NON-INTERVENTIONAL (NI) INTERIM STUDY REPORT

PASS information

Title	Post Conditional Approval Active Surveillance Study Among Individuals in Europe Receiving the Pfizer-BioNTech Coronavirus Disease 2019 (COVID-19) Vaccine
Protocol number	C4591021
Version identifier of the interim study report	2.0
Date	20 March 2023
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), Italy (IT), Spain (ES), United Kingdom (UK), Norway (NO)
Authors	PPD Assistant Professor University Medical Center Utrecht AND PPD Senior Director Epidemiology 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	PPD

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Not applicable.

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Not applicable.

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Not applicable.

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Not applicable.

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	Clinical Practice Research Datalink
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

Abbreviation	Definition
EU	European Union
GOLD	General Practitioner On-line Database (of the CPRD)
GP	General practitioner
GPP	Good Pharmacoepidemiology Practices
GVP	Good Pharmacovigilance Practices
HES	Hospital Episode Statistics
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

Abbreviation	Definition
PASS	Post-authorisation safety study
PHARMO	PHARMO Institute for Drug Outcomes Research or PHARMO Database Network (Netherlands)
PHE	Public Health England
QC	Quality control
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
VAED	Vaccine-associated enhanced disease
VV	Varicella zoster virus
WHO	World Health Organization

3. INVESTIGATORS

The names, affiliations, and contact information of the investigators at each study site are listed Standalone Appendix 3.

Principal Investigator(s) of the Protocol

Name, degree(s)	Job Title	Affiliation
PPD	Senior Director, Safety Surveillance Research	Pfizer, Inc.
	Assistant Professor	University Medical Center Utrecht
	Senior Director, Epidemiology	RTI Health Solutions
	Professor	University Medical Center Utrecht
	Director, Epidemiology	RTI Health Solutions
	Director, Biostatistics	RTI Health Solutions
	Senior Research Epidemiologist	RTI Health Solutions
	Senior Research Epidemiologist	RTI Health Solutions
	Research Epidemiologist	RTI Health Solutions

Lead Country Investigator(s) of the Protocol

Name, degree(s)	Title	Affiliation
PPD	Head Pharmacoepidemiology Unit	Agenzia regionale di sanità della Toscana
	Director	PHARMO Institute for Drug Outcomes Research
	Researcher	
	Researcher	
	President	PENTA Foundation
	Director	Drug Safety Research Unit (DSRU)
	Head of Epidemiology and Research	

Name, degree(s)	Title	Affiliation
PPD	Research Fellow	
	Senior Research Fellow	
	National Health Service (NHS) Senior Researcher	EpiChron Research Group. Instituto Aragonés de Ciencias de la Salud
	Researcher	
	Researcher	
		IDIAP-Jordi Gol
	Researcher	
	Statistician	
	Researcher	University of Oslo

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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
PPD MD, National Taiwan University Children's Hospital, Taipei, Taiwan	Scientific advisory board member
PPD PhD, London School of Hygiene and Tropical Medicine, United Kingdom	Scientific advisory board member
PPD BioNTech Manufacturing GmbH	MAH contact person
PPD , PhD, Teamit Institute S.L	Research Project Manager
PPD , PhD, MediCom Consult	Medical writer

5. MILESTONES

Milestone	Planned date	Actual date	Comments
Date of independent institutional review board (IRB) approval of protocol		05 October 2021	
Registration in the EU PAS register	25 June 2021	25 June 2021	
Start of data collection	30 September 2021	3 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		
Interim report 4	30 September 2023		
Interim report 5	31 March 2024		
Final study report	30 September 2024		

1 Data were not provided in the progress report

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 have identified priority populations for vaccination based on health care or essential worker status, comorbidities, and age.[2] Early distribution of the vaccine may be limited to vulnerable groups at higher risk for COVID-19 infection and COVID-19 complications. As recommendations for vaccination are updated over time, the characteristics of vaccine recipients are expected to vary considerably. Approaches for investigating vaccine safety must flexibly account for changing vaccine distribution, which may vary by country or jurisdiction in Europe.

This non-interventional study was designated as a Post-Authorization Safety Study (PASS) and was a commitment to EMA.

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 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 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.

8. AMENDMENTS AND UPDATES

The following amendments have been made to the protocol:

Table 1.   Amendments to the protocol

Amendment number	Date	Section of protocol changed	Summary of amendment/update	Reason
1	16-Dec-2021	Section 3 Responsible Parties	Updated Pfizer principal investigator	New principal investigator for study
1	16-Dec-2021	Section 6 Milestones	Updated end of data collection date	Incorrect date in initial protocol
1	16-Dec-2021	Section 9.1.1.1 Matching process	Updated Figure 1	The 'V' to symbolize time of vaccination was moved to be consistent with the timeline in the figure. Also, the label 'patient' was changed to 'person' in the figure to align with the description that appears below the figure
1	16-Dec-2021	Section 9.3.1.1 Cohort design	Inclusion of addition sensitivity analysis to assess AESIs after 2nd and 3rd doses	Request from CBER to include dose stratification
1	16-Dec-2021	Section 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-Dec-2021	Section 9.3.3 Covariates definition	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-Dec-2021	Section 9.5 Sample 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-Dec-2021	General	Minor administrative, formatting, and typographical changes have been made	Updated to provide clarity and be consistent with remainder of protocol
1	16-Dec-2021	Section 9.1.1.1 Matching procedure	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

Table 1.   Amendments to the protocol

Amendment number	Date	Section of protocol changed	Summary of amendment/update	Reason
1	16-Dec-2021	Section 9.1.1.1 Matching procedure	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-Dec-2021	Section 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-Dec-2021	Section 9.2.2.1 Cohort and SCRI designs	Added the following two inclusion criteria: Having contact with the health care system within 7 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) 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.	New evidence has been published recommending these two inclusion criteria
1	16-Dec-2021	Section 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.

Table 1.   Amendments to the protocol

Amendment number	Date	Section of protocol changed	Summary of amendment/update	Reason
2	31-Mar-2022	Section 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-Mar-2022	Section 9.1.1.1 Matching process	Added that one individual will be randomly selected if multiple individuals matched a vaccinated individual	To clarify how multiple matches will be handled.
2	31-Mar-2022	Section 9.2.2.1 Cohort and SCRI designs	Removed the exclusion criterion, 'Have contact with the health care system in the 7 days before time zero'	Request from EMA.
2	31-Mar-2022	Section 9.2.2.1.1. Sensitivity analysis	Added a sensitivity analysis excluding individuals who have had contact with the health care system in the 7 days before time zero	Request from EMA to remove from main analysis and add as a sensitivity analysis.
2	31-Mar-2022	Section 9.2.4 Study period	Added 2018-2019 as a historical period	To assess time trends in health seeking behaviour.
2	31-Mar-2022	Section 9.3.2.1 Safety outcomes	Added an additional risk window of 1-21 days for myocarditis and pericarditis	Request from EMA.
2	31-Mar-2022	Section 9.3.2.1 Safety outcomes	Added thrombocytopenia with venous thromboembolism	This outcome is an important AESI to include in the study.
2	31-Mar-2022	Section 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-Mar-2022	Section 9.3.3 Covariate definition	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-Mar-2022	Section 9.3.3 Covariate definition; 9.3.1. Exposure definition, by data source	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.

Table 1.   Amendments to the protocol

Amendment number	Date	Section of protocol changed	Summary of amendment/update	Reason
2	31-Mar-2022	Section 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-Mar-2022	Section 10.4 Ethical conduct of the study	Removed Good Epidemiological Practice guidelines issued by the International Epidemiological Association	Guideline no longer available.
2	31-Mar-2022	Section 11 Management and reporting of adverse events/adverse reactions	Updated name of training	To reflect current training name.
2	31-Mar-2022	General	Minor administrative, formatting, and typographical changes have been made	Updated to provide clarity and be consistent with remainder of protocol.

9. RESEARCH METHODS

Full details of the research methods used can be found in the protocol (Standalone Appendix 3) and are summarized 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. In the final report a self-controlled risk interval (SCRI) design will be used for specific AESIs, as indicated in Table 2. Details about this design are available in the protocol.

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]	1-42[3]	Cohort/SCRI
	Acute disseminated encephalomyelitis	1-42[3]	Cohort/SCRI
	Narcolepsy[a]	1-42[b]	Cohort/SCRI
	Acute aseptic arthritis	1–42[d]	Cohort
	Diabetes (type 1)	1–365	Cohort
	(Idiopathic) thrombocytopenia[a]	1–42[4]	Cohort/SCRI
	Thrombotic thrombocytopenia syndrome (TTS)[a]	1–15[3]	Cohort/SCRI
Cardiovascular system	Acute cardiovascular injury	1–365[e]	Cohort
	Arrhythmia	1–365[e]	Cohort
	Heart failure	1–365[e]	Cohort
	Stress cardiomyopathy	1–365[e]	Cohort
	Coronary artery disease	1–365[e]	Cohort
	Myocarditis	1–7 days	Cohort/SCRI
	Myocarditis	1–14 days	Cohort/SCRI
	Myocarditis	1–21 days	Cohort/SCRI
	Pericarditis	1–7 days	Cohort/SCRI
	Pericarditis	1–14 days	Cohort/SCRI
	Pericarditis	1–21 days	Cohort/SCRI
	Myocarditis and pericarditis	1–7 days	Cohort/SCRI
	Myocarditis and pericarditis	1–14 days	Cohort/SCRI
	Myocarditis and pericarditis	1–21 days	Cohort/SCRI
Circulatory system	Coagulation disorders: thromboembolism, haemorrhage	1–28[3]	Cohort/SCRI
	Single organ cutaneous vasculitis	1–28[f]	Cohort/SCRI
Hepato-gastrointestinal and renal system	Acute liver injury	1–365[h]	Cohort
	Acute kidney injury	1–365[h]	Cohort
	Acute pancreatitis	1–365[h]	Cohort
	Rhabdomyolysis	1–365	Cohort
Nerves and central nervous system	Generalised convulsion	1–42[3]	Cohort/SCRI
	Meningoencephalitis	1–42[3]	Cohort/SCRI
	Transverse myelitis[a]	1–42[3]	Cohort/SCRI
	Bell's palsy	1–42[3]	Cohort/SCRI
Respiratory system	Acute respiratory distress syndrome	1–365	Cohort
Skin and mucous membrane, bone and joints system	Erythema multiforme	1–42[g]	Cohort
	Chilblain-like lesions	1–42[f]	Cohort
Reproductive system	Secondary amenorrhea	1–183	Cohort
Other system	Anosmia, ageusia	1–42	Cohort
	Anaphylaxis[a]	1	Cohort
	Multisystem inflammatory syndrome	1–42[c]	Cohort
	Death (any causes)	1–365	Cohort

Table 2.   List of selected adverse events of special interest

Body system/ classification	Adverse event of special interest	Estimated risk window (days)	Analytic Approach
	Subacute thyroiditis	1–365[d]	Cohort
	Sudden death	1–365	Cohort
Pregnancy outcome, maternal	Gestational diabetes	Any time pregnancy	Sub-cohort
	Preeclampsia	After 20 weeks gestation	Sub-cohort
	Maternal death	Any time pregnancy	Sub-cohort
Pregnancy outcome, neonates	Foetal growth restriction	Any time pregnancy	Sub-cohort
	Spontaneous abortions	At termination	Sub-cohort
	Stillbirth	At birth	Sub-cohort
	Preterm birth	At preterm birth	Sub-cohort
	Major congenital anomalies[a]	1 year after birth	Sub-cohort
	Microcephaly	At birth	Sub-cohort
	Neonatal death	At birth	Sub-cohort
	Termination of pregnancy for foetal anomaly	At termination	Sub-cohort
Any	Vaccine-associated enhanced disease (VAED)[a]	1–365	Cohort

AESI = adverse events of special interest; VAED = vaccine-associated enhanced disease.
Notes:
a.   For this AESI clinical validation will occur.
b.   Published risk and control intervals for demyelinating diseases and cranial disorders were applied to transverse myelitis (TM) and narcolepsy/cataplexy.
c.   As severe COVID-19 ranges from severe pneumonia, acute respiratory distress syndrome, and multisystem organ failure/MIS-A, a 1-42 day risk interval was applied in order to capture the 14-day incubation period of the disease and 4-5 day period from exposure to symptom onset.
d.   Published risk and control intervals for autoimmune disorders were applied to similar autoimmune rheumatic conditions (i.e., fibromyalgia and autoimmune thyroiditis).
e.   Published risk and control intervals for myocarditis and pericarditis were applied to other cardiovascular conditions (i.e., heart failure and cardiogenic shock, stress cardiomyopathy, CAD, arrhythmia, AMI).
f.   Similar risk and control intervals were applied to all cardiovascular and haematological disorders characterized by damage to the blood vessels and/or arteries and clotting (i.e., microangiopathy, DVT, pulmonary embolus, limb ischemia, hemorrhagic disease, DIC, chilblain-like lesions). The published risk and control intervals for Kawasaki disease (KD) were applied to vasculitides given that KD is a form of medium and small-vessel vasculitis.
g.   Published risk and control intervals for non-anaphylactic allergic reactions were applied to hypersensitivity disorders (i.e., erythema multiforme).
h.   Risk intervals of 42 days were applied for acute kidney injury and liver injury to be consistent with other COVID-19 related safety events of interest.

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 AESI among individuals who receive at least one dose of the Pfizer-BioNTech COVID-19 vaccine were calculated.

The primary objective was addressed in a comparative analysis of this incidence with that occurring in an unvaccinated matched comparator group.

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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., recipients of the vaccine) was the day the first vaccination dose was received. Time zero in the unexposed group was a 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 matched comparator in the 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 matched to the vaccinated individual by age, gender, geographical region, previous identified COVID-19 infection, and previous influenza vaccination at time zero. Matched pairs 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 may 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 was used. These assumptions included that the outcome had an acute onset and short latency and had 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 compared 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 was 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 served as a sensitivity analysis and enabled the evaluation of the exclusion of unmatched pairs from the analysis.

The risk windows for each AESI are summarised in Table 2 and the AESI for which a SCRI analysis is a valid approach is indicated.

A prespecified post-vaccination control interval was used for each outcome. This approach minimised 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 was 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
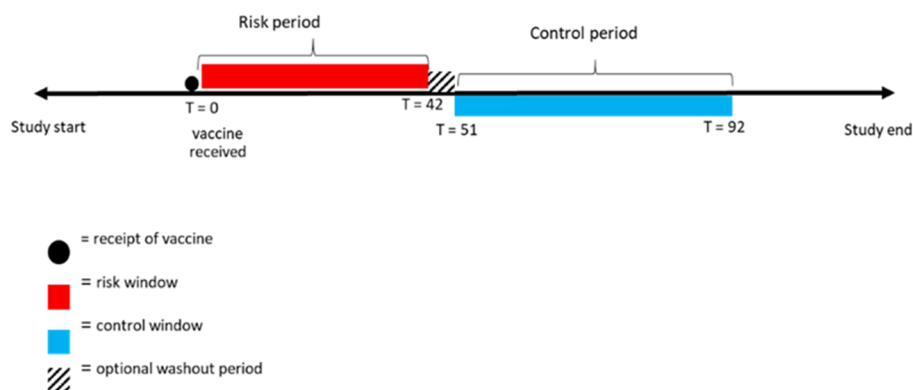
T = time measured in days.
Note: Example with a risk period of 42 days and a control period of 42 days.

9.2. Setting

The study used 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 used as data sources:

- ARS Toscana (Agenzia Regionale di Sanita' della Toscana) [a research institute of the Tuscany region of Italy] (IT)][1]

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[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.

- Pedianet (IT)

- Health Search Database (HSD) (IT)

- PHARMO (PHARMO Institute for Drug Outcomes Research) (NL)

- NRH (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) (UK).

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

NHR (Norway)
5.6 million active individuals

PHARMO (The Netherlands)
2 million active individuals

CPRD (The United Kingdom)
13.3 million active individuals

Pedianet (Italy)
50,000 active individuals

HSD (Italy)
1.2 million active individuals

ARS Toscana (Italy)
3.6 million active individuals

EpiChron (Spain)
1.3 million active individuals

SIDIAP (Spain)
8 million active individuals

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 (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 August 2022
The Netherlands (PHARMO)	06 January 2021	6 January 2021 – 30 Jun 2022
Norway (NHR)	27 December 2020	1 January 2021 – 31 December 2021**
Spain (EpiChron, SIDIAP)	27 December 2020	EpiChron: 27 December 2020 – 31 July 2022 SIDIAP: 01 January 2021 – 30 Jun 2022
UK (CPRD)*	08 December 2020	8 December 2020 – 21 March 2022

* CPRD has not contributed data to this interim report 3;
** NHR results are based on yearly updates of the data sources. The data from 2022 will be available later in 2023.

Figure 3.   Study period and follow-up
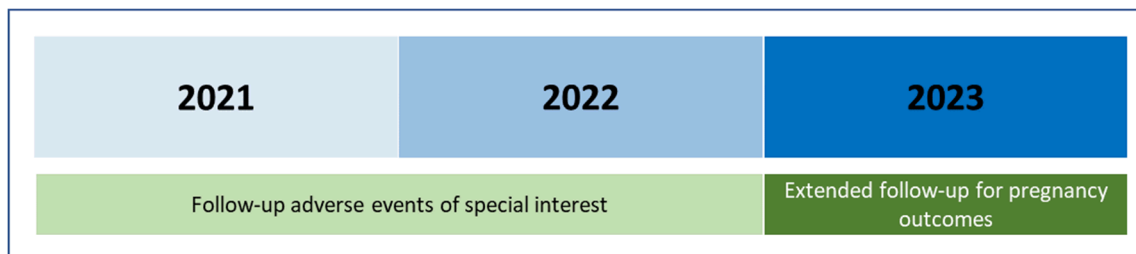
9.3. Subjects

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 point in time, vaccinated individuals may differ from the remaining population in characteristics that may determine their risk of AESI. Measured baseline differences were adjusted for (Section 9.9).

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 following criteria had to be met. Note that the study population for each outcome-specific analysis was therefore 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.

9.3.2. 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. Other exposure groups were also described.

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.

9.4.1.1.1. Sensitivity analyses

The following sensitivity analyses for the cohort design were implemented:

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.

Note that individuals who received a first dose (population studied in the main analysis) may be different from the individuals who received a second dose and different from the individuals receiving subsequent doses (populations studied in this sensitivity analysis). The differences arose from both the national vaccination policies concerning dosing recommendations (i.e., a third dose was indicated for specific at-risk individuals) and the fact that patients who received subsequent doses were survivors who had not suffered any serious adverse reactions that would have contraindicated the continuation of the scheduled vaccination regimen (e.g., an anaphylactic reaction to a first dose). 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

For the SCRI design, for each dose, person-time in the risk interval was considered as 'exposed', while person-time in the control interval was considered 'unexposed'. Risk intervals were specific to the outcome of interest and were 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, but 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 was no known time-limited window after vaccine exposure that the acute event would be expected to occur post-vaccination.

Outcome-specific control intervals were also defined. For outcomes with short risk intervals, the control interval occurred 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 occurred after the risk interval of the second or subsequent dose and did 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).[2]

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

9.4.2.1.1. Outcome identification and validation, by data source

AESIs were identified based on patient profile review of electronic 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 and HSD (IT): In Italy, a validation mechanism including individual linkage with the electronic regional immunisation register was in place. Furthermore, the validation

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

process included the review by clinicians of the individuals' electronic medical records, which contained 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 or PHARMO employees, 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. Validation studies were already available for selected health outcomes (e.g., intracranial haemorrhage, hip fractures, cancer). Depending on the adverse event of interest, validation was possible by comparing the registered diagnosis in two separate registers (e.g., the Norwegian Patient Registry and the Norwegian Stroke Register).

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 (UK): In the United Kingdom (UK), validation was conducted by a review of electronic medical record information for selected endpoints by an adjudication committee 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, 60-69, 70-79, 80+ years)

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- - The age group 0-17 years was further categorised, when feasible, as follows: 0-1, 2-5, 6-11, 12-17

- Sex

- Pregnancy status and pregnancy trimester at time zero

- Race or ethnicity, as appropriate in each country

- Geographic region, as appropriate in each country

- Socioeconomic status, as available in each country (including housing, employment, and income, if available)

- Residency in a long-term care facility

- Health care worker or essential worker status, if available

- Date of vaccination (categorised in trimesters)

- Batch of vaccine received

- 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)

- 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

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- 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

  - Skilled nursing facility, nursing home, or extended care facility stay

  - 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

  - Wheelchair use

- Home hospital bed

- Paralysis

- Parkinson's disease

- Skin ulcer

- Weakness

- Stroke/brain injury

- Ambulance transport

- Dementia

- Difficulty walking

- Home oxygen

- Rehabilitation care

- Psychiatric illness

- Sepsis

- Heart failure

- Podiatric care

- Bladder incontinence

- Diabetes complications

- Arthritis

- Coagulation deficiencies

- Vertigo

- Lipid abnormalities

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. Other exposure groups will also be described.

ARS Toscana (IT): Information on the COVID-19 vaccine was retrieved using the manufacturer code. Information on COVID-19 vaccination included date of immunisation, dose, and vaccine batch number.

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.

HSD (IT): Information on COVID-19 vaccination included date of immunisation, type of vaccine and dose.

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 (UK): The CPRD Aurum database contained information recorded by National Health Service (NHS) primary care GPs; and information on the administration of COVID19

vaccines to individuals. This included, linked to an encrypted unique patient identifier; the name of the vaccine; manufacturing company; dose; stage of the vaccine schedule; administration route; administration location (e.g., general practice); date of administration; and medical observations, events, referrals, test results, and prescribed medications recorded by the GP prior to, on, or after the vaccination date. In addition, patient demographic, practice-level, and staff-level information was also available.

 Standard CPRD-linked data sets also included Hospital Episode Statistics (HES) data sets covering hospital secondary care (accident & emergency, inpatient and outpatient), Office for National Statistics (ONS) data sets for Death Registry information, mother-baby link, and an algorithm-based Pregnancy Register.

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. Exposure identification may 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 will be conducted in a source population of 38.9 million individuals captured in the electronic health care data sources.

Table 4 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 3 for vaccine-associated enhanced disease, (VAED), 44,420 exposed and 44,420 unexposed individuals would need to be included; and assuming a two-sided alpha = 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 4. **Number of individuals needed to detect different risk ratios for selected adverse events of special interest for a range of background rates**

| AESI | Background rate during risk window | Risk ratio | Sample size[a] | |
			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
VAED	1/5,000	1.5	414,643	414,643
VAED	1/5,000	2	128,456	128,456
VAED	1/5,000	2.5	68,045	68,045
VAED	1/5,000	3	44,420	44,420

AESI = adverse event of special interest; VAED = vaccine-associated enhanced disease.
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) = 0.000000137
Guillain-Barré syndrome 1/100,000; (1/100,000)/365 * risk window (risk window 42 days) = 0.00000115
VAED 1/5,000 = 0.0002 (no risk window applied)

9.8. Data transformation

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

9.9. Statistical methods

9.9.1. Main summary measures

In this third interim report, 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 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 gender. 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 measured reported 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 (excluded 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.

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9.9.3. Baseline exchangeability and negative control outcome

Despite matching for potentially relevant confounders, achieve 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.[11] 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). The matching variables were assessed iteratively to get the smallest difference possible. If the 12-day risk difference of symptomatic SARS-CoV-2 infection was ≤0.10%, the matching was considered to be sufficient to achieve baseline exchangeability and if it was >0.1%, the matching was considered not sufficient to achieve baseline exchangeability. In the latter case, the inverse probability of treatment weight (IPTW) would be used to adjust the estimates using propensity score methods. Propensity score methods are appropriate when there is a small number of events for each outcome, which is the case in this study.

The propensity score (PS) is 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 outcome-generic propensity score was estimated and used to adjust all outcomes. 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 propensity score.

The stabilized 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

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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 individuals with extreme weights.

Adjusted HRs and 95% CIs were estimated by including the IPTW in a Cox hazard proportional 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.

As the 12-day risk difference was ≤0.10%, the matching was considered to be sufficient to achieve baseline exchangeability and therefore no propensity score adjustment was necessary in the analyses reported here.

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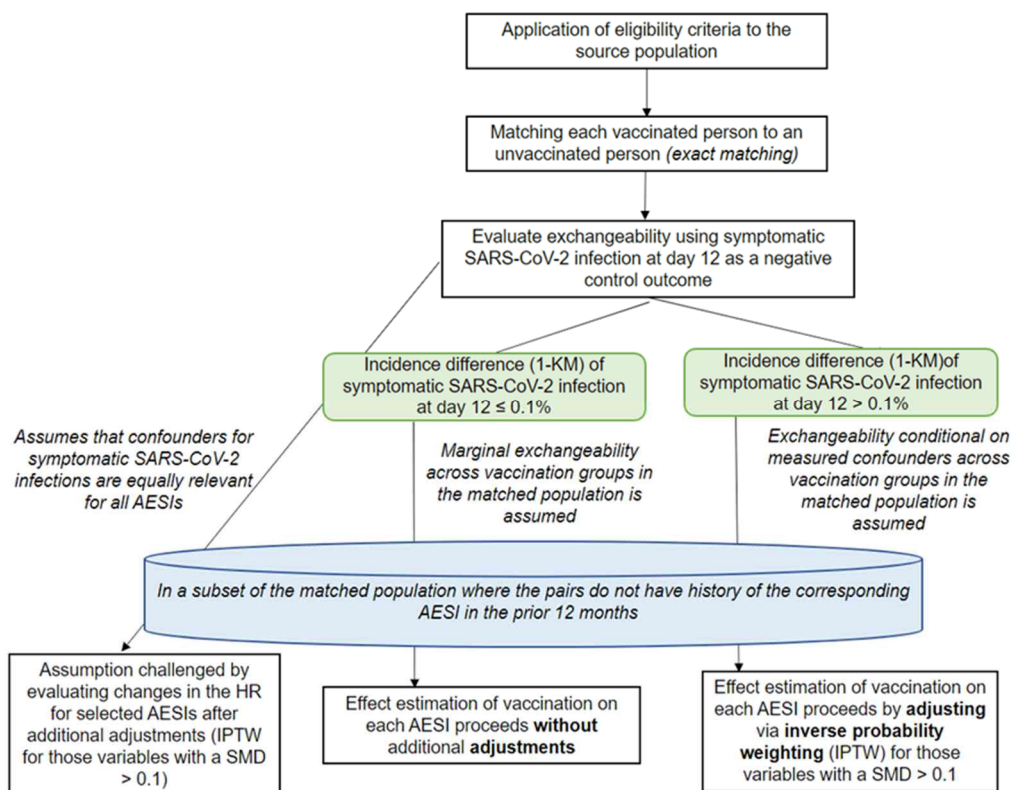
9.9.4. Missing values

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. As the main analysis in this report did not implement further adjustment beyond the baseline matching, approaches to handle the presence of missing data were not needed.

9.9.5. Sensitivity analyses

The sensitivity analyses described above were tested and, for completeness, the tables are included in on-line supplementary data (Table 21). These will be further refined and reported in subsequent reports.

9.9.6. Amendments to the statistical analysis plan

The following amendments have been made to the SAP:

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 analyses 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

Amendment number	Date	Section of SAP changed	Summary of amendment/update	Reason
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 heathcare system in the 7 days before time 0"	Request from EMA
1	15-Apr-2022	2.2.2.1 Inclusion criteria	Removed inclusion criteria, "live in an area where COVID-19 vaccination is under way at baseline"	The criteria 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 following changes to the statistical analysis documented in the protocol were described in the SAP:

- Protocol V4.0, section 9.3.3: age categories have been modified; this change has been communicated to regulatory authorities via an administrative change letter (19 April 2022).

- Protocol V4.0, section 9.7.1.5: quarterly incidence rates in the historical periods will not be compared by calculating standardized differences; the comparison will be made via the matched historical comparators analysis.

- Protocol V4.0, section 9.3.2.1: the AESI, "HIT-like event" is renamed to "'thrombotic thrombocytopenia syndrome (TTS)' and 'thrombocytopenia, venous thromboembolism' is deleted from the list of AESIs; this change has been communicated to regulatory authorities via an administrative change letter (19 April 2022).

9.10. Quality control

Rigorous quality control (QC) was 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. ARS Toscana (IT)

One or two researchers reviewed study documents. ARS Toscana received data bimonthly from the Tuscany region (who performed data QC before sending). The ARS Toscana statistical office appended the data to an Oracle database and checked it using a dashboard to identify any inconsistencies with historical data.

The Pharmacoepidemiology Unit used standardised parametric procedures in Structured Query Language (SQL) and Stata to extract data from the Oracle database. Parametric procedures were also used to convert the data into various CDMs. Study-specific procedures were developed, based on the study protocol and SAP, as well as by composing standard parametric procedures in Stata. Standard procedures in R have been developed in the context of the ConcePTION project. The Unit also regularly generated simulated data sets and double programming in R that were originally developed in SAS or Stata.

9.10.2. 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)*[12] and the *ENCePP Code of Conduct*.[13]

9.10.3. HSD (IT)

HSD 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 Access to extract data from a database.

Quality control of patient general data was conducted through the detection of outlying numerical values and validation rules, checking for duplicate records, grouping of diseases, and regular monitoring of aggregate clinical and drug data. All transformations in the data were logged in SQL scripts through version control. Furthermore, to ensure code reliability, double programming in Stata was used for all scripts. The study was conducted in accordance with the *ENCePP Guide on Methodological Standards in Pharmacoepidemiology*[14] and the *ENCePP Code of Conduct*.[13]

9.10.4. 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*[14] and the *ENCePP Code of Conduct*.[13] 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.

9.10.5. 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)*[14] and the *ENCePP Code of Conduct*.[13] 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.

9.10.6. 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 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.

9.10.7. 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.

9.10.8. CPRD (UK)

The DSRU had information security policies in place to preserve the confidentiality, integrity and availability of the organisation's systems and data. These included ensuring that the premises provide suitable physical and environmental security, all equipment was secure and protected against malicious software, the network was accessed only by authorised staff, telecommunication lines to the premises were protected from interception by being routed overhead or underground, and personnel received training regarding security awareness. The study was conducted according to the *Guidelines for Good Pharmacoepidemiology Practices (GPP)*[14] and according to the *ENCePP Code of Conduct*.[13] Data quality is a high priority at the DSRU and was guaranteed 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 diagnosis of their cause

- System process logs to document staff access, etc.

9.11. Protection of human subjects

9.11.1. Subject information and consent

This study mainly involved data that exist in anonymised structured format and contain no patient personal information.

All parties complied with all applicable laws, including laws regarding the implementation of organisational and technical measures to ensure protection of patient personal data. These measures included omitting patient names or other directly identifiable data in any reports, publications, or other disclosures, except where required by applicable laws.

Patient personal data were stored by the DAPs in encrypted electronic form and were password protected to ensure that only authorised study staff had access.

The DAPs implemented appropriate technical and organisational measures to ensure that personal data could be recovered in the event of disaster. In the event of a potential personal data breach, DAPs were responsible for determining whether a personal data breach had in fact occurred and, if so, provide breach notifications as required by law.

To protect the rights and freedoms of natural persons with regard to the processing of personal data, when study data were compiled for transfer to Pfizer and other authorised parties, any patient names were removed and were replaced by a single, specific, numerical code. All other identifiable data transferred to Pfizer or other authorised parties were identified by this single, patient-specific code. In the case of data transfer, Pfizer maintained high standards of confidentiality and protection of individuals' personal data consistent with the vendor contract and applicable privacy laws.

As this study did not involve data subject to privacy laws according to applicable legal requirements, obtaining informed consent from individuals by Pfizer was not required.

9.12. 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.

9.13. Ethical conduct of the study

The study was conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigour and follow generally accepted research practices described in the *Guidelines for Good Pharmacoepidemiology Practices (GPP)*[14] and according to the *ENCePP Code of Conduct*.[13]

10. RESULTS

10.1. Participants

The study period for this third interim report started in each country with the first Pfizer-BioNTech COVID-19 vaccinations between 8 December 2020 in the UK and 6 January 2021 in the Netherlands (Table 3). The dates for data extraction for this interim report are summarised in Table 3.

Three data sources could not contribute data to this third interim report: CPRD from the UK and ARS and HSD from Italy:

- Although data from CPRD were reported in the first interim report, they could not be included for this third interim report, because the extraction of the updated data with all the covariates took longer than expected due to CPRD server capacity issues. There was also a quality issue with the CPRD data availability that was disclosed in January 2023, and required re-extraction of data.

- Data from ARS were reported in the first and second interim report but could not re-extract data due to national and regional re-assessment of regulations affecting 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 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.

In the other data sources, data for events may originate from different data sources (GP, emergency visits, hospital discharge data sources). This may have an impact on the estimates for the incidence rates as shown in a recent study.[15]

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.

Data from NHR has been included in this third interim analysis for the first time. Data were available up to the end of 2021, and data for 2022 is expected to available for the next interim report since the data access provider receives data once yearly. Also, they have not

received data from all the requested data sources yet, as the hospitalisation data were not available. Hence the data for the events for this report are based on outpatient visits only.

The data in this third interim report from PHARMO were extracted from GP records only, as in the previous interim reports. Data on pregnancy status was not available for this report. The coding system used in the PHARMO databases is ICPC, which is not as granular as ICD coding, and therefore AESIs were identified using free text searching. The identification algorithms have not yet been validated, and this may result in more misclassification than in other data sources. We will investigate this before the next interim report. 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 EpiChron data sources included diagnosis codes from general practitioners and from hospital discharges up to July 2022 for this third interim report.,

The SIDIAP data source included diagnosis codes from general practitioners and from hospital discharges, and data up to June 2022 were included in this third interim report. However, because of differences in lag times in different data banks and delays in notifications about hospitalisations, hospitalization data for the end of the follow-up period, may be incomplete.

In this report we included data up until mid-2022 (i.e., June/July/August depending on the data source, see Table 3) except for NHR, which included data up to end of 2021 as the data for 2022 will only be available in Q2 2023. In this third interim report, we have used all matching criteria and verified the balance between the matched vaccinated and unvaccinated cohorts. Importantly, we also matched on pregnancy status (except in PHARMO, because no pregnancy linkage is currently available and Pedianet which is a paediatric database only) using a pregnancy algorithm developed by the ConcePTION project.

We used a negative control outcome, i.e., COVID-19 disease in the first 12 days after time zero to check if any residual confounding was present and, therefore, if there was a need to adjust the estimates using weights based on the propensity score. 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.

10.1.1. Vaccinated cohort

From among the 9,312,199 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 8,655,088 individuals who received ≥1 dose of Pfizer-BioNTech COVID-19 vaccine (Table 5). These individuals were from Italy (Pedianet 7,427 (<0.1%)); the Netherlands (PHARMO 1,136,778 (13.1%)), Norway (NHR 3,559,909 (41.1%)), and Spain (EpiChron 733,132 (8.5%) and SIDIAP 3,217,842 (37.2%)). The main reason for non-inclusion was the receipt of a COVID-19 vaccine other than Pfizer-BioNTech; the highest non-inclusion rate was in EpiChron (10.6%) and the lowest in SIDIAP (3.0%). A total of 26,814 pregnant

women who had received at least one dose of the Pfizer-BioNTech COVID-19 vaccine were included.

Table 5.   Attrition table for the Pfizer-BioNTech COVID-19 vaccinated cohort (before matching) by data source*

	Pedianet n (%)	PHARMO n (%)	NHR n (%)	EpiChron n (%)	SIDIAP n (%)
Received a first dose of Pfizer-BioNTech COVID-19 vaccine	7,979 (100)	1,267,710 (100)	3,831,685 (100)	830,348 (100)	3,374,477 (100)
Had ≥12 months continuous enrolment[a] AND received a Pfizer-BioNTech vaccine	7,785 (97.57)	1,256,050 (99.08)	3,828,631 (99.92)	816,522 (98.33)	3,315,658 (98.26)
Received no prior COVID-19 vaccination, other than Pfizer-BioNTech vaccine, AND had ≥12 months continuous enrolment AND received a Pfizer-BioNTech vaccine	7,427 (93.08)	1,136,778 (89.67)	3,559,909 (92.91)	733,132 (88.29)	3,217,842 (95.36)
Total first dose Pfizer-BioNTech vaccinated included[b]	7,427 (93.08)	1,136,778 (89.67)	3,559,909 (92.91)	733,132 (88.29)	3,217,842 (95.36)
Pregnant women vaccinated with 1st dose Pfizer-BioNTech vaccinated included	NA	NA**	8,882 (0.23)	4,090 (0.49)	13,842 (0.41)

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;

**Pregnancy data not yet available

10.1.1.1. Number and timing of doses in all vaccinated persons

The number of Pfizer-BioNTech COVID 19 vaccine doses and the timing of vaccination (in weeks) by data source are summarized in Table 6. Overall, 7,127,423 persons received a second dose (82.3%). The interval between the first and second doses was longer than 6 weeks for15.8% of these individuals. This 6-week interval is based on the recommended 4-week scheme, with an additional 2-week security margin. The number of individuals who received a second dose within 6 weeks after the 1st dose varied from 52.2% in NHR to 89.7% in EpiChron. In the paediatric data source, Pedianet, 82.8% of the children received their second dose within six weeks, at the time of database lock. A total of 1,948,651 individuals received a third dose of the Pfizer-BioNTech COVID 19 vaccine, which is 22.5% of the individuals included who had received the 1st dose. The interval between dose 2 and 3 varied between data sources with medians that ranged from 21 weeks (Pedianet) to 29 weeks (EpiChron and SIDIAP). EMA current 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., Comnirnaty 30 micrograms) after primary vaccination for individuals older than 12 years.[16] In Spain (EpiChron and SIDIAP) individuals aged 18 years and older are recommended to receive a first booster (i.e., third dose) 5 months after the last dose of the complete vaccination schedule. In the Netherlands (PHARMO) individuals older than 11 years are recommended to receive repeated vaccinations after at least 3 months after the last vaccination. In Italy and Norway specific recommendations are for at special risk population only.

A total of 6,784 individuals had received a fourth dose, at the time of database lock.

Table 6.   Pfizer-BioNTech COVID-19 vaccine doses received (n,%) and timing (in weeks) by data source*

	Pedianet	NHR	PHARMO	EpiChron	SIDIAP
Total first dose COVID-19 vaccine received, N	7,427 (100)	3,559,909 (100)	1,136,778 (100)	733,132 (100)	3,217,842 (100)
Second dose COVID-19 vaccine received within 6 weeks (completion rate) after 1st dose, n (%)	6,146 (82.75)	1,856,909 (52.16)	764,172 (67.22)	657,348 (89.66)	2,719,601 (84.52)
Second dose COVID-19 vaccine received >6 weeks after 1st dose, n (%)	166 (2.24)	781,668 (21.96)	118,639 (10.44)	25,675 (3.50)	197,099 (6.13)
Interval between first and second dose COVID-19 vaccine (weeks)					
Median (Q1, Q3) (weeks)	3.14 (3.00-3.86)	6 (5.86-7.29)	5 (5.00-5.14)	3 (3.00-3.00)	3 (3.00-3.29)
Minimum, maximum (weeks)	2.57, 45.29	2.14, 51.00	2.14, 71.43	2.14, 78.29	2.14, 74.86
< 2 weeks, n (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
2-4 weeks, n (%)	5,534 (87.67)	414,250 (19.57)	490,016 (18.57)	654,104 (95.77)	2,683,133 (91.99)
5-6 weeks, n (%)	612 (9.70)	1,107,932 (52.34)	1,366,893 (51.80)	3,244 (0.47)	36,468 (1.25)
7-8 weeks, n (%)	18 (0.29)	328,355 (15.51)	420,527 (15.94)	1,300 (0.19)	80,270 (2.75)
9-12 weeks, n (%)	7 (0.11)	219,965 (10.39)	269,133 (10.20)	1,596 (0.23)	54,650 (1.87)
13-18 weeks, n (%)	15 (0.24)	23,824 (1.13)	37,725 (1.43)	2,102 (0.31)	22,963 (0.79)
>18 weeks, n (%)	126 (2)	22,335 (1.06)	54,283 (2.06)	20,677 (3.03)	39,216 (1.34)

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Table 6.   Pfizer-BioNTech COVID-19 vaccine doses received (n,%) and timing (in weeks) by data source*

	Pedianet	NHR	PHARMO	EpiChron	SIDIAP
Third dose COVID-19 received	929 (12.51)	1,087,037 (30.54)	204,773 (18.01)	214,812 (29.30)	441,100 (13.71)
Interval between second and third dose COVID-19 vaccine (weeks)					
Median (Q1, Q3) (weeks)	21.29 (19.00-24.57)	27.14 (25.29 - 30.00)	25.14 (22.71-30.29)	29.14 (27.14-33.00)	29.14 (27.14-33.86)
Minimum, maximum (weeks)	14.14, 48.71	13.00, 48.14	13.00, 73.00	13.00, 78.71	13.00, 74.71
<12 weeks, n (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
12-24 weeks, n (%)	719 (77.40)	232,355 (21.38)	99,849 (48.76)	13,697 (6.38)	19,661 (4.46)
25-37 weeks, n (%)	200 (21.53)	763,744 (70.26)	85,252 (41.63)	172,703 (80.40)	356,294 (80.77)
38-50 weeks, n (%)	10 (1.08)	90,938 (8.37)	18,224 (8.90)	21,889 (10.19)	57,624 (13.06)
>50 weeks, n (%)	0 (0)	0 (0)	1,448 (0.71)	6,523 (3.04)	7,521 (1.71)
Fourth dose COVID-19 vaccine received	0 (0)	203 (0.01)	5,557 (0.49)	526 (0.07)	498 (0.02)
Interval between third and fourth dose COVID-19 vaccine (weeks)					
Median (Q1, Q3) (weeks)	NA	13 (13.57-16.79)	15.29 (14.00-17.86)	28 (24.00-32.36)	29 (27.00-30.00)
Minimum, maximum (weeks)	NA	13.00; 28.14	13.00, 50.71	13.14, 50.57	14.86, 36.86
<12 weeks, n (%)	NA	0 (0)	0 (0)	0 (0)	0 (0)
12-24 weeks, n (%)	NA	198 (97.54)	5,160 (92.86)	154 (29.28)	65 (13.05)
25-37 weeks, n (%)	NA	5 (2.46)	385 (6.93)	353 (67.11)	433 (86.95)

Table 6.   Pfizer-BioNTech COVID-19 vaccine doses received (n,%) and timing (in weeks) by data source*

	Pedianet	NHR	PHARMO	EpiChron	SIDIAP
38-50 weeks, n (%)	NA	0 (0)	12 (0.22)	19 (3.61)	0 (0)
>50 weeks, n (%)	NA	0 (0)	0 (26.06)	0 (0)	0 (0)

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

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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 7. The median age of the vaccinated cohort at first dose ranged from 45 years in SIDIAP to 50 years in PHARMO. The median age at first dose in Pedianet, which contains data only for children, was 10 years. The percentage of females among those who received a 1st dose varied from 48.50% in Pedianet to 52.16% in EpiChron (Table 7).

A total of 110 children under 5 years of age received a first dose of the Pfizer-BioNTech COVID-19 vaccine. A total of 12,753 pregnant women received their first dose during their first trimester of pregnancy and 2,643 during their second trimester.

Most individuals received their first dose in the second quarter of 2021, except in 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, or first quarter 2022 depending on the time of the database lock in the different data sources.

The median age of individuals who received a third dose ranged from 36 years in PHARMO to 77 years in SIDIAP. The percentage of females among those who received a third dose ranged from 49.84% in Pedianet to 58.08% in SIDIAP.

Information on long-term care facility residency and healthcare or essential worker status was not available in the databases. Available data for personal lifestyle variables showed that 6.97% and 4.47% those who received dose 1 and 7.53% and 5.86% of those who received dose 3 in EpiChron and SIDIAP, respectively, were current smokers. In most of the databases BMI data were mainly missing. In SIDIAP most of those who received the 1st and 3rd dose with BMI data available were overweight or obese. Between 61.50% and 79.63% of those vaccinated used primary care at least twice in the year prior to their 1st dose. In the year prior to vaccination, 6.01% and 6.37% of those who had received a first dose in Epichron and SIDIAP, respectively, had been hospitalized once.

Table 7. 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)

Baseline characteristics	Pedianet		NHR		PHARMO	
	1st dose	3rd dose	1st dose	3rd dose	1st dose	3rd dose
Total, n (%)	7,427 (100)	929 (12.51)	3,559,909 (100)	1,087,037 (30.54)	1,136,778 (100)	204,773 (18.01)
Demographics						
Age (years)						
Mean (SD)	9.56 (2.50)	12.29 (0.53)	47.20 (20.93)	66.06 (14.71)	48.90 (21.83)	42.70 (20.22)
Median (Q1, Q3)	10 (7, 12)	12 (12, 13)	47 (29,64)	68 (59,76)	50 (31, 69)	36 (27, 57)
Age groups (years), n (%)						
0-1	0 (0)	0 (0)	<5 (<0.01)	0 (0)	0 (0)	0 (0)
2-4	12 (0.16)	0 (0)	<5 (<0.01)	0 (0)	71 (0.01)	0 (0)
5-11	5,262 (70.85)	37 (3.98)	303 (0.01)	0 (0)	9,820 (0.86)	5 (<0.01))
12-15	2,153 (28.99)	892 (96.02)	199,659 (5.61)	21 (<0.01)	65,275 (5.74)	1,904 (0.93)
16-17	NA	NA	116,610 (3.28)	581 (0.05)	38,118 (3.35)	3,169 (1.55)
18-29	NA	NA	576,282 (16.19)	32,048 (2.95)	156,062 (13.73)	57,656 (28.16)
30-39	NA	NA	489,057 (13.74)	36,253 (3.34)	145,460 (12.80)	56,138 (27.41)
40-49	NA	NA	516,894 (14.52)	71,873 (6.61)	150,324 (13.22)	21,298 (10.40)
50-59	NA	NA	551,053 (15.48)	144,736 (13.31)	191,624 (16.86)	20,142 (9.84)
60-64	NA	NA	243,934 (6.85)	111,015 (10.21)	14,837 (1.31)	1,906 (0.93)
65-69	NA	NA	241,212 (6.78)	186,795 (17.18)	95,332 (8.39)	8,862 (4.33)
70-79	NA	NA	411,374 (11.56)	338,959 (31.18)	188,951 (16.62)	20,349 (9.94)

Table 7. **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)**

Baseline characteristics	Pedianet		NHR		PHARMO	
	1st dose	3rd dose	1st dose	3rd dose	1st dose	3rd dose
80+	NA	NA	213,528 (6.00)	164,756 (15.16)	80,904 (7.12)	13,344 (6.52)
Female, n (%)	3,602 (48.50)	463 (49.84)	1,767,888 (49.66)	583,958 (53.72)	576,560 (50.72)	104,069 (50.82)
Pregnancy status, n (%)	NA	NA	6,176 (0.17)	52 (<0.01)	NA**	NA**
First trimester	NA	NA	1,831 (0.05)	20 (<0.01)	NA	NA
Second trimester	NA	NA	1,367 (0.04)	0 (<0.01)	NA	NA
Third trimester	NA	NA	2,964 (0.08)	32 (<0.01)	NA	NA
Residency in a long-term care facility, n (%)	NA	NA	NA	NA	NA	NA
Healthcare worker or essential worker status, n (%)	NA	NA	NA	NA	NA	NA
Date of vaccination, n (%)						
1 Oct–31 Dec 2020	0 (0)	0 (0)	1,929 (0.05)	0 (0)	0 (0)	0 (0)
1 Jan–31 Mar 2021	0 (0)	0 (0)	488,551 (13.72)	0 (0)	123,987 (10.91)	0 (0)
1 Apr–30 Jun 2021	163 (2.19)	0 (0)	1,673,030 (47)	36 (0)	583,751 (51.35)	147 (0.07)
1 Jul–30 Sep 2021	1,338 (18.02)	0 (0)	1,292,649 (36.31)	7,710 (0.71)	330,593 (29.08)	327 (0.16)
1 Oct–31 Dec 2021	2,295 (30.90)	2 (0.22)	103,750 (2.91)	1,079,291 (99.29)	59,656 (5.25)	50,524 (24.67)
1 Jan–31 Mar 2022	3,511 (47.27)	847 (91.17)	NA**	NA**	35,344 (3.11)	142,857 (69.76)
1 Apr–30 Jun 2022	100 (1.35)	64 (6.89)	NA**	NA**	3,447 (0.30)	10,918 (5.33)
1 Jul–30 Sep 2022	20 (0.27)	16 (1.72)	NA**	NA**	NA	NA
Personal lifestyle characteristics						
Smoking status, n (%)						
Current	NA	NA	NA	NA	0 (0)	31 (0.02)
Former	NA	NA	NA	NA	0 (0)	31 (0.02)

Table 7.   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**
Never	NA	NA	NA	NA	0 (0)	109 (0.05)
Never or former	NA	NA	NA	NA	0 (0)	0 (0)
Unknown	7,427 (100)	929 (100)	2,833,778 (100)	886,387 (100)	1,136,778 (86.74)	204,602 (86.01)
Body Mass Index, n (%)						
Underweight (BMI < 20 kg/m^2)	5,792 (77.99)	546 (58.77)	NA	NA	8,362 (0.74)	1,374 (0.67)
Normal weight (BMI 20 to < 25 kg/m^2)	1,297 (17.46)	303 (32.62)	NA	NA	74,153 (6.52)	10,545 (5.15)
Overweight (BMI 25 to < 30 kg/m^2)	257 (3.46)	63 (6.78)	NA	NA	137,759 (12.12)	17,804 (8.69)
Obese (BMI ≥ 30 kg/m^2)	37 (0.50)	10 (1.08)	NA	NA	99,470 (8.75)	13,572 (6.63)
BMI missing	44 (0.59)	7 (0.75)	NA	NA	817,034 (71.87)	161,478 (78.86)
Obesity diagnosis or obesity surgery	396 (5.33)	62 (6.67)	113,698 (3.19)	45,476 (4.18)	21,460 (1.89)	3,735 (1.82)
Healthcare utilisation						
Number of hospitalisations, n (%)						
0	7,280 (98.02)	917 (98.71)	NA	NA	NA	NA
1	125 (1.68)	11 (1.18)	NA	NA	NA	NA
2+	147 (1.98)	12 (1.29)	NA	NA	NA	NA
Number of emergency department visits, n (%)						
0	NA	NA	NA	NA	NA	NA
1	NA	NA	NA	NA	NA	NA
2+	NA	NA	NA	NA	NA	NA

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Table 7.   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**
Skilled nursing facility, nursing home, or extended care facility stay, n (%)						
0	NA	NA	NA	NA	NA	NA
1	NA	NA	NA	NA	NA	NA
2+	NA	NA	NA	NA	NA	NA
Primary care utilisation, n visits (%)						
0	925 (12.45)	99 (10.66)	NA	NA	274,059 (24.11)	50,074 (24.45)
1	1,210 (16.29)	173 (18.62)	NA	NA	163,629 (14.39)	29,838 (14.57)
2+	5,292 (71.25)	657 (70.72)	NA	NA	699,090 (61.50)	124,861 (60.98)
Cancer screening, n (%)						
0	NA	NA	NA	NA	NA	NA
1	NA	NA	NA	NA	NA	NA
2+	NA	NA	NA	NA	NA	NA
Other preventive health services, n (%)						
COVID-19 tests, n (%)						
0	2,091 (28.15)	136 (14.64)	NA	NA	NA	NA
1-2	4,586 (61.75)	617 (66.42)	NA	NA	NA	NA
3-4	689 (9.28)	159 (17.12)	NA	NA	NA	NA
5+	61 (0.82)	17 (1.83)	NA	NA	NA	NA

*Refer to Table 3 for information on time periods for data; **Data not yet available for 2022

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Table 7. **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)**

Baseline characteristics	EpiChron		SIDIAP	
	1st dose	3rd dose	1st dose	3rd dose
Total, n (%)	733,132 (100)	214,812 (29.30)	3,217,842 (100)	441,100 (13.71)
Demographics				
Age (years)				
Mean (SD)	50.57 (21.68)	59.98 (19.44)	46.16 (23.18)	69.04 (21.32)
Median (Q1, Q3)	49 (35, 70)	58 (46, 76)	45 (28, 61)	77 (56, 84)
Age groups (years), n (%)				
0-1			<5 (0)	
2-4			22 (0)	2 (0)
5-11	2,652 (0.36)	8 (<0.01)	188,092 (5.85)	28 (0.01)
12-15	36,856 (5.03)	269 (0.13)	198,792 (6.18)	1,823 (0.41)
16-17	17,632 (2.41)	1,884 (0.88)	98,822 (3.07)	5,041 (1.14)
18-29	80,816 (11.02)	11,990 (5.58)	355,499 (11.05)	31,987 (7.25)
30-39	92,867 (12.67)	19,260 (8.97)	412,788 (12.83)	25,066 (5.68)
40-49	144,029 (19.65)	37,254 (17.34)	621,710 (19.32)	30,037 (6.81)
50-59	124,921 (17.04)	41,784 (19.45)	525,504 (16.33)	24,372 (5.53)
60-64	13,523 (1.84)	3,658 (1.70)	41,916 (1.30)	4,132 (0.94)
65-69	33,742 (4.60)	14,246 (6.63)	45,754 (1.42)	7,030 (1.59)
70-79	104,733 (14.29)	44,217 (20.58)	407,842 (12.67)	136,397 (30.92)
80+	81,361 (11.10)	40,242 (18.73)	321,099 (9.98)	175,185 (39.72)
Female, n (%)	382,396 (52.16)	113,410 (52.80)	1,671,688 (51.95)	256,059 (58.05)
Pregnancy status, n (%)	3,368 (0.46)	296 (0.14)	9,968 (0.31)	220 (0.05)
First trimester	955 (0.13)	61 (0.03)	9,967 (0.31)	220 (0.05)

Table 7. 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	
Baseline characteristics	**1st dose**	**3rd dose**	**1st dose**	**3rd dose**
Second trimester	1,275 (0.17)	104 (0.05)	<5 (<0.01)	0 (0)
Third trimester	1,129 (0.15)	131 (0.06)	0 (0)	0 (0)
Residency in a long-term care facility, n (%)	0 (0)	0 (0)	0 (0)	0 (0)
Healthcare worker or essential worker status, n (%)				
Date of vaccination, n (%)				
1 Oct–31 Dec 2020	2,299 (0.31)	0 (0)	4,972 (0.15)	0 (0)
1 Jan–31 Mar 2021	106,019 (14.46)	0 (0)	427,697 (13.29)	0 (0)
1 Apr–30 Jun 2021	379,284 (51.73)	8 (0)	1,639,321 (50.94)	17 (0)
1 Jul–30 Sep 2021	223,902 (30.54)	11,668 (5.43)	872,739 (27.12)	32,344 (7.33)
1 Oct–31 Dec 2021	16,233 (2.21)	102,614 (47.77)	172,084 (5.35)	301,700 (68.40)
1 Jan–31 Mar 2022	4,625 (0.63)	81,310 (37.85)	92,503 (2.87)	44,142 (10.01)
1 Apr–30 Jun 2022	574 (0.08)	11,612 (5.41)	8,526 (0.26)	62,897 (14.26)
1 Jul–30 Sep 2022	196 (0.03)	7,600 (3.54)	0 (0)	0 (0)
Personal lifestyle characteristics				
Smoking status, n (%)				
Current	51,105 (6.97)	16,180 (7.53)	143,751 (4.47)	25,838 (5.86)
Former	0 (0)	0 (0)	387,231 (12.03)	27,715 (6.28)
Never	0 (0)	0 (0)	1,590,048 (49.41)	323,371 (73.31)
Never or former	166,813 (22.75)	66,989 (31.18)	0 (0)	0 (0)
Unknown	515,214 (70.28)	131,643 (61.28)	1,096,812 (2.37)	64,176 (3.69)

Table 7. **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	
Baseline characteristics	**1st dose**	**3rd dose**	**1st dose**	**3rd dose**
Body Mass Index, n (%)				
Underweight (BMI < 20 kg/m^2)	18,248 (2.49)	1,351 (0.63)	370,956 (11.53)	14,692 (3.33)
Normal weight (BMI 20 to < 25 kg/m^2)	44,921 (6.13)	9,243 (4.30)	626,229 (19.46)	87,213 (19.77)
Overweight (BMI 25 to < 30 kg/m^2)	48,512 (6.62)	16,830 (7.83)	737,229 (22.91)	156,071 (35.38)
Obese (BMI ≥ 30 kg/m^2)	77,267 (10.54)	31,662 (14.74)	531,993 (16.53)	114,446 (25.95)
BMI missing	544,184 (74.23)	155,726 (72.49)	951,435 (29.57)	68,678 (15.57)
Obesity diagnosis or obesity surgery	47,922 (6.54)	15,818 (7.36)	486,069 (15.11)	98,356 (22.30)
Healthcare utilisation				
Number of hospitalisations, n (%)				
0	677,470 (92.41)	195,225 (90.88)	2,945,284 (91.53)	370,736 (84.05)
1	44,090 (6.01)	14,664 (6.83)	205,067 (6.37)	49,082 (11.13)
2+	11,572 (1.58)	4,923 (2.29)	67,491 (2.10)	21,282 (4.82)
Number of emergency department visits, n (%)				
0	592,442 (80.81)	171,711 (79.94)	NA	NA
1	95,373 (13.01)	29,017 (13.51)	NA	NA
2+	45,317 (6.18)	14,084 (6.56)	NA	NA
Skilled nursing facility, nursing home, or extended care facility stay, n (%)				
0	NA	NA	NA	NA
1	NA	NA	NA	NA
2+	NA	NA	NA	NA

Table 7. **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	
Baseline characteristics	**1st dose**	**3rd dose**	**1st dose**	**3rd dose**
Primary care utilisation, n visits (%)				
0	83,868 (11.44)	14,839 (6.91)	415,448 (12.91)	14,155 (3.21)
1	52,080 (7.10)	12,611 (5.87)	240,058 (7.46)	9,157 (2.08)
2+	597,184 (81.46)	187,362 (87.22)	2,562,336 (79.63)	417,788 (94.72)
Cancer screening, n (%)				
0	NA	NA	NA	NA
1	NA	NA	NA	NA
2+	NA	NA	NA	NA
Other preventive health services, n (%)				
COVID-19 tests, n (%)				
0	513,566 (70.05)	125,184 (58.28)	1,415,552 (43.99)	160,083 (36.29)
1-2	219,566 (29.95)	89,628 (41.72)	1,239,913 (38.53)	155,881 (35.34)
3-4	0 (0)	0 (0)	366,530 (11.39)	57,512 (13.04)
5+	0 (0)	0 (0)	195,847 (6.09)	67,624 (15.33)

10.1.2. Matched cohorts

The attrition data for the matched vaccinated and unvaccinated cohorts are summarised by data source in Table 8. From a total of 8,655,088 vaccinated individuals included 8,352,451 (96.5%) who could be matched with an unvaccinated individual at time zero (Table 8). 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 8.   Attrition table for the matched cohort by data source*

	Pedianet	NHR	PHARMO	EpiChron	SIDIAP
Vaccinated cohort					
Received a Pfizer-BioNTech vaccine, n (%)	7,979 (100)	3,831,685 (100)	1,267,710 (100)	830,348 (100)	3,374,477 (100)
Total vaccinated included, n (%)[a]	7,427 (93.08)	3,559,909 (92.91)	1,136,778 (89.67)	733,132 (88.29)	3,217,842 (95.36)
Pregnant women vaccinated, n (%)	NA	8,882 (0.23)	NA**	4,090 (0.49)	13,842 (0.41)
Matched cohort					
Vaccinees matched, n (%)	7,093 (99.91)	3,542,514	973,685 (85.65)	614,347 (83.80)	3,214,812 (99.91)
Served as control before vaccination, n (%)	1,205 (16.99)	2,420,870	427,345 (43.89)	287,232 (46.75)	1,718,068 (53.44)
Unvaccinated, n (%)	7,093 (95.50)	3,542,514	973,685 (85.65)	614,347 (83.80)	3,214,812 (99.91)
Unique unvaccinated matched included, n (%)	6,017 (84.83)	2,041,298	662,164 (68.01)	387,934 (63.15)	2,049,443 (63.75)
Number of times a comparator selected for matching, n	1.18	1.74	1.47	1.58	1.57
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)
Min-Max	1–5	1–14	1–11	1– 8	1– 14
1, n (%)	5,095 (71.83)	1,163,907 (32.86)	443,109 (45.51)	245,784 (40.01)	1,293,386 (40.23)
2, n (%)	796 (11.22)	506,986 (14.31)	152,094 (15.62)	89,204 (14.52)	488,584 (15.20)
3, n (%)	102 (1.44)	217,782 (6.15)	48,101 (4.94)	33,275 (5.42)	175,535 (5.46)
4, n (%)	20 (0.28)	91,322 (2.58)	13,853 (1.42)	12,427 (2.02)	60,058 (1.87)
5 or more, n (%)	4 (0.06)	61,301 (1.73)	5,007 (0.51)	7,244 (1.18)	31,880 (0.99)

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;
**Pregnancy data not yet available from PHARMO

The median person-months of follow up from first dose until censoring ranged from 0.8 month in NHR to 7.7 months in Pedianet. This was short in all data sources, but similar for vaccinated and unvaccinated cohorts since the censoring date was the same for both (Table 9).

A total of 4,994,594 (59.8%) matched unvaccinated individuals were censored because of receipt of a COVID-19 vaccine (Pfizer-BioNTech COVID-19 or non-Pfizer-BioNTech COVID-19) (Table 9). The percentages of individuals censored for exiting the data sources, end of data availability or death ranged from 0.2% in NHR to 9.4% in PHARMO.

Table 9.   Cohort follow-up and reasons for censoring by vaccination status (matched cohort design), by data source

	Pedianet		NHR		PHARMO		EpiChron		SIDIAP	
	Vac	Unvac	Vac	Vac	Unvac	Vac	Vac	Unvac	Vac	Unvac
Total, n (%)	7,093 (100)	7,093 (100)	3,542,514 (100)	3,542,514 (100)	973,685 (100)	973,685 (100)	614,347 (100)	614,347 (100)	3,214,812 (100)	3,214,812 (100)
Person-months of follow-up										
Median (Q1, Q3) (months)	7.7 (5.2, 8.1)	7.7 (4.8, 8.1)	0.8 (0.3, 2.1)	0.8 (0.3, 2.1)	2.2 (0.4, 7.7)	2.0 (0.4, 7.5)	0.9 (0.3, 7.2)	0.90 (0.3, 7.0)	1.3 (0.3, 6.3)	1.3 (0.3, 6.3)
Min, max (months)	0.1, 14.8	0, 14.9	0, 12.1	0, 12.0	0, 17.6	0, 17.6	0 (19.2)	0 (19.2)	0 (18.1)	0 (18.1)
Reasons for censoring, n (%)										
Non-Pfizer-BioNTech vaccine received	8 (0.1)	145 (2.0)	233,034 (6.6)	323,245 (9.1)	105,543 (10.8)	105,104 (10.8)	35,885 (5.8)	78,308 (12.7)	283,474 (8.8)	571,799 (17.8)
Unvaccinated received Pfizer or non-Pfizer COVID-19 vaccine		1,368 (19.3)		2,406,032 (67.9)		503,869 (51.7)		364,561 (59.3)		1,718,764 (53.5)
Exit from data source[a]	572 (8.1)	592 (8.3)	6,327 (0.2)	14,497 (0.4)	78,264 (8.0)	91,225 (9.4)	3,162 (0.5)	10,764 (1.8)	36,968 (1.10)	37,946 (1.2)

a Administrative end of follow-up, including death (any cause) 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 10. The median age at first dose in the vaccinated and unvaccinated cohorts ranged from 45 years in SIDIAP to 49 years in PHARMO. The median age at first dose in Pedianet, was 10 years. The percentage of females who had received a 1st dose varied from 48.41% in Pedianet to 52.07% in EpiChron (in both cohorts since they were matched on sex) (Table 10). Most first doses of the Pfizer-BioNTech COVID-19 vaccine were administered in the second quarter of 2021, except for the paediatric population in Pedianet when this was in the last quarter of 2021 and 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 NHR and EpiChron and in the first trimester in SIDIAP. Information on long-term care facility residency and healthcare worker or essential worker status could not be identified in the data sources.

In EpiChron and SIDIAP the distributions of smoking status in the vaccinated and unvaccinated cohorts were similar. The number of individuals with unknown smoking status was higher in EpiChron than in SIDIAP (just over 70% in EpiChron and about 35% in SIDIAP). In Pedianet, NHR and PHARMO, the information on smoking status was not collected. BMI data were missing for about 24% of individuals in Pedianet, 30% of individuals in SIDIAP and >70% of individuals in PHARMO and EpiChron; 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. Healthcare use indicators were similar in the vaccinated and unvaccinated cohorts, but these were only successfully assessed in EpiChron and SIDIAP.

Table 10.   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	7,093	7,093		3,542,514	3,542,514		973,685	973,685	
Demographics									
Age (years)			0.06			0.00			0.00
Mean (SD)	9.55 (2.49)	9.41 (2.50)		47.15 (20.90)	47.05 (20.89)		48.24 (21.63)	48.18 (21.61)	
Median (Q1, Q3)	10 (7,12)	10 (7,11)		47 (29,64)	47 (29,64)		49 (30,68)	49 (30,68)	
Age groups (years), n (%)			0.26			0.13			0.05
0-1				<5 (<0.01)	<5 (<0.01)				
2-4	11 (0.16)	213 (3)		<5 (<0.01)	<5 (<0.01)		60 (0.01)	231 (0.02)	
5-11	5,040 (71.06)	5,259 (74.14)		300 (0.01)	30,073 (0.85)		8,720 (0.90)	10,394 (1.07)	
12-15	2,042 (28.79)	1,621 (22.85)		199,243 (5.62)	186,864 (5.27)		58,712 (6.03)	57,752 (5.93)	
16-17	NA	NA		116,188 (3.28)	114,713 (3.24)		34,186 (3.51)	34,716 (3.57)	
18-29	NA	NA		574,025 (16.20)	557,852 (15.75)		137,810 (14.15)	136,672 (14.04)	
30-39	NA	NA		487,344 (13.76)	490,751 (13.85)		123,004 (12.63)	122,195 (12.55)	
40-49	NA	NA		514,926 (14.54)	514,480 (14.52)		128,034 (13.15)	128,592 (13.21)	
50-59	NA	NA		548,899 (15.49)	549,266 (15.50)		169,760 (17.43)	166,110 (17.06)	
60-64	NA	NA		242,808 (6.85)	251,644 (7.10)		11,290 (1.16)	16,444 (1.69)	
65-69	NA	NA		240,043 (6.78)	235,071 (6.64)		82,723 (8.50)	82,269 (8.45)	
70-79	NA	NA		408,959 (11.54)	406,233 (11.47)		160,059 (16.44)	161,896 (16.63)	
80+	NA	NA		209,776 (5.92)	205,561 (5.80)		59,327 (6.09)	56,414 (5.79)	
Female, n (%)	3,434 (48.41)	3,434 (48.41)	0	NA*	NA*	0	493,708 (50.71)	493,708 (50.71)	0
Pregnancy status, n (%)	NA	NA		5,631 (0.16)	5,631 (0.16)	0	NA**	NA**	
First trimester				1,639 (0.05)	490 (0.01)				
Second trimester				1,290 (0.04)	1,466 (0.04)				

Table 10. 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**
Third trimester				2,690 (0.08)	3,525 (0.10)				
Residency in a long-term care facility, n (%)	NA	NA	0	NA	NA	0	NA	NA	0
Healthcare worker or essential worker status, n (%)	NA	NA		NA	NA		NA	NA	
Date of vaccination or matching, n (%)			2.92			1.31			1.39
1 Oct–31 Dec 2020	0 (0)	0 (0)		1,915 (0.05)	12 (<0.01)		0 (0)	0 (0)	
1 Jan–31 March 2021	0 (0)	0 (0)		485,263 (13.70)	227,441 (6.42)		102,348 (10.51)	36,506 (3.75)	
1 Apr–30 Jun 2021	151 (2.13)	1 (0.01)		1,667,431 (47.07)	1,024,043 (28.91)		511,143 (52.50)	239,259 (24.57)	
1 Jul–30 Sep 2021	1,269 (17.89)	182 (2.57)		1,286,321 (36.31)	1,050,659 (29.66)		287,769 (29.55)	158,354 (16.26)	
1 Oct–31 Dec 2021	2,206 (31.10)	279 (3.93)		101,584 (2.87)	145,783 (4.12)		43,846 (4.50)	50,756 (5.21)	
1 Jan–31 Mar 2022	3,359 (47.36)	885 (12.48)		NA	NA		26,005 (2.67)	23,210 (2.38)	
1 Apr–30 Jun 2022	92 (1.30)	21 (0.30)		NA	NA		2,574 (0.26)	2,036 (0.21)	
1 Jul–30 Sep 2022	16 (0.23)	7 (0.10)		NA	NA		0 (0)	0 (0)	
Personal lifestyle characteristics									
Smoking status, n (%)			0			0			0
Current	NA	NA		NA	NA		NA	NA	
Former	NA	NA		NA	NA		NA	NA	
Never	NA	NA		NA	NA		NA	NA	
Never or former	NA	NA		NA	NA		NA	NA	
Unknown	NA	NA		NA	NA		NA	NA	
BMI			0.33			0			0.05
Underweight (BMI <20kg/m^2)	4,043 (57.00)	3,327 (46.91)		NA	NA		6,819 (0.70)	7,907 (0.81)	

Table 10. 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
Normal weight (BMI 20 to <25kg/m^2)	1,109 (15.64)	823 (11.60)		NA	NA		61,326 (6.30)	57,061 (5.86)	
Overweight (BMI 25 to <30kg/m^2)	228 (3.21)	192 (2.71)		NA	NA		115,214 (11.83)	104,582 (10.74)	
Obese (BMI ≥30kg/m^2)	34 (0.48)	20 (0.28)		NA	NA		83,395 (8.56)	78,231 (8.03)	
BMI missing	1,679 (23.67)	2,731 (38.50)		NA	NA		706,931 (72.60)	725,904 (74.55)	
Obesity diagnosis or obesity surgery	365 (5.15)	332 (4.68)		113,145 (3.19)	95,564 (2.70)		17,476 (1.79)	16,471 (1.69)	
Healthcare utilisation									
Number of hospitalisations, n (%)			0.05			0			0
0	6,954 (98.04)	7,000 (98.69)		NA	NA		NA	NA	
1	117 (1.65)	80 (1.13)		NA	NA		NA	NA	
2+	22 (0.31)	13 (0.18)		NA	NA		NA	NA	
Number of emergency department visits, n (%)			0			0			0
0	NA	NA		NA	NA		NA	NA	
1	NA	NA		NA	NA		NA	NA	
2+	NA	NA		NA	NA		NA	NA	
Skilled nursing facility, nursing home, or extended care facility stay, n (%)			0			0			0
0	NA	NA		NA	NA		NA	NA	
1	NA	NA		NA	NA		NA	NA	
2+	NA	NA		NA	NA		NA	NA	
Primary care utilisation, n (%)			0.40			0			0.04

Table 10. 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**
0	909 (12.82)	2,046 (28.85)		NA	NA		245,345 (25.20)	264,542 (27.17)	
1	1,174 (16.55)	1,039 (14.65)		NA	NA		144,079 (14.80)	141,747 (14.56)	
2+	5,010 (70.63)	4,008 (56.51)		NA	NA		584,261 (60.01)	567,396 (58.27)	
Cancer screening, n (%)			0			0			0
0	NA	NA		NA	NA		NA	NA	
1	NA	NA		NA	NA		NA	NA	
2+	NA	NA		NA	NA		NA	NA	
Other preventive health services, n (%)									
COVID-19 tests, n (%)			0.32			0			0
0	2,012 (28.37)	3,078 (43.39)		NA	NA		NA	NA	
1-2	4,387 (61.85)	3,533 (49.81)		NA	NA		NA	NA	
3-5	637 (8.98)	451 (6.36)		NA	NA		NA	NA	
5+	57 (0.80)	31 (0.44)		NA	NA		NA	NA	

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

*percentage of females was not available in the matched cohort, this will be corrected in the next interim report;

**Data not yet available for 2022

Table 10. **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		
	Vac	**Unvac**	**ASD**	**Vac**	**Unvac**	**ASD**
Total, N	614,347	614,347		3,214,812	3,214,812	
Demographics						
Age (years)			0.01			0.00
Mean (SD)	49.38 (21.21)	49.26 (21.16)		46.15 (23.17)	46.06 (23.15)	
Median (Q1, Q3)	48 (34, 68)	48 (34, 68)		45 (28, 61)	45 (28, 61)	
Age groups (years), n (%)			0.06			0.08
0-1				<5 (<0.01)	<5 (<0.01)	
2-4				22 (<0.01)	7,431 (0.23)	
5-11	2,337 (0.38)	5,100 (0.83)		188,064 (5.85)	205,121 (6.38)	
12-15	32,162 (5.24)	30,655 (4.99)		198,664 (6.18)	182,714 (5.68)	
16-17	15,352 (2.50)	14,646 (2.38)		98,745 (3.07)	88,905 (2.77)	
18-29	70,716 (11.51)	70,440 (11.47)		355,194 (11.05)	357,541 (11.12)	
30-39	80,234 (13.06)	80,832 (13.16)		412,520 (12.83)	414,523 (12.89)	
40-49	127,759 (20.80)	128,488 (20.91)		621,375 (19.33)	623,341 (19.39)	
50-59	106,779 (17.38)	104,612 (17.03)		525,135 (16.33)	514,443 (16.00)	
60-64	10,349 (1.68)	10,831 (1.76)		41,848 (1.30)	47,290 (1.47)	
65-69	26,601 (4.33)	29,271 (4.76)		45,686 (1.42)	52,455 (1.63)	
70-79	83,417 (13.58)	83,458 (13.58)		407,505 (12.68)	413,378 (12.86)	
80+	58,641 (9.55)	56,014 (9.12)		320,052 (9.96)	307,669 (9.57)	
Female, n (%)	319,899 (52.07)	319,899 (52.07)	0	1,670,108 (51.95)	1,670,108 (51.95)	0
Pregnancy status, n (%)	1,220 (0.20)	1,220 (0.20)	0	9,369 (0.29)	9,369 (0.29)	0
First trimester	349 (0.06)	303 (0.05)		9,368 (0.29)	9,369 (0.29)	
Second trimester	462 (0.08)	425 (0.07)		<5 (<0.01)	0 (0)	

Table 10. **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		
	Vac	**Unvac**	**ASD**	**Vac**	**Unvac**	**ASD**
Third trimester	405 (0.07)	474 (0.08)		0 (0)	0 (0)	
Residency in a long-term care facility, n (%)	NA	NA	0	NA	NA	0
Healthcare worker or essential worker status, n (%)	NA	NA		NA	NA	
Date of vaccination or matching, n (%)			1.21			1.35
1 Oct–31 Dec 2020	1,902 (0.31)	27 (<0.01)		4,951 (0.15)	28 (<0.01)	
1 Jan–31 March 2021	87,758 (14.28)	29,144 (4.74)		427,097 (13.29)	97,774 (3.04)	
1 Apr–30 Jun 2021	318,876 (51.90)	200,277 (32.60)		1,638,181 (50.96)	960,733 (29.88)	
1 Jul–30 Sep 2021	190,564 (31.02)	112,658 (18.34)		871,829 (27.12)	501,712 (15.61)	
1 Oct–31 Dec 2021	11,352 (1.85)	17,346 (2.82)		171,767 (5.34)	107,869 (3.36)	
1 Jan–31 Mar 2022	3,361 (0.55)	4,965 (0.81)		92,470 (2.88)	45,962 (1.43)	
1 Apr–30 Jun 2022	409 (0.07)	616 (0.10)		8,517 (0.26)	7,122 (0.22)	
1 Jul–30 Sep 2022	125 (0.02)	181 (0.03)		0 (0)	0 (0)	
Personal lifestyle characteristics						
Smoking status, n (%)			0.04			0.05
Current	42,226 (6.87)	40,172 (6.54)		143,588 (4.47)	130,989 (4.07)	
Former	0 (0)	0 (0)		386,969 (12.04)	406,916 (12.66)	
Never	0 (0)	0 (0)		1,588,141 (49.40)	1,531,609 (47.64)	
Never or former	132,208 (21.52)	122,572 (19.95)		NA	NA	
Unknown	439,913 (71.61)	451,603 (73.51)		1,096,114 (34.10)	1,145,298 (35.63)	
BMI			0.05			0.03
Underweight (BMI <20kg/m^2)	15,885 (2.59)	13,470 (2.19)		370,743 (11.53)	377,681 (11.75)	
Normal weight (BMI 20 to <25kg/m^2)	37,721 (6.14)	32,682 (5.32)		625,508 (19.46)	600,590 (18.68)	

Table 10. **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		
	Vac	**Unvac**	**ASD**	**Vac**	**Unvac**	**ASD**
Overweight (BMI 25 to <30kg/m^2)	38,758 (6.31)	36,390 (5.92)		736,297 (22.90)	714,928 (22.24)	
Obese (BMI ≥30kg/m^2)	60,381 (9.83)	58,895 (9.59)		531,514 (16.53)	539,758 (16.79)	
BMI missing	461,602 (75.14)	472,910 (76.98)		950,750 (29.57)	981,855 (30.54)	
Obesity diagnosis or obesity surgery	37,626 (6.12)	38,652 (6.29)		485,769 (15.11)	490,970 (15.27)	
Healthcare utilisation						
Number of hospitalisations, n (%)			0.01			0.00
0	574,301 (93.48)	574,412 (93.50)		2,942,786 (91.54)	2,944,161 (91.58)	
1	32,141 (5.23)	31,495 (5.13)		204,671 (6.37)	201,636 (6.27)	
2+	7,905 (1.29)	8,440 (1.37)		67,355 (2.10)	69,015 (2.15)	
Number of emergency department visits, n (%)			0.02			0
0	503,683 (81.99)	507,110 (82.54)		NA	NA	
1	76,429 (12.44)	72,380 (11.78)		NA	NA	
2+	34,235 (5.57)	34,857 (5.67)		NA	NA	
Skilled nursing facility, nursing home, or extended care facility stay, n (%)			0			0
0	NA	NA		NA	NA	
1	NA	NA		NA	NA	
2+	NA	NA		NA	NA	
Primary care utilisation, n (%)			0.25			0.15
0	79,917 (13.01)	137,179 (22.33)		415,367 (12.92)	593,248 (18.45)	
1	47,220 (7.69)	44,825 (7.30)		239,971 (7.46)	238,618 (7.42)	
2+	487,210 (79.31)	432,343 (70.37)		2,559,474 (79.62)	2,382,946 (74.12)	

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Table 10. **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		
	Vac	**Unvac**	**ASD**	**Vac**	**Unvac**	**ASD**
Cancer screening, n (%)			0			0
0	NA	NA		NA	NA	
1	NA	NA		NA	NA	
2+	NA	NA		NA	NA	
Other preventive health services, n (%)						
COVID-19 tests, n (%)			0.09			0.19
0	446,710 (72.71)	470,407 (76.57)		1,414,798 (44.01)	1,679,196 (52.23)	
1-2	167,637 (27.29)	143,940 (23.43)		1,238,624 (38.53)	1,124,860 (34.99)	
3-5	0 (0)	0 (0)		366,003 (11.38)	295,058 (9.18)	
5+	0 (0)	0 (0)		195,387 (6.08)	115,698 (3.60)	

ASD: absolute standardised difference, 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 11. About 7 to 12% of individuals had a history of either a positive COVID-19 test or a COVID-19 diagnosis. Only NHR reported 1.7%, which is likely to be underestimated due to registration practices in Norway. This was highest in PHARMO and lowest in EpiChron. History of anaphylaxis or allergies was rare, as expected. Cardiovascular disease was the most prevalent comorbidity.

Although the prevalence rates varied between data sources, the comparison between the vaccinated and unvaccinated cohorts showed a good balance since the ASDs were very low for each of the variables.

Table 11.   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 (%)	7,093 (100)	7,093 (100)		3,542,514 (100)	3,542,514 (100)		973,685 (100)	973,685 (100)	
COVID-19 history									
Previous diagnosis of COVID-19	0 (0)	0 (0)		3,495 (0.1)	3,345 (0.1)	<0.01	130,060 (13.4)	130,053 (13.4)	0
Positive test result for COVID-19	640 (9.0)	640 (9.0)	0	58,661 (1.7)	58,702 (1.7)	0	0 (0)	0 (0)	
Comorbidities									
History of anaphylaxis	33 (0.5)	40 (0.6)	0.01	35,255 (1.0)	35,989 (1.0)	<0.01	26,380 (2.7)	25,597 (2.6)	<0.01
History of allergies	55 (0.8)	53 (0.7)	<0.01	39,198 (1.1)	39,554 (1.1)	<0.01	27,023 (2.8)	26,148 (2.7)	0.01
Diabetes mellitus (types 1 and 2)	17 (0.2)	11 (0.2)	0.02	229,047 (6.5)	205,784 (5.8)	0.03	61,099 (6.3)	61,645 (6.3)	<0.01
Hypertension	3 (0)	5 (0.1)	0.01	658,073 (18.6)	639,304 (18.0)	0.01	74,506 (7.7)	73,045 (7.5)	0.01
Cardiovascular disease	259 (3.7)	261 (3.7)	<0.01	1,357,542 (38.3)	1,326,967 (37.5)	0.02	407,093 (41.8)	404,026 (41.5)	0.01
Chronic respiratory disease	4,967 (70.0)	4,888 (68.9)	0.02	507,191 (14.3)	485,083 (13.7)	0.02	195,776 (20.1)	187,911 (19.3)	0.02
Chronic kidney disease	0 (0)	1 (0)	0.02	5,368 (0.2)	4,208 (0.1)	0.01	0 (0)	0 (0)	
Chronic liver disease	0 (0)	0 (0)		18,241 (0.5)	22,412 (0.6)	0.01	466 (<0.1)	514 (0.1)	<0.01
Cancer	9 (0.1)	9 (0.1)	0	206,574 (5.8)	191,678 (5.4)	0.02	58,243 (6.0)	56,454 (5.8)	0.01
Autoimmune disorders	19 (0.3)	12 (0.2)	0.02	285,871 (8.1)	267,536 (7.6)	0.02	36,451 (3.70)	35,420 (3.60)	0.01
Influenza infection or other respiratory infections	4,807 (67.8)	4,536 (64.0)	0.08	364,991 (10.3)	352,334 (9.9)	0.00	85,920 (8.8)	86,328 (8.9)	0.00
Charlson Comorbidity Index Score			0.01			0.03			0.01
0 or 1	7,082 (99.8)	7,082 (99.8)		3,082,317 (87.0)	3,120,694 (88.1)		929,767 (95.5)	929,353 (95.4)	
2	3 (<0.01)	4 (0.10)		175,222 (4.9)	158,286 (4.5)		18,384 (1.9)	17,900 (1.8)	
3	8 (0.10)	7 (0.10)		284,975 (8.0)	263,534 (7.4)		25,534 (2.6)	26,432 (2.7)	

Table 11. 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	0 (0)	0 (0)		13,123 (0.4)	12,607 (0.4)	<0.01	274 (<0.1)	339 (<0.1)	<0.01
Congestive heart failure	0 (0)	0 (0)		78,306 (2.2)	77,325 (2.2)	<0.01	8,164 (0.8)	9,528 (1.0)	0.01
Cerebrovascular disease	0 (0)	1 (<0.01)	0.02	76,233 (2.2)	71,242 (2.0)	0.01	13,759 (1.4)	13,838 (1.4)	<0.01
Peripheral vascular disease	40 (0.6)	44 (0.6)	0.01	138,836 (3.9)	132,831 (3.7)	0.01	28,455 (2.9)	27,158 (2.8)	0.01
Mild to moderate kidney disease	0 (0)	1 (<0.01)	0.02	0 (0)	0 (0)		0 (0)	0 (0)	
Severe kidney disease	0 (0)	0 (0)		4,111 (0.1)	4,196 (0.1)	<0.01	0 (0)	0 (0)	
Mild liver disease	1 (<0.01)	2 (<0.01)	0.01	7,914 (0.2)	8,362 (0.2)	<0.01	0 (0)	0 (0)	
Moderate or severe liver disease	0 (0)	0 (0)		2,927 (0.1)	2,436 (0.1)	<0.01	71 (0)	66 (0)	<0.01
Malignant tumour	7 (0.1	6 (0.10)	<0.01	180,526 (5.1)	165,180 (4.7)	0.02	20,586 (2.1)	21,164 (2.2)	<0.01
Metastasic solid tumour	0 (0)	0 (0)		6,134 (0.2)	5,296 (0.1)	0.01	0 (0)	0 (0)	
HIV/AIDS	2 (<0.01)	0 (0)	0.02	6,242 (0.2)	6,608 (0.2)	<0.01	1,182 (0.1)	1,202 (0.1)	<0.01
Diabetes with complications	0 (0)	0 (0)		185,093 (5.2)	166,726 (4.7)	0.02	7,904 (0.8)	8,315 (0.9)	<0.01
Diabetes no complications	7 (0.1)	5 (0.1)	0.01	0 (0)	0 (0)		0 (0)	0 (0)	
Dementia	0 (0)	0 (0)		30,263 (0.9)	19,195 (0.5)	0.04	0 (0)	0 (0)	
Skin ulcer	0 (0)	0 (0)		35,421 (1.0)	36,208 (1.0)	<0.01	915 (0.1)	967 (0.1)	<0.01
Hemiplegia	2 (<0.01)	2 (0)	0	12,119 (0.3)	9,917 (0.3)	0.01	0 (0)	0 (0)	
Connective tissue disease	35 (0.5)	28 (0.4)	0.01	166,372 (4.7)	158,471 (4.5)	0.01	5,051 (0.5)	4,664 (0.5)	0.01
CDC at-risk groups [a]			0			0			0
Group 0 (no conditions)	1,581 (22.3)	1,581 (22.3)		1,549,758 (43.7)	1,549,758 (43.7)		391,590 (40.2)	391,590 (40.2)	
Group 1 (1 condition)	2,470 (34.8)	2,470 (34.8)		690,171 (19.5)	690,171 (19.5)		213,465 (21.9)	213,465 (21.9)	

Table 11.   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)	3,042 (42.9)	3,042 (42.9)		1,302,585 (36.8)	1,302,585 (36.8)		368,630 (37.9)	368,630 (37.9)	
Immunocompromising conditions	2,612 (36.8)	2,612 (36.8)	0	635,108 (17.9)	635,108 (17.9)	0	220,393 (22.6)	220,393 (22.6)	0
Surrogates of frailty									
Wheelchair use	NA	NA		NA	NA		NA	NA	
Home hospital bed	NA	NA		NA	NA		NA	NA	
Paralysis	2 (<0.01)	2 (<0.01)	0	14,992 (0.4)	12,643 (0.4)	0.01	3,497 (0.4)	3,658 (0.4)	<0.01
Parkinson's disease	0 (0)	0 (0)		13,867 (0.4)	11,499 (0.3)	0.01	1,814 (0.2)	1,957 (0.2)	<0.01
Weakness	0 (0)	0 (0)		349,413 (9.9)	351,050 (9.9)	<0.01	126,629 (13)	130,155 (13.4)	0.01
Stroke/brain injury	0 (0)	0 (0)		49,353 (1.4)	45,714 (1.3)	0.01	4,006 (0.4)	4,192 (0.4)	<0.01
Ambulance transport	NA	NA		NA	NA		NA	NA	
Difficulty walking	51 (0.7)	48 (0.7)	<0.01	0 (0)	0 (0)		0 (0)	0 (0)	
Home oxygen	NA	NA		NA	NA		NA	NA	
Rehabilitation care	NA	NA		NA	NA		NA	NA	
Psychiatric illness	43 (0.6)	23 (0.3)	0.04	660,141 (18.6)	700,646 (19.8)	0.03	150,399 (15.4)	164,197 (16.9)	0.04
Sepsis	1 (<0.01)	1 (<0.01)	0	44,330 (1.3)	42,501 (1.2)	<0.01	18,522 (1.9)	18,296 (1.9)	<0.01
Podiatric care	NA	NA		NA	NA		NA	NA	
Bladder incontinence	139 (2.0)	84 (1.2)	0.06	109,685 (3.1)	105,706 (3.0)	0.01	57,951 (6.0)	58,602 (6.0)	<0.01
Arthritis	301 (4.2)	267 (3.8)	0.02	488,838 (13.8)	478,374 (13.5)	0.01	93,010 (9.6)	88,797 (9.1)	0.01
Coagulation deficiencies	64 (0.9)	65 (0.9)	<0.01	11,660 (0.3)	11,517 (0.3)	<0.01	3,645 (0.4)	3,824 (0.4)	<0.01
Vertigo	42 (0.6)	32 (0.5)	0.02	250,408 (7.1)	246,461 (7.0)	<0.01	65,080 (6.7)	64,848 (6.7)	<0.01
Lipid abnormalities	0 (0)	2 (<0.1)	0.02	189,815 (5.4)	182,673 (5.2)	0.01	9,423 (1.0)	8,978 (0.9)	<0.01

ASD: absolute standardised difference, 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.

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Table 11. **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		
	Vac	**Unvac**	**ASD**	**Vac**	**Unvac**	**ASD**
Total, N	614,347 (100)	614,347 (100)		3,214,812 (100)	3,214,812 (100)	
COVID-19 history						
Previous diagnosis of COVID-19	3,158 (0.5)	3,650 (0.6)	0.01	389,834 (12.1)	388,940 (12.1)	<0.01
Positive test result for COVID-19	43,682 (7.1)	43,682 (7.1)	0	344,727 (10.7)	352,914 (11.0)	0.01
Comorbidities						
History of anaphylaxis	1,485 (0.2)	1,291 (0.2)	0.01	18,999 (0.6)	16,756 (0.5)	0.01
History of allergies	7,078 (1.2)	6,539 (1.1)	0.01	32,748 (1.0)	30,920 (1.0)	0.01
Diabetes mellitus (types 1 and 2)	53,756 (8.8)	56,637 (9.2)	0.02	281,097 (8.7)	291,952 (9.1)	0.01
Hypertension	97,621 (15.9)	97,579 (15.9)	0	471,183 (14.7)	467,014 (14.5)	<0.01
Cardiovascular disease	239,320 (39)	232,719 (37.9)	0.02	1,088,007 (33.8)	1,071,264 (33.3)	0.01
Chronic respiratory disease	68,685 (11.2)	68,604 (11.2)	0	801,855 (24.9)	795,916 (24.8)	<0.01
Chronic kidney disease	22,545 (3.7)	22,451 (3.7)	<0.01	151,846 (4.7)	149,686 (4.7)	<0.01
Chronic liver disease	2,229 (0.4)	2,461 (0.4)	0.01	89,562 (2.8)	94,903 (3.0)	0.01
Cancer	18,931 (3.1)	19,016 (3.1)	<0.01	162,422 (5.1)	161,568 (5.0)	<0.01
Autoimmune disorders	17,980 (2.9)	18,022 (2.9)	0	231,870 (7.2)	232,167 (7.2)	0
Influenza infection or other respiratory infections	103,254 (16.8)	97,126 (15.8)	0.03	939,649 (29.2)	910,348 (28.3)	0.02
Charlson Comorbidity Index Score			0.01			0.01
0 or 1	564,403 (91.9)	563,365 (91.7)		2,762,277 (85.9)	2,755,199 (85.7)	
2	22,075 (3.6)	22,459 (3.7)		203,847 (6.3)	207,514 (6.5)	
3	27,869 (4.5)	28,523 (4.6)		248,688 (7.7)	252,099 (7.8)	
Myocardial infarct	727 (0.1)	928 (0.2)	0.01	22,865 (0.7)	23,901 (0.7)	<0.01
Congestive heart failure	11,168 (1.8)	11,493 (1.9)	<0.01	74,143 (2.3)	74,372 (2.3)	0

Table 11. **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		
	Vac	**Unvac**	**ASD**	**Vac**	**Unvac**	**ASD**
Cerebrovascular disease	9,930 (1.6)	9,783 (1.6)	<0.01	55,210 (1.7)	53,594 (1.7)	<0.01
Peripheral vascular disease	10,024 (1.6)	9,807 (1.6)	<0.01	99,177 (3.1)	98,903 (3.1)	0
Mild to moderate kidney disease	6,025 (1.0)	6,411 (1.0)	0.01	151,346 (4.7)	149,066 (4.6)	<0.01
Severe kidney disease	549 (0.1)	592 (0.1)	<0.01	6,961 (0.2)	5,138 (0.2)	0.01
Mild liver disease	2,003 (0.3)	2,028 (0.3)	<0.01	111,494 (3.5)	116,844 (3.6)	0.01
Moderate or severe liver disease	385 (0.1)	466 (0.1)	<0.01	8,609 (0.3)	9,486 (0.3)	<0.01
Malignant tumour	14,766 (2.4)	15,180 (2.5)	<0.01	86,431 (2.7)	90,158 (2.8)	0.01
Metastasic solid tumour	401 (0.1)	564 (0.1)	0.01	5,011 (0.2)	6,794 (0.2)	0.01
HIV/AIDS	418 (0.1)	626 (0.1)	0.01	1,655 (0.1)	2,608 (0.1)	0.01
Diabetes with complications	5,354 (0.9)	5,652 (0.9)	<0.01	59,816 (1.9)	61,253 (1.9)	<0.01
Diabetes no complications	7,131 (1.2)	7,698 (1.3)	0.01	182,144 (5.7)	188,162 (5.9)	0.01
Dementia	6,196 (1.0)	4,835 (0.8)	0.02	65,354 (2.0)	53,814 (1.7)	0.03
Skin ulcer	3,220 (0.5)	3,288 (0.5)	<0.01	478,488 (14.9)	483,768 (15.0)	<0.01
Hemiplegia	2,318 (0.4)	2,201 (0.4)	<0.01	17,836 (0.6)	15,486 (0.5)	0.01
Connective tissue disease	9,807 (1.6)	9,240 (1.5)	0.01	438,420 (13.6)	436,506 (13.6)	<0.01
CDC at-risk groups [a]			0			0
Group 0 (no conditions)	281,779 (45.9)	281,779 (45.9)		1,276,535 (39.7)	1,276,535 (39.7)	
Group 1 (1 condition)	117,798 (19.2)	117,798 (19.2)		539,982 (16.8)	539,982 (16.8)	
Group 2 (>1 condition)	214,770 (35.0)	214,770 (35.0)		1,398,295 (43.5)	1,398,295 (43.5)	
Immunocompromising conditions	55,433 (9.0)	55,433 (9.0)	0	788,864 (24.5)	788,864 (24.5)	0
Surrogates of frailty						
Wheelchair use	NA	NA		NA	NA	
Home hospital bed	NA	NA		NA	NA	

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Table 11. **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		
	Vac	**Unvac**	**ASD**	**Vac**	**Unvac**	**ASD**
Paralysis	3,308 (0.5)	3,042 (0.5)	0.01	20,654 (0.6)	17,903 (0.6)	0.01
Parkinson's disease	2,880 (0.5)	2,503 (0.4)	0.01	14,285 (0.4)	12,231 (0.4)	0.01
Weakness	5,493 (0.9)	5,602 (0.9)	<0.01	215,550 (6.7)	221,227 (6.9)	0.01
Stroke/brain injury	3,296 (0.5)	3,337 (0.5)	<0.01	37,391 (1.2)	36,387 (1.1)	<0.01
Ambulance transport	NA	NA		NA	NA	
Difficulty walking	1,631 (0.3)	1,447 (0.2)	0.01	38,501 (1.2)	34,913 (1.1)	0.01
Home oxygen	NA	NA		NA	NA	
Rehabilitation care	NA	NA		NA	NA	
Psychiatric illness	117,503 (19.1)	113,011 (18.4)	0.02	688,172 (21.4)	678,236 (21.1)	0.01
Sepsis	3,410 (0.6)	3,357 (0.5)	<0.01	23,410 (0.7)	23,446 (0.7)	0
Podiatric care	NA	NA		NA	NA	
Bladder incontinence	31,916 (5.2)	29,759 (4.8)	0.02	178,088 (5.5)	160,275 (5.0)	0.02
Arthritis	226,664 (36.9)	211,644 (34.5)	0.05	984,935 (30.6)	972,411 (30.2)	0.01
Coagulation deficiencies	14,325 (2.3)	14,047 (2.3)	<0.01	11,735 (0.4)	11,248 (0.3)	<0.01
Vertigo	9,250 (1.5)	9,178 (1.5)	<0.01	425,900 (13.2)	420,588 (13.1)	<0.01
Lipid abnormalities	32,944 (5.4)	32,533 (5.3)	<0.01	302,492 (9.4)	297,324 (9.2)	0.01

ASD: absolute standardised difference, Vac: vaccinated cohort; Unvac: unvaccinated cohort; NA not assessed (correctly)

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.

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10.1.2.3. Baseline comedications

Comedication use for 1 year prior to time zero in the vaccinated and unvaccinated cohorts (with ASDs) is summarised by data source in Table 12. We observed higher use of antibiotics, NSAIs, and psychotropics in SIDIAP compared with PHARMO. Data on other vaccines will not be 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 12.   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 (%)	7,093 (100)	7,093 (100)		3,542,514 (100)	3,542,514 (100)		973,685 (100)	973,685 (100)	
Comedications, n (%)									
Analgesics	17 (0.2)	14 (0.2)	0.01	785,637 (22.2)	756,462 (21.4)	0.02	85,711 (8.8)	89,280 (9.2)	0.01
Antibiotics	694 (9.8)	605 (8.5)	0.04	601,596 (17.0)	581,286 (16.4)	0.01	142,857 (14.7)	145,492 (14.9)	0.01
Antiviral medications	17 (0.2)	14 (0.2)	0.01	45,688 (1.3)	43,597 (1.2)	<0.01	5,332 (0.5)	5,797 (0.6)	0.01
Corticosteroids	226 (3.2)	244 (3.4)	0.01	176,569 (5.0)	175,320 (4.9)	<0.01	45,897 (4.7)	46,981 (4.8)	<0.01
Non-steroidal anti-inflammatory drugs	108 (1.5)	100 (1.4)	0.01	649,308 (18.3)	618,289 (17.5)	0.02	123,025 (12.6)	120,725 (12.4)	0.01
Psychotropics	33 (0.5)	33 (0.5)	0	505,445 (14.3)	515,194 (14.5)	0.01	85,010 (8.7)	90,686 (9.3)	0.02
Statins	0 (0)	0 (0)		513,196 (14.5)	477,515 (13.5)	0.03	151,145 (15.5)	141,235 (14.5)	0.03
Novel oral anticoagulants	0 (0)	3 (<0.1)	0.03	327,281 (9.2)	311,890 (8.8)	0.01	88,715 (9.1)	86,401 (8.9)	0.01
Warfarin	1 (<0.1)	0 (0)	0.02	24,875 (0.7)	23,747 (0.7)	<0.01	5 (<0.1)	<5 (<0.1)	<0.01
Immunosuppressant medications	229 (3.2)	244 (3.4)	0.01	219,291 (6.2)	209,472 (5.9)	0.01	54,345 (5.6)	53,982 (5.5)	<0.01
Other vaccines, n (%)									
Influenza	2,830 (39.9)	2,632 (37.1)	0.06	14,147 (0.4)	13,481 (0.4)	<0.01	NA	NA	
Pneumococcal	4,383 (61.8)	2,963 (41.8)	0.41	302,584 (8.5)	281,263 (7.9)	0.02	NA	NA	
DTP (diphtheria, tetanus, and pertussis)	8 (0.1)	11 (0.2)	0.01	88,397 (2.5)	88,128 (2.5)	0	NA	NA	
TPV (polio)	6,314 (89.0)	3,959 (55.8)	0.80	120,076 (3.4)	113,666 (3.2)	0.01	NA	NA	
TV (MMR) (measles, mumps and rubella)	1,888 (26.6)	1,310 (18.5)	0.20	536,377 (15.1)	523,315 (14.8)	0.01	NA	NA	
Hib (Haemophilus influenzae type b)	3,825 (53.9)	2,674 (37.7)	0.33	3,247 (0.1)	3,308 (0.1)	<0.01	NA	NA	
HepB (hepatitis B virus)	14 (0.2)	15 (0.2)	<0.01	132,691 (3.7)	124,277 (3.5)	0.01	NA	NA	

Table 12.   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**
VZV (varicella-zoster virus)	6,060 (85.4)	3,693 (52.1)	0.77	5,276 (0.1)	5,085 (0.1)	<0.01	NA	NA	
HPV (human papillomavirus)	1,145 (16.1)	410 (5.8)	0.34	0 (0)	0 (0)		NA	NA	
Meningitis	4,379 (61.7)	2,903 (40.9)	0.43	267,694 (7.6)	214,120 (6.0)	0.06	NA	NA	
Rotavirus	506 (7.1)	387 (5.5)	0.07	594 (<0.1)	755 (<0.1)	<0.01	NA	NA	

ASD: absolute standardised difference, Vac: vaccinated cohort; Unvac: unvaccinated cohort

Table 12. **Part 2: Baseline comedications at time zero by exposure group (matched cohort design) by data source (SEE PART 1 ABOVE)**

	EpiChron			SIDIAP		
	Vac	**Unvac**	**ASD**	**Vac**	**Unvac**	**ASD**
Total, n	614,347 (100)	614,347 (100)		3,214,812 (100)	3,214,812 (100)	
Comedications, n (%)						
Analgesics	181,133 (29.5)	170,337 (27.7)	0.04	818,238 (25.5)	805,297 (25.0)	0.01
Antibiotics	116,311 (18.9)	105,071 (17.1)	0.05	499,879 (15.5)	477,453 (14.9)	0.02
Antiviral medications	3,893 (0.6)	3,689 (0.6)	<0.01	19,926 (0.6)	18,112 (0.6)	0.01
Corticosteroids	25,911 (4.2)	26,260 (4.3)	<0.01	122,094 (3.8)	122,077 (3.8)	0
Non-steroidal anti-inflammatory drugs	161,276 (26.3)	142,582 (23.2)	0.07	579,588 (18.0)	562,132 (17.5)	0.01
Psychotropics	133,778 (21.8)	122,983 (20.0)	0.04	520,236 (16.2)	485,744 (15.1)	0.03
Statins	103,434 (16.8)	98,203 (16.0)	0.02	367,477 (11.4)	347,770 (10.8)	0.02
Novel oral anticoagulants	43,627 (7.1)	42,793 (7.0)	<0.01	211,730 (6.6)	203,927 (6.3)	0.01
Warfarin	200 (<0.1)	195 (<0.1)	0	5,002 (0.2)	4,782 (0.1)	<0.01
Immunosuppressant medications	27,808 (4.5)	28,079 (4.6)	<0.01	130,361 (4.1)	129,789 (4.0)	0.00
Other vaccines, n (%)						
Influenza	42,510 (6.9)	37,769 (6.1)	0.03	309,884 (9.6)	285,692 (8.9)	0.03
Pneumococcal	31,863 (5.2)	27,416 (4.5)	0.03	NA	NA	
DTP (diphtheria, tetanus, and pertussis)	137,367 (22.4)	121,321 (19.7)	0.06	NA	NA	
TPV (polio)	1,095 (0.2)	1,486 (0.2)	0.01	NA	NA	
TV (MMR) (measles, mumps and rubella)	24,593 (4.0)	19,849 (3.2)	0.04	NA	NA	
Hib (Haemophilus influenzae type b)	690 (0.1)	649 (0.1)	<0.01	NA	NA	
HepB (hepatitis B virus)	6,476 (1.1)	5,744 (0.9)	0.01	NA	NA	
VZV (varicella-zoster virus)	10,417 (1.7)	8,541 (1.4)	0.02	NA	NA	
HPV (human papillomavirus)	34,326 (5.6)	27,421 (4.5)	0.05	NA	NA	
Meningitis	62,271 (10.1)	49,333 (8.0)	0.07	NA	NA	

Table 12.   Part 2: Baseline comedications at time zero by exposure group (matched cohort design) by data source (SEE PART 1 ABOVE)

	EpiChron			SIDIAP		
	Vac	**Unvac**	**ASD**	**Vac**	**Unvac**	**ASD**
Rotavirus	20 (<0.1)	12 (<0.1)	<0.01	NA	NA	

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

10.1.2.4. Censoring due to prior events of special interest

Prior AESIs (outcome-specific exclusion criteria) at time zero among the Pfizer-BioNTech vaccinated cohort and the matched unvaccinated cohort by data source are summarized in Table 13. 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 13).

Table 13. 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 (%)	7,093 (100)	7,093 (100)		3,542,514 (100)	3,542,514 (100)		973,685 (100)	973,685 (100)	
Autoimmune diseases									
Guillain-Barré syndrome	0 (0)	0 (0)	<0.01	0 (0)	0 (0)	<0.01	6 (<0.1)	14 (<0.1)	0.00
Acute disseminated encephalomyelitis	NA	NA		NA	NA		<5 (<0.1)	0 (0)	0.00
Narcolepsy	NA	NA		NA	NA		8 (<0.1)	6 (<0.1)	0.00
Acute aseptic arthritis	0 (0)	0 (0)	<0.01	30,553 (0.9)	30,838 (0.9)	<0.01	3,979 (0.4)	3,750 (0.4)	0.00
Diabetes mellitus type 1	12 (0.2)	9 (0.1)	0.01	54,837 (1.5)	46,864 (1.3)	0.02	1,155 (0.1)	868 (0.1)	0.01
(Idiopathic) thrombocytopenia	0 (0)	1 (<0.1)	0.02	0 (0)	0 (0)	<0.001	91 (<0.1)	126 (<0.1)	0.00
Thrombotic thrombocytopenia syndrome (TTS)	NA	NA		NA	NA		NA	NA	
Cardiovascular system									
Acute cardiovascular injury[a]	NA	NA		142,174 (4.0)	135,861 (3.8)	0.01	4,871 (0.5)	5,306 (0.5)	0.01
Arrhythmia	19 (0.3)	11 (0.2)	0.02	169,854 (4.8)	165,078 (4.7)	0.01	9,843 (1.0)	9,863 (1.0)	<0.01
Heart failure	NA	NA		40,476 (1.1)	41,247 (1.2)	<0.01	1,661 (0.2)	1,994 (0.2)	0.01
Stress cardiomyopathy	NA	NA		NA	NA		13 (<0.1)	12 (<0.1)	<0.01
Coronary artery disease	NA	NA		94,402 (2.7)	88,753 (2.5)	0.01	1,784 (0.2)	1,817 (0.2)	0.00
Myocarditis	NA	NA		283 (<0.1)	292 (<0.1)	<0.01	89 (<0.1)	111 (<0.1)	<0.01
Pericarditis	0 (0)	0 (0)	<0.01	971 (<0.1)	981 (<0.1)	<0.01	NA	NA	
Circulatory system									
Coagulation disorders: thromboembolism, haemorrhage	2 (<0.1)	3 (<0.1)	0.01	7,627 (0.3)	7,395 (0.3)	0.00	1,886 (0.2)	2,050 (0.2)	<0.01

Table 13. 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**
Single organ cutaneous vasculitis	2 (<0.1)	0 (0)	0.02	NA	NA		20 (<0.1)	17 (<0.1)	<0.01
Hepato-gastrointestinal and renal system									
Acute liver injury	NA	NA		NA	NA		26 (<0.1)	26 (<0.1)	<0.01
Acute kidney injury	0 (0)	0 (0)	<0.01	27,799 (0.8)	26,609 (0.8)	<0.01	4,119 (0.4)	4,247 (0.4)	<0.01
Acute pancreatitis	0 (0)	0 (0)	<0.001	0 (0)	0 (0)	<0.01	224 (<0.1)	266 (<0.1)	<0.01
Rhabdomyolysis	NA	NA		0 (0)	0 (0)	<0.01	6 (<0.1)	7 (<0.1)	<0.01
Nerves and central nervous system									
Generalised convulsion	1 (<0.1)	2 (<0.1)	0.01	2,057 (0.1)	2,109 (0.1)	<0.01	197 (<0.1)	231 (<0.1)	<0.01
Meningoencephalitis	0 (0)	0 (0)	<0.01	813 (<0.1)	673 (<0.1)	<0.01	61 (<0.1)	81 (<0.1)	<0.01
Transverse myelitis	NA	NA		NA	NA		3 (<0.1)	5 (<0.1)	<0.01
Bell's palsy	0 (0)	0 (0)	<0.01	2,137 (0.1)	2,340 (0.1)	<0.01	309 (<0.1)	313 (<0.1)	<0.01
Respiratory system									
Acute respiratory distress syndrome	0 (0)	0 (0)	<0.01	96 (<0.1)	114 (<0.1)	<0.01	30 (<0.1)	46 (<0.1)	<0.01
Skin and mucous membrane, bone, and joints system									
Erythema multiforme	NA	NA		NA	NA		14 (<0.1)	33 (<0.1)	<0.01
Chilblain-like lesions	2 (<0.1)	6 (0.1)	0.02	NA	NA		710 (<0.1)	640 (<0.1)	<0.01
Reproductive system									
Secondary amenorrhea	2 (<0.1)	5 (0.1)	0.02	0 (0)	0 (0)	<0.01	NA	NA	
Other systems									

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Table 13.   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**
Anosmia, ageusia	2 (<0.1)	1 (<0.1)	0.01	2,008 (0.1)	1,920 (0.1)	<0.01	762 (0.1)	719 (0.1)	<0.01
Anaphylaxis	0 (0)	0 (0)	<0.01	NA	NA		7,753 (0.8)	7,571 (0.8)	<0.01
Multisystem inflammatory syndrome				15 (<0.1)	19 (<0.1)	<0.01	<5 (<0.1)	<5 (<0.1)	<0.01
Subacute thyroiditis	0 (0)	0 (0)	<0.01	NA	NA		7 (<0.1)	6 (<0.1)	<0.01
Any									
COVID-19 disease	444 (6.3)	549 (7.7)	0.06	54,700 (1.5)	56,194 (1.6)	0.00	97,452 (10.0)	100,089 (10.3)	0.01

ASD: absolute standardised difference, Vac: vaccinated cohort; Unvac: unvaccinated cohort

a including microangiopathy ASD: Absolute standardised difference

Table 14. 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		
	Vac	**Unvac**	**ASD**	**Vac**	**Unvac**	**ASD**
Total, n	614,347 (100)	614,347 (100)		3,214,812 (100)	3,214,812 (100)	
Autoimmune diseases						
Guillain-Barré syndrome	17 (<0.1)	19 (<0.1)	<0.01	146 (<0.1)	181 (<0.1)	<0.01
Acute disseminated encephalomyelitis	0 (0)	0 (0)	<0.01	<5 (<0.1)	<5 (<0.1)	<0.01
Narcolepsy	5 (<0.1)	<5 (<0.1)	<0.01	49 (<0.1)	43 (<0.1)	<0.01
Acute aseptic arthritis	2,401 (0.4)	2,376 (0.4)	<0.01	16,720 (0.5)	16,382 (0.5)	<0.01
Diabetes mellitus type 1	3,700 (0.6)	3,879 (0.6)	<0.01	8,475 (0.3)	8,903 (0.3)	<0.01
(Idiopathic) thrombocytopenia	392 (0.1)	473 (0.1)	<0.01	4,848 (0.2)	5,072 (0.2)	<0.01
Thrombotic thrombocytopenia syndrome (TTS)	50 (<0.1)	58 (<0.1)	<0.01	551 (<0.01)	617 (<0.01)	<0.01
Cardiovascular system						
Acute cardiovascular injury[a]	8,593 (1.4)	9,447 (1.5)	0.01	50,693 (1.6)	52,425 (1.6)	<0.01
Arrhythmia	10,981 (1.8)	11,020 (1.8)	<0.01	62,645 (1.9)	61,676 (1.9)	<0.01
Heart failure	4,069 (0.7)	4,565 (0.7)	0.01	23,716 (0.7)	24,706 (0.8)	<0.01
Stress cardiomyopathy	33 (<0.1)	41 (<0.1)	<0.01	225 (<0.1)	263 (<0.1)	<0.01
Coronary artery disease	3,368 (0.5)	3,702 (0.6)	0.01	22,975 (0.7)	23,544 (0.7)	<0.01
Myocarditis	25 (<0.1)	23 (<0.1)	<0.01	106 (<0.1)	94 (<0.1)	<0.01
Pericarditis	116 (<0.1)	112 (<0.1)	<0.01	848 (<0.1)	909 (<0.1)	<0.01
Circulatory system						
Coagulation disorders: thromboembolism, haemorrhage	4,218 (0.7)	4,432 (0.7)	<0.01	18,621 (0.6)	19,553 (0.6)	<0.01
Single organ cutaneous vasculitis	35 (<0.1)	27 (<0.1)	<0.01	189 (<0.01)	211 (<0.1)	<0.01
Hepato-gastrointestinal and renal system						
Acute liver injury	430 (0.1)	446 (0.1)	<0.01	5,136 (0.2)	5,519 (0.2)	<0.01
Acute kidney injury	2,160 (0.4)	2,570 (0.4)	0.01	15,654 (0.5)	16,805 (0.5)	<0.01
Acute pancreatitis	430 (0.1)	504 (0.1)	<0.01	2,263 (0.1)	2,525 (0.1)	<0.01
Rhabdomyolysis	150 (<0.1)	175 (<0.1)	<0.01	823 (<0.1)	839 (<0.1)	<0.01

Table 14. 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		
	Vac	**Unvac**	**ASD**	**Vac**	**Unvac**	**ASD**
Nerves and central nervous system						
Generalised convulsion	375 (0.1)	355 (0.1)	<0.01	1,305 (<0.1)	1,360 (<0.1)	<0.01
Meningoencephalitis	46 (<0.1)	39 (<0.1)	<0.01	183 (<0.1)	221 (<0.1)	<0.01
Transverse myelitis	<5 (<0.1)	<5 (<0.1)	<0.01	16 (<0.1)	21 (<0.1)	<0.01
Bell's palsy	382 (0.1)	446 (0.1)	<0.01	2,864 (0.1)	3,039 (0.1)	<0.01
Respiratory system						
Acute respiratory distress syndrome	486 (0.1)	709 (0.1)	0.01	2,912 (0.1)	3,514 (0.1)	0.01
Skin and mucous membrane, bone, and joints system						
Erythema multiforme	32 (<0.1)	16 (<0.1)	<0.01	165 (<0.1)	163 (<0.1)	<0.01
Chilblain-like lesions	281 (<0.1)	220 (<0.1)	<0.01	1,833 (0.1)	1,782 (0.1)	<0.01
Reproductive system						
Secondary amenorrhea	1,183 (0.2)	1,061 (0.2)	<0.01	7,200 (0.2)	7,802 (0.2)	<0.01
Other systems						
Anosmia, ageusia	841 (0.1)	763 (0.1)	<0.01	2,401 (0.1)	2,227 (0.1)	<0.01
Anaphylaxis	42 (<0.1)	56 (<0.1)	<0.01	514 (<0.1)	538 (<0.1)	<0.01
Multisystem inflammatory syndrome	7 (<0.1)	7 (<0.1)	<0.01	59 (<0.1)	86 (<0.1)	<0.01
Subacute thyroiditis	109 (<0.1)	129 (<0.1)	<0.01	908 (<0.1)	880 (<0.1)	<0.01

ASD: absolute standardised difference, Vac: vaccinated cohort; Unvac: unvaccinated cohort

a including microangiopathy ASD: Absolute standardised difference

10.2. Outcome data in the unmatched cohort

Incidence rates (95% CI) of 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) of 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).

10.3. Main results

The main results for this third interim report are the following two secondary analyses:

- Estimated incidence rates of prespecified AESI among individuals who receive at least one dose of the Pfizer-BioNTech COVID-19 vaccine compared with a matched comparator unvaccinated cohort using a cohort study design.

- Description of incidence rates and assessment of potential 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.

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 10.3.1 below). The analyses for VAED are not presented in this report as the algorithms to identify these events require further development.

10.3.1. Results from negative control

To assess baseline exchangeability, the incidences of COVID-19 disease in the first 12 days after vaccination in the vaccinated and unvaccinated cohorts were compared. In NHR, EpiChron and SIDIAP the differences for the incidences were less than 1 per 1000 cases. In PHARMO, the incidence of COVID-19 disease in the first 12 days after vaccination was 5 per 1000 cases higher in the vaccinated cohort than in the unvaccinated cohort. However, the difference occurred on day 1 after time zero and did not subsequently increase or decrease, probably reflecting a known misclassification of COVID-19 cases in vaccinated individuals (see Figure 5). In Pedianet, the difference for the incidences of COVID-19 disease in the first 12 days were 2 per 1000 cases (see Figure 5) However cumulative incidence curves for vaccinated and unvaccinated cohorts increase similarly in the first 12 days after time zero, and the differential factor was the high background incidence of COVID-19 disease in the first 12 days in Pedianet (350 per 10,000 individuals) compared with the background incidences in the other data sources (around 40 per 10,000 individuals). Therefore, this is

also not suggestive of confounding. Consequently, we considered that the matching process achieved the required balance between the cohorts, and the analyses were performed in the matched cohorts without further adjustments.

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 in PHARMO and Pedianet**

PHARMO

Number at risk

Unvaccinated	853011	852340	785276	736045	697712	666516	641143
Vaccinated	853011	849231	782176	733167	695127	664215	639155

Cumulative number of events

Unvaccinated	0	952	1934	2821	3572	4300	4985
Vaccinated	0	4634	5817	6883	7795	8671	9455

Pedianet

Number at risk

Unvaccinated	6496	6476	6363	6233	6109	5993	5886
Vaccinated	6496	6495	6394	6286	6149	6005	5879

Cumulative number of events

Unvaccinated	0	27	63	112	131	160	200
Vaccinated	0	5	24	60	112	168	228

10.3.2. Guillain-Barré syndrome

Guillain-Barré syndrome was a very rare event that was observed in four of the five data sources. The IRs ranged from 0 per 10,000 person-years (95% CI: 0–0.9) in EpiChron to 0.3 per 10,000 person-years (95% CI: 0.1; 0.6) in SDIAP in the vaccinated cohorts and from 0.1 per 10,000 person-years (95% CI: 0.0; 0.9) in PHARMO to 0.7 per 10,000 person-years (95% CI: 0.2; 2.2) in EpiChron in the unvaccinated cohorts. The cumulative incidence was below 1 per 10,000 individuals in both cohorts in all data sources. Due to the absence of cases in EpiChron, PHARMO and Pedianet age-related effects on incidence were only observed in SIDIAP, with increased incidence at higher age. The matched HR for GBS in SIDIAP was 1.75 (95% CI 0.51, 5.97) and 0.99 (95% CI 0.06, 15.96) in PHARMO. No differences were observed for the incidence of Guillain-Barré syndrome between the vaccinated and unvaccinated cohorts.

Table 15. **Risk estimates (95% CI) per 10,000 person-years (PY) for Guillain-Barré syndrome among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source (risk window: 42 days after dose 1)**

Data source	Vaccinated				Unvaccinated			
	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 (Italy)	0	0 (0, 0)	738.7	0 (0, 49.9)	0	0 (0, 0)	735.8	NA
NHR (Norway)	0	0 (0, 0)	240,851.2	0 (0, 0.2)	0	0 (0, 0)	240,559.3	NA
PHARMO (Netherlands)	<5	0 (0, 0)	79,659.7	0.1 (0, 0.7)	<5	0 (0, 0.1)	79,234.2	0.1 (0, 0.9)
EpiChron (Spain)	0	0 (0, 0)	42,606.7	0 (0, 0.9)	<5	0.1 (0, 0.2)	42,465.3	0.7 (0.2, 2.2)
SIDIAP (Spain)	7	0 (0, 0.1)	241,338.4	0.3 (0.10, 0.6)	<5	0 (0, 0)	241,179.3	0.2 (0.1, 0.4)

Note: Estimation of confidence intervals differs between vaccinated and unvaccinated, since the unvaccinated estimate is a 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, gender, 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 Guillain-Barré syndrome among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source (risk window: 42 days after dose 1**
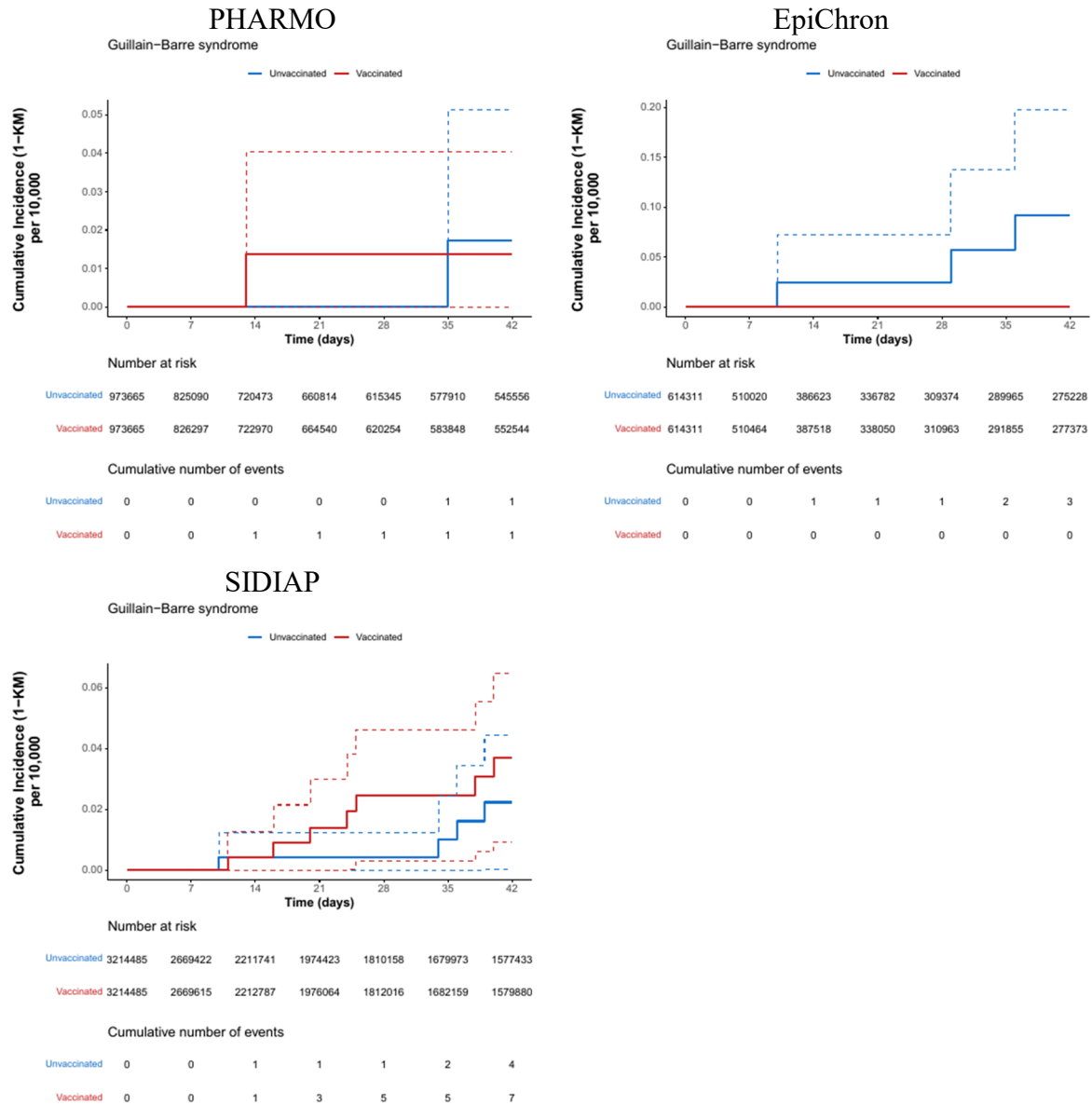
Cumulative incidence curves (1 – Kaplan–Meier risk) starting from the day of administration of the first dose of vaccine up to 42 days follow-up. Dotted lines represent 95% confidence intervals. The number at risk at each time point and the cumulative number of events are also shown for each time point. 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 Guillain-Barré syndrome 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: 42 days after dose 1)**
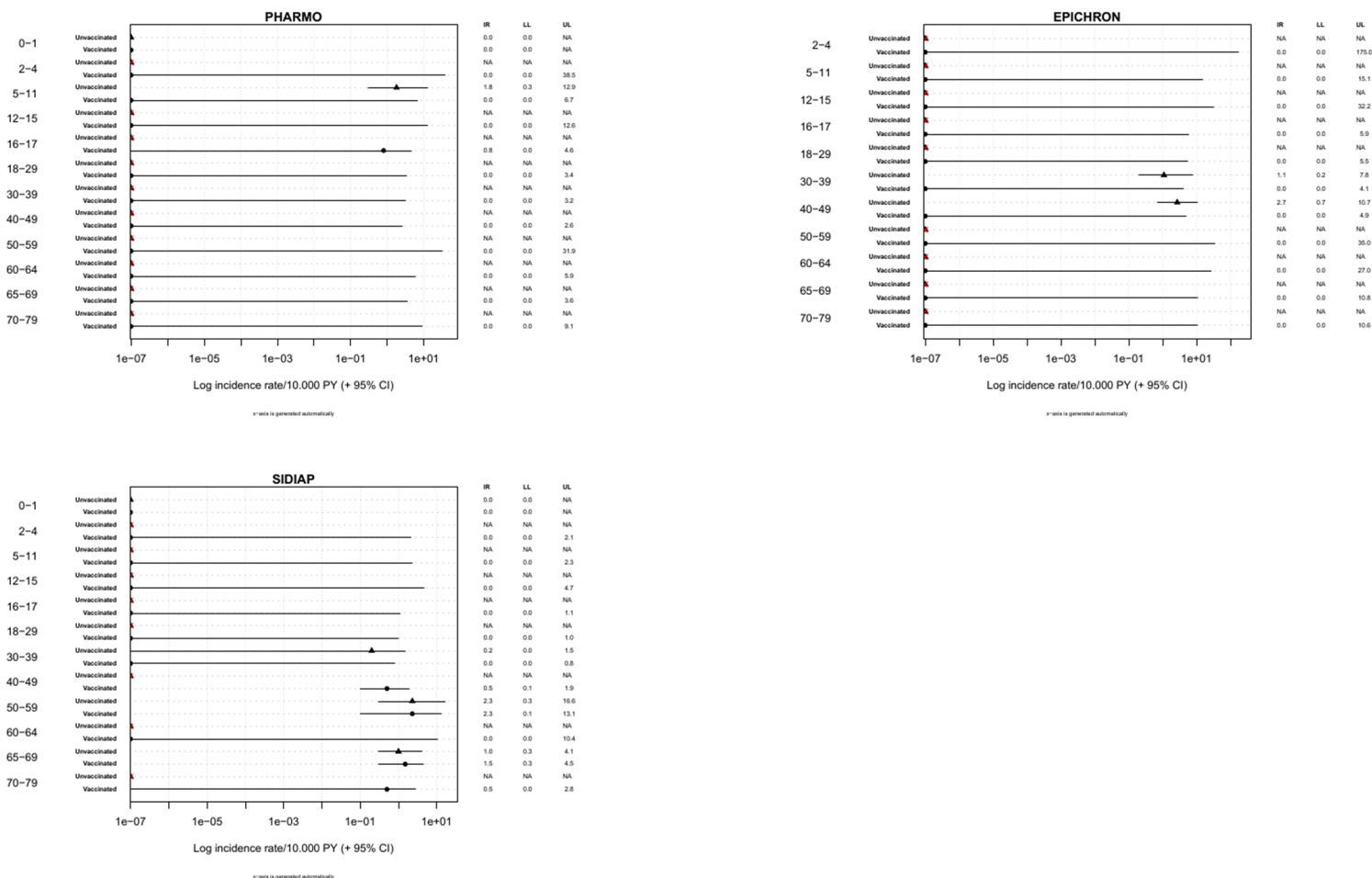
Table 16. **Matched and adjusted hazard ratios (HRs) and matched risk differences (RDs) per 10,000 person-years and their 95% CIs for Guillain-Barré syndrome among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source (at 42 days after dose 1)**

	Matched HR (95% CI)	Matched RD
Pedianet	NA	NA
NHR	NA	NA
PHARMO	0.99 (0.06, 15.96)	NA
EpiChron	NA	-0.09
SIDIAP	1.75 (0.51, 5.97)	0.01

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

10.3.3. Acute disseminated encephalomyelitis

Acute disseminated encephalomyelitis was a very rare event with only one case observed in the vaccinated cohort in SIDIAP in the 42-day risk window. Due to the low number of cases in the risk window, no age-related patterns were observed in the matched cohorts. No differences were observed for the incidence of acute disseminated encephalomyelitis within the 42-day risk window, between the vaccinated and unvaccinated cohorts.

Table 17. **Risk estimates (95% CI) per 10,000 person-years (PY) for acute disseminated encephalomyelitis among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source (risk window: 42 days after dose 1)**

Data source	Vaccinated				Unvaccinated			
	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 (Italy)	NA	NA	NA	NA	NA	NA	NA	NA
NHR (Norway)	NA	NA	NA	NA	NA	NA	NA	NA
PHARMO (Netherlands)	0	0 (0, 0)	79,661.60	0 (0, 0.5)	0	0 (0, 0)	79,236	NA
EpiChron (Spain)	0	0 (0, 0)	42,609.90	0 (0, 0.9)	0	0 (0, 0)	42,468.70	NA
SIDIAP (Spain)	<5	0 (0, 0)	241,364.10	0 (0, 0.2)	0	0 (0, 0)	241,204.90	NA

NA: Not available

Note: Estimation of confidence intervals differs between vaccinated and unvaccinated, since the unvaccinated estimate is a 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, gender, 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+).

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Figure 8. **Cumulative incidence of acute disseminated encephalomyelitis among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source (risk window: 42 days after dose 1**
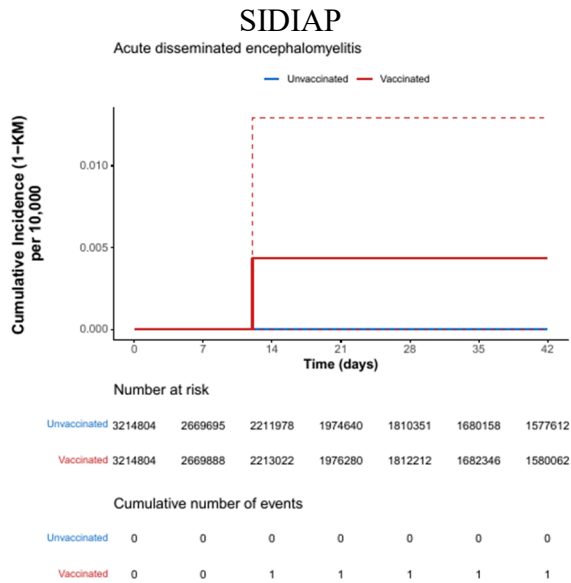
Cumulative incidence curves (1 – Kaplan–Meier risk) starting from the day of administration of the first dose of vaccine up to 42 days of follow-up. Dotted lines represent 95% confidence intervals. The number at risk at each time point and the cumulative number of events are also shown for each time 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 acute disseminated encephalomyelitis 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: 42 days after dose 1)**
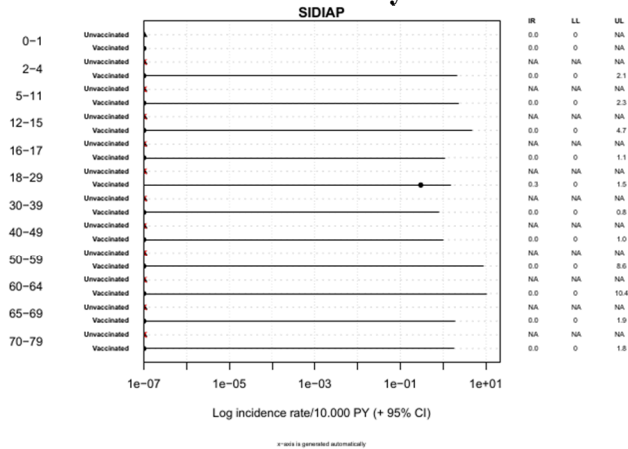
Table 18. Matched hazard ratios (HRs) and matched risk differences (RDs) per 10,000 person-years and their 95% CIs for acute disseminated encephalomyelitis among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source (risk window: 42 days after dose 1)

	Matched HR (95% CI)	Matched RD
Pedianet	NA	NA
NHR	NA	NA
PHARMO	NA	NA
EpiChron	NA	NA
SIDIAP	NA	NA

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

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10.3.4. Narcolepsy

Narcolepsy was rarely observed during the study risk window of 42 days. The incidence rates were 0.2 (95% CI 0, 1.3) per 10,000 person-years in EpiChron and 0.2 (95% CI 0, 0.4) per 10,000 person-years in SIDIAP in the vaccinated cohorts and 0.3 (95% CI 0.1, 0.7) per 10,000 person-years in SIDIAP in the unvaccinated cohort. Due to the low number of cases in the 42-day risk window no age-related incidence patterns were observed. No differences were observed for the incidence of narcolepsy in the vaccinated and unvaccinated cohorts during the 42-day risk window.

Table 19. Risk estimates (95% CI) per 10,000 person-years (PY) for narcolepsy among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source (risk window: 42 days after dose 1)

Data source	Vaccinated				Unvaccinated			
	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 (Italy)	NA	NA	NA	NA	NA	NA	NA	NA
NHR (Norway)	NA	NA	NA	NA	NA	NA	NA	NA
PHARMO (Netherlands)	0	0 (0, 0)	79,660.5	0 (0, 0.50)	0	0 (0, 0)	79,234.9	NA
EpiChron (Spain)	<5	0 (0, 0.1)	42,609.4	0.2 (0, 1.3)	0	0 (0, 0)	42,468.2	NA
SIDIAP (Spain)	<5	0 (0, 0)	241,357.3	0.2 (0, 0.4)	7	0 (0, 0.1)	241,198.0	0.3 (0.1, 0.7)

NA: Not available

Note: Estimation of confidence intervals differs between vaccinated and unvaccinated, since the unvaccinated estimate is a 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, gender, 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 narcolepsy among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source (risk window: 42 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 42-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 narcolepsy 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: 42 days after dose 1)**

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Table 20. **Matched hazard ratios (HRs) and matched risk differences (RDs) per 10,000 person-years and their 95% CIs for narcolepsy among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source (risk window: 42 days after dose 1)**

	Matched HR (95% CI)	Matched RD
Pedianet	NA	NA
NHR	NA	NA
PHARMO	NA	NA
EpiChron	NA	0.03
SIDIAP	0.57 (0.16, 1.98)	-0.02

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

10.3.5. Acute aseptic arthritis

Acute aseptic arthritis was observed in both the vaccinated and unvaccinated cohorts in PHARMO, EpiChron and SIDIAP and in the unvaccinated cohort in Pedianet. In the vaccinated cohorts, the incidences ranged from 13.5 per 10,000 person-years (95% CI 0.3, 75.4) in Pedianet, which has data for children up to 14 years old, to 51.5 per 10,000 person-years (95% CI: 48.6; 54.4) in SIDIAP. The cumulative incidence (1-KM) over the 42-day risk window was below 7 per 10,000 individuals in both the vaccinated and unvaccinated cohorts. IRs of acute aseptic arthritis increased in adolescents and remained relatively stable after this age. All matched HRs were around 1 and the 95% CIs included 1. No differences were observed for the incidence of acute aseptic arthritis between the vaccinated and unvaccinated cohorts during the 42-day risk window.

Table 21. **Risk estimates (95% CI) per 10,000 person-years (PY) for acute aseptic arthritis among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source (risk window: 42 days after dose 1)**

Data source	Vaccinated				Unvaccinated			
	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 (Italy)	1	1.6 (0, 4.7)	738.7	13.5 (0.3, 75.4)	0	0 (0, 0)	735.8	NA
NHR (Norway)	1,396	6.5 (6.2, 6.9)	237,132.7	58.9 (55.8, 62.0)	1,244	5.9 (5.4, 6.4)	236,865.3	52.5 (48.6, 56.8)
PHARMO (Netherlands)	335	4.8 (4.3, 5.3)	79,059.5	42.4 (38.0, 47.2)	293	4.3 (3.6, 4.9)	78,640.7	37.3 (32.3, 42.9)
EpiChron (Spain)	189	5.0 (4.3, 5.8)	42,316.2	44.7 (38.5, 51.5)	194	5.0 (3.9, 6.1)	42,177.0	46.0 (37.4, 56.5)
SIDIAP (Spain)	1,231	5.8 (5.5, 6.2)	239,255.2	51.5 (48.6, 54.4)	1,223	5.7 (5.3, 6.2)	239,111.7	51.1 (47.3, 55.3)

NA: Not available

Note: Estimation of confidence intervals differs between vaccinated and unvaccinated, since the unvaccinated estimate is a 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, gender, 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 acute aseptic arthritis among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source (risk window: 42 days after dose 1)**

Figure 12. **Cumulative incidence of acute aseptic arthritis among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source (risk window: 42 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 42-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 acute aseptic arthritis 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: 42 days after dose 1)
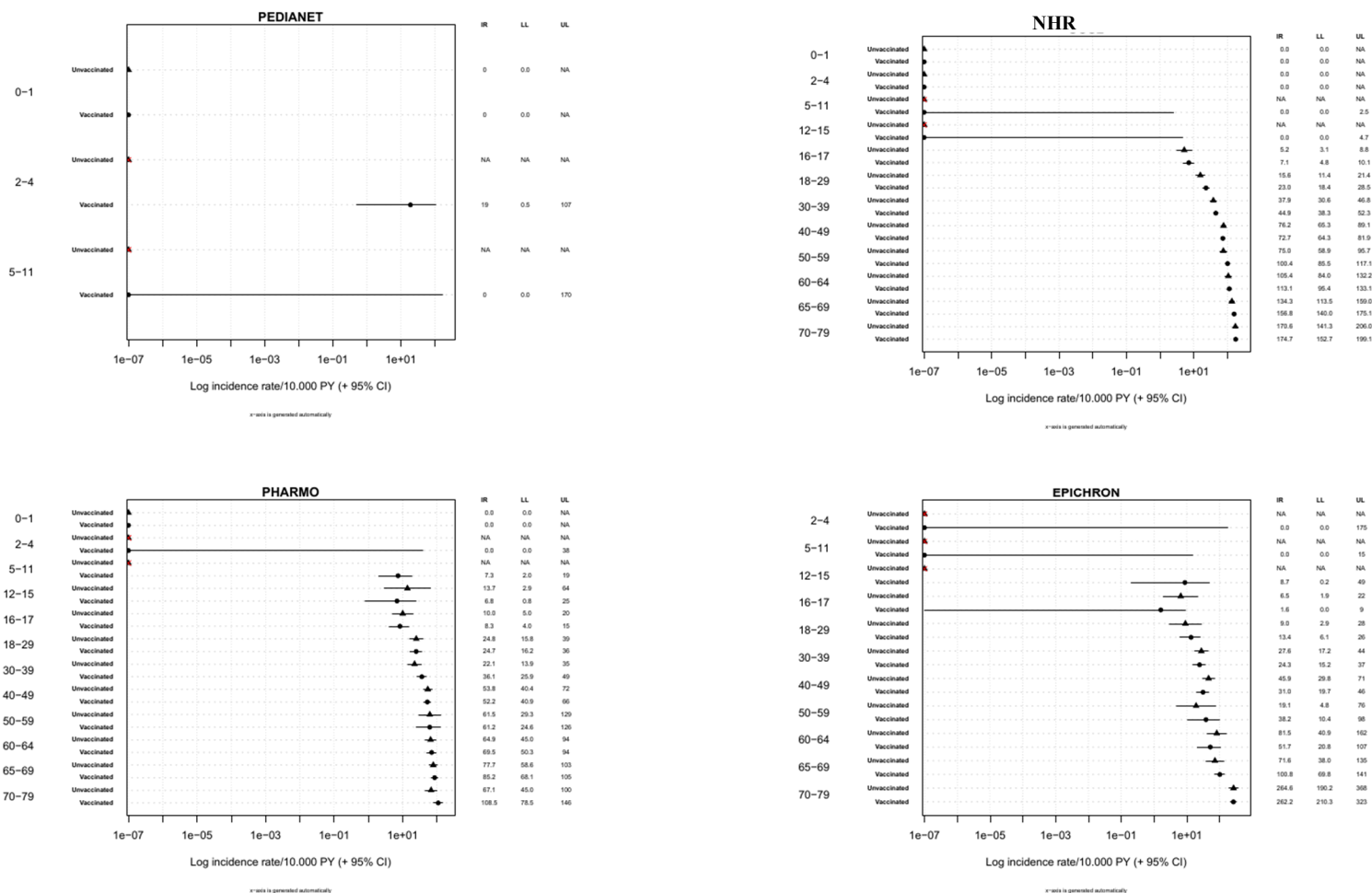
Figure 13. **Forest plot showing incidence rates and 95% confidence intervals for acute aseptic arthritis among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source and by age groups (risk window: 42 days after dose 1)**

Table 22. Matched hazard ratios (HRs) and matched risk differences (RDs) per 10,000 person-years and their 95% CIs for acute aseptic arthritis among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source (risk window: 42 days after dose 1)

	Matched HR (95% CI)	Matched RD
Pedianet	NA	1.59
NHR	1.12 (1.02, 1.23)	0.64
PHARMO	1.14 (0.95, 1.36)	0.55
EpiChron	0.97 (0.76, 1.25)	0.03
SIDIAP	1.01 (0.91, 1.11)	0.11

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

10.3.6. Diabetes mellitus type 1

Diabetes mellitus type 1 was observed in both the vaccinated and unvaccinated cohorts in NHR, PHARMO, EpiChron and SIDIAP and one event was reported in the unvaccinated cohort in Pedianet. The IRs ranged from 0 per 10,000 person-years (95% CI 0, 9.5) in Pedianet to 9.1 per 10,000 person-years (95% CI 8.2, 9.9) in NHR in the vaccinated cohorts and from 0.9 per 10,000 person-years (95% CI 0.5, 1.4) in PHRAMO to 7.8 per 10,000 person-years (95% CI 6.7, 9.2) in NHR in the unvaccinated cohorts. The cumulative incidence (1-KM) per 10,000 individuals at any time during follow-up was constant over time in the vaccinated and unvaccinated cohorts. The incidence was similar in the different age groups. The matched HRs were 1.16 (95% CI: 0.96; 1.38) in NHR, 0.70 (95% CI: 0.37; 1.34) in PHARMO, 0.69 (95% CI: 0.42; 1.14) in EpiChron, and 1.75 (0.51, 5.97) in SIDIAP, but were not significantly elevated.

Table 23.   Risk estimates (95% CI) per 10,000 person-years (PY) for diabetes mellitus type 1 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)

Data source	Vaccinated				Unvaccinated			
	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 (Italy)	0	0 (0, 0)	3,871.1	0 (0, 9.5)	1	1.7 (0, 5.00)	3,824.2	2.6 (0.4, 18.6)
NHR (Norway)	449	13.3 (6.2, 20.3)	495,154.3	9.1 (8.2, 9.9)	385	8.7 (1.8, 15.7)	490,503.0	7.8 (6.7, 9.2)
PHARMO (Netherlands)	21	0.7 (0.3, 1.0)	346,080.1	0.6 (0.4, 0.9)	29	0.7 (0.3, 1.1)	336,466.2	0.9 (0.5, 1.4)
EpiChron (Spain)	41	2.3 (1.5, 3.1)	190,236.8	2.2 (1.5, 2.9)	58	3.1 (1.7, 4.5)	185,682.7	3.1 (2.1, 4.7)
SIDIAP (Spain)	374	3.9 (3.4, 4.4)	924,943.5	4.0 (3.6, 4.5)	355	3.7 (3.0, 4.3)	923,200.6	3.8 (3.3, 4.5)

NA: Not available

Note: Estimation of confidence intervals differs between vaccinated and unvaccinated, since the unvaccinated estimate is a 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, gender, 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 diabetes mellitus type 1 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 diabetes mellitus type 1 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 diabetes mellitus type 1 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 diabetes mellitus type 1 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 hazard ratios (HRs) and matched risk differences (RDs) per 10,000 person-years and their 95% CIs for diabetes mellitus type 1 within any time 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 (risk window: 365 days after dose 1)**

	Matched HR (95% CI)	Matched RD
Pedianet	NA	-1.69
NHR	1.16 (0.96, 1.38)	4.54
PHARMO	0.70 (0.37, 1.34)	-0.02
EpiChron	0.69 (0.42, 1.14)	-0.80
SIDIAP	1.75 (0.51, 5.97)	0.01

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

10.3.7. (Idiopathic) thrombocytopenia

(Idiopathic) thrombocytopenia was observed in the vaccinated and unvaccinated cohorts in PHARMO, EpiChron and SIDIAP and no events were observed in Pedianet or NHR. The incidence rates in the vaccinated cohorts ranged from 1.4 per 10,000 person-years (95% CI 0.7, 2.5) in PHARMO to 17.3 per 10,000 person-years (95% CI 15.7, 19.1) in SIDIAP and from 1.1 per 10,000 person-years (95% CI 0.6, 2.2 in PHARMO to 18.1 per 10,000 person-years (95% CI 16.1, 20.5) in SIDIAP in the unvaccinated cohorts. The cumulative incidence (1-KM) per 10,000 individuals at any time after follow-up showed a constant increase in incidence over the 365-day risk window and was less than 2.5 per 10,000 individuals in the vaccinated and unvaccinated cohorts. The incidences were slightly higher in the older age groups in each of the data sources. The matched HRs were 1.22 (95% CI: 0.50; 2.94) in PHARMO, 0.53 (95% CI: 0.32; 0.88) in EpiChron, and 0.96 (95% CI: (0.82: 1.11) in SIDIAP.

Table 25.   Risk estimates (95% CI) per 10,000 person-years (PY) for (idiopathic) thrombocytopenia among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source (risk window: 42 days after dose 1)

| Data source	Vaccinated				Unvaccinated			
	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 (Italy)	0	0 (0, 0)	738.6	0 (0, 49.9)	0	0 (0, 0)	735.7	NA
NHR (Norway)	0	0 (0, 0)	240,851.2	0 (0, 0.2)	0	0 (0, 0)	240,559.3	NA
PHARMO (Netherlands)	11	0.2 (0.1, 0.2)	79,643.9	1.4 (0.7, 2.5)	9	0.1 (0, 0.2)	79,218.3	1.1 (0.6, 2.2)
EpiChron (Spain)	33	0.9 (0.6, 1.2)	42,547.7	7.8 (5.3, 10.9)	62	1.7 (1.1, 2.3)	42,406.7	14.6 (1, 21.3)
SIDIAP (Spain)	417	2.0 (1.8, 2.2)	240,649.2	17.3 (15.7, 19.1)	436	2.0 (1.8, 2.3)	240,497.1	18.1 (16.1, 20.5)

NA: Not available

Note: Estimation of confidence intervals differs between vaccinated and unvaccinated, since the unvaccinated estimate is a 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, gender, 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 (idiopathic) thrombocytopenia among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source (risk window: 42 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 42-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 (idiopathic) thrombocytopenia 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: 42 days after dose 1)

Table 26. **Matched hazard ratios (HRs) and matched risk differences (RDs) per 10,000 person-years and their 95% CIs for (idiopathic) thrombocytopenia among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source (risk window: 42 days after dose 1)**

	Matched HR (95% CI)	Matched RD
Pedianet	NA	NA
NHR	NA	NA
PHARMO	1.22 (0.50, 2.94)	0.04
EpiChron	0.53 (0.32, 0.88)	-0.79
SIDIAP	0.96 (0.82, 1.11)	-0.04

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

10.3.8. Thrombotic thrombocytopenia syndrome (TTS)

Thrombotic thrombocytopenia syndrome (TTS) is defined as the occurrence of a venous or arterial thrombotic event and thrombocytopenia within 10 days of the occurrence of a thrombotic event. It was rarely observed in the vaccinated and unvaccinated cohorts in EpiChron and SIDIAP. The incidence rates were 1.5 per 10,000 person-years (95% CI 0.3, 4.4) in EpiChron and 2.1 per 10,000 person-years (95% CI 1.4, 3.2) in SIDIAP in the vaccinated cohorts and 1.3 per 10,000 person-years (95% CI <0.1, 2.0) in SIDIAP and 6.1 per 10,000 person-years (95% CI 2.1, 18.0) in EpiChron in the unvaccinated cohorts. The cumulative incidence was less than 1 per 10,000 individuals in both the vaccinated and unvaccinated cohorts during the 15-day risk window. The matched HRs were 0.25 (95% CI: 0.05; 1.20) in EpiChron and 1.64 (95% CI: 0.82; 3.29) in SIDIAP. No significant differences were observed in the incidence of TTS between the vaccinated and unvaccinated cohorts in the data sources reporting data.

Table 27. Risk estimates (95% CI) per 10,000 person-years (PY) for thrombotic thrombocytopenia syndrome (TTS) among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source (risk window: 15 days after dose 1)

Data source	Vaccinated				Unvaccinated			
	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 (Italy)	NA	NA	NA	NA	NA	NA	NA	NA
NHR (Norway)	NA	NA	NA	NA	NA	NA	NA	NA
PHARMO (Netherlands)	NA	NA	NA	NA	NA	NA	NA	NA
EpiChron (Spain)	<5	0.1 (0, 0.1)	19,720.7	1.5 (0.3, 4.4)	12	0.3 (0, 0.6)	19,699.9	6.1 (2.1, 18.0)
SIDIAP (Spain)	23	0.1 (0.1, 0.1)	107,687.2	2.1 (1.4, 3.2)	14	0.1 (0, 0.0)	107,672.0	1.3 (0.0, 2.0)

NA: Not available

Note: Estimation of confidence intervals differs between vaccinated and unvaccinated, since the unvaccinated estimate is a 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, gender, 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 thrombotic thrombocytopenia syndrome (TTS) among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source (risk window: 15 days after dose 1)
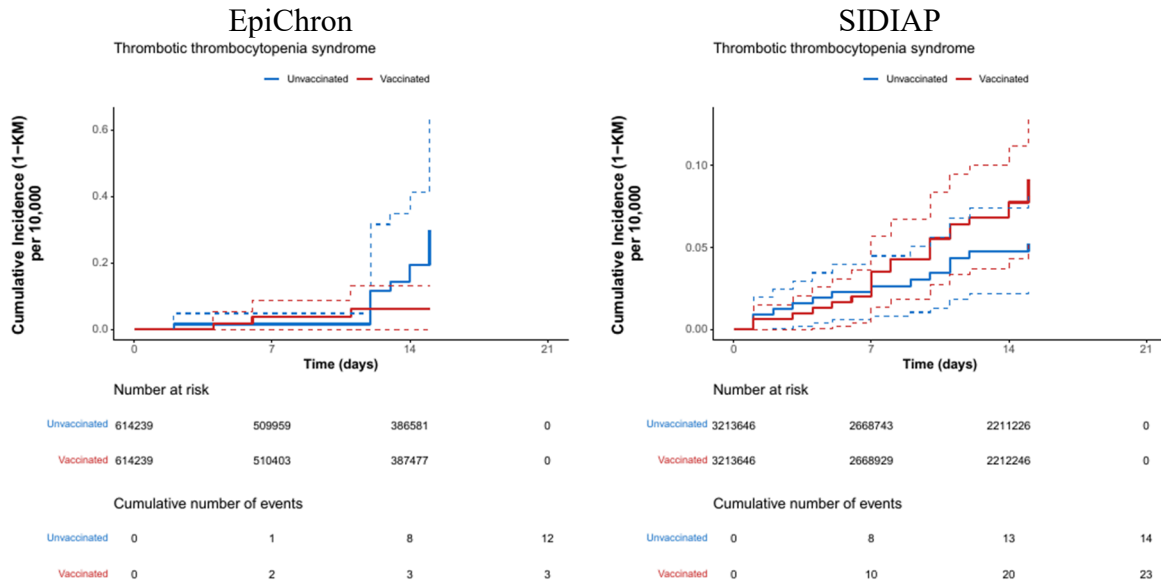
Cumulative incidence curves (1 – Kaplan–Meier risk) starting from the day of administration of the first dose of vaccine. Dotted lines represent 95% confidence intervals. The number at risk at each time point and the cumulative number of events are also shown for each time point. The numerical data correspond to the days indicated by the tick marks on the x-axis.

Figure 19. Forest plot showing incidence rates and 95% confidence intervals for thrombotic thrombocytopenia syndrome (TTS) 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: 15 days after dose 1)
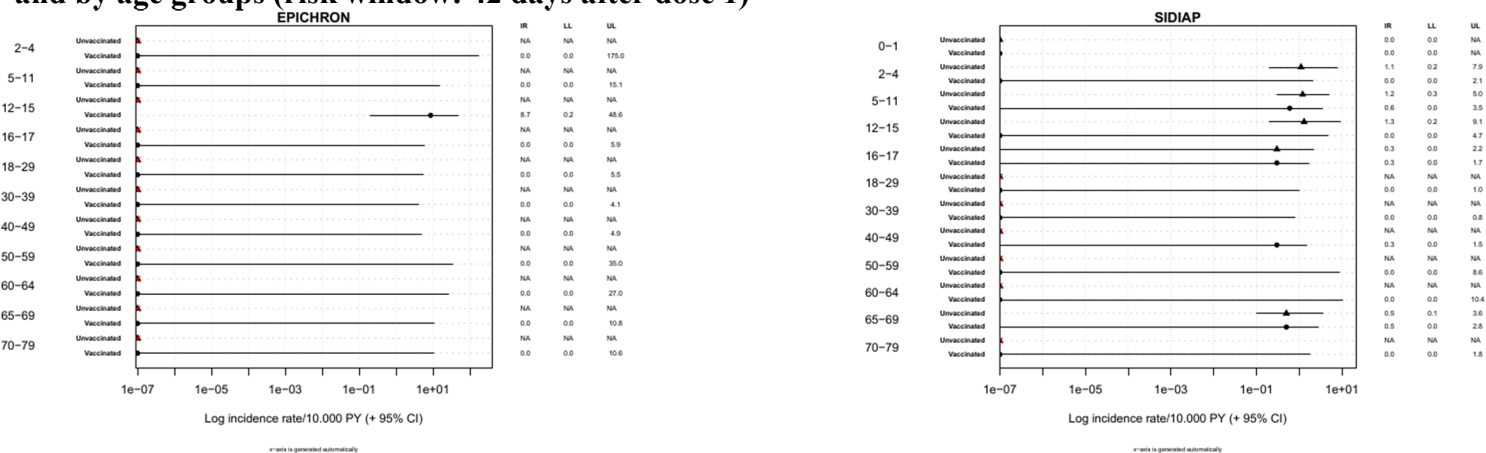
Table 28. **Matched hazard ratios (HRs) and matched risk differences (RDs) per 10,000 person-years and their 95% CIs for thrombotic thrombocytopenia syndrome (TTS) among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source (risk window: 15 days after dose 1)**

	Matched HR (95% CI)	Matched RD
Pedianet	NA	NA
NHR	NA	NA
PHARMO	NA	NA
EpiChron	0.25 (0.05, 1.20)	-0.24
SIDIAP	1.64 (0.82, 3.29)	0.04

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

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10.3.9. Acute cardiovascular injury

Acute cardiovascular injury events were observed in both the vaccinated and unvaccinated cohorts in all data sources, except Pedianet, which has data for children only. The incidence rates ranged from 41.3 per 10,000 person-years (95% CI 39.2, 43.5) in PHARMO to 180.8 per 10,000 person-years (95% CI 177.0, 184.7) in NHR in the vaccinated cohorts and from 47.2 per 10,000 person-years (95% CI 44.0, 50.6) in PHARMO to 185.4 per 10,000 person-years (95% CI 179.3, 191.8) in NHR in the unvaccinated cohorts.

The incidence of acute cardiovascular injury (including microangiopathy, heart failure, stress cardiomyopathy, coronary artery disease, arrhythmia) 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 0.97 (95% CI: 0.94; 1.01) in NHR, 0.88 (95% CI: 0.80; 0.96) in PHARMO, 0.94 (95% CI: 0.86; 1.03) in EpiChron and 1.14 (95% CI: 1.09; 1.18) in SIDIAP. The cumulative incidence risk curves showed that the risk between the vaccinated and unvaccinated cohorts diverged after day 100 in SIDIAP.

Table 29. **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)**

Data source	Vaccinated				Unvaccinated			
	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 (Italy)	NA	NA	NA	NA	NA	NA	NA	NA
NHR (Norway)	8,533	270.1 (239.7, 300.5)	471,987.9	180.8 (177.0, 184.7)	8,693	286.6 (241.5, 331.5)	468,807.7	185.4 (179.3, 191.8)
PHARMO (Netherlands)	1,420	39.6 (37.1, 42)	343,516.9	41.3 (39.2, 43.5)	1,578	41.3 (38.1, 44.5)	334,114.5	47.2 (44.0, 50.6)
EpiChron (Spain)	1,610	75.3 (71.3, 79.3)	188,266.1	85.5 (81.4, 89.8)	1,684	78.3 (71.9, 84.6)	184,065.2	91.5 (84.9, 98.6)
SIDIAP (Spain)	10,355	115.6 (112.7, 118.4)	907,893.3	114.1 (111.9, 116.3)	9,116	92.3 (88.5, 96.1)	907,972.0	100.4 (97.2, 103.7)

NA: Not available

Note: Estimation of confidence intervals differs between vaccinated and unvaccinated, since the unvaccinated estimate is a 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, gender, 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 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)
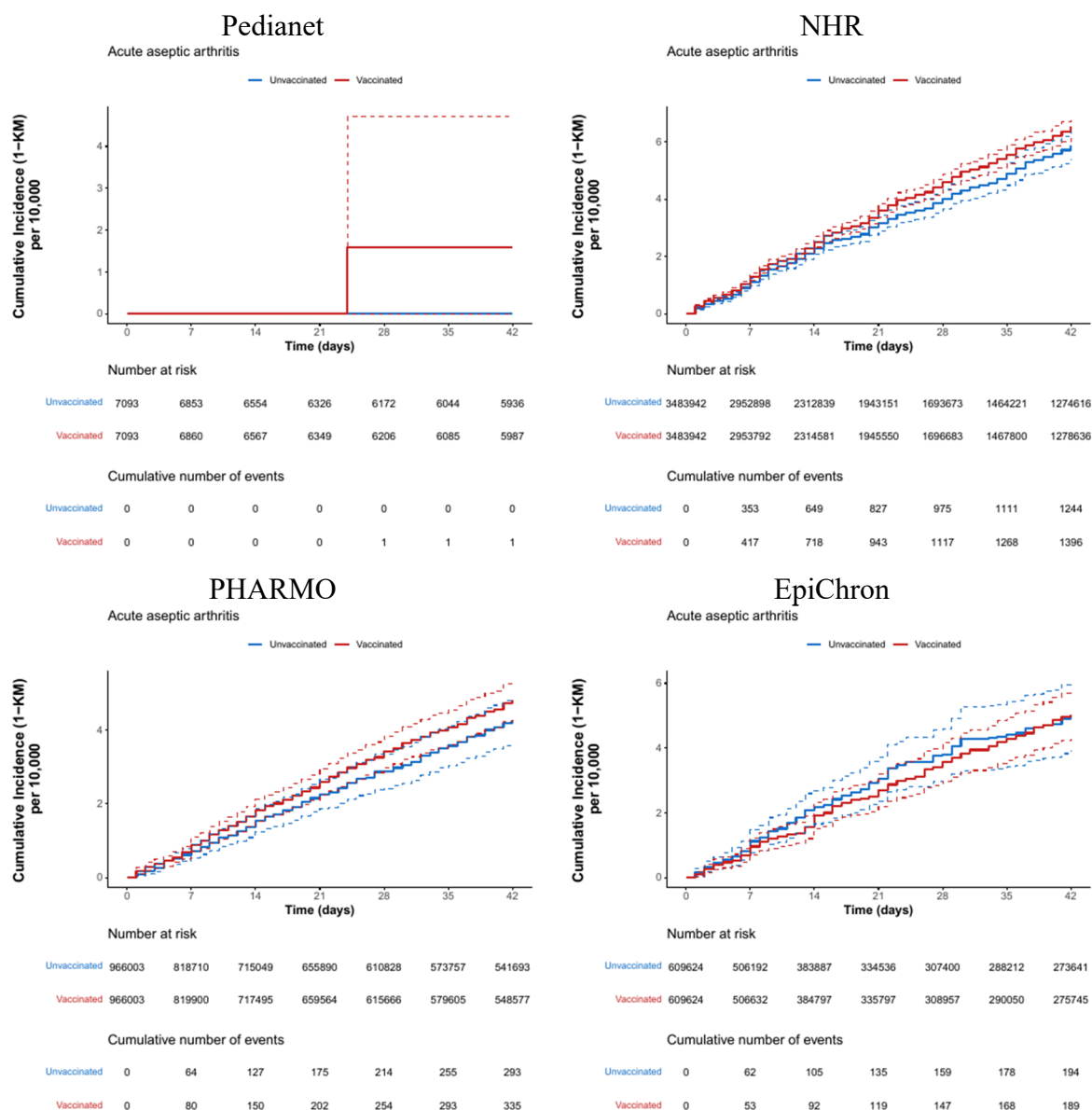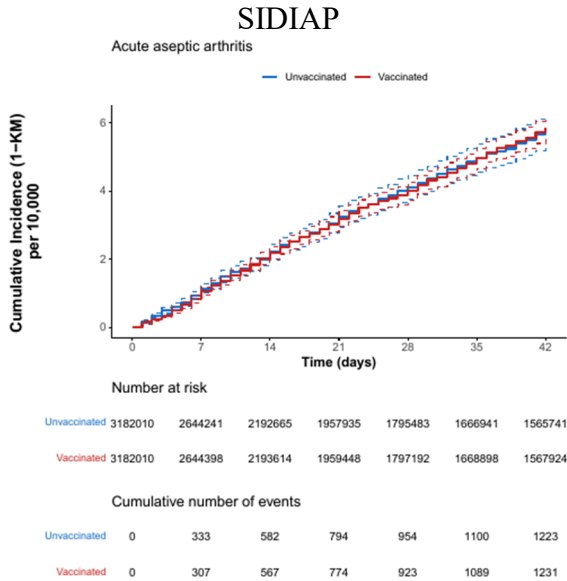

Cumulative incidence curves (1 – Kaplan–Meier risk) starting from the day of administration of the first dose of vaccine up to 365 days. Dotted lines represent 95% confidence intervals. The number at risk at each time point and the cumulative number of events during the 365-day risk window are also shown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

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Figure 21. 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)
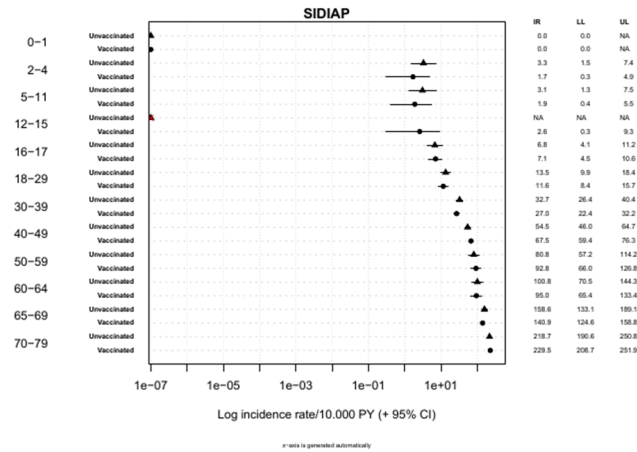
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Table 30. **Matched hazard ratios (HRs) and matched risk differences (RDs) per 10,000 person-years and their 95% CIs for acute cardiovascular injury among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source (risk window: 365 days after dose 1)**

	Matched HR (95% CI)	Matched RD
Pedianet	NA	NA
NHR	0.97 (0.94, 1.01)	-16.43
PHARMO	0.88 (0.80, 0.96)	-1.69
EpiChron	0.94 (0.86, 1.03)	-3.00
SIDIAP	1.14 (1.09, 1.18)	23.21

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

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10.3.10. Arrhythmia

Arrhythmia was observed in the vaccinated and unvaccinated cohorts in all data sources. The incidence rates ranged from 20.7 per 10,000 person-years (95% CI 8.9, 40.8) in Pedianet (children only) to 244.8 per 10,000 person-years (95% CI 240.3, 249.4) in NHR in the vaccinated cohorts and from 21.0 per 10,000 person-years (95% CI 7.9, 55.9) in Pedianet to 231.7 per 10,000 person-years (95% CI 225.0, 238.6) in NHR in the unvaccinated cohorts. The cumulative incidences during the 365-day risk window ranged from 14.5 per 10,000 person-years (95% CI 4.4, 24.5) in Pedianet to 273.5 per 10,000 person-years (95% CI 253.5, 293.5) in NHR in the vaccinated cohorts and from 17.0 per 10,000 person-years (95% CI 1.1, 32.9) in Pedianet to 269.8 per 10,000 person-years (95% CI 227.5, 311.9) in NHR in the unvaccinated cohorts.

The incidence rates were higher in the older age groups. The matched HRs were 0.99 (95% CI: 0.30; 3.27) in Pedianet, 1.06 (95% CI: 1.02; 1.09) in NHR, 1.04 (95% CI: 0.98; 1.10) in PHARMO, 1.19 (95% CI: 1.11; 1.29) in EpiChron and 1.21 (95% CI: 1.17; 1.25) in SIDIAP.

Table 31. 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)

Data source	Vaccinated				Unvaccinated			
	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 (Italy)	8	14.5 (4.4, 24.5)	3,859.7	20.7 (8.9, 40.8)	8	17.0 (1.1, 32.9)	3,815.4	21.0 (7.9, 55.9)
NHR (Norway)	11,355	273.5 (253.5, 293.5)	463,789.7	244.8 (240.3, 249.4)	10,673	269.8 (227.5, 311.9)	460,649.9	231.7 (225.0, 238.6)
PHARMO (Netherlands)	3,197	93.5 (89.7, 97.4)	339,292.7	94.2 (91, 97.5)	3,000	88.5 (83.5, 93.4)	330,035.7	90.9 (86.6, 95.4)
EpiChron (Spain)	2,532	123.3 (118.1, 128.4)	186,829.2	135.5 (130.3, 140.9)	2,082	100.5 (93.3, 107.7)	182,882.3	113.8 (106.6, 121.6)
SIDIAP (Spain)	13,504	148.9 (145.7, 152.2)	903,128.4	149.5 (147, 152.1)	11,195	111.5 (107.4, 115.5)	903,670.7	123.9 (120.3, 127.5)

Note: Estimation of confidence intervals differs between vaccinated and unvaccinated, since the unvaccinated estimate is a 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, gender, 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 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)**
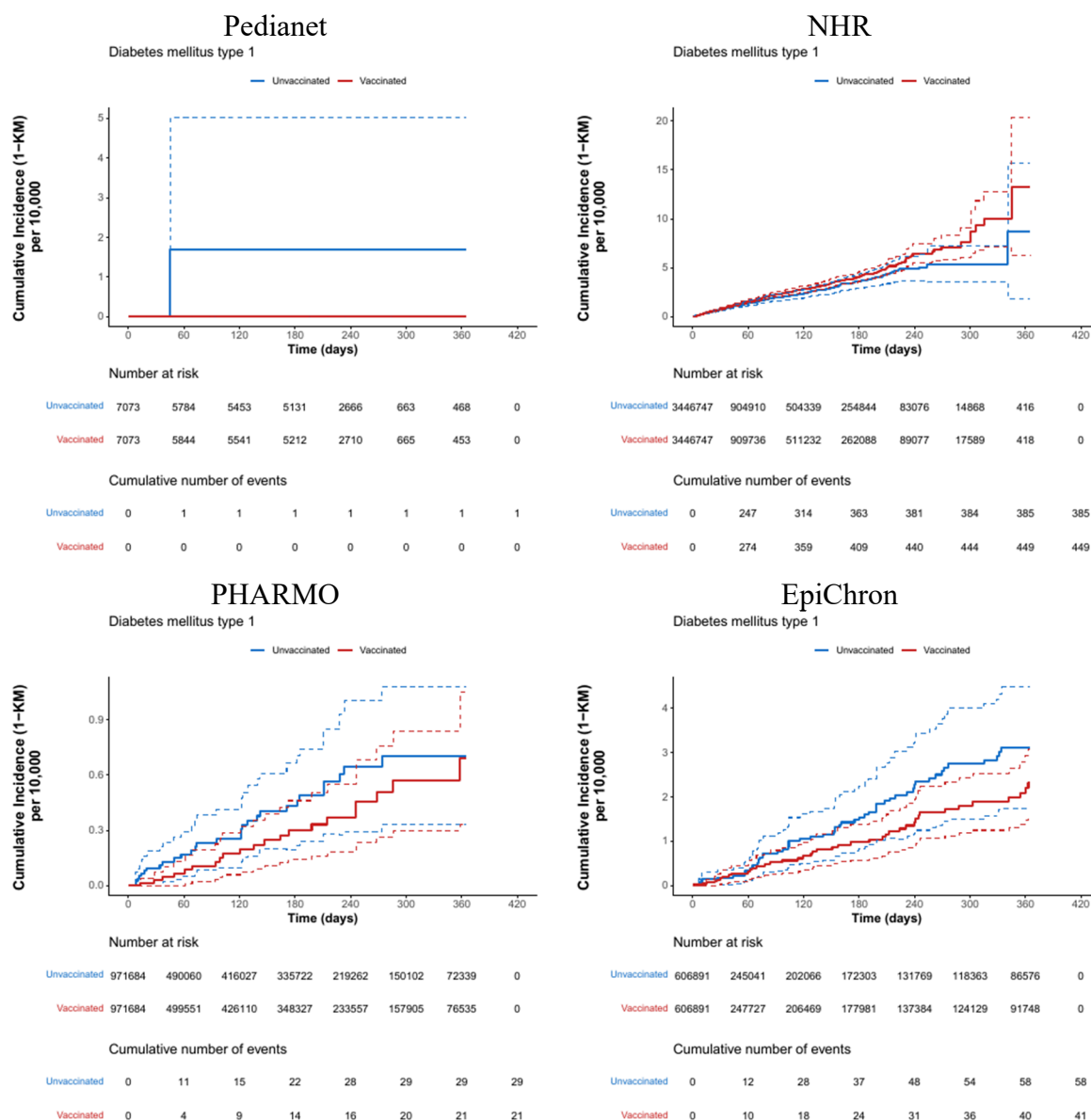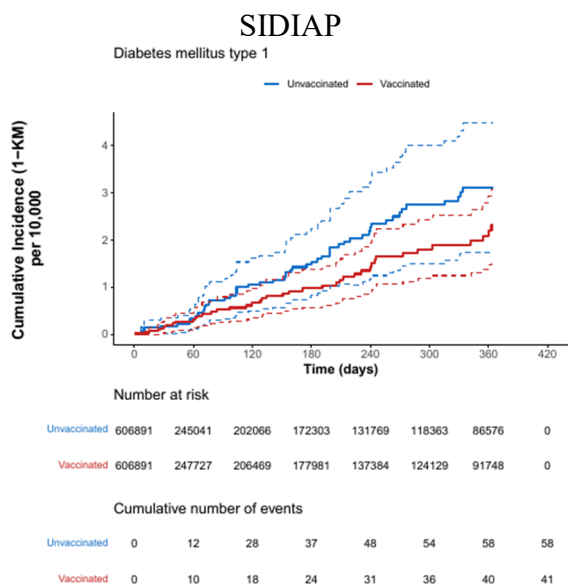
Figure 22. **Cumulative incidence of arrhythmia among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source (risk window: 365 days after dose 1)**

SIDIAP

Arrhythmia

Number at risk

Unvaccinated	3095581	1379650	1113484	857162	514838	390564	171797	0
Vaccinated	3095581	1380751	1114596	857637	513192	387360	169176	0

Cumulative number of events

Unvaccinated	0	5279	7255	8734	9977	10656	11164	11195
Vaccinated	0	5317	7978	10007	11709	12703	13450	13504

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 23. **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)**
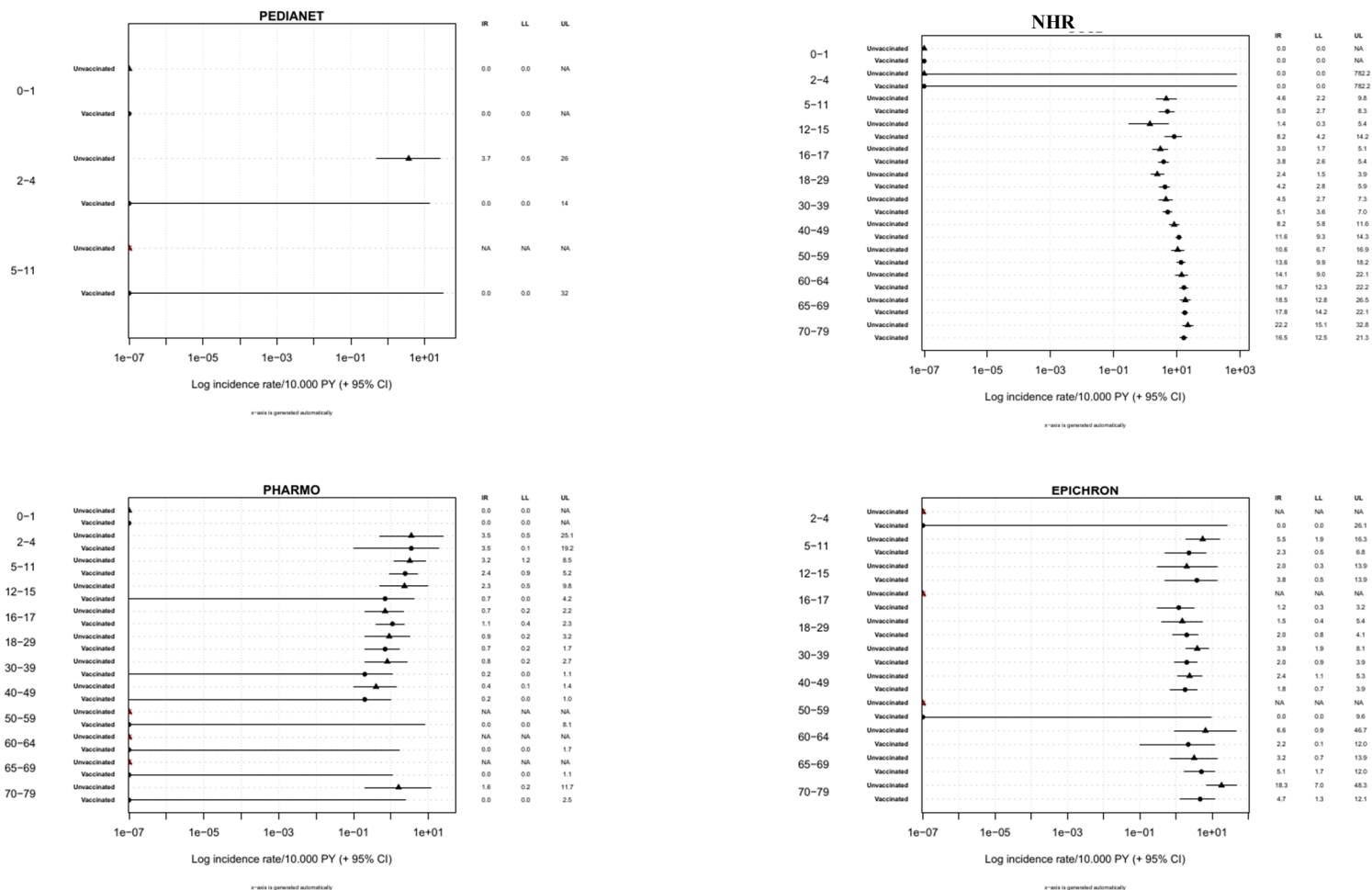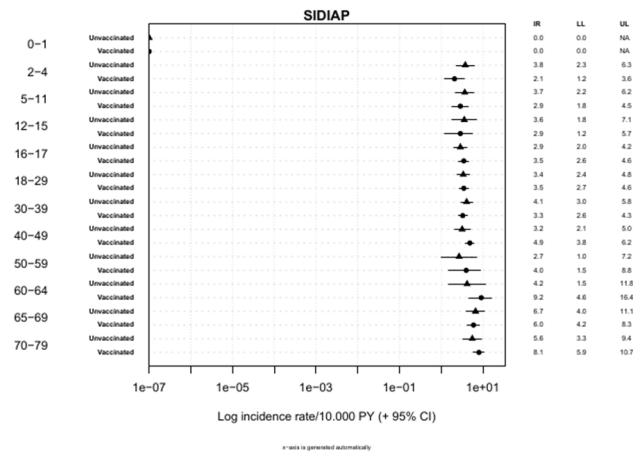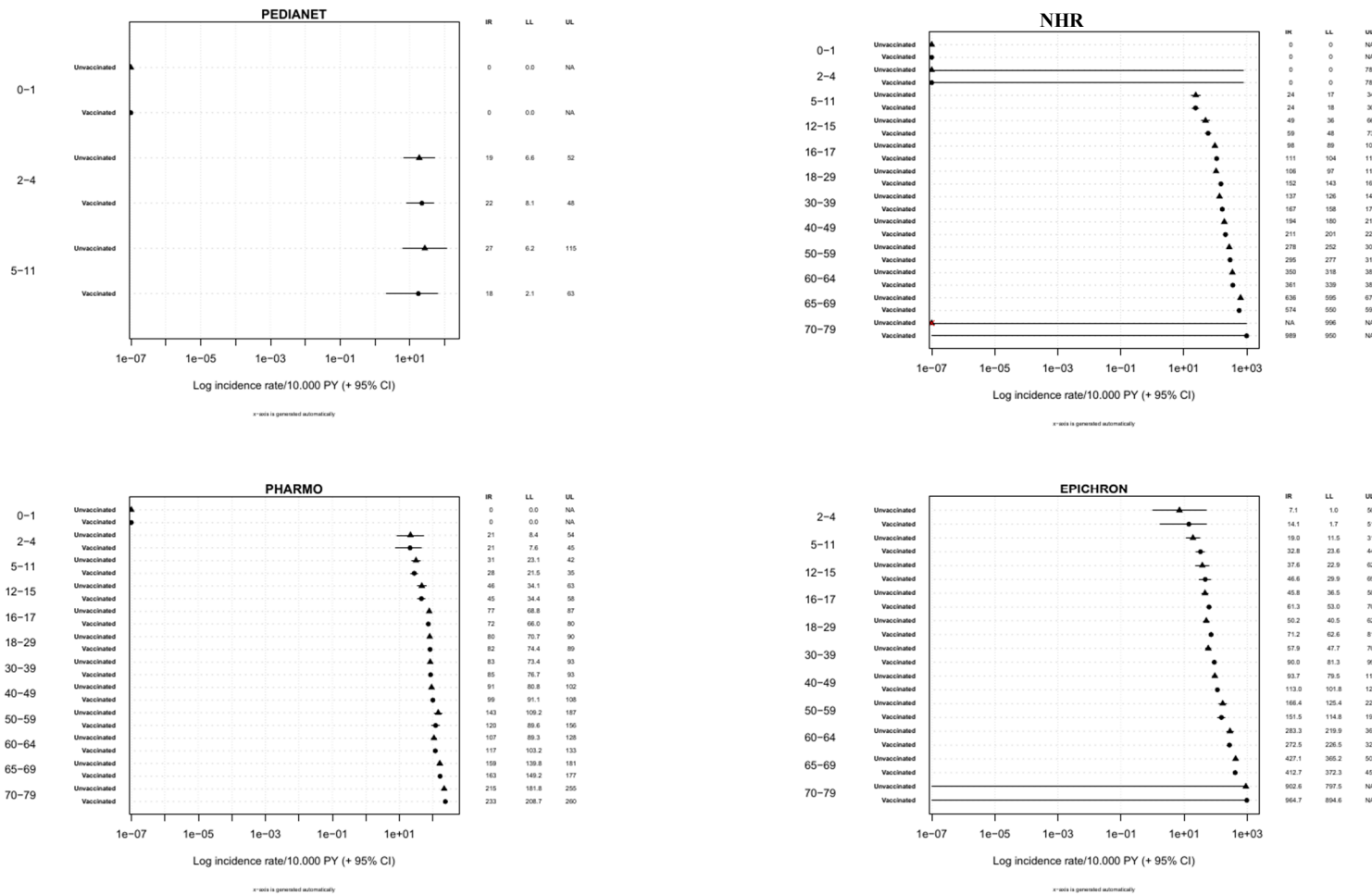
Figure 23. Forest plot showing incidence rates and 95% confidence intervals for arrhythmia among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source and by age groups (risk window: 365 days after dose 1)
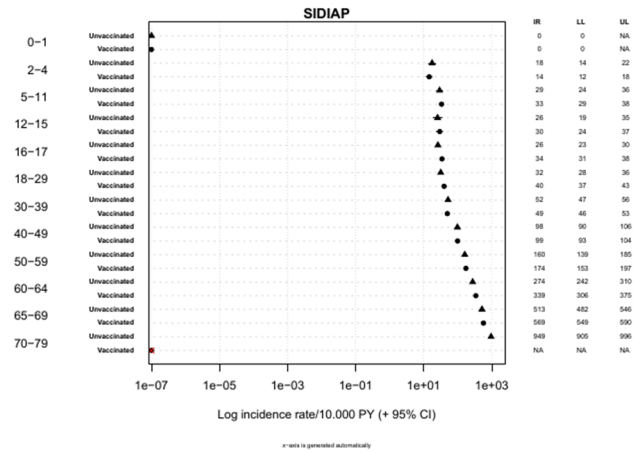
Table 32. **Matched hazard ratios (HRs) and matched risk differences (RDs) per 10,000 person-years and their 95% CIs for arrhythmia among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source (risk window: 365 days after dose 1)**

	Matched HR (95% CI)	Matched RD
Pedianet	0.99 (0.30, 3.27)	-2.53
NHR	1.06 (1.02, 1.09)	3.72
PHARMO	1.04 (0.98, 1.10)	5.05
EpiChron	1.19 (1.11, 1.29)	22.78
SIDIAP	1.21 (1.17, 1.25)	37.49

10.3.11. Heart failure

The incidence rates of heart failure ranged from 15.6 per 10,000 person-years (95% CI 14.3, 17.0) in PHARMO to 63.0 (95% CI 60.8, 65.3) per 10,000 person-years in NHR in the vaccinated cohorts and from 19.8 per 10,000 person-years (95% CI 17.7, 22.1) in PHARMO to 76.9 per 10,000 person-years (95% CI 72.9, 81.1) in NHR in the unvaccinated cohorts. The cumulative incidence of heart failure during the 365-day risk window showed a separation between vaccinated and non-vaccinated in all data sources. The incidence of heart failure was higher in the older age groups in all data sources. The matched HRs were 0.82 (95% CI; 0.76: 0.87) in NHR, 0.79 (95% CI; 0.69; 0.91) in PHARMO, 0.90 (95% CI; 0.79: 1.03) in EpiChron, and 1.29 (95% CI; 1.22; 1.36) in SIDIAP.

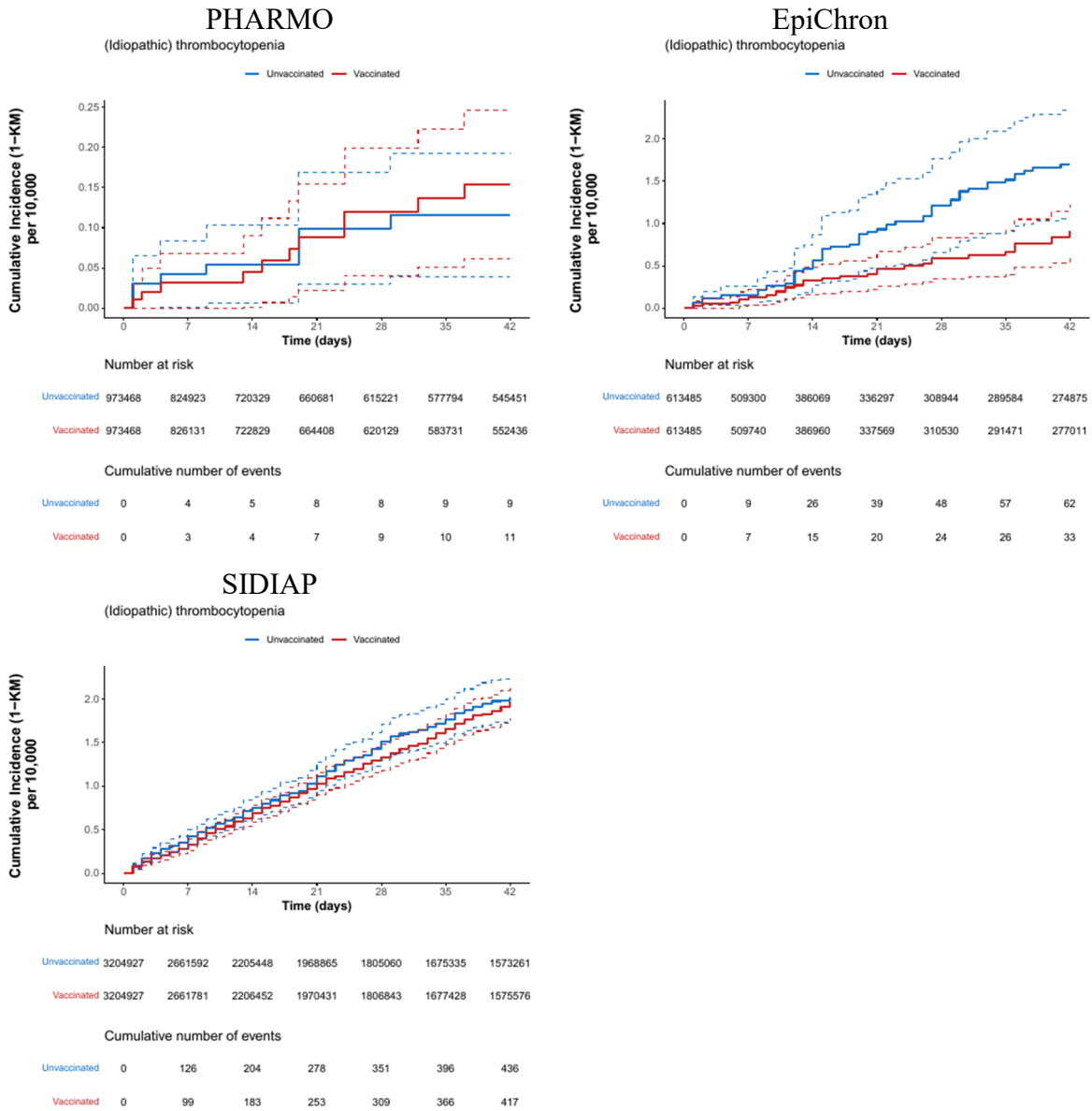**Table 33.** **Risk estimates (95% CI) per 10,000 person-years (PY) for heart failure among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source (risk window: 365 days after dose 1)**

Data source	Vaccinated				Unvaccinated			
	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 (Italy)	NA	NA	NA	NA	NA	NA	NA	NA
NHR (Norway)	3,126	122.3 (100.1, 144.5)	496,169.6	63.0 (60.8, 65.3)	3,783	153.1 (124.4, 181.6)	492,111.0	76.9 (72.9, 81.1)
PHARMO (Netherlands)	539	15.4 (13.8, 16.9)	345,683.4	15.6 (14.3, 17.0)	665	17.2 (15.0, 19.3)	336,230.2	19.8 (17.7, 22.1)
EpiChron (Spain)	821	38.2 (35.4, 41.1)	190,180.9	43.2 (40.3, 46.2)	894	39.5 (34.8, 44.2)	185,830.0	48.1 (43.2, 53.6)
SIDIAP (Spain)	5,701	65.7 (63.5, 68.0)	919,055.9	62.0 (60.4, 63.7)	4,433	45.9 (43.0, 48.8)	918,659.4	48.3 (46.0, 50.6)

NA: Not available

Note: Estimation of confidence intervals differs between vaccinated and unvaccinated, since the unvaccinated estimate is a 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, gender, 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 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 25. 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)
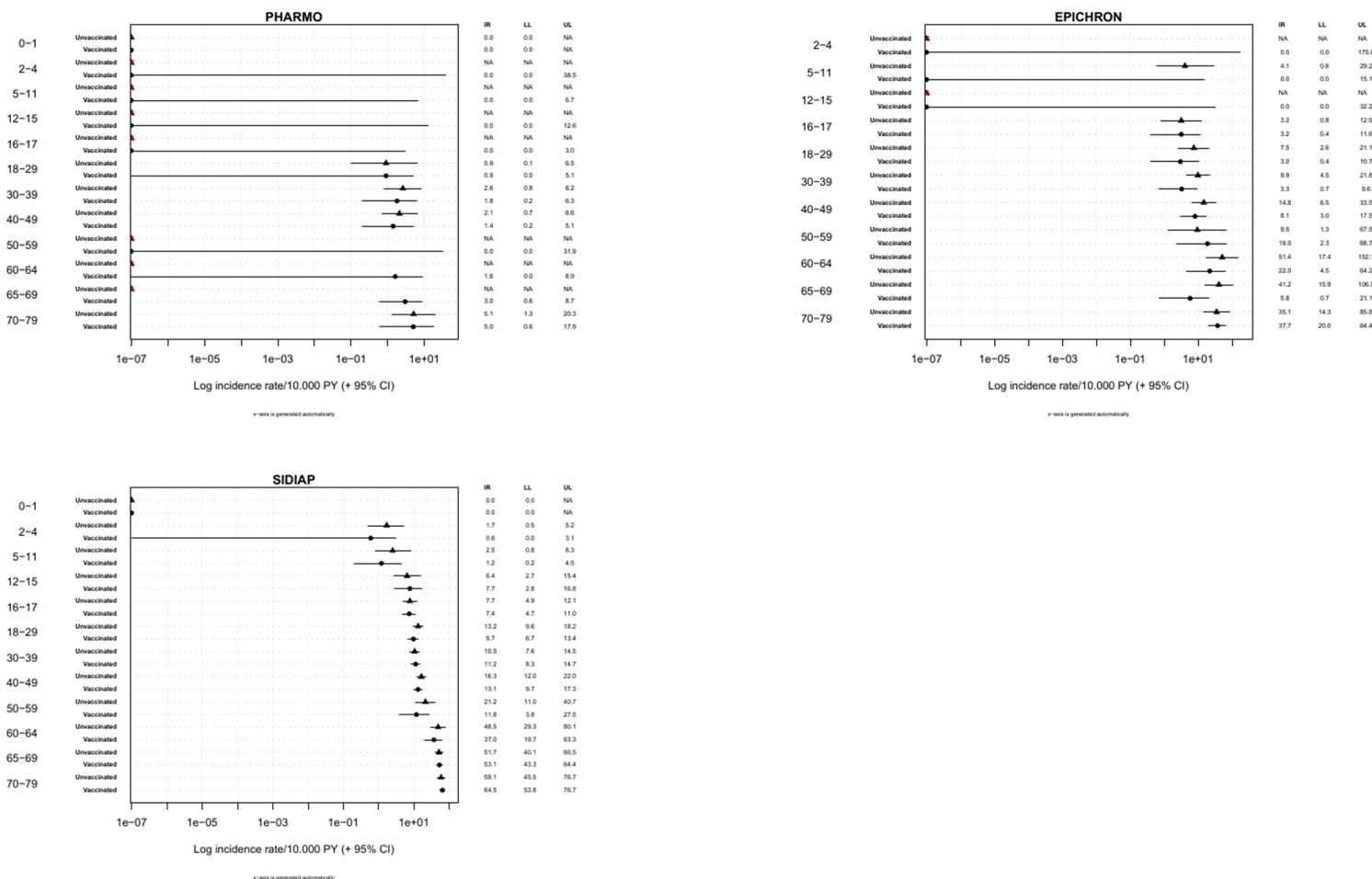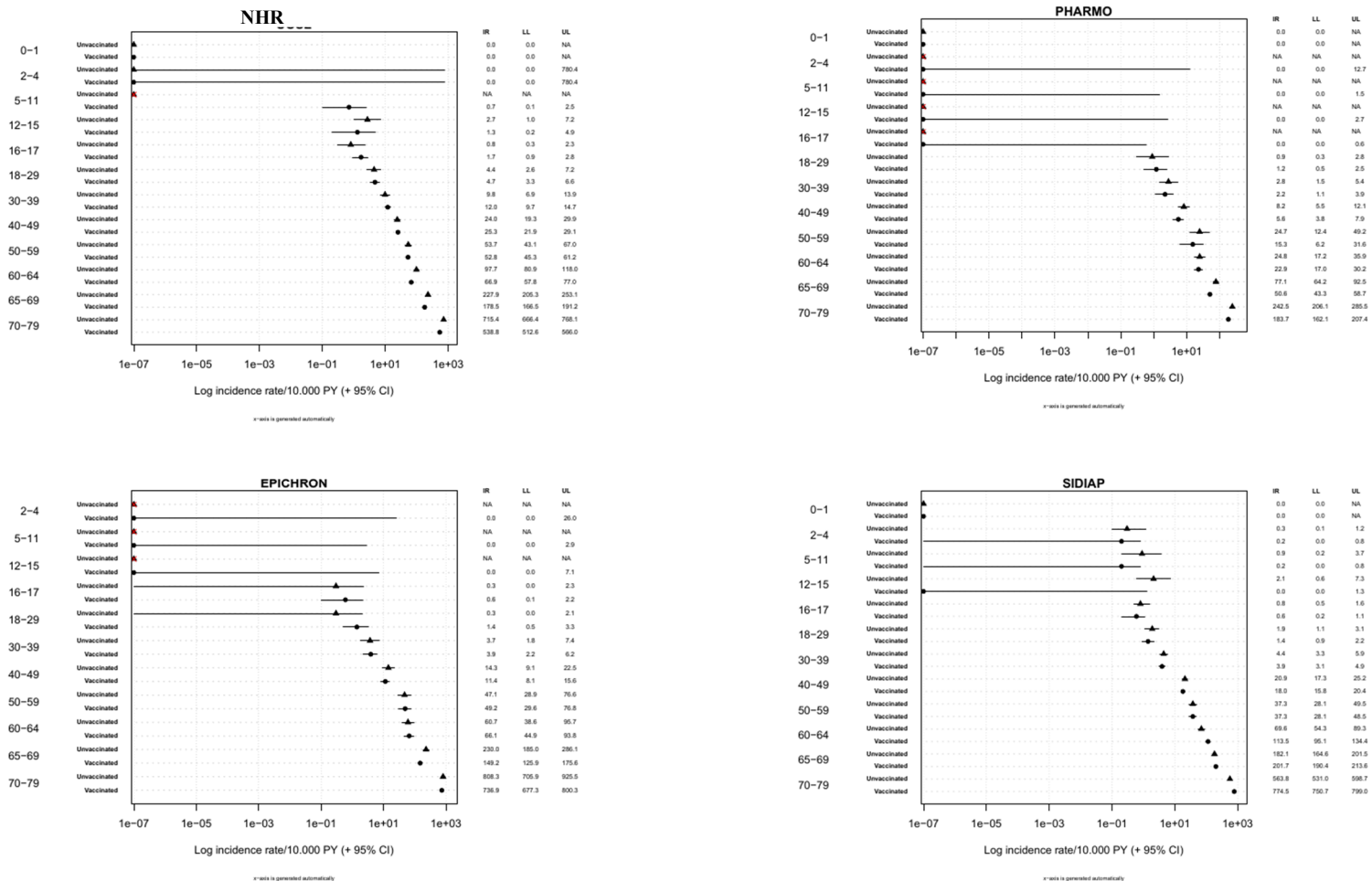
Table 34. **Matched hazard ratios (HRs) and matched risk differences (RDs) per 10,000 person-years and their 95% CIs for heart failure among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source (risk window: 365 days after dose 1)**

	Matched HR (95% CI)	Matched RD
Pedianet	NA	NA
NHR	0.82 (0.76, 0.87)	30.73
PHARMO	0.79 (0.69, 0.91)	-1.76
EpiChron	0.90 (0.79, 1.03)	-1.30
SIDIAP	1.29 (1.22, 1.36)	19.81

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

10.3.12. Stress cardiomyopathy

Stress cardiomyopathy was a very rare event in the three data sources in which events could be identified (i.e., PHARMO, EpiChron, and SIDIAP). The incidence rates for stress cardiomyopathy ranged from 0.1 per 10,000 person-years (95% CI 0, 0.3) in PHARMO to 0.6 per 10,000 person-years (95% CI 0.4, 0.7) in SIDIAP in the vaccinated cohorts and from 0.1 per 10,000 person-years (95% CI 0, 0.4) in PHARMO to 0.4 per 10,000 person-years (95% CI 0.2, 0.6) in SIDIAP in the unvaccinated cohorts. The cumulative incidence during the 365-day risk window was less than 1 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 0.73 (95% CI: 0.14; 3.75) in PHARMO, 1.63 (95% CI: 0.39; 6.78) in EpiChron and 1.53 (95% CI: 0.88; 2.64) in SIDIAP.

Table 35. 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)

Data source	Vaccinated				Unvaccinated			
	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 (Italy)	NA	NA	NA	NA	NA	NA	NA	NA
NHR (Norway)	NA	NA	NA	NA	NA	NA	NA	NA
PHARMO (Netherlands)	<5	0.1 (0, 0.2)	346,858.0	0.1 (0, 0.3)	<5	0.1 (0, 0.10)	337,230.3	0.1 (0, 0.4)
EpiChron (Spain)	5	0.3 (0, 0.5)	191,765.3	0.3 (0.1, 0.6)	<5	0.1 (0, 0.3)	187,138.9	0.2 (0.0, 0.5)
SIDIAP (Spain)	52	0.5 (0.3, 0.7)	929,351.3	0.6 (0.4, 0.7)	34	0.3 (0.2, 0.5)	927,519.6	0.4 (0.2, 0.6)

NA: Not available

Note: Estimation of confidence intervals differs between vaccinated and unvaccinated, since the unvaccinated estimate is a 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, gender, 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 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 27. 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)
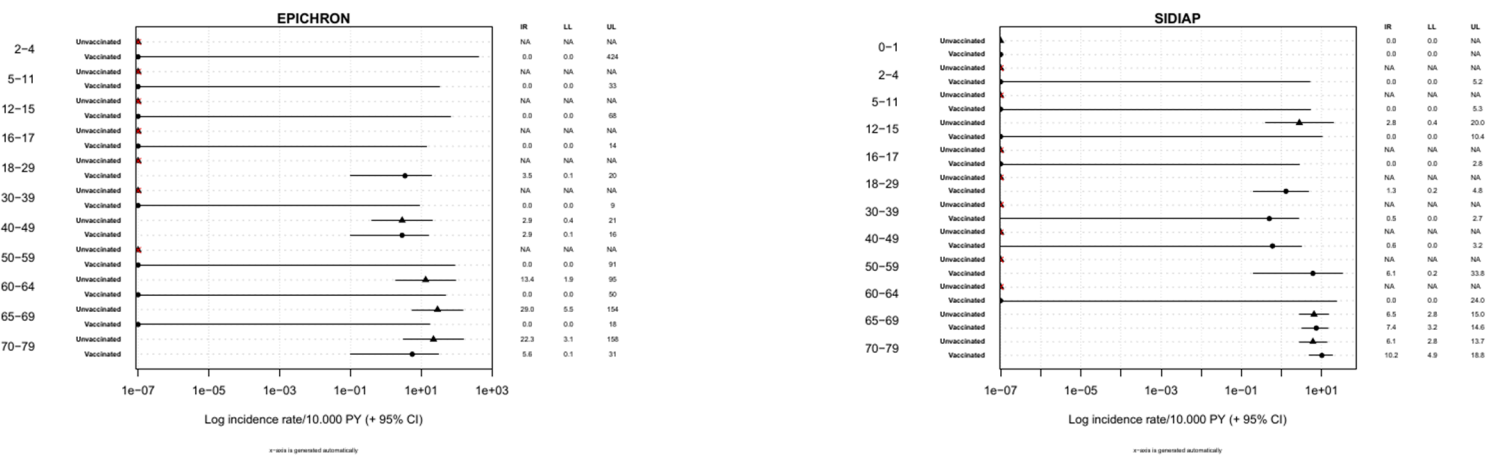
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Table 36. Matched hazard ratios (HRs) and matched risk differences (RDs) per 10,000 person-years and their 95% CIs for stress cardiomyopathy among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source (risk window: 365 days after dose 1)

	Matched HR (95% CI)	Matched RD
Pedianet	NA	NA
NHR	NA	NA
PHARMO	0.73 (0.14, 3.75)	0.03
EpiChron	1.63 (0.39, 6.78)	0.17
SIDIAP	1.53 (0.88, 2.64)	0.16

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

10.3.13. 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 13.4 per 10,000 person-years (95% CI 12.2, 14.7) in PHARMO to 118.1 per 10,000 person-years (95% CI 115.1, 121.2) in NHR in the vaccinated cohorts and from 13.0 per 10,000 person-years (95% CI 11.4, 14.8) in PHARMO to 120.2 per 10,000 person-years (95% CI 115.2, 125.4) 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 unadjusted HRs of coronary artery disease was 0.98 (95% CI: 0.93, 1.03) in NHR, 1.04 (95% CI: 0.88; 1.22) in PHARMO, 0.86 (95% CI: 0.74; 1.00) in Epichron and 1.15 (95% CI: 1.08; 1.22) in SIDIAP.
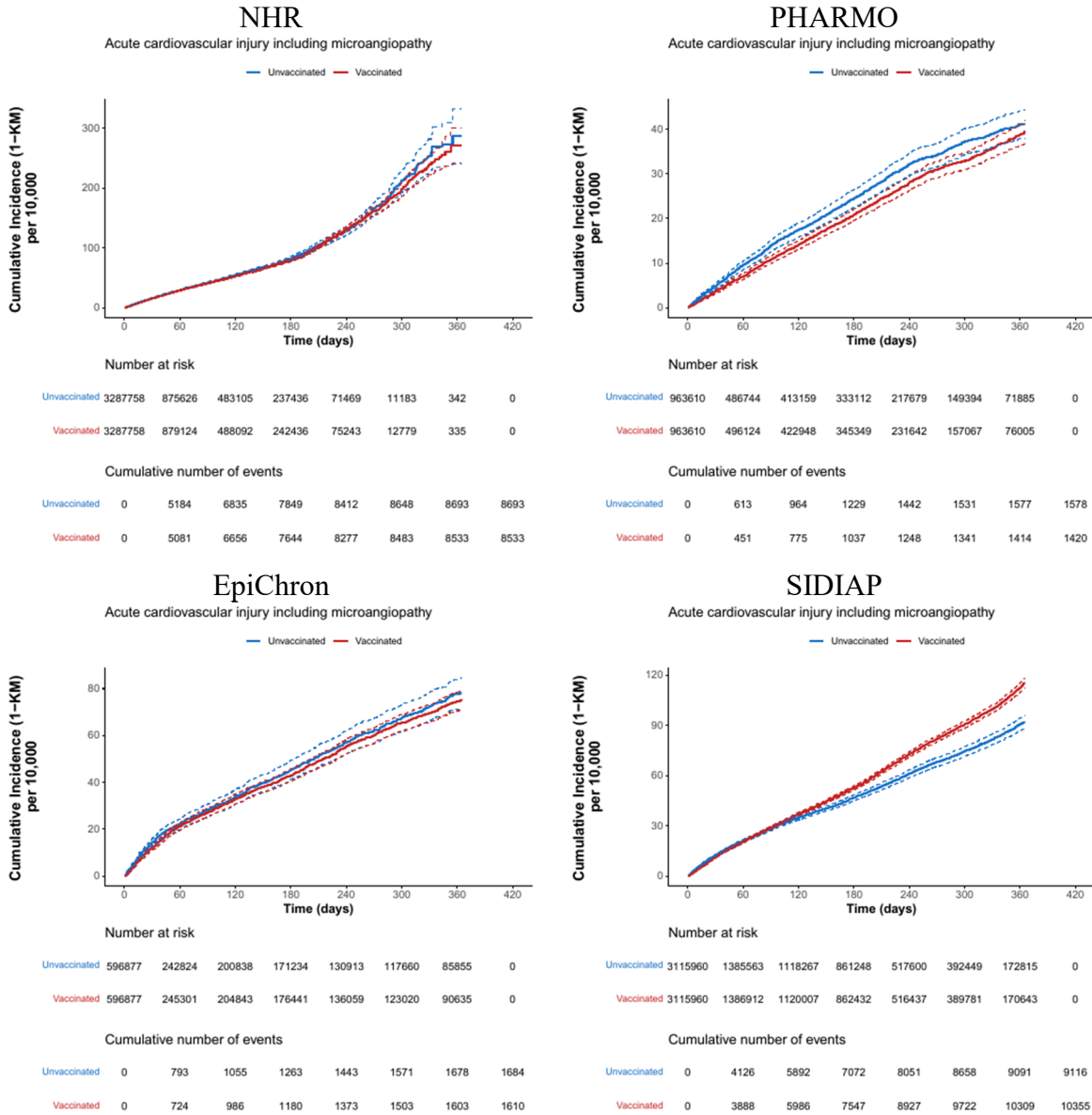
Table 37.   **Risk estimates (95% CI) per 10,000 person-years (PY) for coronary artery disease among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source (risk window: 365 days after dose 1)**

Data source	Vaccinated				Unvaccinated			
	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 (Italy)	NA	NA	NA	NA	NA	NA	NA	NA
NHR (Norway)	5,739	190.3 (159.8, 220.7)	485,745.6	118.1 (115.1, 121.2)	5,791	198.2 (161.5, 234.7)	481,660.5	120.2 (115.2, 125.4)
PHARMO (Netherlands)	464	12.4 (11.1, 13.8)	345,712.8	13.4 (12.2, 14.7)	436	11.1 (9.5, 12.7)	336,140.9	13.0 (11.4, 14.8)
EpiChron (Spain)	571	26.6 (24.2, 29.0)	190,437.7	30.0 (27.6, 32.5)	651	30.1 (26.1, 34.2)	185,944.4	35.0 (31.0, 39.6)
SIDIAP (Spain)	4,359	46.9 (45.1, 48.7)	920,196.4	47.4 (46.0, 48.8)	3,785	37.6 (35.2, 4)	919,129.8	41.2 (39.1, 43.4)

NA: Not available

Note: Estimation of confidence intervals differs between vaccinated and unvaccinated, since the unvaccinated estimate is a 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, gender, 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 28. **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 29. **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)**
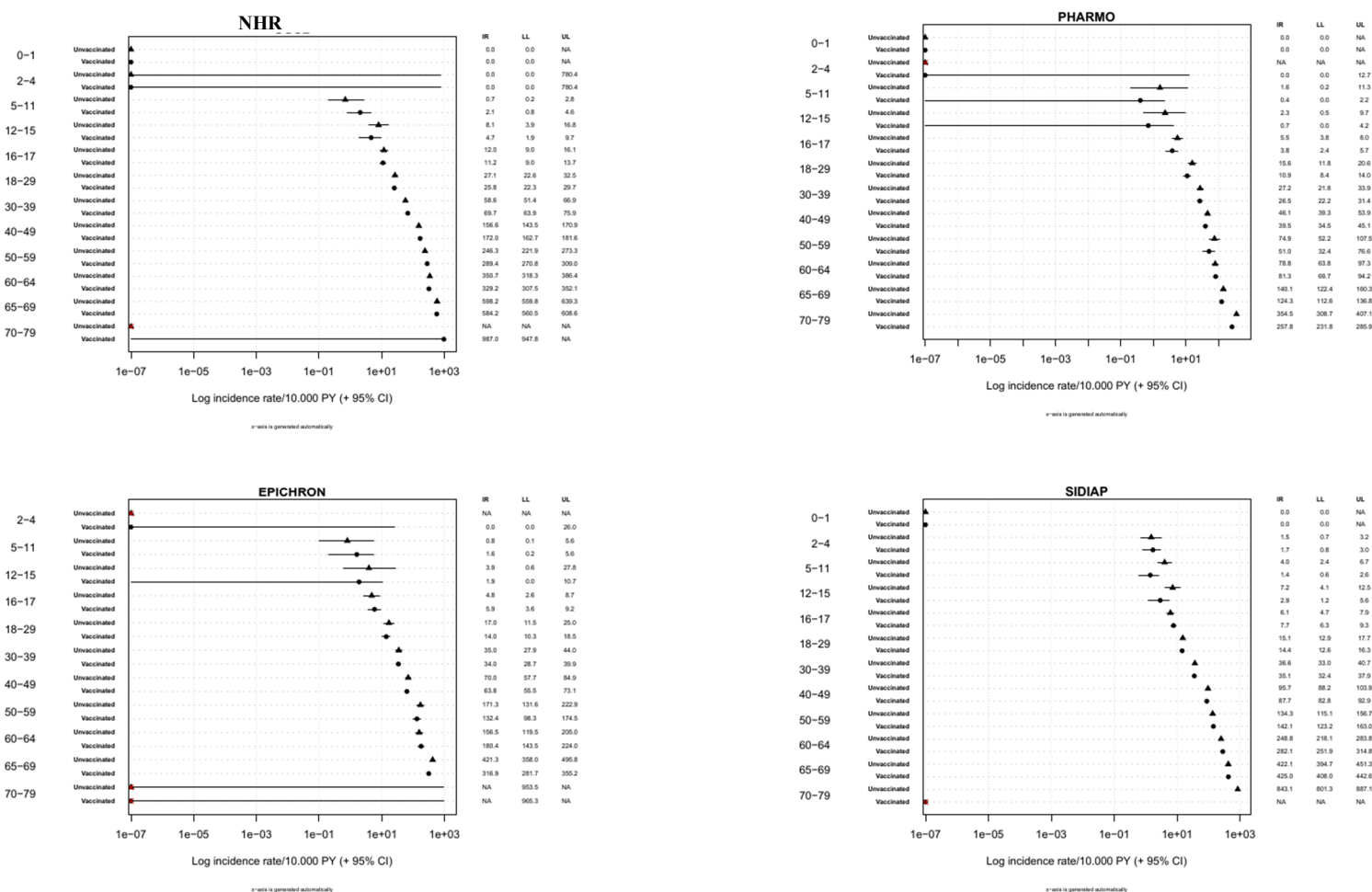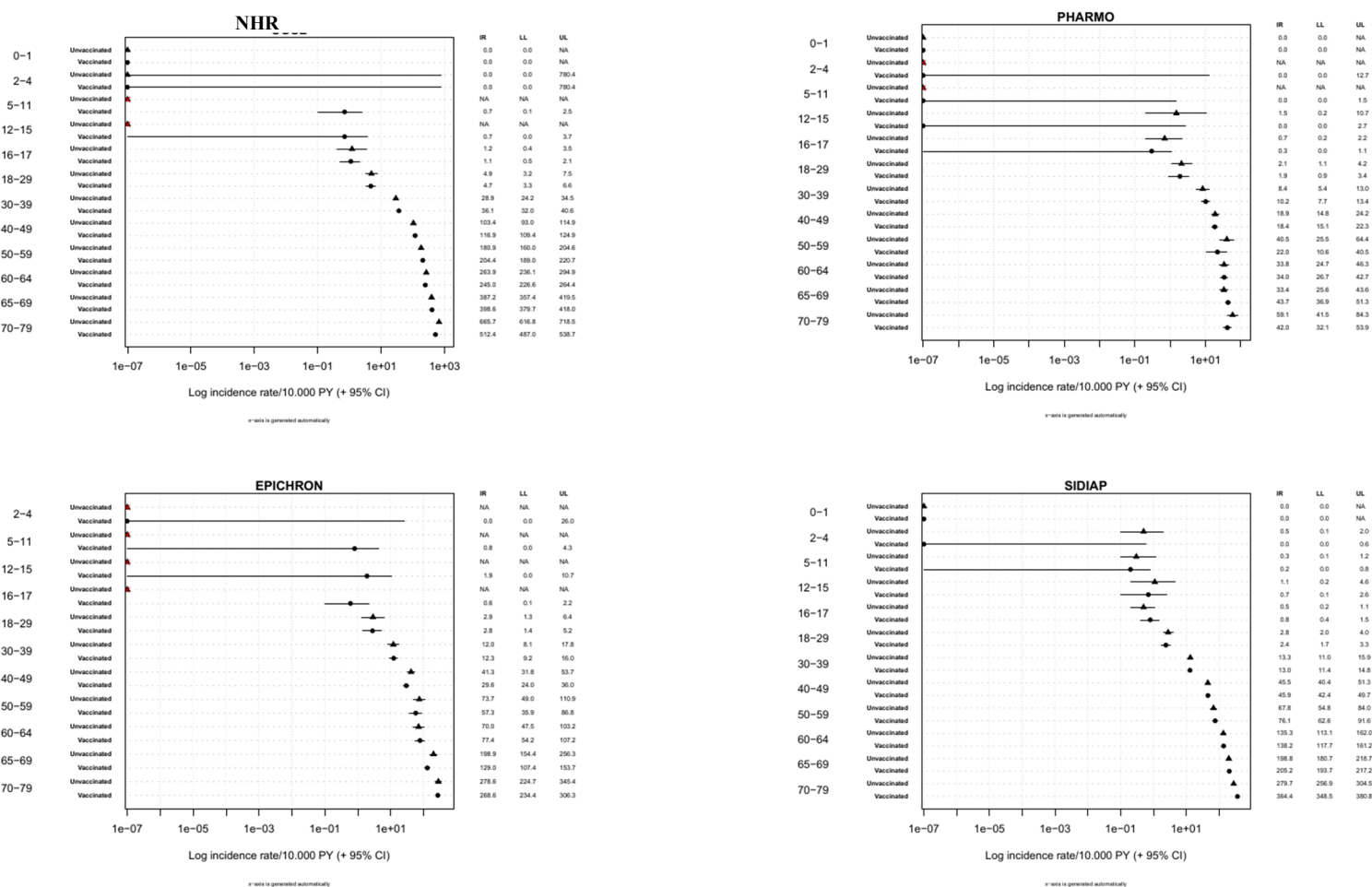
Table 38. Matched hazard ratios (HRs) and matched risk differences (RDs) per 10,000 person-years and their 95% CIs for coronary artery disease among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source (risk window: 365 days after dose 1)

	Matched HR (95% CI)	Matched RD
Pedianet	NA	NA
NHR	0.98 (0.93, 1.03)	--7.84
PHARMO	1.04 (0.88, 1.22)	1.32
EpiChron	0.86 (0.74, 1.00)	-3.56
SIDIAP	1.15 (1.08, 1.22)	9.33

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

10.3.14. Myocarditis

Myocarditis events were identified in all data sources, except Pedianet. Myocarditis events are not identifiable in Pedianet because they have to use a free-text algorithm.

During the 7-day risk window after the start of follow-up, the incidence rates ranged from 0 per 10,000 person-years (95% CI 0, 0.7) in SIDIAP to 1.2 per 10,000 person-years (95% CI 0.1, 4.2) in PHARMO in the vaccinated cohorts and from 0 per 10,000 person-years in EpiChron to 2.3 per 10,000 person-years (95% CI 0.7, 7.7) in PHARMO in the unvaccinated cohorts. No events were reported in the vaccinated cohort in SIDIAP or in the unvaccinated cohort in EpiChron during this risk window. The cumulative incidence during the 7-day risk window was below 1 per 10,000 individuals in both cohorts in each data source. No age-related variation in incidence was observed during the 7-day period due to the small number of events. The matched HRs were 0.57 (0.13, 2.46) in NHR and 0.50 (0.08, 3.12) in PHARMO.

During the 14-day risk window after the start of follow-up, the incidence rates ranged from 0.5 per 10,000 person-years (95% CI 0, 3.0) in EpiChron to 0.9 per 10,000 person-years (95% CI 0.4, 1.7) in NHR in the vaccinated cohorts and from 0.3 per 10,000 person-years (95% CI 0.1, 0.9) in SIDIAP to 2.2 per 10,000 person-years (95% CI 0.9, 5.1) in PHARMO in the unvaccinated cohorts. The cumulative incidence during the 14-day risk window was below 1 per 10,000 individuals in both cohorts in each data source. The incidence was higher in age groups over 17 years. The matched HRs were 0.91 (95% CI: 0.34; 2.45) in NHR, 0.29 (95% CI: 0.06, 1.44) in PHARMO and 2.00 (95% CI: 0.50, 7.99) in SIDIAP.

During the 21-day risk window after the start of follow-up, the incidence rates were 0.4 per 10,000 person-years (95% CI 0.1, 1.6) in PHARMO, 0.4 per 10,000 person-years (95% CI 0.2, 0.9) in SIDIAP and 1.2 per 10,000 person-years in EpiChron in the vaccinated cohorts and ranged from 0.4 per 10,000 person-years (95% CI 0.1, 0.9) in SIDIAP to 1.8 per 10,000 person-years (95% CI 0.8, 3.9) in PHARMO in the unvaccinated cohorts. The cumulative incidence was below 1 per 10,000 individuals in both cohorts in each data source. The incidence of myocarditis was higher in age groups over 17 years. The matched HRs were 1.00 (95% CI: 0.40; 2.52) in NHR, 0.25 (95% CI: 0.05, 1.22) in PHARMO and 1.20 (95% CI: 0.37, 3.93) in SIDIAP.

Table 39. **Risk estimates (95% CI) per 10,000 person-years (PY) for myocarditis within 7 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**

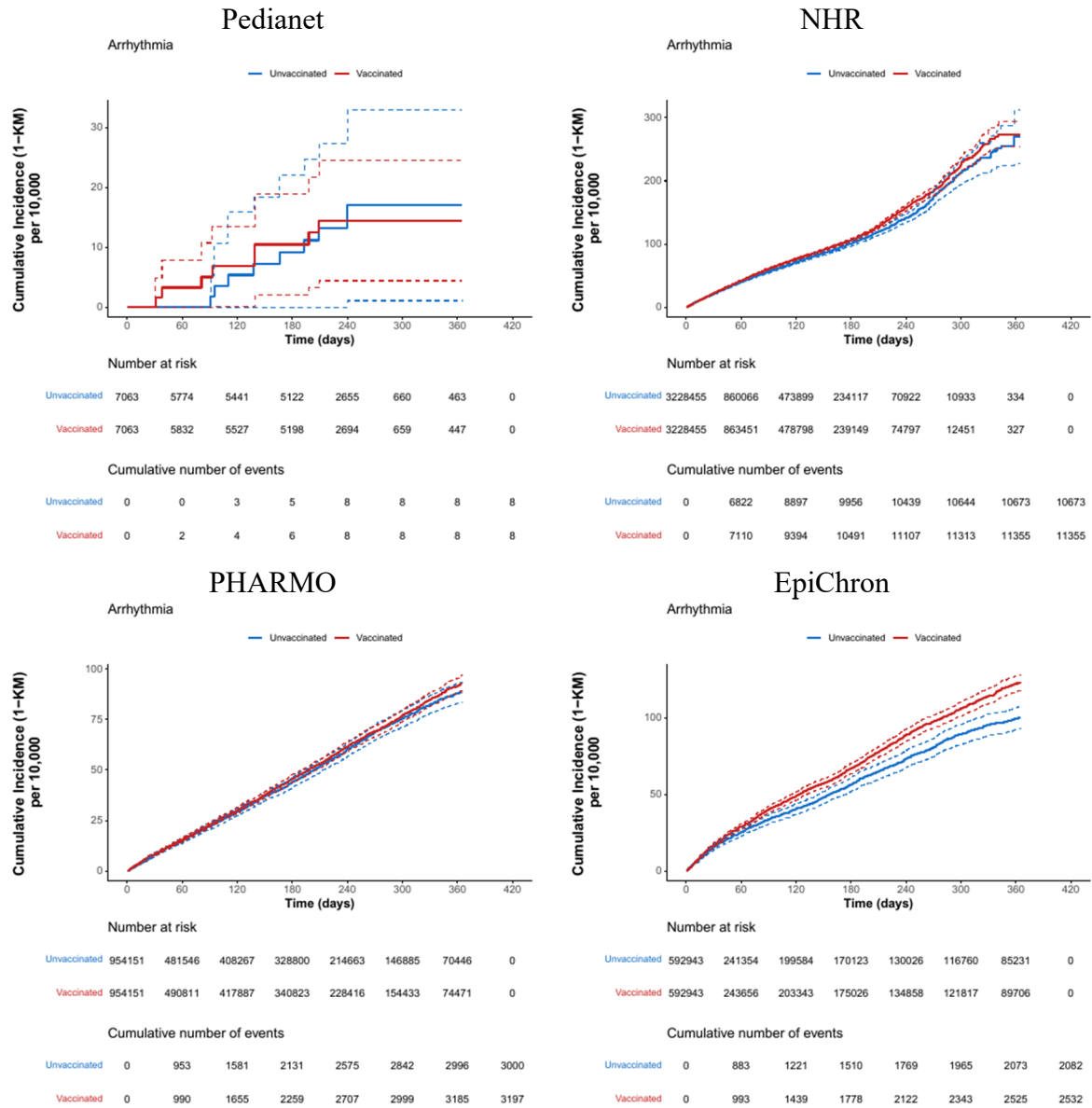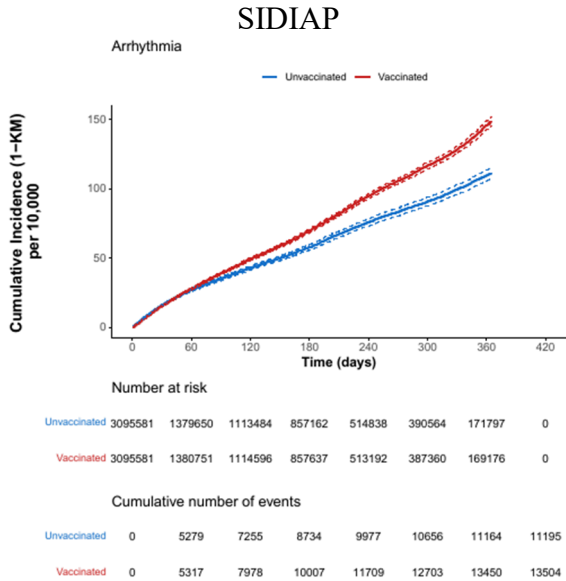| Data source	Vaccinated				Unvaccinated			
	Events (n)	Cumulative incidence (95% CI)	Person-years (PY)	Incidence rate (95% CI)	Events (n)	Cumulative incidence (95% CI)	Person-years (PY)	Incidence rate (95% CI)
Pedianet (Italy)	NA	NA	NA	NA	NA	NA	NA	NA
NHR (Norway)	<5	0 (0, 0)	62,543.3	0.6 (0.2, 1.6)	7	0 (0, 0)	62,533.4	1.1 (0.4, 3.3)
PHARMO (Netherlands)	<5	0 (0, 0.1)	17,327.4	1.2 (0.1, 4.2)	<5	0 (0, 0.1)	17,315.1	2.3 (0.7, 7.7)
EpiChron (Spain)	<5	0 (0, 0.1)	10,732.5	0.9 (0, 5.2)	0	0 (0, 0)	10,728.0	NA
SIDIAP (Spain)	0	0 (0, 0)	56,545.4	0 (0, 0.7)	<5	0 (0, 0)	56,546.7	0.2 (0, 1.3)

NA: Not available

Note: Estimation of confidence intervals differs between vaccinated and unvaccinated, since the unvaccinated estimate is a 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, gender, 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+).

Table 40. Risk estimates (95% CI) per 10,000 person-years (PY) for myocarditis within 14 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

Data source	Vaccinated				Unvaccinated			
	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 (Italy)	NA	NA	NA	NA	NA	NA	NA	NA
NHR (Norway)	10	0 (0, 0.1)	110,821.4	0.9 (0.4, 1.7)	11	0 (0, 0.1)	110,782.2	1.0 (0.5, 2.2)
PHARMO (Netherlands)	2	0 (0, 0.1)	31,915.0	0.6 (0.1, 2.3)	7	0.10 (0, 0.1)	31,865.6	2.2 (0.9, 5.1)
EpiChron (Spain)	1	0 (0, 0.1)	18,694.2	0.5 (0, 3.0)	0	0 (0, 0)	18,676.0	
SIDIAP (Spain)	6	0 (0, 0)	101,779.5	0.6 (0.2, 1.3)	3	0 (0, 0)	101,766.9	0.3 (0.1, 0.9)

NA: Not available

Note: Estimation of confidence intervals differs between vaccinated and unvaccinated, since the unvaccinated estimate is a 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, gender, 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+).

Table 41. **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**

Data source	Vaccinated				Unvaccinated			
	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 (Italy)	NA	NA	NA	NA	NA	NA	NA	NA
NHR (Norway)	12	0 (0, 0.1)	150,629.3	0.8 (0.4, 1.4)	12	0 (0, 0.1)	150,545.9	0.8 (0.4, 1.7)
PHARMO (Netherlands)	2	0 (0, 0.1)	45,089.4	0.4 (0.1, 1.6)	8	0.1 (0, 0.2)	44,978.7	1.8 (0.8, 3.9)
EpiChron (Spain)	3	0.1 (0, 0.2)	25,414.6	1.2 (0.2, 3.4)	0	0 (0, 0)	25,374.7	
SIDIAP (Spain)	6	0 (0, 0)	141,297.5	0.4 (0.2, 0.9)	5	0 (0, 0)	141,257.4	0.4 (0.1, 0.9)

NA: Not available

Note: Estimation of confidence intervals differs between vaccinated and unvaccinated, since the unvaccinated estimate is a 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, gender, 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 30. Cumulative incidence of myocarditis within 7 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 7-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 31. Cumulative incidence of myocarditis within 14 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 14-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 32. 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 33. **Forest plot showing incidence rates and 95% confidence intervals for myocarditis within 7 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**
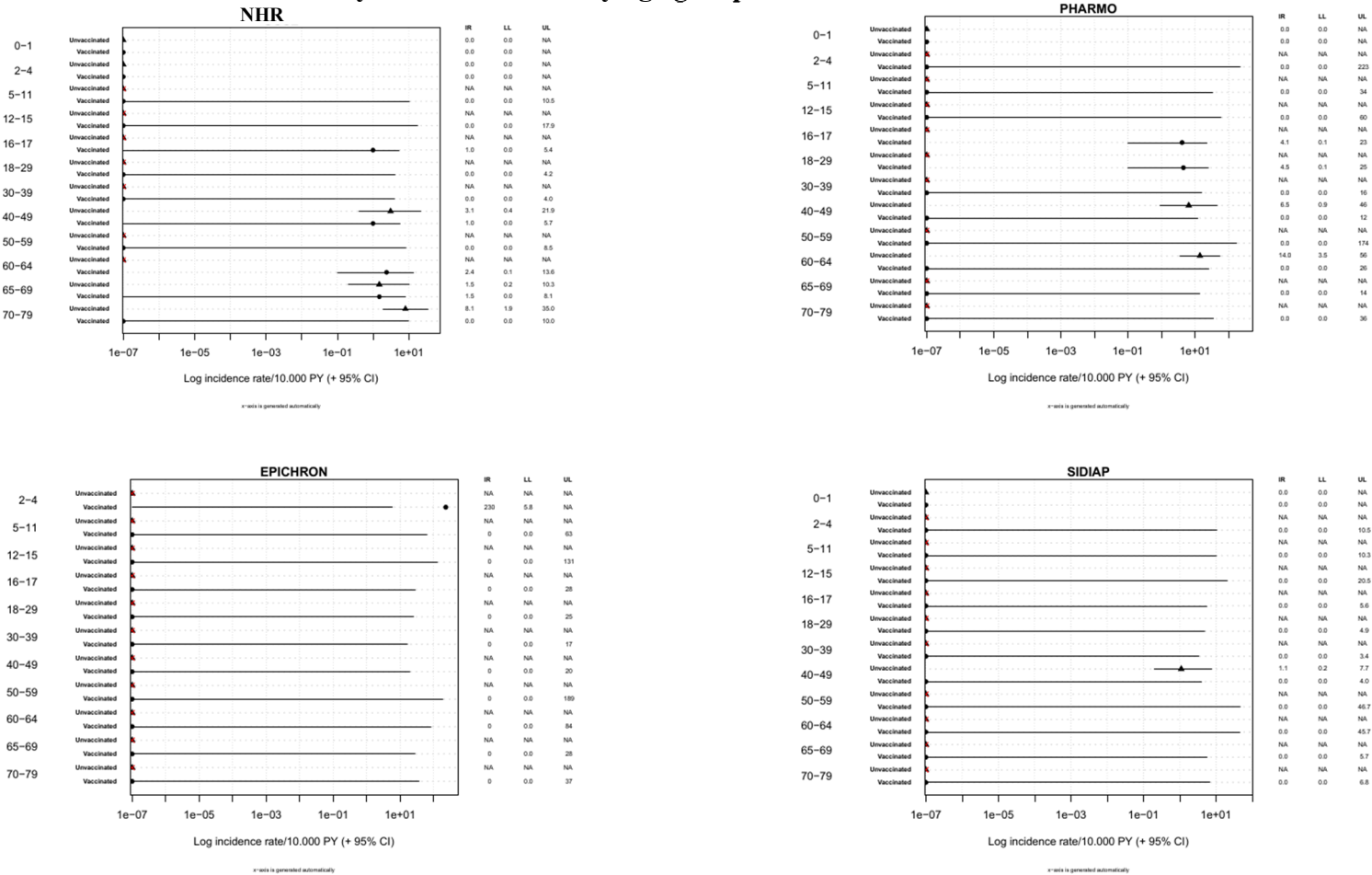
Figure 34. Forest plot showing incidence rates and 95% confidence intervals for myocarditis within 14 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source and by age groups
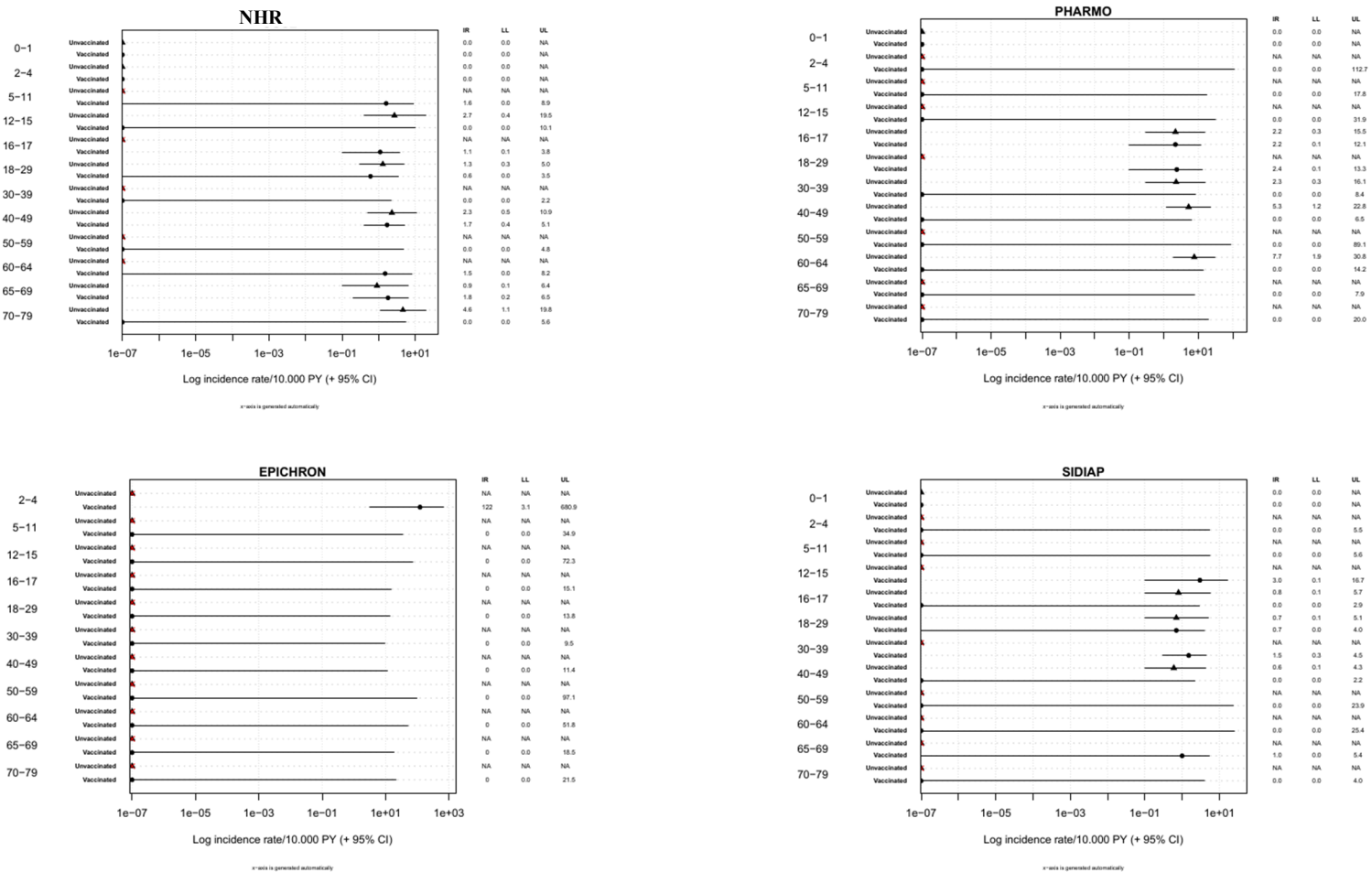
Figure 35. Forest plot showing incidence rates and 95% confidence intervals for myocarditis within 21 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source and by age groups
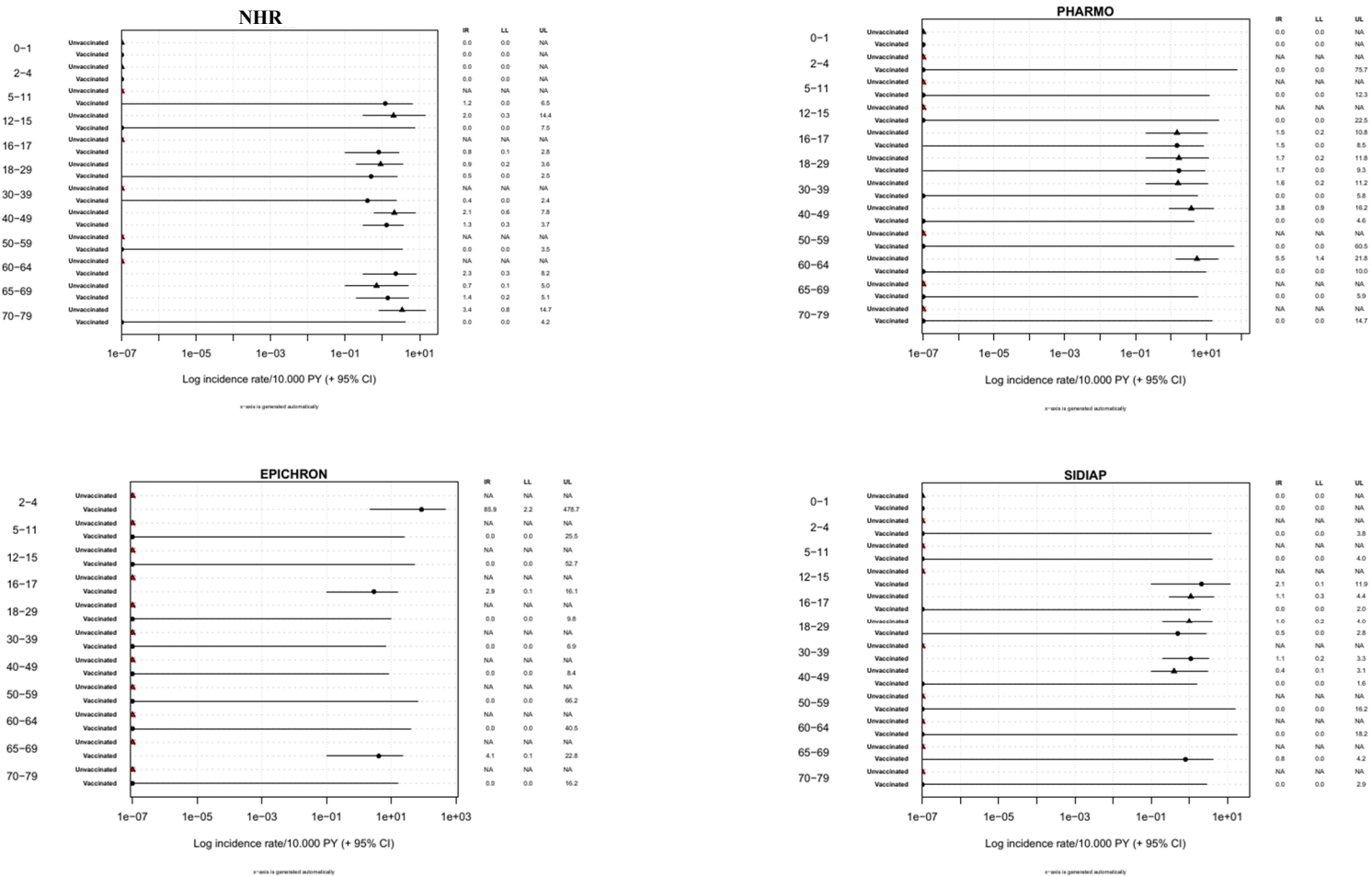
Table 42. **Matched hazard ratios (HRs) and matched risk differences (RDs) per 10,000 person-years and their 95% CIs for myocarditis within 7 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source**

	Matched HR (95% CI)	Matched RD
Pedianet	NA	NA
NHR	0.57 (0.13, 2.46)	-0.01
PHARMO	0.50 (0.08, 3.12)	-0.02
EpiChron	NA	0.02
SIDIAP	NA	0

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

Table 43. **Matched hazard ratios (HRs) and matched risk differences (RDs) per 10,000 person-years and their 95% CIs for myocarditis within 14 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)	Matched RD
Pedianet	NA	NA
NHR	0.91 (0.34, 2.45)	0
PHARMO	0.29 (0.06, 1.44)	-0.06
EpiChron	NA	0.02
SIDIAP	2.00 (0.50, 7.99)	0.01

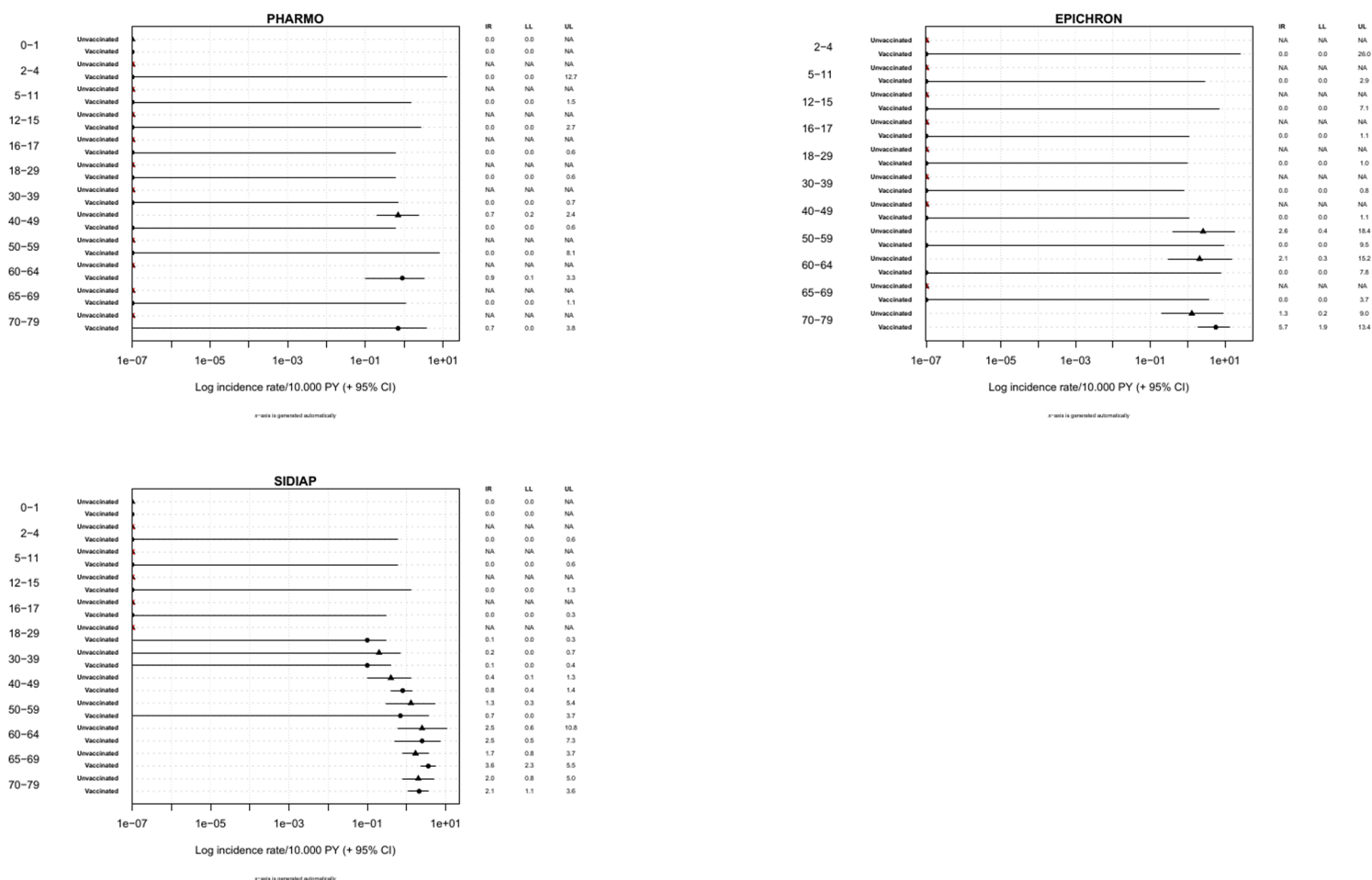NA: not assessable due to zero cases in the vaccinated or unvaccinated cohorts for HR or in both cohorts for RD

Table 44. **Matched hazard ratios (HRs) and matched 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)	Matched RD
Pedianet	NA	NA
NHR	1.00 (0.40, 2.52)	0
PHARMO	0.25 (0.05, 1.22)	-0.07
EpiChron	NA	0.07
SIDIAP	1.20 (0.37, 3.93)	0

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

10.3.15. Pericarditis

Pericarditis events were identified in all data sources except PHARMO.

In the 7-day risk window, the incidence rates ranged from 0 per 10,000 person-years (95% CI 0, 275.2) in Pedianet to 3.7 per 10,000 person-years (95% CI 1.0, 9.5) in EpiChron and 3.7 per 10,000 person-years (95% CI 2.3, 5.7) in SIDIAP in the vaccinated cohorts and from 2.1 per 10,000 person-years in SIDIAP to 3.0 per 10,000 person-years (95% CI 1.7, 5.3) in NHR in the unvaccinated cohorts. No events were reported observed in either cohort in Pedianet during this risk window. The cumulative incidence was below 1 per 10,000 individuals in both cohorts in all data sources. The incidence was higher in age groups over about 11 years old than in the younger age groups. The matched HRs for pericarditis were 0.84 (95% CI: 0.40; 1.37) in NHR, 1.33 (95% CI: 0.30; 5.95) in EpiChron and 1.75 (95% CI: 0.75; 4.08) in SIDIAP for the 7-day risk window.

In the 14-day risk window, the incidence rates ranged from 2.9 per 10,000 person-years (95% CI: 2.0, 4.1) in NHR to 3.6 per 10,000 person-years (95% CI: 2.6, 5.0) in SIDIAP in the vaccinated cohorts and was 2.3 per 10,000 person-years (95% CI: 1.3, 4.1) in NHR, 2.7 per 10,000 person-years (95% CI: 0.9, 7.6) in EpiChron and 2.7 per 10,000 person-years (95% CI: 1.7, 4.2) in SIDIAP in the unvaccinated cohorts. In Pedianet the incidence rate in the vaccinated cohort was 38.1, but this corresponded to only one event. The cumulative incidence was below 1 per 10,000 individuals in both cohorts in all data sources, except for Pedianet. The incidence was higher in age groups over 11 years compared with those under 11 years old. The matched HRs for pericarditis within the 14-day risk window were 1.23 (95% CI: 0.64; 2.36) in NHR, 1.20 (95% CI: 0.32; 4.44) in Epichron and 1.37 (95% CI: 0.78; 2.41) in SIDIAP.

In the 21-day risk window, the incidence rates ranged from 2.4 per 10,000 person-years (95% CI 0.9, 5.1) in EpiChron to 3.5 per 10,000 person-years (95% CI 2.6, 4.7) in SIDIAP in the vaccinated cohorts and from 2.2 per 10,000 person-years (95% CI 1.3, 3.7) in NHR to 3.2 per 10,000 person-years (95% CI 1.2, 8.4) in EpiChron in the unvaccinated cohorts. In the vaccinated cohort in Pedianet, the incidence rate was 25.9 per 10,000 person-years (corresponding to one event). The cumulative incidence was below 1 per 10,000 individuals in both cohorts in all data sources, except for Pedianet. The incidence was higher in age groups over 11 years compared with those under 11 years old. The matched HRs for pericarditis within 21 days after start of follow-up were 1.42 (95% CI: 0.79; 2.56) in NHR, 0.75 (95% CI: 0.21; 2.65) in EpiChron and 1.35 (95% CI: 0.83; 2.20) in SIDIAP. The IRs for pericarditis in the first 14-day and first 21-day follow-up periods were similar.

Table 45. **Risk estimates (95% CI) per 10,000 person-years (PY) for pericarditis within 7 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**

Data source	Vaccinated				Unvaccinated			
	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 (Italy)	0	0 (0, 0)	134.1	0 (0, 275.2)	0	0 (0, 0)	134.0	NA
NHR (Norway)	16	0.1 (0, 0.1)	62,518.7	2.6 (1.5, 4.2)	19	0.1 (0, 0.1)	62,508.8	3.0 (1.7, 5.3)
PHARMO (Netherlands)	NA	NA	NA	NA	NA	NA	NA	NA
EpiChron (Spain)	<5	0.1 (0, 0.2)	10,729.5	3.7 (1.0, 9.5)	<5	0.1 (0, 0.1)	10,724.9	2.8 (0.9, 8.7)
SIDIAP (Spain)	21	0.1 (0, 0.1)	56,518.1	3.7 (2.3, 5.7)	12	0 (0, 0.1)	56,519.3	2.1 (1.0, 4.4)

NA: Not available

Note: Estimation of confidence intervals differs between vaccinated and unvaccinated, since the unvaccinated estimate is a 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, gender, 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+).

Table 46. **Risk estimates (95% CI) per 10,000 person-years for pericarditis within 14 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**

Data source	Vaccinated				Unvaccinated			
	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 (Italy)	1	1.5 (0, 4.40)	262.20	38.1 (1.00, 212.50)	0	0 (0, 0)	261.9	NA
NHR (Norway)	32	0.1 (0.1, 0.2)	110,777.3	2.9 (2.0, 4.1)	26	0.1 (0, 0.1)	110,738.2	2.3 (1.3, 4.1)
PHARMO (Netherlands)	NA	NA	NA	NA	NA	NA	NA	NA
EpiChron (Spain)	6	0.1 (0, 0.2)	18,689.0	3.2 (1.2, 7.0)	5	0.1 (0, 0.2)	18,670.8	2.7 (0.9, 7.6)
SIDIAP (Spain)	37	0.1 (0.1, 0.2)	101,730.3	3.6 (2.6, 5.0)	27	0.1 (0.1, 0.1)	101,717.8	2.7 (1.7, 4.2)

NA: Not available

Note: Estimation of confidence intervals differs between vaccinated and unvaccinated, since the unvaccinated estimate is a 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, gender, 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+).

Table 47. Risk estimates (95% CI per 10,000 person-years) for pericarditis 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

Data source	Vaccinated				Unvaccinated			
	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 (Italy)	1	1.5 (0, 4.4)	385.5	25.9 (0.7, 144.5)	0	0 (0, 0)	384.9	NA
NHR (Norway)	47	0.2 (0.1, 0.2)	150,569.2	3.1 (2.3, 4.2)	33	0.1 (0.1, 0.2)	150,486.1	2.2 (1.3, 3.7)
PHARMO (Netherlands)	NA	NA	NA	NA	NA	NA	NA	NA
EpiChron (Spain)	6	0.1 (0, 0.2)	25,407.7	2.4 (0.9, 5.1)	8	0.2 (0, 0.4)	25,367.7	3.2 (1.2, 8.4)
SIDIAP (Spain)	50	0.2 (0.1, 0.3)	141,229.1	3.5 (2.6, 4.7)	37	0.2 (0.1, 0.2)	141,189.1	2.6 (1.8, 3.9)

NA: Not available

Note: Estimation of confidence intervals differs between vaccinated and unvaccinated, since the unvaccinated estimate is a 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, gender, 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 36. Cumulative incidence of pericarditis within 7 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

NHR

EpiChron

SIDIAP

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 7-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 37. Cumulative incidence of pericarditis within 14 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 14-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 38. Cumulative incidence of pericarditis 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 39. Forest plot showing incidence rates and 95% confidence intervals for pericarditis within 7 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

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Figure 40. Forest plot showing incidence rates and 95% confidence intervals for pericarditis within 14 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 41. Forest plot showing incidence rates and 95% confidence intervals for pericarditis 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

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Table 48. Matched hazard ratios (HRs) and matched risk differences (RDs) per 10,000 person-years and their 95% CIs for pericarditis within 7 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
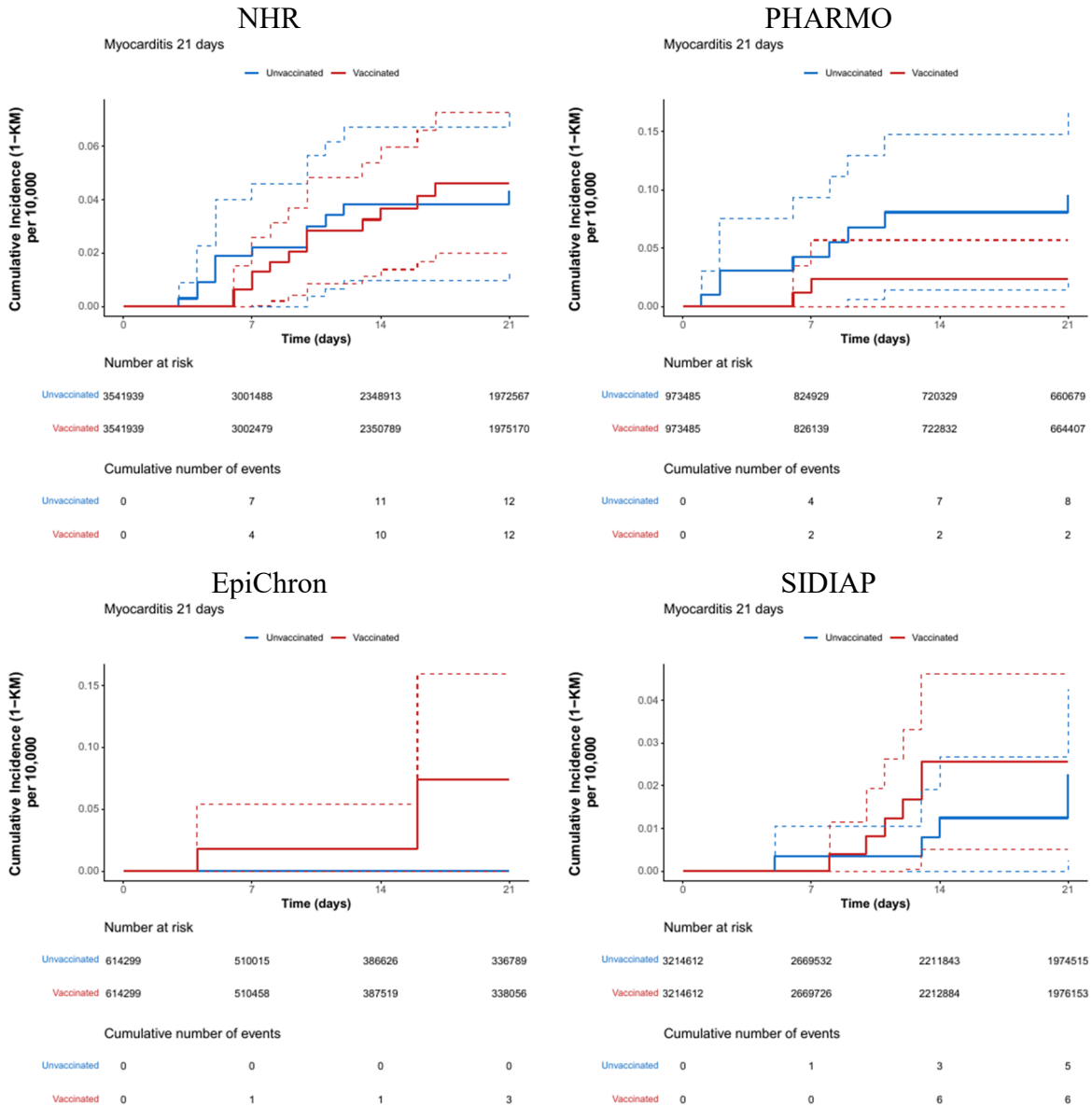
	Matched HR (95% CI)	Matched RD
Pedianet	NA	NA
NHR	0.84 (0.40, 1.77)	-0.01
PHARMO	NA	NA
EpiChron	1.33 (0.30, 5.95)	0.02
SIDIAP	1.75 (0.75, 4.08)	0.03

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

Table 49. Matched hazard ratios (HRs) and matched risk differences (RDs) per 10,000 person-years and their 95% CIs for pericarditis within 14 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)	Matched RD
Pedianet	NA	NA
NHR	1.23 (0.64, 2.36)	0.02
PHARMO	NA	NA
EpiChron	1.20 (0.32, 4.44)	0.03
SIDIAP	1.37 (0.78, 2.41)	0.04

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

Table 50. Matched hazard ratios (HRs) and matched risk differences (RDs) per 10,000 person-years and their 95% CIs for pericarditis 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)	Matched RD
Pedianet	NA	NA
NHR	1.42 (0.79, 2.56)	0.06
PHARMO	NA	NA
EpiChron	0.75 (0.21, 2.65)	-0.06
SIDIAP	1.35 (0.83, 2.20)	0.05

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

10.3.16. Myocarditis or pericarditis

Combined myocarditis or pericarditis events were identified in all data sources.

In the 7-day risk window, the incidence rates ranged from 1.2 per 10,000 person-years (95% CI 0.1, 4.2) in PHARMO to 4.7 per 10,000 person-years (95% CI 1.5, 10.9) in EpiChron in the vaccinated cohorts and from 1.9 per 10,000 person-years (95% CI 0.5, 7.5) in EpiChron and 1.9 per 10,000 person-years (95% CI 0.9, 4.2) in SIDIAP to 4.0 per 10,000 person-years (95% CI 2.4, 6.7) in NHR in the unvaccinated cohorts. No events were reported in either cohort in Pedianet during this risk window. The cumulative incidence was below 1 per 10,000 individuals in both cohorts in all data sources. The incidence was higher in age groups over about 11 years old than in the younger age groups. The matched HRs during the 7-day risk window were 0.80 (95% CI: 0.41; 1.57) in NHR, 0.50 (95% CI: 0.08; 3.12) in PHARMO, 2.50 (95% CI: 0.48; 12.88) in EpiChron and 2.09 (95% CI: 0.87; 5.03) in SIDIAP.

In the 14-day risk window, the incidence rates ranged 0.6 per 10,000 person-years (95% CI 0.1, 2.3) in PHARMO to 4.5 per 10,000 person-years (95% CI 3.3, 6.0) in SIDIAP in the vaccinated cohorts and from 2.2 per 10,000 person-years (95% CI 0.9, 5.1) in PHARMO to 3.3 per 10,000 person-years (95% CI 2.0, 5.2) in NHR in the unvaccinated cohorts. In Pedianet the incidence rate in the vaccinated cohort was 38.1, but this corresponded to only one event. The cumulative incidence was below 1 per 10,000 individuals in both cohorts in all data sources, except for Pedianet. The incidence was higher in age groups over about 11 years old than in the younger age groups. The matched unadjusted HRs for combined myocarditis and pericarditis events during the 14-day risk window were 1.17 (95% CI: 0.67; 2.03) in NHR, 0.29 (95% CI: 0.06; 1.44) in PHARMO, 1.40 (95% CI: 0.39; 5.00) in EpiChron and 1.64 (95% CI: 0.96; 2.81) in SIDIAP.

In the 21-day risk window, the incidence rates ranged from 0.4 per 10,000 person-years (95% CI 0.1, 1.6) in PHARMO to 4.3 per 10,000 person-years (95% CI 3.3, 5.5) in SIDIAP in the vaccinated cohorts and from 1.8 per 10,000 person-years (95% CI 0.8, 3.9) in PHARMO to 4.3 per 10,000 person-years (95% CI 1.9, 9.8) in EpiChron in the unvaccinated cohorts. In the vaccinated cohort in Pedianet, the incidence rate was 25.9 per 10,000 person-years (corresponding to one event) The cumulative incidence was below 1 per 10,000 individuals in both cohorts in all data sources, except for the vaccinated cohort in Pedianet with a cumulative incidence of 1.5 (corresponding to one event). The incidence was higher in age groups over about 11 years old than in the younger age groups. The matched unadjusted HRs during the 21-day risk window after dose 1 were 1.40 (95% CI: 0.84; 2.35) in NHR, 0.25 (95% CI: 0.05; 1.22) in PHARMO, 0.91 (95% CI: 0.33; 2.53) in EpiChron and 1.45 (95% CI: 0.93; 2.27) in SIDIAP.

Table 51. **Risk estimates (95% CI) per 10,000 person-years (PY) for myocarditis/pericarditis within 7 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**

| Data source	Vaccinated				Unvaccinated			
	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 (Italy)	0	0 (0, 0)	134.1	0 (0, 275.2)	0	0 (0, 0)	134.0	NA
NHR (Norway)	20	0.1 (0, 0.1)	62,510.8	3.2 (2.0, 4.9)	25	0.1 (0, 0.1)	62,500.8	4.0 (2.4, 6.7)
PHARMO (Netherlands)	<5	0 (0, 0.1)	17,327.4	1.2 (0.1, 4.2)	<5	0 (0, 0.1)	17,315.1	2.3 (0.7, 7.7)
EpiChron (Spain)	5	0.1 (0, 0.2)	10,727.7	4.7 (1.5, 10.9)	<5	0 (0, 0.1)	10,723.1	1.9 (0.5, 7.5)
SIDIAP (Spain)	23	0.1 (0, 0.1)	56,513.7	4.1 (2.6, 6.1)	11	0 (0, 0.1)	56,515.0	1.9 (0.9, 4.2)

Note: Estimation of confidence intervals differs between vaccinated and unvaccinated, since the unvaccinated estimate is a 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, gender, 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+).

Table 52. Risk estimates (95% CI) per 10,000 person-years (PY) for myocarditis/pericarditis within 14 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 (Italy)	1	1.5 (0, 4.4)	262.2	38.1 (1.0, 212.5)	0	0 (0, 0)	261.90.0	NA
NHR (Norway)	42	0.1 (0.1, 0.2)	110,762.8	3.8 (2.7, 5.1)	36	0.1 (0.1, 0.2)	110,723.7	3.3 (2.0, 5.2)
PHARMO (Netherlands)	2	0 (0, 0.1)	31,915.0	0.6 (0.1, 2.3)	7	0.1 (0, 0.1)	31,865.6	2.2 (0.9, 5.1)
EpiChron (Spain)	7	0.1 (0, 0.3)	18,685.9	3.7 (1.5, 7.7)	5	0.1 (0, 0.2)	18,667.7	2.7 (0.9, 7.6)
SIDIAP (Spain)	46	0.2 (0.1, 0.2)	101,722.5	4.5 (3.3, 6.0)	28	0.1 (0.1, 0.2)	101,710.0	2.8 (1.7, 4.3)

Note: Estimation of confidence intervals differs between vaccinated and unvaccinated, since the unvaccinated estimate is a 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, gender, 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+).

Table 53. **Risk estimates (95% CI) per 10,000 person-years (PY) for myocarditis/pericarditis 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**

Data source	Vaccinated				Unvaccinated			
	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 (Italy)	1	1.5 (0, 4.4)	385.5	25.9 (0.7, 144.5)	0	0 (0, 0)	384.9	NA
NHR (Norway)	59	0.2 (0.1, 0.3)	150,549.0	3.9 (3.0, 5.1)	42	0.2 (0.1, 0.2)	150,465.9	2.8 (1.8, 4.4)
PHARMO (Netherlands)	2	0 (0, 0.1)	45,089.4	0.4 (0.1, 1.6)	8	0.1 (0, 0.2)	44,978.7	1.8 (0.8, 3.9)
EpiChron (Spain)	10	0.2 (0.1, 0.4)	25,403.5	3.9 (1.9, 7.2)	11	0.3 (0, 0.5)	25,363.5	4.3 (1.9, 9.8)
SIDIAP (Spain)	61	0.3 (0.2, 0.3)	141,218.0	4.3 (3.3, 5.5)	42	0.2 (0.1, 0.2)	141,178.3	3.0 (2.1, 4.3)

Note: Estimation of confidence intervals differs between vaccinated and unvaccinated, since the unvaccinated estimate is a 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, gender, 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+).
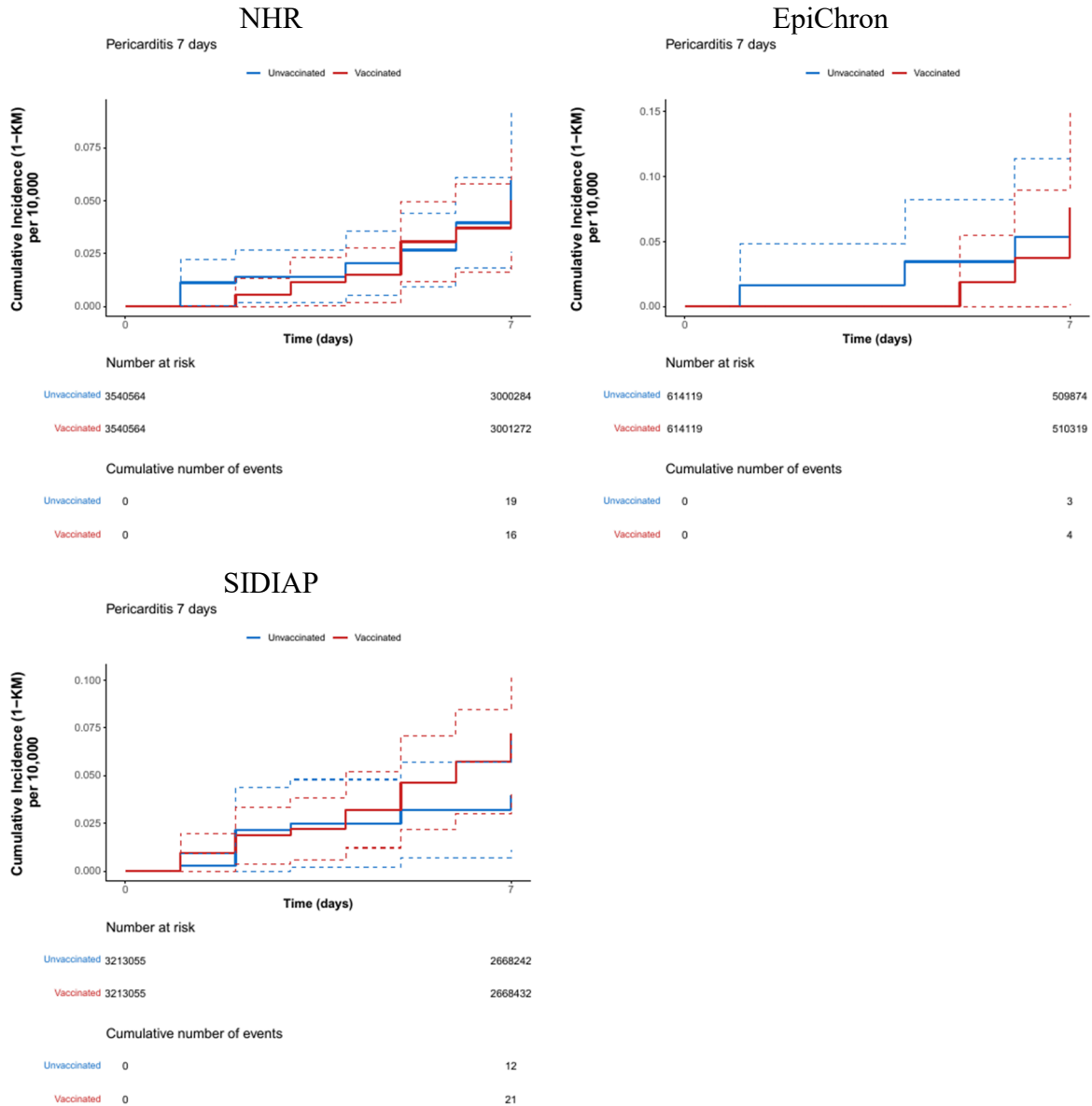
LL: lower limit of 95% CI; UL: upper lower limit of 95% CI.

Figure 42.   Cumulative incidence of myocarditis/pericarditis within 7 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 7-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 43. Cumulative incidence of myocarditis/pericarditis within 14 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 43. **Cumulative incidence of myocarditis/pericarditis within 14 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 14-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 44. **Cumulative incidence of myocarditis/pericarditis 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 44. **Cumulative incidence of myocarditis/pericarditis 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**
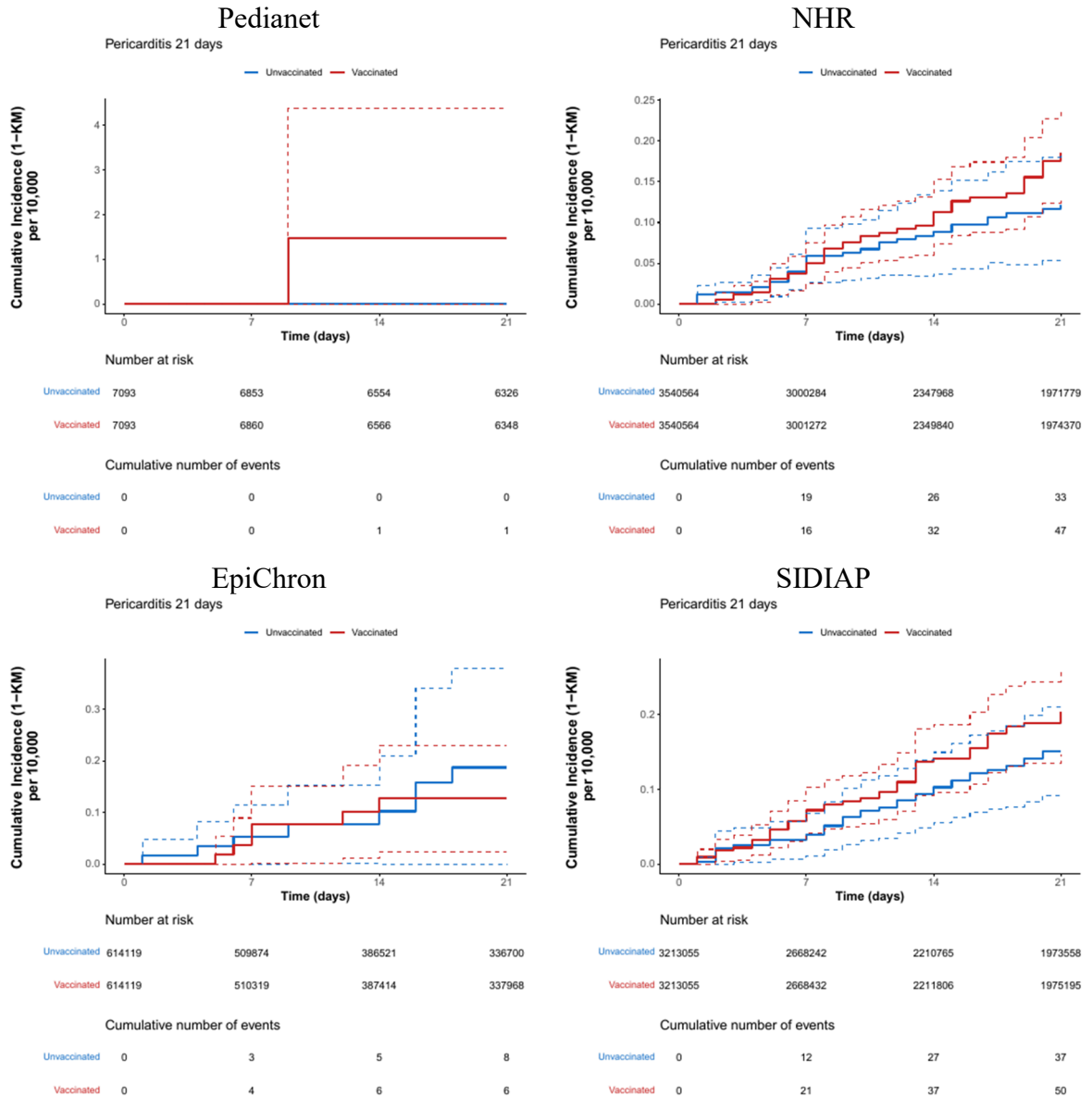

Cumulative incidence curves (1 – Kaplan–Meier risk) starting from the day of administration of the first dose of vaccine. Dotted lines represent 95% confidence intervals. The number at risk at each time point and the cumulative number of events during the 21-day risk window are also shown for each time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

Figure 45. **Forest plot showing incidence rates and 95% confidence intervals for myocarditis or pericarditis within 7 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 46. Forest plot showing incidence rates and 95% confidence intervals for myocarditis or pericarditis within 14 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 46. Forest plot showing incidence rates and 95% confidence intervals for myocarditis or pericarditis within 14 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 47. Forest plot showing incidence rates and 95% confidence intervals for myocarditis or pericarditis 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
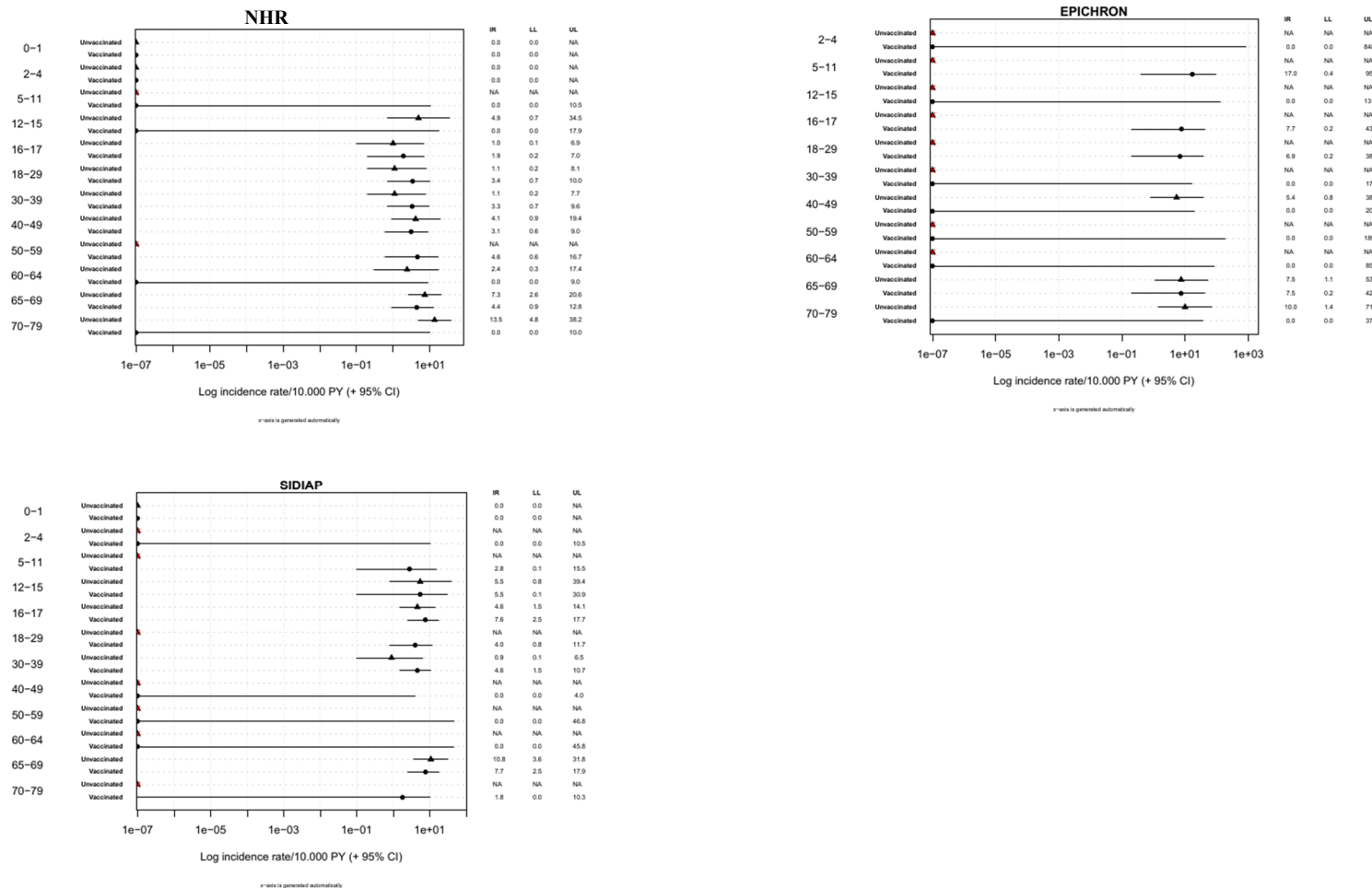
Figure 47. Forest plot showing incidence rates and 95% confidence intervals for myocarditis or pericarditis within 21 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source and by age groups
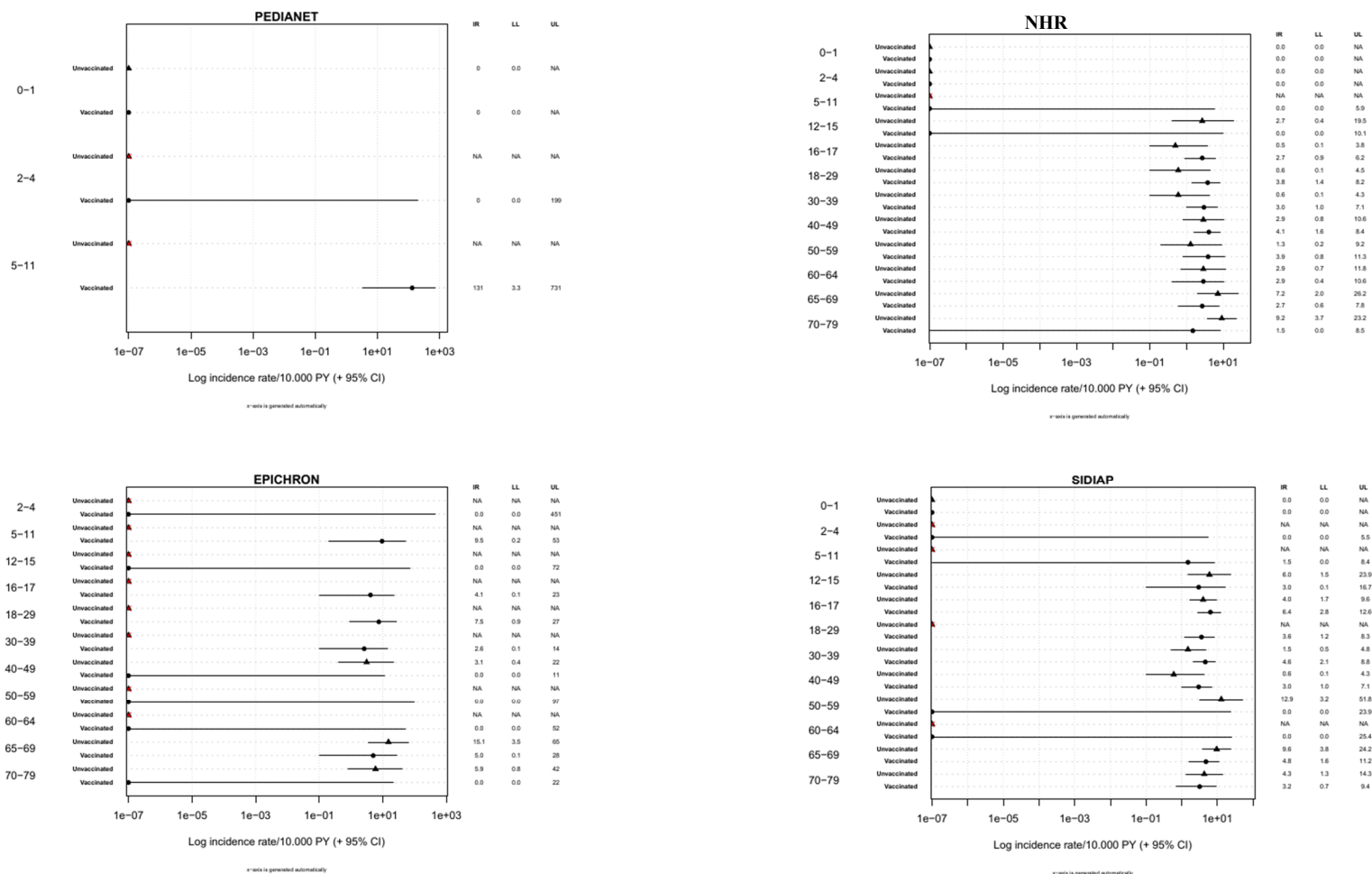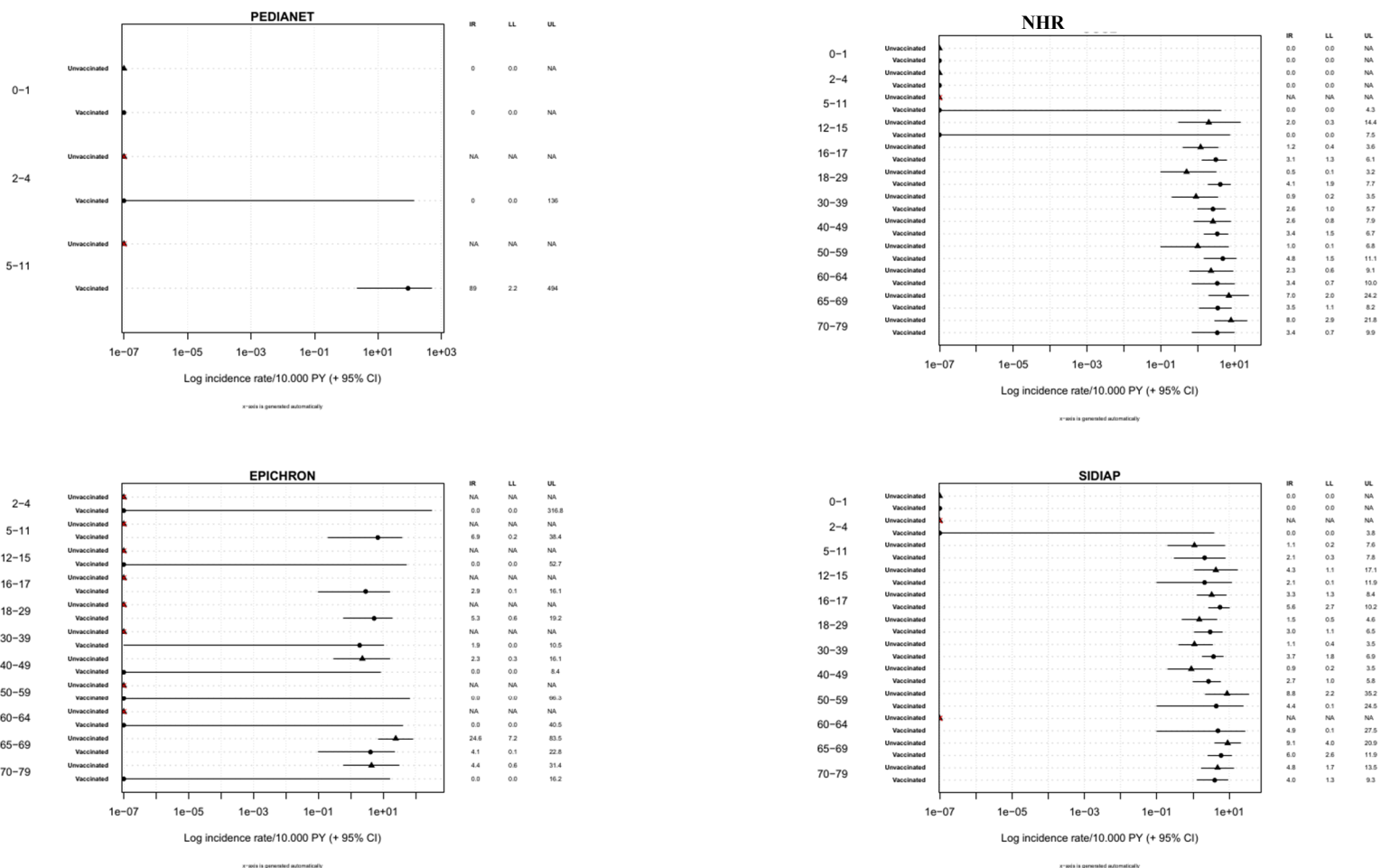
Table 54. **Matched hazard ratios (HRs) and matched risk differences (RDs) per 10,000 person-years and their 95% CIs for myocarditis or pericarditis within 7 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source**

	Matched HR (95% CI)	Matched RD
Pedianet	NA	NA
NHR	0.80 (0.41, 1.57))	-0.02
PHARMO	0.50 (0.08, 3.12)	-0.02
EpiChron	2.50 (0.48, 12.88)	0.06
SIDIAP	2.09 (0.87, 5.03)	0.04

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

Table 55. **Matched hazard ratios (HRs) and matched risk differences (RDs) per 10,000 person-years and their 95% CIs for myocarditis or pericarditis within 14 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)	Matched RD
Pedianet	NA	NA
NHR	1.17 (0.67, 2.03)	0.03
PHARMO	0.29 (0.06, 1.44)	-0.06
EpiChron	1.40 (0.39, 5.00)	0.04
SIDIAP	1.64 (0.96, 2.81)	0.07

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

Table 56.   Matched hazard ratios (HRs) and matched risk differences (RDs) per 10,000 person-years and their 95% CIs for myocarditis or pericarditis 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)	Matched RD
Pedianet	NA	NA
NHR	1.40 (0.84, 2.35)	0.08
PHARMO	0.25 (0.05, 1.22)	-0.07
EpiChron	0.91 (0.33, 2.53)	-0.05
SIDIAP	1.45 (0.93, 2.27)	0.08

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

10.3.17. Coagulation disorders (thromboembolism, haemorrhage)

Coagulation disorders were identified in all data sources, except Pedianet. The incidence rates ranged from 21.4 per 10,000 person-years (95% CI 17.7, 25.5) in PHARMO to 75.9 per 10,000 person-years (95% CI 66.5, 86.2) in EpiChron in the vaccinated cohorts and from 24.4 per 10,000 person-years (95% CI 20.2, 29.6) in PHARMO to 96.3 per 10,000 person-years (95% CI 82.4, 112.5) in EpiChron in the unvaccinated cohorts. The cumulative incidence was less than 7.5 per 10,000 individuals in both cohorts in all data sources. The increases in cumulative incidence of coagulation disorders within the 28-day follow-up period were similar in the vaccinated and unvaccinated cohorts and constant during the risk window in all databases.

The incidence of coagulation disorders was higher in older age groups. The matched unadjusted HRs for coagulation disorders were 0.91 (95% CI: 0.83, 1.00) in NHR, 0.87 (95% CI: 0.67; 1.14) in PHARMO, 0.79 (95% CI: 0.65; 0.96) in EpiChron and 0.78 (95% CI: 0.71; 0.86) in SIDIAP.

Table 57. **Risk estimates (95% CI) per 10,000 person-years (PY) for coagulation disorders (thromboembolism, haemorrhage) 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**

Data source	Vaccinated				Unvaccinated			
	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 (Italy)	0	0 (0, 0)	505.2	0 (0, 73.0)	0	0 (0, 0)	504.0	NA
NHR (Norway)	1,097	4.6 (4.3, 4.9)	182,281.1	60.2 (56.7, 63.9)	1,200	5.0 (4.6, 5.4)	182,146.2	65.9 (61.1, 71.1)
PHARMO (Netherlands)	122	1.6 (1.3, 1.9)	57,105.0	21.4 (17.7, 25.5)	139	1.9 (1.5, 2.2)	56,910.3	24.4 (20.2, 29.6)
EpiChron (Spain)	236	5.8 (5.1, 6.6)	31,109.1	75.9 (66.5, 86.2)	299	7.3 (6.1, 8.4)	31,041.0	96.3 (82.4, 112.5)
SIDIAP (Spain)	1,040	4.6 (4.3, 4.9)	175,220.3	59.4 (55.8, 63.1)	1,329	5.7 (5.3, 6.1)	175,144.7	75.9 (70.7, 81.5)

Note: Estimation of confidence intervals differs between vaccinated and unvaccinated, since the unvaccinated estimate is a 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, gender, 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 48. **Cumulative incidence of coagulation disorders (thromboembolism, haemorrhage) 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**

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 28-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 49. Forest plot showing incidence rates and 95% confidence intervals for coagulation disorders (thromboembolism, haemorrhage) 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
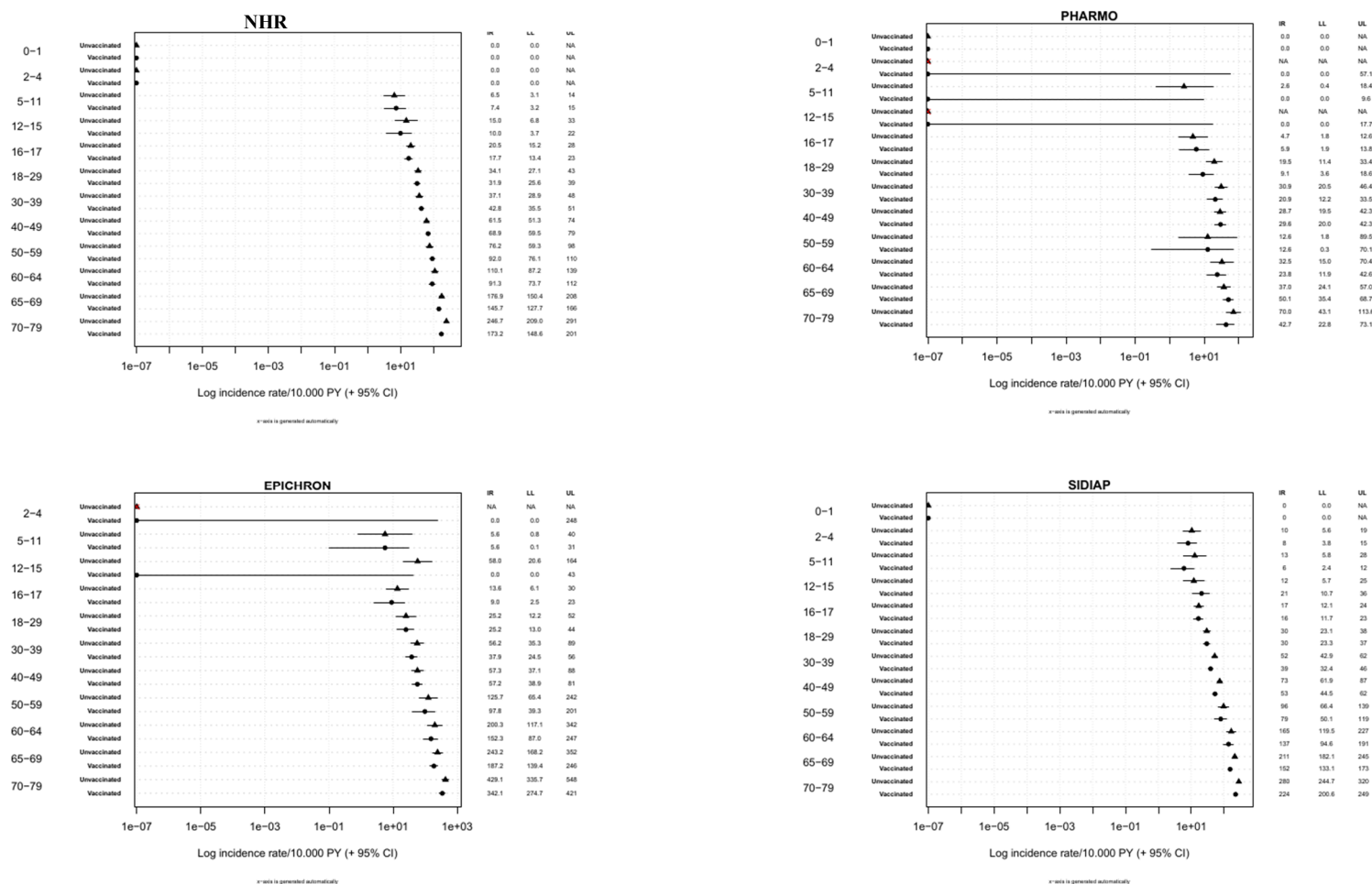
Table 58. **Matched hazard ratios (HRs) and matched risk differences (RDs) per 10,000 person-years and their 95% CIs for coagulation disorders (thromboembolism, haemorrhage) within 28 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source**

	Matched HR (95% CI)	Matched RD
Pedianet	NA	NA
NHR	0.91 (0.83, 1.00)	-0.42
PHARMO	0.87 (0.67, 1.14)	-0.28
EpiChron	0.79 (0.65, 0.96)	-1.46
SIDIAP	0.78 (0.71, 0.86)	-1.09

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

10.3.18. Single organ cutaneous vasculitis

Single organ cutaneous vasculitis within the 28-day risk window was a very rare event identified in PHARMO, EpiChron, and SIDIAP but not Pedianet or NHR. The incidence rates ranged from 0.2 per 10,000 person-years (95% CI 0, 1.0) in PHARMO to 0.7 per 10,000 person-years (95% CI 0.3, 1.2) in SIDIAP in the vaccinated cohorts. In SIDIAP the incidence rate was 0.6 per 10,000 person-years (95% CI 0.3, 1.1) in the unvaccinated cohort. No events were identified in the 28-day risk window in the unvaccinated cohorts in the other data sources.

The matched adjusted HR was 1.20 (95% CI: 0.50; 2.90) in SIDIAP.

Table 59. **Risk estimates (95% CI) per 10,000 person-years (PY) for single organ cutaneous vasculitis 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**

Data source	Vaccinated				Unvaccinated			
	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 (Italy)	0	0 (0, 0)	505.4	0 (0, 73.0)	0	0 (0, 0)	504.2	NA
NHR (Norway)	0	0 (0, 0)	185,056.0	0 (0, 0.2)	0	0 (0, 0)	184,914.7	NA
PHARMO (Netherlands)	<5	0 (0, 0)	57,333.8	0.2 (0, 1.0)	0	0 (0, 0)	57,138.4	NA
EpiChron (Spain)	<5	0 (0, 0.1)	31,517.9	0.3 (0, 1.8)	0	0 (0, 0)	31,449.7	NA
SIDIAP (Spain)	12	0.1 (0, 0.1)	177,200.6	0.7 (0.3, 1.2)	10	0 (0, 0.1)	177,125.8	0.6 (0.3, 1.1)

Note: Estimation of confidence intervals differs between vaccinated and unvaccinated, since the unvaccinated estimate is a 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, gender, 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+).
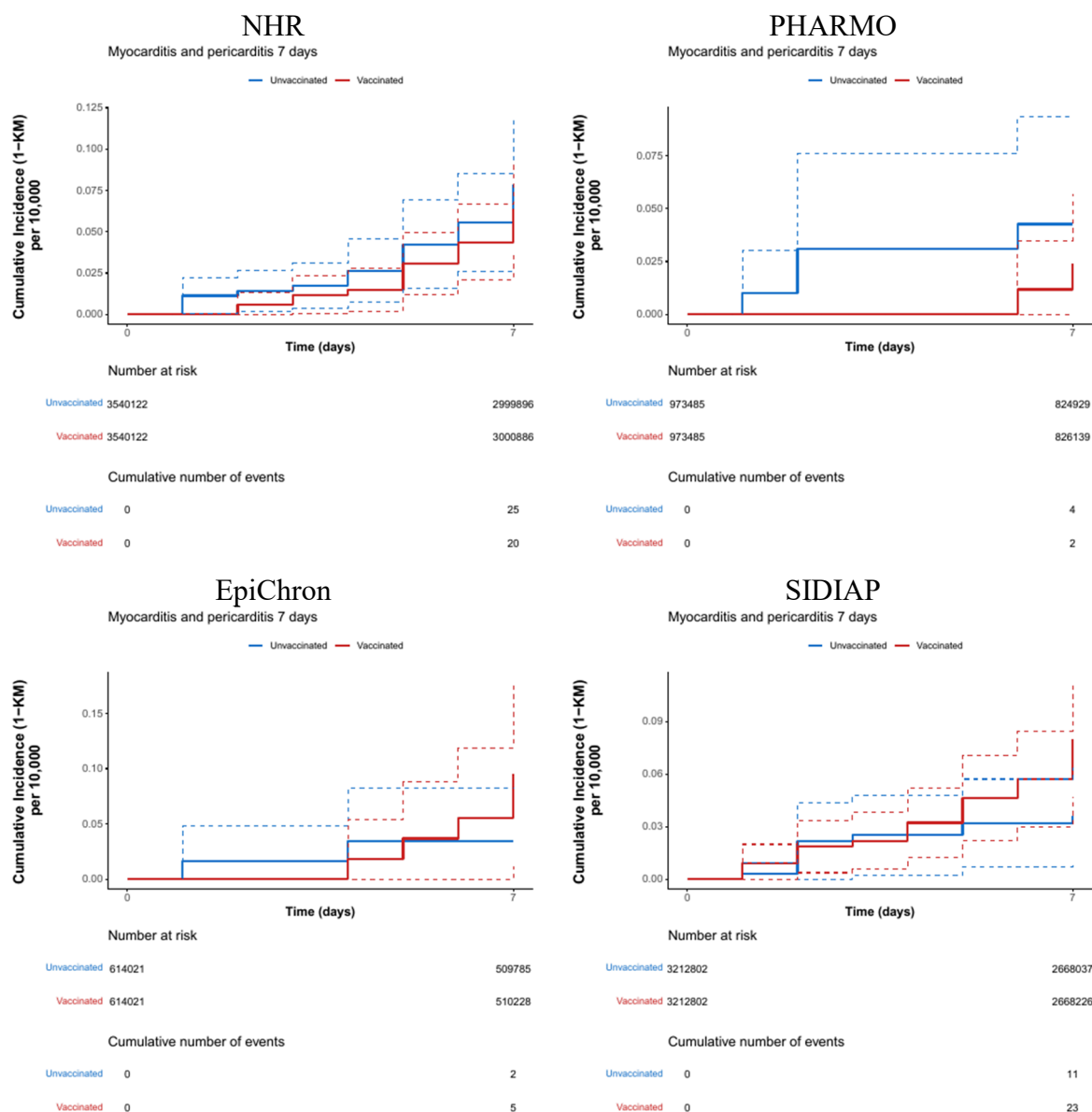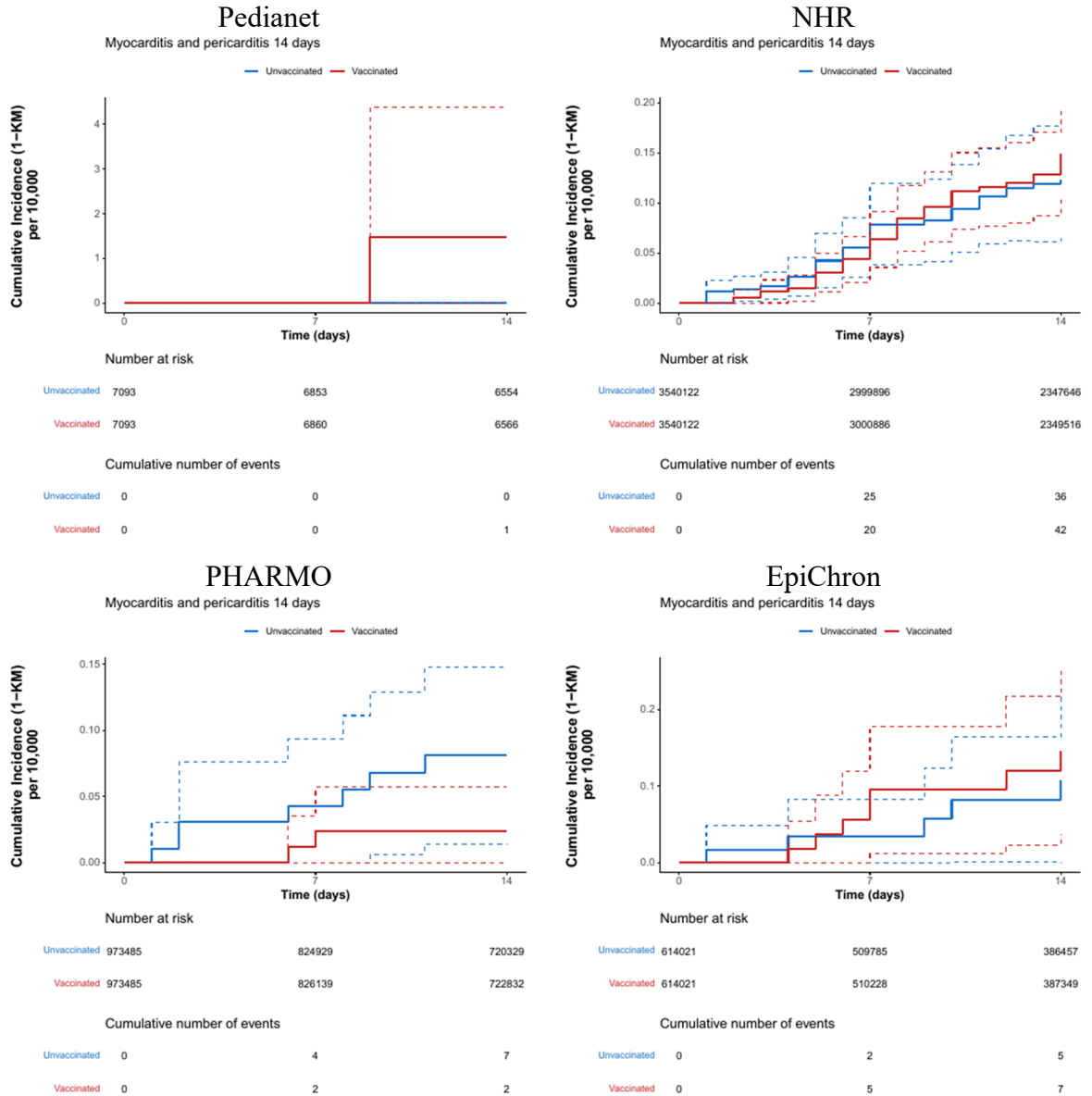
Figure 50. **Cumulative incidence of single organ cutaneous vasculitis within 28 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source**

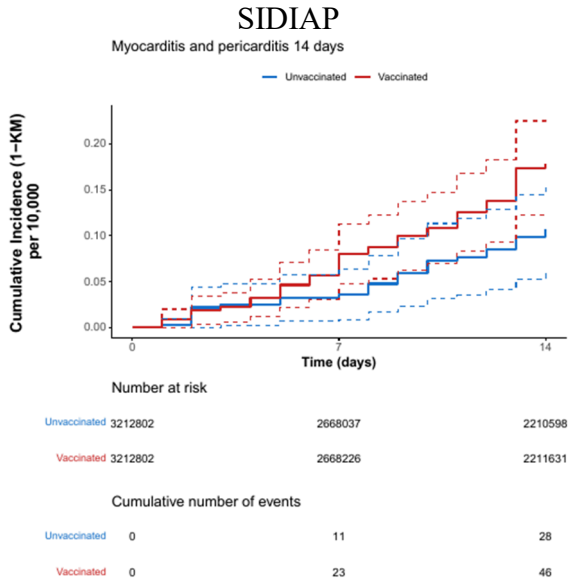

Cumulative incidence curves (1 – Kaplan–Meier risk) starting from the day of administration of the first dose of vaccine. Dotted lines represent 95% confidence intervals. The number at risk at each time point and the cumulative number of events during the 28-day risk window are also shown for each time point. The numerical data correspond to the days indicated by the tick marks on the x-axis.

Figure 51. Forest plot showing incidence rates and 95% confidence intervals for single organ cutaneous vasculitis 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

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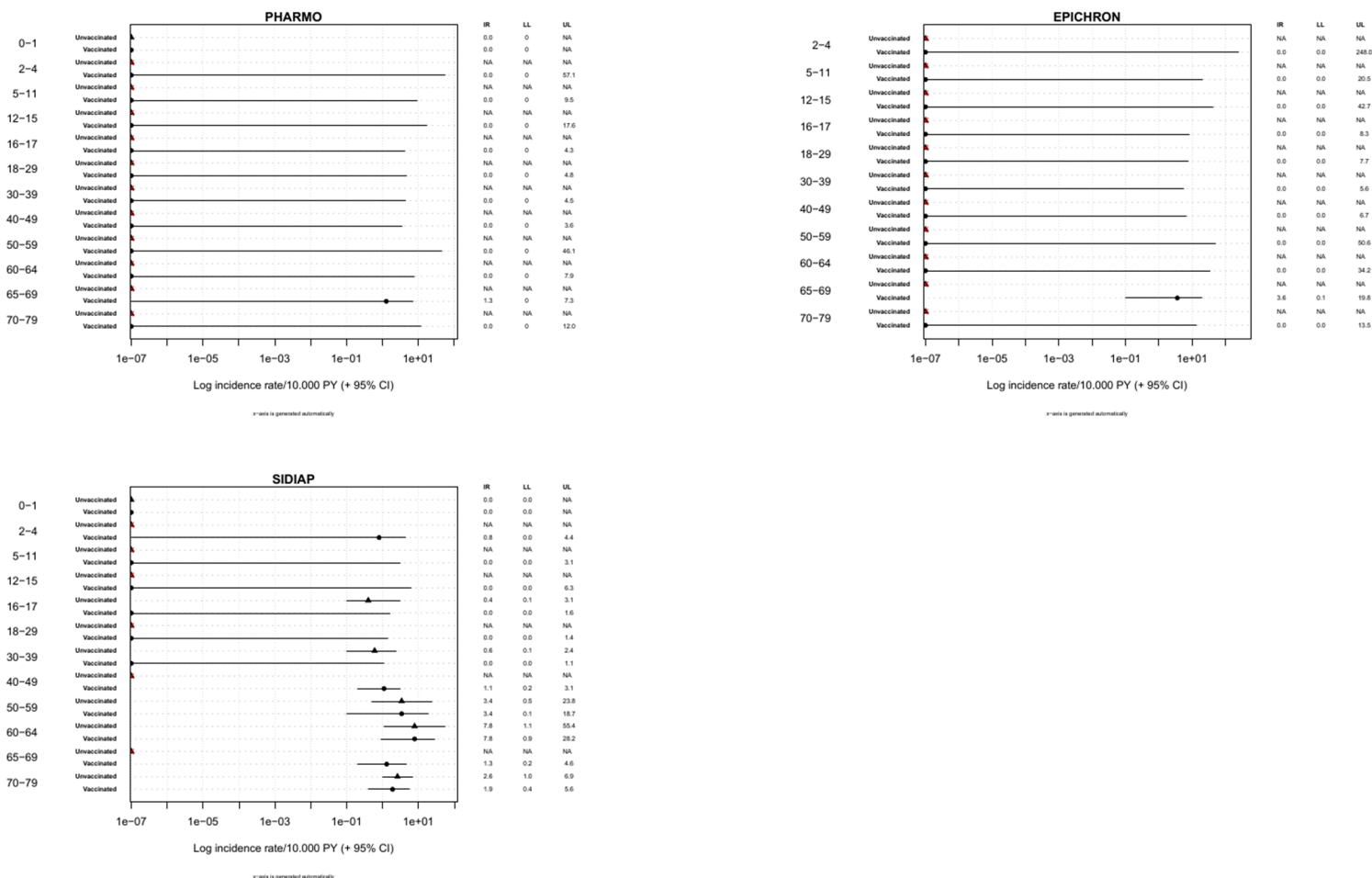
Table 60. Matched hazard ratios (HRs) and matched risk differences (RDs) per 10,000 person-years and their 95% CIs for single organ cutaneous vasculitis within 28 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source

	Matched HR (95% CI)	Matched RD
Pedianet	NA	NA
NHR	NA	NA
PHARMO	NA	NA
EpiChron	NA	NA
SIDIAP	1.20 (0.50, 2.90)	0.01

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

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10.3.19. Acute liver injury

Acute liver injury events were identified in all data sources except Pedianet. The incidence rates ranged from 0.1 per 10,000 person-years (95% CI 0, 0.3) in NHR to 17.0 per 10,000 person-years (95% CI 16.2, 17.9) in SIDIAP in the vaccinated cohorts and between 0.4 per 10,000 person-years (95% CI 0.2, 0.9) in NHR and 14.6 per 10,000 person-years (95% CI 13.5, 15.9) in SIDIAP in the unvaccinated cohorts. The cumulative incidence during the 365-day risk window was below 18.0 per 10,000 individuals in the vaccinated cohorts and below 13.0 per 10,000 individuals in the unvaccinated cohorts.

The matched HRs for acute liver injury were 0.29 (0.10, 0.87) in NHR, 0.73 (95% CI: 0.33; 1.62) in PHARMO, 0.86 (95% CI: 0.64, 1.15) in EpiChron and 1.16 (95% CI: 1.06, 1.28) in SIDIAP.

Table 61. Risk estimates (95% CI) per 10,000 person-years (PY) for acute liver injury 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
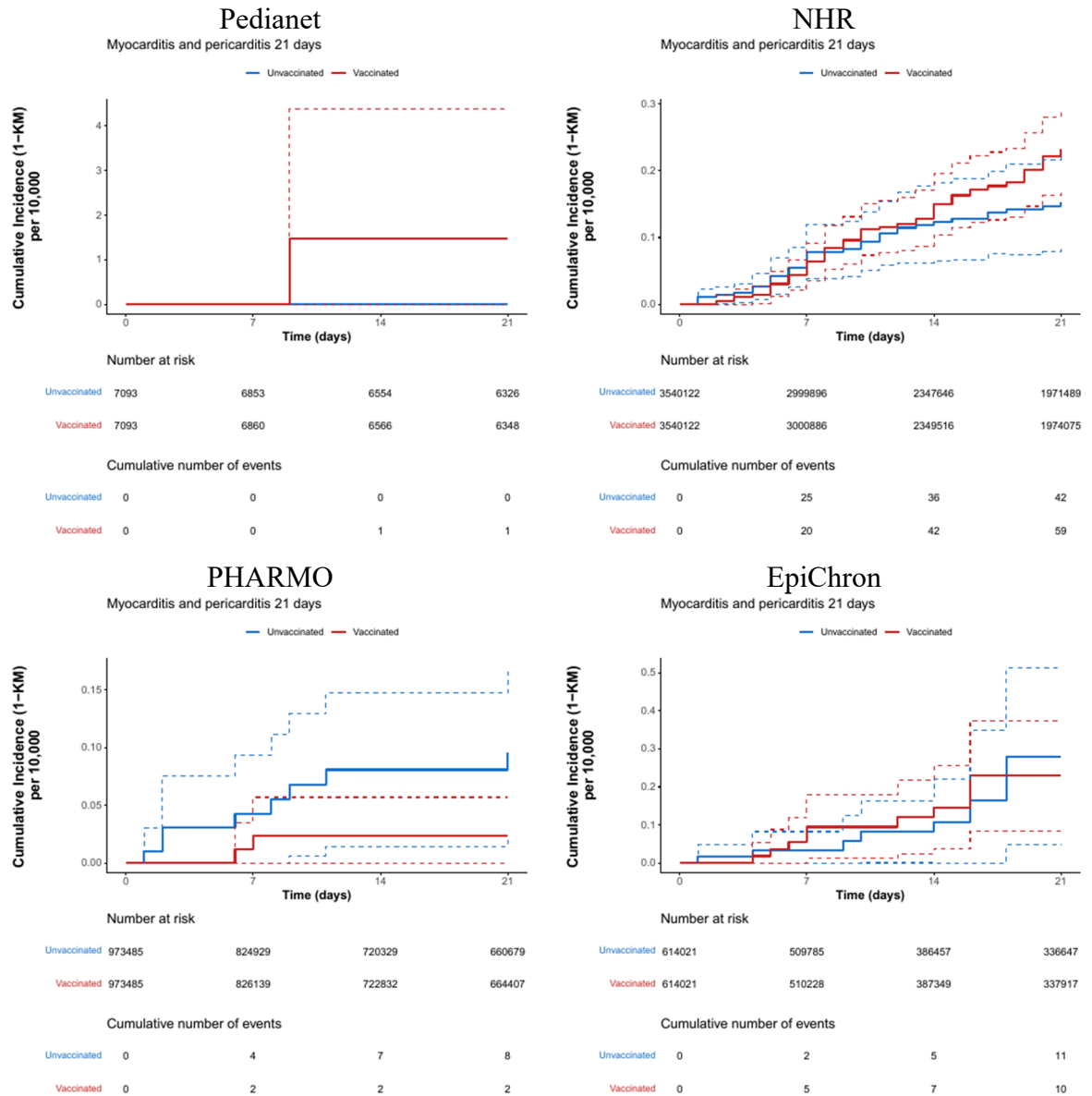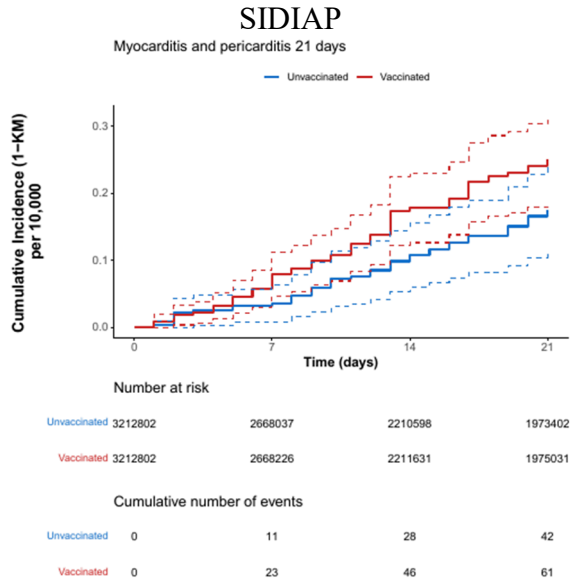
Data source	Vaccinated				Unvaccinated			
	Events (n)	Cumulative incidence (95% CI)	Person-years (PY)	Incidence rate (95% CI)	Events (n)	Cumulative incidence (95% CI)	Person-years (PY)	Incidence rate (95% CI)
Pedianet (Italy)	NA	NA	NA	NA	NA	NA	NA	NA
NHR (Norway)	6	0.3 (0, 0.8)	509,660.4	0.1 (0, 0.3)	20	0.5 (0, 1.2)	504,574.7	0.4 (0.2, 0.9)
PHARMO (Netherlands)	15	0.4 (0.2, 0.7)	346,837.1	0.4 (0.2, 0.7)	20	0.6 (0.2, 0.9)	337,211.2	0.6 (0.3, 1.1)
EpiChron (Spain)	127	5.9 (4.8, 7.0)	191,551.3	6.6 (5.5, 7.9)	146	6.0 (4.4, 7.5)	186,944.4	7.8 (6.2, 9.9)
SIDIAP (Spain)	1,577	17.1 (16.0, 18.1)	926,674.2	17.0 (16.2, 17.9)	1,353	12.3 (11.1, 13.5)	925,036.9	14.6 (13.5, 15.9)

Note: Estimation of confidence intervals differs between vaccinated and unvaccinated, since the unvaccinated estimate is a 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, gender, 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 52. **Cumulative incidence of acute liver injury 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**
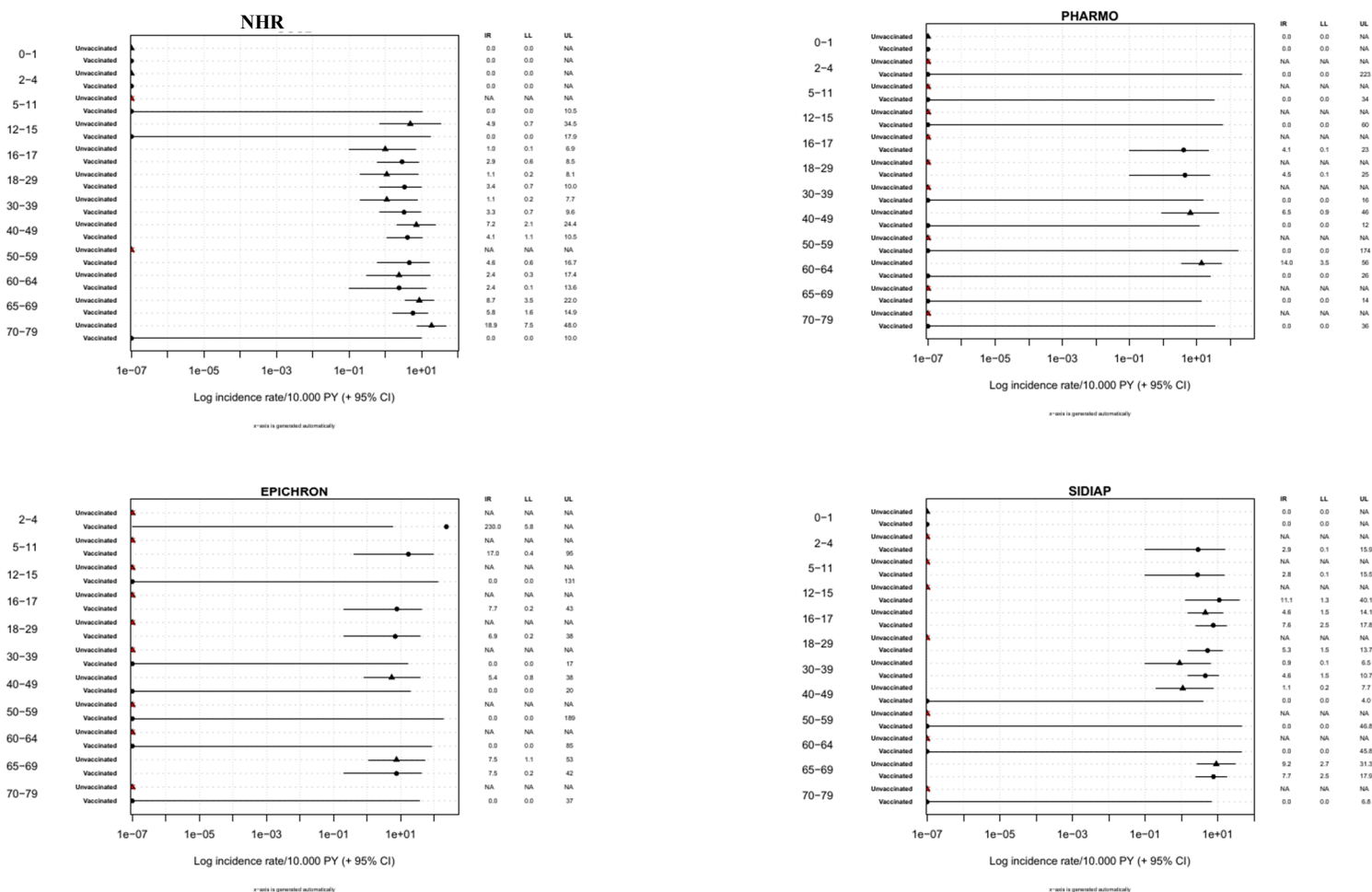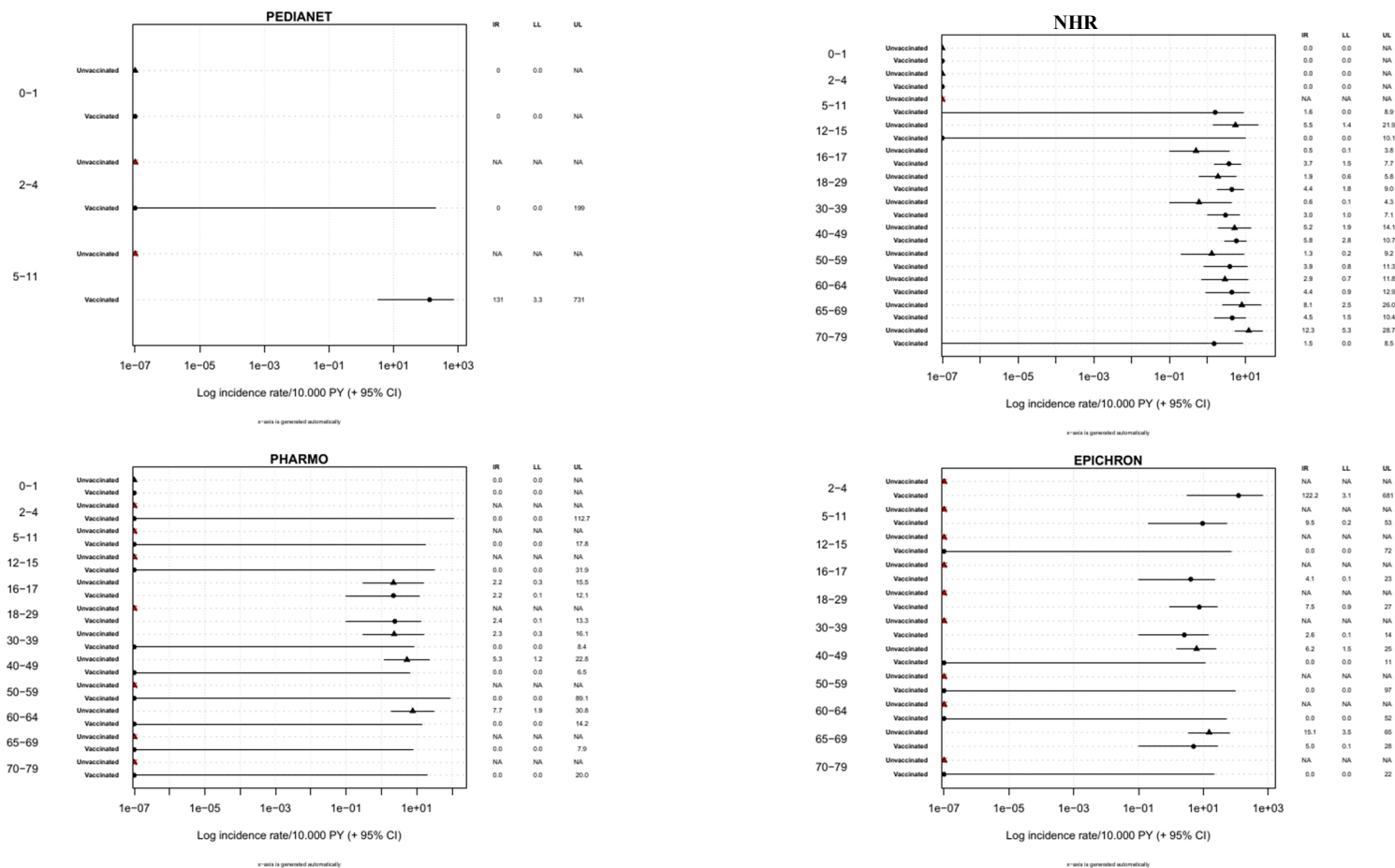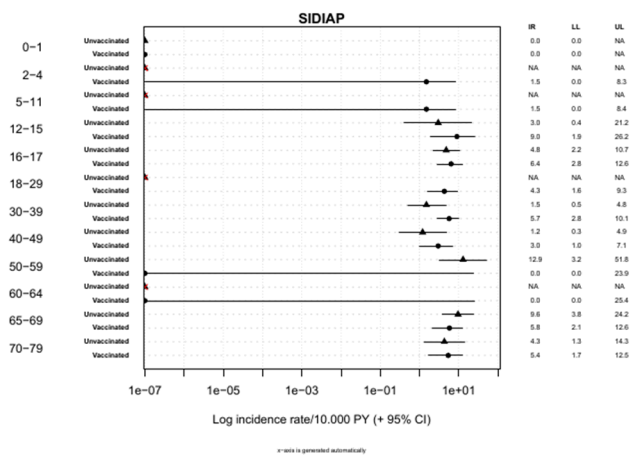

Cumulative incidence curves (1 – Kaplan–Meier risk) starting from the day of administration of the first dose of vaccine. Dotted lines represent 95% confidence intervals. The number at risk at each time point and the cumulative number of events during the 365-day risk window are also shown for each time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

Figure 53. Forest plot showing incidence rates and 95% confidence intervals for acute liver injury 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
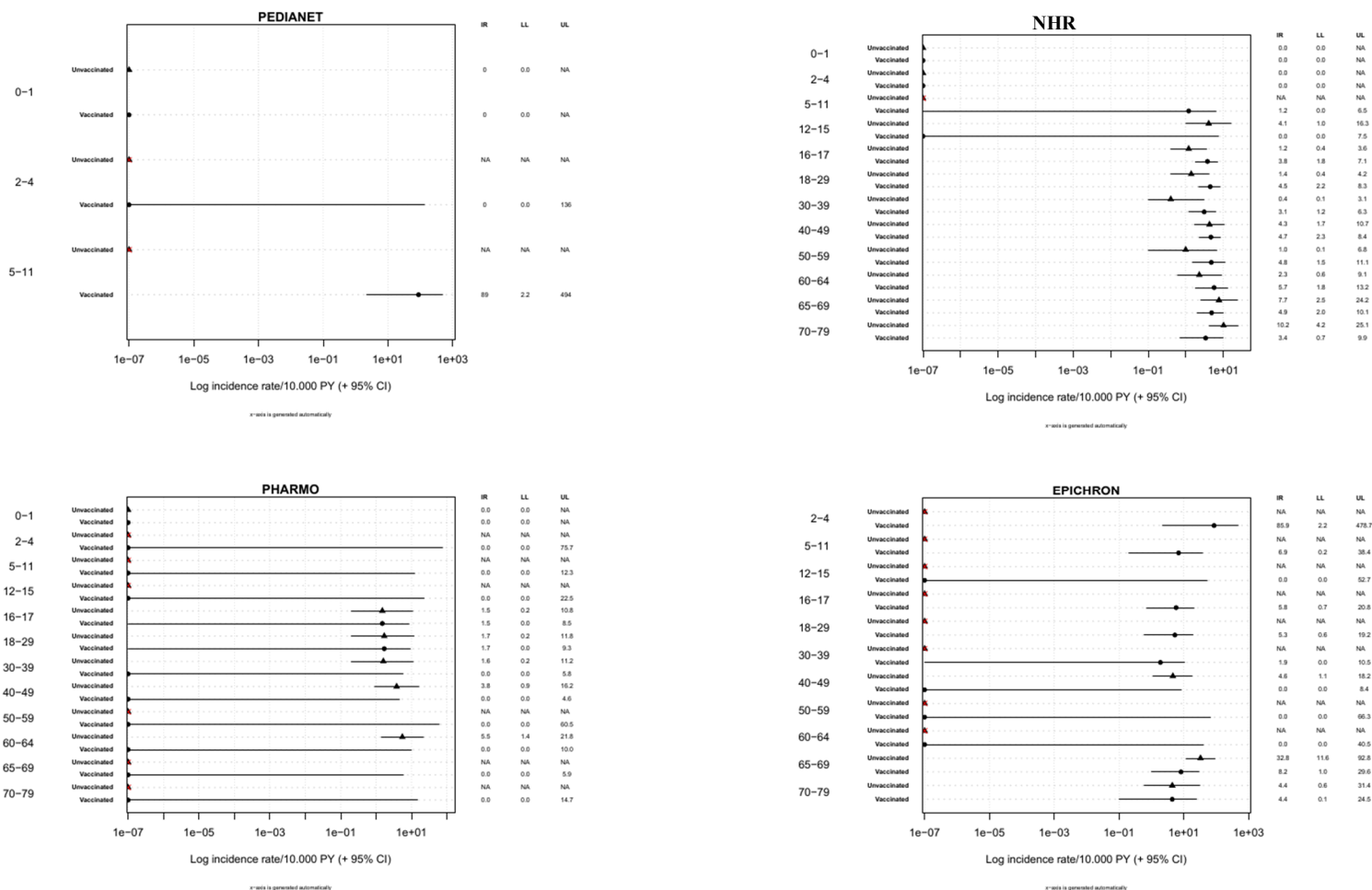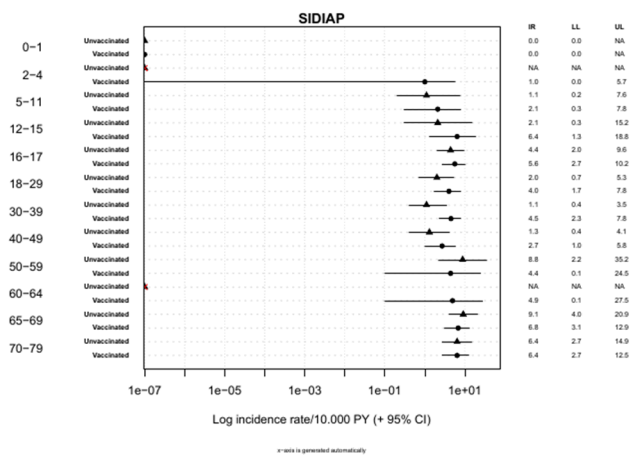
Table 62.   Matched hazard ratios (HRs) and matched risk differences (RDs) per 10,000 person-years and their 95% CIs for acute liver injury within 365 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source

	Matched HR (95% CI)	Matched RD
Pedianet	NA	NA
NHR	0.29 (0.10, 0.87)	-0.16
PHARMO	0.73 (0.33, 1.62)	-0.12
EpiChron	0.86 (0.64, 1.15)	-0.08
SIDIAP	1.16 (1.06, 1.28)	4.72

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

10.3.20. Acute kidney injury

Acute kidney injury events within 365 days after the start of follow-up were identified in all data sources, except Pedianet. The incidence rates ranged from 16.1 per 10,000 person-years (95% CI 15.0, 17.3) in NHR to 55.4 per 10,000 person-years (95% CI 53.9, 57.0) in SIDIAP in the vaccinated cohorts and from 21.9 per 10,000 person-years (95% CI 19.7, 24.3) in NHR to 43.4 per 10,000 person-years (95% CI 41.3, 45.5) in SIDIAP in the unvaccinated cohorts.

The incidence of acute kidney injury was highest in older age groups in both the vaccinated and unvaccinated cohorts. The matched unadjusted HRs were 0.73 (95% CI: 0.64; 0.83) in NHR, 1.06 (95% CI: 0.95; 1.18) in PHARMO, 0.88 (95% CI: 0.77; 1.02) in EpiChron and 1.28 (95% CI: 1.21; 1.35) in SIDIAP.

Table 63. Risk estimates (95% CI) per 10,000 person-years (PY) for acute kidney injury 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

Data source	Vaccinated				Unvaccinated			
	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 (Italy)	0	0 (0, 0)	3,878.5	0 (0, 9.5)	0	0 (0, 0)	3,833.6	NA
NHR (Norway)	819	41.8 (30.4, 53.2)	507,565.9	16.1 (15.0, 17.3)	1,101	48.6 (32.4, 64.8)	502,669.6	21.9 (19.7, 24.3)
PHARMO (Netherlands)	1,154	30.4 (28.4, 32.4)	344,457.0	33.5 (31.6, 35.5)	1,066	27.0 (24.2, 29.7)	335,113.3	31.8 (29.1, 34.8)
EpiChron (Spain)	667	32.0 (29.3, 34.6)	190,759.5	35.0 (32.4, 37.7)	740	34.2 (29.6, 38.8)	186,319.0	39.7 (35.2, 44.8)
SIDIAP (Spain)	5,105	60.8 (58.6, 62.9)	921,283.7	55.4 (53.9, 57.0)	3,990	40.4 (37.8, 42.9)	920,407.7	43.4 (41.3, 45.5)

Note: Estimation of confidence intervals differs between vaccinated and unvaccinated, since the unvaccinated estimate is a 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, gender, 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 54. Cumulative incidence of acute kidney injury 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
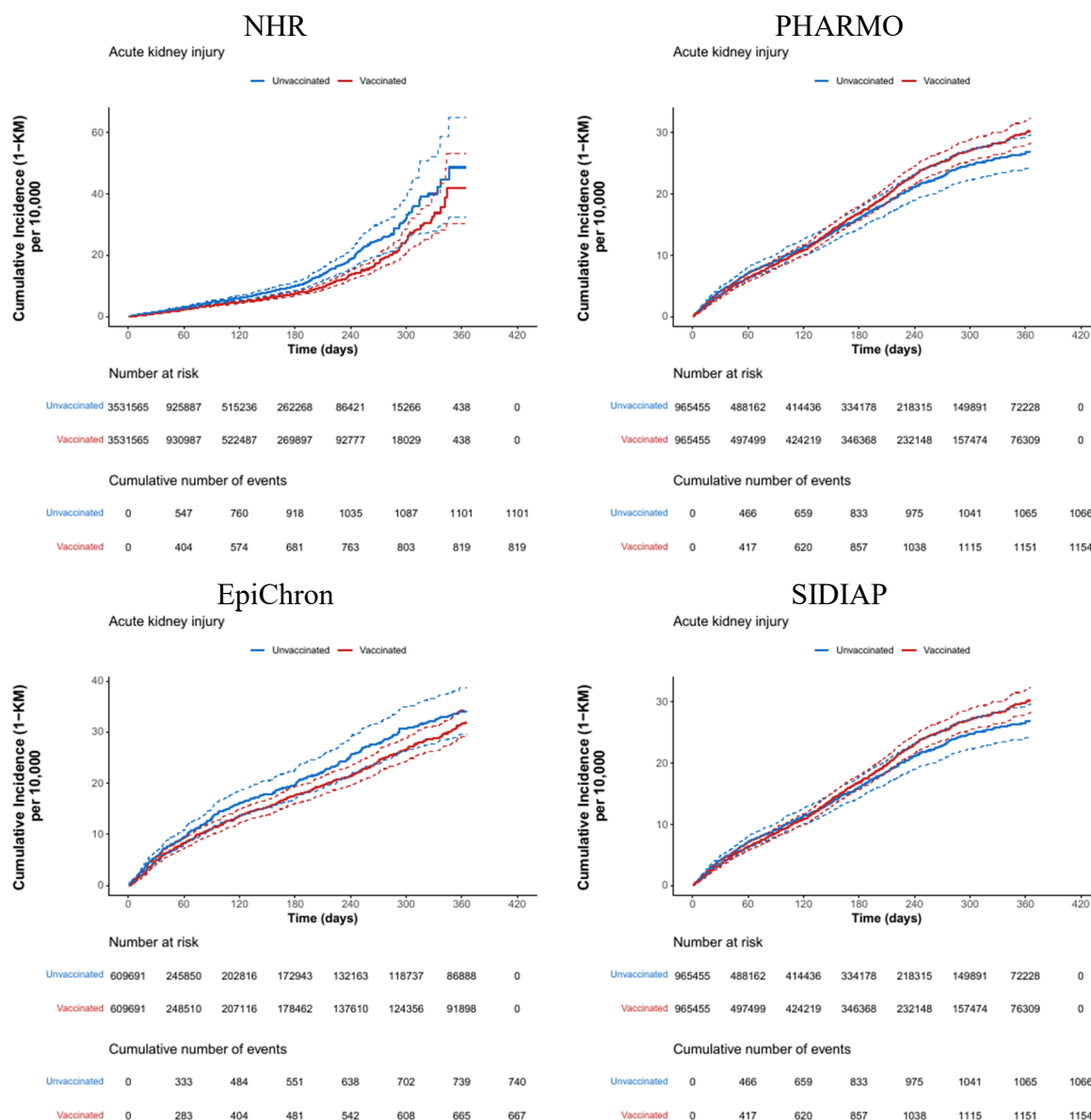
Cumulative incidence curves (1 – Kaplan–Meier risk) starting from the day of administration of the first dose of vaccine. Dotted lines represent 95% confidence intervals. The number at risk at each time point and the cumulative number of events within the 365-day risk window are also shown for each time point. The numerical data correspond to the days indicated by the tick marks on the x-axis.

Figure 55. **Forest plot showing incidence rates and 95% confidence intervals for acute kidney injury 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 64. Matched hazard ratios (HRs) and matched risk differences (RDs) per 10,000 person-years and their 95% CIs for acute kidney injury 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)	Matched RD
Pedianet	NA	NA
NHR	0.73 (0.64, 0.83)	-6.79
PHARMO	1.06 (0.95, 1.18)	3.42
EpiChron	0.88 (0.77, 1.02)	-2.27
SIDIAP	1.28 (1.21, 1.35)	20.42

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

10.3.21. Acute pancreatitis

Acute pancreatitis events were identified in all data sources except Pedianet. The incidence rates ranged from 0.2 per 10,000 person-years (95% CI 0.1, 0.3) in NHR to 6.2 per 10,000 person-years (95% CI 5.7, 6.7) in SIDIAP in the vaccinated cohorts and from 0.2 per 10,000 person-years (95% CI 0.1, 0.5) in NHR to 5.4 per 10,000 person-years (95% CI 4.7, 6.2) in SIDIAP in the unvaccinated cohorts. The cumulative incidence during the 365-day risk window was less than 6.5 per 10,000 individuals in the vaccinated cohorts and less than 5.0 per 10,000 individuals in the unvaccinated cohorts.

The incidence rate of acute pancreatitis was highest in the older age groups in both the vaccinated and unvaccinated cohorts. The matched unadjusted HRs were 0.66 (95% CI 0.24, 1.86) in NHR, 0.71 (95% CI: 0.48; 1.03) in PHARMO, 1.32 (95% CI: 0.89, 1.94) in EpiChron and 1.15 (95% CI: 0.98, 1.34) in SIDIAP.

Table 65. Risk estimates (95% CI) per 10,000 person-years (PY) for acute pancreatitis 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

| Data source	Vaccinated				Unvaccinated			
	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 (Italy)	0	0 (0, 0)	3,878.5	0 (0, 9.50)	0	0 (0, 0)	3,833.6	NA
NHR (Norway)	8	0.2 (0, 0.3)	509,660.4	0.2 (0.1, 0.3)	12	0.1 (0, 0.2)	504,574.7	0.2 (0.1, 0.5)
PHARMO (Netherlands)	69	2.0 (1.4, 2.5)	346,687.5	2.0 (1.5, 2.5)	95	2.5 (1.7, 3.3)	337,056.0	2.8 (2.1, 3.8)
EpiChron (Spain)	94	4.3 (3.4, 5.3)	191,534.6	4.9 (4.0, 6.0)	70	3.3 (2.1, 4.5)	186,928.9	3.7 (2.7, 5.2)
SIDIAP (Spain)	575	6.0 (5.4, 6.6)	928,255.7	6.2 (5.7, 6.7)	500	4.5 (3.8, 5.2)	926,488.6	5.4 (4.7, 6.2)

Note: Estimation of confidence intervals differs between vaccinated and unvaccinated, since the unvaccinated estimate is a 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, gender, 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+).
LL: lower limit of 95% CI; UL: upper lower limit of 95% CI.

Figure 56. Cumulative incidence of acute pancreatitis 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 365-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 57. Forest plot showing incidence rates and 95% confidence intervals for acute pancreatitis 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 66. Matched hazard ratios (HRs) and matched risk differences (RDs) per 10,000 person-years and their 95% CIs for acute pancreatitis 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)	Matched RD
Pedianet	NA	NA
NHR	0.66 (0.24, 1.86)	0.07
PHARMO	0.71 (0.48, 1.03)	-0.56
EpiChron	1.32 (0.89, 1.94)	0.99
SIDIAP	1.15 (0.98, 1.34)	1.46

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

10.3.22. Rhabdomyolysis

Rhabdomyolysis events were reported in all data sources except Pedianet. The incidence rates ranged from <0.1 per 10,000 person-years (95% CI <0.1, <0.1) in NHR to 2.5 per 10,000 person-years (95% CI 2.2, 2.9) in SIDIAP in the vaccinated cohorts. The incidence rates were 3.2 per 10,000 person-years (95% CI 2.0, 4.9) in Epichron and 3.4 per 10,000 person-years (95% CI 2.9, 4.1) in SIDIAP in the unvaccinated cohorts, with no events observed in NHR or PHARMO. The cumulative incidence was below 4 per 10,000 individuals in both cohorts in all three data sources.

The matched HRs were 0.50 (95% CI: 0.28; 0.87) in EpiChron and 0.73 (95% CI: 0.59; 0.91) in SIDIAP.

Table 67. **Risk estimates (95% CI) per 10,000 person-years (PY) for rhabdomyolysis 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)**

Data source	Vaccinated				Unvaccinated			
	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 (Italy)	NA	NA	NA	NA	NA	NA	NA	NA
NHR (Norway)	<5	<0.1 (<0.1, <0.1)	509,660.4	0 (0, 0.1)	0	0 (0, 0)	504,574.7	NA
PHARMO (Netherlands)	<5	0.1 (0, 0.2)	346,857.7	0.1 (0, 0.3)	0	0 (0, 0)	337,231.6	NA
EpiChron (Spain)	30	1.4 (0.9, 2.0)	191,707.6	1.6 (1.1, 2.2)	59	2.8 (1.5, 4.0)	187,075.4	3.2 (2.0, 4.9)
SIDIAP (Spain)	234	2.8 (2.4, 3.3)	928,961.8	2.5 (2.2, 2.9)	319	3.6 (2.8, 4.3)	927,151.6	3.4 (2.9, 4.1)

Note: Estimation of confidence intervals differs between vaccinated and unvaccinated, since the unvaccinated estimate is a 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, gender, 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 58. Cumulative incidence of rhabdomyolysis 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.

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Figure 59. **Forest plot showing incidence rates and 95% confidence intervals for rhabdomyolysis 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)**
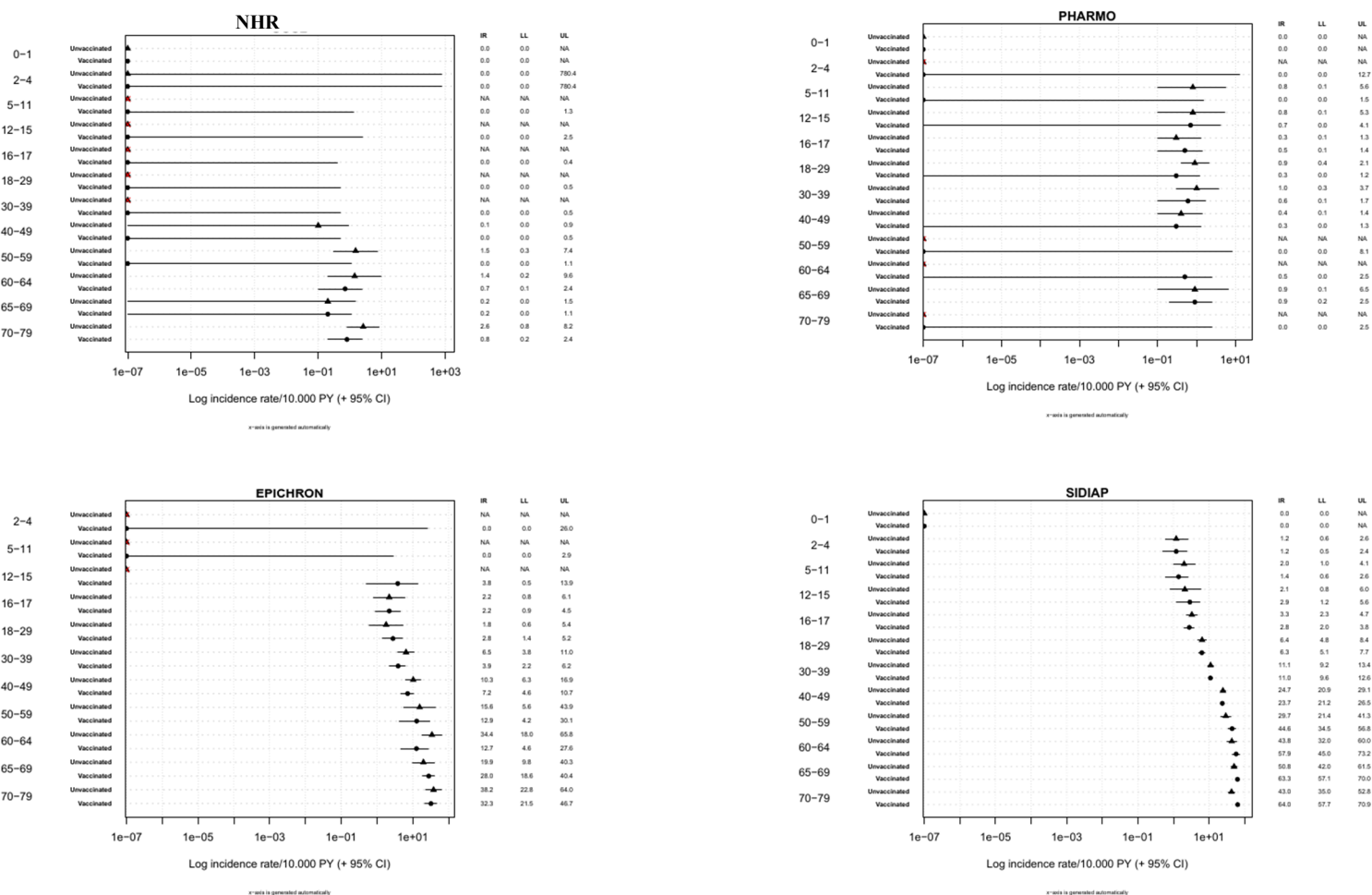
PFIZER CONFIDENTIAL
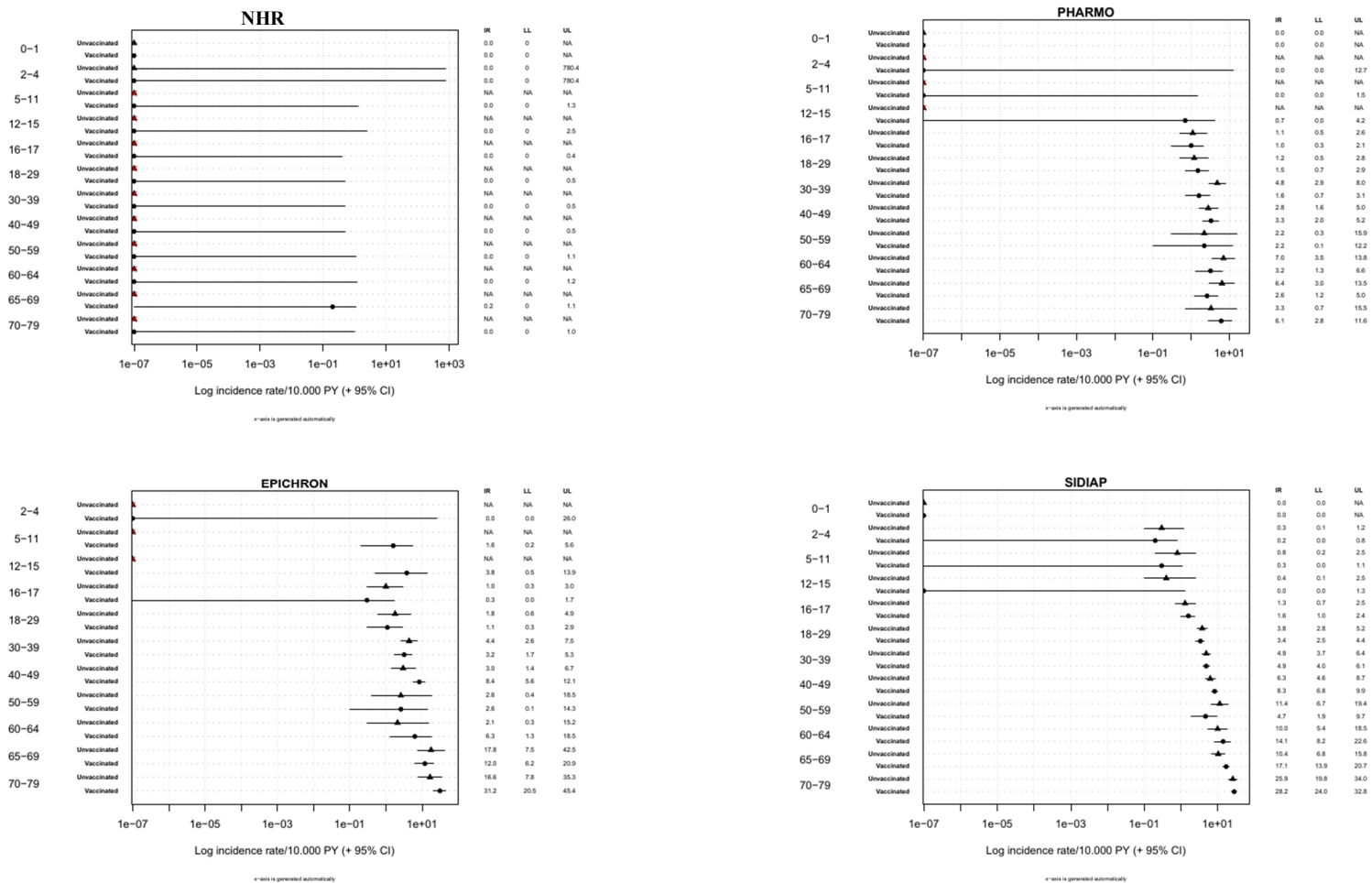
Table 68. Matched hazard ratios (HRs) and matched risk differences (RDs) per 10,000 person-years and their 95% CIs for rhabdomyolysis among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source (risk window: 365 days after dose 1)

	Matched HR (95% CI)	Matched RD
Pedianet	NA	NA
NHR	NA	NA
PHARMO	NA	0.08
EpiChron	0.50 (0.28, 0.87)	-1.36
SIDIAP	0.73 (0.59, 0.91)	-0.77

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

10.3.23. Generalised convulsions

Generalised convulsion events were identified in all data sources, except Pedianet. The incidence rates ranged from 1.8 per 10,000 person-years (95% CI 1.0, 3.0) in PHARMO to 7.8 per 10,000 person-years (95% CI 5.3, 10.9) in EpiChron in the vaccinated cohorts and from 3.4 per 10,000 person-years (95% CI 2.1, 5.6) in PHARMO to 6.4 per 10,000 person-years (95% CI 4.0, 10.2) in EpiChron in the unvaccinated cohorts. The cumulative incidence was below 1 per 10,000 individuals in both cohorts in all data sources.

The matched HRs were 0.89 (95% CI: 0.68; 1.17) in NHR, 0.52 (95% CI: 0.25; 1.06) in PHARMO, 1.22 (95% CI: 0.68; 2.19) in EpiChron and 1.23 (95% CI: 0.94; 1.61) in SIDIAP.

Table 69. **Risk estimates (95% CI) per 10,000 person-years (PY) for generalised convulsions 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**

Data source	Vaccinated				Unvaccinated			
	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 (Italy)	0	0 (0, 0)	738.5	0 (0, 50)	0	0 (0, 0)	735.6	NA
NHR (Norway)	135	0.6 (0.5, 0.8)	240,531.4	5.6 (4.7, 6.6)	151	0.7 (0.5, 0.9)	240,240.2	6.3 (5.1, 7.8)
PHARMO (Netherlands)	14	0.2 (0.1, 0.3)	79,625.3	1.8 (1.0, 3.0)	27	0.4 (0.2, 0.6)	79,198.8	3.4 (2.1, 5.6)
EpiChron (Spain)	33	0.9 (0.6, 1.2)	42,557.1	7.8 (5.3, 10.9)	27	0.7 (0.4, 1.0)	42,417.0	6.4 (4.0, 10.2)
SIDIAP (Spain)	153	0.8 (0.6, 0.9)	241,141.4	6.3 (5.4, 7.4)	124	0.6 (0.5, 0.7)	240,985.8	5.1 (4.1, 6.4)

Note: Estimation of confidence intervals differs between vaccinated and unvaccinated, since the unvaccinated estimate is a 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, gender, 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+).
LL: lower limit of 95% CI; UL: upper lower limit of 95% CI.

Figure 60. **Cumulative incidence of generalised convulsions 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**

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 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 61. Forest plot showing incidence rates and 95% confidence intervals for generalised convulsions 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
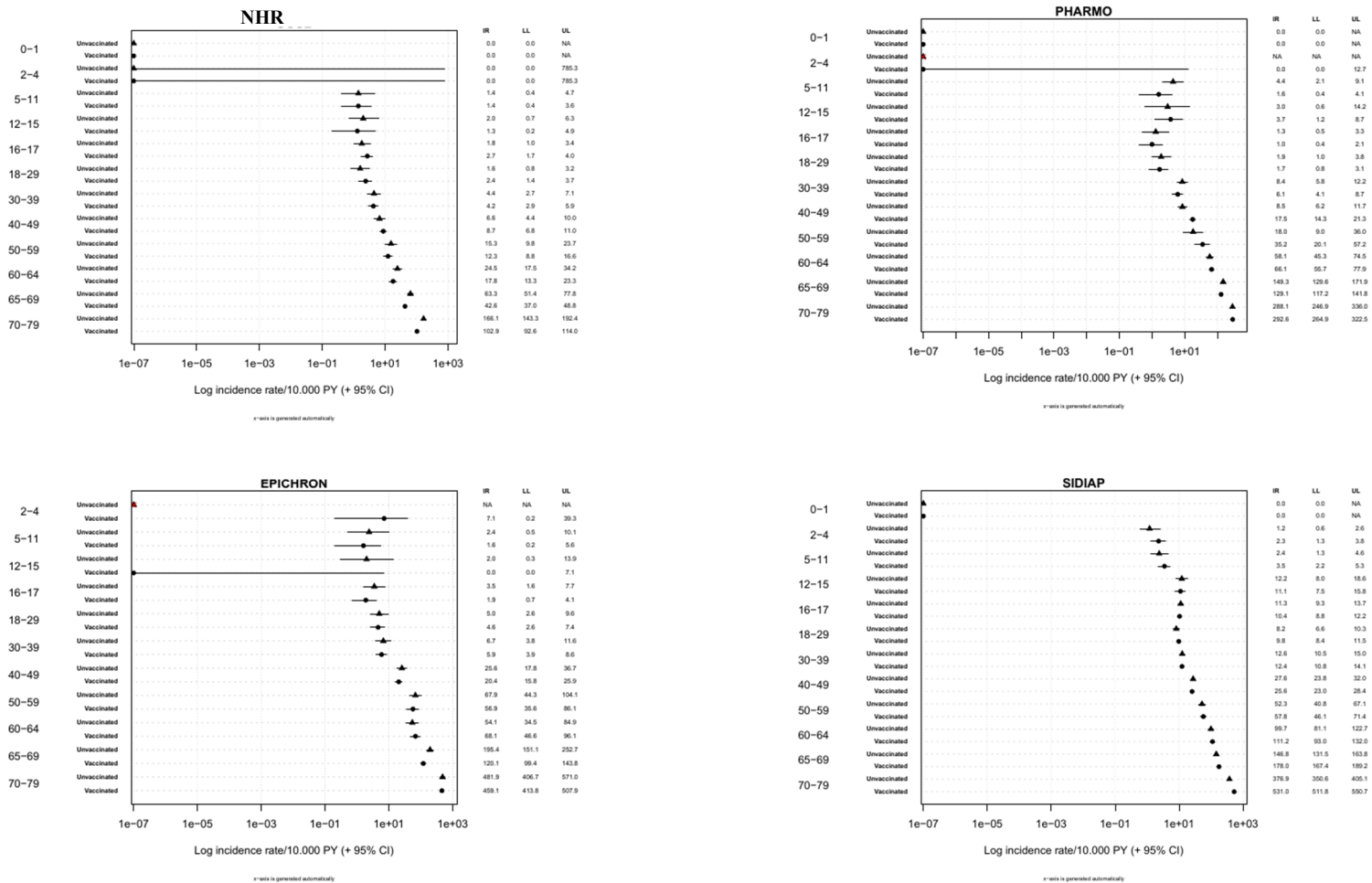
Table 70. Matched hazard ratios (HRs) and matched risk differences (RDs) per 10,000 person-years and their 95% CIs for generalised convulsions within 42 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source

	Matched HR (95% CI)	Matched RD
Pedianet	NA	NA
NHR	0.89 (0.68, 1.17)	-0.06
PHARMO	0.52 (0.25, 1.06)	-0.19
EpiChron	1.22 (0.68, 2.19)	0.22
SIDIAP	1.23 (0.94, 1.61)	0.15

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

10.3.24. Meningoencephalitis

Meningoencephalitis was a rare event in all data sources, with no events identified in Pedianet. The incidence rates ranged from 0.6 per 10,000 person-years (95% CI 0.3, 1.0) in SIDIAP to 1.9 per 10,000 person-years (95% CI 1.4, 2.5) in NHR in the vaccinated cohorts and from 0.7 per 10,000 person-years (95% CI 0.2, 3.0) in EpiChron and 0.7 per 10,000 person-years (95% CI 0.4, 1.2) in SIDIAP to 1.9 per 10,000 person-years (95% CI 1.3, 2.8) in NHR in the unvaccinated cohorts. The cumulative incidence was below 1 per 10,000 individuals in both cohorts in all data sources.

The matched HRs were 1.02 (95% CI: 0.64; 1.63) in NHR, 0.54 (95% CI: 0.18; 1.65) in PHARMO, 1.33 (95% CI: 0.23; 7.69) in EpiChron and 0.94 (95% CI: 0.44; 2.01) in SIDIAP.
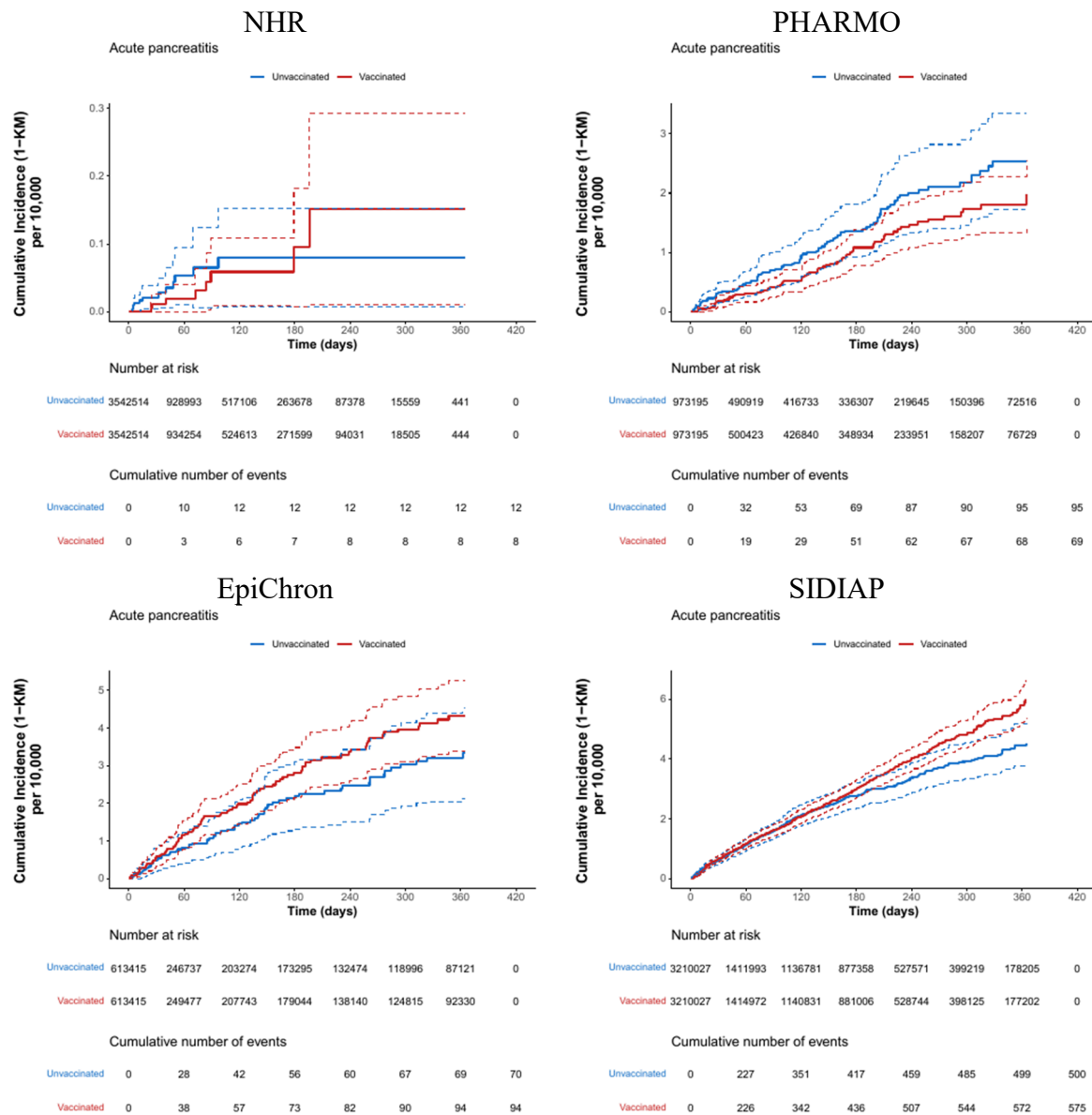
Table 71. **Risk estimates (95% CI) per 10,000 person-years (PY) for meningoencephalitis within 42 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source**

Data source	Vaccinated				Unvaccinated			
	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 (Italy)	0	0 (0, 0)	738.7	0 (0, 49.9)	0	0 (0, 0)	735.8	NA
NHR (Norway)	46	0.2 (0.2, 0.3)	240,742.5	1.9 (1.4, 2.5)	45	0.2 (0.1, 0.3)	240,451.4	1.9 (1.3, 2.8)
PHARMO (Netherlands)	6	0.1 (0, 0.2)	79,649.2	0.8 (0.3, 1.6)	11	0.2 (0, 0.3)	79,223.5	1.4 (0.6, 3.0)
EpiChron (Spain)	<5	0.1 (0, 0.3)	42,603.4	0.9 (0.3, 2.4)	<5	0.1 (0, 0.2)	42,462.2	0.7 (0.2, 3.0)
SIDIAP (Spain)	15	0.1 (0, 0.1)	241,331.5	0.6 (0.3, 1.0)	16	0.1 (0, 0.1)	241,172.2	0.7 (0.4, 1.2)

Note: Estimation of confidence intervals differs between vaccinated and unvaccinated, since the unvaccinated estimate is a 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, gender, 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 62. Cumulative incidence of meningoencephalitis 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

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 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 63. Forest plot showing incidence rates and 95% confidence intervals for meningoencephalitis 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
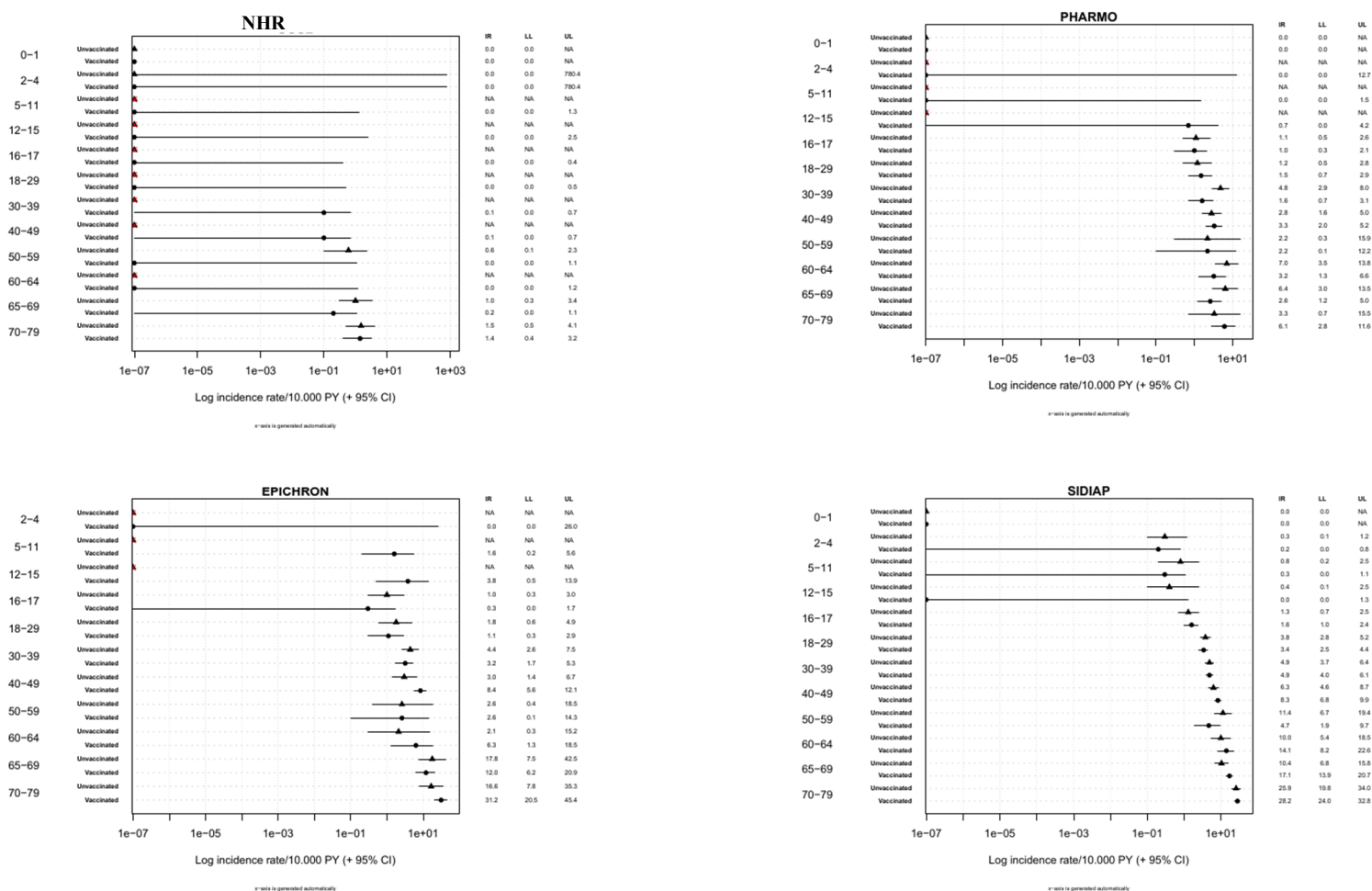
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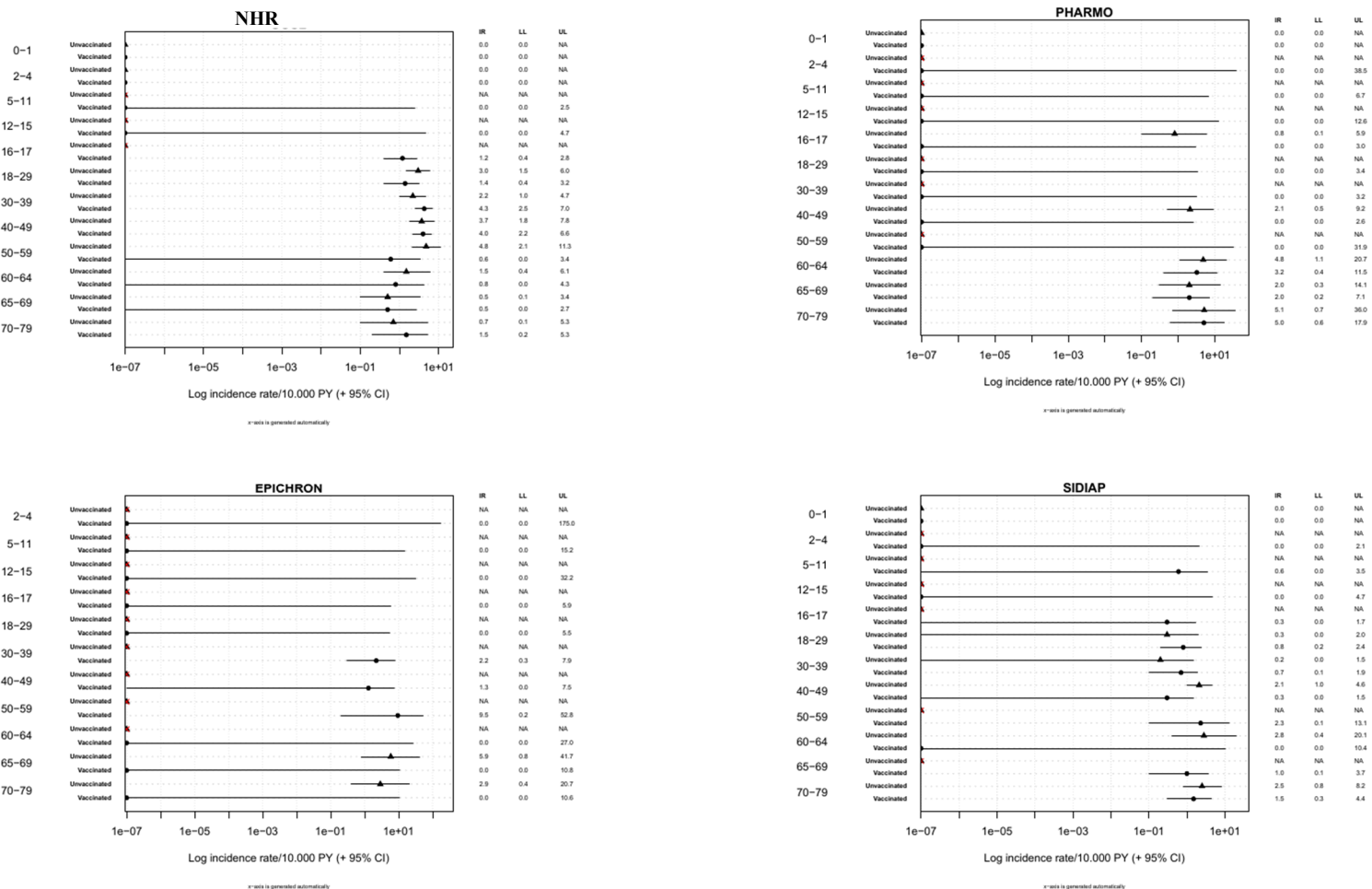
Table 72. **Matched hazard ratios (HRs) and matched risk differences (RDs) per 10,000 person-years and their 95% CIs for meningoencephalitis within 42 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source**

	Matched HR (95% CI)	Matched RD
Pedianet	NA	NA
NHR	1.02 (0.64, 1.63)	0.01
PHARMO	0.54 (0.18, 1.65)	-0.08
EpiChron	1.33 (0.23, 7.69)	0.07
SIDIAP	0.94 (0.44, 2.01)	0

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

10.3.25. Transverse myelitis

Transverse myelitis within 42 days after start of follow-up was a very rare event identified in PHARMO, EpiChron and SIDIAP, with all incidence rates less than 1 per 10,000 person-years. The incidence rates in SIDIAP, based on <5 events was 0.1 per 10,000 person-years (95% CI 0, 0.4) in the vaccinated cohort and was 0.1 (95% CI 0, 0.9) and 0.2 (95% CI 0, 1.7) per 10,000 person-years in the unvaccinated cohort in PHARMO and EpiChron, respectively.

No HRs were estimated due to the low number of events.

Table 73. **Risk estimates (95% CI) per 10,000 person-years (PY) for transverse myelitis 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**

Data source	Vaccinated				Unvaccinated			
	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 (Italy)	NA	NA	NA	NA	NA	NA	NA	NA
NHR (Norway)	NA	NA	NA	NA	NA	NA	NA	NA
PHARMO (Netherlands)	0	0 (0, 0)	79,661.0	0 (0, 0.5)	<5	0 (0, 0)	79,235.3	0.1 (0, 0.9)
EpiChron (Spain)	0	0 (0, 0)	42,609.8	0 (0, 0.9)	<5	0 (0, 0.1)	42,468.5	0.2 (0, 1.7)
SIDIAP (Spain)	<5	0 (0, 0)	241,361.4	0.1 (0, 0.4)	0	0 (0, 0)	241,202.2	

Note: Estimation of confidence intervals differs between vaccinated and unvaccinated, since the unvaccinated estimate is a 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, gender, 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+).
LL: lower limit of 95% CI; UL: upper lower limit of 95% CI.

Figure 64. Cumulative incidence of transverse myelitis 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

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 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 65. Forest plot showing incidence rates and 95% confidence intervals for transverse myelitis 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

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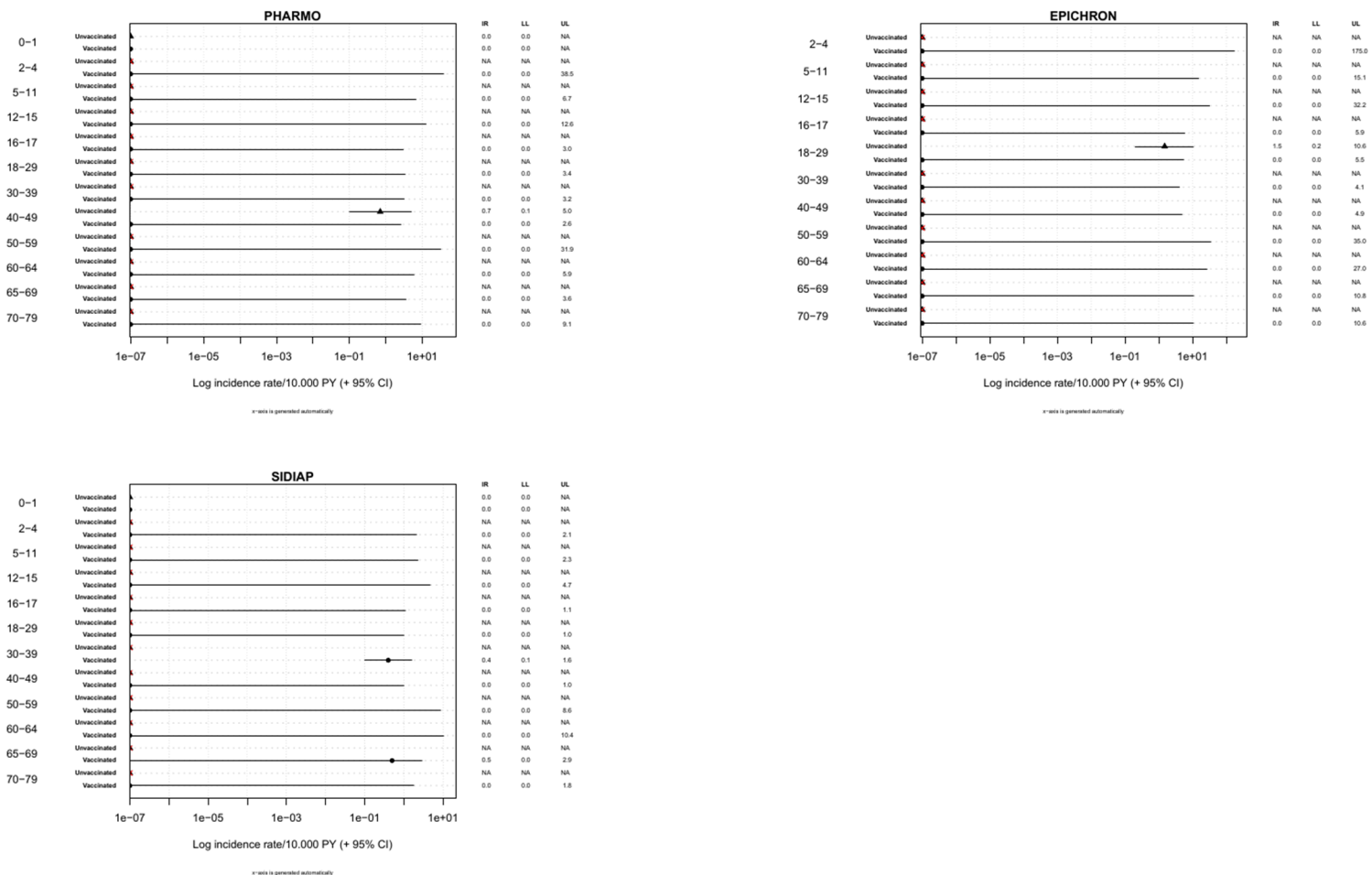
10.3.26. Bell's palsy

Bell's palsy events were identified in all data sources, except Pedianet. The incidence rates ranged from 2.6 per 10,000 person-years (95% CI 1.6, 4.0) in PHARMO to 8.5 per 10,000 person-years (95% CI 7.3, 9.7) in SIDIAP in the vaccinated cohorts and from 2.3 per 10,000 person-years (95% CI 1.4, 3.7) in PHARMO to 8.2 per 10,000 person-years (95% CI 6.8, 9.9) in SIDIAP in the unvaccinated cohorts. The cumulative incidence was below 1 per 10,000 individuals in both cohorts in all data sources except SIDIAP where it was 1.0 in the vaccinated cohort.

The matched HRs were 1.00 (95% CI: 0.73; 1.37) in NHR, 1.16 (95% CI: 0.62: 2.19) in PHARMO, 1.03 (95% CI: 0.52; 2.04) in EpiChron and 1.03 (95% CI: 0.82; 1.30) in SIDIAP.
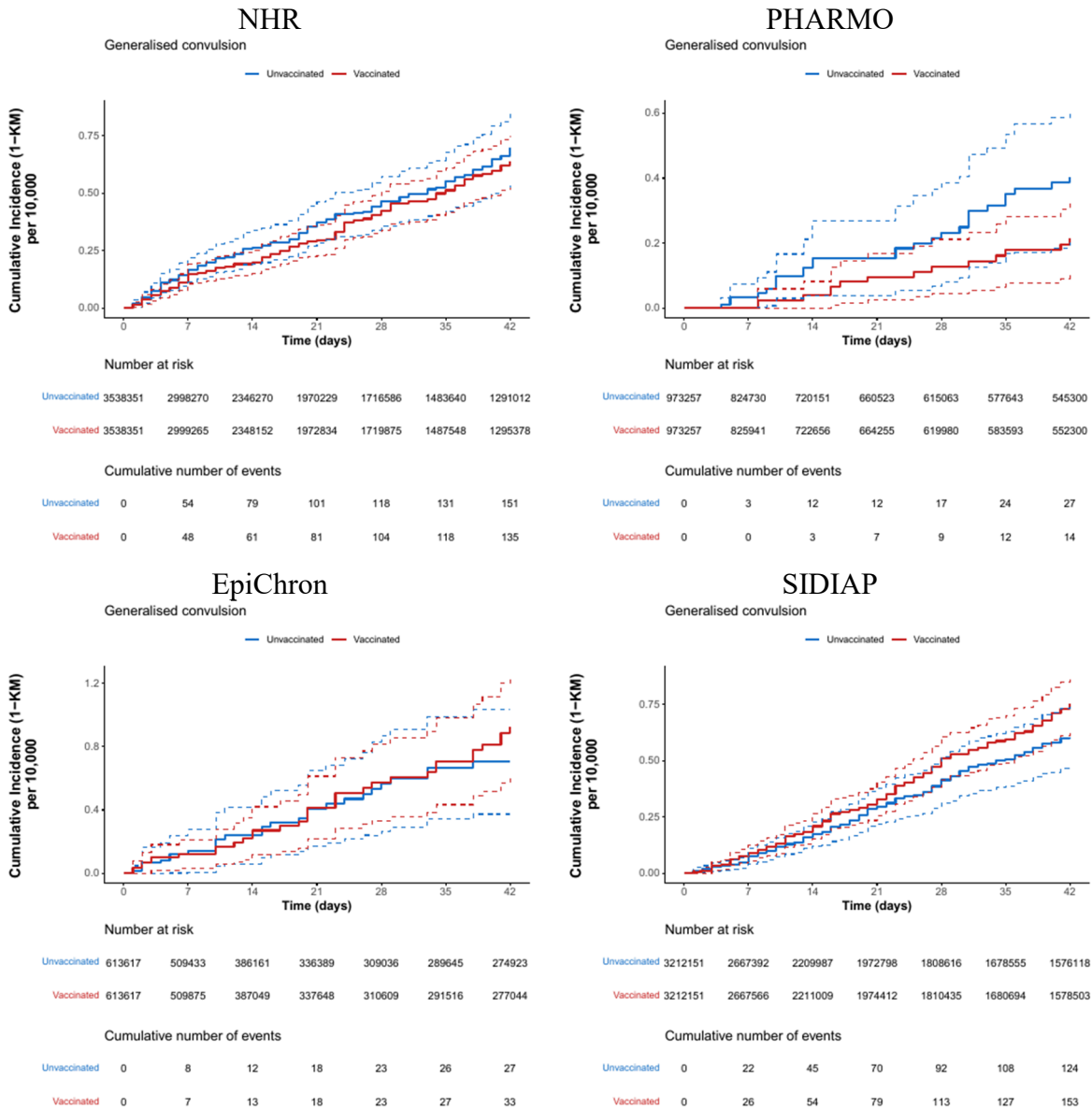
Table 74. **Risk estimates (95% CI) per 10,000 person-years (PY) for Bell's palsy within 42 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source**

Data source	Vaccinated				Unvaccinated			
	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 (Italy)	0	0 (0, 0)	738.7	0 (0, 49.9)	0	0 (0, 0)	735.8	NA
NHR (Norway)	122	0.6 (0.5, 0.7)	240,530.3	5.1 (4.2, 6.1)	122	0.6 (0.4, 0.7)	240,238.3	5.1 (3.9, 6.6)
PHARMO (Netherlands)	21	0.3 (0.2, 0.4)	79,610.7	2.6 (1.6, 4.0)	18	0.3 (0.1, 0.4)	79,185.6	2.3 (1.4, 3.7)
EpiChron (Spain)	29	0.8 (0.5, 1.1)	42,554.2	6.8 (4.6, 9.8)	28	0.8 (0.3, 1.3)	42,413.9	6.6 (3.7, 11.8)
SIDIAP (Spain)	204	1.0 (0.8, 1.1)	240,938.2	8.5 (7.3, 9.7)	198	0.9 (0.7, 1.1)	240,782.6	8.2 (6.8, 9.9)

Note: Estimation of confidence intervals differs between vaccinated and unvaccinated, since the unvaccinated estimate is a 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, gender, 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 66. **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**

NHR

Bell's palsy

Number at risk

Unvaccinated	3538040	2998114	2346205	1970251	1716643	1483729	1291116
Vaccinated	3538040	2999102	2348075	1972857	1719953	1487652	1295497

Cumulative number of events

Unvaccinated	0	36	54	79	97	112	122
Vaccinated	0	36	59	81	94	109	122

PHARMO

Bell's palsy

Number at risk

Unvaccinated	973063	824566	720021	660416	614977	577566	545241
Vaccinated	973063	825769	722516	664136	619882	583496	552225

Cumulative number of events

Unvaccinated	0	7	7	8	13	14	18
Vaccinated	0	10	13	14	17	20	21

EpiChron

Bell's palsy

Number at risk

Unvaccinated	613523	509384	386141	336369	309008	289635	274923
Vaccinated	613523	509823	387024	337626	310588	291513	277057

Cumulative number of events

Unvaccinated	0	4	8	11	21	22	28
Vaccinated	0	4	10	15	21	25	29

SIDIAP

Bell's palsy

Number at risk

Unvaccinated	3208916	2664856	2208068	1971166	1807215	1677354	1575031
Vaccinated	3208916	2665040	2209085	1972772	1809029	1679489	1577435

Cumulative number of events

Unvaccinated	0	51	95	132	157	171	198
Vaccinated	0	45	94	130	157	183	204

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.

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Figure 67. 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
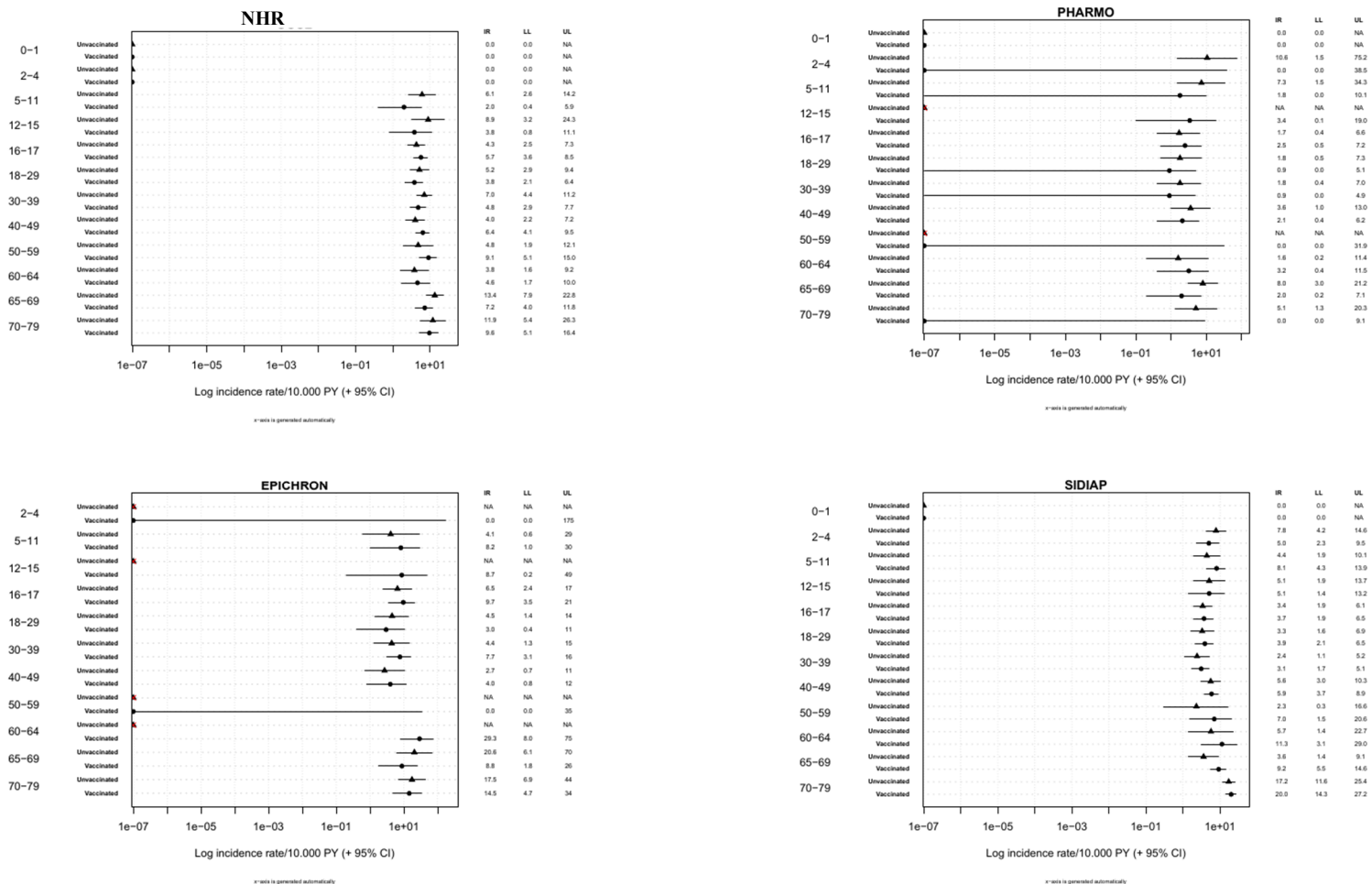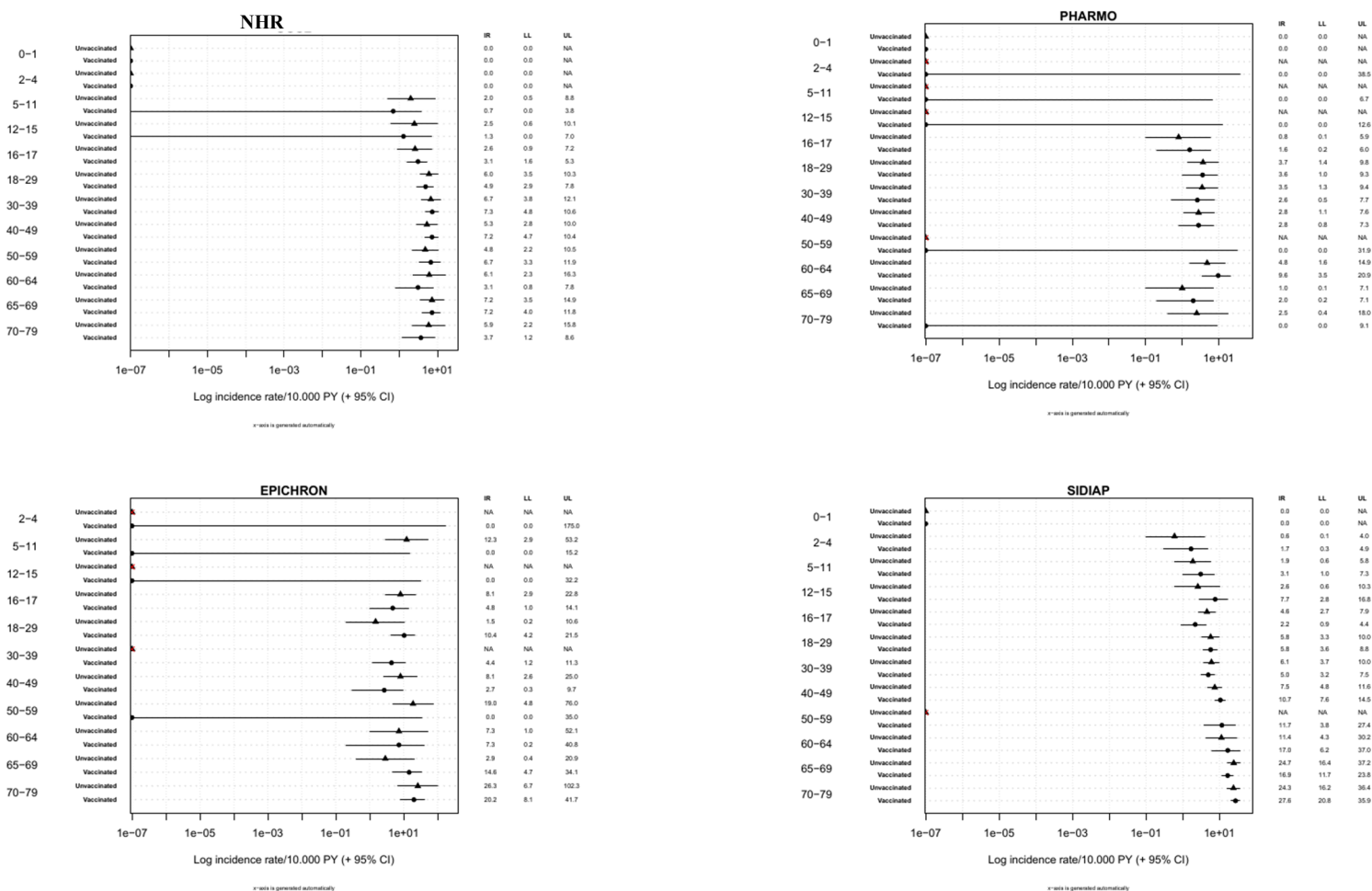
Table 75. **Matched hazard ratios (HRs) and matched risk differences (RDs) per 10,000 person-years and their 95% CIs for Bells Palsy within 42 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source**

	Matched HR (95% CI)	Matched RD
Pedianet	NA	NA
NHR	1.00 (0.73, 1.37)	NA
PHARMO	1.16 (0.62, 2.19)	0.01
EpiChron	1.03 (0.52, 2.04)	NA
SIDIAP	1.03 (0.82, 1.30)	0.04

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

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10.3.27. Acute respiratory distress syndrome

Acute respiratory distress syndrome events were identified in all data sources except Pedianet. The incidence rates ranged from 0.3 per 10,000 person-years (95% CI 0.2, 0.6) in PHARMO to 9.1 per 10,000 person-years (95% CI 7.8, 10.6) in EpiChron in the vaccinated cohorts and from 0.9 per 10,000 person-years (95% CI 0.6, 1.5) in PHARMO to 19.4 per 10,000 person-years (95% CI 16.5, 22.9) in EpiChron in the unvaccinated cohorts. The cumulative incidence was below 11 per 10,000 individuals in the vaccinated cohorts and below 18 per 10,000 individuals in the unvaccinated cohorts in all data sources.

The incidence of acute respiratory distress syndrome was highest in the older age groups, in both the unvaccinated and vaccinated cohorts. The matched HRs were 0.23 (95% CI: 0.15; 0.36) in NHR, 0.35 (95% CI: 0.16; 0.74) in PHARMO, 0.47 (95% CI: 0.38; 0.59) in EpiChron and 0.63 (95% CI: 0.56; 0.70) in SIDIAP.

Table 76. **Risk estimates (95% CI) per 10,000 person-years (PY) for acute respiratory distress syndrome 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)**

Data source	Vaccinated				Unvaccinated			
	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 (Italy)	0	0 (0, 0)	3,878.5	0 (0, 9.5)	0	0 (0, 0)	3,833.6	NA
NHR (Norway)	33	0.9 (0.3, 1.6)	509,617.0	0.6 (0.4, 0.9)	139	4.7 (2.8, 6.7)	504,526.8	2.8 (2.1, 3.7)
PHARMO (Netherlands)	11	0.4 (0.1, 0.6)	346,831.7	0.3 (0.2, 0.6)	31	0.8 (0.4, 1.2)	337,203.3	0.9 (0.6, 1.5)
EpiChron (Spain)	175	7.7 (6.5, 9.0)	191,486.8	9.1 (7.8, 10.6)	363	17.2 (14.1, 20.2)	186,851.9	19.4 (16.5, 22.9)
SIDIAP (Spain)	814	10.0 (9.1, 10.9)	927,769.9	8.8 (8.2, 9.4)	1,296	13.7 (12.2, 15.1)	925,882.1	14.0 (12.9, 15.2)

Note: Estimation of confidence intervals differs between vaccinated and unvaccinated, since the unvaccinated estimate is a 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, gender, 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 68. Cumulative incidence of acute respiratory distress syndrome 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 69. Forest plot showing incidence rates and 95% confidence intervals for acute respiratory distress syndrome 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)
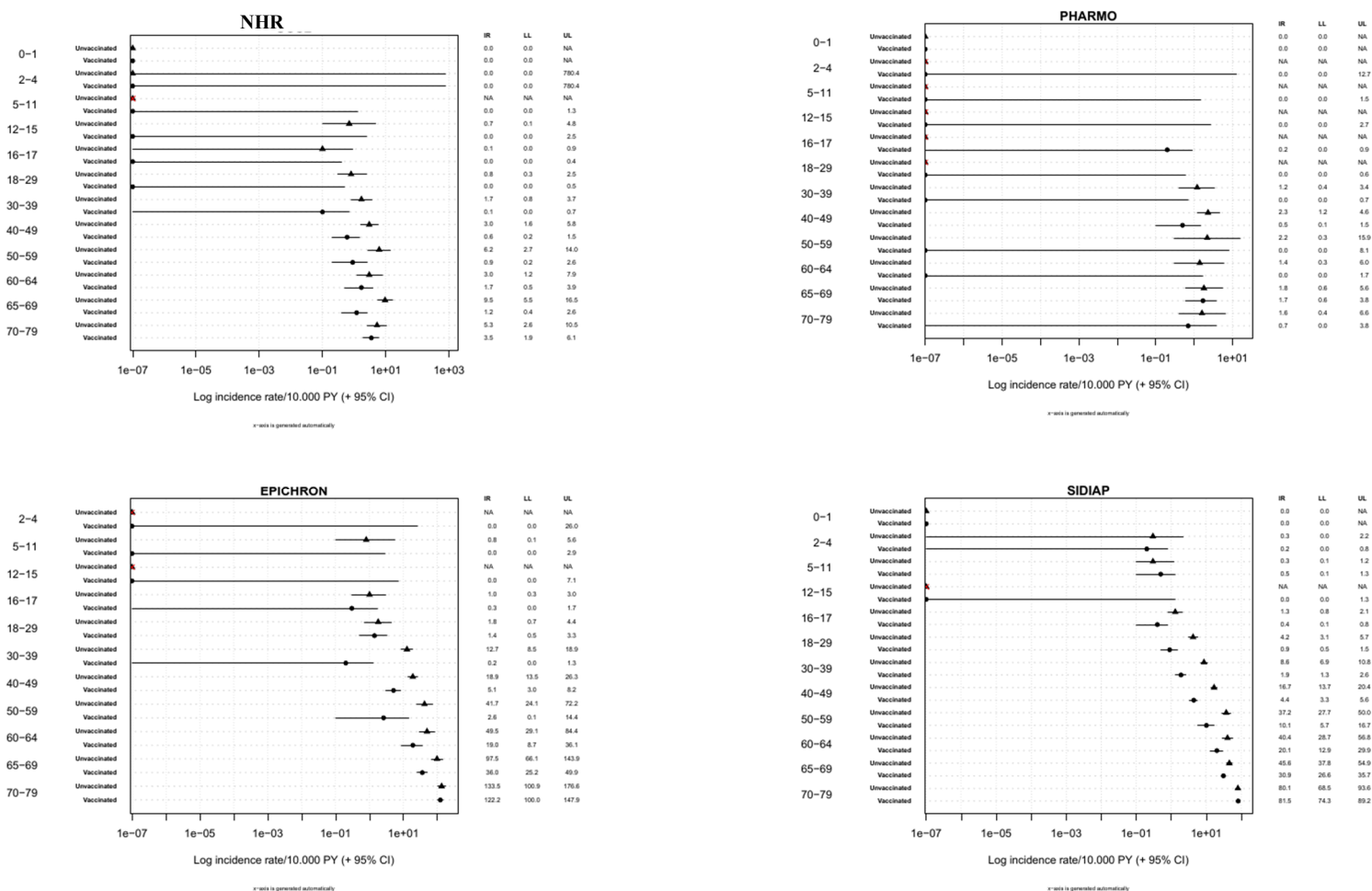
Table 77. **Matched hazard ratios (HRs) and matched risk differences (RDs) per 10,000 person-years and their 95% CIs for acute respiratory distress syndrome among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source (risk window: 365 days after dose 1)**

	Matched HR (95% CI)	Matched RD
Pedianet	NA	NA
NHR	0.23 (0.15, 0.36)	-3.81
PHARMO	0.35 (0.16, 0.74)	-0.41
EpiChron	0.47 (0.38, 0.59)	-9.42
SIDIAP	0.63 (0.56, 0.70)	-3.65

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

10.3.28. Erythema multiforme

Erythema multiforme events were a rare event and were identified in PHARMO, EpiChron and SIDIAP. The incidence rates were 0.3 per 10,000 person-years (95% CI 0, 0.9) in PHARMO and 0.6 per 10,000 person-years (95% CI 0.3, 1.0) in SIDIAP (no events in EpiChron) in the vaccinated cohorts and from 0.2 per 10,000 person-years (95% CI 0, 1.7) in EpiChron to 0.6 per 10,000 person-years (95% CI 0.3, 1.1) in SIDIAP in the unvaccinated cohorts. The cumulative incidence was less than 1 per 10,000 individuals in both cohorts in the three data sources.

The incidence was higher in the younger age groups, but the number of events was low. The matched unadjusted HRs were 0.50 (95% CI: 0.09; 2.72) in PHARMO and 1.07 (95% CI: 0.49; 2.34) in SIDIAP.

Table 78. Risk estimates (95% CI) per 10,000 person-years (PY) for erythema multiforme 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

Data source	Vaccinated				Unvaccinated			
	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 (Italy)	NA	NA	NA	NA	NA	NA	NA	NA
NHR (Norway)	NA	NA	NA	NA	NA	NA	NA	NA
PHARMO (Netherlands)	<5	0 (0, 0.1)	79,657.5	0.3 (0, 0.9)	<5	0.1 (0, 0.1)	79,231.8	0.5 (0.2, 1.3)
EpiChron (Spain)	0	0 (0, 0)	42,607.0	0 (0, 0.9)	<5	0 (0, 0)	42,465.6	0.2 (0, 1.7)
SIDIAP (Spain)	15	0.1 (0, 0.1)	241,338.5	0.6 (0.3, 1.0)	14	0.1 (0, 0.1)	241,179.6	0.6 (0.3, 1.1)

Note: Estimation of confidence intervals differs between vaccinated and unvaccinated, since the unvaccinated estimate is a 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, gender, 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 70. **Cumulative incidence of erythema multiforme 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**

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 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 71. **Forest plot showing incidence rates and 95% confidence intervals for erythema multiforme 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 79. **Matched hazard ratios (HRs) and matched risk differences (RDs) per 10,000 person-years and their 95% CIs for erythema multiforme 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)	Matched RD
Pedianet	NA	NA
NHR	NA	NA
PHARMO	0.50 (0.09, 2.72)	-0.04
EpiChron	NA	-0.02
SIDIAP	1.07 (0.49, 2.34)	-0.01

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

10.3.29. Chilblain-like lesions

Chilblain-like lesions were identified in all data sources except NHR. The incidence rates ranged from 1.4 per 10,000 person-years (95% CI 0.5, 3.1) in EpiChron to 2.6 per 10,000 person-years (95% CI 1.6, 4.0) in PHARMO in the vaccinated cohorts and from 2.0 per 10,000 person-years (95% CI 1.2, 3.4) in PHARMO to 3.5 per 10,000 person-years (95% CI 2.7, 4.6) in SIDIAP in the unvaccinated cohorts. The incidence rate in the vaccinated cohort of Pedianet was 27.1 per 10,000 person-years, but there were only two events, compared with no events in the unvaccinated cohort. The cumulative incidences during the 42-day risk window were less than 0.3 per 10,000 individuals in the vaccinated cohorts and less than 0.5 per 10,000 individuals in the unvaccinated cohorts.

The matched unadjusted HRs were 1.31 (95% CI: 0.67; 2.56) in PHARMO, 0.67 (95% CI: 0.24; 1.87) in EpiChron and 0.65 (95% CI: 0.45; 0.94) in SIDIAP.

Table 80. **Risk estimates (95% CI) per 10,000 person-years (PY) for chilblain-like lesions 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**

Data source	Vaccinated				Unvaccinated			
	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 (Italy)	2	3.1 (0, 7.4)	737.9	27.1 (3.3, 97.9)	0	0 (0, 0)	735.0	NA
NHR (Norway)	NA	NA	NA	NA	NA	NA	NA	NA
PHARMO (Netherlands)	21	0.3 (0.2, 0.4)	79,549.4	2.6 (1.6, 4.0)	16	0.2 (0.1, 0.3)	79,124.8	2.0 (1.2, 3.4)
EpiChron (Spain)	6	0.1 (0, 0.2)	42,577.1	1.4 (0.5, 3.1)	9	0.2 (0.1, 0.4)	42,435.8	2.1 (1.1, 4.1)
SIDIAP (Spain)	55	0.3 (0.2, 0.3)	241,090.8	2.3 (1.7, 3.0)	85	0.4 (0.3, 0.5)	240,930.5	3.5 (2.7, 4.6)

Note: Estimation of confidence intervals differs between vaccinated and unvaccinated, since the unvaccinated estimate is a 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, gender, 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 72. Cumulative incidence of chilblain-like lesions 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

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 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 73. Forest plot showing incidence rates and 95% confidence intervals for chilblain-like lesions 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

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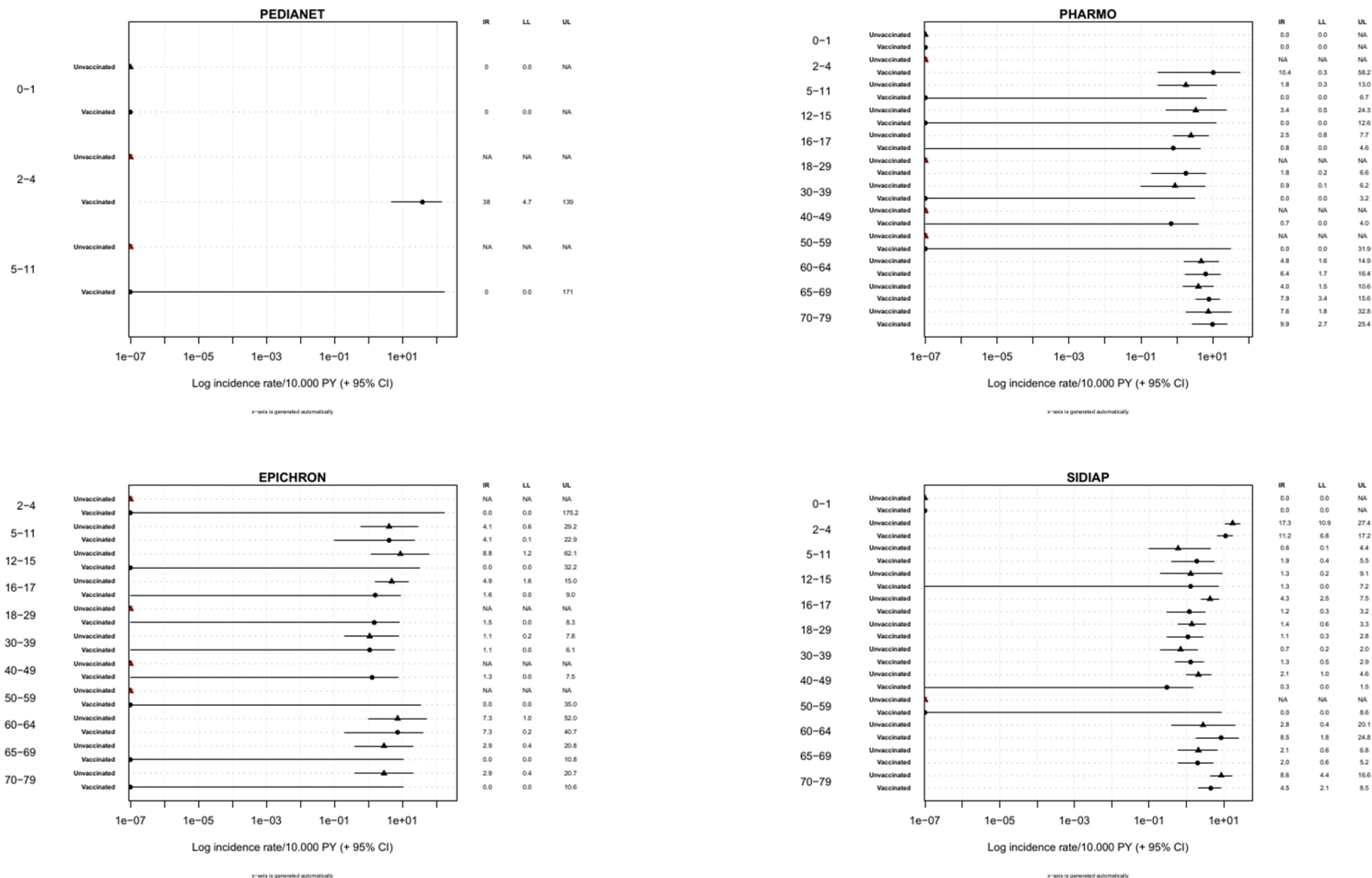
Table 81. **Matched hazard ratios (HRs) and matched risk differences (RDs) per 10,000 person-years and their 95% CIs for chilblain-like lesions within 42 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source**

	Matched HR (95% CI)	Matched RD
Pedianet	NA	NA
NHR	NA	NA
PHARMO	1.31 (0.67, 2.56)	0.07
EpiChron	0.67 (0.24, 1.87)	-0.09
SIDIAP	0.65 (0.45, 0.94)	-0.15

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

10.3.30. Secondary amenorrhea

Secondary amenorrhea events were identified in Pedianet, EpiChron, and SIDIAP. In Pedianet one event was observed in each of the vaccinated and unvaccinated cohorts. The incidence rates were 3.5 per 10,000 person-years (95% CI 0.1, 19.3) in Pedianet, 24.9 per 10,000 person-years (95% CI 23.8, 26.1) in SIDIAP and 25.6 per 10,000 person-years (95% CI 22.9, 28.6) in EpiChron in the vaccinated cohorts. The incidence rates were 3.5 per 10,000 person-years (95% CI 0.5, 24.9) in Pedianet, 15.3 per 10,000 person-years (95% CI 12.6, 18.5) in EpiChron and 24.6 per 10,000 person-years (95% CI 23.1, 26.3) in SIDIAP in the unvaccinated cohorts. The cumulative incidence was around 13 per 10,000 individuals in the vaccinated cohorts and between 7.5 and 12.3 per 10,000 individuals in the unvaccinated cohorts in EpiChron and SIDIAP, respectively.

The incidence rates were assessed only in females in age groups considered to be of child-bearing potential. The matched HR were 1.00 (95% CI: 0.06; 15.89) in Pedianet, 1.68 (95% CI: 1.34; 2.09) in EpiChron and 1.01 (95% CI: 0.93; 1.10) in SIDIAP.

Table 82. Risk estimates (95% CI) per 10,000 person-years (PY) for secondary amenorrhea 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

Data source	Vaccinated				Unvaccinated			
	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 (Italy)	1	1.6 (0, 4.7)	2,889.6	3.5 (0.1, 19.3)	1	1.4 (0, 4.2)	2,856.6	3.5 (0.5, 24.9)
NHR (Norway)	0	0 (0, 0)	478,517.4	0 (0, 0.10)	0	0 (0, 0)	475,551.2	NA
PHARMO (Netherlands)	NA	NA	NA	NA	NA	NA	NA	NA
EpiChron (Spain)	321	13.0 (11.5, 14.5)	125,159.5	25.6 (22.9, 28.6)	189	7.5 (6.0, 9.0)	123,430.7	15.3 (12.6, 18.5)
SIDIAP (Spain)	1,729	12.8 (12.2, 13.4)	693,446.2	24.9 (23.8, 26.1)	1,705	12.3 (11.4, 13.1)	691,862.6	24.6 (23.1, 26.3)

Note: Estimation of confidence intervals differs between vaccinated and unvaccinated, since the unvaccinated estimate is a 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, gender, 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+).

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Figure 74. **Cumulative incidence of secondary amenorrhea 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**
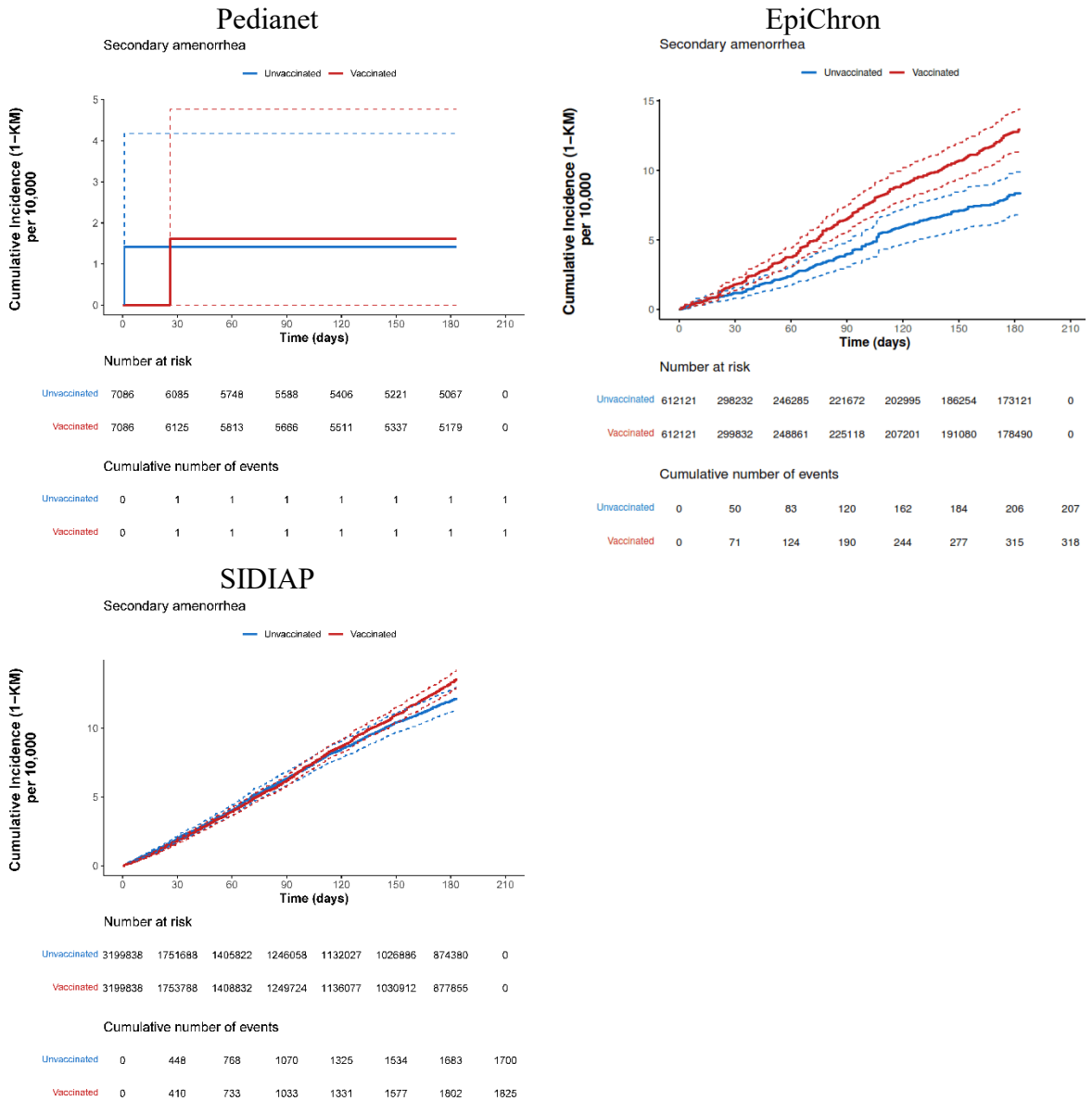
Cumulative incidence curves (1 – Kaplan–Meier risk) starting from the day of administration of the first dose of vaccine. Dotted lines represent 95% confidence intervals. The number at risk at each time point and the cumulative number of events during the 183-day risk window are also shown for each time point. The numerical data correspond to the days indicated by the tick marks on the x-axis.

Figure 75. **Forest plot showing incidence rates and 95% confidence intervals for secondary amenorrhea 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**
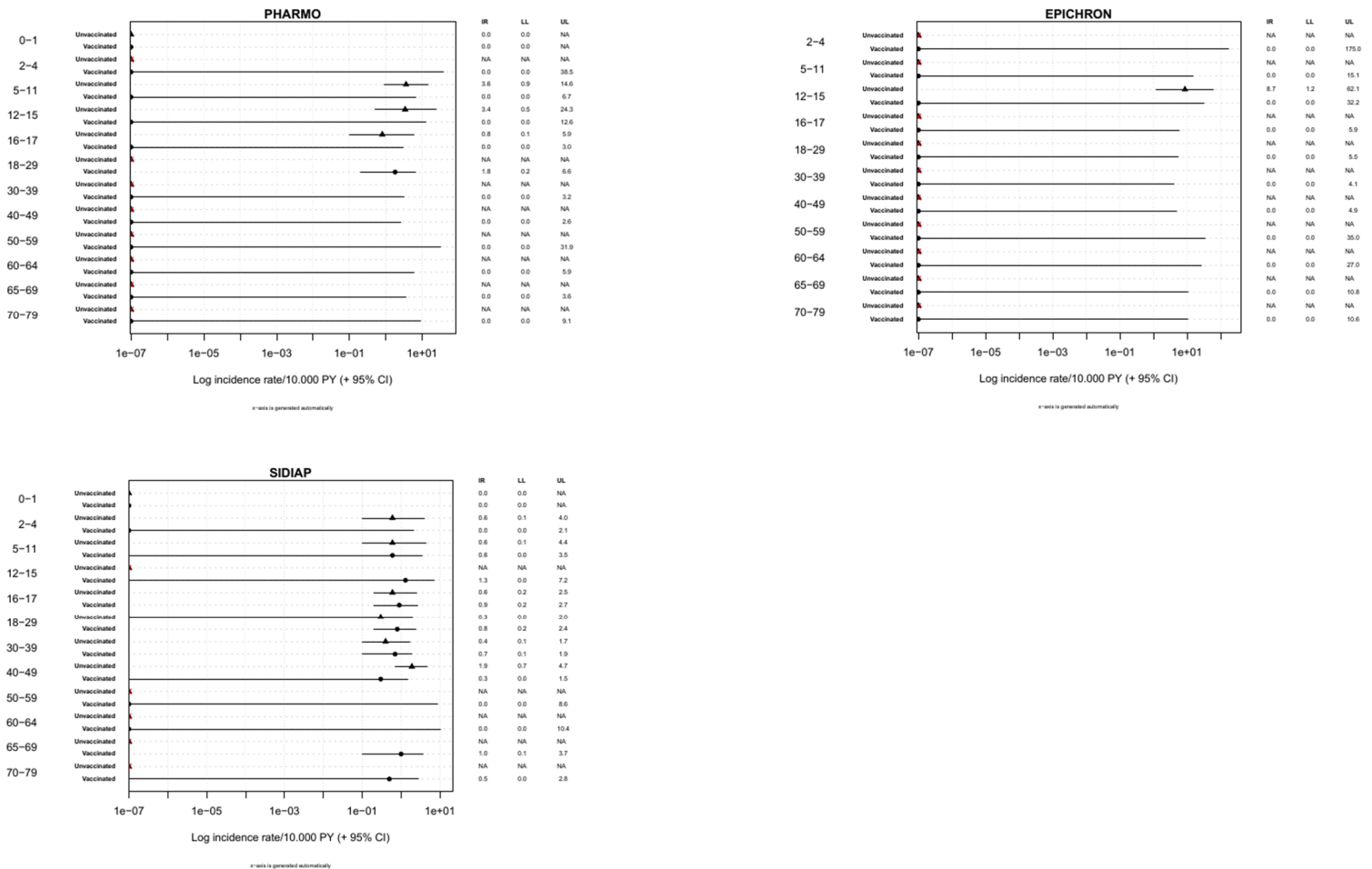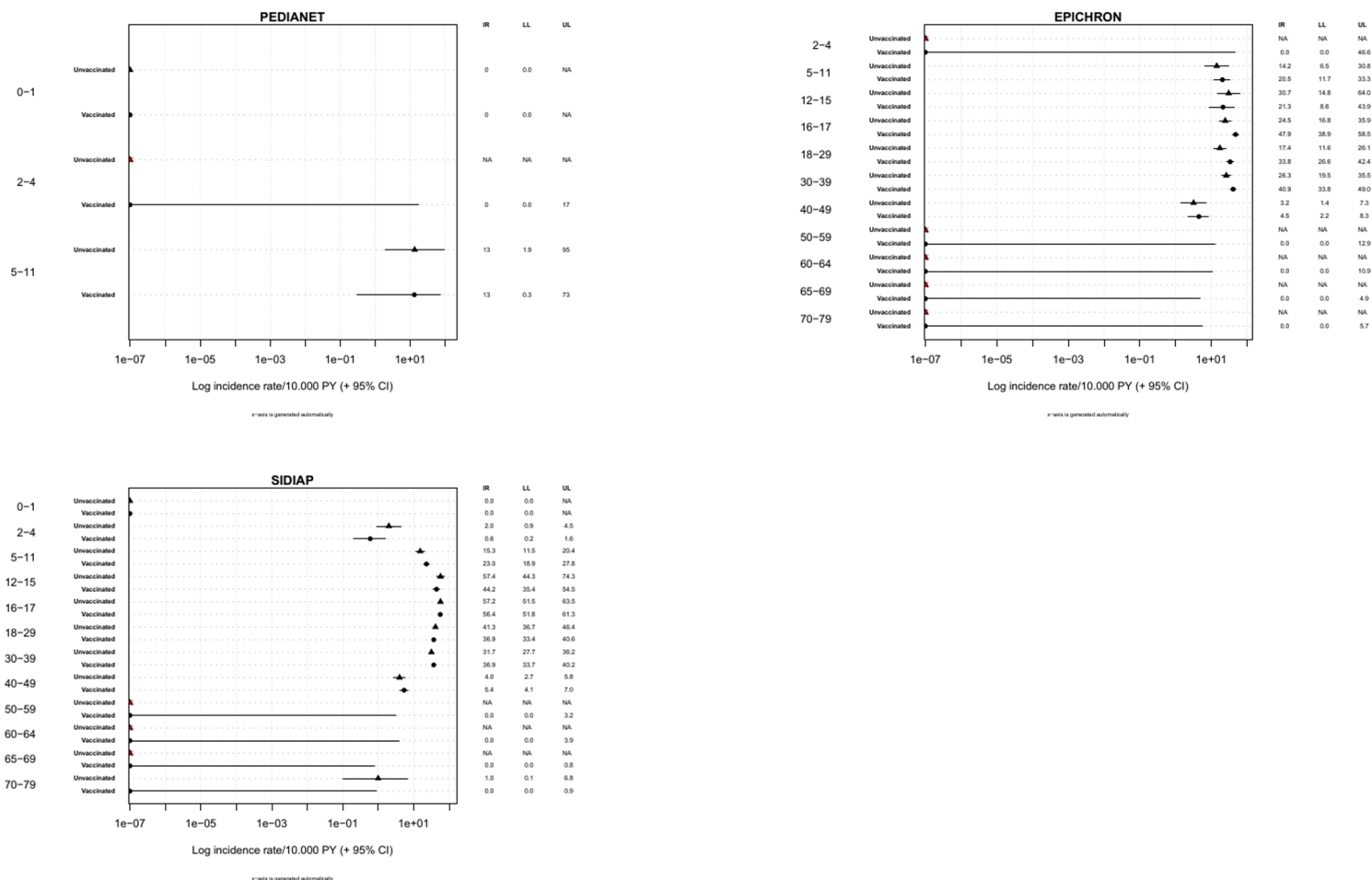
Table 83. **Matched hazard ratios (HRs) and matched risk differences (RDs) per 10,000 person-years and their 95% CIs for secondary amenorrhea within 183 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source**

	Matched HR (95% CI)	Matched RD
Pedianet	1.00 (0.06, 15.89)	0.19
NHR	NA	NA
PHARMO	NA	NA
EpiChron	1.68 (1.34, 2.09)	5.47
SIDIAP	1.01 (0.93, 1.10)	0.54

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

10.3.31. Anosmia, ageusia

Anosmia, ageusia events were identified in all data sources. The incidence rates ranged from 3.9 per 10,000 person-years (95% CI 3.1, 4.7) in NHR to 16.2 per 10,000 person-years (95% CI 12.6, 20.6) in EpiChron in the vaccinated cohorts and from 4.0 per 10,000 person-years (95% CI 3.1, 5.2) in NHR to 27.2 per 10,000 person-years (95% CI.6.8, 108.8) in Pedianet in the unvaccinated cohorts. The cumulative incidence was less than 2 per 10,000 individuals in the vaccinated cohorts and less than 3.5 per 10,000 individuals in the unvaccinated cohorts in all data sources.
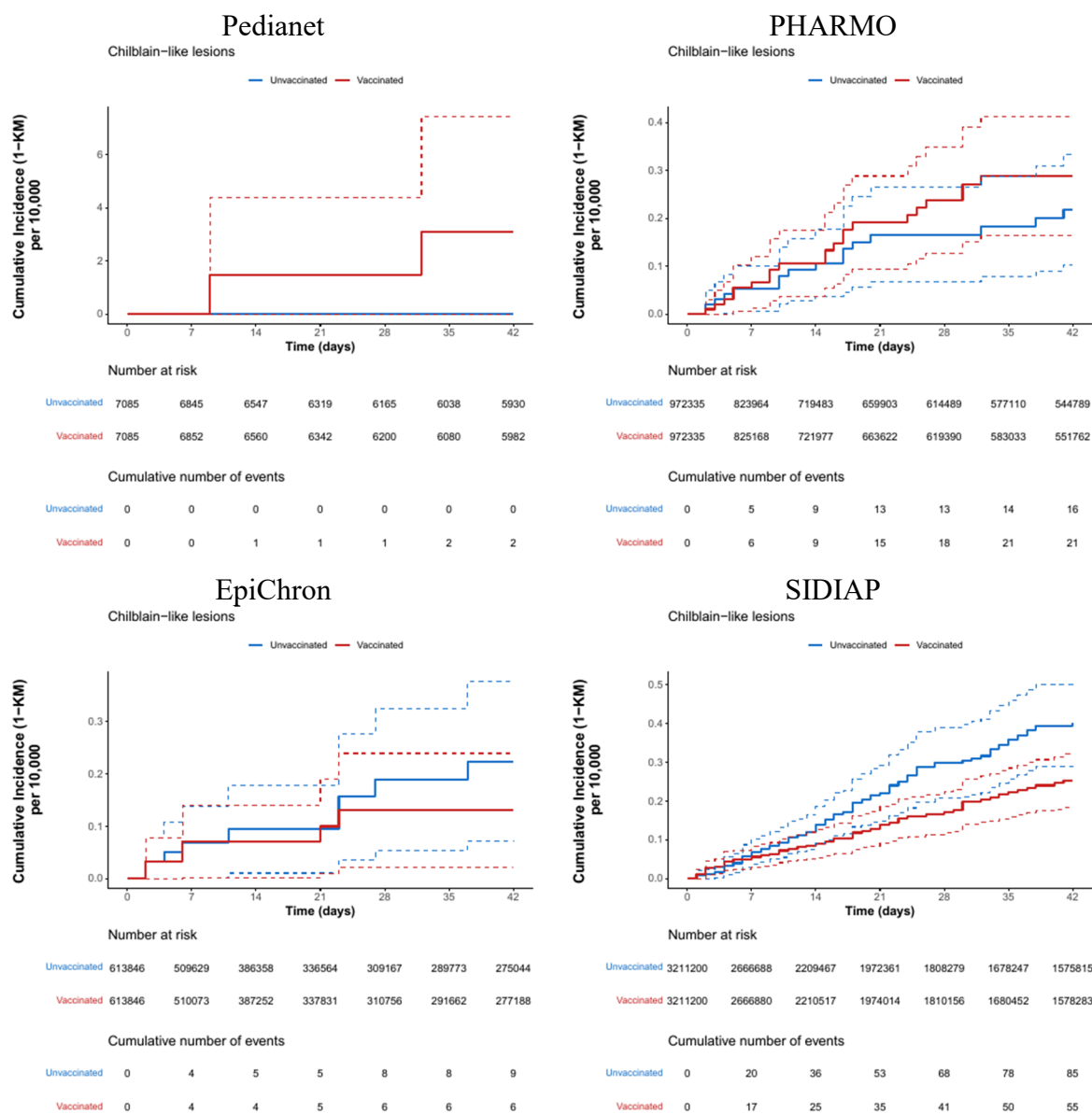
The matched HR for anosmia/ageusia was 0.97 (95% CI: 0.70; 1.34) in NHR, 1.00 (95% CI:0.69; 1.44) in PHARMO, 1.17 (95% CI:0.78; 1.75) in EpiChron and 0.88 (95% CI:0.71; 1.09) in SIDIAP.

Table 84. **Risk estimates (95% CI) per 10,000 person-years (PY) for anosmia, ageusia 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**

Data source	Vaccinated				Unvaccinated			
	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 (Italy)	0	0 (0, 0)	738.40	0 (0, 5)	2	3.1 (0, 7.4)	735.40	27.2 (6.8, 108.8)
NHR (Norway)	93	0.4 (0.3, 0.5)	240,582.90	3.9 (3.1, 4.7)	96	0.5 (0.4, 0.6)	240,292.30	4.0 (3.1, 5.2)
PHARMO (Netherlands)	71	1.0 (0.8, 1.3)	79,532.20	8.9 (7.0, 11.3)	71	1.0 (0.7, 1.3)	79,106.10	9.0 (6.7, 12.0)
EpiChron (Spain)	69	1.8 (1.4, 2.3)	42,483	16.2 (12.6, 20.6)	59	1.6 (1.1, 2.2)	42,342.80	13.9 (1, 19.3)
SIDIAP (Spain)	183	0.8 (0.7, 1.0)	240,974.30	7.6 (6.5, 8.8)	208	1.0 (0.8, 1.2)	240,814.60	8.6 (7.3, 10.2)

Note: Estimation of confidence intervals differs between vaccinated and unvaccinated, since the unvaccinated estimate is a 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, gender, 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+).
LL: lower limit of 95% CI; UL: upper lower limit of 95% CI.

Figure 76. Cumulative incidence of anosmia, ageusia 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 76. Cumulative incidence of anosmia, ageusia 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

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 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 77. **Forest plot showing incidence rates and 95% confidence intervals for anosmia, ageusia 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 77. Forest plot showing incidence rates and 95% confidence intervals for anosmia, ageusia 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
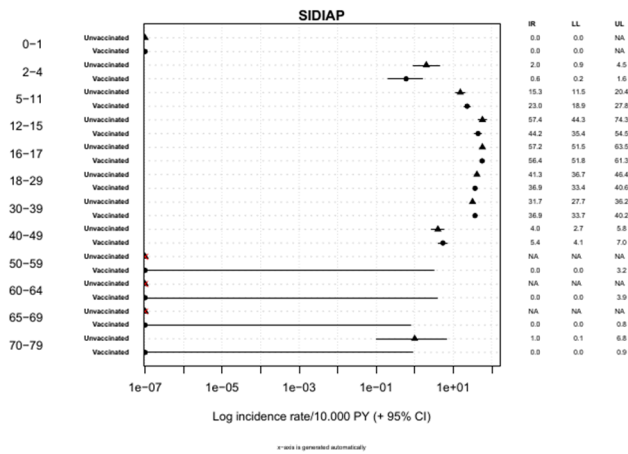
Table 85. **Matched hazard ratios (HRs) and matched risk differences (RDs) per 10,000 person-years and their 95% CIs for anosmia, ageusia within 42 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source**

	Matched HR (95% CI)	Matched RD
Pedianet	NA	NA
NHR	0.97 (0.70, 1.34)	-0.08
PHARMO	1.00 (0.69, 1.44)	0.02
EpiChron	1.17 (0.78, 1.75)	0.20
SIDIAP	0.88 (0.71, 1.09)	-0.15

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

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10.3.32. Anaphylaxis

Anaphylaxis was a rare event in all data sources, with a total of 50 events identified in the vaccinated cohorts and 14 events in unvaccinated cohorts. The prevalence rate was highest in PHARMO. Matched hazard ratios were 3.31 (95% CI: 1.78; 6.15) in PHARMO and 6.00 (95% CI: 0.72; 49.84) in SIDIAP.

Table 86.   Prevalence rate (95% CI) for anaphylaxis within 1 day 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

Data source	Vaccinated				Unvaccinated			
	Events (n)	Cumulative incidence (95% CI)	Person-years (PY)	Prevalence rate (95% CI)	Events (n)	Cumulative incidence (95% CI)	Person-years (PY)	Prevalence rate (95% CI)
Pedianet (Italy)	0	NA	NA	0 (0, 5.4)	0	NA	NA	NA
NHR (Norway)	NA	NA	NA	NA	NA	NA	NA	NA
PHARMO (Netherlands)	43	NA	NA	0.40 (0.30, 0.6)	13	NA	NA	0.1 (0.1, 0.2)
EpiChron (Spain)	<5	NA	NA	0 (0, 0.1)	0	NA	NA	NA
SIDIAP (Spain)	6	NA	NA	0 (0, 0)	<5	NA	NA	0 (0, 0)

Note: Estimation of confidence intervals differs between vaccinated and unvaccinated, since the unvaccinated estimate is a 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, gender, 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 78. Forest plot showing prevalence rates and 95% confidence intervals for anaphylaxis within 1 day 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 87. Matched hazard ratios (HRs) and matched risk differences (RDs) per 10,000 person-years and their 95% CIs for anaphylaxis within 1 day 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)	Matched RD
Pedianet	NA	NA
NHR	NA	NA
PHARMO	3.31 (1.78, 6.15)	0.31
EpiChron	NA	0.02
SIDIAP	6.00 (0.72, 49.84)	0.02

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

10.3.33. Multisystem inflammatory syndrome

Multisystem inflammatory syndrome events were rare and were identified in all data sources except Pedianet. The incidence rates ranged from 0.1 per 10,000 person-years (95% CI 0, 0.7) in PHARMO to 0.9 per 10,000 person-years (95% CI 0.3, 2.4) in EpiChron in the vaccinated cohorts and were 0.2 per 10,000 person-years (95% CI 0.1, 0.5) in NHR, 0.2 per 10,000 person-years (95% CI 0.1, 1.7) in EpiChron and 0.9 per 10,000 person-years (95% CI 0.6, 1.5) in SIDIAP in the unvaccinated cohorts. The cumulative incidences were 0.1 per 10,000 individuals in the vaccinated and unvaccinated cohorts in EpiChron and SIDIAP. The matched HRs were 0.20 (95% CI: 0.02, 1.71) in NHR, 3.98 (95% CI: 0.44; 35.62) in EpiChron and 0.64 (95% CI: 0.31; 1.32) in SIDIAP.

Table 88. **Risk estimates (95% CI) per 10,000 person-years (PY) for multisystem inflammatory syndrome 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**

| Data source	Vaccinated				Unvaccinated			
	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 (Italy)	NA	NA	NA	NA	NA	NA	NA	NA
NHR (Norway)	<5	0 (0, 0)	240,847.8	0 (0, 0.2)	5	0 (0, 0)	240,556.0	0.2 (0.1, 0.5)
PHARMO (Netherlands)	<5	0 (0, 0.1)	79,661.5	0.1 (0, 0.7)	0	0 (0, 0)	79,235.9	NA
EpiChron (Spain)	<5	0.1 (, 0.2)	42,608.8	0.9 (0.3, 2.4)	<5	0 (0, 0.1)	42,467.7	0.2 (0, 1.7)
SIDIAP (Spain)	14	0.1 (, 0.1)	241,351.6	0.6 (0.3, 1.0)	22	0.1 (0, 0.2)	241,192.3	0.9 (0.6, 1.5)

Note: Estimation of confidence intervals differs between vaccinated and unvaccinated, since the unvaccinated estimate is a 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, gender, 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+).
LL: lower limit of 95% CI; UL: upper lower limit of 95% CI.

Figure 79. **Cumulative incidence of multisystem inflammatory syndrome 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**

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 window are also shown for each time point. The numerical data correspond to the days indicated by the tick marks on the x-axis.

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Figure 80. Forest plot showing incidence rates and 95% confidence intervals for multisystem inflammatory syndrome 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
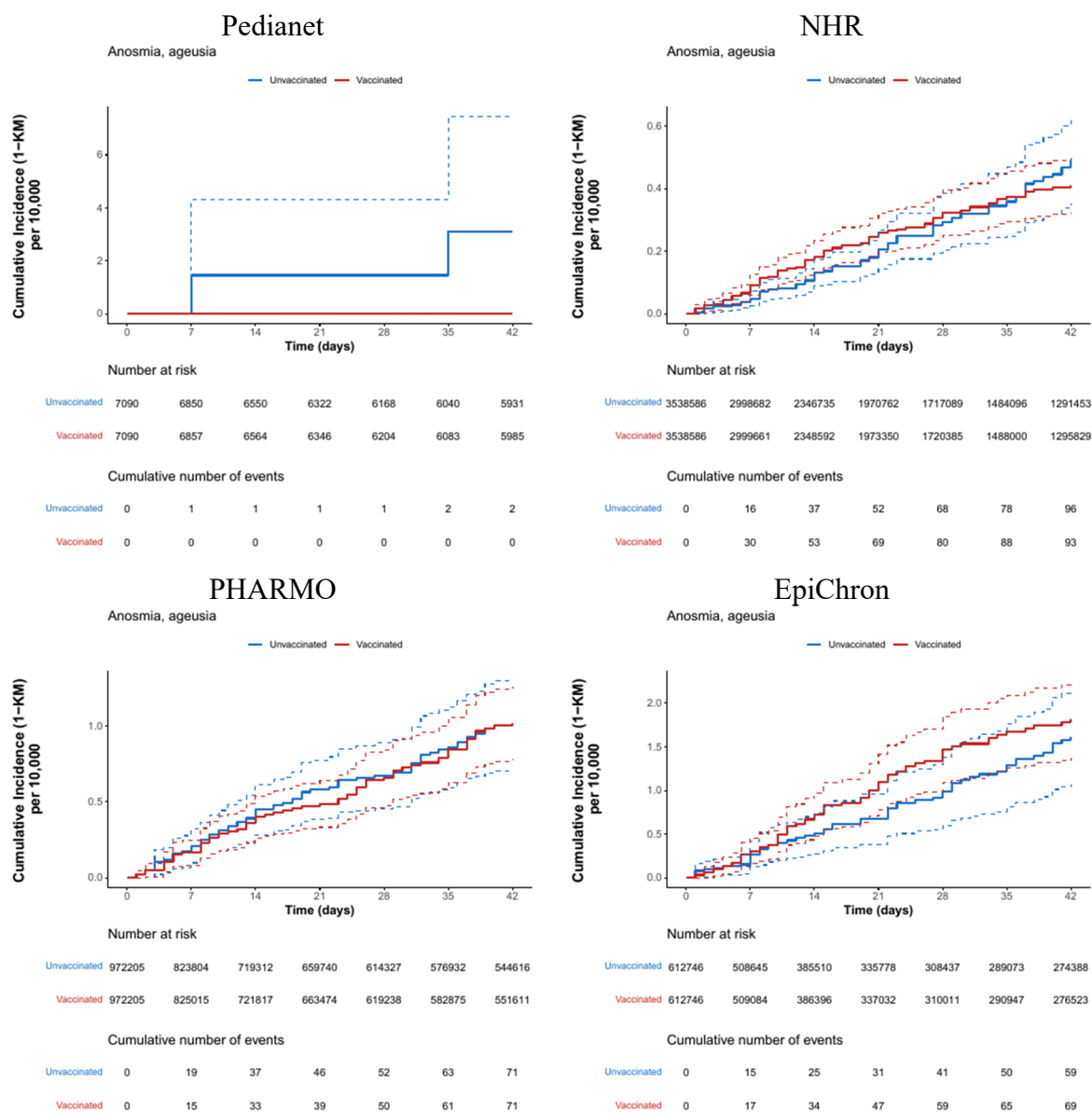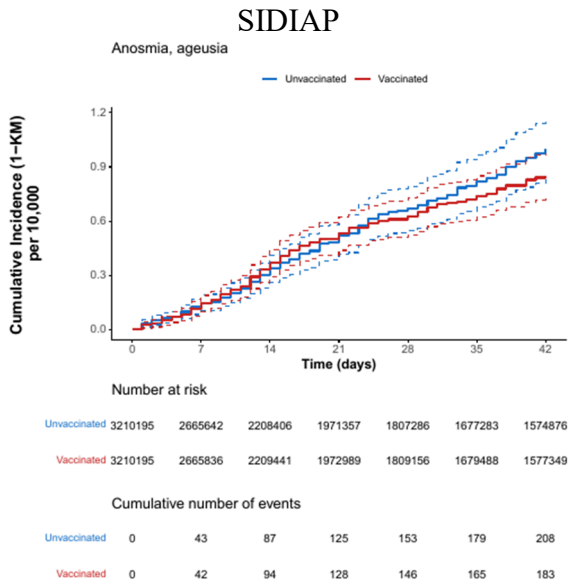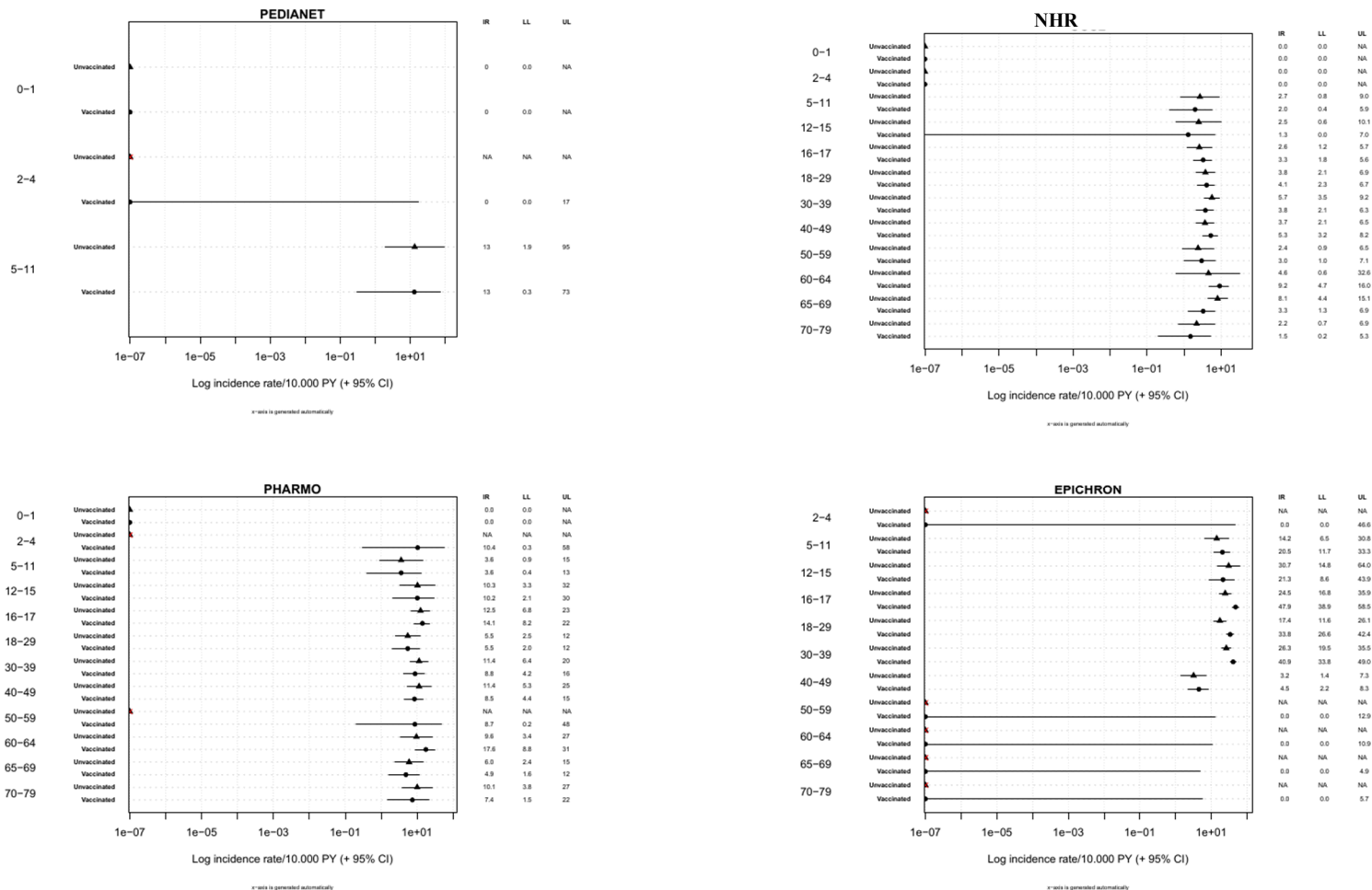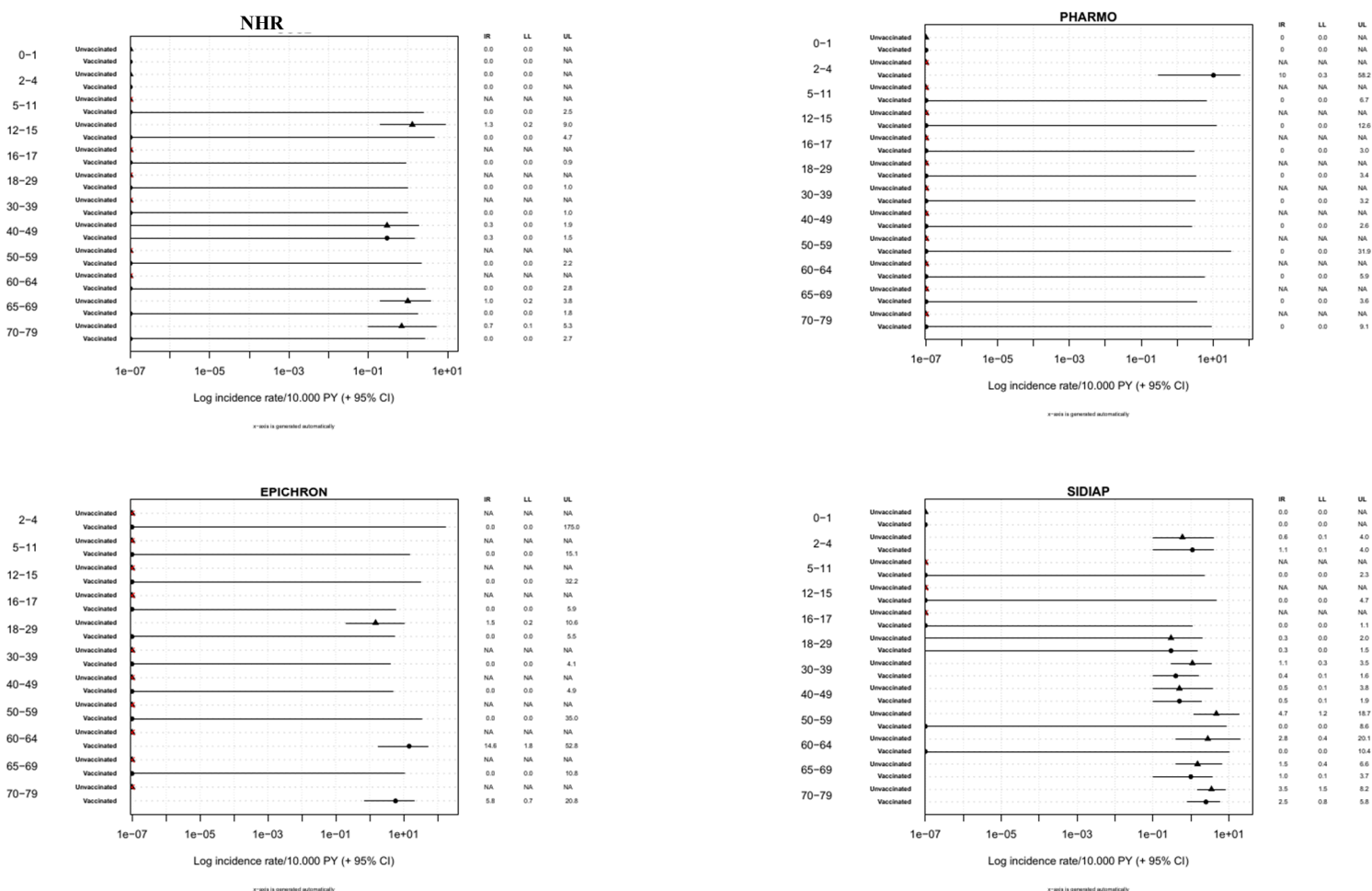
Table 89. Matched hazard ratios (HRs) and matched risk differences (RDs) per 10,000 person-years and their 95% CIs for multisystem inflammatory syndrome within 42 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source

	Matched HR (95% CI)	Matched RD
Pedianet	NA	NA
NHR	0.20 (0.02, 1.71)	-0.02
PHARMO	NA	0.02
EpiChron	3.98 (0.44, 35.62)	0.09
SIDIAP	0.64 (0.31, 1.32)	-0.03

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

10.3.34. Death (any cause)

Deaths (any cause) were identified in all data sources. Pedianet reported one death in the vaccinated cohort. The cumulative incidences in the vaccinated cohorts ranged from 34.9 per 10,000 individuals (95% CI 32.6, 37.2) in PHARMO to 590.4 per 10,000 individuals (95% CI 525.9, 654.5) in NHR and from 82.5 per 10,000 individuals (95% CI 78.1, 86.8) in PHARMO to 839.3 per 10,000 individuals (95% CI 735.4, 941.9) in NHR in the unvaccinated cohorts.

The incidence rates ranged from 38.1 per 10,000 person-years (95% CI 36.1, 40.2) in PHARMO to 155.2 per 10,000 person-years (95% CI 152.7, 157.8) in SIDIAP in the vaccinated cohorts and from 109.1 per 10,000 person-years (95% CI 103.9, 114.6) in PHARMO to 222.6 per 10,000 person-years (95% CI 215.3, 230.3) in NHR in the unvaccinated cohorts. In PHARMO the cumulative incidence of deaths remained constant from day 150 onwards, as more deaths may not have been registered yet.

The incidences of death (any cause) were highest in the oldest age groups. The matched unadjusted HRs were 0.49 (95% CI: 0.47; 0.51) in NHR, 0.35 (95% CI: 0.33; 0.38) in PHARMO, 0.55 (95% CI: 0.51; 0.60) in EpiChron and 0.99 (95% CI: 0.96; 1.02) in SIDIAP.

Table 90. **Risk estimates (95% CI) per 10,000 person-years (PY) for death (any cause) 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)**

Data source	Vaccinated				Unvaccinated			
	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 (Italy)	1	1.9 (0, 5.5)	3,878.5	2.6 (0.1, 14.4)	0	0 (0, 0)	3,833.6	NA
NHR (Norway)	5,623	590.4 (525.9, 654.5)	509,660.4	110.3 (107.5, 113.3)	11,234	839.3 (735.4, 941.9)	504,574.7	222.6 (215.3, 230.3)
PHARMO (Netherlands)	1,322	34.9 (32.6, 37.2)	346,865.0	38.1 (36.1, 40.2)	3,680	82.5 (78.1, 86.8)	337,237.8	109.1 (103.9, 114.6)
EpiChron (Spain)	1,395	68.5 (64.6, 72.4)	191,778.8	72.7 (69.0, 76.7)	2,475	111.4 (103.5, 119.3)	187,152.7	132.2 (123.9, 141.2)
SIDIAP (Spain)	14,429	223.9 (219.4, 228.5)	929,451.1	155.2 (152.7, 157.8)	14,533	171.1 (165.5, 176.6)	927,611.9	156.7 (152.8, 160.6)

Note: Estimation of confidence intervals differs between vaccinated and unvaccinated, since the unvaccinated estimate is a 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, gender, 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+).
LL: lower limit of 95% CI; UL: upper lower limit of 95% CI.

Figure 81. **Cumulative incidence of death (any cause) 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)**
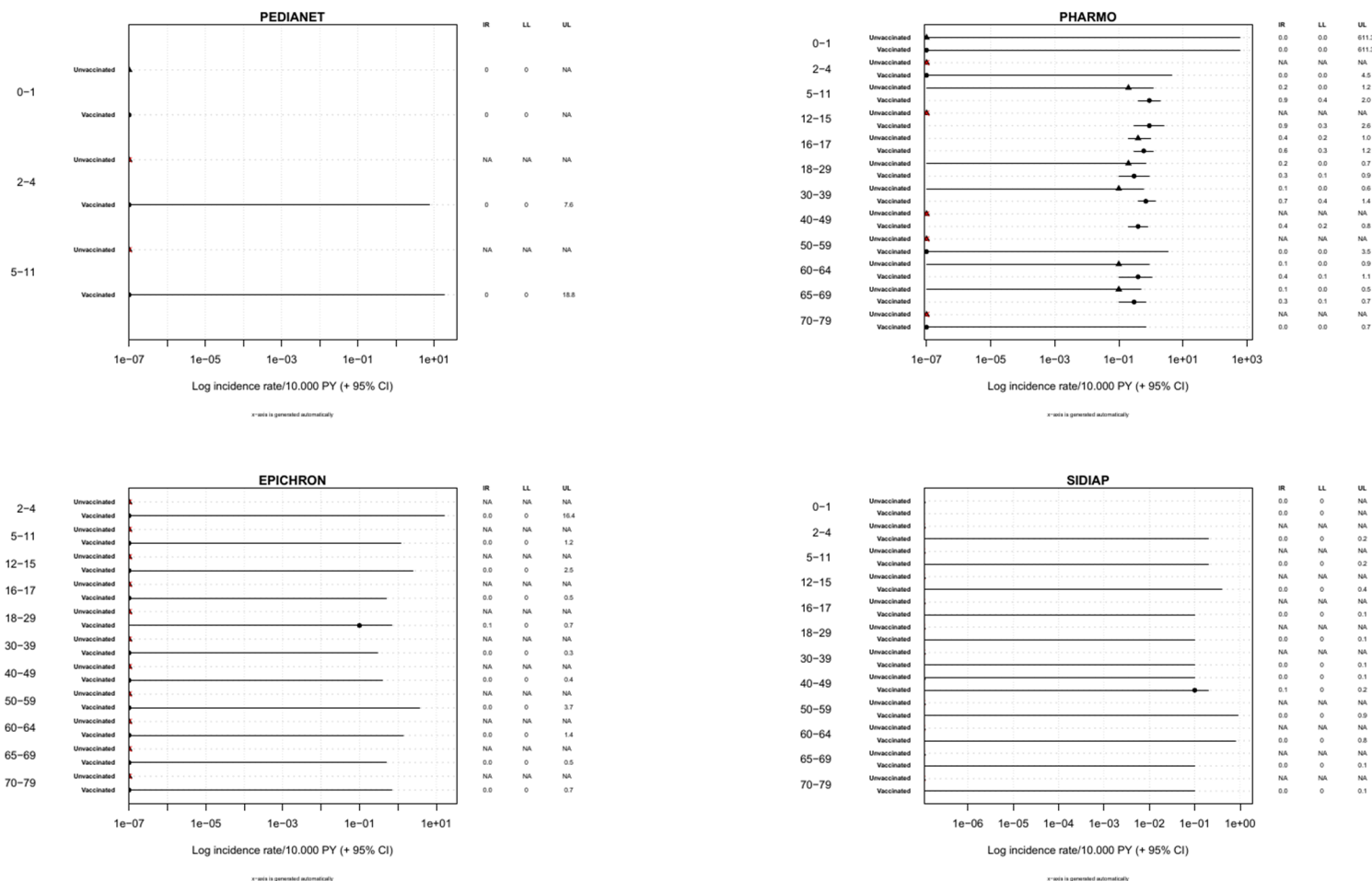
Figure 81. **Cumulative incidence of death (any cause) among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source (risk window: 365 days after dose 1)**
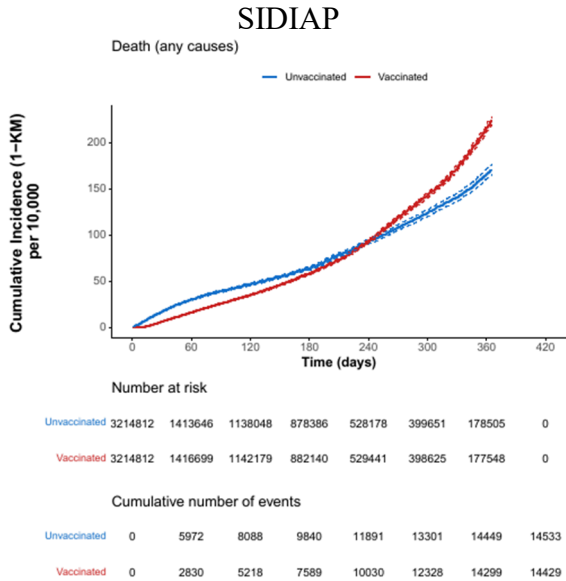
Cumulative incidence curves (1 – Kaplan–Meier risk) starting from the day of administration of the first dose of vaccine. Dotted lines represent 95% confidence intervals. The number at risk at each time point and the cumulative number of events with the 365-day risk interval are also shown for each time point. The numerical data correspond to the days indicated by the tick marks on the x-axis.

Figure 82. Forest plot showing incidence rates and 95% confidence intervals for death (any cause) 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 82. **Forest plot showing incidence rates and 95% confidence intervals for death (any cause) 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)**
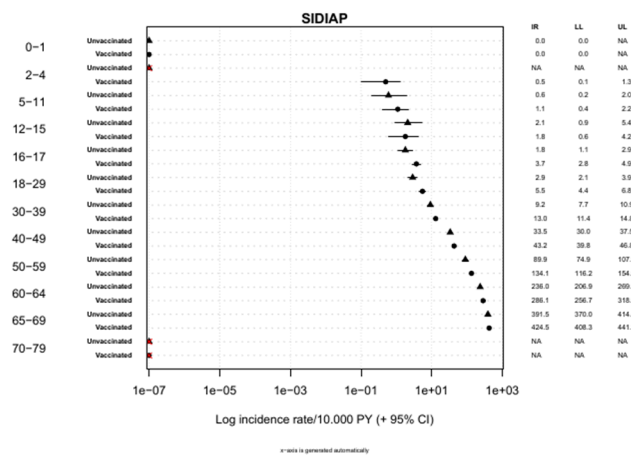
Table 91. Matched hazard ratios (HRs) and matched risk differences (RDs) per 10,000 person-years and their 95% CIs for death (any cause) among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source (risk window: 365 days after dose 1)

	Matched HR (95% CI)	Matched RD
Pedianet	NA	NA
NHR	0.49 (0.47, 0.51)	-248.89
PHARMO	0.35 (0.33, 0.38)	-47.57
EpiChron	0.55 (0.51, 0.60)	-42.91
SIDIAP	0.99 (0.96, 1.02)	52.88

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

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10.3.35. Subacute thyroiditis

Subacute thyroiditis events were identified in all data sources but no events were reported in Pedianet or NHR. The incidence rates 0.1 per 10,000 person-years (95% CI 0, 0.2) in PHARMO, 1.6 per 10,000 person-years (95% CI 1.1, 2.3) in EpiChron and 3.0 per 10,000 person-years (95% CI 2.7, 3.4) in SIDIAP in the vaccinated cohorts and 0.1 per 10,000 person-years (95% CI 0, 0.4) in PHARMO, 1.4 per 10,000 person-years (95% CI 0.8, 2.3) in EpiChron and 3.2 per 10,000 person-years (95% CI 2.7, 3.8) in SIDIAP in the unvaccinated cohorts. The cumulative incidence during the 42-day risk window was less than 3.5 per 10,000 individuals in the vaccinated cohorts and less than 3 per 10,000 individuals in the unvaccinated cohorts.

The incidence of acute thyroiditis was highest in older age groups in both the vaccinated and unvaccinated cohorts. The matched HRs were 0.98 (95% CI: 0.09; 10.88) in PHARMO, 1.17 (95% CI: 0.63; 2.15) in EpiChron and 0.95 (95% CI: 0.78; 1.16) in SIDIAP.

Table 92. **Risk estimates (95% CI) per 10,000 person-years (PY) for subacute thyroiditis 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)**

Data source	Vaccinated				Unvaccinated			
	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 (Italy)	0	0 (0, 0)	3,878.5	0 (0, 9.5)	0	0 (0, 0)	3,833.6	NA
NHR (Norway)	0	0 (0, 0)	509,660.4	0 (0, 0.1)	0	0 (0, 0)	504,574.7	NA
PHARMO (Netherlands)	<5	0 (0, 0.1)	346,859.0	0.1 (0, 0.2)	<5	0.1 (0, 0.2)	337,232.6	0.1 (0, 0.4)
EpiChron (Spain)	31	1.4 (0.9, 2.0)	191,715.2	1.6 (1.1, 2.3)	26	1.2 (0.6, 1.8)	187,098.2	1.4 (0.8, 2.3)
SIDIAP (Spain)	281	3.2 (2.7, 3.7)	928,888.7	3.0 (2.7, 3.4)	296	2.9 (2.3, 3.4)	927,043.3	3.2 (2.7, 3.8)

Note: Estimation of confidence intervals differs between vaccinated and unvaccinated, since the unvaccinated estimate is a 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, gender, 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 83. Cumulative incidence of subacute thyroiditis 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 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 84. Forest plot showing incidence rates and 95% confidence intervals for subacute thyroiditis 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
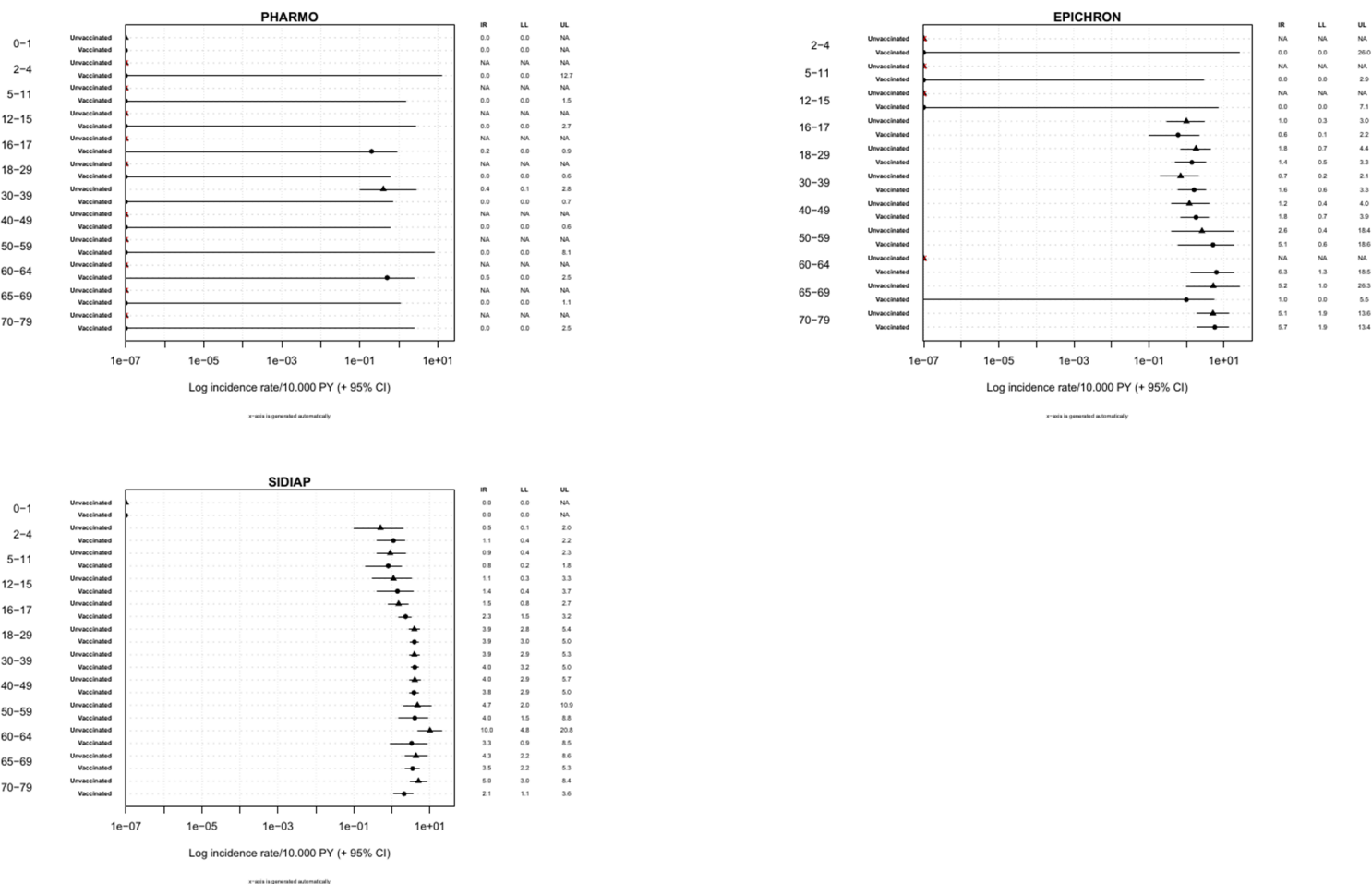
Table 93. **Matched hazard ratios (HRs) and matched risk differences (RDs) per 10,000 person-years and their 95% CIs for subacute thyroiditis within 365 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source**

	Matched HR (95% CI)	Matched RD
Pedianet	NA	NA
NHR	NA	NA
PHARMO	0.98 (0.09, 10.88)	-0.01
EpiChron	1.17 (0.63, 2.15)	0.22
SIDIAP	0.95 (0.78, 1.16)	0.33

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

10.3.36. Sudden death

Sudden death (based on diagnostic codes of sudden death) during a 365-day risk window were identified in NHR, PHARMO and EpiChron. The incidence rates in the vaccinated cohorts were 2.1 per 10,000 person-years (95% CI 1.8, 2.6) in NHR and 0.1 per 10,000 person-years (95% CI 0, 0.3) in PHARMO (no events in the EpiChron vaccinated cohort). The incidence rates in the unvaccinated cohorts were 0.2 per 10,000 person-years (95% CI 0.1, 0.6) in PHARMO, 0.2 per 10,000 person-years (95% CI 0, 0.7) in EpiChron and 2.9 per 10,000 person-years (95% CI 2.2, 3.8) in NHR. The cumulative incidence was less than 1 per 10,000 individuals in the vaccinated and unvaccinated cohorts.

The matched HRs were 0.72 (95% CI: 0.52; 1.01) in NHR and 0.42 (95% CI: 0.09; 1.92) in PHARMO.

Table 94.   Risk estimates (95% CI) per 10,000 person-years (PY) for sudden death 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)
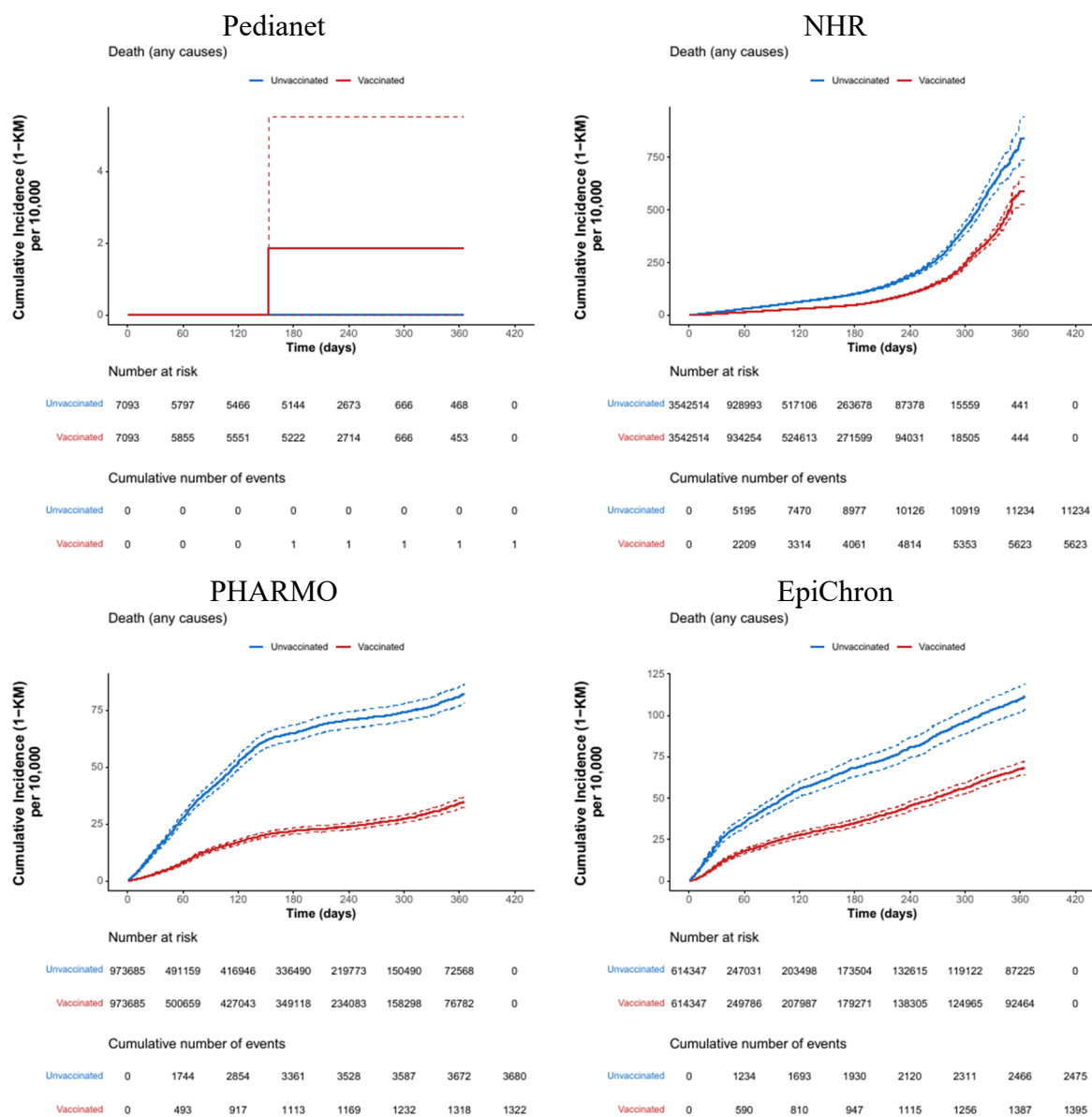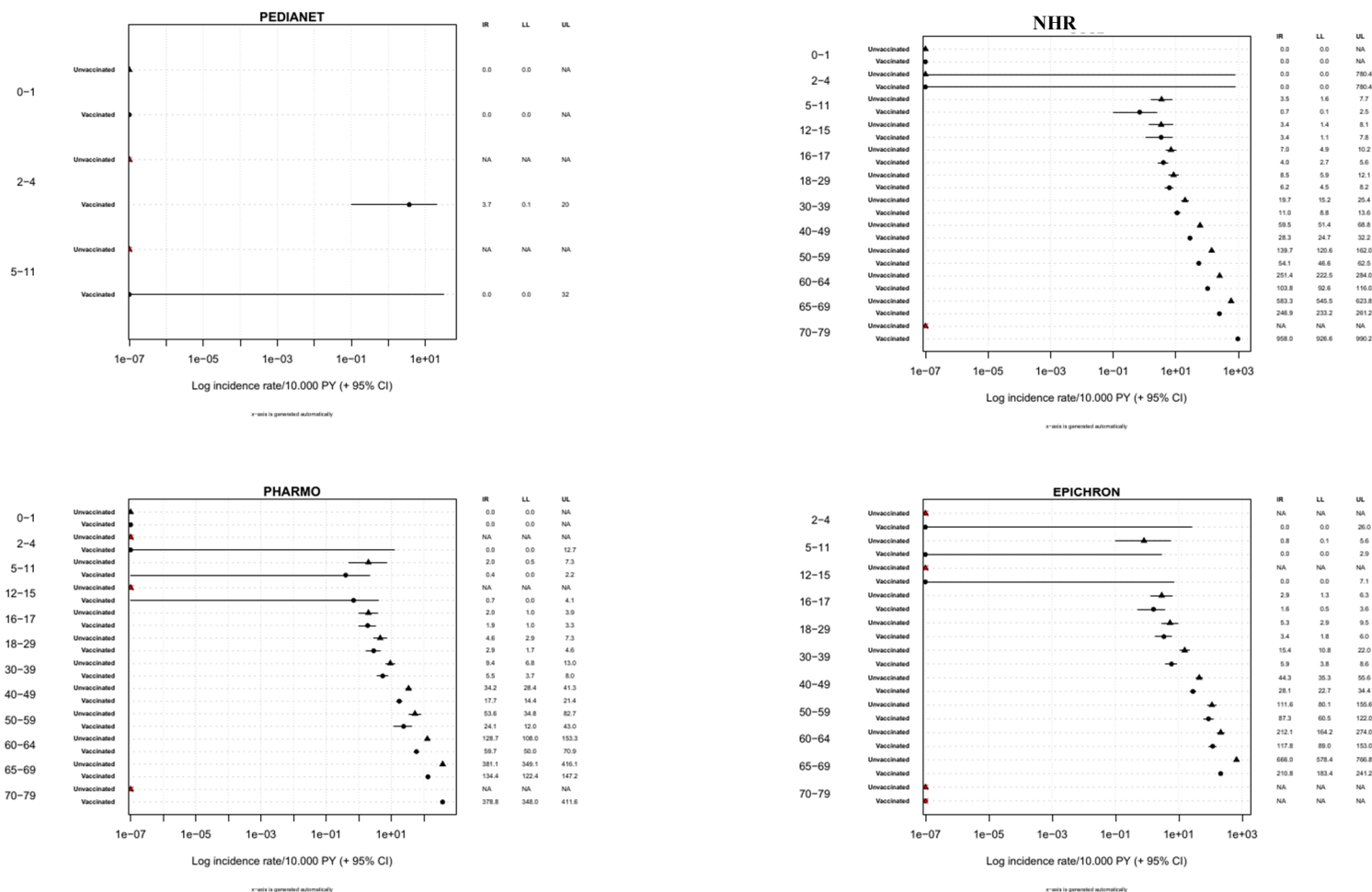
Data source	Vaccinated				Unvaccinated			
	Events (n)	Cumulative incidence (95% CI)	Person-years (PY)	Incidence rate (95% CI)	Events (n)	Cumulative incidence (95% CI)	Person-years (PY)	Incidence rate (95% CI)
Pedianet (Italy)	NA	NA	NA	NA	NA	NA	NA	NA
NHR (Norway)	109	7.4 (4.1, 10.8)	509,570.5	2.1 (1.8, 2.6)	146	20.2 (3.5, 36.8)	504,481.8	2.9 (2.2, 3.8)
PHARMO (Netherlands)	<5	0.1 (0, 0.1)	346,864.8	0.10 (0, 0.3)	7	0.2 (0, 0.5)	337,237.2	0.2 (0.1, 0.6)
EpiChron (Spain)	0	0 (0, 0)	191,778.8	0 (0, 0.2)	<5	0.2 (0, 0.5)	187,152.7	0.2 (0, 0.7)
SIDIAP (Spain)	NA	NA	NA	NA	NA	NA	NA	NA

Note: Estimation of confidence intervals differs between vaccinated and unvaccinated, since the unvaccinated estimate is a 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, gender, 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+).

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Figure 85. Cumulative incidence of sudden death 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)

NHR

Sudden death

— Unvaccinated — Vaccinated

Cumulative Incidence (1–KM) per 10,000

Number at risk

Unvaccinated	3541929	928843	517006	263601	87332	15551	441	0
Vaccinated	3541929	934102	524518	271526	93994	18500	444	0

Cumulative number of events

Unvaccinated	0	53	89	109	129	141	146	146
Vaccinated	0	51	66	78	95	106	109	109

PHARMO

Sudden death

— Unvaccinated — Vaccinated

Cumulative Incidence (1–KM) per 10,000

Number at risk

Unvaccinated	973685	491159	416946	336489	219772	150489	72568	0
Vaccinated	973685	500659	427043	349117	234083	158298	76782	0

Cumulative number of events

Unvaccinated	0	1	1	3	5	7	7	7
Vaccinated	0	2	2	3	3	3	3	3

EpiChron

Sudden death

— Unvaccinated — Vaccinated

Cumulative Incidence (1–KM) per 10,000

Number at risk

Unvaccinated	614347	247031	203498	173504	132615	119122	87225	0
Vaccinated	614347	249786	207987	179271	138305	124965	92464	0

Cumulative number of events

Unvaccinated	0	0	0	0	2	3	3	3
Vaccinated	0	0	0	0	0	0	0	0

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.

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Figure 86. Forest plot showing incidence rates and 95% confidence intervals for sudden death 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)
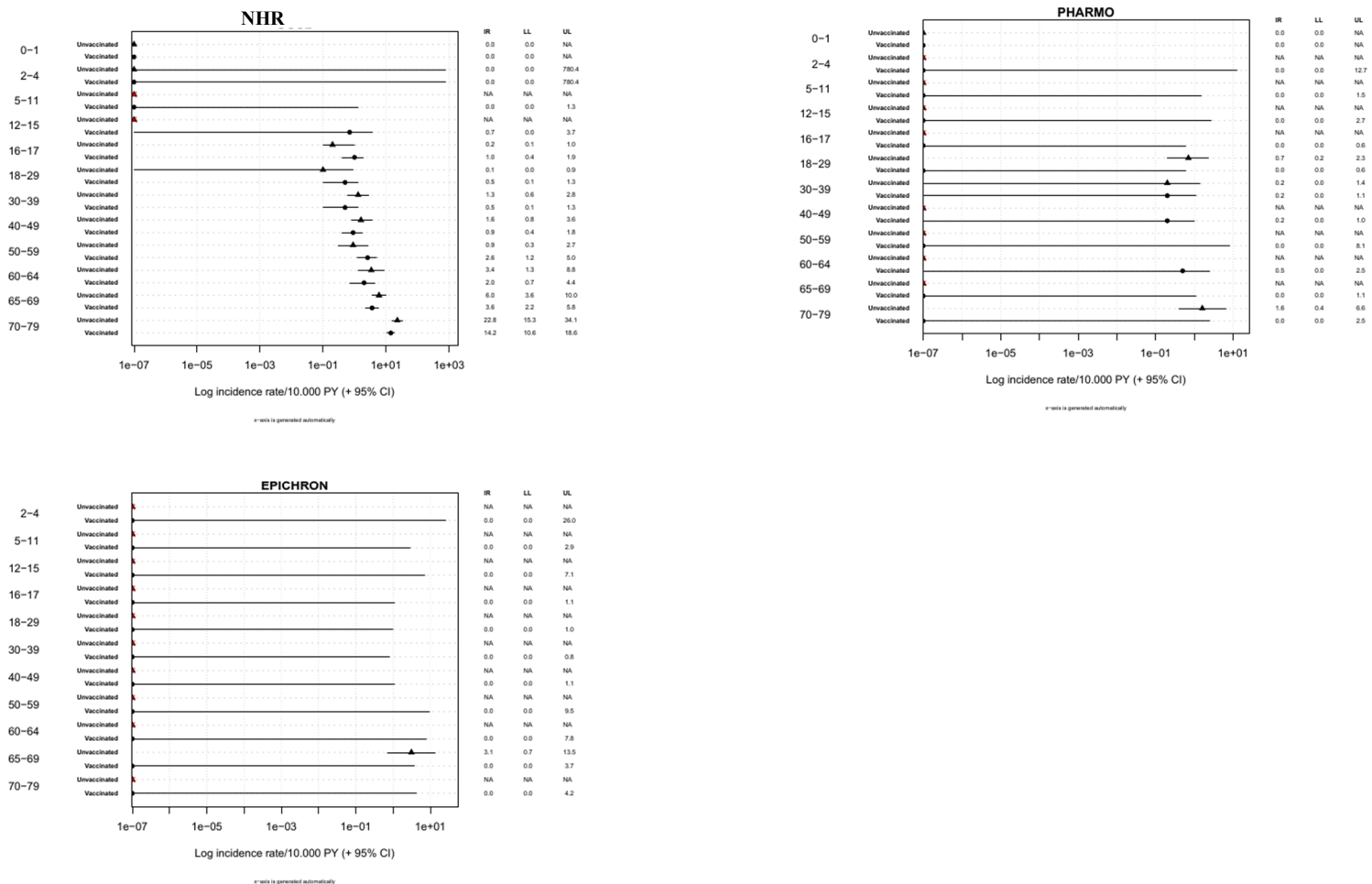
Table 95. **Matched hazard ratios (HRs) and matched risk differences (RDs) per 10,000 person-years and their 95% CIs for sudden death among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source (risk window: 365 days after dose 1)**

	Matched HR (95% CI)	Matched RD
Pedianet	NA	NA
NHR	0.72 (0.52, 1.01)	-12.77
PHARMO	0.42 (0.09, 1.92)	-0.17
EpiChron	NA	NA
SIDIAP	NA	NA

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

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10.3.37. Vaccine-associated enhanced disease (VAED)

It was not possible to assess VAED in the unvaccinated cohort. We, therefore, used severe COVID-19 disease as a proxy for VAED and this could only be assessed in NHR and PHARMO,

Table 96. **Risk estimates (95% CI) per 10,000 person-years (PY) for vaccine-associated enhanced disease (VAED) within any time 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**

Data source	Vaccinated				Unvaccinated			
	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)
NHR (Norway)	131	18.3 (10.4, 26.3)	509,607.50	2.6 (2.1, 3.1)	502	78.0 (55.2, 100.8)	504,522.90	9.9 (8.5, 11.7)
PHARMO (Netherlands)	23,716	732.5 (722.1, 742.8)	301,778.50	785.9 (775.9, 795.9)	25,527	801.2 (786.8, 815.6)	291,913.40	874.5 (860.0, 889.2)

Note: Estimation of confidence intervals differs between vaccinated and unvaccinated, since the unvaccinated estimate is a 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, gender, 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 87. Cumulative incidence of vaccine-associated enhanced disease (VAED) within any time 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
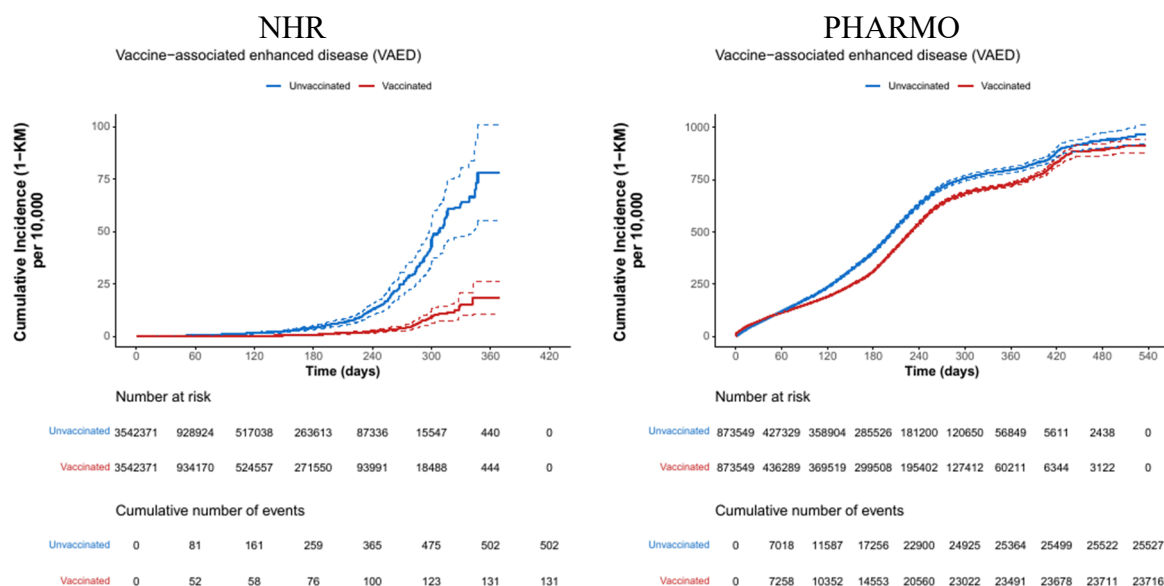
Cumulative incidence curves (1 – Kaplan–Meier risk) starting from the day of administration of the first dose of vaccine. Dotted lines represent 95% confidence intervals. The number at risk at each time point and the cumulative number of events within any time after start of follow-up are also shown for each time point. The numerical data correspond to the days indicated by the tick marks on the x-axis.

Figure 88. Forest plot showing incidence rates and 95% confidence intervals for vaccine-associated enhanced disease (VAED) within any time 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
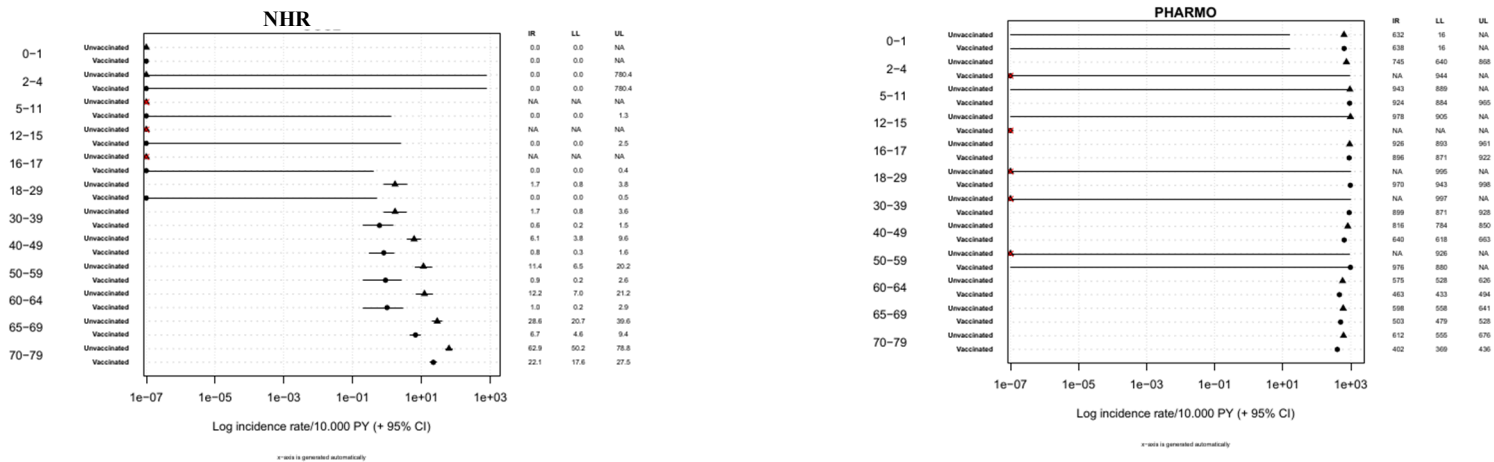
10.4. Other analyses

None

10.5. Adverse events / adverse reactions

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

This study involves a combination of existing structured data and unstructured data, which was 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 third interim report provides updated results on the estimated incidence rates (IRs) and hazard ratios (HRs) for 35 prespecified AESIs 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. These data are from five data sources in four countries; Pedianet in Italy, PHARMO in the Netherlands, NHR in Norway and SIDIAP and EpiChron in Spain, that passed the quality checks. No data from the UK (CRPD) were included because the data extraction with all the covariates included for this report took longer than expected due to CPRD server capacity issues which will be resolved for the next interim report. No new data from ARS could be extracted and analysed for the third interim report because of national and regional re-assessment of their ability to provide public data to PASS studies.

In this report we included data up until mid-year 2022 (i.e., June/July/August depending on data source) except for NHR, which included data up to end of 2021 as the data for 2022 will only be available in Q2 2023. In this third interim report, we have used all matching criteria and verified the balance between the matched vaccinated and unvaccinated cohorts. Importantly, we also matched on pregnancy status (except in PHARMO, because no pregnancy linkage is currently available and Pedianet which is a paediatric database only) using a pregnancy algorithm developed by the ConcePTION project. We used a negative control outcome, i.e., COVID-19 disease in the first 12 days after time zero to check if any residual confounding was present and, therefore, if there was a need to adjust the estimates using weights based on the propensity score. 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.

These results should still be considered as interim results from a long-term safety surveillance study. For this third data extraction we included extraction, transformation and harmonisation of outcomes and some covariates. Limitations from prior reports have been identified and issues corrected, when possible. We will continue to work on resolving issues for the fourth interim report.

11.1.1. Important information on data sources

Three data sources could not contribute data to this third interim report: CPRD from the UK and ARS and HSD from Italy:

- Although data from CPRD were reported in the first interim report, they could not be included for this third interim report, since the extraction of the updated data with all the covariates took longer than expected due to CPRD server capacity issues and infrastructure development issues. In addition, there was also a CPRD data quality issue affecting data availability that was declared by CPRD in January 2023, which required a re-extraction of data.

- Data from ARS were reported in the first and second interim report but could not re-extract data due to national and regional re-assessment 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 (Italian GP databases) data source, and it was, therefore, not considered as 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 for the coming six-monthly updates. However, we cannot exclude the possibility that recording of vaccine brand may be selective. We will monitor data in HSD on vaccine uptake to assess whether data are fit for purpose.

In the other data sources, data for events may originate from different data sources (GP, emergency visits, hospital discharge data sources). This may have an impact on the estimates for the incidence rates as shown in a recent study.[15]

Pedianet is a pediatric 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 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 the reason why Pedianet could not contribute data for all AESIs.

NHR contributed data for the first time in this third interim analysis. The data access provider has not received data from all the requested data sources yet, as the hospitalisation data were not available. Hence the data for the events for this report are based on outpatient visits only.

The data in this third interim report from PHARMO were extracted from GP records only, as for the previous reports. The coding system used in the PHARMO databanks is ICPC, which is not as granular as ICD coding, and therefore free text identification of AESIs was conducted. The identification algorithms have not yet been validated, which may result in more misclassification than in other data sources, but this will be investigated before the next interim report. 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 EpiChron data sources included diagnosis codes from general practitioners and from hospital discharges up to July 2022 for this third interim report.

The SIDIAP data source included diagnosis codes from general practitioners and from hospital discharges, and data up to June 2022 were included in this third interim report. However, because of differences in lag times in different data banks and delays in

notifications about hospitalisations, these data for the end of the follow-up period may be incomplete.

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 decreased from 10.3 million for the second interim (8.4 million 1st interim report) to 8,644,088 individuals in this third interim report. This decrease is due to inability to include updated data from ARS and CPRD. A total of 7,127,423 (82.3%) individuals received a second dose of the Pfizer-BioNTech COVID-19 vaccine. The second dose was mainly administered within six weeks following the first dose; 14.17% individuals had an interval of more than six weeks between the first and second doses. The percentage of individuals with a longer interval between the first and second doses was highest in Norway (28.1%), where the COVID-19 vaccination campaign prioritised the administration of first doses to a large percentage of the population, before administrating the second dose. In other data sources the percentage of individuals who had an interval longer than six weeks between the first and second doses varied between 2.6 and 13.4%.

A total of 1,948,651 individuals had a recorded third dose of the Pfizer vaccine which is 22.5% of the persons who received a 1st dose. The mean age of these individuals was higher than those who had received at least a first dose (except PHARMO), reflecting the targeted roll out of booster doses to elderly individuals first. At the time of database lock, 6,784 individuals had received a fourth dose of the Pfizer-BioNTech COVID-19 vaccine. The interval between the second and third doses varied between data sources with the median interval ranging from 21 weeks in Pedianet to 29 weeks in EpiChron and SIDIAP. A total of 26,814 pregnant women received a first dose of the Pfizer-BioNTech COVID-19 vaccine and satisfied the inclusion criteria. Among these women 12,753 (67.71%) received the dose during their first trimester of pregnancy and 2,643 in their second trimester.

11.1.3. Matched cohorts

In this third 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, pregnancy, immunocompromised status, pre-existing conditions considered as risk factors for severe COVID-19 disease by the Centers for Disease Control and Prevention (CDC) and socio-economic status.

From a total of 8,655,088 individuals who received a first dose of the Pfizer-BioNTech COVID-19 vaccine, 8,352,451 (96.5%) could be matched with an unvaccinated individual. Many individuals who were initially included in the matched unvaccinated cohort subsequently received a 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. 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 follow-up time after the first dose was extended for most data sources and varied between 1 month in NHR to 7.5 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. The median age of vaccinated individuals was highest in PHARMO (50 years), followed by EpiChron (48 years), NHR (47 years), and SIDIAP (45 years). The median age in Pedianet, a paediatric database, was 10 years, with only a few children under 5 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 EpiChron and SIDIAP, and the healthcare use indicators showed a similar distribution in the vaccinated and unvaccinated cohorts. This should be interpreted cautiously because of the high percentage of missing data for these variables.

Some data sources had missing data on other vaccines (SIDIAP, PHARMO), but these data will be included in the next interim report. 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 8 million vaccinated and 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%.

The third interim data and results are an improvement compared with those in the first two interim reports, in terms of size, follow-up and harmonisation of AESIs, as well as the first inclusion of many covariates, and more detailed matching on pre-specified covariates.

11.1.4. Incidence rates and hazard ratios for AESIs

In comparison with the second interim report, the codelists of AESIs were thoroughly 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.

Negative control

To assess baseline exchangeability, we compared the incidences of COVID-19 disease in the first 12 days after vaccination in the vaccinated and unvaccinated cohorts. In NHR, EpiChron and SIDIAP the differences for the incidences were not greater than 1 per 1000 individuals. In PHARMO and Pedianet differences were 5 and 2 per 1,000 but not suggestive of confounding. Consequently, we considered that the matching process achieved the required

balance between the cohorts, and the analyses could be performed in the matched cohorts without further adjustments.

AESIs with long time window (1 year) in SIDIAP

The cumulative incidence curves for a series of cardiovascular and metabolic AESIs with a risk window of 365 days in SIDIAP show a differentiation in risk between the vaccinated and unvaccinated cohorts that occurred after day 100. This was observed for acute cardiovascular injury, arrhythmia, heart failure, stress cardiomyopathy, coronary artery disease, acute liver injury and acute kidney injury. This finding, which was not observed in any of the other data sources for these outcomes, has not been reported in the literature and it is not expected under the actual knowledge on the safety of the vaccines. The fact that this was observed for most of the cardiovascular and metabolic outcomes with a long risk window is suggestive of a particular characteristic of the database, including data collection and management that is currently being investigated. This finding has been communicated to the Scientific Advisory Board whose member agree with our interpretation and encourage investigators to further analyse the data.

Guillain-Barré syndrome

The age-specific background rates for Guillain-Barré syndrome published in the ACCESS database are between 0.5 per 100,000 person-years for individuals under 19 years of age and 10 per 100,000 person-years in those 70-79 years of age. It also shows that rates are higher when using in-patient diagnosis codes as compared with GP only.[15] In the vaccinated cohorts, the IRs ranged from 0 per 10,000 person-years (95% CI: 0–0.9) in EpiChron to 0.3 per 10,000 person-years (95% CI: 0.1; 0.6) in SDIAP and from 0.1 per 10,000 person-years (95% CI: 0.0; 0.9) in PHARMO to 0.7 per 10,000 person-years (95% CI: 0.2; 2.2) in EpiChron in the unvaccinated cohorts. The cumulative incidence was below 1 per 10,000 individuals in both cohorts in all data sources. Due to the low number or absence of cases in Epichron, PHARMO and Pedianet, age-related effects on incidence were only observed in SIDIAP, with greater incidence at higher age, consistent with the known epidemiology. The matched hazard ratio for GBS in SIDIAP was 1.75 (95% CI 0.51, 5.97) and 0.99 (95% CI 0.06, 15.96) in PHARMO. No differences were observed in the incidence of Guillain-Barré syndrome between the vaccinated and unvaccinated cohorts during the risk window.

Acute disseminated encephalomyelitis

Acute disseminated encephalomyelitis was a very rare event. Only one case was observed in the vaccinated cohort in SIDIAP therefore, the incidence was very rare (1 per 10,000 person-years), which is consistent with published background rates in the ACCESS report, that reported age-specific rates were below 1 per 10,000 person-years in each age group. The acute disseminated encephalomyelitis rates in ACCESS showed that rates are substantially higher when in-patient data are used. Rates were lower in GP data sources only.

Narcolepsy

The incidence rates in the vaccinated cohorts were 0.2 (95% CI 0, 1.3) per 10,000 person-years in EpiChron and 0.2 (95% CI 0, 0.4) per 10,000 person-years in SIDIAP and 0.3 per 10,000 person-years in the unvaccinated cohort in SIDIAP, which is consistent with published background rates in the ACCESS report, that showed that age-specific rates varied from 0.1 to 3 per 100,000 person-years with a high rate of 6 per100,000 person-years in Denmark for individuals aged 20-29 years of age. The ACCESS data also showed that the incidence rates are highest in data sources with GP and outpatient data, the rate is lower in data sources with only in-hospital data. No differences were observed for the incidence of narcolepsy in the vaccinated and unvaccinated cohorts during 42 days of follow-up.

Acute aseptic arthritis

No specific codes for acute aseptic arthritis were available and therefore a broad definition was applied including possible (more sensitive) codes, which means that the event included cases of new arthritis and gout. This broad definition produced incidence rates of acute aseptic arthritis that ranged from 13.5 per 10,000 person-years (95% CI 0.3, 75.4) in Pedianet, which has data for children up to 14 years old, to 51.5 per 10,000 person-years (95% CI: 48.6; 54.4) in SIDIAP in the vaccinated cohorts and from 37.30 per 10,000 person-years (95% CI 32.3; 42.9) in PHARMO to 52.50 (95% CI 48.6; 56.8) in NHR in the unvaccinated cohort. The cumulative incidence during the 42-day risk window was below 7 per 10,000 individuals in the vaccinated and unvaccinated cohorts. No differences were observed for the incidence of acute aseptic arthritis between the vaccinated and unvaccinated cohorts during the 42 days risk window, all HR were around 1 and confidence intervals were narrow. ACCESS did not report IRs for acute aseptic arthritis for PHARMO, Pedianet, or SIDIAP because it focused on the narrow definition only, for which there are no codes.

Diabetes mellitus type 1

Diabetes mellitus type 1 was observed in both the vaccinated and unvaccinated cohorts in all data sources. The IRs in the vaccinated cohorts ranged from 0 per 10,000 person-years (95% CI 0, 9.5) in Pedianet to 9.1 per 10,000 person-years (95% CI 8.2, 9.9) in NHR and from 0.9 per 10,000 person-years (95% CI 0.5, 1.4) in PHARMO to 7.8 (95% CI 6.7, 9.2) per 10,000 person-years in NHR in the unvaccinated cohort.

The cumulative incidence (1-KM) per 10,000 individuals at any time during follow-up was constant over time in the vaccinated and unvaccinated cohorts. The incidence was stable over different age groups. The matched HRs were 1.16 0.70 (95% CI: 0.96; 1.38) in NHR, 0.70 (95% CI: 0.37; 1.34) in PHARMO, 0.69 (95% CI: 0.42; 1.14) in EpiChron, and 1.75 (0.51, 5.97) in SIDIAP, but were not significantly elevated.

Based on the age-related incidence we observed diabetes mellitus type 1 is likely to be misclassified by having included type 2 diabetes, since type 2 diabetes is more common in adults than type 1 diabetes.[17,18] For the fourth interim report, we will create an algorithm

with insulin medication as inclusion, and presence of non-insulin glucose lowering agents as an exclusion.

(Idiopathic) thrombocytopenia:

(Idiopathic) thrombocytopenia was observed in the vaccinated and unvaccinated cohorts in all data sources, with no events in Pedianet and NHR. The incidence rates in the vaccinated cohorts varied between 1.4 per 10,000 person-years in PHARMO and 17.3 per 10,000 person-years in SIDIAP and between 1.1 per 10,000 person-years in PHARMO and 18.1 per 10,000 person-years in SIDIAP in the unvaccinated cohorts. The cumulative incidence (1-KM) per 10,000 individuals at any time during follow-up showed a constant increase in incidence over the risk window time and was less than 2.5 per 10,000 individuals in the vaccinated and unvaccinated cohorts after 42 days. The matched HRs were 1.22 (95% CI: 0.50; 2.94) in PHARMO, 0.53 (95% CI: 0.32; 0.88) in EpiChron, and 0.96 1 (95% CI: (0.82: 1.11) in SIDIAP.

We are exploring why (idiopathic) thrombocytopenia rates in EpiChron were half the rates in SIDIAP. The ACCESS data showed that the incidence rates of thrombocytopenia increased rapidly with increasing age. The IRs were below 10 per 10,000 person-years below 50 years of age and increased to 50 per 10,000 person-years in those aged 80 years and older. The IRs were highest in SIDIAP, which is consistent with the study findings in this third interim report. The identification of thrombocytopenia events is based on laboratory testing, but for this report we only used diagnostic codes to identify the event, but for next reports we may explore use of laboratory data as well, which will improve our ability to identify idiopathic thrombocytopenia. SIDIAP, EpiChron, PHARMO, Pedianet and CPRD all have access to laboratory results. The ACCESS data showed that inclusion of GP data is important for the incidence rates.

Thrombotic thrombocytopenia syndrome (TTS)

Thrombotic thrombocytopenia syndrome (TTS) is a condition that is defined as the occurrence of a venous or arterial thrombotic event and thrombocytopenia within 10 days of the occurrence of a thrombotic event. It is a rarely occurring event which was observed in the vaccinated and unvaccinated cohorts in EpiChron and SIDIAP. The incidence rates in the vaccinated cohorts varied between 1.5 per 10,000 person-years in EpiChron and 2.1 per 10,000 person-years in SIDIAP and between 1.3 per 10,000 person-years in SIDIAP and 6.1 per 10,000 person-years in EpiChron in the unvaccinated cohorts. The cumulative incidence was less than 1 per 10,000 individuals in both the vaccinated and unvaccinated cohorts over a 15-day risk window after dose 1. Due to the low number of cases no clear patterns of age-related differences in incidences could be observed in either the vaccinated or unvaccinated cohorts in the forest plots. The matched HRs were 0.25 (95% CI 0.05; 1.20) in EpiChron and 1.64 (95% CI: 0.82; 3.29) in SIDIAP. No significant differences were observed in the incidence of TTS between the vaccinated and unvaccinated cohorts in the data sources that could identify the events.

Acute cardiovascular injury

Acute cardiovascular injury events were observed in both the vaccinated and unvaccinated cohorts in all data sources, except in Pedianet (only children). The incidence rates in the vaccinated cohorts varied between 41.3 per 10,000 person-years in PHARMO and 180.8 per 10,000 person-years in NHR and between 47.2 per 10,000 person-years in PHARMO and 185.4 per 10,000 person-years in NHR in the unvaccinated cohorts.

The incidence of acute cardiovascular injury (including microangiopathy, heart failure, stress cardiomyopathy, coronary artery disease, arrhythmia) was higher among older age groups in all data sources, both in the vaccinated and unvaccinated cohorts. The matched HRs were 0.97 (95% CI: 0.94; 1.01) in NHR, 0.88 (95%CI: 0.80; 0.96) in PHARMO, 0.94 (95% CI: 0.86; 1.03) in EpiChron and 1.14 (95% CI: 1.09; 1.18) in SIDIAP. The cumulative incidence curves show that the differentiation in risk of ACI between vaccinated and non-vaccinated occurs after day 100 in SIDIAP. As mentioned above this finding was observed only in SIDIAP but not in the data sources participating in this study and has not been reported in the literature, what is suggestive of a particular characteristic of the database, including data collection and management that is currently being investigated.

Arrhythmia

Arrhythmia is part of the acute cardiovascular injury event, but is also included separately.

Arrhythmia events were reported observed in vaccinated and unvaccinated cohorts in all data sources bases. The incidence rates in the vaccinated cohorts varied between 20.7 per 10,000 person-years in Pedianet (children only) and 244.8 per 10,000 person-years in NHR and between 21.0 per 10,000 person-years in Pedianet and 231.7 per 10,000 person-years in NHR in the unvaccinated cohorts. Rates were comparable to those reported in ACCESS, which also showed the strong age relationship, and the impact of having both primary care and hospital data in PHARMO.

The cumulative incidences over 365 days of follow-up in the vaccinated cohorts varied between 14.5 per 10,000 person-years in Pedianet and 273.5 per 10,000 person-years in NHR and between 17 per 10,000 person-years in Pedianet and 269.8 per 10,000 person-years in NHR in the unvaccinated cohorts.

The incidence rates were generally higher among older age groups. The matched unadjusted HRs were 0.99 (95% CI: 0.30; 3.27) in Pedianet, 1.06 (95%: CI 1.02; 1.09) in NHR, 1.04 (95% CI: 0.98; 1.10) in PHARMO, 1.19 (95% CI: 1.11; 1.29) in EpiChron and 1.21 (95% CI: 1.17; 1.25) in SIDIAP.

Heart failure

Heart failure is part of the acute cardiovascular injury event, but is also included separately.

The incidence rates of heart failure in the vaccinated cohorts varied between 15.6 per 10,000 person-years in PHARMO and 63.0 per 10,000 person-years in NHR and between 19.8 per 10,000 person-years in PHARMO and 76.9 per 10,000 person-years in NHR in the unvaccinated cohorts. The cumulative incidence within one year after dose 1, showed a separation between vaccinated and non-vaccinated in all data sources. The matched HRs were 0.82 (95% CI; 0.76: 0.87) in NHR, 0.79 (95% CI; 0.69; 0.91) in PHARMO, 0.90 (95% CI; 0.79: 1.03) in EpiChron, and 1.29 (95% CI; 1.22; 1.36) in SIDIAP

Stress cardiomyopathy

Stress cardiomyopathy is part of the acute cardiovascular injury event, but is also included separately.

Stress cardiomyopathy was a very rare event in the three data sources in which events could be identified (i.e., PHARMO, EpiChron, and SIDIAP). The incidence rates of stress cardiomyopathy in the vaccinated cohorts varied between 0.1 per 10,000 person-years in PHARMO and 0.6 per 10,000 person-years in SIDIAP and between 0.1 per 10,000 person-years in PHARMO and 0.4 per 10,000 person-years in SIDIAP in the unvaccinated cohorts, which is consistent with the results from ACCESS where it was also showed that stress cardiomyopathy could only be detected in data sources with hospitalisation data.

The cumulative incidence within one year after dose 1 was less than 1 per 10,000 person-years in both cohorts in all three data sources. The incidence of stress cardiomyopathy was higher in the age groups over 40 years. The matched HRs for stress cardiomyopathy were 0.73 (95% CI: 0.14; 3.75) in PHARMO, 1.63 (95% CI: 0.39; 6.78) in EpiChron and 1.53 (95% CI: 0.88; 2.64) in SIDIAP. The ACCESS data showed that the incidence was underestimated when relying on GP data only, which is consistent with our findings

Coronary artery disease

Coronary artery disease was reported in both the vaccinated and unvaccinated cohorts in all data sources, except Pedianet. The incidence rates in the vaccinated cohorts varied between 13.4 per 10,000 person-years in PHARMO and 118.1 per 10,000 person-years in NHR and between 13.0 per 10,000 person-years in PHARMO and 120.2 per 10,000 person-years in NHR in the unvaccinated cohorts. These IRs are similar to those reported in ACCESS. No differences were observed in the incidence of coronary artery disease in the vaccinated and unvaccinated cohorts.

The incidence of coronary artery disease was higher in older age groups in all data sources, in both the vaccinated and unvaccinated cohorts. The matched unadjusted HRs of coronary artery disease was 0.98 (95% CI: 0.93; 1.03) in NHR, 1.04 (95% CI: 0.88; 1.22) in PHARMO, 0.86 (95% CI: 0.74; 1.00) in Epichron and 1.15 (95% CI: 1.08; 1.22) in SIDIAP.

Myocarditis

For the 7-day risk window after start of follow-up (dose 1), the incidence rates in the vaccinated cohorts varied from 0 per 10,000 person-years in SIDIAP to 1.2 per 10,000 person-years in PHARMO and between 0 per 10,000 person-years in EpiChron and 2.3 per 10,000 person-years in PHARMO in the unvaccinated cohorts. The cumulative incidences during the 7-day risk window were below 1 per 10,000 individuals in both cohorts in each data source. Age-related changes in incidence could not be clearly observed over the 7-day period. The matched HRs were 0.57 in NHR and 0.50 in PHARMO, with 95% CIs that included 1.

In the 14-day risk window after start of follow-up, the incidence rates in the vaccinated cohorts varied from 0.5 per 10,000 person-years in EpiChron to 0.9 per 10,000 person-years in NHR, and between 0.3 per 10,000 person-years in SIDIAP and 2.2 per 10,000 person-years in PHARMO in the unvaccinated cohorts. The cumulative incidence was below 1 per 10,000 individuals in both cohorts in all data sources. The incidence was higher in age groups over 17 years. The matched HRs were 0.91 (95% CI: 0.34; 2.45) for NHR, 0.29 (95% CI: 0.06; 1.44) for PHARMO and 2.0 (95% CI: 0.50; 7.99) in SIDIAP

In the 21-day risk window, the incidence rates in the vaccinated cohorts varied between 0.4 per 10,000 person-years in SIDIAP and PHARMO and 1.2 per 10,000 person-years in EpiChron and between 0.4 per 10,000 person-years in SIDIAP and 1.8 per 10,000 person-years in PHARMO in the unvaccinated cohorts. The cumulative incidence was below 1 per 10,000 individuals in both cohorts in all data sources. The incidence of myocarditis was higher after adolescence. The matched unadjusted HRs were 1.00 (95% CI: 0.40; 2.52) in NHR, 0.25 (95% CI: 0.05; 1.22) in PHARMO and 1.20 (95% CI: 0.37; 3.93)

The risk of myocarditis in the 7-, 14- and 21-day intervals after start of follow-up were similar in the vaccinated and unvaccinated cohorts in all databases.

Myocarditis has been associated with mRNA vaccines in several studies, in young adults, after the second dose of the vaccine, which is typically administered 28 days after the first dose, and therefore not observed in the 7-, 14- and 21-day risk windows analysed here.

Pericarditis

Pericarditis events could be identified in all data sources, except PHARMO.

In the 7-day risk window, the incidence rates in the vaccinated cohorts varied between 0 per 10,000 person-years in Pedianet and 3.7 per 10,000 person-years in EpiChron and SIDIAP and between 2.1 per 10,000 person-years in EpiChron and 3.0 per 10,000 person-years in NHR in the unvaccinated cohorts. No events were reported observed in either cohort in Pedianet during this risk window. The cumulative incidence was below 1 per 10,000 individuals in both cohorts in all data sources. The incidence was higher in age groups over about 11 years old than in the younger age groups. The matched unadjusted HRs for

pericarditis were 1.84 (95% CI: 0.40, 1.77) in NHR, 1.33 (95% CI: 0.30, 5.95) in EpiChron and 1.75 (95% CI: 0.75, 4.08) in SIDIAP for the 7-day risk window.

In the 14-day risk window, the incidence rates in the vaccinated cohorts varied between 2.9 per 10,000 person-years in NHR and 3.6 per 10,000 person-years in SIDIAP and was 2.3 per 10,000 person-years in NHR, and 2.7 per 10,000 person-years in EpiChron and SIDIAP in the unvaccinated cohorts. In Pedianet the incidence rate in the vaccinated cohort was 38.1, but corresponded to one event only. The cumulative incidence was below 1 per 10,000 individuals in both cohorts in all data sources, except for Pedianet. The incidence increased after childhood and remained relatively stable afterwards. The matched unadjusted HRs of pericarditis within the risk window of 14 days were 1.23 (95% CI: 0.64; 2.36) in NHR, 1.20 (95% CI: 0.32; 4.44) in Epichron and 1.37 (95% CI: 0.78; 2.41) in SIDIAP.

In the 21-day risk window, the incidence rates in the vaccinated cohorts varied between 2.4 per 10,000 person-years in EpiChron and 3.5 per 10,000 person-years in SIDIAP and between 2.2 per 10,000 person-years in NHR and 3.2 per 10,000 person-years in EpiChron in the unvaccinated cohorts. In the vaccinated cohort in Pedianet, the incidence rate was 25.9 per 10,000 person-years (corresponding to one event) The cumulative incidence was below 1 per 10,000 individuals in both cohorts in all data sources, except for Pedianet. The incidence was higher in age groups over 11 years compared with those under 11 years old. The matched unadjusted HRs for pericarditis within 21 days after start of follow-up were 1.42 (95% CI: 0.79; 2.56) in NHR, 0.75 (95% CI: 0.21; 2.65) in EpiChron and 1.35 (95% CI: 0.83; 2.20) in SIDIAP.

Myocarditis or pericarditis

The myocarditis or pericarditis outcome showed similar results to those observed for the separate outcomes.

In the 7-day risk window, the incidence rates in the vaccinated cohorts varied between 1.2 per 10,000 person-years in PHARMO and 4.7 per 10,000 person-years in EpiChron and between 1.9 per 10,000 person-years in EpiChron and SIDIAP and 4.0 per 10,000 person-years in NHR in the unvaccinated cohorts. No events were reported in either cohort in Pedianet during this risk window. The cumulative incidence was below 1 per 10,000 individuals in both cohorts in all data sources. The incidence was higher in age groups over about 11 years old than in the younger age groups. The matched unadjusted HRs were 0.80 (95% CI: 0.41; 1.57) in NHR, 0.50 (95% CI: 0.08; 3.12) in PHARMO, 2.50 (95% CI: 0.48; 12.88) in EpiChron and 2.09 (95% CI: 0.87; 5.03) in SIDIAP.

In the 14-day risk window, the incidence rates in the vaccinated cohorts varied between 0.6 per 10,000 person-years in PHARMO and 4.5 per 10,000 person-years in SIDIAP and between 2.2 per 10,000 person-years in PHARMO and 3.3 per 10,000 person-years in NHR in the unvaccinated cohorts. In Pedianet the incidence rate in the vaccinated cohort was 38.1, but corresponded to one event. The cumulative incidence was below 1 per 10,000 individuals in both cohorts in all data sources, except for Pedianet. The incidence was higher in age groups over about 11 years old than in the younger age groups. The matched unadjusted HRs

of myo- or pericarditis were 1.17 (95% CI: 0.67; 2.03) in NHR, 0.29 (95% CI: 0.06; 1.44) in PHARMO, 1.40 (0.39; 5.00) in EpiChron and 1.64 (95% CI: 0.96; 2.81) in SIDIAP.

In the 21-day risk window, the incidence rates in the vaccinated cohorts varied between 0.4 per 10,000 person-years in PHARMO and 4.3 per 10,000 person-years in SIDIAP and between 1.8 per 10,000 person-years in PHARMO and 4.3 per 10,000 person-years in EpiChron in the unvaccinated cohorts. In the vaccinated cohort in Pedianet, the incidence rate was 25.9 per 10,000 person-years (corresponding to one event) The cumulative incidence was below 1 per 10,000 individuals in both cohorts in all data sources, except for the vaccinated cohort in Pedianet with a cumulative incidence of 1.5 (corresponding to one event). The incidence was higher in age groups over about 11 years old than in the younger age groups. The matched unadjusted HRs for myocarditis or pericarditis during the 21-day risk window after dose 1 were 1.40 (95% CI: 0.84; 2.35) in NHR, 0.25 (95% CI: 0.05; 1.22) in PHARMO, 0.91 (95% CI: 0.33; 2.53) in EpiChron and 1.45 (95% CI: 0.93; 2.27) in SIDIAP.

Coagulation disorders

The incidence rates in the vaccinated cohorts varied between 21.4 per 10,000 person-years in PHARMO and 75.9 per 10,000 person-years in EpiChron and between 24.4 per 10,000 person-years in PHARMO and 96.3 per 10,000 person-years in EpiChron in the unvaccinated cohorts. The cumulative incidence was less than 7.5 per 10,000 individuals in both cohorts in all data sources. The increases in cumulative incidence of coagulation disorders within 28 days after start of follow-up, in the vaccinated and unvaccinated cohorts were similar and constant during the risk window in all databases.

The incidence of coagulation disorders was higher in older age groups in both the vaccinated and unvaccinated cohorts and based on the ACCESS data, is highest when both GP and in-patient diagnoses are used to identify the events. The matched HRs for coagulation disorders were 0.91 (95% CI: 0.65; 0.96) in NHR, 0.87 (95% CI: 0.67; 1.14) in PHARMO, 0.79 (95% CI: 0.65; 0.96) in EpiChron and 0.78 (95% CI: 0.71; 0.86) in SIDIAP.

Single organ cutaneous vasculitis

Single organ cutaneous vasculitis within the 28-day risk window was a very rare event and could be identified in PHARMO, EpiChron, and SIDIAP, and not in Pedianet or NHR. The incidence rates in the vaccinated cohorts ranged from 0.2 per 10,000 person-years in PHARMO to 0.7 per 10,000 person-years in SIDIAP. In SIDIAP the incidence rate per 10,000 person-years was 0.6 in the unvaccinated cohorts, in the other data sources no event was identified in the 28-day risk window in the unvaccinated cohort. The matched HR for single organ cutaneous vasculitis was 1.20 (95% CI: 0.50; 2.90) in SIDIAP.

ACCESS reported IRs for single organ cutaneous vasculitis per 100,000 for the years 2017 – 2020 for PHARMO, ARS, Pedianet, and SIDIAP ranging from 4.03 (ARS) to 30.10 (Pedianet). The ACCESS data showed that the rates are higher when outpatient and GP data used.

Acute liver injury

Acute liver injury events were identified in PHARMO, EpiChron and, SIDIAP. The incidence rates in the vaccinated cohorts varied between 0.1 per 10,000 person-years in NHR and 17.0 per 10,000 person-years in SIDIAP and between 0.4 per 10,000 person-years in NHR and 14.6 per 10,000 person-years in SIDIAP in the unvaccinated cohorts. The cumulative incidence over the 365-day risk window was below 18 per 10,000 individuals in the vaccinated cohorts and below 15 per 10,000 individuals in the unvaccinated cohorts.

The matched HRs for acute liver injury were 0.29 (95% CI: 0.10; 0.87) in NHR, 0.73 (95% CI: 0.33; 1.62) in PHARMO, 0.86 (95% CI: 0.64; 1.15) in EpiChron and 1.16 (95% CI: 1.06; 1.28) in SIDIAP.

ACCESS reported IRs for acute liver injury per 100,000 for the years 2017 – 2020 for PHARMO, ARS, Pedianet, and SIDIAP ranging from 2.51 (Pedianet) to 46.55 (SIDIAP). The ACCESS rates showed the increase in incidence when both outpatient and inpatient data are used, GP only data leads to underestimation of the incidence

Acute kidney injury

Acute kidney injury events within 365 days after the start of follow-up were reported identified in all data sources, except Pedianet. The incidence rates in the vaccinated cohorts varied between 16.1 per 10,000 person-years in NHR and 55.4 per 10,000 person-years in SIDIAP and between 21.9 per 10,000 person-years in NHR and 43.4 per 10,000 person-years in SIDIAP in the unvaccinated cohorts.

The incidence of acute kidney injury was highest in older age groups in both the vaccinated and unvaccinated cohorts. The matched unadjusted HRs were 0.73 (95% CI: 0.64; 0.83) in NHR, 1.06 (95% CI: 0.95; 1.18) in PHARMO, 0.88 (95% CI: 0.77; 1.02) in EpiChron and 1.28 (95% CI: 1.21; 1.35) in SIDIAP.

ACCESS reported IRs for acute kidney injury per 100,000 for the years 2017–2020 for PHARMO, ARS, and SIDIAP from 239.62 (ARS) to 992.56 (SIDIAP). Acute kidney injury rates depended largely on availability of inpatient diagnosis data, and was underestimated in sources using only GP data.

Acute pancreatitis

Acute pancreatitis events were reported identified in all data sources except Pedianet. The incidence rates in the vaccinated cohorts varied between 0.2 per 10,000 person-years in NHR and 6.2 per 10,000 person-years in SIDIAP and between 0.2 per 10,000 person-years in NHR and 5.4 per 10,000 person-years in SIDIAP in the unvaccinated cohorts. The cumulative incidence was under 6.5 per 10,000 individuals in the vaccinated cohorts and under 5 per 10,000 individuals in the unvaccinated cohorts

The incidence rate of acute pancreatitis was highest in the older age groups in both the vaccinated and unvaccinated cohorts. The matched unadjusted HRs were 0.66 (95% CI 0.24, 1.86) in NHR, 0.71 (95% CI: 0.48; 1.03) in PHARMO, 1.32 (95% CI: 0.89; 1.94) in EpiChron and 1.15 (0.98; 1.34) in SIDIAP.

ACCESS has not reported any IRs for acute pancreatitis. Rates may be lower in PHARMO, since acute pancreatitis is typically a diagnosis made in hospital and hospital data may not be complete in PHARMO since the data for this report are based on GP data only. For the next interim report hospital data may be linked until end of 2021.

Rhabdomyolysis

The incidence rates for rhabdomyolysis in the vaccinated cohorts varied between <0.1 per 10,000 person-years in NHR and 2.5 per 10,000 person-years in SIDIAP and between 3.2 per 10,000 person-years in Epichron and 3.4 per 10,000 person-years in SIDIAP in the unvaccinated cohorts. The cumulative incidence was below 4 per 10,000 individuals in both cohorts in all three data sources.

The matched HRs were 0.50 (95% CI: 0.28; 0.87) in EpiChron and 0.73 (95% CI: 0.59; 0.91) in SIDIAP. Rates were lower in PHARMO, since rhabdomyolysis is typically a diagnosis made in hospital which may not be complete in PHARMO since the data for this report are based on GP only. For the next interim report hospital data may be linked until end of 2021.

ACCESS has not produced IR for rhabdomyolysis.

Generalised convulsion

Generalised convulsion events were identified in all data sources, except Pedianet, which had stated they cannot accurately extract these data as this typically leads to an emergency visit. The incidence rates in the vaccinated cohorts varied between 1.8 per 10,000 person-years in PHARMO and 7.8 per 10,000 person-years in EpiChron and between 3.4 per 10,000 person-years in PHARMO and 6.4 per 10,000 person-years in EpiChron in the unvaccinated cohorts. The cumulative incidence was below 1 per 10,000 individuals in both cohorts in all data sources.

The matched HR were 0.89 (95% CI: 0.68; 1.17) in NHR, 0.52 (95% CI: 0.25; 1.06) in PHARMO, 1.22 (95% CI: 0.68; 2.19) in EpiChron and 1.23 (95% CI: 0.94; 1.61) in SIDIAP.

ACCESS reported IRs for generalised convulsion per 100,000 for the years 2017–2020 for PHARMO, ARS, Pedinaet, and SIDIAP from 114.02 (ARS) to 165.34 (ARS). It is an event that typically is seen in emergency units and therefore underestimated in data sources with only GP data.

Meningoencephalitis

Meningoencephalitis was a rare event in all data sources, with no events identified in Pedianet (as this is not a diagnosis for primary care). The incidence rates in the vaccinated cohorts varied between 0.6 per 10,000 person-years in SIDIAP and 1.9 per 10,000 person-years in NHR and between 0.7 per 10,000 person-years in EpiChron and SIDIAP and 1.9 per 10,000 person-years in NHR in the unvaccinated cohorts. The cumulative incidence was below 1 per 10,000 individuals in both cohorts in all data sources.

The matched HRs were 1.02 (95% CI: 0.64; 1.63) in NHR, 0.54 (0.18; 1.65) in PHARMO, 1.33 (95% CI: 0.23; 7.69) in EpiChron and 0.94 (95% CI: 0.44; 2.01) in SIDIAP.

Rates in data sources with hospital diagnoses were similar to ACCESS. Rates were lower in GP-based data sources.

Transverse myelitis

Transverse myelitis within 42 days after the start of follow-up was a very rare event observed in PHARMO, EpiChron and SIDIAP, with all incidence rates less than 1 per 10,000 person-years. The incidence rates in the vaccinated cohort in SIDIAP, based on <5 events was 0.1 per 10,000 person-years and was 0.1 and 0.2 per 10,000 person-years in the unvaccinated cohort in PHARMO and EpiChron.

No HRs were estimated due to the low number of events.

ACCESS shows IRs for transverse myelitis per 100,000 for the years 2017–2020 for PHARMO, ARS, Pedinaet, and SIDIAP from 0.33 (PHARMO) to 1.52 (ARS), showing that in hospital and emergency room visit data are important to capture cases Rates are underestimated in GP only data sources.

Bell's palsy

Bell's palsy events were identified in all data sources, except Pedianet. The incidence rates in the vaccinated cohorts varied between 2.6 per 10,000 person-years in PHARMO and 8.5 per 10,000 person-years in SIDIAP and between 2.3 per 10,000 person-years in PHARMO and 8.2 per 10,000 person-years in SIDIAP in the unvaccinated cohorts. The cumulative incidence was below 1 per 10,000 individuals in both cohorts in all data sources except SIDIAP where it was 1.0 in the vaccinated.

The matched HRs were 1.00 (95% CI: 0.73; 1.37) in NHR, 1.16 (95% CI: 0.62; 2.19) in PHARMO, 1.03 (95% CI: 0.52; 2.04) in EpiChron and 1.03 (95% CI: 0.82; 1.30) in SIDIAP.

ACCESS has not reported IRs for Bell's palsy.

Acute respiratory distress syndrome

Acute respiratory distress syndrome events were identified in NHR, PHARMO, EpiChron and SIDIAP. The incidence rates in the vaccinated cohorts varied between 0.3 per 10,000 person-years in PHARMO and 9.1 per 10,000 person-years in EpiChron and between 0.9 per 10,000 person-years in PHARMO and 19.4 per 10,000 person-years in EpiChron in the unvaccinated cohorts. The cumulative incidence was below 11 per 10,000 individuals in the vaccinated cohorts and below 18 per 10,000 individuals in the unvaccinated cohorts in all data sources.

The incidence of acute respiratory distress syndrome was highest in the older age groups, in both the unvaccinated and vaccinated cohorts. The matched HRs were 0.23 (0.15, 0.36) in NHR, 0.35 (95% CI: 0.16; 0.74) in PHARMO, 0.47 (0.38; 0.59) in EpiChron and 0.63 (95% CI: 0.56; 0.70) in SIDIAP, thus showing consistent protective effects of vaccination.

ACCESS reported IRs for acute respiratory distress syndrome per 100,000 for the years 2017–2020 for PHARMO, ARS, Pedianet, and SIDIAP from 2.31 (PHARMO) to 1.52 (ARS). It also showed that in and outpatient data are needed for an accurate estimation of the incidence.

Erythema multiforme

Erythema multiforme events were identified in PHARMO, EpiChron and SIDIAP and it is a rare event in all data sources. The incidence rates in the vaccinated cohorts varied between 0.3 per 10,000 person-years in PHARMO and 0.6 per 10,000 person-years in SIDIAP and between 0.2 per 10,000 person-years in EpiChron and 0.6 per 10,000 person-years in SIDIAP in the unvaccinated cohorts. The cumulative incidence was less than 1 per 10,000 individuals in both cohorts in the three data sources.

The incidence was highest in younger age, but the low number of events did not allow to inspect clear age patterns. The matched unadjusted HRs were 0.50 (95% CI: 0.09; 2.72) in PHARMO and 1.07 (95% CI: 0.49; 2.34) in SIDIAP.

ACCESS reported IRs for erythema multiforme syndrome per 100,000 for the years 2017–2020 of 6 per 100,000 person-years in GP data sources only to 9.7 per 100,000 in data sources with hospitalisation and emergency diagnoses.

Chilblain-like lesions

Chilblain-like lesions were identified in all data sources except NHR. The incidence rates in the vaccinated cohorts varied between 1.4 per 10,000 person-years in EpiChron and 2.6 per 10,000 person-years in PHARMO and between 2.0 per 10,000 person-years in PHARMO and 3.5 per 10,000 person-years in SIDIAP in the unvaccinated cohorts. The incidence rate in the vaccinated cohort of Pedianet was 27.1, but there were only two events, compared with no events in the unvaccinated cohort. The cumulative incidences in the 42 days after start of

follow-up were as less than 0.3 per 10,000 individuals in the vaccinated cohorts and less than 0.5 per 10,000 individuals in the unvaccinated cohorts.

The incidence of chilblain-like lesions did not show a clear age pattern. The matched unadjusted HRs were 1.31 (95% CI: 0.67; 2.56) in PHARMO, 0.67 (95% CI: 0.24; 1.87) in EpiChron and 0.65 (95% CI: 0.45; 0.94) in SIDIAP.

ACCESS showed IRs for chilblain-like lesions per 100,000 for the years 2017–2020 for PHARMO, ARS, Pedianet, and SIDIAP from 0.04 (ARS) to 15.97 (SIDIAP) and the need for GP diagnoses.

Secondary amenorrhea

Secondary amenorrhea events were identified in Pedianet, EpiChron, and SIDIAP. In Pedianet one event in the vaccinated and one event in the non- vaccinated was identified. The incidence rates in the vaccinated cohorts were 3.5 per 10,000 person-years in Pedianet, 24.9 per 10,000 person-years in SIDIAP and 25.6 per 10,000 person-years in EpiChron. In the unvaccinated cohorts the incidence rates were 3.5 per 10,000 person-years in Pedianet, 25.6 per 10,000 person-years in EpiChron and 24.6 per 10,000 person-years in SIDIAP. The cumulative incidence was around 13 per 10,000 individuals in the vaccinated cohorts and between 7.5 per 10,000 individuals in the unvaccinated cohorts in EpiChron and 12.3 in SIDIAP.

The matched HR were 1.00 (95% CI: 0.06; 15.89) in Pedianet, 1.68 (95% CI: 1.34; 2.09) in EpiChron and 1.01 (95% CI: 0.93; 1.10) in SIDIAP.

We further investigated the nature of the result obtained in EpiChron. We restricted the population to women of childbearing age and calculated the 1-KM curves and obtained the same differences between the vaccinated and unvaccinated cohorts.

We checked the codes that corresponded to the translation of the secondary amenorrhea definition to EpiChron specific codes and found that many codes for dysmenorrhea, primary amenorrhea and menopause had been included. Therefore, we think that the findings correspond more to an outcome that could be named as menstrual disorders than secondary amenorrhea. To take into account the effect of menopause and primary amenorrhea we stratified the female population in age groups and for each age group the 1-KM curves obtained reflected the same differences between vaccinated and unvaccinated diminishing the potential effect modification of the primary amenorrhea and menopause codes. We aim to refine the definition of the event to reflect secondary amenorrhea and evaluate it in the rest of the databases.to get additional insight on the research question

Anosmia, ageusia

Anosmia, ageusia events were reported in all data sources. The incidence rates in the vaccinated cohorts varied between 3.9 per 10,000 person-years in NHR and 16.2 per 10,000 person-years in EpiChron and between 4.0 per 10,000 person-years in NHR and 27.2 per

10,000 person-years in Pedianet in the unvaccinated cohorts. The cumulative incidence was less than 2 per 10,000 individuals in the vaccinated cohorts and less than 3.5 per 10,000 individuals in the unvaccinated cohorts in all data sources.

The matched HR for anosmia/ageusia was 0.97 (95% CI: 0.70; 1.34) in NHR, 1.00 (95% CI: 0.69; 1.44) in PHARMO, 1.17 (95% CI: 0.78; 1.75) in EpiChron and 0.88 (95% CI: 0.71; 1.09) in SIDIAP.

In the ACCESS project SIDIAP identified IRs between 1.9 and 3.5 per 10,000 years for SIDIAP between 2017 and 2020. It also showed the need for GP diagnoses to identify this event, which could not be identified in hospital.

Anaphylaxis

Anaphylaxis was a rare event in all data sources, with a total of 50 events identified in the vaccinated cohorts and 14 events in unvaccinated cohorts. The incidence rate was highest in PHARMO. Matched hazard ratios were 3.31 (1.78, 6.15) in PHARMO and 6.00 (0.72, 49.84) in SIDIAP.

More events will be collected for subsequent interim reports. We expect that the results for the prevalence of anaphylaxis in a one-day risk period will become more robust.

Multisystem inflammatory syndrome

Multisystem inflammatory syndrome events were reported identified in all data sources except Pedianet and were very rare. The incidence rates in the vaccinated cohorts ranged from 0.1 per 10,000 person-years in PHARMO to 0.9 per 10,000 person-years in EpiChron and were 0.2 per 10,000 person-years in NHR and EpiChron, and 0.9 per 10,000 person-years in SIDIAP in the unvaccinated cohorts. The cumulative incidences were 0.1 per 10,000 individuals in the vaccinated and unvaccinated cohorts as available in EpiChron and SIDIAP. The matched HRs were 0.20 (95% CI: 0.02, 1.71) in NHR, 3.98 (95% CI: 0.44; 35.62) in EpiChron and 0.64 (95% CI: 0.31; 1.32) in SIDIAP.

The ACCESS project reported background IRs between 2.3 and 4.6 per 100,000 person-years for SIDIAP from 2017 to 2020.

Death (any cause)

Death (any cause) were identified in all data sources. Pedianet reported one death only in the vaccinated cohort. The cumulative incidences in the vaccinated cohorts ranged from 34.9 per 10,000 individuals in PHARMO to 590.4 per 10,000 individuals in NHR and from 82.5 per 10,000 individuals in PHARMO to 839.3 per 10,000 individuals in NHR in the unvaccinated cohorts. The incidence rates in the vaccinated cohorts varied between 38.1 per 10,000 person-years in PHARMO and 155.2 per 10,000 person-years in SDIAP and between 109.1 per 10,000 person-years in PHARMO and 222.6 per 10,000 person-years in NHR in the

unvaccinated cohorts. In PHARMO the cumulative incidence of deaths remained constant from day 150 onwards, as more deaths have not yet been registered.

The incidences of death (any cause) were highest in the oldest age groups. The matched unadjusted HRs were 0.49 (95% CI: 0.47; 0.51) in NHR, 0.35 (95% CI: 0.33; 0.38) in PHARMO, 0.55 (95% CI: 0.51; 0.60) in EpiChron and 0.99 (95% CI: 0.96; 1.02) in SIDIAP.

Subacute thyroiditis

Subacute thyroiditis events were reported identified in all data sources, but no events were reported in Pedianet or NHR. The incidence rates in the vaccinated cohorts varied between 0.1 per 10,000 person-years in PHARMO and 3.0 per 10,000 person-years in SIDIAP and between 0.1 per 10,000 person-years in PHARMO and 3.2 per 10,000 person-years in SIDIAP in the unvaccinated cohorts. The cumulative incidence within 42 days was less than 3.5 per 10,000 individuals in the vaccinated cohorts and less than 3 per 10,000 individuals in the unvaccinated cohorts.

The incidence of acute thyroiditis was highest in older age groups in both the vaccinated and unvaccinated cohorts. The matched HRs were 0.98 (95% CI: 0.09; 10.88) in PHARMO, 1.17 (95% CI: 0.63; 2.15) in EpiChron and 0.95 (95% CI: 0.78; 1.16) in SIDIAP.

ACCESS has not reported IRs for subacute thyroiditis.

Sudden death

Sudden death (based on diagnostic codes of sudden death) at any time after the start of follow-up were identified in for NHR, PHARMO and EpiChron. The incidence rates in the vaccinated cohorts were 0.1 per 10,000 person-years in PHARMO and 2.1 per 10,000 person-years in NHR. The cumulative incidence was less than 1 per 10,000 individuals in the vaccinated and unvaccinated cohorts in both data sources.

The matched HRs were 0.72 (95% CI: 0.52, 1.01) in NHR and 0.42 (95% CI: 0.09, 1.92) in PHARMO.

ACCESS shows IRs for sudden death per 100,000 for the years 2017–2020 for PHARMO, ARS, Pedianet, and SIDIAP from 0.77 (Pedianet) to 330.30 (SIDIAP).

COVID-19 disease

COVID-19 disease is not one of the AESI studied and was used as a negative test to evaluate the balance between matched cohorts. The evolution of the pandemic makes it very difficult to interpret the IRs over time. COVID-19 disease rates were high and differed between data sources, which may be due to the source of the collected data, e.g., PCR test, symptomatic COVID-19.

Vaccine-associated enhanced disease

Vaccine-associated enhanced disease (VAED), which is defined as a COVID-19 event that is more clinically severe than expected following vaccination, is a difficult event to study, as it cannot be assessed in unvaccinated individuals.VAED could only be assessed in NHR and PHARMO although COVID-19 events could be identified in all data sources. Consistency of definitions will be verified and reported in the next interim reports.

1.1   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). Data from PHARMO showed lower than expected estimates of vaccine uptake, but the rates are improving. NHR data had substantial missing data for the COVID-19 vaccine brand.

Although no data from HSD were included in this report, when they will be included, a potential limitation for HSD is that general practitioners were only involved in the COVID vaccination campaign for patients aged 80 or older in March 2021. Given that there is no automated system to collect data on patients' vaccination status, GPs might have under- or mis-registered COVID-19 vaccines because the GPs were not the primary vaccinators. We will explore options to improve this and benchmark against known vaccination uptake prior to deciding whether data on vaccination are fit for purpose in the future. HSD data is not included in this interim report.

In PHARMO, data on COVID-19 vaccinations were entered in the GP medical record through various routes, including directly by the GPs who vaccinated, which was not done using the Pfizer-BioNTech COVID-19 vaccine because of the cold chain requirements, or through the public health vaccination register if an individual was vaccinated by the public health institute. This resulted either in some missing vaccination data from the public health vaccination register because they have not yet been registered at the GP level or in a multitude of entries that require cleaning and deduplication. Over time this problem will be reduced and for the final results, PHARMO hopes to have linkage with the vaccination register established.

Definition of AESIs

AESIs were identified through diagnostic codes, which can be tagged as narrow (specific) and possible (sensitive). In this third 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 PHARMO, NHR and Pedianet, the codes reflected those in general practitioners' records, which may include specialist or hospital diagnostic codes, but these may not be complete or delayed. This may be the reason that the rates are lower for some rare events that require hospitalization. SIDIAP and EpiChron contain inpatient and outpatient diagnoses. NHR is based on primary care (GP) and outpatient specialist data. Registers, codes and PCR testing were used for COVID-19 diagnoses and tests. PHARMO

and Pedianet used free text searching for COVID-19 disease as well as for other events. The quality of the free text identification will be assessed, and modified if needed, for future reports.

1.2   Interpretation

The data on the vaccinated and matched unvaccinated cohorts captured a large population of more than 8 million individuals who had received at least one dose of the Pfizer-BioNTech vaccine, who were matched with unvaccinated individuals. The matching was successful, both in terms of finding an appropriate matched as well as minimising confounding. However, several matching variables were not measurable in all data sources (e.g. socio-economic status), and rather than deleting these, which may cause selection bias, we matched on the unknown status. In future analyses we plan to investigate the impact of this. In this third interim report, follow-up has been extended which impacted especially the events for long term follow-up. Some associations were seen for these events in SIDIAP, and we are currently exploring the impact of lag times of hospital data reporting during the later part of the follow-up.

1.3   Generalizability

Our quality checks showed that the distribution of age and sex of the source populations closely resembles the national statistics in each country. The study population for this 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 third interim report provide characteristics and incidence rates for 35 AESIs in more than 8 million vaccinated individuals and 8 million unvaccinated controls, although the data were not pooled but were analysed per data source 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. Long term follow-up for some event rates introduced challenges that will need further exploration and refinement in the future interim reports and the final report.

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15. LIST OF SOURCE TABLES AND FIGURES

Not applicable.

Document Approval Record

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