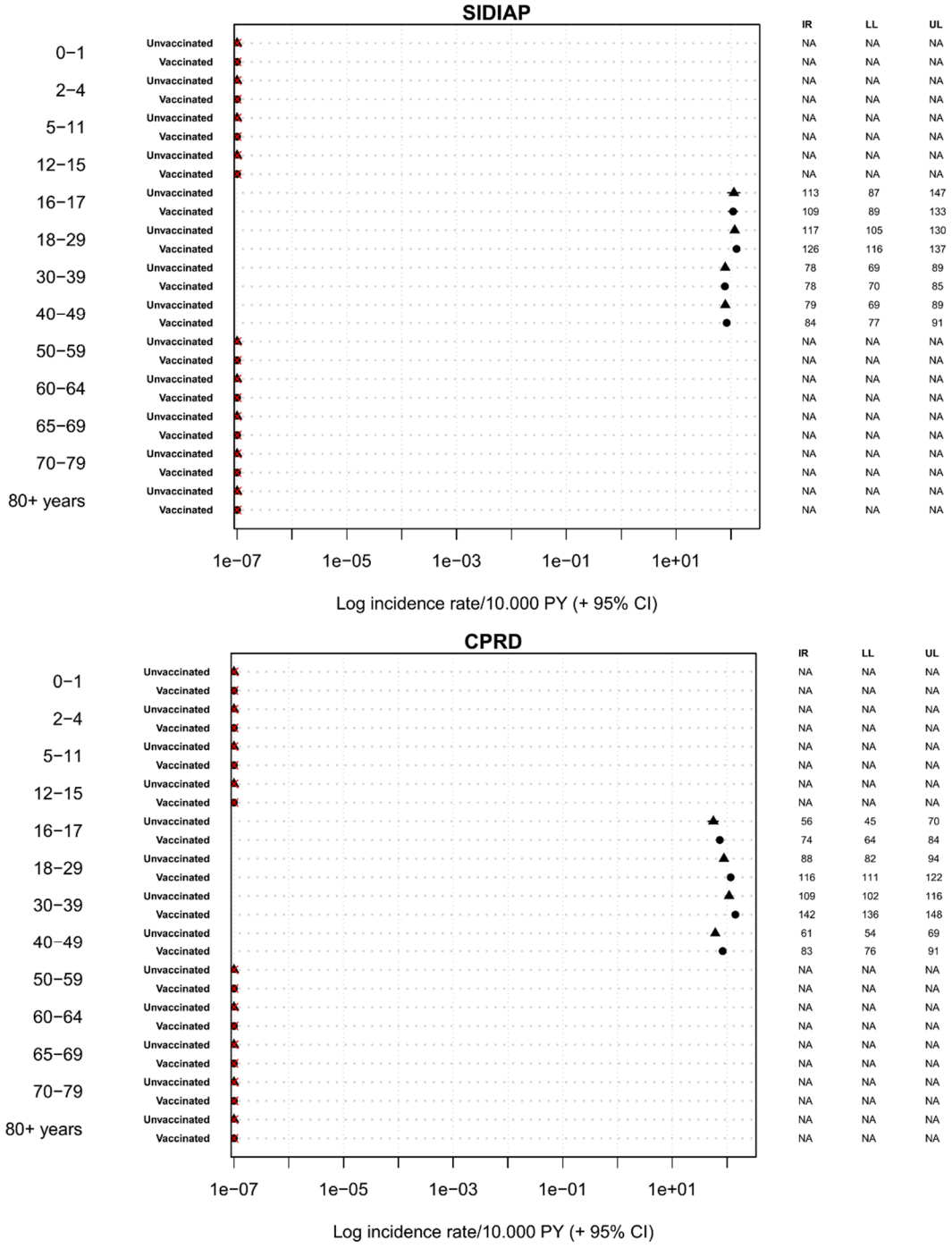


Table 36. Matched hazard ratios (HRs) and matched risk differences (RDs) per 10,000 person-years and their 95% CIs for secondary amenorrhoea within 183 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source

	Matched HR (95% CI)	Adjusted HR (95% CI)	Matched RD	Adjusted RD
Pedianet	NA	NA	1.23	1.11
NHR	0.91 (0.69, 1.22)	0.91 (0.69, 1.21)	-0.54	-0.55
PHARMO	0.99 (0.06, 15.60)	0.77 (0.05, 11.99)	0.01	0
EpiChron	1.91 (1.50, 2.43)	1.71 (1.34, 2.18)	17.14	14.62
SIDIAP	1.05 (0.97, 1.14)	0.99 (0.91, 1.07)	2.76	0.08
CPRD Aurum	1.32 (1.25, 1.39)	1.24 (1.17, 1.30)	11.69	8.39

NA: not assessable due to zero cases in the vaccinated or unvaccinated cohorts for HR or in both cohorts for RD

10.2.3.11. Hypermenorrhoea

Hypermenorrhoea events were identified in Pedianet, EpiChron, and SIDIAP. The incidence rates were 5.15 per 10,000 person-years (95% CI: 0.62, 18.62) in Pedianet, 142.88 per 10,000 person-years (95% CI: 137.34, 148.59) in SIDIAP, and 230.91 per 10,000 person-years (95% CI: 215.72, 246.89) in EpiChron in the vaccinated cohorts. In the unvaccinated cohorts the incidence rates were 7.70 per 10,000 person-years (95% CI: 1.79, 33.20) in Pedianet, 130.74 per 10,000 person-years (95% CI: 123.61, 138.29) in SIDIAP, and 143.95 per 10,000 person-years (95% CI: 128.81, 160.87) in EpiChron. In PHARMO, incidence rates were below 1 with very few cases identified in both cohorts. The cumulative incidence varied between 2.57 per 10,000 individuals (95% CI: 0, 6.15) in Pedianet and 114.59 per 10,000 individuals (95% CI: 106.80, 122.37) in EpiChron in the vaccinated cohorts and between 3.21 per 10,000 individuals (95% CI: 0, 7.99) in Pedianet and 69.56 per 10,000 individuals (95% CI: 61.61, 77.50) in EpiChron in the unvaccinated cohorts. The cumulative incidence curves for the vaccinated and unvaccinated cohorts diverged during follow up in EpiChron and SIDIAP.

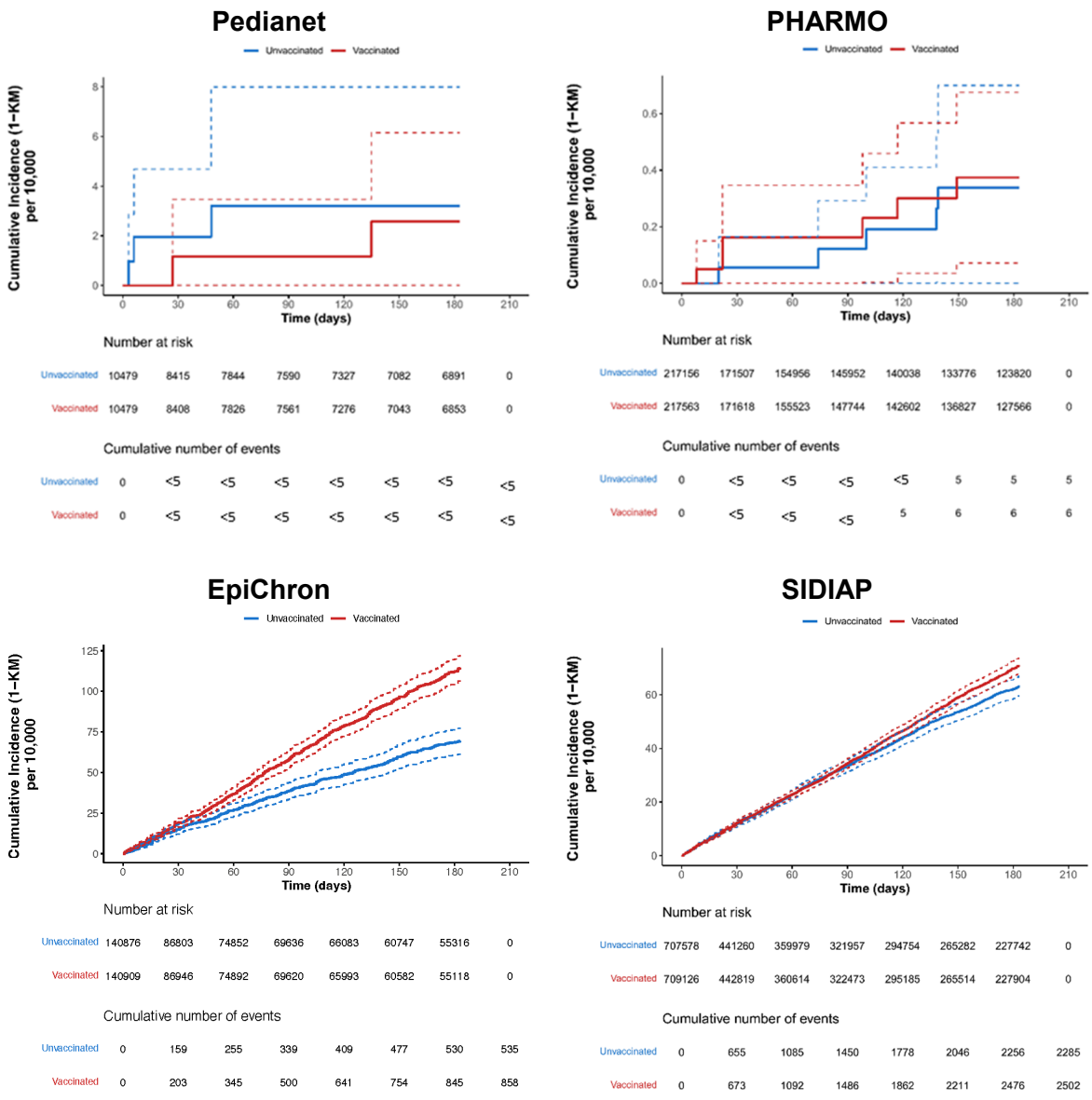
The matched HRs were 0.67 (95% CI: 0.09, 5.01) in Pedianet, 1.60 (95% CI: 1.41, 1.83) in EpiChron, and 1.09 (95% CI: 1.02, 1.17) in SIDIAP. The adjusted HRs were 0.62 (95% CI: 0.08, 4.66) in Pedianet, 1.40 (95% CI: 1.23, 1.60) in EpiChron, and 1.02 (95% CI: 0.95, 1.09) in SIDIAP. In EpiChron the adjusted HRs were above 1 and the lower limits of the 95% Cis were >1.

Table 37. Risk estimates (95% CI) per 10,000 person-years (PY) for hypermenorrhea within 183 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source

	Vaccinated				Unvaccinated			
Data source	**Events (n)**	**Cumulative incidence (95% CI)**	**Person-years (PY)**	**Incidence rate (95% CI)**	**Events (n)**	**Cumulative incidence (95% CI)**	**Person-years (PY)**	**Incidence rate (95% CI)**
Pedianet	<5	2.57 (0, 6.15)	NR	5.15 (0.62, 18.62)	<5	3.21 (0, 7.99)	NR	7.70 (1.79, 33.20)
NHR	NA	NA	NA	NA	NA	NA	NA	NA
PHARMO	6	0.37 (0.07, 0.68)	76,532	0.78 (0.29, 1.71)	5	0.34 (0, 0.70)	75,683	0.66 (0.23, 1.86)
EpiChron	858	114.59 (106.80, 122.37)	37,157	230.91 (215.72, 246.89)	535	69.56 (61.61, 77.50)	37,166	143.95 (128.81, 160.87)
SIDIAP	2,502	70.96 (68.09, 73.83)	175,111	142.88 (137.34, 148.59)	2,285	63.45 (59.74, 67.15)	174,773	130.74 (123.61, 138.29)
CPRD Aurum	NA	NA	NA	NA	NA	NA	NA	NA

NA: not available; NR: not reportable due to masking numbers of events <5
Note: Estimation of confidence intervals differs between vaccinated and unvaccinated, since the unvaccinated estimate is a generalised estimating equation (GEE) estimates (to account for individuals who were matched to more than one vaccinated individual). When NA (not-assessable) is listed for the 1-KM it means that there is no estimate for the duration of follow-up specified as risk interval, meaning that there was not any patient who reached the end of the risk window. The vaccinated and unvaccinated cohorts were matched on age, sex, geographical region, prior identified COVID-19 infection, prior influenza vaccination, pregnancy, immunocompromised and number of pre-existing conditions considered by the Centers for Disease Control and Prevention (CDC) as risk criteria (0, 1, 2, 3, 4+).

Figure 26. Cumulative incidence of hypermenorrhoea within 183 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source



Cumulative incidence curves (1 – Kaplan–Meier risk) starting from the day of administration of the first dose of vaccine. Dotted lines represent 95% confidence intervals. The number at risk at each time point and the cumulative number of events during the 183-day risk window are also shown for each time point. The numerical data correspond to the days indicated by the tick marks on the x-axis.

Figure 27. Forest plot showing incidence rates and 95% confidence intervals for hypermenorrhoea within 183 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source and by age groups

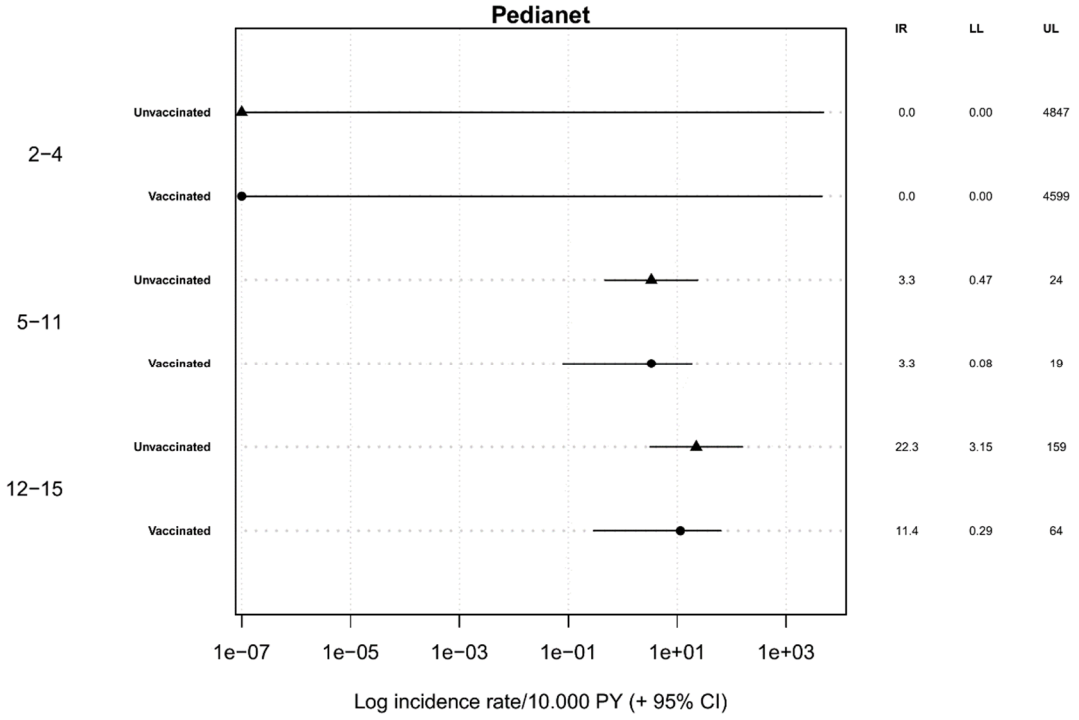


Figure 27. Forest plot showing incidence rates and 95% confidence intervals for hypermenorrhoea within 183 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source and by age groups

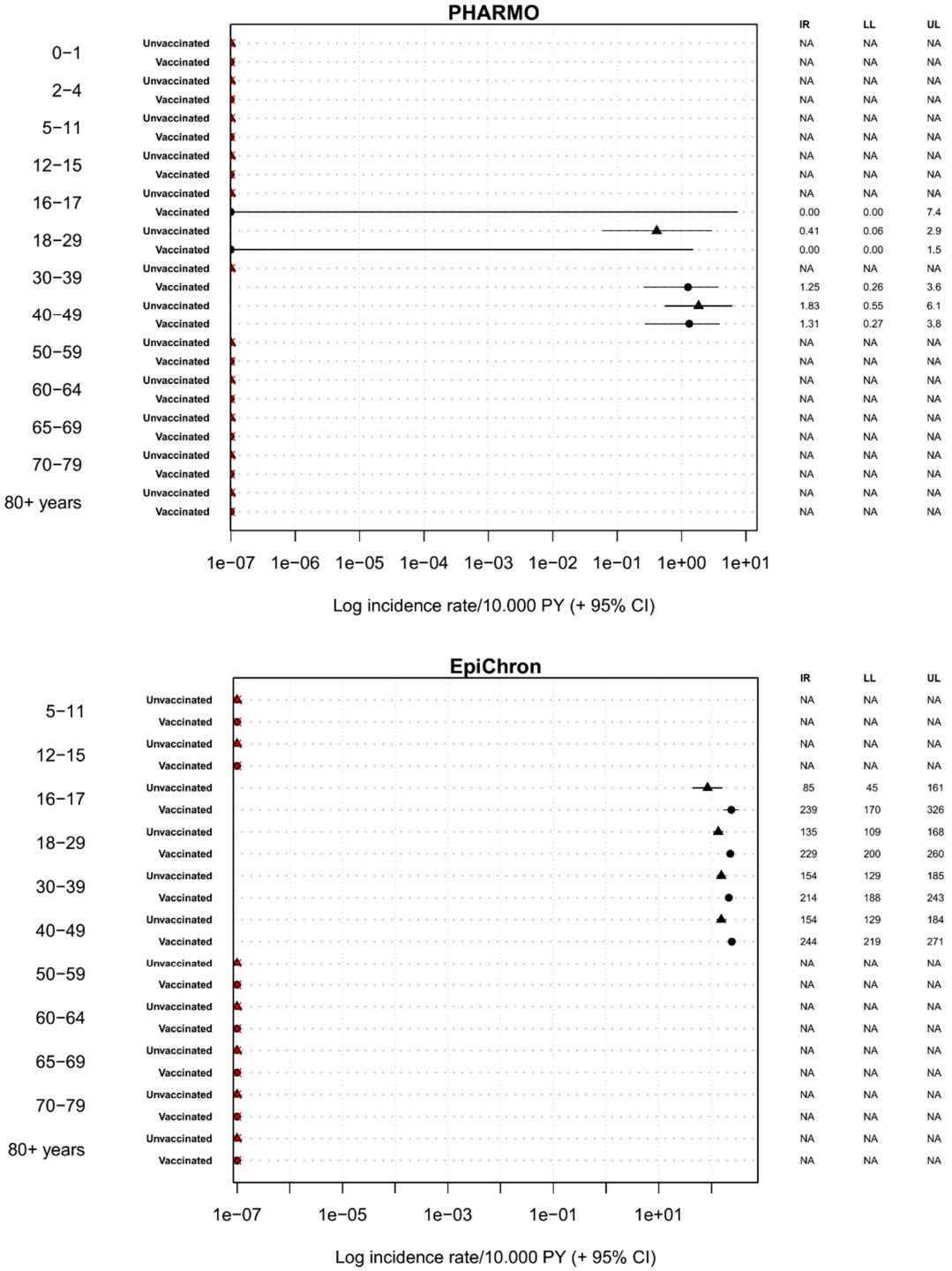


Figure 27. Forest plot showing incidence rates and 95% confidence intervals for hypermenorrhoea within 183 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source and by age groups

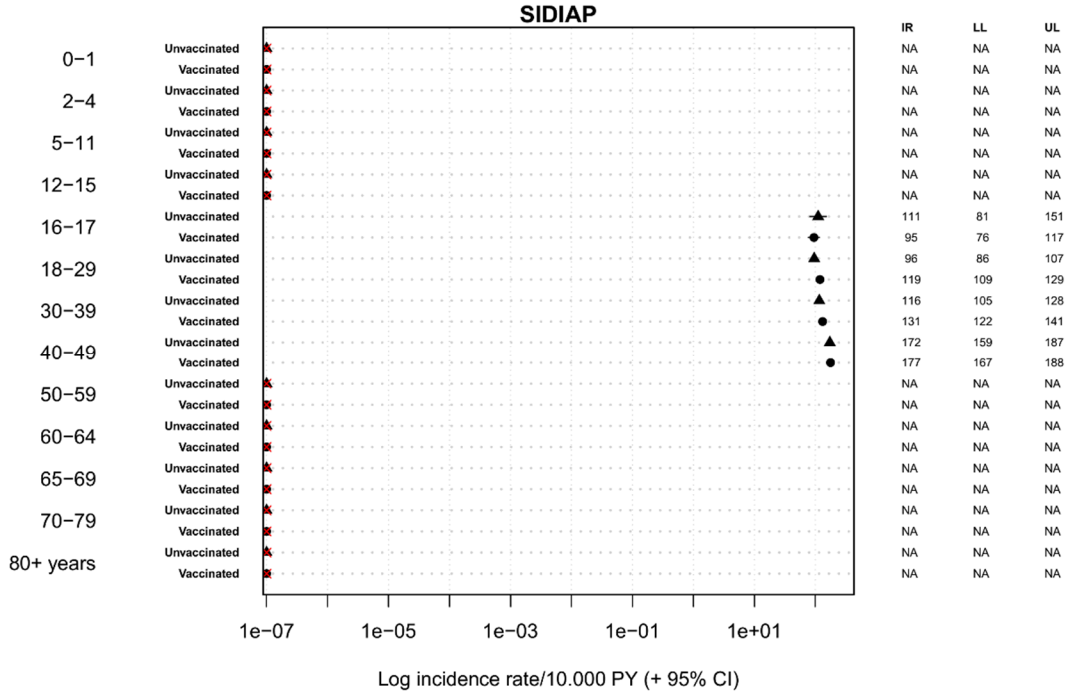


Table 38. Matched and adjusted hazard ratios (HRs) and matched and adjusted risk differences (RDs) per 10,000 person-years and their 95% CIs for hypermenorrhoea within 183 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source

	Matched HR (95% CI)	Adjusted HR (95% CI)	Matched RD	Adjusted RD
Pedianet	0.67 (0.09, 5.01)	0.62 (0.08, 4.66)	-0.64	-0.87
NHR	NA	NA	NA	NA
PHARMO	1.19 (0.32, 4.41)	1.18 (0.31, 4.47)	0.04	0.04
EpiChron	1.60 (1.41, 1.83)	1.40 (1.23, 1.60)	45.03	33.57
SIDIAP	1.09 (1.02, 1.17)	1.02 (0.95, 1.09)	7.52	2.94
CPRD Aurum	NA	NA	NA	NA

NA: not assessable due to zero cases in the vaccinated or unvaccinated cohorts for HR or in both cohorts for RD

10.3. Other analyses

None.

10.4. Adverse events / adverse reactions

No adverse events (AEs), other than those reported in aggregated data, 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. Key results

This fifth interim report provides updated results on the estimated incidence rates (IRs) and hazard ratios (HRs) for the 37 prespecified AESIs (Table 16) in a vaccinated cohort of individuals who received at least one dose of the Pfizer-BioNTech COVID-19 vaccine and in a matched unvaccinated comparator cohort. Results are reported for two recently added AESIs, i.e., glomerulonephritis and cerebral venous sinus thrombosis (CVST).

These results are based on data from six data sources in five countries: Pedianet in Italy, PHARMO in the Netherlands, NHR in Norway, EpiChron and SIDIAP in Spain and CPRD Aurum in the UK. No data from ARS (IT) could be extracted and analysed for this fifth interim report because of national and regional reassessment of their ability to provide public data for PASS. Results from HSD (IT) have also not been included because of data validity concerns regarding misclassification of exposure due to Pfizer-BioNTech COVID-19 vaccine registration practices among GP practices in the data source coverage area.

In this report we included data up to 31 December 2022 from Pedianet, 30 June 2023 (i.e., GP data) and 31 December 2022 (i.e., hospital data) from PHARMO, 30 June 2023 from SIDIAP, 31 July 2023 from EpiChron, 31 December 2022 from NHR, and 21 March 2022 from CPRD Aurum. The period covered in the analysed data included months when participants could receive up to five doses of the Pfizer-BioNTech COVID-19 vaccine, which was implemented in many countries end of summer 2022. Hence, data for individuals who had received up to three booster doses of the Pfizer-BioNTech COVID-19 vaccine have also been included.

In this fifth interim report, we have used all matching criteria except pregnancy for CPRD and PHARMO for reasons of ongoing pregnancy data and script validations and for PEDIANET which is a paediatric database only, socio-economic status for CPRD, and influenza vaccination for NHR. The balance between the matched vaccinated and unvaccinated cohorts was verified. Matching on pregnancy status was done using a pregnancy algorithm developed by the ConcePTION project.[18] We used a negative control outcome, i.e., COVID-19 in the first 12 days after time zero and the results are compatible

with the absence of relevant baseline residual confounding. Because the use of this negative control outcome assumes that the confounders for COVID-19 disease are equally relevant for all AESIs, effect estimates were additionally adjusted via IPT weighting, since similar estimates with and without IPT weighting would support this assumption. This was what we observed, thus our matching process generated comparable cohorts.

These results should be considered as the last interim results from a long-term safety surveillance study. Limitations from prior reports have been identified and issues have been corrected, such as the inclusion of IPT adjusted results, improved algorithms to clean the vaccination information, refined and more specific disease code lists, and performance of matching based on all matching variables, including socio-economic status. We will continue to work on resolving outstanding issues for the final report.

11.1.1. Important information on data sources

Two data sources, ARS and HSD from Italy, could not contribute data to this fifth interim report:

- Data from ARS were reported in interim reports 1 and 2, but since then data have not been re-extracted due to national and regional reassessment of their ability to provide public data for PASS studies.

- Data on COVID-19 vaccination were missing for a high percentage of individuals in the HSD data source (Italian GP databases), and it was, therefore, not considered as fit for purpose. In Italy, GPs were involved in the COVID-19 vaccination campaign only for their patients aged 80 years and older in March 2021. There was no automated system to collect data on patients' vaccination status, and recording this information depended entirely on the efforts of the GPs. Since it is mandatory for Italian GPs to collect vaccine-related information for their own electronic dossiers, the accuracy of vaccine registration is expected to improve over time. However, we cannot exclude the possibility that recording of the vaccine brand may be selective. We will continue to monitor data on vaccine uptake in HSD to assess whether they are fit for purpose.

In the other data sources, data for events can originate from different data sources (i.e., GP, emergency visits, hospital discharge data sources, outpatient specialist diagnoses). This may have an impact on the estimates for the incidence rates as shown in a recent study.[19]

Pedianet is an Italian paediatric general practice research database that includes children until the age of 14, after which they are transferred to general practitioners. The vaccination campaign for children in Italy started on 31 May 2021, which is reflected by the different calendar time of first vaccination. AESIs are based on diagnoses in the paediatricians' record, which may include information from hospitalisation, when it is reported back to them, but this may not be complete, which is why Pedianet could not contribute data for all AESIs.

The data from PHARMO in this fifth interim report were extracted from GP records up to 30 June 2023 and from hospital records up to 31 December 2022. The coding system used in the PHARMO GP databases is ICPC, which is not as granular as ICD coding. Additional AESI events were identified using free text searching. Although substantial improvements in the free text identification and the ETL script for variables and AESIs have been made, the

number of events and event rates tend to be lower in this GP data source compared with the other data sources, that also include data from secondary care settings.

The EpiChron data source included diagnosis codes from general practitioners and from hospital discharges up to 31 July 2023 for this fifth interim report.

The SIDIAP data source included data from general practitioner and hospital discharge records up to 30 June 2023 for this report.

The NHR data source provided GP data from the Norway Control and Payment of Primary Health Care Refunds (KUHR) and hospital data from the Norwegian Patient Registry up to 31 December 2022 for this report. The KUHR GP data source is at max 4 digits for ICPC2 codes because more details digits are not used in the KUHR GP data source. This can lead to a less specific identification of events resulting in higher event and incident numbers from Norway.

The CPRD Aurum data source provided data from primary care medical records up to 21 March 2022 for this report. Only information which has been coded in the medical records, including information from hospital discharge letters, can be used. A coding system specific to CPRD Aurum is used to determine event diagnoses, prescriptions, and vaccine administration (MedCodeID for diagnoses and ProdCodeID for medicinal products). No free text is available.

11.1.2. Total vaccinated population and vaccination patterns

The number of individuals who received a first dose of Pfizer-BioNTech COVID-19 vaccine and were included in this fifth report was 12,613,349. A total of 10,665,306 (84.6%) individuals received a second dose of the Pfizer-BioNTech COVID-19 vaccine. The second dose was mainly administered within six weeks after the first dose; 16.6% individuals had an interval of more than six weeks between the first and second doses in all data sources, except CPRD Aurum where 81.27% were vaccinated with the second dose outside the 6-week window. This longer interval between the doses in the UK is explained by The higher percentage of individuals with a longer interval between the first and second doses in the UK (CPRD Aurum) is because the Joint Committee on Vaccination and Immunisation (JCVI) recommended a 12-week interval between the first and second doses in order to prioritised the administration of first doses to a large percentage of the population, before administering the second dose.[20] In other data sources the percentage of individuals who had an interval longer than six weeks between the first and second doses varied from 2.34% in Pedianet to 22.75% in PHARMO.

A total of 26,980 pregnant women in the NHR, EpiChron and SIDIAP data sources received a first dose of the Pfizer-BioNTech COVID-19 vaccine and satisfied the inclusion criteria. Among these women 9,234 (34.23%) received the dose during their first trimester of pregnancy and 9,763 (36.19%) in their second trimester. Pregnancy data were not available from PHARMO or CPRD Aurum for this report, but they are expected to be available for the final report.

Overall, 4,642,445 individuals had a recorded third dose of the Pfizer vaccine which is 36.81% of those who received a 1st dose. The mean age of these individuals was higher than those who had received at least a first dose (except in PHARMO), reflecting the

targeted roll out of booster doses to elderly individuals first. The interval between the second and third doses varied between data sources with the median interval ranging from 21 weeks in Pedianet to 31 weeks in SIDIAP.

At the time of database lock, 1,021,555 (8.10%) individuals had received a fourth dose and 7,801 (0.06%) a fifth dose of the Pfizer-BioNTech COVID-19 vaccine.

11.1.3. Matched cohorts

In this fifth interim report, individuals were matched in each data source on the following pre-specified matching variables: calendar date of time zero, age, sex, prior COVID-19 diagnosis, place of residence, at least one influenza vaccine (not in NHR), pregnancy (not in PHARMO, CPRD Aurum, and Pedianet), immunocompromised status, pre-existing conditions considered as risk factors for severe COVID-19 by the Centers for Disease Control and Prevention (CDC) and socio-economic status (not in CPRD).

From a total of 12,613,349 individuals who received a first dose of the Pfizer-BioNTech COVID-19 vaccine and were included in the study, 12,400,847 (98.32%) could be matched with an unvaccinated individual. The median follow-up time after the first dose varied from 0.9 months in NHR to 11.3 months in Pedianet. Censoring of follow-up was mostly due to unvaccinated individuals being vaccinated with a COVID-19 vaccine, which also resulted in the censoring of the matched vaccinated individual.

Many individuals who were initially included in the matched unvaccinated cohort subsequently received a Pfizer-BioNTech COVID-19 vaccine. A total of 6,217,296 (50.14%) matched unvaccinated individuals were censored because of receipt of a COVID-19 vaccine (Pfizer-BioNTech COVID-19 vaccine or a non-Pfizer-BioNTech COVID-19 vaccine) When this occurred, the follow-up of the unvaccinated individual was censored (as was that for the matched vaccinated individual), and the unvaccinated individual entered the vaccinated cohort with time zero as the date of vaccination if an unvaccinated individual could be matched to them. This had an impact on the duration of follow-up, especially for events with long risk windows. However, this is inevitable since COVID-19 vaccination uptake rates are high in the participating countries.

The median age of matched vaccinated individuals was highest in PHARMO (49 years), followed by EpiChron (48 years), NHR (47 years), SIDIAP (45 years), and CPRD Aurum (36 years). The median age in Pedianet, a paediatric database, was 10 years, with only a few children aged under 5 years captured. We assessed lifestyle factors, healthcare use, prevalence of comorbidity and comorbidity summary scores, as well as the use of comedications and vaccines prior to time zero. Information on long-term care facility residency and healthcare worker or essential worker status could not be identified in the data sources. The lifestyle indicators (i.e., smoking status and BMI), which were available from PHARMO for about 26% and 21% of the vaccinated and unvaccinated cohorts, respectively, EpiChron for about 24% and 23% of the vaccinated and unvaccinated cohorts, respectively and SIDIAP for about 55% and 54% of the vaccinated and unvaccinated cohorts, respectively. This should be interpreted cautiously because of the high percentage of missing data for these variables. The healthcare use indicators showed a similar distribution between the vaccinated and unvaccinated cohorts.

PHARMO had missing data on almost all other vaccines, as these vaccinations are not registered by the GPs in the Netherlands. Despite the differences in prevalence of covariates between data sources, which may be explained by the type of data source, the age of the population and experience with using ETL, the assessment of the absolute standardised differences (ASDs) between the vaccinated and unvaccinated cohorts within each data source for the prevalence of baseline demographic characteristics, comorbidities and comedications did not show differences or imbalance.

There are now more than 12 million vaccinated individuals and 12 million unvaccinated individuals in the study, which, in the pooled analysis that is planned for the final report, would be sufficient to detect a risk ratio of 3 for Guillain-Barré syndrome (incidence rate of 1 in 100,000 person-years and a risk window of 42 days), assuming a two-sided alpha of 0.95 and a power of 80%.

11.1.4. Negative control

A difference in the cumulative incidence of symptomatic SARS-CoV-2 infections at day 12 of approximately 0.1% was considered as proof of non-relevant residual confounding based on an observational study of the effectiveness of the Pfizer-BioNTech COVID-19 vaccine in adults.[13]. We compared the incidences of COVID-19 in the first 12 days after vaccination in the vaccinated and unvaccinated cohorts to assess baseline exchangeability. In NHR, PHARMO, EpiChron SIDIAP and CPRD Aurum the differences for the incidences were less than 1 per 1,000 individuals. In Pedianet the difference between the incidences of COVID-19 in the first 12 days was 2 per 1,000 cases but this is not suggestive of confounding as incidence rates in the pediatric population were 10 times those in the adult population and the Kaplan-Meier curves showed similar increases in vaccinated and unvaccinated. Consequently, we considered that the matching process achieved the required balance between the cohorts. Regardless of the negative control results, as we are dealing with outcomes that have long risk windows, the analyses were performed in the matched cohorts with PS adjustments to control for the effect of potential confounding.

11.1.5. Incidence rates and hazard ratios for AESIs

Since the analyses in previous interim reports, the AESIs code lists have been re-reviewed by clinical epidemiologists within VAC4EU, and tags for specific and sensitive codes were assessed per descendant code, instead of at the concept level. This may have led to changes in some of the event rates.

The following 11 AESIs, are discussed below either at the request of EMA or because they have been recently included in the list of AESIs.

11.1.5.1. Acute cardiovascular injury

Acute cardiovascular injury (ACI) was defined as a composite endpoint. The definition is based on American College of Cardiology/American Heart Association Task Force definition, i.e., acute cardiovascular injury is an acute illness that is physician-diagnosed as a cardiovascular injury.[21] Acute cardiovascular injury refers to a broad spectrum of cardiac pathology including microangiopathy, heart failure, stress cardiomyopathy, coronary artery disease, myocarditis, pericarditis and cardiac arrhythmias, usually associated with abnormalities on ECG, echocardiography or cardiac MRI, and elevated biochemical markers. The study variable is operationalised as an algorithm including diagnostic codes

identifying microangiopathy, acute myocardial infarction, stress cardiomyopathy, heart failure, coronary artery disease, myocarditis, pericarditis, and arrhythmia.

In this report, the adjusted HRs and the lower limits of the 95% CIs for ACI were above 1 in PHARMO with a HR of 1.38 (95% CI: 1.31, 1.45), in EpiChron with a HR of 1.10 (95% CI: 1.03, 1.18), and in CPRD Aurum with a HR of 1.23 (95% CI: 1.18, 1.27) in CPRD Aurum. In CPRD Aurum and EpiChron the cumulative incidence showed divergence between vaccinated and unvaccinated from around day 80 within the 365 days risk window and in PHARMO from around day 30.

In PHARMO the identification of ACI was mainly driven by events identified with the ICPC GP symptom code 'palpitations' (K04) and ICD10 hospital code for atrial fibrillation and atrial flutter unspecified (I489), and acute subendocardial myocardial infarction (I214), followed by ICD10 heart failure unspecified (I509), and ICPC code for acute myocardial infarction (K75) and atrial fibrillation/flutter (K78). In CPRD Aurum the highest code counts were for MedCodelds for atrial fibrillation (MedCodeId 82343012) and ischaemic heart disease (MedCodeId 2534664018). In EpiChron, ACI was mainly identified through the ICD9CM codes for atrial fibrillation (427.31) and tachycardia unspecified (785.0) followed by ICD10CM codes for heart failure unspecified (I50.9) and unspecified atrial fibrillation (I48.91) and ICD9CM codes for acute myocardial infarction of unspecified site episode of care unspecified (410.90), and heart failure unspecified (428.9).

Some of these events may have presented with mild symptoms that did not require immediate medical attention, and healthcare may have been sought in a delayed manner. The differences in incidence between vaccinated and unvaccinated could be partly due to vaccinated individuals seeking medical attention more frequently than those who were unvaccinated.

Another plausible explanation is the difference in the composition of the unvaccinated cohort as follow-up increases. Follow-up for unvaccinated individuals is censored in the unvaccinated cohort if they are vaccinated and they are then followed up from that time point in the vaccinated cohort. Therefore, long term follow-up in the unvaccinated cohort is restricted to individuals who are never vaccinated and who are possibly less likely to seek medical attention if not urgently needed. This difference between the vaccinated and unvaccinated individuals may be minimal in the earlier periods of follow-up after vaccination, during which time proportionally more unvaccinated persons intend to be vaccinated. The Kaplan-Meier curves show that, generally, the differences between vaccinated and unvaccinated cohorts are driven by the divergence in cumulative incidence over time, particularly for AESIs with a long follow up time of 365 days. We will further assess the numbers of individuals switching from the unvaccinated to vaccinated cohorts in relation to follow up time. Also, we plan to analyse differences in baseline characteristics between those unvaccinated that remain in the unvaccinated cohort for a long follow up period (e.g., at day 100, 200, 300, and 365) and the unvaccinated that get vaccinated during follow up period at different time points at the same timepoints. In addition, a negative control event, with the characteristics of cardiovascular disease, will be identified and analysed to explore the behaviour of the incidence rate in relation to follow-up time.

Another reason that may explain the divergence, could be that cardiovascular events occur due to COVID-19, which is considered to be a risk factor for cardiovascular events. As COVID-19 infection is only assessed at baseline at the time of vaccination there is no

information about COVID-19 infections occurring during the 365 day follow up that potentially could trigger cardiovascular events in vaccinated or unvaccinated individuals within 365 days after the first dose.

11.1.5.2. Arrhythmia

In this report, the adjusted HRs and the lower limits of the 95% CIs for arrhythmia were above 1 in NHR, PHARMO, EpiChron, and CPRD Aurum with a HR of 1.03 (95% CI: 1, 1.05) in NHR, 1.36 (95% CI: 1.29, 1.44) in PHARMO, 1.12 (95% CI: 1.04, 1.21) in EpiChron, and 1.27 (95% CI: 1.21, 1.33) in CPRD Aurum. In all data sources the cumulative incidence showed divergence between vaccinated and unvaccinated from around day 60 within the 365 days risk window. Arrythmia is the main driver of results for acute cardiovascular injury and all the discussion points mentioned above apply specifically to this AESI.

In NHR and PHARMO the identification of arrhythmia was mainly driven through ICPC GP codes for atrial fibrillation/flutter (K78) and 'palpitations (K04), and ICD10 code for atrial fibrillation and atrial flutter unspecified (I489). In EpiChron arrhythmia was identified mainly through ICD9CM codes for atrial fibrillation 427.3, and tachycardia unspecified 785.0, and the ICD10CM code for unspecified atrial fibrillation (I48.91). In CPRD Aurum the MedCodeId 82343012 for atrial fibrillation was the most frequent code.

These results show higher cumulative incidence rates of arrhythmia in vaccinated cohorts compared with those in unvaccinated cohorts, increasing with time since vaccination. The matched HRs were higher in CPRD Aurum than in the other data sources.

In all data sources except NHR, adjustment (PS control of confounding) resulted in a lowering of the HR. suggesting some residual confounding present in the matched HRs. Vaccinated and unvaccinated individuals may be different in their frequency of use of healthcare services (i.e., a healthy vaccinee effect) (i.e., a healthy vaccinee effect). It is possible that vaccinated individuals were more likely to seek health care than unvaccinated individuals, and thus have this condition diagnosed.

The EMA COVID Vaccine Monitoring (CVM) final report showed background incidence rates in unvaccinated individuals comparable to those found in this fifth interim report with diagnoses more frequently originating from primary care.[22]

11.1.5.3. Heart failure

Heart failure was part of the acute cardiovascular injury composite event but was also analysed separately.

In this report, the adjusted HRs and the lower limits of the 95% CIs for heart failure were above 1 in PHARMO with a HR of 1.29 (95% CI: 1.13, 1.47) and showed a divergence between vaccinated and unvaccinated from around day 60 within the 365 days risk window.

Heart failure in PHARMO was mainly identified by ICD10 hospital codes for heart failure unspecified (I509) and left ventricular failure (I501) followed by ICPC GP codes decompensation of the heart (K77). In PHARMO hospital codes are being added to complete the primary care ICPC GP codes and will be further investigated for the final report.

11.1.5.4. Stress cardiomyopathy

Stress cardiomyopathy was part of the acute cardiovascular injury composite event, but was also analysed separately.

No differences were observed for the incidence of stress cardiomyopathy between the vaccinated and unvaccinated cohorts during the 365-day risk window.

ACCESS data showed that the incidence was underestimated when relying on GP data only.

11.1.5.5. Coronary artery disease

Coronary artery disease is part of the acute cardiovascular injury composite event, but was also analysed separately.

In this report, the adjusted HRs and the lower limits of the 95% CIs for coronary artery disease were above 1 in PHARMO with a HR of 1.49 (95% CI: 1.31, 1.69) and in CPRD Aurum with a HR of 1.40 (95% CI: 1.30, 1.50). The cumulative incidence showed a divergence between vaccinated and unvaccinated cohorts from around day 30 in PHARMO and CPRD within the 365 days risk window. The potentials reasons for these results are discussed above in Section 11.1.5.1.

Coronary artery disease in PHARMO was mainly identified with ICD10 hospital codes for angina pectoris unspecified (I209) and acute subendocardial myocardial infarction (I214), Unstable angina (I200), Acute transmural myocardial infarction of inferior wall (I211) and with ICPC codes for Acute myocardial infarction (K75), and angina pectoris (K74). In CPRD Aurum the main codes identifying CAD were Ischaemic heart disease (MedCodeId 2534664018) and angina pectoris (MedCodeId 299757012).

11.1.5.6. Myocarditis (21-day risk window)

The lower limits of the 95% CIs for the myocarditis HRs occurring in a risk window of 21 days were below 1. There were no differences observed for myocarditis between vaccinated and unvaccinated in a 21-day risk window.

Myocarditis has been associated with COVID-19 mRNA vaccines in several studies in young adults, after the second dose of the vaccine.[23] This second dose is typically administered 28 days after the first dose, and therefore was not observed in the during the 21-day risk window analysed here.

11.1.5.7. Cerebral venous sinus thrombosis

Cerebral venous sinus thrombosis (CVST) has been added to the list of AESIs for this fifth interim report. CVST had been operationalised as cerebral venous thrombosis (CVT) in the prior interim reports. No differences between vaccinated and unvaccinated have been observed for CVST.

11.1.5.8. Glomerulonephritis

The lower limits of the CIs for the glomerulonephritis HRs assessed in a risk window of 365 days were below 1. There were no differences observed for glomerulonephritis between the vaccinated and unvaccinated cohorts.

Glomerulonephritis has been added for the first time for this fifth interim report as an AESI. No glomerulonephritis events were identified in Pedianet, NHR, or PHARMO. In PHARMO, the use of a single ICD-10 code only capturing hospital-based diagnoses, may explain the lack of glomerulonephritis events identified since PHARMO predominantly contributed GP data. This and other potential causes for the lack of results from NHR and PHARMO for glomerulonephritis are under investigation and will be reported in the final report. This will be done by reviewing definitions, algorithms and diagnostic ICD10 and ICPC codes. Additionally, the impact of partial ICD10 hospital registration coverage in PHARMO will be assessed, as glomerulonephritis is more likely to be detected in hospital settings. As glomerulonephritis is more likely to be detected in hospital settings and in adults, we did not expect to identify glomerulonephritis events in Pedianet.

11.1.5.9. Bell's palsy

In this interim report 5 we did not observe any differences between the vaccinated and unvaccinated cohorts for Bell's palsy assessed in a risk window of 42 days. The adjusted HR was 0.65 (95% CI: 0.28, 1.51). The lower limits of the 95% CIs for the HRs were all below 1. This is different from interim report 4, for PHARMO where the lower limits of the 95% CIs for the HRs were above 1, with an adjusted HR of 3.08 (95% CI: 1.24, 7.62). In interim report 4, there were 24 and 7 events within the 42 days risk window in the vaccinated and unvaccinated cohorts, respectively in PHARMO compared with 10 and 14, respectively, in interim report 5. We compared the code lists and did not detect any changes in diagnostic codes between interim report 4 and interim report 5. However, the reduction of cases identified could be due to an improved case identification algorithm introduced in interim report 5 or due to the continued efforts of PHARMO to clean COVID-19 vaccine exposure registration in removing potential duplicate vaccination entries originating from different data bases.

11.1.5.10. Secondary amenorrhoea

Secondary amenorrhoea events were identified in EpiChron, SIDIAP, and CPRD Aurum. Pedianet, which covers a paediatric population, is not suitable for the assessment of secondary amenorrhoea. Detection of this event may have been limited overall since codes did not include the underlying diseases to which amenorrhoea could be secondary; Codes for these underlying diseases were not included in the definition because it was felt they were not only specific for secondary amenorrhoea. PHARMO and NHR had low numbers of cases. The lack of GP-based ICPC codes to define secondary amenorrhoea for these countries, where this event is likely to be managed primarily by GPs, may explain the low numbers of events.

In this report, the adjusted HRs and the lower limits of the 95% CIs for secondary amenorrhoea within 183 days were above 1 in EpiChron with an adjusted HR of 1.71 (95% CI: 1.34, 2.18) and in CPRD Aurum with an adjusted HR of 1.24 (95% CI: 1.17, 1.30). The cumulative incidence showed a divergence between vaccinated and unvaccinated from

around day 15 in EpiChron and CPRD Aurum within the 183 days risk window. However, the observed occurrence of a menstrual disorder event as early as 15 days after vaccination does not appear to be biologically plausible and this is currently being investigated. The inclusion of biologically plausible lag time in the risk window from start of follow up after vaccination is needed.

Menstrual problems are mainly identified in GP practices and the ICPC codes in NHR and PHARMO are not granular enough to separate secondary amenorrhoea from amenorrhoea or even hypermenorrhoea. The codes available usually cover unspecified menstrual problems. Additionally, in the case of secondary amenorrhoea, the more specific underlying diagnosis will be coded in hospital settings. A possible next step would be to broaden the definition with a more sensitive definition for the identification of 'menstrual problems' in general. This is also partly reflected in some inconsistent published reports about the association of COVID-19 vaccines and menstrual disorders.[23-26]. Similar to the cardiovascular events, the differences between the vaccinated and unvaccinated cohorts could be explained by different healthcare seeking behaviour. In light of this and the limitations described above, the apparent differences in the incidences of secondary amenorrhoea in vaccinated and unvaccinated cohorts is inconclusive. Further investigations will be carried out and presented in the final report.

11.1.5.11. Hypermenorrhoea

Hypermenorrhoea events were identified in EpiChron, and SIDIAP. No events were identified in CPRD Aurum as there are no MedCodeId codes. As a limitation in this interim report 5, the incidence rates and HRs were assessed in the overall population and not restricted to only females in age groups considered to be of child-bearing potential. Pedianet (restricted to a paediatric population) is not suitable for the assessment of hypermenorrhoea.

In this report, the adjusted HR and the lower limits of the 95% CIs for hypermenorrhoea within 183 days were above 1 in EpiChron with a HR of 1.60 (95% CI: 1.41, 1.83). The cumulative incidence showed a divergence between vaccinated and unvaccinated from around day 30 in EpiChron. This observed occurrence of a menstrual disorder event beginning 30 days after vaccination seems too early to be biological plausible associated with the vaccine and is being investigated further. The inclusion of biologically plausible lag time in the risk window from start of follow up after vaccination is needed.

Recent publications suggest that menstrual problems have been observed following COVID-19 vaccination but further longitudinal studies are needed to confirm the causal relationship between COVID-19 vaccination and menstrual irregularities.[23-26] The definition used for hypermenorrhoea was very specific, with very few codes in each dictionary. For instance, only one ICD10 code -N92.1 (Excessive and frequent menstruation with irregular cycle) was used for hypermenorrhoea. amenorrhoea This is an inconsistent finding since the higher risk of hypermenorrhoea in the vaccinated cohort was only observed in EpiChron; this will be further investigated and discussed in the final report.

11.1.5.12. Comparison of adjusted hazard ratios between interim reports 4 and 5

Higher adjusted HRs were observed in interim report 5 than in interim report 4 for acute cardiovascular injury, including microangiopathy in NHR, PHARMO, EpiChron and SIDIAP (Table 39). This is most likely to be due to an adaptation of the identification algorithm. In

interim 4 this algorithm included stress cardiomyopathy, heart failure, coronary artery disease, other thromboembolic venous events, and cardiogenic shock. In interim report 5 the algorithm included microangiopathy, acute myocardial infarction, stress cardiomyopathy, heart failure, coronary artery disease, myocarditis, pericarditis, and arrhythmia. This adaptation was based on the definition from the American College of Cardiology/American Heart Association Task Force, stating that acute cardiovascular injury is an acute illness that is physician-diagnosed as a cardiovascular injury. [21] Acute cardiovascular injury refers to a broad spectrum of cardiac pathology including microangiopathy, heart failure, stress cardiomyopathy, coronary artery disease, myocarditis, pericarditis and cardiac arrhythmias, usually associated with abnormalities on ECG, echocardiography or cardiac MRI, and elevated biochemical markers."

The adjusted HRs for arrhythmia, heart failure, stress cardiomyopathy, coronary artery disease, and myocarditis were similar for the interim reports 4 and 5 and are consistent across all data sources.

Cerebral venous sinus thrombosis and glomerulonephritis included for the first time in this interim report 5, so no comparisons with interim report 4 are possible.

No consistent differences in the adjusted HRs for Bell's palsy between interim reports 4 and 5 were observed. More specific identification codes were used in the algorithm in PHARMO which may have led to the lower adjusted HR, but this is under investigation for the final report.

No differences in the adjusted HRs for secondary amenorrhoea and between interim reports 4 and 5 were observed, except in EpiChron for secondary amenorrhoea and PHARMO for hypermenorrhoea. The adjusted HR in interim report 4 for secondary amenorrhoea in EpiChron was lower than that observed in SIDIAP and in interim report 5 the adjusted HR was higher than in SIDIAP. The adjusted HR for hypermenorrhoea in PHARMO in interim report 4 was higher than those observed in the other data sources, but in interim report 5 the adjusted HR is similar to those seen in the other data sources. The case identification algorithm that includes ICPC and ICD10 codes for these menstrual events will be further refined for the final report.

Table 39. Comparison of adjusted hazard ratios in interim reports 4 and 5 for selected AESIs

	Interim report 4	Interim report 5
Acute cardiovascular injury including microangiopathy		
Pedianet	NA	1.38 (0.73, 2.61)
NHR	0.94 (0.90, 0.98)	1.01 (0.99, 1.04)
PHARMO	1.20 (1.08, 1.33)	1.38 (1.31, 1.45)
EpiChron	0.91 (0.82, 1.00)	1.10 (1.03, 1.18)
SIDIAP	0.93 (0.89, 0.99)	0.99 (0.96, 1.03)
CPRD Aurum	NA	1.23 (1.18, 1.27)
Arrhythmia		
Pedianet	1.73 (0.79, 3.78)	1.75 (0.88, 3.49)
NHR	1.04 (1.00, 1.07)	1.03 (1.00, 1.05)

Table 39. Comparison of adjusted hazard ratios in interim reports 4 and 5 for selected AESIs

	Interim report 4	Interim report 5
PHARMO	1.28 (1.19, 1.38)	1.36 (1.29, 1.44)
EpiChron	1.07 (0.98, 1.17)	1.12 (1.04, 1.21)
SIDIAP	1.02 (0.98, 1.06)	0.99 (0.96, 1.03)
CPRD Aurum	NA	1.27 (1.21, 1.33)
Heart failure		
Pedianet	NA	NA
NHR	0.80 (0.75, 0.85)	0.77 (0.73, 0.82)
PHARMO	1.13 (0.97, 1.31)	1.29 (1.13, 1.47)
EpiChron	0.88 (0.78, 0.99)	0.90 (0.80, 1.01)
SIDIAP	0.87 (0.81, 0.93)	0.89 (0.82, 0.96)
CPRD Aurum	NA	1.02 (0.95, 1.09)
Stress cardiomyopathy		
Pedianet	NA	NA
NHR	NA	0.69 (0.18, 2.67)
PHARMO	1.34 (0.23, 7.82)	1.49 (0.33, 6.69)
EpiChron	3.12 (0.38, 25.82)	0.85 (0.21, 3.47)
SIDIAP	1.55 (0.82, 2.91)	1.51 (0.75, 3.04)
CPRD Aurum	NA	NA
Coronary artery disease		
Pedianet	NA	NA
NHR	0.99 (0.94, 1.05)	0.99 (0.94, 1.04)
PHARMO	1.36 (1.15, 1.60)	1.49 (1.31, 1.69)
EpiChron	0.84 (0.69, 1.02)	0.97 (0.80, 1.17)
SIDIAP	1.06 (0.97, 1.16)	1.00 (0.91, 1.10)
CPRD Aurum	NA	1.40 (1.30, 1.50)
Myocarditis (21 days)		
Pedianet	NA	0
NHR	0.91 (0.35, 2.38)	0.94 (0.46, 1.94)
PHARMO	NA	1.23 (0.13, 11.84)
EpiChron	2.82 (0.29, 27.15)	3.64 (0.41, 32.53)
SIDIAP	2.71 (0.71, 10.30)	1.05 (0.35, 3.16)
CPRD Aurum	NA	2.30 (0.94, 5.66)
Cerebral venous sinus thrombosis		
Pedianet	NA	0
NHR	NA	0.63 (0.23, 1.74)
PHARMO	NA	NA
EpiChron	NA	0.90 (0.06, 14.09)
SIDIAP	NA	0.68 (0.11, 4.20)
CPRD Aurum	NA	0.43 (0.14, 1.27)
Glomerulonephritis		
Pedianet	NA	0
NHR	NA	NA
PHARMO	NA	NA

Table 39. Comparison of adjusted hazard ratios in interim reports 4 and 5 for selected AESIs

	Interim report 4	Interim report 5
EpiChron	NA	0.59 (0.22, 1.55)
SIDIAP	NA	1.29 (0.88, 1.87)
CPRD Aurum	NA	0.88 (0.67, 1.16)
Bell's palsy		
Pedianet	NA	0
NHR	1.01 (0.76, 1.35)	1.15 (0.88, 1.50)
PHARMO	3.08 (1.24, 7.62)	0.65 (0.28, 1.51)
EpiChron	0.89 (0.40, 2.00)	0.84 (0.34, 2.09)
SIDIAP	0.91 (0.71, 1.16)	0.96 (0.75, 1.24)
CPRD Aurum	NA	0.99 (0.75, 1.29)
Secondary amenorrhoea		
Pedianet	1.78 (0.16, 19.84)	NA
NHR	NA	0.91 (0.69, 1.21)
PHARMO	NA	0.77 (0.05, 11.99)
EpiChron	0.34 (0.07, 1.76)	1.71 (1.34, 2.18)
SIDIAP	1.07 (0.99, 1.16)	0.99 (0.91, 1.07)
CPRD Aurum	NA	1.24 (1.17, 1.30)
Hypermenorrhoea		
Pedianet	0.33 (0.08, 1.42)	0.62 (0.08, 4.66)
NHR	NA	NA
PHARMO	6.62 (0.80, 54.62)	1.18 (0.31, 4.47)
EpiChron	1.38 (1.21, 1.57)	1.40 (1.23, 1.60)
SIDIAP	1.09 (1.03, 1.16)	1.02 (0.95, 1.09)
CPRD Aurum	NA	NA

NA: not available

11.2. Limitations

Vaccination data and coverage were consistent with ECDC coverage data in Pedianet and EpiChron, SIDIAP (https://vaccinetracker.ecdc.europa.eu/public/extensions/covid-19/vaccine-tracker.html#uptake-tab). Information on the COVID-19 vaccine brand was considerably missing in NHR. Data from PHARMO showed lower than expected estimates of vaccine uptake, they are improving.

The contributing data sources, differed in the point of care from where they sampled their populations (GP, emergency visits, hospital discharge data bases) which could have an impact on the estimates for the incidence rates as shown in a recent study.[19]

Pedianet is a paediatric general practice research database, that includes children until the age of 14, after which they are transferred to general practitioners. Vaccination of children started later in 2021, which is reflected by the different calendar time of first vaccination. AESIs were based on diagnoses in the paediatricians' records, which may include information from hospitalisation when it is reported back to them. However, this reporting may not be complete, which is why Pedianet could not contribute data for all AESIs.

In PHARMO, data on COVID-19 vaccinations were entered in the GP medical record through various routes, including directly by the GPs who administered the vaccine or occasionally by manual linkage of information from a nationwide vaccination registry (CIMS) maintained by public health institutes, for individuals vaccinated at a public health institute. Registering vaccines administered at public health institutes in the GP EHR was not mandatory. Additionally, the requirements for the supply chain for the Pfizer-BioNTech COVID-19 vaccine such as refrigeration made it unsuitable for use in GP practices. Together, these factors could have resulted in underestimated numbers of individuals vaccinated with the Pfizer-BioNTech COVID-19 vaccine, or in duplicate entries. Throughout the duration of this study the registration of vaccination improved in the GP EHR, possibly due to delays in GPs obtaining nationwide vaccination registry data, or delayed entry into the EHR, if any central information was obtained at all. Correspondingly, vaccine uptake rates for the Netherlands are more in line with national data. A direct link between the PHARMO Data Network with the nationwide vaccination registry in the Netherlands could not be established.

Data from NHR were available up to the end of 2022. Since the previous interim reports, NHR have continuously updated previously missing COVID-19 vaccine brand information. Additionally, hospital event information has been included, in addition to the primary care data. Previously, events were not identified with full ICD10 codes. Full ICD10 codes are now available with the new data extraction conducted in 2023 and are included in this fifth interim report. However, the KUHR GP data source only has a maximum of 4 digits for ICPC2 codes because more detailed digits are not used in this data source. This could lead to less specific identification of events resulting in higher event counts and incident rates from Norway for events identified mainly in the GP setting using ICPC2 codes.

Risk differences were provided without an estimation of their precision which is a limitation. Bootstrapping methods for the calculation of the risk difference are being tested and will be implemented in future analysis.

The missing data for death (any cause) in SIDIAP are under investigation and will be corrected in the next draft of this fifth interim report.

As stated previously in the discussion section, further investigations into diagnostic codes and case definitions, differential baseline characteristics in unvaccinated individuals, compared with vaccinated individuals, at longer follow time points, differential healthcare seeking patterns and adherence, (i.e., cardiovascular acute injury, arrhythmia, glomerulonephritis, secondary amenorrhoea, and hypermenorrhoea) will be undertaken and the findings will be discussed in the final report.

Definition of AESIs

AESIs were identified through diagnostic codes, which can be tagged as narrow (specific) and possible (sensitive). In this fifth interim report, we used only narrow (specific) codes. For the final comparative analyses, AESIs cases will be validated. The provenance of the diagnostic codes also differs. In Pedianet and partly in PHARMO, where only a minority of the study population had linked hospital data, AESIs were coded in primary care. Patients with severe events may not have consulted their GP, or, if they did, the GP may not have included the codes for the final diagnoses that were determined in the hospital setting. Also, feedback from hospital records into the GP record may not be complete, or easily accessible

in the GP databases. This could be the reason why rates are lower for some rare events that require hospitalisation in these data sources. SIDIAP and EpiChron contain inpatient and outpatient diagnoses. The NHR results are based on primary care (GP), hospital and outpatient specialist data. Registers, codes and PCR testing were used for COVID-19 diagnoses and tests. PHARMO and Pedianet used additional free text searching for COVID-19 as well as for other events. CPRD Aurum used only primary care coded records.

11.3. Interpretation

These analyses were performed on data from more than 12 million individuals who had received at least one dose of the Pfizer-BioNTech COVID-19 vaccine (vaccinated cohorts) and from an equal number of matched unvaccinated individuals (unvaccinated cohorts). The matching was successful, both in terms of the identification of an appropriately matched pair as well as minimised confounding. In this fifth interim report, follow-up has been extended which has had a positive impact on the detection of AESIs, particularly for those with longer risk windows.

11.4. Generalisability

The distribution of age and sex of the data source populations were compatible with the national statistics in each country. The study population for this fifth interim report included a large percentage of all individuals who received the Pfizer-BioNTech COVID-19 vaccine, in the setting of vaccination programmes that began with elderly and frail individuals in very late 2020 and early 2021 and expanded to younger, healthier individuals later in 2021. This report includes all individuals.

12. OTHER INFORMATION

Not Applicable.

13. CONCLUSIONS

The results in this fifth interim report describe the characteristics and incidence rates for the 37 AESIs (Table 16) in more than 12 million vaccinated individuals and 12 million matched unvaccinated controls.

The data were analysed by data source and were not pooled in this report. The incidence rates of AESIs were generally very low in the risk intervals studied and were comparable with available published background incidence rates from previous studies in unvaccinated cohorts.

Among the 11 AESIs that were highlighted for further discussion, the divergence in cumulative incidence observed for several of the cardiovascular events with long risk windows (eg. 365 days) resulted in small increases in risk in some of the data sources. These increases could be explained by a number of factors. Some of these events have presented with mild symptoms that did not require immediate medical attention, and vaccinated individuals may have sought medical attention more frequently than those who were unvaccinated (healthy vaccinee effect). Another plausible explanation is differences in the composition of the unvaccinated cohort as follow-up progresses. Unvaccinated individuals were censored in the unvaccinated cohort if they were vaccinated and were then followed up in the vaccinated cohort from that time point. Hence, the individuals who remained in the unvaccinated cohort were those who were never vaccinated and who were

possibly less likely seek medical attention at all if it was not urgently needed. These differences may have been minimal earlier in follow-up, but may have become more pronounced as follow-up progressed.

Results for CVST, Bell's Palsy and glomerulonephritis all showed no evidence of an increased risk in the vaccinated cohort based on adjusted HRs. Adjusted HRs for secondary amenorrhea were slightly elevated in EpiChron and CPRD Aurum. For hypermenorhea, only the adjusted HR in Epichron was slightly elevated. These events, along with the cardiovascular events described above, will continue to be monitored and further refined for inclusion in the final study report.

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15. LIST OF SOURCE TABLES AND FIGURES

Not applicable.

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