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	V1.0
Date	15 September 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.

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)

Abbreviation	Definition
EU PAS Register	European Union electronic register of post-authorisation studies
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)

Abbreviation	Definition
ONS	Office for National Statistics
PASS	Post-authorisation safety study
PHARMO	PHARMO Institute for Drug Outcomes Research or PHARMO Database Network (Netherlands)
PHE	Public Health England
PS	Propensity score
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 in the 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	Health Search Research
	Director	PHARMO Institute for Drug Outcomes Research
	Researcher	
	Researcher	
	Researcher	
	President	PENTA Foundation

Name, degree(s)	Title	Affiliation
PPD	Director	Drug Safety Research Unit (DSRU)
	Head of Epidemiology and Research	
	Research Fellow	
	Senior Research Fellow	
	Researcher	EpiChron Research Group. Instituto Aragonés de Ciencias de la Salud
	Researcher	
	Researcher	IDIAP-Jordi Gol
	Statistician	
	Statistician	
	Data Scientist	
	Data Scientist	
	Researcher	University of Oslo
	Researcher	

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	Programme Manager
PPD, PhD, Teamit Institute S.L	Study 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	30 September 2021	
End of study data collection	31 March 2024		
Study progress report [1]	30 September 2021	27 September 2021	
Interim report I	31 March 2022	23 March 2022	
Interim report 2	30 September 2022	15 September 2022	
Interim report 3	31 March 2023	20 March 2023	
Interim report 4	30 September 2023	15 September 2023	
Interim report 5	31 March 2024		
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 is 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 sub-cohorts of interest (i.e., individuals who are immunocompromised, individuals who are frail and have comorbidities, individuals diagnosed with previous COVID-19 infection, and age-specific groups) in Europe using a cohort study design and/or a SCRI design.

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

- To characterise utilisation patterns of Pfizer-BioNTech COVID-19 vaccine among individuals within Europe, including estimating the proportion of individuals receiving the vaccine; two-dose vaccine completion rate and distribution of time gaps between the first and second doses; and demographics and clinical characteristics of recipients, overall and among sub-cohorts of interest, such as individuals who are immunocompromised, elderly, or have specific comorbidities.

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.
3	11-Apr-2023	General	Administrative, formatting, and typographical corrections have been made	Updated to provide clarity and to be consistent with remainder of protocol
3	11-Apr-2023	9.3.2.1 Safety Outcomes	New AESI added: secondary amenorrhea	Request from European Medicines Agency (EMA)
3	11-Apr-2023	9.3.2.1 Safety Outcomes	COVID-19 disease removed as a safety outcome	COVID-19 disease is not an AESI and COVID-19 testing is not systematically performed in the healthcare systems of the study data sources
3	11-Apr-2023	9.3.2.1 Safety Outcomes	Table 1, AESI 'Thrombocytopenia with venous thromboembolism' was removed and the AESI 'Heparin-induced thrombocytopenia (HIT)-like event' was renamed 'Thrombosis thrombocytopenia syndrome (TTS)'	These three events are equivalent and have the same definition, but TTS is the preferred name

Table 1. Amendments to the protocol

Amendment number	Date	Section of protocol changed	Summary of amendment/update	Reason
3	11-Apr-2023	7 Rationale and Background 8.2 Objectives 9.2 Setting 9.7 Data Analysis	Add new secondary objective: To describe the rate of cardiac imaging use among vaccinated and unvaccinated individuals each calendar month of the study period, before and after distribution of the direct healthcare professional communication (DHPC) letter	Request from EMA
3	11-Apr-2023	9.3.2.3 Cardiac imaging	Cardiac imaging defined	Needed for the added secondary objective.
3	11-Apr-2023	9.3.1 Exposure definition, 9.4.8 CPRD	Update sources of data for CPRD	Some COVID-19 specific databases linked to CPRD were identified as not necessary to obtain study variables based on recent experience in the study
3	11-Apr-2023	9.4 Data sources	Re-ordered data sources to be consistent with order in other studies	Consistency
3	11-Apr-2023	9.4.4 PHARMO	Update sources of data for PHARMO	Outpatient Pharmacy Database will not be used
3	11-Apr-2023	9.3.2.2 Outcome identification and validation, by data source	Add description of the validation process for HSD	This was previously combined with the description for Pedianet
3	11-Apr-2023	9.3.3 Covariate definition	Covariate definition will be updated to the following age groups: 0-1, 2-4, 5-11, 12-15, 16-17,18-29, 30-39, 40-49, 50-59, 60-64, 65-69, 70-79, and 80+ years.	These categories were chosen to align with age groups as authorized and prioritized during vaccine rollout indications of the vaccine in children younger than 16 years old
4	Pending	9.3.2.1 Safety Outcomes	New AESIs added: myositis, hypermenorrhea	Request from European Medicines Agency (EMA). Pending protocol amendment
4	Pending	9.3.2.1 Safety Outcomes	VAED changed to Severe COVID-19 defined as either COVID-19 hospitalisation or death	Pending protocol amendment. Updated to provide clarity

Table 1. Amendments to the protocol

Amendment number	Date	Section of protocol changed	Summary of amendment/update	Reason
4	Pending	9.7.1 and 9.7.2	Sections: Comparison with historical comparators, and Time trends in AESI in pre-pandemic, post-pandemic, and post-vaccination periods have been further developed and clarified Section on age-standardised outcome measures removed	Pending protocol amendment. Updated to provide clarity

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

Table 2. List of selected adverse events of special interest

Body system/ classification	Adverse event of special interest	Estimated risk window (days)	Analytic Approach
Pregnancy outcome, maternal	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	Severe COVID-19 [h]	365	Cohort

Notes:
a This AESI will undergo clinical validation.
b Published risk and control intervals for demyelinating diseases and cranial disorders were applied to TM and narcolepsy/cataplexy.
c Published risk and control intervals for autoimmune disorders were applied to similar autoimmune rheumatic conditions (i.e., fibromyalgia and autoimmune thyroiditis).
d Published risk and control intervals for myocarditis and pericarditis were applied to other cardiovascular conditions (i.e., heart failure and cardiogenic shock, stress cardiomyopathy, CAD, arrhythmia, AMI).
e Similar risk and control intervals were applied to all cardiovascular and haematological disorders characterised by damage to the blood vessels and/or arteries and clotting (i.e., microangiopathy, DVT, pulmonary embolus, limb ischaemia, haemorrhagic disease, DIC, chilblain-like lesions). The published risk and control intervals for KD were applied to vasculitides given that KD is a type of medium and small-vessel vasculitis.
f Published risk and control intervals for non-anaphylactic allergic reactions were applied to hypersensitivity disorders (i.e., erythema multiforme).
g 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.
h Severe COVID-19 defined as either COVID-19 hospitalisation or death

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.

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, previous influenza vaccination at time zero, pregnancy, immunocompromised, CDC risk criteria and socioeconomic status/education level. 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 will be used in the final analysis. These assumptions will include that the outcome has an acute onset and short latency and has relatively well-known risk intervals; the design is less suited to study outcomes that affect the probability of exposure, but this potential bias was reduced by the use of a post-vaccination control interval.

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

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

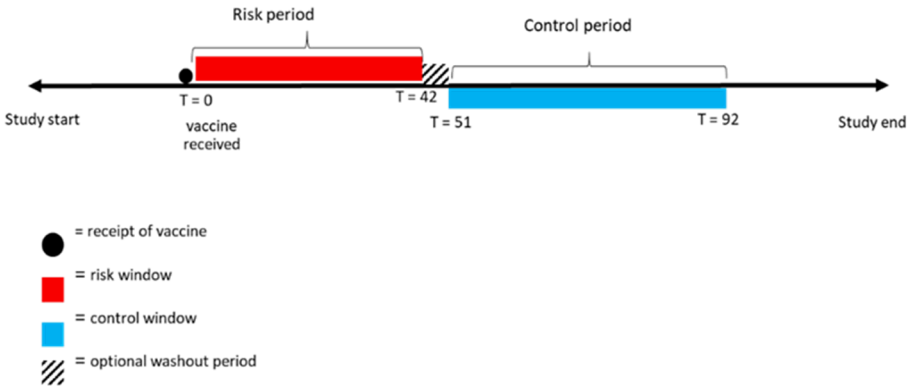
The SCRI design will be performed in the overall vaccinated population, including among vaccinated individuals not included in the retrospective cohort analysis because a matching comparator was not found. This design will serve as a sensitivity analysis and will enable the evaluation of the exclusion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

The 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 will be used for each outcome. This approach will minimise bias because of outcomes affecting the probability of exposure (e.g., the outcome is a contraindication for exposure or delayed exposure). For individuals who received more than one dose of the vaccine, the risk interval will be extended beyond each dose.

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

Figure 1. Self-controlled risk interval design



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

9.2. Setting

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

9.2.1. Data sources

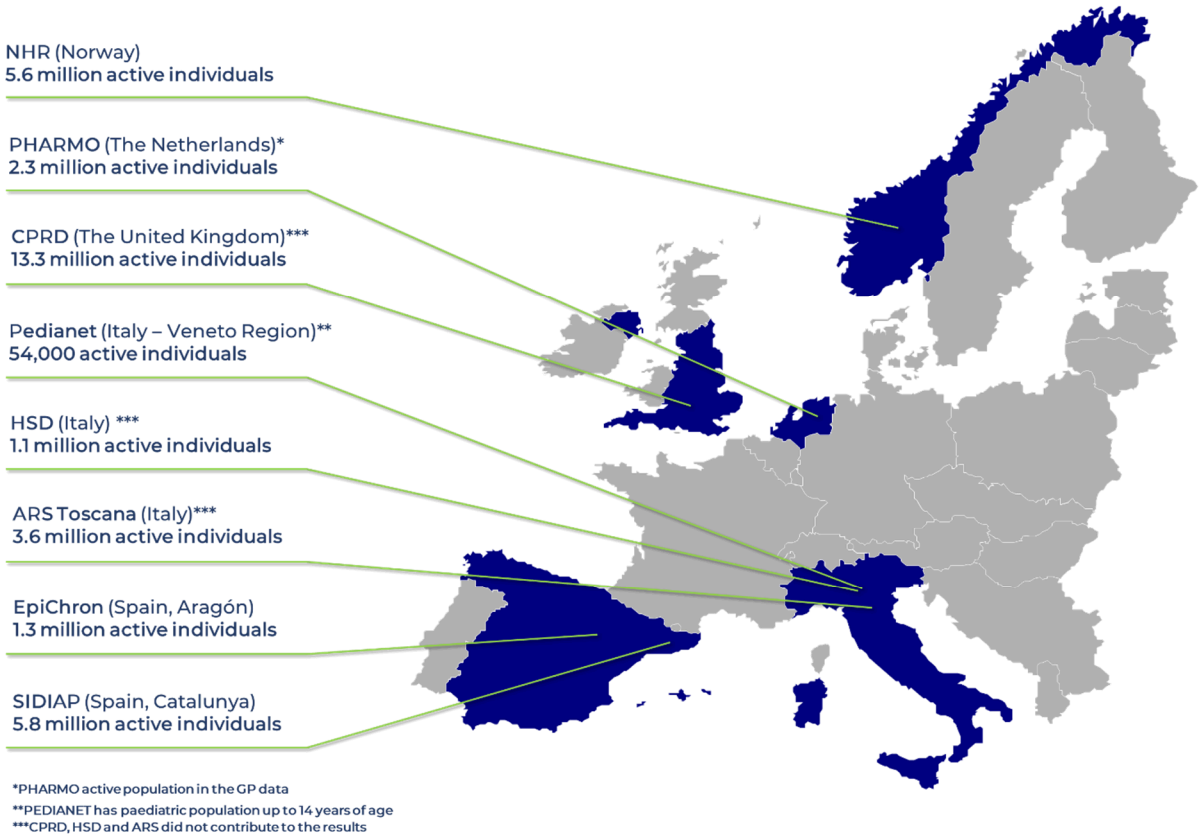
The following European electronic health care databases and two-letter country codes were used as data sources (Figure 2):

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

[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.

- PHARMO (PHARMO Data Network) (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



9.2.2. Study period and follow-up

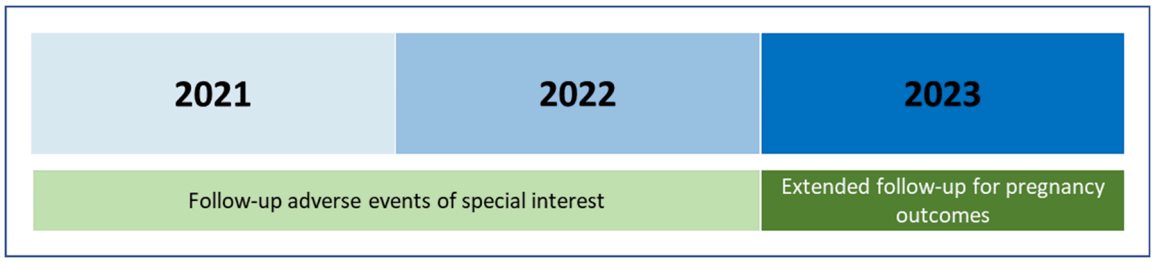
The study period for both the cohort and SCRI designs started on the date of administration of the first dose of the Pfizer-BioNTech COVID-19 vaccine in each country participating in the study (Table 3) and will end on the date of the latest data availability. Follow-up will last for two years for AESIs. 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 Dec 2022
The Netherlands (PHARMO)	06 January 2021	GP data: 6 January 2021 – 31 Dec 2022 Hospital data: 6 January 2021 – 31 Dec 2021
Norway (NHR)	27 December 2020	1 January 2021 – 31 December 2021*
Spain (EpiChron, SIDIAP)	27 December 2020	EpiChron: 27 December 2020 – 31 Dec 2022 SIDIAP: 01 January 2021 – 31 Dec 2022
UK (CPRD)**	08 December 2020	8 December 2020 – 21 March 2022

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

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 in the analysis (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 criteria below 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. Cohorts of individuals exposed to a third dose of the Pfizer-BioNTech COVID-19 vaccine were also analysed.

9.4.1.1. Cohort design

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

1. Receipt of at least one dose of the Pfizer-BioNTech COVID-19 vaccine, followed or not by a second dose or booster of the Pfizer-BioNTech COVID-19 vaccine. Individuals were censored if and when they received a non–Pfizer-BioNTech COVID-19 vaccine during follow-up.

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

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.

Individuals who received a first dose (population studied in the main analysis) may be different from the individuals who received a second dose and they may also be different

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

9.4.1.2. Self-controlled risk interval design

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

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

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

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

Standard algorithms for each outcome definition were applied to participant data sources, based on the results of the ACCESS project. Algorithms were tailored to the data source to take into consideration the nature of the records that identified the outcome, e.g., primary care, access to hospital care, and access to emergency care.[10] Multiple algorithms for the same outcome were included in the analysis, to assess the potential impact of differential misclassification.

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

HSD (IT): The validation process includes the review by clinicians of the individuals' EHRs, which contain information from primary care reports.

PHARMO (NL): In the Netherlands, for the validation study, information on selected endpoints from patient medical records were abstracted by local medical professionals 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, 60-64, 65-69, 70-79, 80+ years)
        - The age group 0-17 years was further categorised, when feasible, as follows: 0-1, 2-4, 5-11, 12-15, 16-17
    - Sex
    - Pregnancy status and pregnancy trimester at time zero
    - Geographic region, as appropriate in each country
    - Socioeconomic status, as available in each country (including housing, employment, and income, if available)
    - Date of vaccination (categorised in trimesters)
- COVID-19 history, as available in each data source (used to define subgroups of interest)
    - Previous diagnosis of COVID-19

- Positive test result for COVID-19

- Personal lifestyle characteristics
  - Smoking status (if available)
  - Body mass index (if available)
- Comorbidities
  - History of anaphylaxis
  - History of allergies
  - Diabetes mellitus (types 1 and 2)
  - Hypertension
  - Cardiovascular disease
  - Cerebrovascular disease
  - Chronic respiratory disease
  - Chronic kidney disease
  - Chronic liver disease
  - Cancer
  - Autoimmune disorders
  - Influenza infection or other respiratory infections
  - Charlson Comorbidity Index (reported as individual items and as a composite score)
- Immunocompromising conditions (used to define subgroups for secondary analyses)
  - Immunodeficiencies
  - Immunosuppressant medication use
  - Human immunodeficiency virus and other immunosuppressing conditions

- Comedication use during the year before time zero (prescriptions or dispensing, no over-the-counter medication use). For this report, comedication use was assessed for ten years prior to time zero, but this will be corrected in the next interim report.
    - Analgesics
    - Antibiotics
    - Antiviral medications
    - Corticosteroids
    - Non-steroidal anti-inflammatory drugs
    - Psychotropics
    - Statins
    - Novel oral anticoagulants
    - Warfarin
- Health care utilisation in the year before time zero and in the 2 weeks before time zero
    - Number of hospitalisations
    - Number of emergency department visits
    - Primary care utilisation
    - Cancer screening
    - Other preventive health services, as appropriate
    - COVID-19 tests
- Other vaccinations
    - Influenza
    - Pneumococcal
    - DTP (diphtheria, tetanus, and pertussis)
    - TPV (polio)

- TV (MMR) (measles, mumps and rubella)
- Hib (Haemophilus influenzae type b)
- HB (hepatitis B virus)
- VV (varicella zoster virus)
- HZ (herpes-zoster virus)
- HPV (human papillomavirus)
- Meningococcal
- Rotavirus

- Surrogates of frailty
  - 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.

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

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

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

EpiChron (ES): The Aragon Health System (Aragon, Spain) implemented a specific vaccination register embedded in the electronic health record (EHR) system. The COVID-19 vaccination was systematically registered in this register by health care professionals. This register collected all the relevant information regarding the vaccination process, such as patient's identifier; date of administration and due date for next dose, when applicable; centre of administration; injection site; name of the vaccine; brand (laboratory); batch number;

dose; and vaccination criteria (risk group to which the patient belongs). There was also a free-text section in which health professionals included their observations (e.g., presence or not of an allergic reaction).

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

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 since the medical records could be incomplete. 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 is 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 severe COVID-19, 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

			Sample size[a]	
AESI	**Background rate during risk window**	**Risk ratio**	**Exposed**	**Unexposed**
Anaphylaxis	1/40,000	5	25,164,513	25,164,513
Anaphylaxis	1/40,000	7	15,147,759	15,147,759
Anaphylaxis	1/40,000	10	9,341,969	9,341,969
Anaphylaxis	1/40,000	50	1,081,289	1,081,289
Guillain-Barré syndrome	1/100,000	2	22,340,153	22,340,153
Guillain-Barré syndrome	1/100,000	3	7,725,193	7,725,193
Guillain-Barré syndrome	1/100,000	5	2,997,860	2,997,860
Guillain-Barré syndrome	1/100,000	10	1,112,913	1,112,913
Severe COVID-19	1/5,000	1.5	414,643	414,643
Severe COVID-19	1/5,000	2	128,456	128,456
Severe COVID-19	1/5,000	2.5	68,045	68,045
Severe COVID-19	1/5,000	3	44,420	44,420

AESI = adverse event of special interest; Severe COVID-19 defined as COVID-19-related hospitalisation or death.
a Assuming a two-sided alpha = 0.95, power of 80%, and a ratio of 1:1 exposed to unexposed.
Background incidence rate (IR) taking into account the risk window (source: https://doi.org/10.1093/infdis/jiab628):
Anaphylaxis 1/40,000; (1/40,000)/365 * risk window (risk window 2 days) = <0.010000137
Guillain-Barré syndrome 1/100,000; (1/100,000)/365 * risk window (risk window 42 days) = <0.01000115
Severe COVID-19 1/5,000 = <0.0102 (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 Interim Report (IR) #4, 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 (exclusion criteria for the AESI-specific analysis).
- Cohort follow-up and reasons for censoring.
- Population description at time zero by cohort (age groups, sex, age groups by sex, influenza vaccination, COVID-19 infection, history of AESI – exclusion criteria with prior history within one year – documented for the previous 10 years).

9.9.2. Main statistical methods

- The IR of all AESIs by different time windows after dose 1.
- The IR of all AESIs within the risk windows after dose 1, dose 2, and dose 3.
- The number of cases, and risk estimates (IR, Kaplan-Meier (KM) for all AESI (identified electronically) in each matched exposure group, overall and by subgroups.
- The crude cumulative incidence (1- KM) curves for each AESI by exposure group taking risk windows in consideration.
- Cumulative incidence curves (1 - KM) for the negative control outcome, starting from the day of administration of the first dose of vaccine.

9.9.3. Baseline exchangeability and negative control outcome

Despite matching for potentially relevant confounders, 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). It was stablished a priori that, if the 12-day

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

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

The stabilized weights were calculated as:

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

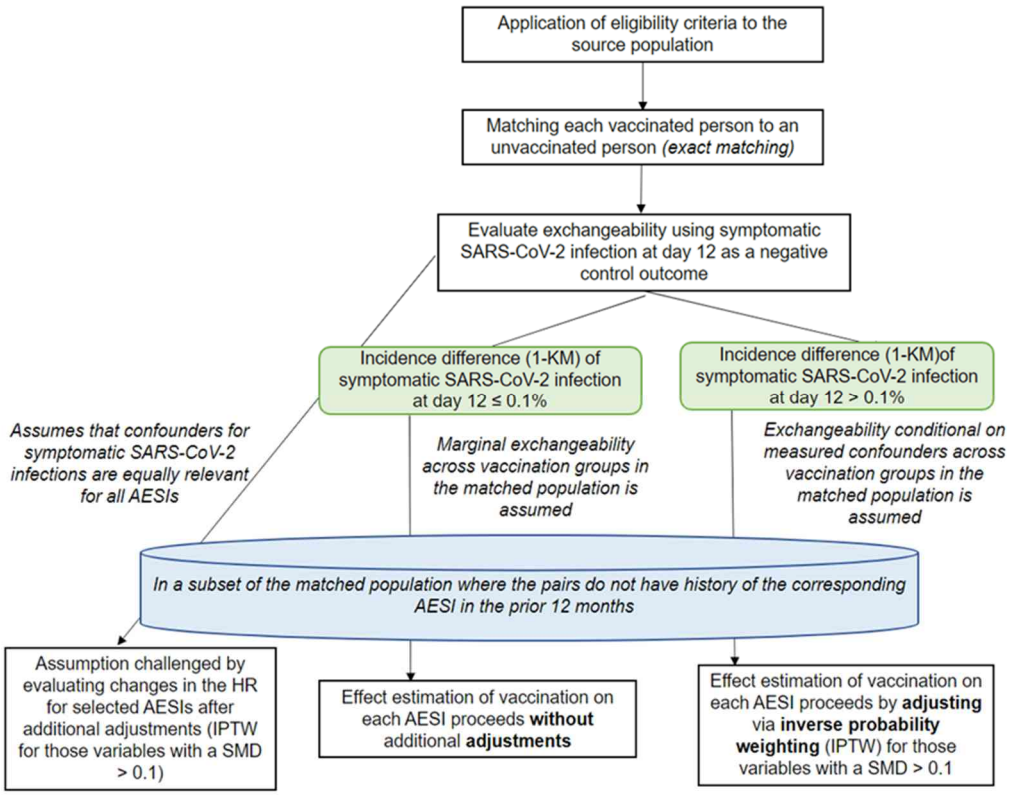
Where PS is the propensity score and A is the vaccination status at baseline (vaccinated: A=1, unvaccinated: A=0), i.e., the weight for the vaccinated cohort was 0.5/PS and for the unvaccinated cohort it was 0.5/(1-PS). Since, by design, the marginal probability of being exposed is ½, the weights were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

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

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

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

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



9.9.4. Missing values

Patients with missing data for the matching variables and those with missing exposure status or any of the outcome data were not included in the analyses. We assumed that the absence of information on clinical events meant that the event did not occur. 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 available on request. 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 analysis for the cohort design excluding individuals who have had contact with the healthcare system in the seven days before time zero	Request from EMA to remove from main analysis and add as a sensitivity analysis
1	15-Apr-2022	2.2.2.4.1. Matching process	Added the variable 'Immunocompromised (yes/no) – exact matching' to the list of matching variables	To align with the latest version of the study protocol
1	15-Apr-2022	2.2.2.2 Exclusion criteria; 2.2.6.2. Exclusion criteria	Removed exclusion criteria, "have had been in contact with the 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

Amendment number	Date	Section of SAP changed	Summary of amendment/update	Reason
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
2	17-Jul-2023	2	Updated introduction	To describe new objective i.e., assessment of the effectiveness of the direct healthcare professional communication (DHPC) letter
2	17-Jul-2023	2.1	Update list of outcomes to include myositis, secondary amenorrhea and hypermenorrhea to be consistent with changes to protocol V5.0, section 9.3.2.1	Request by EMA
2	17-Jul-2023	2.2.6.3	Removed 'verified' from AESIs in Table 3	
2	17-Jul-2023	2.4.2	Added new secondary objective described in protocol V5.0, section 8.2: to assess the effectiveness of the direct healthcare professional communication (DHPC) letter by describing the rate of cardiac imaging use for vaccinated and unvaccinated individuals each calendar month of the study period, before and after distribution of the DHPC letter	Included in European risk management plan as an additional risk minimization measure
2	17-Jul-2023	5.2.1	Added myocarditis/pericarditis to Table 6	
2	17-Jul-2023	5.3	Added cardiac imaging as additional endpoint	Inclusion of endpoints for new objective described above related to DHPC

Amendment number	Date	Section of SAP changed	Summary of amendment/update	Reason
2	17-Jul-2023	5.4.1	Demographic variables removed from list: • race/ethnicity • residency in long-term care facility healthcare worker or essential worker status	DAPs have confirmed these variables are not available.
2	17-Jul-2023	5.4.4	Added additional conditions to the CDC at risk-groups	
2	17-Jul-2023	5.4.7	Healthcare use variable deleted • skilled nursing facility	DAPs confirmed variable not available
2	17-Jul-2023	5.4.12	Added additional respiratory conditions in Table 8	
2	17-Jul-2023	7.2.5	Added section in Final Report	Include analysis of new objective related to DHPC
2	17-Jul-2023	7.2.8	Added section on Description of cardiac imaging use before and after the issue of the direct healthcare professional communication letter	Analysis of new objective related to DHPC
2	17-Jul-2023	2.2.5 4.1 7.2.5 7.2.7	Updated sections • Comparison with historical controls, • Study period • Analysis. Final Report • Comparison with historical comparators.	The comparison with historical periods will be made via the matched historical comparators analysis
2	17-Jul-2023	5.4.1 Demographics	Protocol V4.0, section 9.3.3: age categories have been modified;	To be consistent with the change in age categories that has been communicated to regulatory authorities via an administrative change letter

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

9.10. Quality control

Rigorous quality control (QC) 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. 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]

9.10.2. PHARMO (NL)

PHARMO adhered to high standards throughout the research process based on robust methodologies, transparency, and scientific independence, in accordance with the *ENCePP Guide on Methodological Standards in Pharmacoepidemiology*[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.

9.10.3. NHR (University of Oslo) (NO)

The University of Oslo had centralised information security policies in place to preserve the confidentiality, integrity and availability of the organisation's systems and data. All data are stored and analyzed within the TSD platform, a service for sensitive data at the University of Oslo (https://www.uio.no/english/services/it/research/sensitive-data/). Only authorized researchers can access and handle the data within TSD. A two-step authentication process is in place to access TSD. The study was conducted according to the *Guidelines for Good*

Pharmacoepidemiology Practices (GPP)[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.

9.10.4. EpiChron (ES)

The EpiChron Cohort is built from the BIGAN platform which integrates a technical infrastructure and a data lake gathering individual patient data from the regional health service information systems. The completion of the hospital CMBD register and the drug dispensation database, is systematic, uniform, and normative, in compliance with legal requirements. Specific on-line training and chart documentation on the use of EHR software was regularly provided to physicians and nurses in Aragon. The BIGAN platform includes several processes to control and improve the quality of its data, mainly in the ETL processes of capture and persistence in the data lake. Among these mechanisms, there are validation rules (for example, for dates and time intervals) or cross-checks with master tables, requiring that certain coded data exist in a standardised dictionary. Analysis of the distribution of variables is also carried out periodically, in search of 'outliers' that identify errors in the data capture or transformation processes. As a rule, records that do not validate QA procedures are kept in a 'holding area to be reviewed and discarded or reprocessed. The resulting databases are pseudonymised to encrypt individual-level identification codes, protecting individuals' privacy and complying with data protection laws, and they are stored on a central computer server, with restricted access by members of the research group, using a double-entry password. The research group was a multidisciplinary qualified team including public health specialists, epidemiologists, clinicians, pharmacists, statisticians, and data managers, who were all trained in data management and patient data protection.

9.10.5. SIDIAP (ES)

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

9.11. 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

Five of the eight data sources contributed data for this interim report (Section 9.2):

- Pedianet (IT)
- PHARMO (NL)

- NHR (NO)
- EpiChron (ES)
- SIDIAP (ES).

The study period for this fourth interim report started in each country with the first Pfizer-BioNTech COVID-19 vaccinations between 27 December 2020 in EpiChron (Spain) and 6 January 2021 in PHARMO (The Netherlands) (Table 3). Data collection started on 31 May 2021 in Pedianet (Italy) because vaccination in children started later. The end dates for data extraction for this IR are summarised in Table 3.

Data from NHR were available up to the end of 2021. Since the last interim report, NHR has completed missing COVID-19 vaccine brand information. Additionally, some hospital event information has been added, in addition to the existing primary care data.

The data in this interim report from PHARMO were extracted from GP records up to 31 March 2023 and hospital records up to 31 December 2021. Data on pregnancy status was available for the first time 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 31 December 2022 for this interim report.

The SIDIAP data source included diagnosis codes from general practitioners and from hospital discharges, and data up to 31 December 2022 were included in this IR #4. However, because of differences in lag times in different data banks and delays in notifications about hospitalisations, hospitalisation data for the end of the follow-up period, may be incomplete.

In this IR #4, we have used all matching criteria, verified the balance between the matched vaccinated and unvaccinated cohorts and included PS adjusted risk estimates.

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.

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

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

- There was a quality issue with the CPRD data availability that was discovered in January 2023, and which required re-extraction of data. This took time because an extensive pre-matching procedure had to be followed before data for matched patient IDs could be requested from CPRD. Analyses using the re-extracted data showed results that differed from published incidence rates. This may be due to incorrect reading of the data from study scripts. A new updated CPRD data instance became available in July/August 2023, and analyses are being done in preparation for the next interim report.

10.1.1. Vaccinated cohort

From among the 9,698,097 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 8,139,239 eligible individuals (Table 5). These individuals were from Italy (Pedianet 10,546 (0.1% of the total study population); the Netherlands (PHARMO 721,076 (8.9%)) Norway (NHR 3,559,920 (43.7%)), Spain (EpiChron 734,326 (8.9%) and SIDIAP 3,113,371 (38.3%)). The main reason for exclusion was the receipt of a COVID-19 vaccine other than Pfizer-BioNTech; the highest exclusion rate was in PHARMO (43.6%) and the lowest in NHR (7.1%). A total of 25,290 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 (%)	NHR n (%)	PHARMO n (%)	EpiChron n (%)	SIDIAP n (%)
Received a first dose of Pfizer-BioNTech COVID-19 vaccine	12,046 (100)	3,831,694 (100)	1,279,343 (100)	870,551 (100)	3,704,463 (100)
Had ≥12 months continuous enrolment[a] AND received a Pfizer-BioNTech vaccine	11,034 (91.60)	3,828,686 (99.92)	1,269,992 (99.27)	855,583 (98.28)	3,637,575 (98.19)
Received no prior COVID-19 vaccination, other than Pfizer-BioNTech vaccine, AND had ≥12 months continuous enrolment AND received a Pfizer-BioNTech vaccine	10,546 (87.55)	3,559,920 (92.91)	721,076 (56.36)	734,326 (84.35)	3,113,371 (84.04)
Total Pfizer-BioNTech COVID-19 vaccinated cohort[b]	10,546 (87.55)	3,559,920 (92.91)	721,076 (56.36)	734,326 (84.35)	3,113,371 (84.04)
Pregnant women vaccinated with 1st dose Pfizer-BioNTech vaccinated included	0 (0)	6,716 (0.18)	564 (0.04)	7,750 (0.89)	10,260 (0.28)

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;

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

The number of Pfizer-BioNTech COVID 19 vaccine doses and the timing of vaccination (in weeks) by data source are summarized in Table 6. Overall, 6,704,067 persons received a second dose (82.4%). The interval between the first and second doses was longer than 6 weeks for 16.5% 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 89.5% in EpiChron. In the paediatric data source, Pedianet, 83.1% of the children received their second dose within six weeks, at the time of database lock.

At the time of database lock (Table 3), a total of 1,959,413 individuals received a third dose of the Pfizer-BioNTech COVID 19 vaccine, which is 24.1% of the individuals included who had received the 1st dose. The interval between doses 2 and 3 varied between data sources with medians that ranged from 21 weeks (Pedianet) to 31 weeks (SIDIAP). The current EMA guidelines recommend 28 days between 2nd and 3rd dose for individuals older than 5 years and at least 3 months for the booster dose (i.e., Comirnaty 30 micrograms) after primary vaccination for individuals older than 12 years.[15] In Spain (EpiChron and SIDIAP) individuals aged 18 years and older were recommended to receive a first booster (i.e., third dose) five months after the last dose of the complete vaccination schedule. In the Netherlands (PHARMO) individuals older than 11 years were recommended to receive repeated vaccinations after at least 3 months after the last vaccination. In Italy (Pedianet) and Norway (NHR) specific recommendations are for at special risk population only.

A total of 324,290 individuals had received a fourth dose, at the time of database lock, with 77.9% of these reported in SIDIAP.

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	10,546 (100)	3,559,920 (100)	721,076 (100)	734,326 (100)	3,113,371 (100)
Second dose COVID-19 vaccine received					
Within 6 weeks (completion rate) after 1st dose, n (%)	8,761 (83.07)	1,856,909 (52.16)	453,708 (62.92)	657,457 (89.53)	2,619,838 (84.15)
>6 weeks after 1st dose, n (%)	247 (2.34)	781,671 (21.96)	88,608 (12.29)	27,078 (3.69)	209,790 (6.74)
Total second dose received, n (%)	9,008 (85.42)	2,638,580 (74.12)	542,316 (75.21)	684,535 (93.22)	2,829,628 (90.89)
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 (5.00-5.29)	3 (3.00-3.00)	3 (3.00-3.29)
Minimum, maximum (weeks)	2.29, 45.86	2.14, (51.00)	2.14, 96.00	2.29, 97.43	2.14, 101.00
< 2 weeks, n (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
2-4 weeks, n (%)	7,975 (88.53)	490,016 (18.57)	89,116 (16.43)	654,184 (95.57)	2,584,768 (91.35)
5-6 weeks, n (%)	786 (8.73)	1,366,893 (51.80)	364,592 (67.23)	3,273 (0.48)	35,070 (1.24)
7-8 weeks, n (%)	25 (0.28)	420,527 (15.94)	6,344 (1.17)	1,314 (0.19)	80,236 (2.84)
9-12 weeks, n (%)	9 (0.10)	269,133 (10.20)	5,362 (0.99)	1,601 (0.23)	54,658 (1.93)
13-18 weeks, n (%)	24 (0.27)	37,725 (1.43)	4,886 (0.90)	2,108 (0.31)	23,055 (0.81)
>18 weeks, n (%)	189 (2.10)	54,286 (2.06)	72,016 (13.28)	22,055 (3.22)	51,841 (1.83)

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 vaccine received	1,230 (11.66)	1,087,037 (30.54)	148,846 (20.64)	231,078 (31.47	491,222 (15.78)
Interval between second and third dose COVID-19 vaccine (weeks)					
Median (Q1, Q3) (weeks)	21.43 (19.14-24.86)	27.14 (25.29-30.00)	26.71 (22.86-34.29)	29.71 (27.29-34.29)	30.71 (27.29-41.43)
Minimum, maximum (weeks)	14.14, 55.57	13.00, 48.14	13.00, 107.00	19.43, 100.86	13.00, 100.29
<12 weeks, n (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
12-24 weeks, n (%)	925 (75.20)	232,355 (21.38)	62,705 (42.13)	12,463 (5.39)	19,234 (3.92)
25-37 weeks, n (%)	277 (22.52)	763,744 (70.26)	59,862 (40.22)	173,013 (74.87)	331,763 (67.54)
38-50 weeks, n (%)	24 (1.95)	90,938 (8.37)	18,606 (12.50)	23,818 (10.31)	75,214 (15.31)
>50 weeks, n (%)	4 (0.33)	0 (0)	7,673 (5.15)	21,784 (9.43)	65,011 (13.23)
Fourth dose COVID-19 vaccine received	16 (0.15)	203 (0.01)	16,750 (2.32)	54,861 (7.47)	252,460 (8.11)
Interval between third and fourth dose COVID-19 vaccine (weeks)					
Median (Q1, Q3) (weeks)	41.43 (40.61-44.25)	14 (13.57-16.79)	40.14 (22.29-43.43)	48.86 (47.00-50.14)	49.71 (47.71-52.14)
Minimum, maximum (weeks)	32.57, 45.86	13.00, 28.14	13.00, 73.43	19.43 (65)	13.00, 70.86
<12 weeks, n (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
12-24 weeks, n (%)	0 (0)	198 (97.54)	4,644 (27.73)	449 (0.82)	1,946 (0.77)
25-37 weeks, n (%)	2 (12.50)	5 (2.46)	2,664 (15.90)	1,078 (1.96)	4,454 (1.76)
38-50 weeks, n (%)	14 (87.50)	0 (0)	8,800 (52.54)	42,886 (78.17)	152,789 (60.52)

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

	Pedianet	NHR	PHARMO	EpiChron	SIDIAP
>50 weeks, n (%)	0 (0)	0 (0)	642 (3.83)	10,448 (19.04)	93,271 (36.94)

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

10.1.1.2. Baseline characteristics of vaccinated cohort (before matching)

The baseline characteristics of those who received at least one dose and three doses of the Pfizer-BioNTech COVID-19 vaccine in the vaccinated cohort are summarised in Table 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, that contains data for children only, was 10 years. The percentage of females among those who received a 1st dose varied from 49.11% in Pedianet to 52.16% in EpiChron (Table 7).

A maximum (i.e., with masking of numbers under five) of 102 children under 5 years of age received a first dose of the Pfizer-BioNTech COVID-19 vaccine.

A total of 7,555 pregnant women received their first dose during their first trimester of pregnancy and 8,851 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, except in PHARMO where it was received in the first quarter 2022.

The median age of individuals who received a third dose ranged from 38 years in PHARMO to 74 years in SIDIAP. The percentages of females among those who received a third dose ranged from 49.43% in Pedianet to 57.00% 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 28.50% of those who received dose 1 and 35.11% of those who received dose 3 in EpiChron were current smokers. BMI data were missing in most of the databases. In SIDIAP 12.69% of those who received dose 1 and 21.17% of those who received dose 3 had been diagnosed as obese. In the other data sources the percentages were below 8% for both doses. Between 51.77% in PHARMO and 81.42% in EpiChron of those vaccinated had used primary care at least twice in the year prior to their 1st dose. In the year prior to vaccination, between 0.84% in Pedianet and 2.29% in NHR of those who had received a first dose had been hospitalised at least two times.

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**
Total, n (%)	10,546	1,230	3,559,920	1,087,037	721,076	148,846
Demographics						
Age (years)						
Mean (SD)	9.40 (2.48)	12.28 (0.55)	47.20 (20.93)	66.06 (14.71)	48.88 (21.97)	44.11 (20.97)
Median (Q1, Q3)	10 (7,12)	12 (12,13)	47 (29,64)	68 (59,76)	50 (30,69)	38 (28,59)
Age groups (years), n (%)						
0-1	0 (0)	0 (0)	<5 (NR)	0 (0)	0 (0)	0 (0)
2-4	17 (0.16)	0 (0)	<5 (NR)	0 (0)	54 (0.01)	0 (0)
5-11	7,756 (73.54)	58 (4.72)	303 (0.01)	0 (0)	6,653 (0.92)	68 (0.05)
12-15	2,773 (26.29)	1,172 (95.28)	199,659 (5.61)	21 (< 0.01)	41,919 (5.81)	2,766 (1.86)
16-17	NA	NA	116,610 (3.28)	581 (0.05)	24,522 (3.40)	3,206 (2.15)
18-29	NA	NA	576,282 (16.19)	32,048 (2.95)	98,807 (13.70)	37,127 (24.94)
30-39	NA	NA	489,057 (13.74)	36,253 (3.34)	93,119 (12.91)	37,354 (25.10)
40-49	NA	NA	516,894 (14.52)	71,873 (6.61)	95,220 (13.21)	16,111 (10.82)
50-59	NA	NA	551,053 (15.48)	144,736 (13.31)	119,221 (16.53)	15,905 (10.69)
60-64	NA	NA	243,934 (6.85)	111,015 (10.21)	10,107 (1.40)	1,602 (1.08)
65-69	NA	NA	241,212 (6.78)	186,795 (17.18)	57,808 (8.02)	7,158 (4.81)
70-79	0 (0)	0 (0)	411,374 (11.56)	338,959 (31.18)	119,661 (16.59)	16,154 (10.85)

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**
80+	0 (0)	0 (0)	213,528 (6)	164,756 (15.16)	53,985 (7.49)	11,395 (7.66)
Female, n (%)	5,179 (49.11)	608 (49.43)	1,767,893 (49.66)	583,958 (53.72)	367,745 (51.00)	76,919 (51.68)
Females aged 14 to 50 years, n (%)	0 (0)	0 (0)	881,139 (49.84)	93,807 (16.06)	167,150 (45.45)	48,086 (62.52)
Pregnancy status, n (%)	NA	NA	6,716 (0.76)	52 (0.06)	564 (0.34)	<5 (NR)
First trimester	NA	NA	2,113 (0.24)	11 (0.01)	34 (0.02)	<5 (NR)
Second trimester	NA	NA	1,629 (0.18)	8 (0.01)	270 (0.16)	0 (0)
Third trimester	NA	NA	2,960 (0.34)	33 (0.04)	257 (0.15)	0 (0)
Residency in a long-term care facility, n (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
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)	488,552 (13.72)	0 (0)	82,060 (11.38)	0 (0)
1 Apr–30 Jun 2021	198 (1.88)	0 (0)	1,673,032 (47)	36 (0)	353,986 (49.09)	52 (0.03)
1 Jul–30 Sep 2021	1,679 (15.92)	0 (0)	1,292,653 (36.31)	7,710 (0.71)	206,198 (28.60)	113 (0.08)
1 Oct–31 Dec 2021	3,326 (31.54)	<5	103,754 (2.91)	1,079,291 (99.29)	41,684 (5.78)	40,078 (26.93)
1 Jan–31 Mar 2022	5,133 (48.67)	1,087 (88.37)	NA**	NA**	26,879 (3.73)	85,817 (57.65)
1 Apr–30 Jun 2022	139 (1.32)	92 (7.48)	NA**	NA**	2,573 (0.36)	7,824 (5.26)
1 Jul–30 Sep 2022	57 (0.54)	29 (2.36)	NA**	NA**	1,986 (0.28)	4,147 (2.79)
Personal lifestyle characteristics						
Smoking status, n (%)						
Current	0 (0)	0 (0)	0 (0)	0 (0)	185,505 (25.73)	30,579 (20.54)

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**
Former	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Never	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Never or former	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Unknown	10,546 (100)	1,230 (100)	3,559,920 (100)	1,087,037 (100)	535,571 (74.27)	118,267 (79.46)
Body Mass Index, n (%)						
Underweight (BMI < 20 kg/m2)	5,861 (55.58) ***	512 (41.63) ***	NA	NA	1,709 (0.24)	369 (0.25)
Normal weight (BMI 20 to < 25 kg/m2)	1,509 (14.31)	325 (26.42)	NA	NA	15,732 (2.18)	3,534 (2.37)
Overweight (BMI 25 to < 30 kg/m2)	319 (3.02)	77 (6.26)	NA	NA	30,406 (4.22)	6,369 (4.28)
Obese (BMI ≥ 30 kg/m2)	56 (0.53)	22 (1.79)	NA	NA	21,763 (3.02)	4,525 (3.04)
BMI missing	2,801 (26.56)	294 (23.90)	3,559,920 (100)	1,087,037 (100)	651,466 (90.35)	134,049 (90.06)
Obesity diagnosis or obesity surgery	581 (5.51)	90 (7.32)	113,699 (3.19)	45,476 (4.18)	7,096 (0.98)	1,588 (1.07)
Healthcare utilisation						
Number of hospitalisations, n (%)						
0	10,158 (96.32)	1,184 (96.26)	3,310,495 (92.99)	968,721 (89.12)	NA	NA
1	299 (2.84)	39 (3.17)	168,029 (4.72)	71,520 (6.58)	NA	NA
2+	89 (0.84)	7 (0.57)	81,396 (2.29)	46,796 (4.30)	NA	NA
Number of emergency department visits, n (%)						
0	9,303 (88.21)	1,073 (87.24)	3,559,920 (100)	1,087,037 (100)	NA	NA
1	984 (9.33)	122 (9.92)	0 (0)	0 (0)	NA	NA
2+	259 (2.46)	35 (2.85)	0 (0)	0 (0)	NA	NA

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**
Primary care utilisation, n visits (%)						
0	1,295 (12.28)	136 (11.06)	322,517 (9.06)	62,102 (5.71)	237,319 (32.91)	39,758 (26.71)
1	1,746 (16.56)	201 (16.34)	313,065 (8.79)	66,418 (6.11)	110,422 (15.31)	21,891 (14.71)
2+	7,505 (71.16)	893 (72.60)	2,924,338 (82.15)	958,517 (88.18)	373,335 (51.77)	87,197 (58.58)
Cancer screening, n (%)						
0	10,546 (100)	1,230 (100)	3,559,920 (100)	1,087,037 (100)	721,076 (100)	148,846 (100)
1	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
2+	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
COVID-19 tests, n (%)						
0	2,963 (28.10)	173 (14.07)	3,494,325 (98.16)	1,084,504 (99.77)	NA	NA
1-2	6,521 (61.83)	836 (67.97)	65,595 (1.84)	2,533 (0.23)	NA	NA
3-4	976 (9.25)	203 (16.50)	0 (0)	0 (0)	NA	NA
5+	86 (0.82)	18 (1.46)	0 (0)	0 (0)	NA	NA

*Refer to Table 3 for information on time periods for data; **Data not yet available for 2022, *** Child-specific BMI algorithm is pending validation
NR: not reportable;

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**
Total, n (%)	734,326	231,078	3,113,371	491,222
Demographics				
Age (years)				
Mean (SD)	50.57 (21.68)	59.72 (19.60)	45.36 (22.77)	63.82 (22.98)
Median (Q1, Q3)	49 (35, 70))	58 (45, 76))	45 (28,59)	74 (44,82)
Age groups (years), n (%)				
0-1	0 (0)	0 (0)	<5	<5
2-4	0 (0)	0 (0)	16 (< 0.01)	<5
5-11	2,651 (0.36)	31 (0.01)	190,402 (6.12)	189 (0.04)
12-15	36,879 (5.02)	619 (0.27)	197,685 (6.35)	3,434 (0.70)
16-17	17,650 (2.40)	2,175 (0.94)	98,177 (3.15)	9,290 (1.89)
18-29	81,117 (11.05)	13,465 (5.83)	348,968 (11.21)	46,988 (9.57)
30-39	93,081 (12.68)	21,051 (9.11)	402,597 (12.93)	40,185 (8.18)
40-49	144,190 (19.64)	39,775 (17.21)	610,587 (19.61)	47,937 (9.76)
50-59	125,013 (17.02)	44,199 (19.13)	517,693 (16.63)	38,162 (7.77)
60-64	13,545 (1.84)	4,291 (1.86)	41,044 (1.32)	5,214 (1.06)
65-69	33,818 (4.61)	15,170 (6.56)	44,465 (1.43)	7,691 (1.57)

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**
70-79	104,890 (14.28)	47,466 (20.54)	393,261 (12.63)	135,923 (27.67)
80+	81,492 (11.10)	42,836 (18.54)	268,474 (8.62)	156,204 (31.80)
Female, n (%)	383,042 (52.16)	122,468 (53)	1,617,589 (51.96)	279,986 (57.00)
Females aged 14 to 50 years, n (%)	179,583 (46.88)	41,394 (33.80)	780,762 (48.27)	79,111 (28.26)
Pregnancy status, n (%)	7,750 (4.32)	954 (2.30)	10,260 (1.31)	651 (0.82)
First trimester	1,815 (1.01)	83 (0.20)	3,593 (0.46)	206 (0.26)
Second trimester	3,227 (1.80)	443 (1.07)	3,725 (0.48)	244 (0.31)
Third trimester	2,708 (1.51)	428 (1.03)	2,919 (0.37)	200 (0.25)
Residency in a long-term care facility, n (%)	0 (0)	0 (0)	0 (0)	0 (0)
Date of vaccination, n (%)				
1 Oct–31 Dec 2020	2,298 (0.31)	0 (0)	3,696 (0.12)	0 (0)
1 Jan–31 Mar 2021	106,042 (14.44)	0 (0)	378,221 (12.15)	0 (0)
1 Apr–30 Jun 2021	379,271 (51.65)	0 (0)	1,596,237 (51.27)	14 (0)
1 Jul–30 Sep 2021	224,079 (30.51)	11,416 (4.94)	856,310 (27.50)	23,834 (4.85)
1 Oct–31 Dec 2021	16,327 (2.22)	101,683 (44)	170,174 (5.47)	282,746 (57.56)
1 Jan–31 Mar 2022	4,707 (0.64)	81,205 (35.14)	92,120 (2.96)	43,650 (8.89)

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**
1 Apr–30 Jun 2022	599 (0.08)	11,610 (5.02)	8,618 (0.28)	63,851 (13)
1 Jul–30 Sep 2022	431 (0.06)	12,218 (5.29)	4,468 (0.14)	49,312 (10.04)
Personal lifestyle characteristics				
Smoking status, n (%)				
Current	209,299 (28.50)	81,130 (35.11)	0 (0)	0 (0)
Former	0 (0)	0 (0)	0 (0)	0 (0)
Never	0 (0)	0 (0)	1,402,744 (45.06)	296,606 (60.38)
Never or former	0 (0)	0 (0)	0 (0)	0 (0)
Unknown	525,027 (71.50)	149,948 (64.89)	1,710,627 (54.94)	194,616 (39.62)
Body Mass Index, n (%)				
Underweight (BMI < 20 kg/m2)	16,803 (2.29)	1,548 (0.67)	216,878 (6.97)	8,140 (1.66)
Normal weight (BMI 20 to < 25 kg/m2)	45,867 (6.25)	10,606 (4.59)	358,354 (11.51)	62,409 (12.70)
Overweight (BMI 25 to < 30 kg/m2)	50,279 (6.85)	18,878 (8.17)	487,881 (15.67)	124,718 (25.39)
Obese (BMI ≥ 30 kg/m2)	40,791 (5.55)	17,637 (7.63)	394,954 (12.69)	99,078 (20.17)
BMI missing	580,586 (79.06)	182,409 (78.94)	1,655,304 (53.17)	196,877 (40.08)
Obesity diagnosis or obesity surgery	47,904 (6.52)	17,213 (7.45)	467,888 (15.03)	104,451 (21.26)
Healthcare utilisation				
Number of hospitalisations, n (%)				

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**
0	674,800 (91.89)	207,967 (90)	2,864,642 (92.01)	425,127 (86.54)
1	47,470 (6.46)	17,539 (7.59)	190,789 (6.13)	47,380 (9.65)
2+	12,056 (1.64)	5,572 (2.41)	57,940 (1.86)	18,715 (3.81)
Number of emergency department visits, n (%)				
0	593,396 (80.81)	183,792 (79.54)	NA	NA
1	95,514 (13.01)	31,676 (13.71)	NA	NA
2+	45,416 (6.18)	15,610 (6.76)	NA	NA
Primary care utilisation, n visits (%)				
0	84,236 (11.47)	15,384 (6.66)	400,271 (12.86)	20,199 (4.11)
1	52,191 (7.11)	13,270 (5.74)	235,607 (7.57)	14,692 (2.99)
2+	597,899 (81.42)	202,424 (87.60)	2,477,493 (79.58)	456,331 (92.90)
Cancer screening, n (%)				
0	734,326 (100)	231,078 (100)	3,113,371 (100)	491,222 (100)
1	0 (0)	0 (0)	0 (0)	0 (0)
2+	0 (0)	0 (0)	0 (0)	0 (0)
COVID-19 tests, n (%)				
0	515,950 (70.26)	130,167 (56.33)	1,382,439 (44.40)	172,249 (35.07)
1-2	218,376 (29.74)	100,911 (43.67)	1,213,338 (38.97)	179,898 (36.62)

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**
3-4	0 (0)	0 (0)	348,937 (11.21)	70,543 (14.36)
5+	0 (0)	0 (0)	168,657 (5.42)	68,532 (13.95)

NR: not reportable

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 8,139,239 vaccinated individuals included, 7,923,975 (97.36%) 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 (%)	12,046 (100)	3,831,694 (100)	1,279,343 (100)	870,551 (100)	3,704,463 (100)
Total vaccinated included, n (%)[a]	10,546 (87.55)	3,559,920 (92.91)	721,076 (56.36)	734,326 (84.35)	3,113,371 (84.04)
Pregnant women vaccinated, n (%)	0 (0)	6,716 (0.18)	679 (0.05)	10,055 (1.16)	14,320 (0.39)
Matched cohort					
Vaccinees matched, n (%)	10,478 (99.36)	3,542,453 (99.51)	648,737 (89.97)	611,445 (83.27)	3,110,862 (99.92)
Served as control before vaccination, n (%)	3,066 (29.26)	2,419,949 (68.31)	247,629 (38.17)	282,843 (46.26)	1,671,250 (53.72)
Unvaccinated, n	10,478	3,542,453	648,737	611,445	3,110,862
Unique unvaccinated matched included, n (%)	8,057 (76.89)	2,040,999 (57.62)	462,813 (71.34)	387,055 (63.30)	1,976,723 (63.55)
Number of times a comparator selected for matching, Mean	1.30	1.74	1.40	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, 6	1, 17	1, 14	1, 20	1, 15
1, n (%)	6,161 (58.80)	1,163,811 (32.85)	326,262 (50.29)	245,543 (40.16)	1,241,075 (39.89)
2, n (%)	1,483 (14.15)	506,771 (14.31)	99,388 (15.32)	89,218 (14.59)	475,276 (15.28)
3, n (%)	326 (3.11)	217,557 (6.14)	27,789 (4.28)	33,192 (5.43)	170,919 (5.49)
4, n (%)	63 (0.60)	91,341 (2.58)	7,159 (1.10)	11,984 (1.96)	58,480 (1.88)
5 or more, n (%)	24 (0.23)	61,519 (1.74)	2,215 (0.34)	7,118 (1.16)	30,973 (1.00)

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

The median months of follow up from first dose until censoring ranged from 0.8 months in NHR to 11.3 months in Pedianet and SIDIAP. The follow-up time was short in all data sources, but was similar for vaccinated and unvaccinated cohorts since the censoring date was the same for both (Table 9).

A total of 4,711,117 (63.43%) matched unvaccinated individuals were censored because of receipt of a COVID-19 vaccine (Pfizer-BioNTech COVID-19 vaccine or a non-Pfizer-BioNTech COVID-19 vaccine) (Table 9). The percentages of individuals censored for exiting the data sources or end of data availability ranged from 0.2% in the vaccinated cohort in NHR to 36.00% in unvaccinated cohort 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**	**Unvac**	**Vac**	**Unvac**	**Vac**	**Unvac**	**Vac**	**Unvac**
Total, N	10,478	10,478	3,542,453	3,542,453	648,737	648,737	611,445	611,445	3,110,862	3,110,862
Person-months of follow-up										
Median (Q1, Q3) (months)	11.30 (1.90, 11.90)	11.30 (2.00, 11.90)	0.80 (0.30, 2.10)	0.80 (0.30, 2.10)	5.50 (0.60, 11.80)	4.70 (0.60, 8.80)	1.00 (0.30, 7.50)	1.00 (0.30, 7.40)	1.30 (0.30, 7.10)	1.30 (0.30, 7.10)
Min, max (months)	0.10, 18.70	0.10, 18.90	0, 12.10	0, 12.10	0, 26.50	0, 26.50	0, 24.30	0, 24.30	0.10, 24.10	0.10, 24.10
Reasons for censoring, n (%)										
Non-Pfizer-BioNTech vaccine received	8 (0.10)	332 (3.20)	232,853 (6.60)	323,408 (9.10)	102,910 (15.90)	59,773 (9.20)	37,078 (6.10)	77,979 (12.80)	275,797 (8.90)	561,253 (18.00)
Unvaccinated received Pfizer or non-Pfizer COVID-19 vaccine	NA	3,098 (29.60)	NA	2,405,616 (67.90)	NA	272,644 (42.00)	NA	360,992 (59.00)	NA	1,668,767 (53.60))
Exit from data source[a]	717 (6.80)	606 (5.80)	6,357 (0.20)	14,522 (0.40)	215,532 (33.20)	233,581 (36.00)	1,933 (0.30)	2,743 (0.40)	0 (0)	0 (0)

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

10.1.2.1. Baseline characteristics

The prevalence of the baseline characteristics in the vaccinated and unvaccinated cohorts, and their absolute standardised differences (ASDs) for each data source are summarised in Table 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 (in both cohorts since they were matched on sex) who had received a 1st dose varied from 49.04% in Pedianet to 51.95% in EpiChron and SIDIAP (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, PHARMO, EpiChron and SIDIAP. Pregnant women were more frequently vaccinated in the second trimester in PHARMO, EpiChron and SIDIAP and in the third trimester in NHR. Information on long-term care facility residency and healthcare worker or essential worker status could not be identified in the data sources.

In PHARMO and EpiChron the distributions of smoking status in the vaccinated and unvaccinated cohorts were similar. The number of individuals with unknown smoking status was higher in PHARMO than in EpiChron (<1% in EpiChron and between 75% and 79% in PHARMO). In Pedianet, NHR and PHARMO, the information on smoking status was not collected. BMI data were missing for about 27% of individuals in Pedianet, 53% of individuals in SIDIAP, about 80% of individuals in EpiChron and about 90% of individuals in PHARMO; BMI data were not available in NHR. The percentages of individuals with an obesity diagnosis or obesity surgery were similar between the vaccinated and unvaccinated cohorts. Healthcare use indicators were similar in the vaccinated and unvaccinated cohorts in all data sources.

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	10,478	10,478		3,542,453	3,542,453		648,737	648,737	
Demographics									
Age (years)			0.09			<0.01			<0.01
Mean (SD)	9.40 (2.48)	9.16 (2.45)		47.15 (20.90)	47.05 (20.89)		48.29 (21.82)	48.23 (21.80)	
Median (Q1, Q3)	10 (7,12)	10 (7,11)		47 (29,64)	47 (29,64)		49 (30,69)	49 (30,68)	
Age groups (years), n (%)			0.30			0.13			0.07
0-1	0 (0)	0 (0)		<5	<5		0 (0)	0 (0)	
2-4	17 (0.16)	375 (3.58)		<5	<5		52 (0.01)	209 (0.03)	
5-11	7,718 (73.66)	8,216 (78.41)		300 (0.01)	30,031 (0.85)		6,202 (0.96)	9,517 (1.47)	
12-15	2,743 (26.18)	1,887 (18.01)		199,248 (5.62)	186,928 (5.28)		39,423 (6.08)	36,474 (5.62)	
16-17	NA	NA		116,183 (3.28)	114,467 (3.23)		22,808 (3.52)	22,889 (3.53)	
18-29	NA	NA		574,047 (16.20)	558,201 (15.76)		90,105 (13.89)	89,651 (13.82)	
30-39	NA	NA		487,396 (13.76)	491,203 (13.87)		84,898 (13.09)	84,721 (13.06)	
40-49	NA	NA		514,911 (14.54)	513,992 (14.51)		86,484 (13.33)	86,500 (13.33)	
50-59	NA	NA		548,924 (15.50)	549,279 (15.51)		108,897 (16.79)	106,571 (16.43)	
60-64	NA	NA		242,812 (6.85)	251,836 (7.11)		8,319 (1.28)	11,803 (1.82)	
65-69	NA	NA		240,081 (6.78)	234,749 (6.63)		51,886 (8)	51,334 (7.91)	
70-79	NA	NA		408,973 (11.54)	406,449 (11.47)		106,145 (16.36)	107,080 (16.51)	
80+	NA	NA		209,575 (5.92)	205,315 (5.80)		43,518 (6.71)	41,988 (6.47)	
Female, n (%)	5,138 (49.04)	5,138 (49.04)	0	1,758,735 (49.65)	1,758,735 (49.65)	0	330,413 (50.93)	330,413 (50.93)	0
Females aged 14 to 50 years, n (%)	0 (0)	0 (0)	0	877,433 (49.89)	873,519 (49.67)	0	151,804 (45.94)	151,587 (45.88)	0

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**
Pregnancy status, n (%)									
Pregnant	NA	NA		6,124 (0.70)	6,124 (0.70)		226 (0.15)	226 (0.15)	
First trimester	NA	NA		1,915 (0.22)	539 (0.06)		6 (<0.01)	17 (0.01)	
Second trimester	NA	NA		1,516 (0.17)	1,670 (0.19)		117 (0.08)	86 (0.06)	
Third trimester	NA	NA		2,681 (0.31)	3,715 (0.43)		101 (0.07)	117 (0.08)	
Date of vaccination or matching, n (%)			2.22			0.97			1.66
1 Oct–31 Dec 2020	0 (0)	0 (0)		1,914 (0.05)	1,914 (0.05)		0 (0)	0 (0)	
1 Jan–31 March 2021	0 (0)	0 (0)		485,117 (13.69)	485,117 (13.69)		71,596 (11.04)	71,596 (11.04)	
1 Apr–30 Jun 2021	197 (1.88)	197 (1.88)		1,667,635 (47.08)	1,667,635 (47.08)		322,686 (49.74)	322,686 (49.74)	
1 Jul–30 Sep 2021	1,665 (15.89)	1,665 (15.89)		1,286,271 (36.31)	1,286,271 (36.31)		190,789 (29.41)	190,789 (29.41)	
1 Oct–31 Dec 2021	3,308 (31.57)	3,308 (31.57)		101,516 (2.87)	101,516 (2.87)		34,633 (5.34)	34,633 (5.34)	
1 Jan–31 Mar 2022	5,101 (48.68)	5,101 (48.68)		NA*	NA*		21,695 (3.34)	21,695 (3.34)	
1 Apr–30 Jun 2022	138 (1.32)	138 (1.32)		NA*	NA*		2,002 (0.31)	2,002 (0.31)	
1 Jul–30 Sep 2022	55 (0.52)	55 (0.52)		NA*	NA*		1,495 (0.23)	1,495 (0.23)	
Personal lifestyle characteristics									
Smoking status, n (%)									
Current	NA	NA		NA	NA		162,471 (25.04)	133,415 (20.57)	
Former	NA	NA		NA	NA		0 (0)	0 (0)	
Never	NA	NA		NA	NA		0 (0)	0 (0)	
Never or former	NA	NA		NA	NA		0 (0)	0 (0)	
Unknown	NA	NA		NA	NA		486,266 (74.96)	515,322 (79.43)	
BMI			0.05			0			0.06

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**
Underweight (BMI <20kg/m^2)	5,815 (55.50)**	5,751 (54.89) **		NA	NA		1,466 (0.23)	1,491 (0.23)	
Normal weight (BMI 20 to <25kg/m^2)	1,499 (14.31)**	1,447 (13.81) **		NA	NA		13,817 (2.13)	11,395 (1.76)	
Overweight (BMI 25 to <30kg/m^2)	316 (3.02) **	261 (2.49) **		NA	NA		26,711 (4.12)	21,509 (3.32)	
Obese (BMI ≥30kg/m^2)	56 (0.53) **	45 (0.43) **		NA	NA		19,156 (2.95)	16,039 (2.47)	
BMI missing	2,792 (26.65)	2,974 (28.38)		NA	NA		587,587 (90.57)	598,303 (92.23)	
Obesity diagnosis or obesity surgery	577 (5.51)	511 (4.88)		113,134 (3.19)	95,019 (2.68)		5,709 (0.88)	5,859 (0.90)	
Healthcare utilisation									
Number of hospitalisations, n (%)			0.01			<0.01			0
0	10,095 (96.34)	10,128 (96.66)		3,295,514 (93.03)	3,290,797 (92.90)		648,737 (100)	648,737 (100)	
1	297 (2.83)	288 (2.75)		166,415 (4.70)	170,389 (4.81)		0 (0)	0 (0)	
2+	86 (0.82)	83 (0.79)		80,524 (2.27)	81,267 (2.29)		0 (0)	0 (0)	
Number of emergency department visits, n (%)			0.01			0			0
0	9,242 (88.20)	9,290 (88.66)		3,542,453 (100)	3,542,453 (100)		648,737 (100)	648,737 (100)	
1	979 (9.34)	940 (8.97)		0 (0)	0 (0)		0 (0)	0 (0)	
2+	257 (2.45)	248 (2.37)		0 (0)	0 (0)		0 (0)	0 (0)	
Primary care utilisation, n (%)			0.04			0.09			0.21
0	1,292 (12.33)	1,439 (13.73)		321,900 (9.09)	414,150 (11.69)		221,042 (34.07)	287,918 (44.38)	
1	1,740 (16.61)	1,667 (15.91)		312,366 (8.82)	322,344 (9.10)		101,042 (15.58)	84,856 (13.08)	
2+	7,446 (71.06)	7,372 (70.36)		2,908,187 (82.10)	2,805,959 (79.21)		326,653 (50.35)	275,963 (42.54)	
Cancer screening, n (%)			0			0			0

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	10,478 (100)	10,478 (100)		NA	NA		648,737 (100)	648,737 (100)	
1	0 (0)	0 (0)		NA	NA		0 (0)	0 (0)	
2+	0 (0)	0 (0)		NA	NA		0 (0)	0 (0)	
COVID-19 tests, n (%)			0.08			0			0
0	2,953 (28.18)	3,295 (31.45)		3,484,025 (98.35)	3,483,794 (98.34)		648,737 (100)	648,737 (100)	
1-2	6,478 (61.82)	6,305 (60.17)		58,428 (1.65)	58,659 (1.66)		0 (0)	0 (0)	
3-5	962 (9.18)	794 (7.58)		0 (0)	0 (0)		0 (0)	0 (0)	
5+	85 (0.81)	84 (0.80)		0 (0)	0 (0)		0 (0)	0 (0)	

ASD: absolute standardised difference; NR: not reportable; Vac: vaccinated cohort; Unvac: unvaccinated cohort; NA: not available
* Data extracted only up to 31 December 2021 for this report
** Child-specific BMI algorithm is pending validation

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	611,445	611,445		3,110,862	3,110,862	
Demographics						
Age (years)			<0.01			<0.01
Mean (SD)	49.47 (21.21)	49.35 (21.17)		45.34 (22.76)	45.25 (22.74)	
Median (Q1, Q3)	48 ((34,68))	48 ((34,68))		45 ((28,58))	45 ((28,59))	
Age groups (years), n (%)			0.06			0.08
0-1	0 (0)	0 (0)		<5 (NR)	<5 (NR)	
2-4	0 (0)	0 (0)		16 (< 0.01)	8,068 (0.26)	
5-11	2,319 (0.38)	5,031 (0.82)		190,369 (6.12)	206,624 (6.64)	
12-15	31,883 (5.21)	30,372 (4.97)		197,600 (6.35)	181,565 (5.84)	
16-17	15,200 (2.49)	14,546 (2.38)		98,130 (3.15)	88,432 (2.84)	
18-29	70,088 (11.46)	69,905 (11.43)		348,712 (11.21)	351,079 (11.29)	
30-39	79,157 (12.95)	79,520 (13.01)		402,379 (12.93)	404,276 (13)	
40-49	127,135 (20.79)	127,848 (20.91)		610,344 (19.62)	612,787 (19.70)	
50-59	106,590 (17.43)	104,571 (17.10)		517,466 (16.63)	506,679 (16.29)	
60-64	10,313 (1.69)	10,906 (1.78)		40,975 (1.32)	46,185 (1.48)	
65-69	26,624 (4.35)	29,165 (4.77)		44,397 (1.43)	51,114 (1.64)	
70-79	83,410 (13.64)	83,358 (13.63)		392,932 (12.63)	398,503 (12.81)	
80+	58,726 (9.60)	56,223 (9.20)		267,540 (8.60)	255,546 (8.21)	
Female, n (%)	317,629 (51.95)	317,629 (51.95)	0	1,616,225 (51.95)	1,616,225 (51.95)	0
Females aged 14 to 50 years, n (%)	152,645 (48.06)	152,883 (48.13)	0	780,253 (48.28)	778,028 (48.14)	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**
Pregnancy status, n (%)						
Pregnant	3,620 (2.37)	3,620 (2.37)		9,992 (1.28)	9,992 (1.28)	
First trimester	876 (0.57)	808 (0.53)		3,501 (0.45)	3,076 (0.40)	
Second trimester	1,475 (0.97)	1,295 (0.85)		3,632 (0.47)	3,326 (0.43)	
Third trimester	1,269 (0.83)	1,517 (0.99)		2,837 (0.36)	3,483 (0.45)	
Date of vaccination or matching, n (%)			1.22			1.34
1 Oct–31 Dec 2020	1,903 (0.31)	1,903 (0.31)		3,680 (0.12)	3,680 (0.12)	
1 Jan–31 March 2021	87,569 (14.32)	87,569 (14.32)		377,774 (12.14)	377,774 (12.14)	
1 Apr–30 Jun 2021	317,993 (52.01)	317,993 (52.01)		1,595,321 (51.28)	1,595,321 (51.28)	
1 Jul–30 Sep 2021	188,536 (30.83)	188,536 (30.83)		855,558 (27.50)	855,558 (27.50)	
1 Oct–31 Dec 2021	11,167 (1.83)	11,167 (1.83)		169,888 (5.46)	169,888 (5.46)	
1 Jan–31 Mar 2022	3,314 (0.54)	3,314 (0.54)		92,086 (2.96)	92,086 (2.96)	
1 Apr–30 Jun 2022	420 (0.07)	420 (0.07)		8,609 (0.28)	8,609 (0.28)	
1 Jul–30 Sep 2022	285 (0.05)	285 (0.05)		4,460 (0.14)	4,460 (0.14)	
Personal lifestyle characteristics						
Smoking status, n (%)						
Current	167,506 (27.40)	156,046 (25.52)		0 (0)	0 (0)	
Former	0 (0)	0 (0)		0 (0)	0 (0)	
Never	0 (0)	0 (0)		1,401,376 (45.05)	1,379,012 (44.33)	
Never or former	0 (0)	0 (0)		0 (0)	0 (0)	
Unknown	1,903 (0.31)	1,903 (0.31)		1,709,486 (54.95)	1,731,850 (55.67)	

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**
BMI			0.04			0.02
Underweight (BMI <20kg/m^2)	14,418 (2.36)	12,327 (2.02)		216,778 (6.97)	221,681 (7.13)	
Normal weight (BMI 20 to <25kg/m^2)	37,661 (6.16)	33,262 (5.44)		357,902 (11.50)	345,304 (11.10)	
Overweight (BMI 25 to <30kg/m^2)	39,774 (6.50)	37,410 (6.12)		487,288 (15.66)	475,178 (15.27)	
Obese (BMI ≥30kg/m^2)	31,773 (5.20)	31,702 (5.18)		394,656 (12.69)	398,951 (12.82)	
BMI missing	487,819 (79.78)	496,744 (81.24)		1,654,238 (53.18)	1,669,748 (53.67)	
Obesity diagnosis or obesity surgery	37,270 (6.10)	37,958 (6.21)		467,667 (15.03)	472,591 (15.19)	
Healthcare utilisation						
Number of hospitalisations, n (%)			0.01			<0.01
0	569,524 (93.14)	570,353 (93.28)		2,862,573 (92.02)	2,864,018 (92.07)	
1	33,812 (5.53)	32,353 (5.29)		190,460 (6.12)	188,294 (6.05)	
2+	8,109 (1.33)	8,739 (1.43)		57,829 (1.86)	58,550 (1.88)	
Number of emergency department visits, n (%)			0.02			0
0	502,110 (82.12)	505,904 (82.74)		3,110,862 (100)	3,110,862 (100)	
1	75,773 (12.39)	71,539 (11.70)		0 (0)	0 (0)	
2+	33,562 (5.49)	34,002 (5.56)		0 (0)	0 (0)	
Primary care utilisation, n (%)			0.25			0.15
0	80,066 (13.09)	138,150 (22.59)		400,224 (12.87)	566,384 (18.21)	
1	47,143 (7.71)	44,472 (7.27)		235,540 (7.57)	234,568 (7.54)	
2+	484,236 (79.20)	428,823 (70.13)		2,475,098 (79.56)	2,309,910 (74.25)	

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	611,445 (100)	611,445 (100)		3,110,862 (100)	3,110,862 (100)	
1	0 (0)	0 (0)		0 (0)	0 (0)	
2+	0 (0)	0 (0)		0 (0)	0 (0)	
COVID-19 tests, n (%)			0.09			0.18
0	446,739 (73.06)	470,384 (76.93)		1,381,801 (44.42)	1,624,263 (52.21)	
1-2	164,706 (26.94)	141,061 (23.07)		1,212,221 (38.97)	1,101,538 (35.41)	
3-5	0 (0)	0 (0)		348,509 (11.20)	284,005 (9.13)	
5+	0 (0)	0 (0)		168,331 (5.41)	101,056 (3.25)	

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

10.1.2.2. Baseline comorbidities

The prevalence of baseline comorbidities in the 10 years prior to time zero in the vaccinated and unvaccinated cohorts with absolute standardised differences (ASDs) are summarised by data source in Table 11. About 7 to 12% of individuals had a history of either a positive COVID-19 test or a COVID-19 diagnosis. Both NHR and PHARMO reported <1.7%, which is likely to be underestimated due to registration practices in Norway and The Netherlands. Histories of anaphylaxis or allergies were rare, as expected. Cardiovascular disease, hypertension and chronic respiratory disease were the most prevalent comorbidities.

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

Table 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 (%)	10,478 (100)	10,478 (100)		3,542,453 (100)	3,542,453 (100)		648,737 (100)	648,737 (100)	
COVID-19 history									
Previous diagnosis of COVID-19	0 (0)	0 (0)		4,029 (0.11)	3,657 (0.10)	<0.01	8,825 (1.36)	8,830 (1.36)	0
Positive test result for COVID-19	1,046 (10)	1,046 (10)	0	58,428 (1.65)	58,659 (1.66)	<0.01	NA	NA	
Comorbidities									
History of anaphylaxis	18 (0.17)	10 (0.10)	0.02	0 (0)	0 (0)	0	38 (0.01)	28 (0)	<0.01
History of allergies	154 (1.47)	124 (1.18)	0.02	39,208 (1.11)	38,864 (1.10)	<0.01	4,091 (0.63)	3,934 (0.61)	<0.01
Diabetes mellitus (types 1 and 2)	28 (0.27)	33 (0.31)	0.01	246,743 (6.97)	222,625 (6.28)	0.03	28,602 (4.41)	29,975 (4.62)	0.01
Hypertension	<5 (0.03)	7 (0.07)	0.02	675,873 (19.08)	656,305 (18.53)	0.01	37,614 (5.80)	36,050 (5.56)	0.01
Cardiovascular disease	400 (3.82)	343 (3.27)	0.03	1,368,101 (38.62)	1,335,631 (37.70)	0.02	192,549 (29.68)	183,299 (28.25)	0.03
Chronic respiratory disease	6,123 (58.44)	6,183 (59.01)	0.01	507,158 (14.32)	485,043 (13.69)	0.02	65,328 (10.07)	62,576 (9.65)	0.01
Chronic kidney disease	0 (0)	0 (0)		5,370 (0.15)	4,260 (0.12)	0.01	6,864 (1.06)	6,175 (0.95)	0.01
Chronic liver disease	<5 (0.01)	<5 (0.02)	0.01	18,223 (0.51)	22,340 (0.63)	0.01	638 (0.10)	981 (0.15)	0.01
Cancer	25 (0.24)	26 (0.25)	0.00	210,916 (5.95)	197,085 (5.56)	0.02	24,976 (3.85)	27,535 (4.24)	0.02
Autoimmune disorders	211 (2.01)	197 (1.88)	0.01	419,202 (11.83)	405,772 (11.45)	0.01	9,701 (1.50)	9,390 (1.45)	<0.01
Influenza infection or other respiratory infections	6,218 (59.34)	6,240 (59.55)	0.00	364,974 (10.30)	351,879 (9.93)	0.01	19,837 (3.06)	19,121 (2.95)	0.01

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
Charlson Comorbidity Index Score			0.03			0.03			0.05
0 or 1	9,776 (93.30)	9,718 (92.75)		2,874,198 (81.14)	2,913,691 (82.25)		609,784 (94)	604,668 (93.21)	
2	689 (6.58)	752 (7.18)		436,862 (12.33)	417,699 (11.79)		23,092 (3.56)	22,493 (3.47)	
3	13 (0.12)	8 (0.08)		231,393 (6.53)	211,063 (5.96)		15,861 (2.44)	21,576 (3.33)	
Myocardial infarct	<5 (NR)	<5 (NR)	0	13,118 (0.37)	12,642 (0.36)	<0.01	662 (0.10)	648 (0.10)	0
Congestive heart failure	0 (0)	0 (0)		78,303 (2.21)	77,198 (2.18)	<0.01	4,664 (0.72)	6,176 (0.95)	0.03
Cerebrovascular disease	4 (0.04)	8 (0.08)	0.02	109,727 (3.10)	102,771 (2.90)	0.01	8,460 (1.30)	9,452 (1.46)	0.01
Peripheral vascular disease	51 (0.49)	47 (0.45)	0.01	115,540 (3.26)	110,214 (3.11)	0.01	21,808 (3.36)	18,922 (2.92)	0.03
Mild to moderate kidney disease	0 (0)	0 (0)		0 (0)	0 (0)		682 (0.11)	863 (0.13)	0.01
Severe kidney disease	0 (0)	0 (0)		4,114 (0.12)	4,054 (0.11)	0	239 (0.04)	341 (0.05)	0.01
Mild liver disease	<5 (NR)	<5 (NR)	0	7,908 (0.22)	8,421 (0.24)	<0.01	151 (0.02)	240 (0.04)	0.01
Moderate or severe liver disease	0 (0)	0 (0)		12,581 (0.36)	12,356 (0.35)	<0.01	106 (0.02)	143 (0.02)	<0.01
Malignant tumour	9 (0.09)	10 (0.10)	<0.01	180,564 (5.10)	165,695 (4.68)	0.02	12,241 (1.89)	15,485 (2.39)	0.04
Metastasic solid tumour	0 (0)	0 (0)		8,659 (0.24)	7,394 (0.21)	0.01	817 (0.13)	1,009 (0.16)	0.01
HIV/AIDS	6 (0.06)	<5 (NR)	0.02	6,283 (0.18)	6,380 (0.18)	<0.01	496 (0.08)	510 (0.08)	<0.01
Diabetes with complications	0 (0)	0 (0)		<5 (0)	<5 (0)		1,652 (0.25)	2,096 (0.32)	0.01
Diabetes no complications	7 (0.07)	<5 (NR)	0.02	<5 (0)	0 (0)		1,927 (0.30)	2,063 (0.32)	<0.01
Dementia	0 (0)	0 (0)		43,094 (1.22)	29,950 (0.85)	0.04	1,695 (0.26)	2,919 (0.45)	0.03
Skin ulcer	<5 (NR)	5 (0.05)	<0.01	44,411 (1.25)	45,237 (1.28)	<0.01	1,007 (0.16)	1,168 (0.18)	0.01
Hemiplegia	6 (0.06)	5 (0.05)	<0.01	12,124 (0.34)	9,933 (0.28)	0.01	1,028 (0.16)	1,608 (0.25)	0.02
Connective tissue disease	142 (1.36)	145 (1.38)	<0.01	271,364 (7.66)	265,279 (7.49)	0.01	4,490 (0.69)	3,704 (0.57)	0.01

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
CDC at-risk groups [a]			<0.01			<0.01			0
Group 0 (no conditions)	3,487 (33.28)	3,487 (33.28)		1,546,571 (43.66)	1,546,571 (43.66)		384,623 (59.29)	384,623 (59.29)	
Group 1 (1 condition)	3,315 (31.64)	3,318 (31.67)		683,845 (19.30)	683,816 (19.30)		128,243 (19.77)	128,225 (19.77)	
Group 2 (>1 condition)	3,676 (35.08)	3,673 (35.05)		1,312,037 (37.04)	1,312,066 (37.04)		135,871 (20.94)	135,889 (20.95)	
Immunocompromising conditions	3,191 (30.45)	3,191 (30.45)	0	746,531 (21.07)	746,531 (21.07)	0	70,980 (10.94)	70,980 (10.94)	0
Surrogates of frailty									
Wheelchair use	0 (0)	0 (0)		NA	NA		NA	NA	
Home hospital bed	0 (0)	0 (0)		NA	NA		NA	NA	
Paralysis	6 (0.06)	5 (0.05)	0.01	14,995 (0.42)	12,681 (0.36)	0.01	1,635 (0.25)	2,140 (0.33)	0.01
Parkinson’s disease	0 (0)	0 (0)		13,852 (0.39)	11,324 (0.32)	0.01	894 (0.14)	1,139 (0.18)	0.01
Weakness	0 (0)	<5 (NR)	0.01	349,328 (9.86)	351,334 (9.92)	<0.01	29,360 (4.53)	25,215 (3.89)	0.03
Stroke/brain injury	<5 (NR)	<5 (NR)	0.01	49,352 (1.39)	45,670 (1.29)	0.01	3,271 (0.50)	3,873 (0.60)	0.01
Ambulance transport	NA	NA		NA	NA		NA	NA	
Difficulty walking	61 (0.58)	66 (0.63)	0.01	NA	NA		534 (0.08)	800 (0.12)	0.01
Home oxygen	NA	NA		NA	NA		NA	NA	
Rehabilitation care	NA	NA		NA	NA		NA	NA	
Psychiatric illness	61 (0.58)	56 (0.53)	0.01	665,806 (18.80)	707,125 (19.96)	0.03	55,115 (8.50)	62,161 (9.58)	0.04
Sepsis	<5 (NR)	6 (0.06)	0.03	44,320 (1.25)	42,886 (1.21)	<0.01	4,544 (0.70)	4,387 (0.68)	<0.01
Podiatric care	NA	NA		NA	NA		NA	NA	
Bladder incontinence	200 (1.91)	206 (1.97)	<0.01	109,649 (3.10)	105,710 (2.98)	0.01	13,942 (2.15)	11,732 (1.81)	0.02
Arthritis	375 (3.58)	357 (3.41)	0.01	482,334 (13.62)	478,242 (13.50)	<0.01	32,638 (5.03)	28,014 (4.32)	0.03
Coagulation deficiencies	82 (0.78)	67 (0.64)	0.02	11,657 (0.33)	11,803 (0.33)	<0.01	1,361 (0.21)	1,446 (0.22)	<0.01

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
Vertigo	58 (0.55)	48 (0.46)	0.01	250,334 (7.07)	247,046 (6.97)	<0.01	15,790 (2.43)	12,873 (1.98)	0.03
Lipid abnormalities	0 (0)	0 (0)		189,761 (5.36)	183,198 (5.17)	0.01	2,452 (0.38)	2,028 (0.31)	0.01

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

Table 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	611,445 (100)	611,445 (100)		3,110,862 (100)	3,110,862 (100)	
COVID-19 history						
Previous diagnosis of COVID-19	3,147 (0.51)	3,679 (0.60)	0.01	380,788 (12.24)	377,993 (12.15)	<0.01
Positive test result for COVID-19	42,918 (7.02)	42,914 (7.02)	0	327,745 (10.54)	338,393 (10.88)	0.01
Comorbidities						
History of anaphylaxis	5,145 (0.84)	4,792 (0.78)	0.01	502 (0.02)	500 (0.02)	0
History of allergies	48,419 (7.92)	44,809 (7.33)	0.02	31,266 (1.01)	29,724 (0.96)	<0.01
Diabetes mellitus (types 1 and 2)	53,891 (8.81)	56,990 (9.32)	0.02	256,567 (8.25)	267,660 (8.60)	0.01
Hypertension	97,516 (15.95)	98,119 (16.05)	<0.01	433,544 (13.94)	428,913 (13.79)	<0.01
Cardiovascular disease	231,931 (37.93)	225,902 (36.95)	0.02	1,017,636 (32.71)	999,338 (32.12)	0.01
Chronic respiratory disease	68,342 (11.18)	68,361 (11.18)	0	763,670 (24.55)	758,498 (24.38)	<0.01
Chronic kidney disease	22,574 (3.69)	22,511 (3.68)	<0.01	127,984 (4.11)	126,536 (4.07)	<0.01
Chronic liver disease	2,234 (0.37)	2,516 (0.41)	0.01	84,709 (2.72)	89,587 (2.88)	0.01
Cancer	20,437 (3.34)	20,524 (3.36)	<0.01	153,207 (4.92)	150,725 (4.85)	<0.01
Autoimmune disorders	22,693 (3.71)	22,504 (3.68)	<0.01	139,067 (4.47)	139,596 (4.49)	<0.01
Influenza infection or other respiratory infections	57,482 (9.40)	53,253 (8.71)	0.02	899,603 (28.92)	872,685 (28.05)	0.02
Charlson Comorbidity Index Score			0.01			0.01
0 or 1	540,043 (88.32)	537,582 (87.92)		2,481,360 (79.76)	2,473,182 (79.50)	
2	44,800 (7.33)	46,574 (7.62)		399,368 (12.84)	409,311 (13.16)	
3	26,602 (4.35)	27,289 (4.46)		230,134 (7.40)	228,369 (7.34)	
Myocardial infarct	737 (0.12)	886 (0.14)	0.01	3,970 (0.13)	4,176 (0.13)	0
Congestive heart failure	11,716 (1.92)	12,239 (2)	0.01	56,563 (1.82)	56,436 (1.81)	0
Cerebrovascular disease	12,520 (2.05)	12,275 (2.01)	<0.01	66,642 (2.14))	64988 (2.09)	<0.01

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**
Peripheral vascular disease	10,055 (1.64)	10,119 (1.65)	<0.01	89,525 (2.88)	89,389 (2.87)	<0.01
Mild to moderate kidney disease	6,049 (0.99)	6,377 (1.04)	<0.01	26,726 (0.86)	25,868 (0.83)	
Severe kidney disease	545 (0.09)	584 (0.10)	<0.01	1,910 (0.06)	1,098 (0.04)	0.01
Mild liver disease	2,034 (0.33)	2,189 (0.36)	0.01	20,196 (0.65)	21,116 (0.68)	<0.01
Moderate or severe liver disease	529 (0.09)	678 (0.11)	0.01	1,833 (0.06)	2,138 (0.07)	<0.01
Malignant tumour	14,570 (2.38)	15,015 (2.46)	<0.01	76,397 (2.46)	78,528 (2.52)	<0.01
Metastasic solid tumour	485 (0.08)	597 (0.10)	0.01	919 (0.03)	1,312 (0.04)	0.01
HIV/AIDS	75 (0.01)	86 (0.01)	<0.01	0 (0)	0 (0)	
Diabetes with complications	4,733 (0.77)	4,929 (0.81)	<0.01	51,221 (1.65)	53,139 (1.71)	<0.01
Diabetes no complications	7,240 (1.18)	7,818 (1.28)	0.01	38,667 (1.24)	39,433 (1.27)	<0.01
Dementia	5,422 (0.89)	4,270 (0.70)	0.02	46,899 (1.51)	38,880 (1.25)	0.02
Skin ulcer	16,824 (2.75)	15,757 (2.58)	0.01	15,754 (0.51)	16,013 (0.51)	<0.01
Hemiplegia	2,298 (0.38)	2,135 (0.35)	<0.01	15,201 (0.49)	13,270 (0.43)	0.01
Connective tissue disease	80,845 (13.22)	72,428 (11.85)	0.04	211,937 (6.81)	206,762 (6.65)	0.01
CDC at-risk groups [a]			0			0
Group 0 (no conditions)	281,872 (46.10)	281,872 (46.10)		1,253,422 (40.29)	1,253,422 (40.29)	
Group 1 (1 condition)	116,130 (18.99)	116,100 (18.99)		531,208 (17.08)	531,208 (17.08)	
Group 2 (>1 condition)	213,443 (34.91)	213,473 (34.91)		1,326,232 (42.63)	1,326,232 (42.63)	
Immunocompromising conditions	59,574 (9.74)	59,574 (9.74)	0	703,176 (22.60)	703,176 (22.60)	0
Surrogates of frailty						
Wheelchair use	NA	NA		NA	NA	
Home hospital bed	NA	NA		NA	NA	
Paralysis	3,271 (0.53)	2,976 (0.49)	0.01	17,258 (0.55)	14,948 (0.48)	0.01

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**
Parkinson's disease	2,852 (0.47)	2,541 (0.42)	0.01	11,235 (0.36)	9,987 (0.32)	0.01
Weakness	5,469 (0.89)	5,567 (0.91)	<0.01	207,426 (6.67)	213,811 (6.87)	0.01
Stroke/brain injury	3,276 (0.54)	3,249 (0.53)	<0.01	31,253 (1)	30,689 (0.99)	<0.01
Ambulance transport	NA	NA		NA	NA	
Difficulty walking	1,624 (0.27)	1,491 (0.24)	<0.01	32,030 (1.03)	29,471 (0.95)	0.01
Home oxygen	NA	NA		NA	NA	
Rehabilitation care	NA	NA		NA	NA	
Psychiatric illness	117,143 (19.16)	112,936 (18.47)	0.02	639,860 (20.57)	635,065 (20.41)	<0.01
Sepsis	3,402 (0.56)	3,436 (0.56)	<0.01	19,344 (0.62)	19,075 (0.61)	<0.01
Podiatric care	NA	NA		NA	NA	
Bladder incontinence	31,747 (5.19)	29,639 (4.85)	0.02	147,308 (4.74)	134,853 (4.33)	0.02
Arthritis	223,610 (36.57)	208,657 (34.13)	0.05	775,338 (24.92)	772,403 (24.83)	<0.01
Coagulation deficiencies	14,215 (2.32)	14,175 (2.32)	0	10,904 (0.35)	10,350 (0.33)	<0.01
Vertigo	8,735 (1.43)	8,600 (1.41)	<0.01	405,749 (13.04)	401,970 (12.92)	<0.01
Lipid abnormalities	32,972 (5.39)	32,802 (5.36)	<0.01	276,865 (8.90)	273,009 (8.78)	<0.01

ASD: absolute standardised difference; NR: not reportable; 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.

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 (%)	10,478 (100)	10,478 (100)		3,542,453 (100)	3,542,453 (100)		648,737 (100)	648,737 (100)	
Comedications, n (%)									
Analgesics	18 (0.17)	20 (0.19)	<0.01	785,319 (22.17)	757,539 (21.38)	0.02	31,557 (4.86)	29,305 (4.52)	0.02
Antibiotics	1,048 (10.00)	1,123 (10.72)	0.02	601,616 (16.98)	579,791 (16.37)	0.02	43,628 (6.73)	39,376 (6.07)	0.03
Antiviral medications	26 (0.25)	33 (0.31)	0.01	45,713 (1.29)	43,593 (1.23)	<0.01	1,647 (0.25)	1,567 (0.24)	<0.01
Corticosteroids	329 (3.14)	422 (4.03)	0.05	176,644 (4.99)	175,546 (4.96)	<0.01	14,585 (2.25)	13,869 (2.14)	0.01
Non-steroidal anti-inflammatory drugs	113 (1.08)	143 (1.36)	0.03	649,173 (18.33)	618,679 (17.46)	0.02	40,477 (6.24)	34,797 (5.36)	0.04
Psychotropics	60 (0.57)	81 (0.77)	0.02	505,318 (14.26)	517,137 (14.60)	0.01	27,738 (4.28)	26,875 (4.14)	0.01
Statins	0 (0)	0 (0)		516,866 (14.59)	481,037 (13.58)	0.03	50,487 (7.78)	41,738 (6.43)	0.05
Novel oral anticoagulants	<5 (NR)	<5 (NR)	0.02	433,415 (12.23)	415,043 (11.72)	0.02	40,269 (6.21)	34,853 (5.37)	0.04
Warfarin	<5 (NR)	<5 (NR)	0.01	24,868 (0.70)	23,611 (0.67)	<0.01	<5 (NR)	0 (0)	0
Immunosuppressant medications	336 (3.21)	428 (4.08)	0.05	219,549 (6.20)	209,276 (5.91)	0.01	17,315 (2.67)	16,129 (2.49)	0.01
Other vaccines, n (%)									
Influenza	NA	NA		NA	NA		NA	NA	
Pneumococcal	5,285 (50.44)	5,338 (50.94)	0.01	302,690 (8.54)	280,560 (7.92)	0.02	NA	NA	
DTP (diphtheria, tetanus, and pertussis)	<5 (NR)	<5 (NR)	<0.01	88,401 (2.50)	88,148 (2.49)	<0.01	NA	NA	
TPV (polio)	8,010 (76.45)	7,830 (74.73)	0.04	120,069 (3.39)	113,132 (3.19)	0.01	NA	NA	
TV (MMR) (measles, mumps and rubella)	2,821 (26.92)	2,701 (25.78)	0.03	536,363 (15.14)	523,637 (14.78)	0.01	NA	NA	
Hib (Haemophilus influenzae type b)	4,605 (43.95)	4,805 (45.86)	0.04	3,245 (0.09)	3,230 (0.09)	<0.01	NA	NA	
HepB (hepatitis B virus)	40 (0.38)	65 (0.62)	0.03	132,701 (3.75)	124,243 (3.51)	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)	7,718 (73.66)	7,350 (70.15)	0.08	5,285 (0.15)	5,084 (0.14)	<0.01	NA	NA	
HPV (human papillomavirus)	1,442 (13.76)	997 (9.52)	0.13	NA	NA		NA	NA	
Meningitis	5,723 (54.62)	5,535 (52.82)	0.04	267,688 (7.56)	214,202 (6.05)	0.06	NA	NA	

ASD: absolute standardised difference, NR: not reportable; 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	611,445 (100)	611,445 (100)		3,110,862 (100)	3,110,862 (100)	
Comedications, n (%)						
Analgesics	180,276 (29.48)	169,336 (27.69)	0.04	769,072 (24.72)	760,691 (24.45)	0.01
Antibiotics	115,639 (18.91)	104,068 (17.02)	0.05	468,108 (15.05)	451,706 (14.52)	0.01
Antiviral medications	3,867 (0.63)	3,624 (0.59)	<0.01	18,854 (0.61)	17,168 (0.55)	0.01
Corticosteroids	25,864 (4.23)	26,379 (4.31)	<0.01	112,638 (3.62)	113,389 (3.64)	<0.01
Non-steroidal anti-inflammatory drugs	160,272 (26.21)	141,109 (23.08)	0.07	568,621 (18.28)	553,016 (17.78)	0.01
Psychotropics	133,466 (21.83)	122,560 (20.04)	0.04	481,692 (15.48)	453,514 (14.58)	0.02
Statins	113,536 (18.57)	108,452 (17.74)	0.02	357,708 (11.50)	337,941 (10.86)	0.02
Novel oral anticoagulants	54,562 (8.92)	53,831 (8.80)	<0.01	223,746 (7.19)	217,309 (6.99)	0.01
Warfarin	199 (0.03)	189 (0.03)	<0.01	4,310 (0.14)	4,270 (0.14)	0
Immunosuppressant medications	27,771 (4.54)	28,277 (4.62)	<0.01	120,519 (3.87)	120,619 (3.88)	0
Other vaccines, n (%)						
Influenza	NA	NA		NA	NA	
Pneumococcal	31,868 (5.21)	27,233 (4.45)	0.04	NA	NA	
DTP (diphtheria, tetanus, and pertussis)	135,291 (22.13)	118,790 (19.43)	0.07	NA	NA	
TPV (polio)	1,098 (0.18)	1,452 (0.24)	0.01	NA	NA	
TV (MMR) (measles, mumps and rubella)	24,314 (3.98)	19,739 (3.23)	0.04	NA	NA	
Hib (Haemophilus influenzae type b)	692 (0.11)	600 (0.10)	0	NA	NA	
HepB (hepatitis B virus)	6,361 (1.04)	5,659 (0.93)	0.01	NA	NA	
VZV (varicella-zoster virus)	10,242 (1.68)	8,543 (1.40)	0.02	NA	NA	
HPV (human papillomavirus)	33,955 (5.55)	27,089 (4.43)	0.05	NA	NA	
Meningitis	61,671 (10.09)	48,778 (7.98)	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**

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 (%)	10,478 (100)	10,478 (100)		3,542,453 (100)	3,542,453 (100)		648,737 (100)	648,737 (100)	
Autoimmune diseases									
Guillain-Barré syndrome	<5 (NR)	<5 (NR)	<0.01	0 (0)	0 (0)	<0.01	10 (0)	7 (0)	<0.01
Acute disseminated encephalomyelitis	NA	NA		NA	NA		0 (0)	0 (0)	<0.01
Narcolepsy	0 (0)	0 (0)	<0.01	<5 (0)	5 (0)	<0.01	<5 (NR)	<5 (NR)	<0.01
Acute aseptic arthritis	36 (0.34)	40 (0.38)	0.01	30,715 (0.87)	30,586 (0.86)	<0.01	1,263 (0.19)	1,086 (0.17)	<0.01
Diabetes mellitus type 1	14 (0.13)	15 (0.14)	<0.01	49,302 (1.39)	41,029 (1.16)	0.02	662 (0.10)	682 (0.11)	<0.01
(Idiopathic) thrombocytopenia	<5 (NR)	<5 (NR)	0.01	0 (0)	0 (0)	<0.01	107 (0.02)	116 (0.02)	<0.01
Thrombotic thrombocytopenia syndrome (TTS)	TBR	TBR		TBR	TBR		9 (<0.01)	<5 (NR)	<0.01
Myositis	0 (0)	0 (0)	<0.01	470 (0.01)	402 (0.01)	<0.01	8 (<0.01)	16 (<0.01)	<0.01
Cardiovascular system									
Acute cardiovascular injury[a]	<5 (NR)	<5 (NR)	<0.01	108,623 (3.07)	104,523 (2.95)	0.01	2,877 (0.44)	2,793 (0.43)	<0.01
Arrhythmia	22 (0.21)	21 (0.20)	<0.01	169,811 (4.79)	164,193 (4.64)	0.01	5,700 (0.88)	5,102 (0.79)	0.01
Heart failure	NA	NA		40,474 (1.14)	41,409 (1.17)	<0.01	1,151 (0.18)	1,274 (0.20)	0.01
Stress cardiomyopathy	NA	NA		NA	NA		14 (<0.01)	13 (<0.01)	<0.01
Coronary artery disease	NA	NA		74,445 (2.10)	69,804 (1.97)	0.01	1,556 (0.24)	1,412 (0.22)	<0.01
Myocarditis	6 (0.06)	6 (0.06)	<0.01	285 (0.01)	290 (0.01)	<0.01	29 (<0.01)	40 (0.01)	<0.01
Pericarditis	<5 (NR)	<5 (NR)	0.01	969 (0.03)	960 (0.03)	<0.01	14 (<0.01)	20 (<0.01)	<0.01
Circulatory system									
Coagulation disorders: thromboembolism, haemorrhage	6 (0. 06)	6 (0. 06)	<0.01	27,799 (0.78)	26,658 (0.75)	<0.01	860 (0.13)	914 (0.14)	<0.01
Single organ cutaneous vasculitis	<5 (NR)	<5 (NR)	0.01	0 (0)	0 (0)	<0.01	7 (<0.01)	17 (<0.01)	<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**
Hepato-gastrointestinal and renal system									
Acute liver injury	0 (0)	0 (0)	<0.01	362 (0.01)	389 (0.01)	<0.01	8 (<0.01)	10 (<0.01)	<0.01
Acute kidney injury	0 (0)	0 (0)	<0.01	0 (0)	0 (0)	<0.01	328 (0.05)	432 (0.07)	0.01
Acute pancreatitis	NA	NA		0 (0)	0 (0)	<0.01	149 (0.02)	142 (0.02)	<0.01
Rhabdomyolysis	NA	NA		0 (0)	0 (0)	<0.01	10 (<0.01)	<5 (<0.01)	<0.01
Nerves and central nervous system									
Generalised convulsion	<5 (NR)	<5 (NR)	<0.01	0 (0)	0 (0)	<0.01	48 (0.01)	36 (0.01)	<0.01
Meningoencephalitis	0	0	<0.01	1,056 (0.03)	962 (0.03)	<0.01	18 (<0.01)	23 (<0.01)	<0.01
Transverse myelitis	<5 (NR)	0 (0)	0.01				<5 (NR)	<5 (NR)	<0.01
Bell's palsy	<5 (NR)	<5 (NR)	0.01	2,139 (0.06)	2,400 (0.07)	<0.01	157 (0.02)	150 (0.02)	<0.01
Respiratory system									
Acute respiratory distress syndrome	NA	NA		99 (<0.01)	112 (<0.01)	<0.01	14 (<0.01)	19 (<0.01)	<0.01
Skin and mucous membrane, bone, and joints system									
Erythema multiforme	<5 (NR)	0	0.01	NA	NA		5 (<0.01)	<5 (NR)	<0.01
Chilblain-like lesions	<5 (NR)	<5 (NR)	<0.01	NA	NA		393 (0.06)	287 (0.04)	0.01
Reproductive system									
Secondary amenorrhea	<5	<5	<0.01	0 (0)	0 (0)	<0.01	0 (0)	0 (0)	<0.01
Hypermenorrhea	14 (0.10)	6 (0.10)	0.01	NA	NA		12 (<0.01)	8 (<0.01)	<0.01
Other systems									
Anosmia, ageusia	<5 (NR)	<5 (NR)	<0.01	2,011 (0.06)	1,842 (0.05)	<0.01	304 (0.05)	266 (0.04)	<0.01
Anaphylaxis	18 (0.14)	10 (0.10)	0.02				38 (0.01)	28 (<0.01)	<0.01
Multisystem inflammatory syndrome	NA	NA		15 (<0.01)	18 (<0.01)	<0.01	<5 (NR)	<5 (NR)	<0.01
Subacute thyroiditis	NA	NA		NA	NA		<5 (NR)	5 (NR)	<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
Any									
Severe COVID-19 disease	739 (7.05)	893 (8.52)	0.06	54,893 (1.55)	56,366 (1.59)	<0.01	8,108 (1.25)	8,233 (1.27)	<0.01

ASD: absolute standardised difference; NR: not reportable; 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	611,445 (100)	611,445 (100)		3,110,862 (100)	3,110,862 (100)	
Autoimmune diseases						
Guillain-Barré syndrome	14 (<0.01)	16 (<0.01)	<0.01	138 (<0.01)	165 (0.01)	<0.01
Acute disseminated encephalomyelitis	0 (0)	<5 (NR)	<0.01	<5 (NR)	<5 (NR)	<0.01
Narcolepsy	8 (<0.01)	<5 (NR)	<0.01	49 (<0.01)	39 (<0.01)	<0.01
Acute aseptic arthritis	2,236 (0.37)	2,195 (0.36)	<0.01	15,491 (0.50)	14,937 (0.48)	<0.01
Diabetes mellitus type 1	3,695 (0.60)	3,918 (0.64)	<0.01	7,949 (0.26)	8,446 (0.27)	<0.01
(Idiopathic) thrombocytopenia	391 (0.06)	461 (0.08)	<0.01	4,207 (0.14)	4,214 (0.14)	<0.01
Thrombotic thrombocytopenia syndrome (TTS)	26 (<0.01)	32 (0.01)	<0.01	186 (0.01)	204 (0.01)	<0.01
Myositis	42 (0.01)	41 (0.01)	<0.01	464 (0.01)	435 (0.01)	<0.01
Cardiovascular system						
Acute cardiovascular injury[a]	6,478 (1.06)	7,223 (1.18)	0.01	25,394 (0.82)	26,011 (0.84)	<0.01
Arrhythmia	8,778 (1.44)	9,012 (1.47)	<0.01	52,399 (1.68)	51,151 (1.64)	<0.01
Heart failure	4,180 (0.68)	4,684 (0.77)	0.01	17,044 (0.55)	17,265 (0.55)	<0.01
Stress cardiomyopathy	33 (0.01)	32 (0.01)	<0.01	202 (0.01)	196 (0.01)	<0.01
Coronary artery disease	1,568 (0.26)	1,783 (0.29)	0.01	7,496 (0.24)	7,781 (0.25)	<0.01
Myocarditis	27 (<0.01)	31 (0.01)	<0.01	126 (<0.01)	104 (<0.01)	<0.01
Pericarditis	120 (0.02)	133 (0.02)	<0.01	772 (0.02)	877 (0.03)	<0.01
Circulatory system						
Coagulation disorders: thromboembolism, haemorrhage	3,960 (0.65)	4,219 (0.69)	<0.01	13,778 (0.44)	14,307 (0.46)	<0.01
Single organ cutaneous vasculitis	332 (0.05)	274 (0.04)	<0.01	111 (<0.01)	118 (<0.01)	<0.01
Hepato-gastrointestinal and renal system						
Acute liver injury	173 (0.03)	212 (0.03)	<0.01	473 (0.02)	560 (0.02)	<0.01
Acute kidney injury	1,994 (0.33)	2,352 (0.38)	0.01	14,136 (0.45)	14,833 (0.48)	<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**
Acute pancreatitis	430 (0.07)	479 (0.08)	<0.01	2,067 (0.07)	2,249 (0.07)	<0.01
Rhabdomyolysis	132 (0.02)	135 (0.02)	<0.01	554 (0.02)	585 (0.02)	<0.01
Nerves and central nervous system						
Generalised convulsion	78 (0.01)	78 (0.01)	<0.01	319 (0.01)	348 (0.01)	<0.01
Meningoencephalitis	50 (0.01)	58 (0.01)	<0.01	250 (0.01)	306 (0.01)	<0.01
Transverse myelitis	<5 (NR)	<5 (NR)	<0.01	16 (<0.01)	17 (<0.01)	<0.01
Bell's palsy	272 (0.04)	318 (0.05)	<0.01	2,628 (0.08)	2,774 (0.09)	<0.01
Respiratory system						
Acute respiratory distress syndrome	115 (0.02)	192 (0.03)	0.01	1,068 (0.03)	1,439 (0.05)	0.01
Skin and mucous membrane, bone, and joints system						
Erythema multiforme	32 (0.01)	27 (<0.01)	<0.01	161 (0.01)	168 (0.01)	<0.01
Chilblain-like lesions	281 (0.05)	235 (0.04)	<0.01	1,791 (0.06)	1,766 (0.06)	<0.01
Reproductive system						
Secondary amenorrhea	24 (<0.01)	16 (<0.01)	<0.01	7,665 (0.25)	8,432 (0.27)	<0.01
Hypermenorrhea	3,103 (0.51)	2,842 (0.46)	0.01	12,420 (0.40)	12,541 (0.40)	<0.01
Other systems						
Anosmia, ageusia	974 (0.16)	922 (0.15)	<0.01	2,493 (0.08)	2,264 (0.07)	<0.01
Anaphylaxis	5,145 (0.84)	4,792 (0.78)	0.01	502 (0.02)	500 (0.02)	<0.01
Multisystem inflammatory syndrome	0 (0)	0 (0)	<0.01	5 (<0.01)	<5 (<0.01)	<0.01
Subacute thyroiditis	<5 (NR)	6 (<0.01)	<0.01	11 (<0.01)	9 (<0.01)	<0.01
Any						
Severe COVID-19 disease	40,873 (6.68)	40,699 (6.66)	<0.01	347,990 (11.19)	361,929 (11.63)	0.01

ASD: absolute standardised difference; NR: not reportable; 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 IR #4 are the following two secondary analyses:

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

- Description of incidence rates and assessment of a potential increased risk of prespecified AESI following the administration of at least one dose of the Pfizer-BioNTech COVID-19 vaccine compared with a matched comparator group with no COVID-19 vaccination. in Europe using a cohort study design and/or a SCRI design.

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

The results are summarized for each data source, per AESI, in the following tables and figures. The data for COVID-19 disease in the first 12 days after vaccination were used for the negative control (see Section 10.3.1 below).

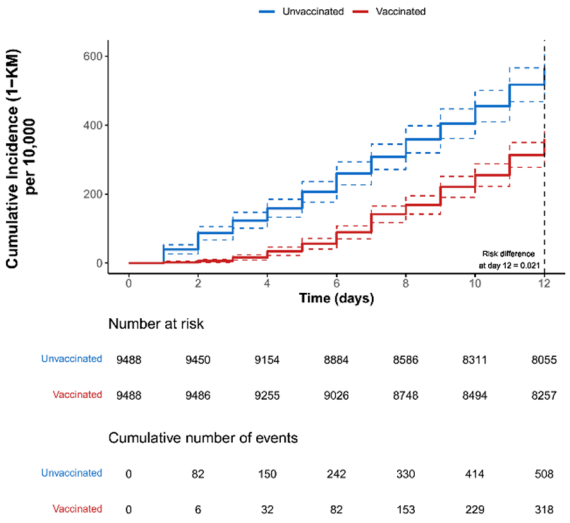
10.3.1. Results from negative control

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, PHARMO, EpiChron and SIDIAP the differences between the incidences were less than 1 per 1000 cases, which was the a-priori set threshold for baseline exchangeability. Figure 5difference between. In Pedianet, the difference between the incidences of COVID-19 disease in the first 12 days was 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. Although we considered that the matching process achieved the required balance between the cohorts, the analyses were performed in the matched cohorts with additional control for confounding to evaluate the effect of the PS adjustment.

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

Pedianet



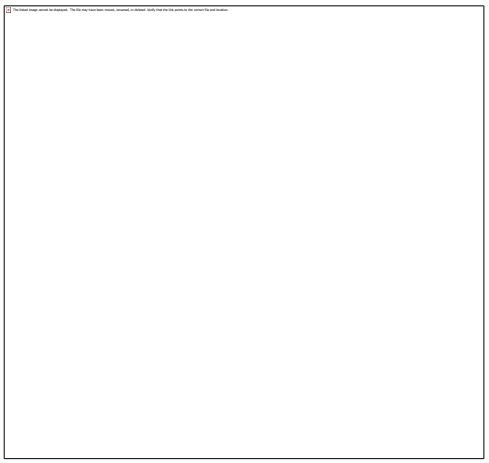
Number at risk

Unvaccinated	9488	9450	9154	8884	8586	8311	8055
Vaccinated	9488	9486	9255	9026	8748	8494	8257

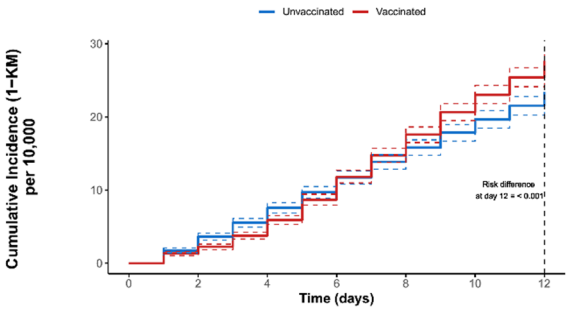
Cumulative number of events

Unvaccinated	0	82	150	242	330	414	508
Vaccinated	0	6	32	82	153	229	318

NHR



PHARMO



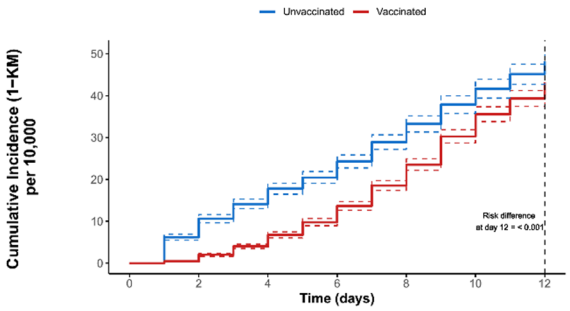
Number at risk

Unvaccinated	639992	639651	601180	572838	550349	531133	515929
Vaccinated	639992	635561	597733	569875	547670	529549	514682

Cumulative number of events

Unvaccinated	0	232	473	713	941	1148	1342
Vaccinated	0	143	364	706	1024	1317	1558

EpiChron



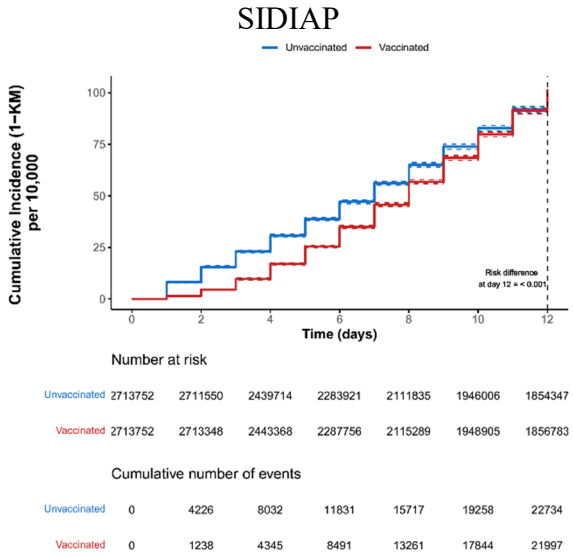
Number at risk

Unvaccinated	568603	568213	502855	486245	437624	373707	361341
Vaccinated	568603	568577	503500	486969	438410	374496	362130

Cumulative number of events

Unvaccinated	0	606	972	1291	1699	2025	2264
Vaccinated	0	115	357	698	1145	1611	1887

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



10.3.2. Guillain-Barré syndrome

Guillain-Barré syndrome was a very rare event that was observed in two of the five data sources. In SIDIAP events occurred in both the vaccinated and unvaccinated cohorts and in EpiChron only in the unvaccinated cohort. The IRs were 0.3 per 10,000 person-years (95% CI: 0.13, 0.70) in SIDIAP in the vaccinated cohort and were 0.30 per 10,000 person-years (95% CI: 0.20, 0.80) in SIDIAP and 0.47 per 10,000 person-years (95% CI: 0.12; 1.88) in EpiChron in the unvaccinated cohorts. The cumulative incidence was below 1 per 10,000 individuals in both cohorts in both data sources. Due to the absence of events in the vaccinated cohorts in Pedianet, NHR, PHARMO, and EpiChron, age-related effects on incidence were only observed in SIDIAP, with a trend for increased incidence at higher age groups. The matched HR for Guillain-Barré syndrome in SIDIAP was 1.14 (95% CI: 0.38, 3.40) and the adjusted HR was 1.11 (95% CI: 0.37, 3.31). 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)

	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)	0	0 (0, 0)	1,034.33	0 (0, 35.66)	0	0 (0, 0)	1,034.89	NA
NHR (Norway)	0	0 (0, 0)	240,790.32	0 (0, 0.15)	0	0 (0, 0)	240,499.36	NA
PHARMO (Netherlands)	0	0 (0, 0)	56,853.81	0 (0, 0.65)	<5	0.02 (0, 0.05)	56,954.14	0.18 (0.02, 1.25)
EpiChron (Spain)	0	0 (0, 0)	42,607.99	0 (0, 0.87)	<5	0.05 (0, 0.11)	42,560.24	0.47 (0.12, 1.88)
SIDIAP (Spain)	8	0 (0, 0.10)	233,106.17	0.34 (0.15, 0.68)	7	0.03 (0, 0.06)	233,106.18	0.30 (0.13, 0.70)

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

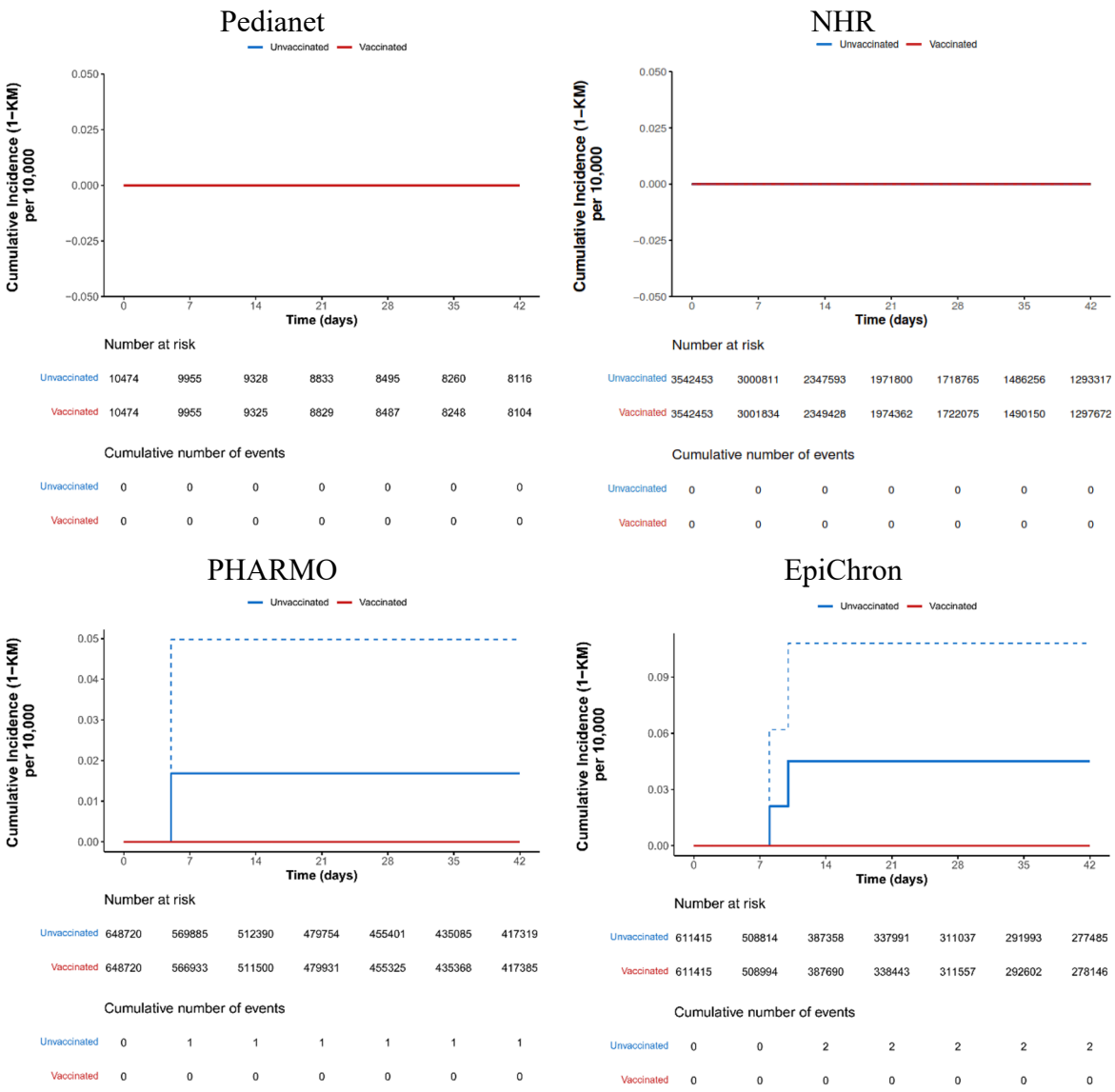
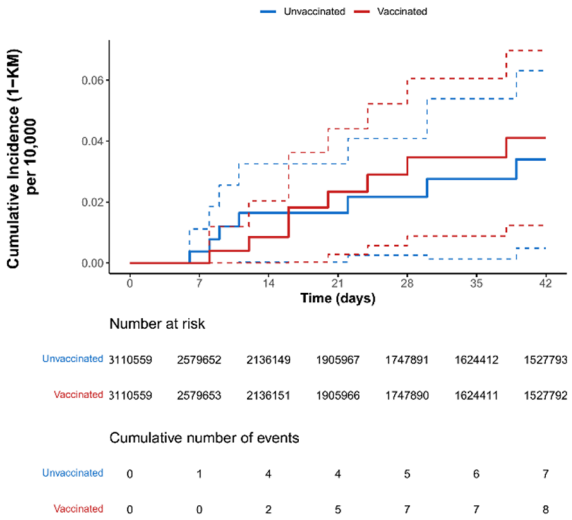


Figure 6. Cumulative incidence of Guillain-Barré syndrome among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source (risk window: 42 days after dose 1

SIDIAP



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)

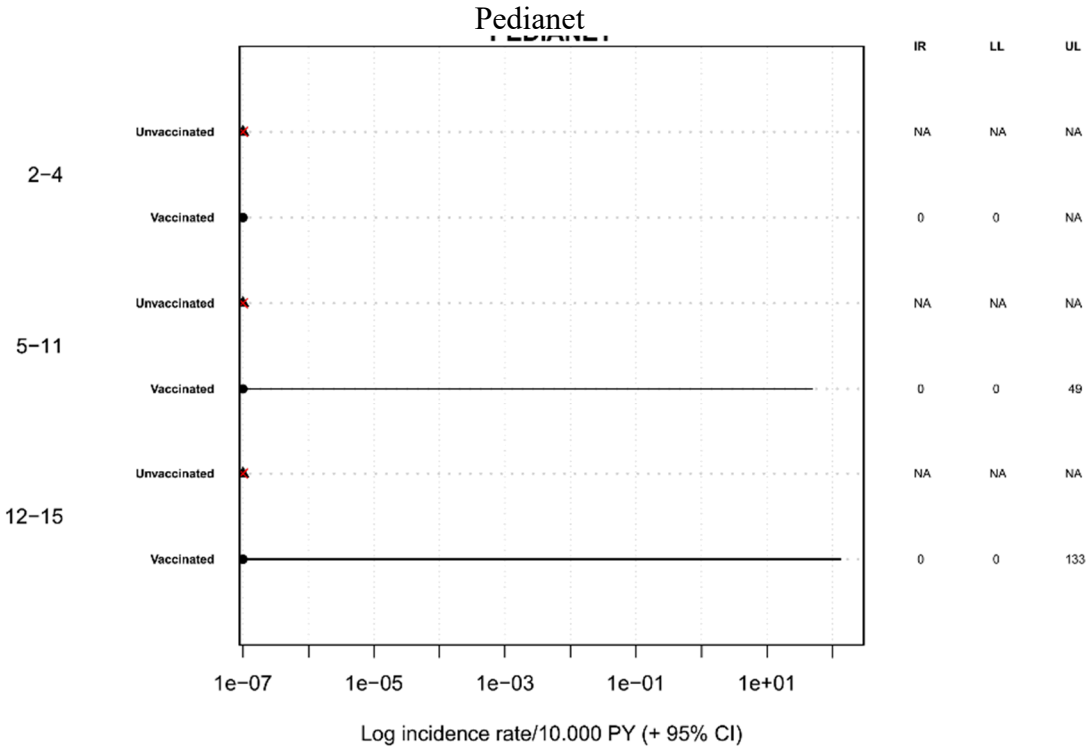


Figure 7. Forest plot showing incidence rates and 95% confidence intervals for Guillain-Barré syndrome among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source and by age groups (risk window: 42 days after dose 1)

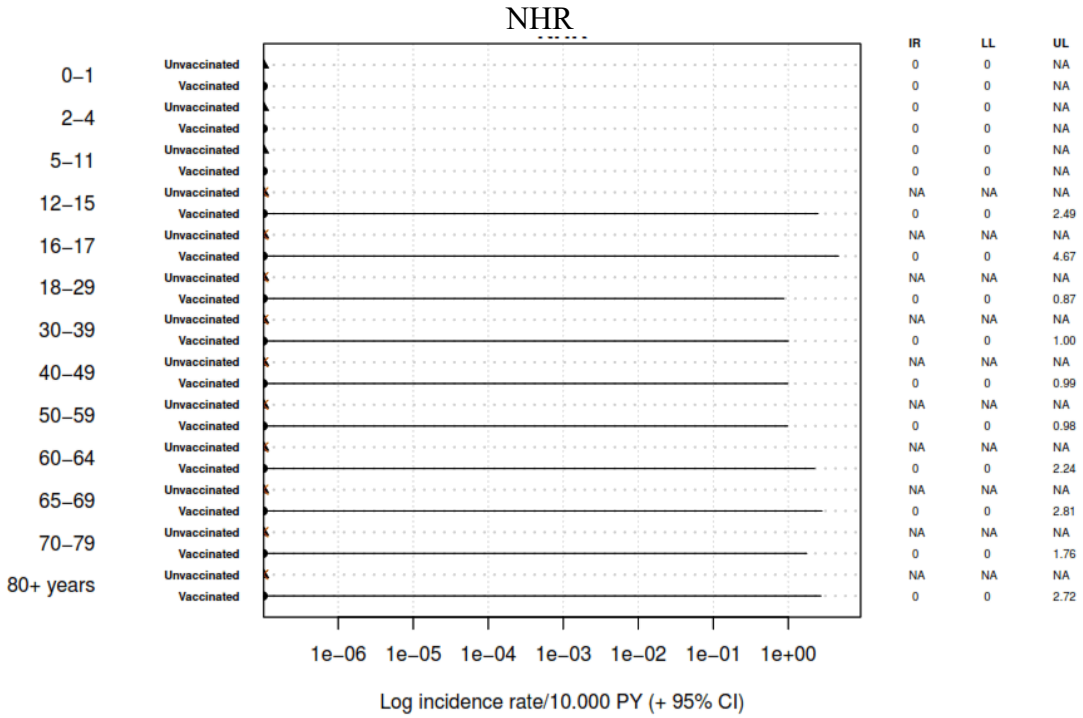


Figure 7. Forest plot showing incidence rates and 95% confidence intervals for Guillain-Barré syndrome among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source and by age groups (risk window: 42 days after dose 1)

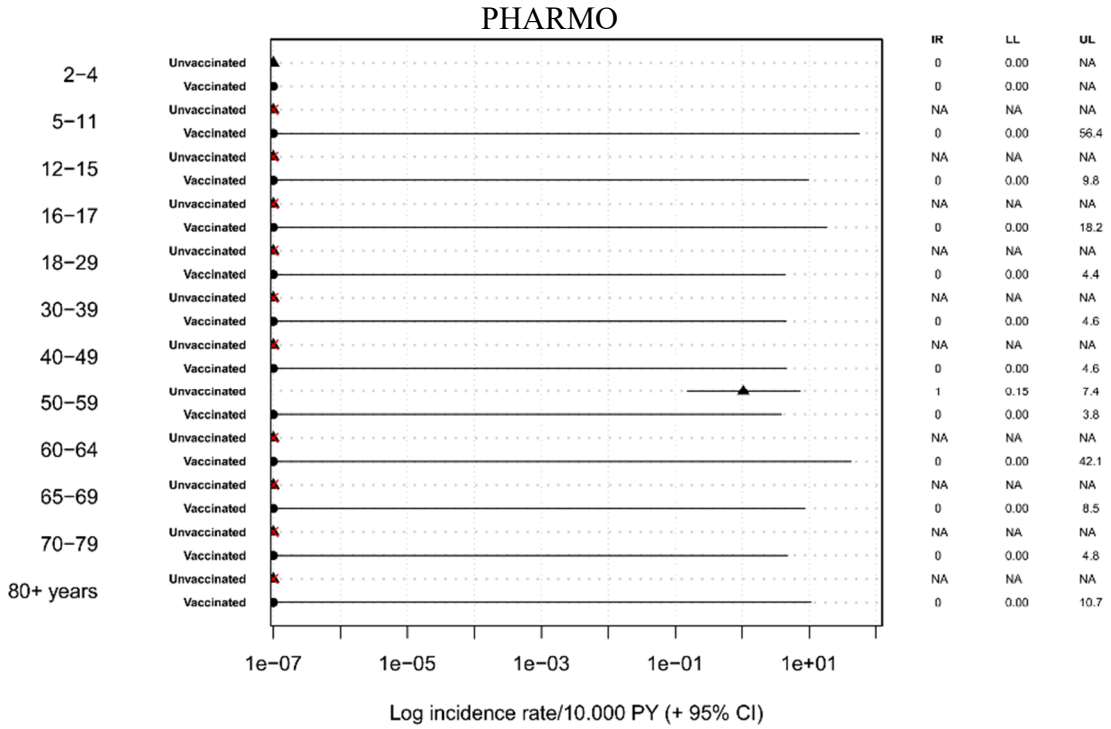


Figure 7. Forest plot showing incidence rates and 95% confidence intervals for Guillain-Barré syndrome among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source and by age groups (risk window: 42 days after dose 1)

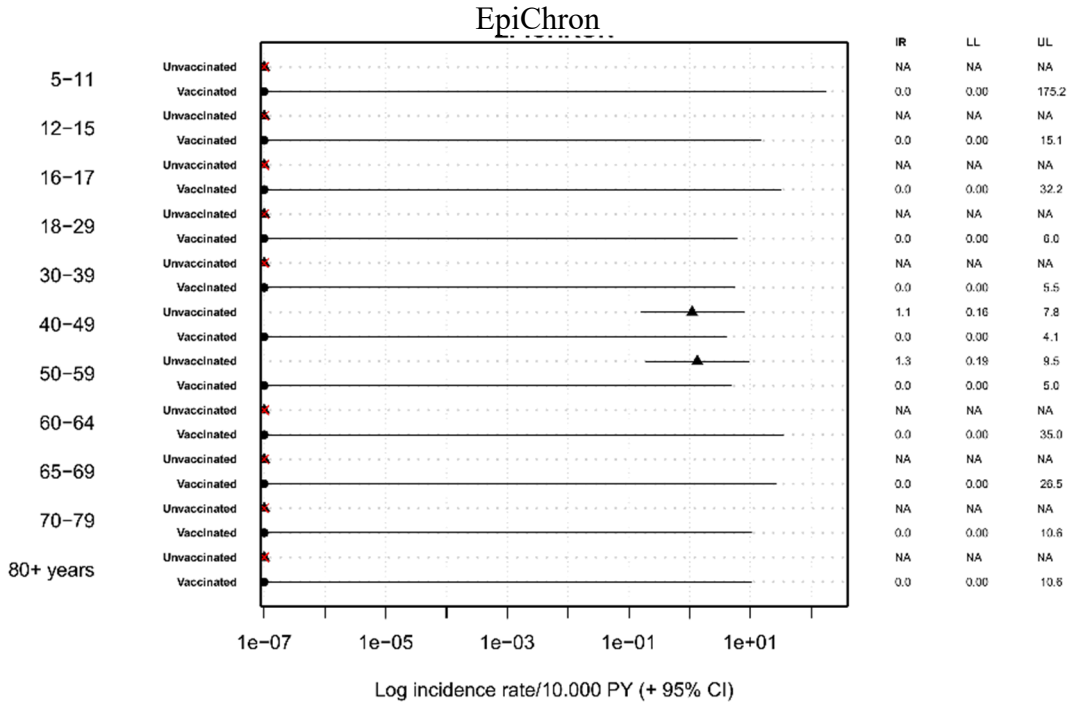


Figure 7. Forest plot showing incidence rates and 95% confidence intervals for Guillain-Barré syndrome among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source and by age groups (risk window: 42 days after dose 1)

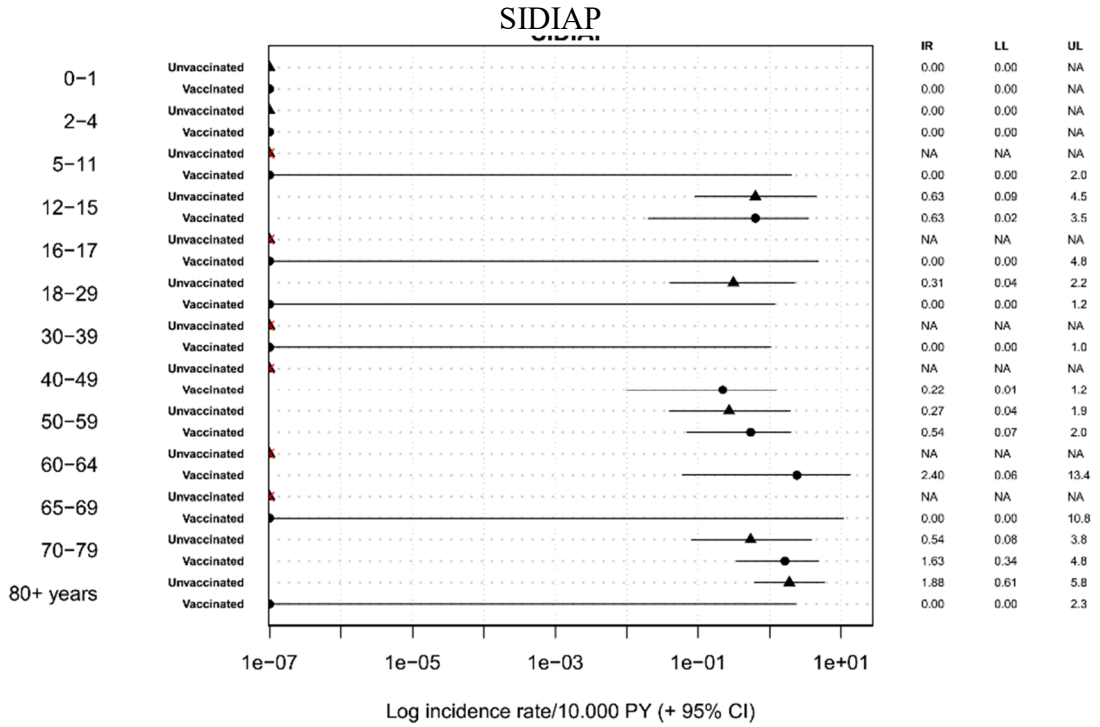


Table 16. Matched and adjusted hazard ratios (HRs) and matched and adjusted risk differences (RDs) per 10,000 person-years and their 95% CIs for Guillain-Barré syndrome among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source (at 42 days after dose 1)

	Matched HR (95% CI)	Adjusted HR (95% CI)	Matched RD	Adjusted RD
Pedianet	NA	NA	NA	NA
NHR	NA	NA	NA	NA
PHARMO	NA	NA	-0.02	-0.02
EpiChron	NA	NA	-0.05	-0.05
SIDIAP	1.14 (0.38, 3.40)	1.11 (0.37, 3.31)	0.01	0.01

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

10.3.3. Acute disseminated encephalomyelitis

Acute disseminated encephalomyelitis was a very rare event with <5 events 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.

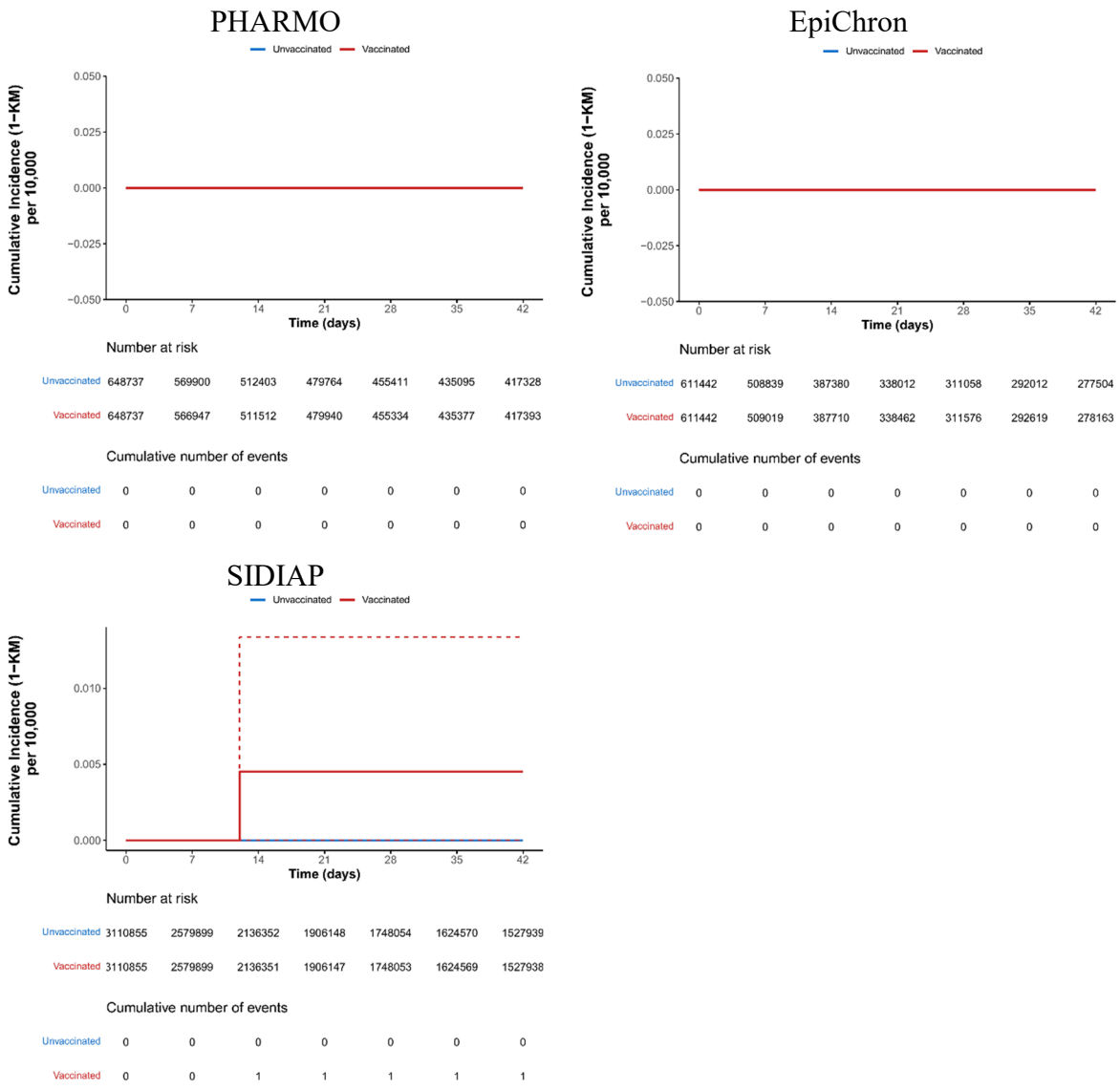
Table 17. Risk estimates (95% CI) per 10,000 person-years (PY) for acute disseminated encephalomyelitis among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source (risk window: 42 days after dose 1)

	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)	NA	NA	NA	NA	NA	NA	NA	NA
NHR (Norway)	NA	NA	NA	NA	NA	NA	NA	NA
PHARMO (Netherlands)	0	0 (0, 0)	56,855.08	0 (0, 0.65)	0	0 (0, 0)	56,955.51	NA
EpiChron (Spain)	0	0 (0, 0)	42,610.30	0 (0, 0.87)	0	0 (0, 0)	42,562.73	NA
SIDIAP (Spain)	<5	0 (0, 0.01)	233,128.29	0 (0, 0.24)	0	0 (0, 0)	233,128.37	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+).

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)

PHARMO

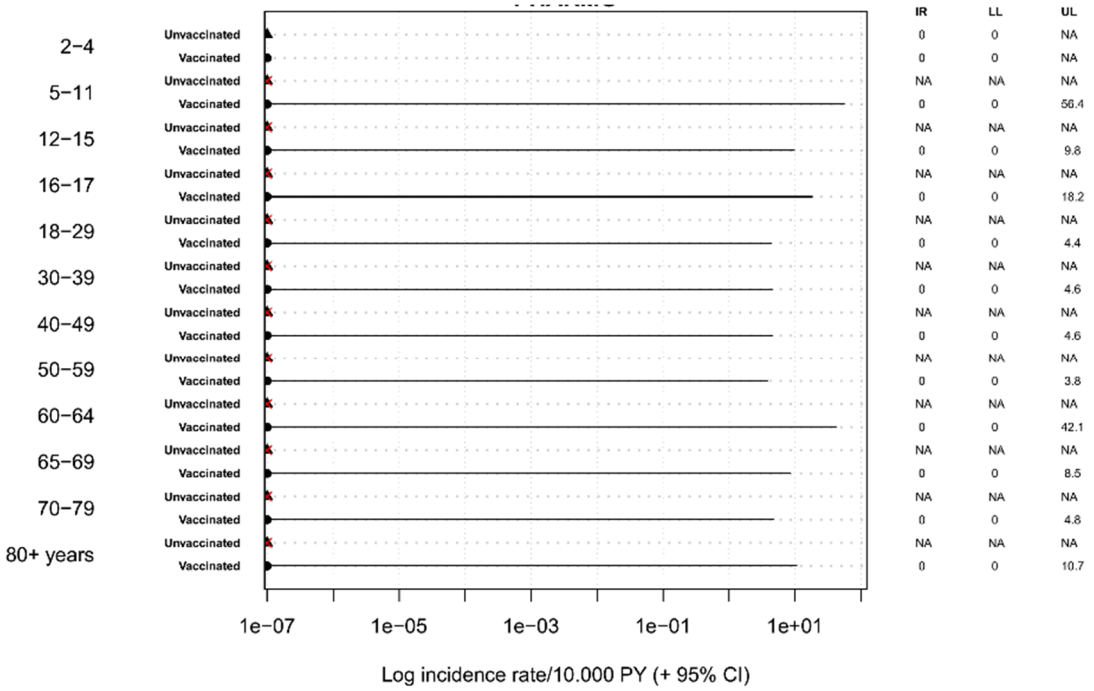


Figure 9. Forest plot showing incidence rates and 95% confidence intervals for acute disseminated encephalomyelitis among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source and by age groups (risk window: 42 days after dose 1)

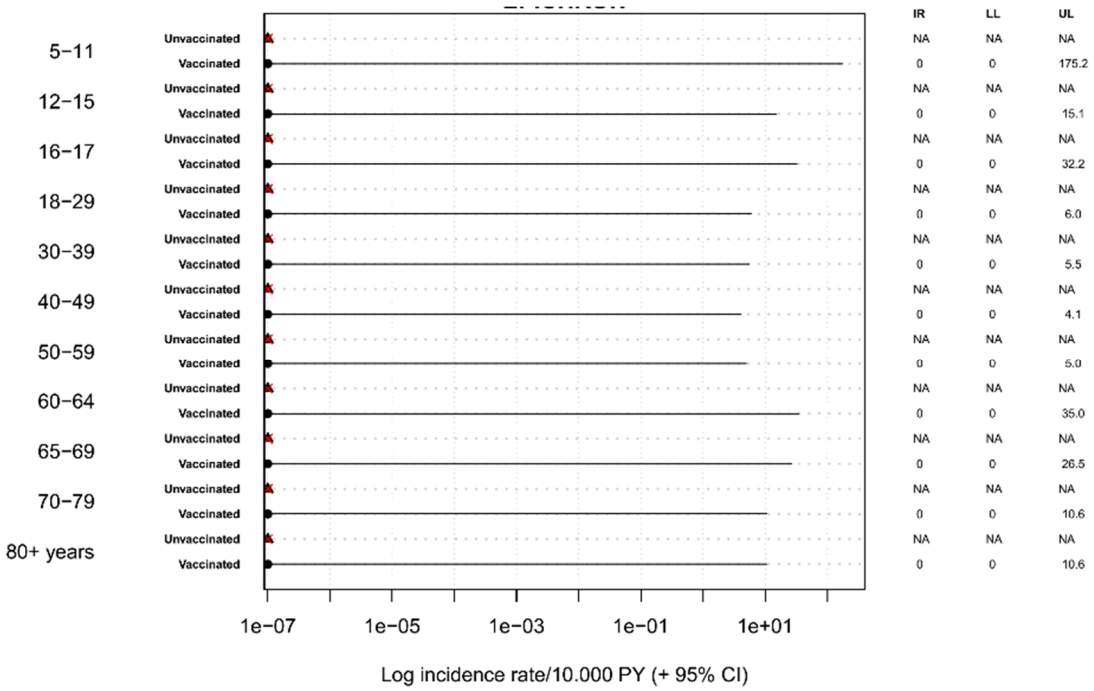


Figure 9. Forest plot showing incidence rates and 95% confidence intervals for acute disseminated encephalomyelitis among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source and by age groups (risk window: 42 days after dose 1)

SIDIAP

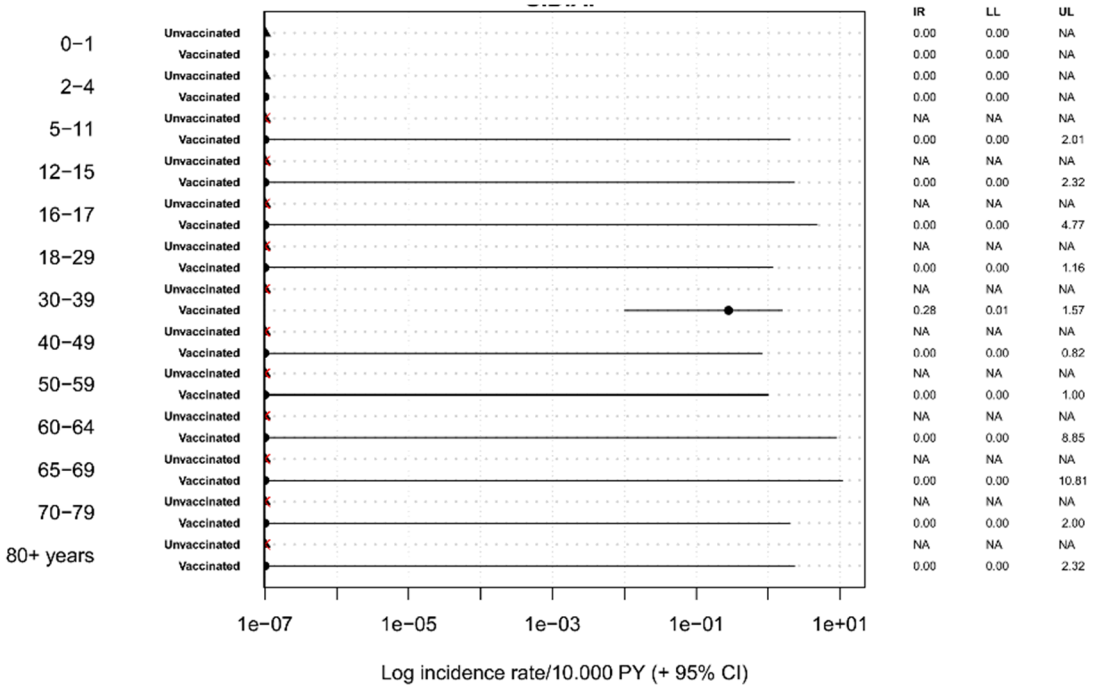


Table 18. Matched and adjusted hazard ratios (HRs) and matched and adjusted risk differences (RDs) per 10,000 person-years and their 95% CIs for acute disseminated encephalomyelitis among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source (risk window: 42 days after dose 1)

	Matched HR (95% CI)	Adjusted HR (95% CI)	Matched RD	Adjusted RD
Pedianet	NA	NA	NA	NA
NHR	NA	NA	NA	NA
PHARMO	NA	NA	NA	NA
EpiChron	NA	NA	NA	NA
SIDIAP	NA	NA	0	0

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

10.3.4. Narcolepsy

Narcolepsy was only observed in SIDIAP during the study risk window of 42 days. The incidence rates were 0.13 (95% CI: 0.03, 0.38) per 10,000 person-years in SIDIAP in the vaccinated cohorts and 0.21 (95% CI: 0.08, 0.61) per 10,000 person-years in the unvaccinated cohort. Due to the low number of events in the 42-day risk window no age-related incidence patterns were observed. The matched HR for narcolepsy in SIDIAP was 0.60 (95% CI: 0.13, 2.78) and the adjusted HR was 0.56 (95% CI: 0.12, 2.66). 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)

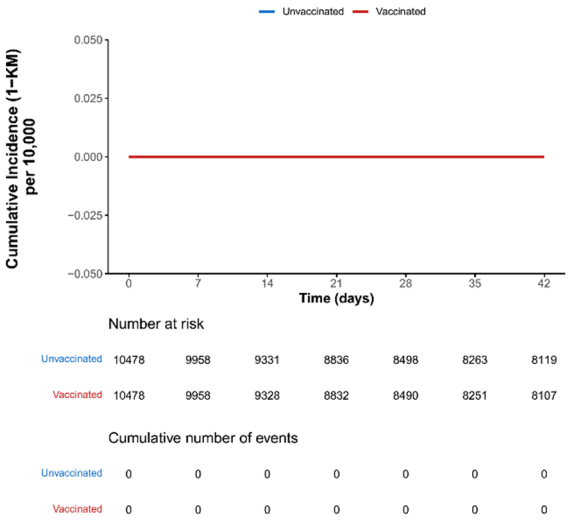
	Vaccinated				Unvaccinated			
Data source	**Events (n)**	**Cumulative incidence (95% CI)**	**Person-years (PY)**	**Incidence rate (95% CI)**	**Events (n)**	**Cumulative incidence (95% CI)**	**Person-years (PY)**	**Incidence rate (95% CI)**
Pedianet (Italy)	0	0 (0, 0)	1,034.69	0 (0, 35.65)	0	0 (0, 0)	1,035.25	NA
NHR (Norway)	0	0 (0, 0)	240,789.81	0 (0, 0.15)	0	0 (0, 0)	240,498.85	NA
PHARMO (Netherlands)	0	0 (0, 0)	56,854.84	0 (0, 0.65)	0	0 (0, 0)	56,955.27	NA
EpiChron (Spain)	0	0 (0, 0)	42,609.75	0 (0, 0.87)	0	0 (0, 0)	42,562.18	NA
SIDIAP (Spain)	<5	0.01 (0, 0.03)	233,122	0.13 (0.03, 0.38)	5	0.03 (0, 0.06)	233,122.03	0.21 (0.08, 0.61)

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)

Pedianet



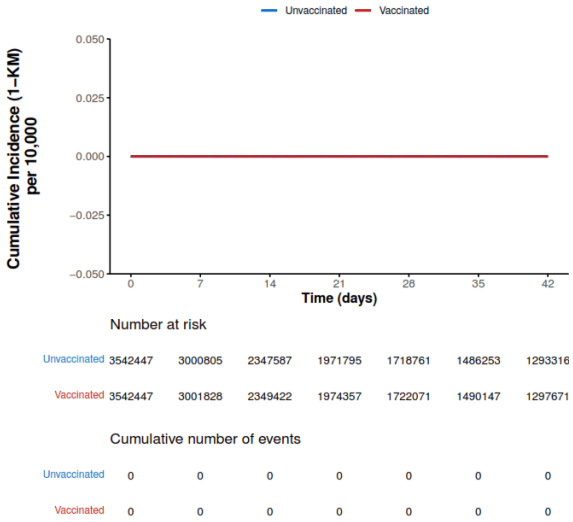
Number at risk

Unvaccinated	10478	9958	9331	8836	8498	8263	8119
Vaccinated	10478	9958	9328	8832	8490	8251	8107

Cumulative number of events

Unvaccinated	0	0	0	0	0	0	0
Vaccinated	0	0	0	0	0	0	0

NHR



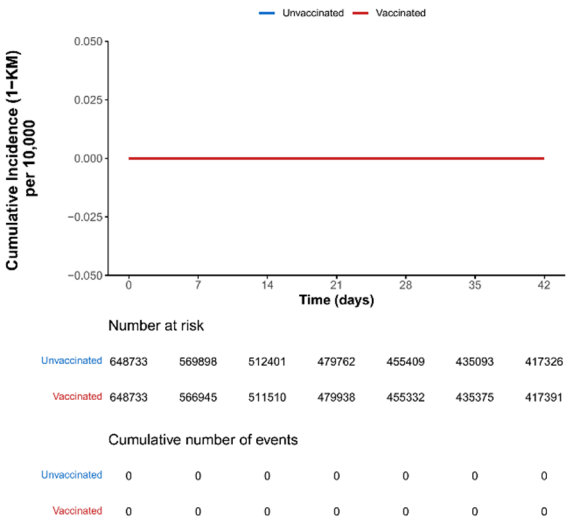
Number at risk

Unvaccinated	3542447	3000805	2347587	1971795	1718761	1486253	1293316
Vaccinated	3542447	3001828	2349422	1974357	1722071	1490147	1297671

Cumulative number of events

Unvaccinated	0	0	0	0	0	0	0
Vaccinated	0	0	0	0	0	0	0

PHARMO



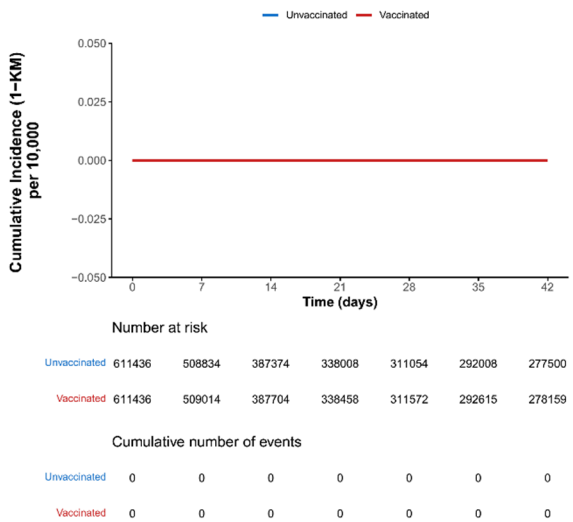
Number at risk

Unvaccinated	648733	569898	512401	479762	455409	435093	417326
Vaccinated	648733	566945	511510	479938	455332	435375	417391

Cumulative number of events

Unvaccinated	0	0	0	0	0	0	0
Vaccinated	0	0	0	0	0	0	0

EpiChron



Number at risk

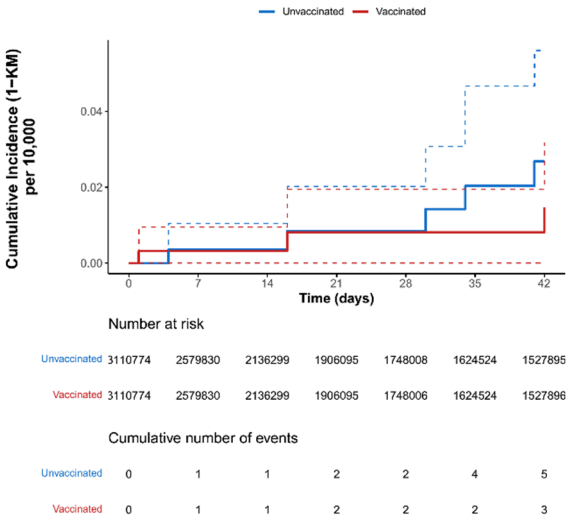
Unvaccinated	611436	508834	387374	338008	311054	292008	277500
Vaccinated	611436	509014	387704	338458	311572	292615	278159

Cumulative number of events

Unvaccinated	0	0	0	0	0	0	0
Vaccinated	0	0	0	0	0	0	0

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)

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 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)

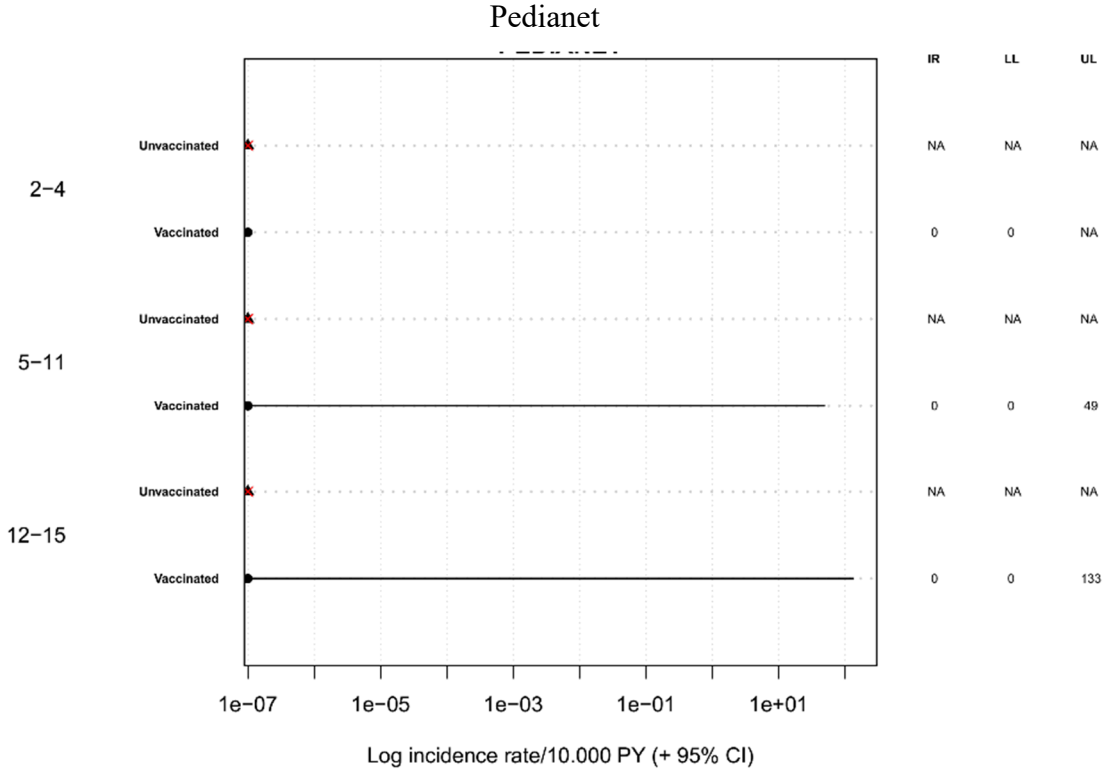


Figure 11. Forest plot showing incidence rates and 95% confidence intervals for narcolepsy among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source and by age groups (risk window: 42 days after dose 1)

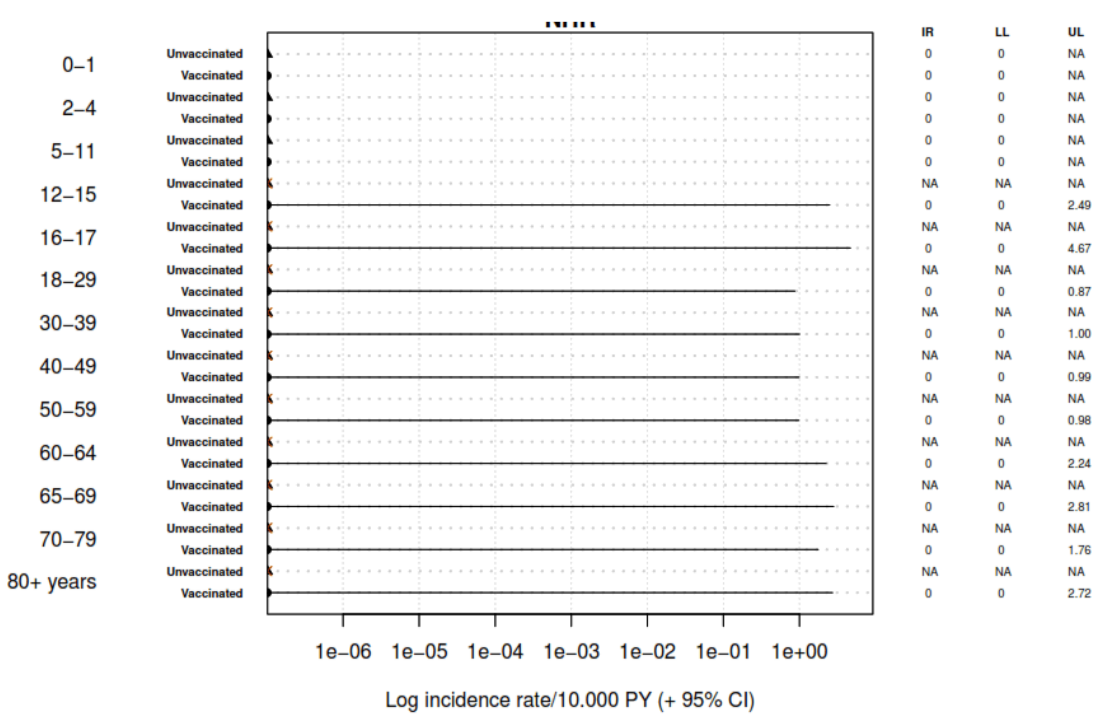


Figure 11. Forest plot showing incidence rates and 95% confidence intervals for narcolepsy among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source and by age groups (risk window: 42 days after dose 1)

PHARMO

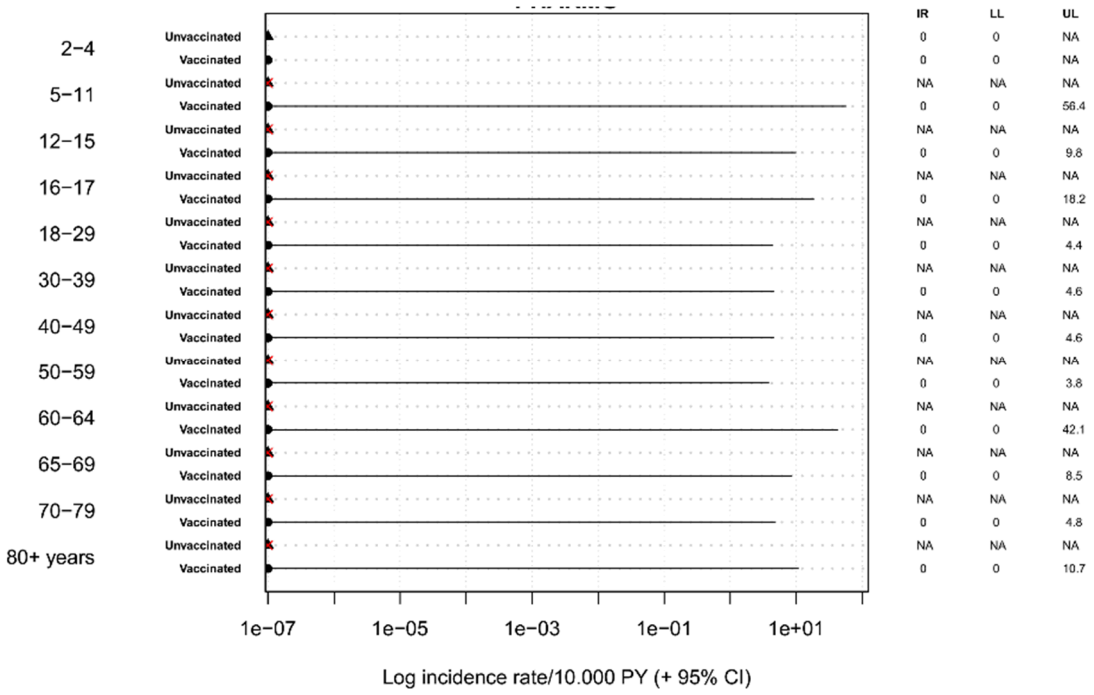


Figure 11. Forest plot showing incidence rates and 95% confidence intervals for narcolepsy among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source and by age groups (risk window: 42 days after dose 1)

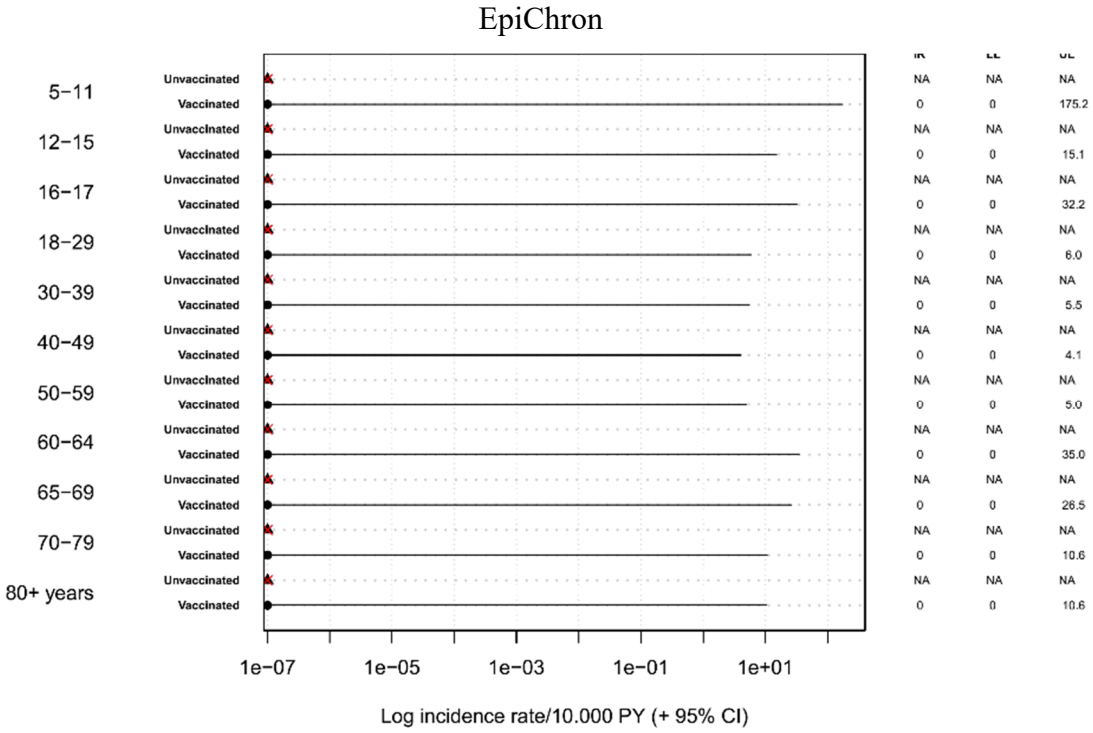


Figure 11. Forest plot showing incidence rates and 95% confidence intervals for narcolepsy among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source and by age groups (risk window: 42 days after dose 1)

SIDIAP

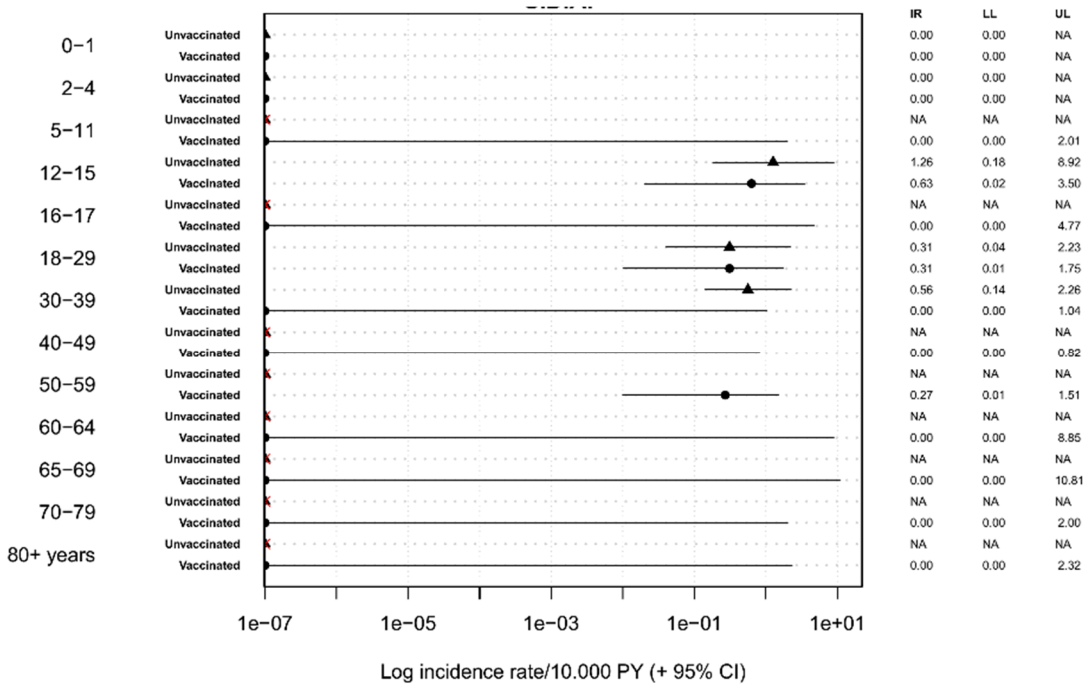


Table 20. Matched and adjusted hazard ratios (HRs) and matched and adjusted risk differences (RDs) per 10,000 person-years and their 95% CIs for narcolepsy among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source (risk window: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

	Matched HR (95% CI)	Adjusted HR (95% CI)	Matched RD	Adjusted RD
Pedianet	NA	NA	NA	NA
NHR	NA	NA	NA	NA
PHARMO	NA	NA	NA	NA
EpiChron	NA	NA	NA	NA
SIDIAP	0.60 (0.13, 2.78)	0.56 (0.12, 2.66)	-0.01	-0.01

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

10.3.5. Acute aseptic arthritis

Acute aseptic arthritis was observed in both the vaccinated and unvaccinated cohorts in all data sources. In the vaccinated cohorts, the incidences ranged from 22.7 per 10,000 person-years (95% CI: 19, 27) in PHARMO to 60.57 per 10,000 person-years (95% CI: 57.48, 63.79) in NHR. The cumulative incidences (1-KM) were less than 7 per 10,000 individuals over the 42-day risk window in both the vaccinated and unvaccinated cohorts. IRs for 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. The matched HRs were 0.50 (95% CI: 0.12, 2.16) in Pedianet, 1.09 (95% CI: 0.99, 1.20) in NHR, 1.17 (95% CI: 0.88, 1.55) in PHARMO, 1.16 (95% CI: 0.92, 1.47) in EpiChron, and 0.95 (95% CI: 0.86, 1.05) in SIDIAP. The adjusted HR were 0.48 (95% CI: 0.11, 2.10) in Pedianet, 1.09 (95% CI: 0.99, 1.19) in NHR, 1.06 (95% CI: 0.80, 1.40) in PHARMO, 1.10 (95% CI: 0.87, 1.39) in EpiChron, and 0.90 (95% CI: 0.81, 0.99) in SIDIAP. All matched and adjusted HRs were around 1 and the 95% CIs included 1. No differences were observed for the incidence of acute aseptic arthritis during the 42-day risk window between the vaccinated and unvaccinated cohorts.

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)

	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)	<5	3.26 (0, 6.95)	1,027.49	29.20 (6.02, 85.33)	6	6.90 (0.56, 13.23)	1,027.98	58.37 (23.17, 147.01)
NHR (Norway)	1,436	6.74 (6.38, 7.11)	237,079.71	60.57 (57.48, 63.79)	1,316	6.20 (5.69, 6.71)	236,809.77	55.57 (51.39, 60.10)
PHARMO (Netherlands)	120	2.44 (2.00, 2.87)	56,658.37	21.18 (17.56, 25.33)	103	2.02 (1.57, 2.47)	56,760.62	18.15 (14.59, 22.56)
EpiChron (Spain)	24.	6.48 (5.64, 7.32)	42,342.07	57.39 (50.40, 65.08)	209	5.49 (4.36, 6.62)	42,298.22	49.41 (40.44, 60.38)
SIDIAP (Spain)	1,063	5.21 (4.89, 5.53)	231,237.92	45.97 (43.25, 48.82)	1,123	5.39 (4.95, 5.83)	231,233.75	48.57 (44.84, 52.60)

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)

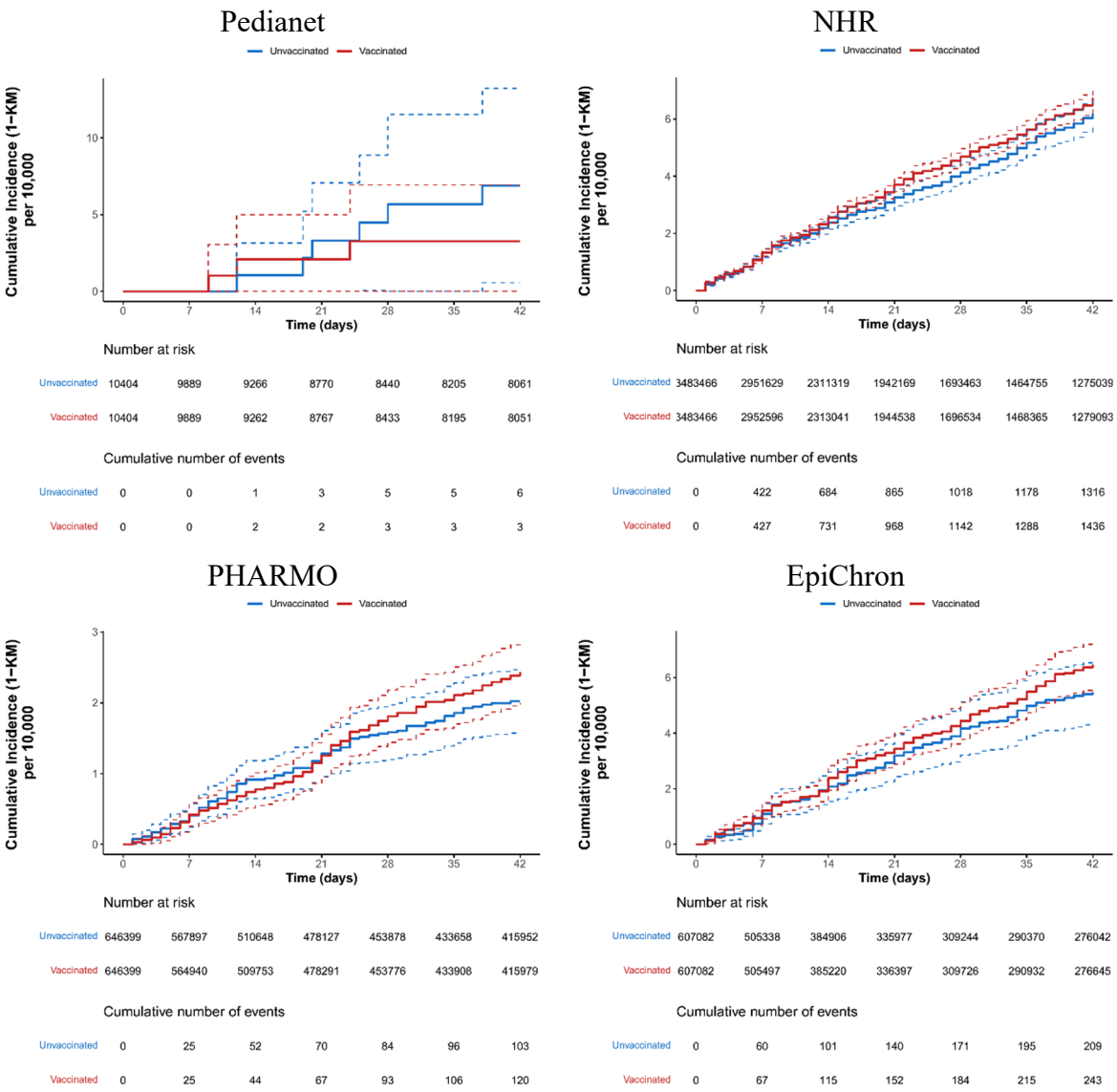
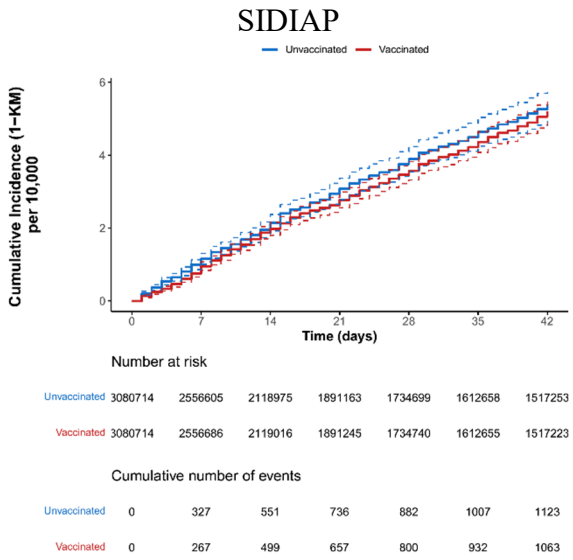


Figure 12. Cumulative incidence of acute aseptic arthritis among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source (risk window: 42 days after dose 1)



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)

Pedianet

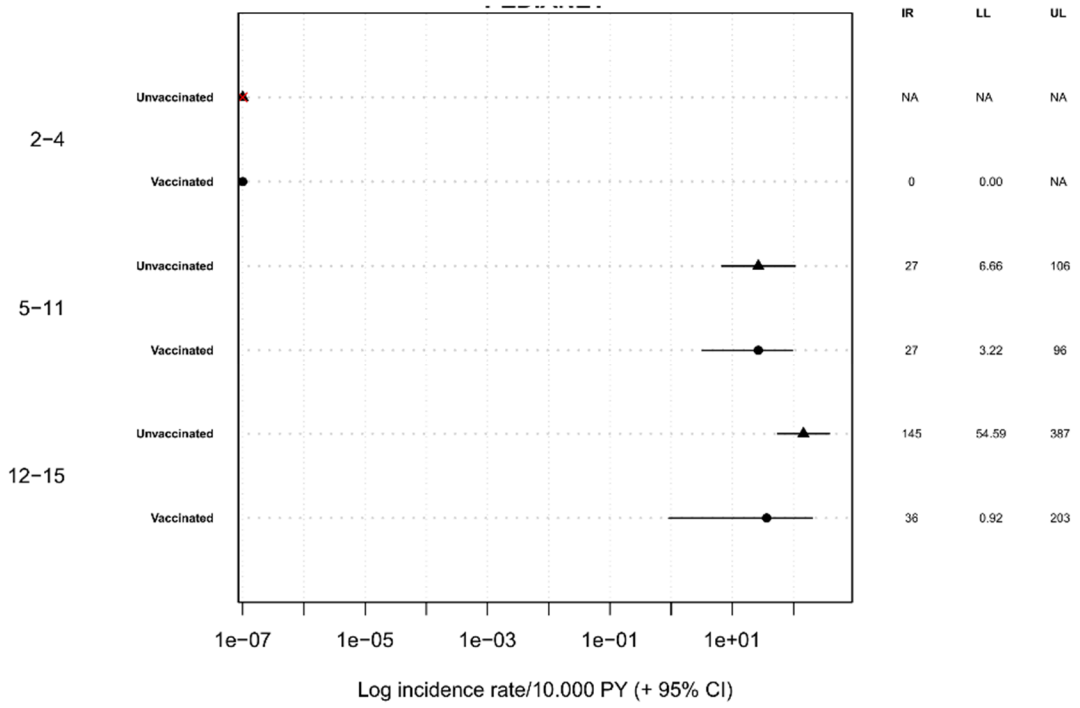


Figure 13. Forest plot showing incidence rates and 95% confidence intervals for acute aseptic arthritis among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source and by age groups (risk window: 42 days after dose 1)

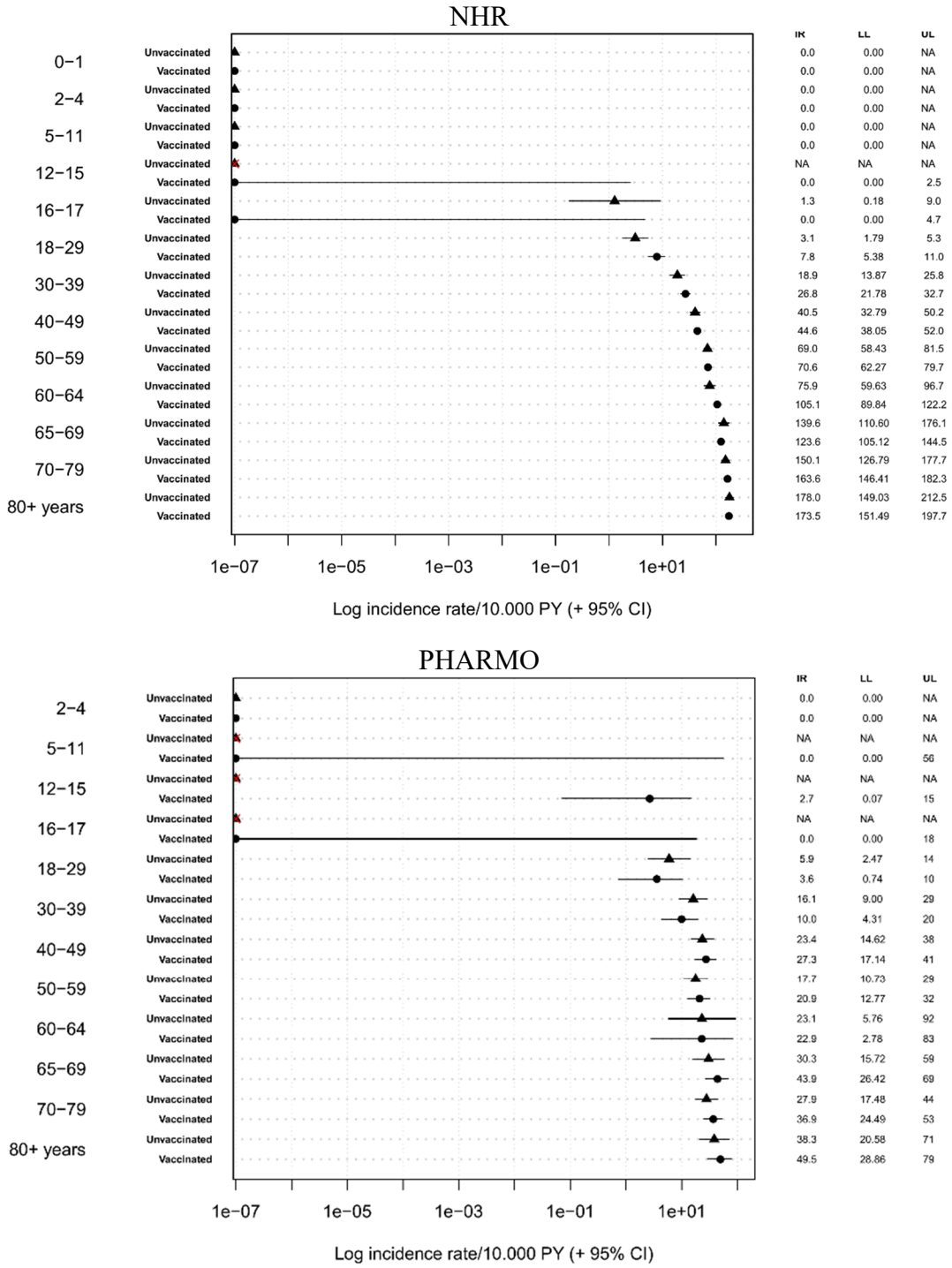


Figure 13. Forest plot showing incidence rates and 95% confidence intervals for acute aseptic arthritis among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source and by age groups (risk window: 42 days after dose 1)

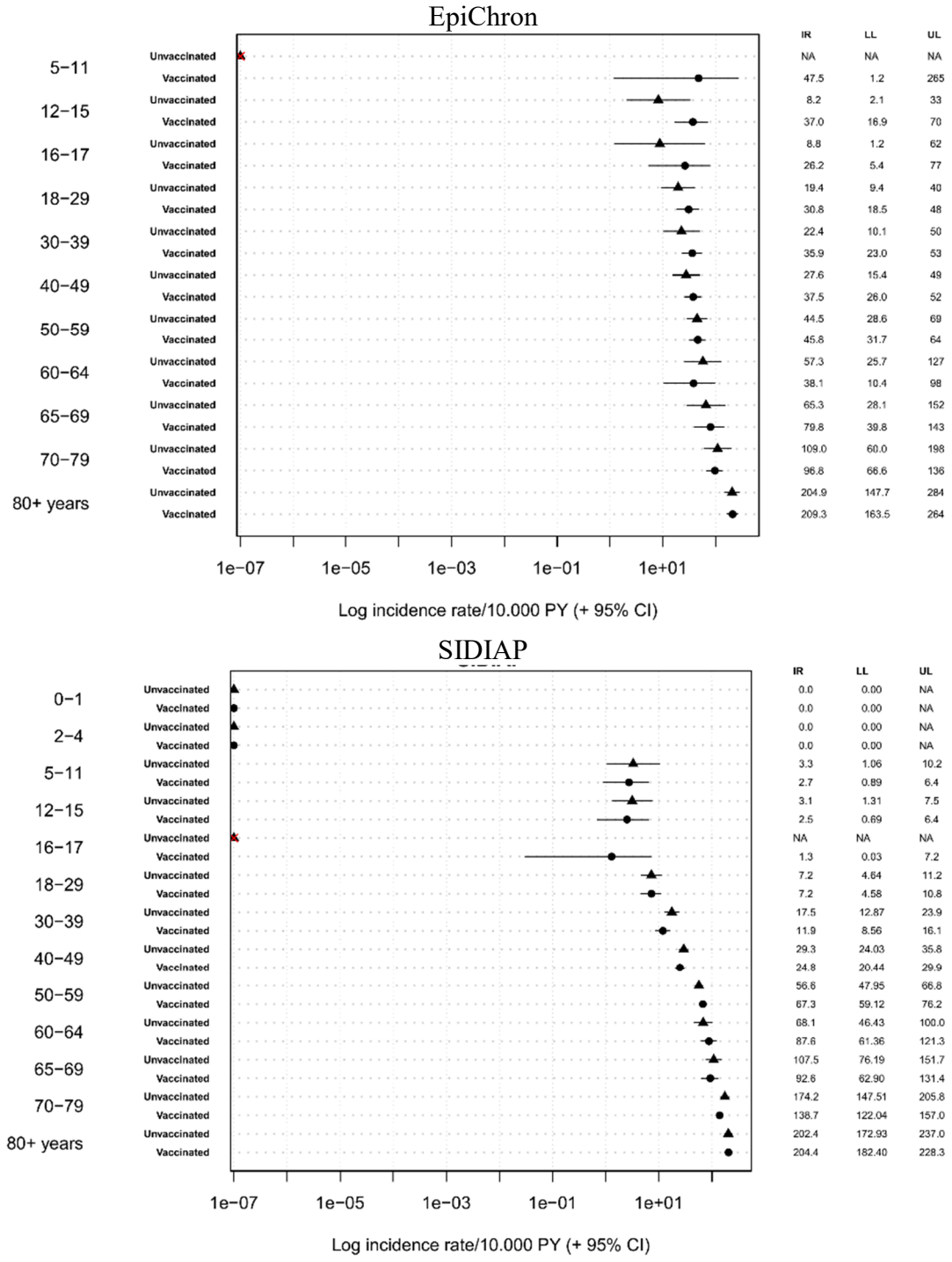


Table 22. Matched hazard and adjusted ratios (HRs) and matched and adjusted risk differences (RDs) per 10,000 person-years and their 95% CIs for acute aseptic arthritis among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source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

	Matched HR (95% CI)	Adjusted HR (95% CI)	Matched RD	Adjusted RD
Pedianet	0.50 (0.12, 2.16)	0.48 (0.11, 2.10)	-3.64	-3.72
NHR	1.09 (0.99, 1.20)	1.09 (0.99, 1.19)	0.54	0.51
PHARMO	1.17 (0.88, 1.55)	1.06 (0.80, 1.40)	0.42	0.20
EpiChron	1.16 (0.92, 1.47)	1.10 (0.87, 1.39)	0.99	0.66
SIDIAP	0.95 (0.86, 1.05)	0.90 (0.81, 0.99)	-0.18	-0.45

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. The IRs ranged from 1.16 per 10,000 person-years (95% CI: 0.81, 1.61) in PHARMO to 6.30 per 10,000 person-years (95% CI: 5.62, 7.04) in NHR in the vaccinated cohorts and from 1.09 per 10,000 person-years (95% CI: 0.70, 1.70) in PHRAMO to 5.26 per 10,000 person-years (95% CI: 4.39, 6.31) in NHR in the unvaccinated cohorts. The incidence was similar in the different age groups. The matched HRs were 1.19 (95% CI: 0.97, 1.48) in NHR, 1.08 (95% CI: 0.62, 1.85) in PHARMO, 0.69 (95% CI: 0.43, 1.09) in EpiChron, and 1.00 (95% CI: 0.84, 1.20) in SIDIAP. The adjusted HR were 1.19 (95% CI: 0.97, 1.48) in NHR, 1.06 (95% CI: 0.62, 1.84) in PHARMO, 0.70 (95% CI: 0.44, 1.11) in EpiChron, and 0.97 (95% CI: 0.81, 1.16) in SIDIAP, but were not significantly elevated. In NHR the lower limits of the 95% CIs for both the matched and adjusted HRs were >1.

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)

	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)	0	0 (0, 0)	6,957.49	0 (0, 5.30)	0	0 (0, 0)	7,000.16	NA
NHR (Norway)	313	12.54 (2.58, 22.50)	496,947.59	6.30 (5.62, 7.04)	259	6.95 (3.30, 10.60)	492,167.79	5.26 (4.39, 6.31)
PHARMO (Netherlands)	35	1.23 (0.81, 1.66)	302,274.56	1.16 (0.81, 1.61)	30	0.86 (0.46, 1.27)	275,619.29	1.09 (0.70, 1.70)
EpiChron (Spain)	49	2.50 (1.77, 3.24)	198,374.18	2.47 (1.83, 3.27)	71	3.44 (2.10, 4.78)	197,397.80	3.60 (2.49, 5.20)
SIDIAP (Spain)	384	3.71 (3.31, 4.11)	1,009,335.38	3.80 (3.43, 4.20)	383	3.67 (3.10, 4.24)	1,009,348.92	3.79 (3.28, 4.39)

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)

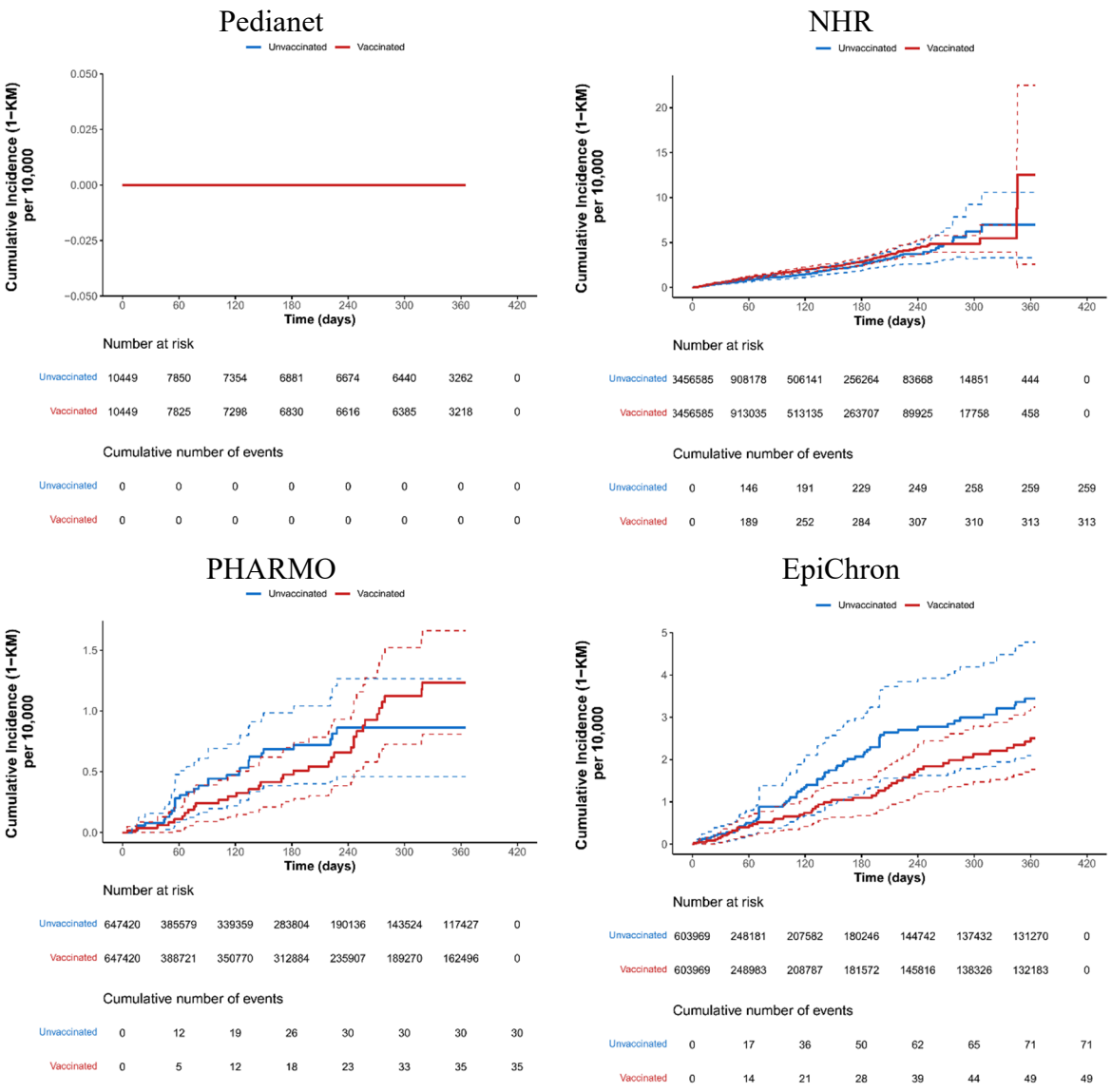
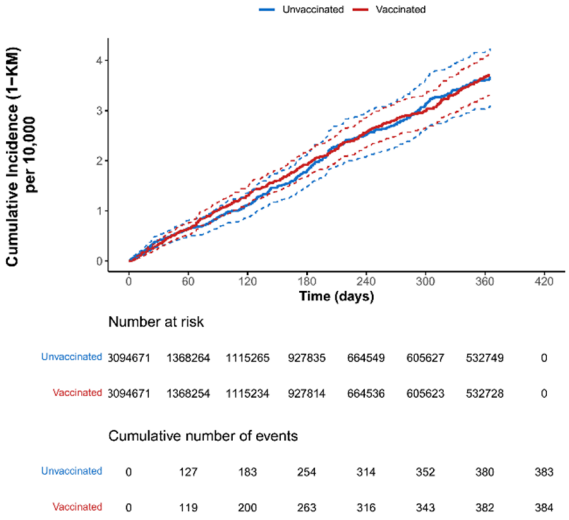


Figure 14. Cumulative incidence of diabetes mellitus type 1 among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source (risk window: 365 days after dose 1)

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 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)

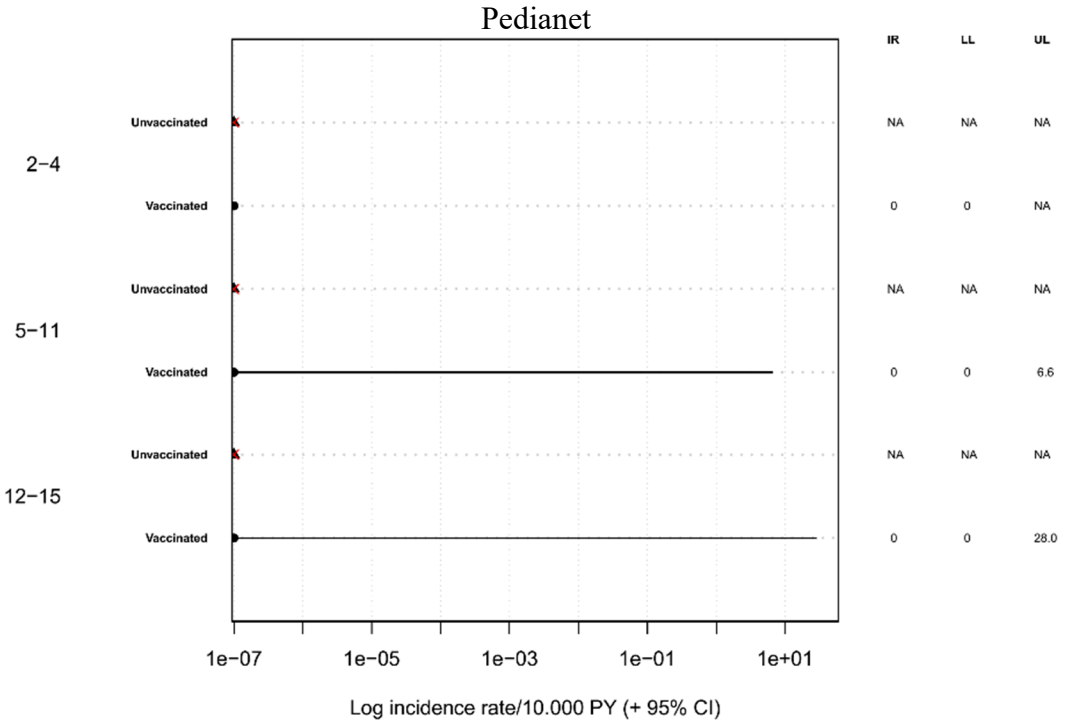


Figure 15. Forest plot showing incidence rates and 95% confidence intervals for diabetes mellitus type 1 among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source and by age groups (risk window: 365 days after dose 1)

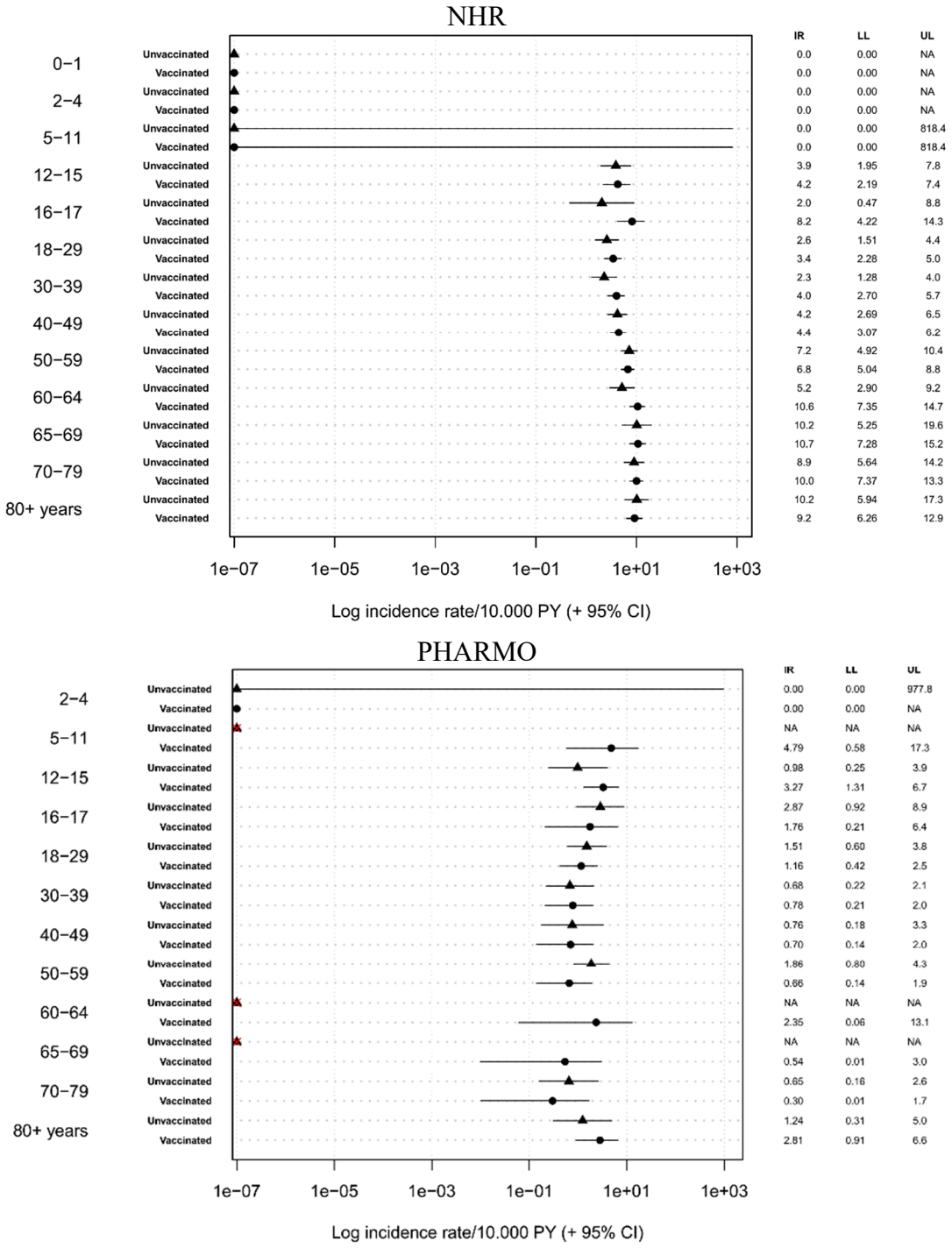


Figure 15. Forest plot showing incidence rates and 95% confidence intervals for diabetes mellitus type 1 among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source and by age groups (risk window: 365 days after dose 1)

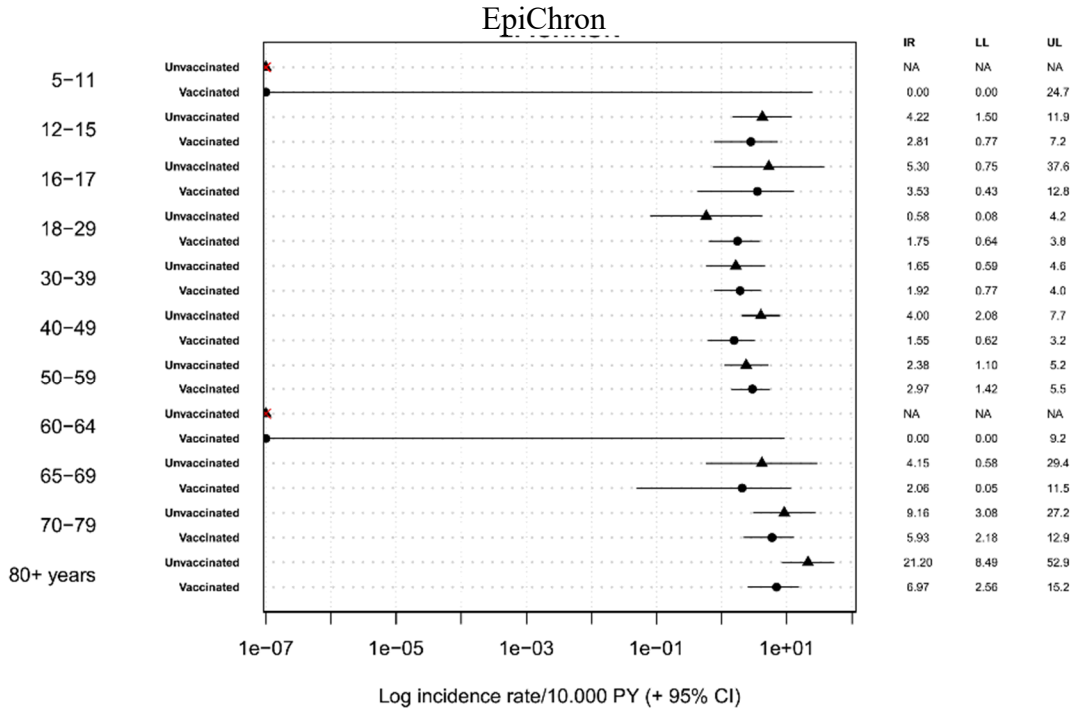


Figure 15. Forest plot showing incidence rates and 95% confidence intervals for diabetes mellitus type 1 among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source and by age groups (risk window: 365 days after dose 1)

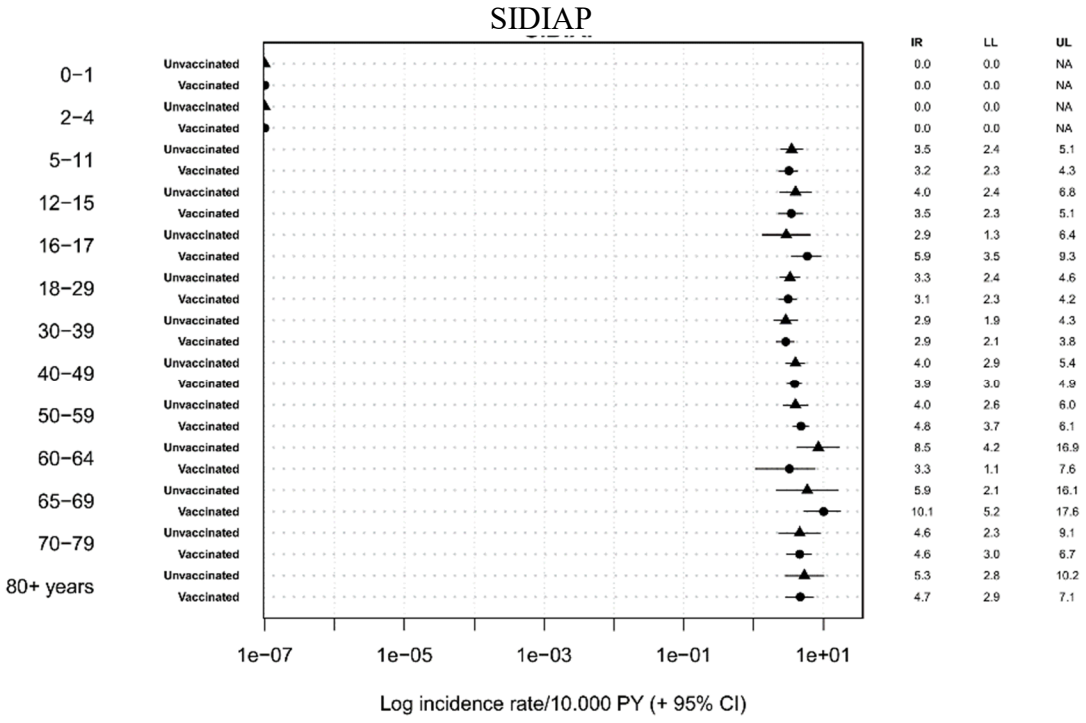


Table 24. Matched and adjusted hazard ratios (HRs) and matched and adjusted risk differences (RDs) per 10,000 person-years and their 95% CIs for diabetes mellitus type 1 within any time after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched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

	Matched HR (95% CI)	Adjusted HR (95% CI)	Matched RD	Adjusted RD
Pedianet	NA	NA	NA	NA
NHR	1.19 (0.97, 1.48)	1.19 (0.97, 1.48)	5.59	5.58
PHARMO	1.08 (0.62, 1.85)	1.06 (0.62, 1.84)	0.37	0.37
EpiChron	0.69 (0.43, 1.09)	0.70 (0.44, 1.11)	-0.93	-0.88
SIDIAP	1.00 (0.84, 1.20)	0.97 (0.81, 1.16)	0.04	-0.10

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 1.76 per 10,000 person-years (95% CI: 0.84, 3.24) in PHARMO to 13.55 per 10,000 person-years (95% CI: 12.09, 15.13) in SIDIAP and in the unvaccinated cohorts from 2.99 per 10,000 person-years (95% CI: 1.81, 4.94) in PHARMO to 16.13 per 10,000 person-years (95% CI: 14.14, 18.40) in SIDIAP. 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 1.8 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 0.59 (95% CI: 0.27, 1.31) in PHARMO, 0.49 (95% CI: 0.28, 0.85) in EpiChron, and 0.84 (95% CI: 0.71, 1) in SIDIAP. The adjusted HRs were 0.55 (0.25, 1.22) in PHARMO, 0.46 (0.26, 0.78) in EpiChron, and 0.78 (0.66, 0.93) in SIDIAP.

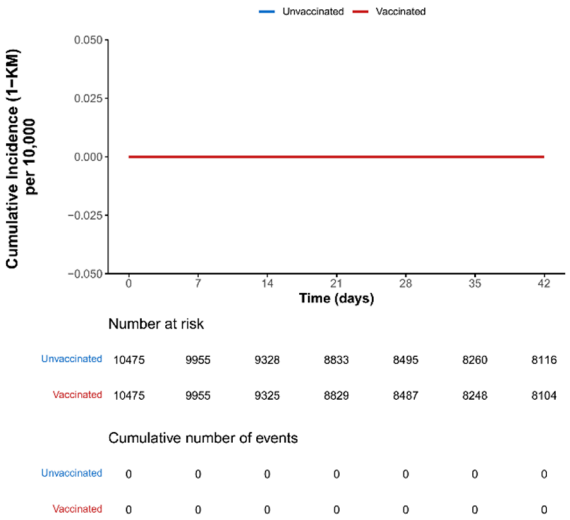
Table 25. Risk estimates (95% CI) per 10,000 person-years (PY) for (idiopathic) thrombocytopenia among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source (risk window: 42 days after dose 1)

	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)	0	0 (0, 0)	1,034.35	0 (0, 35.66)	0	0 (0, 0)	1,034.91	NA
NHR (Norway)	0	0 (0, 0)	202,695.80	0 (0, 0.20)	0	0 (0, 0)	202,436.30	NA
PHARMO (Netherlands)	10	0.20 (0.08, 0.33)	56,834.57	1.76 (0.84, 3.24)	17	0.35 (0.17, 0.53)	56,935.49	2.99 (1.81, 4.94)
EpiChron (Spain)	29	0.80 (0.50, 1.10)	42,550.34	6.82 (4.56, 9.79)	59	1.62 (0.95, 2.30)	42,502.57	13.88 (9.16, 21.05)
SIDIAP (Spain)	315	1.52 (1.35, 1.69)	232,540.45	13.55 (12.09, 15.13)	375	1.77 (1.53, 2.01)	232,536.13	16.13 (14.14, 18.40)

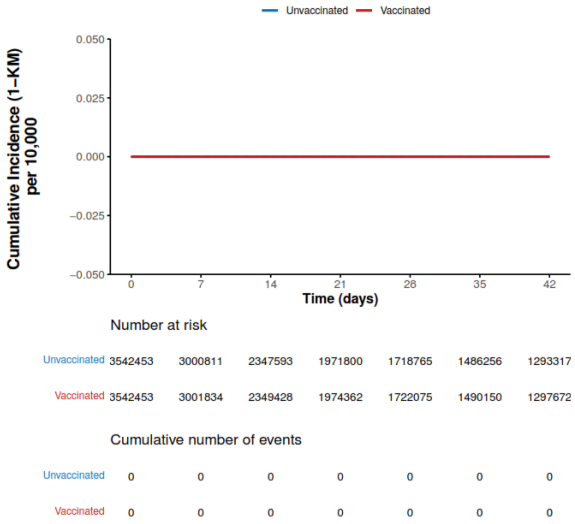
Note: Estimation of confidence intervals differs between vaccinated and unvaccinated, since the unvaccinated estimate is a GEE estimates (to account for individuals who were matched to more than one vaccinated individual). When NA (not-assessable) is listed for the 1-KM it means that there is no estimate 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)

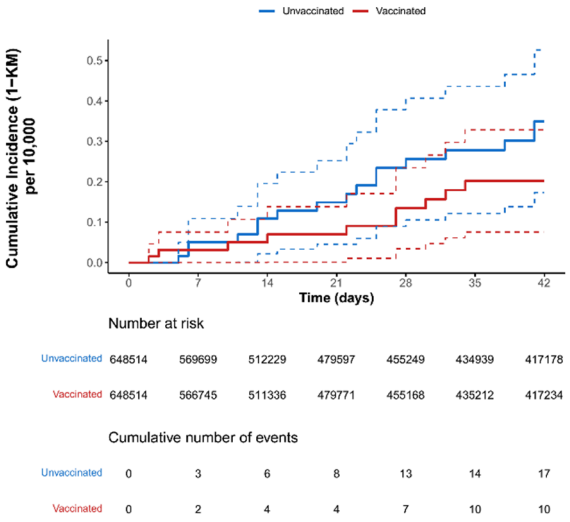
Pedianet



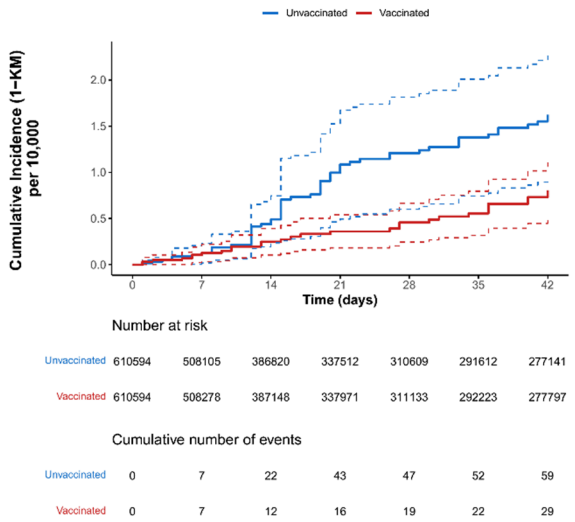
NHR



PHARMO

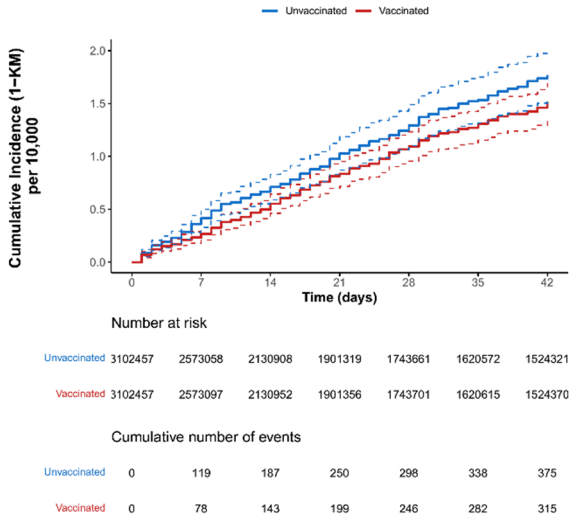


EpiChron



SIDIAP

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)

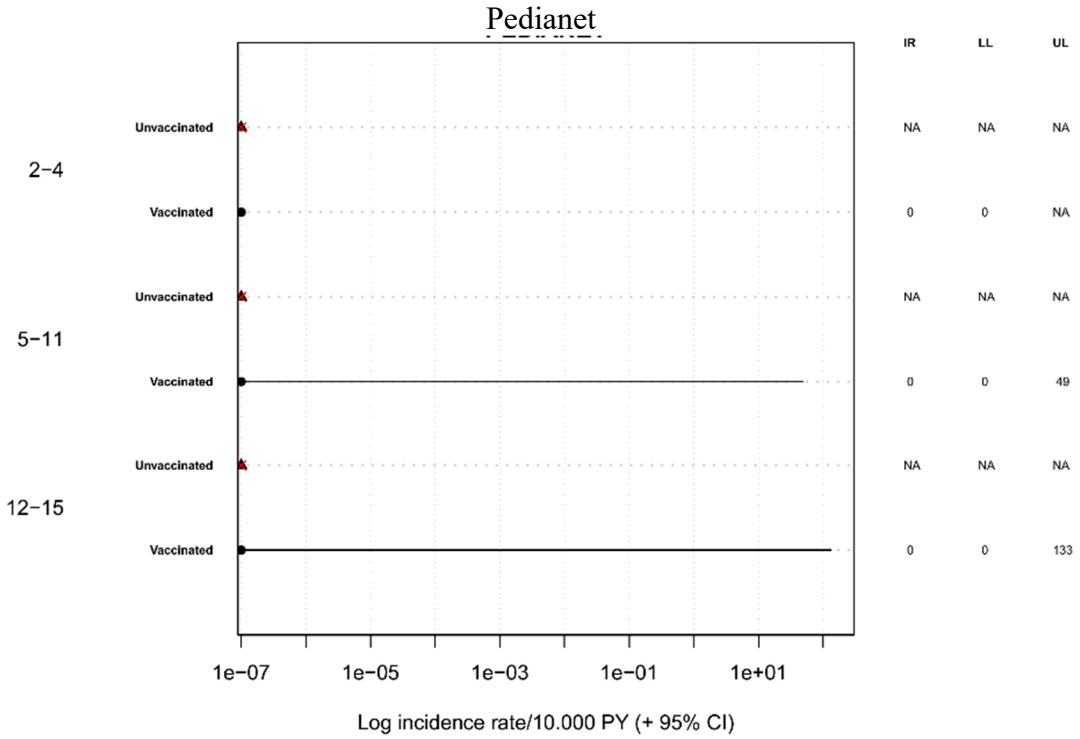


Figure 17. Forest plot showing incidence rates and 95% confidence intervals for (idiopathic) thrombocytopenia among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source and by age groups (risk window: 42 days after dose 1)

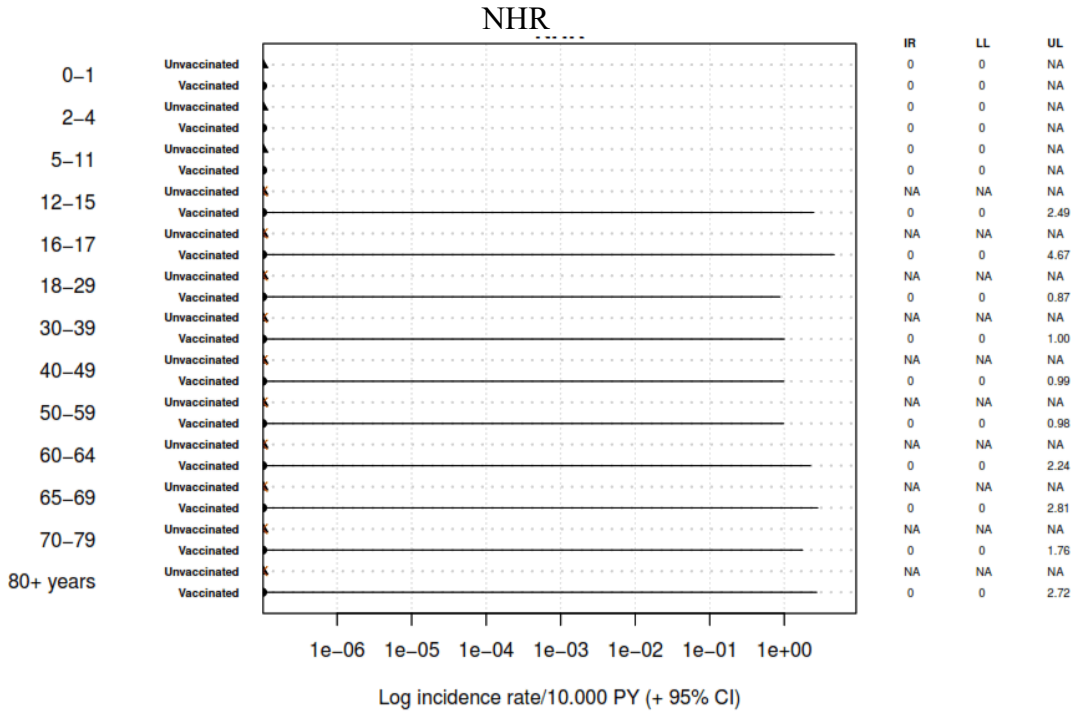
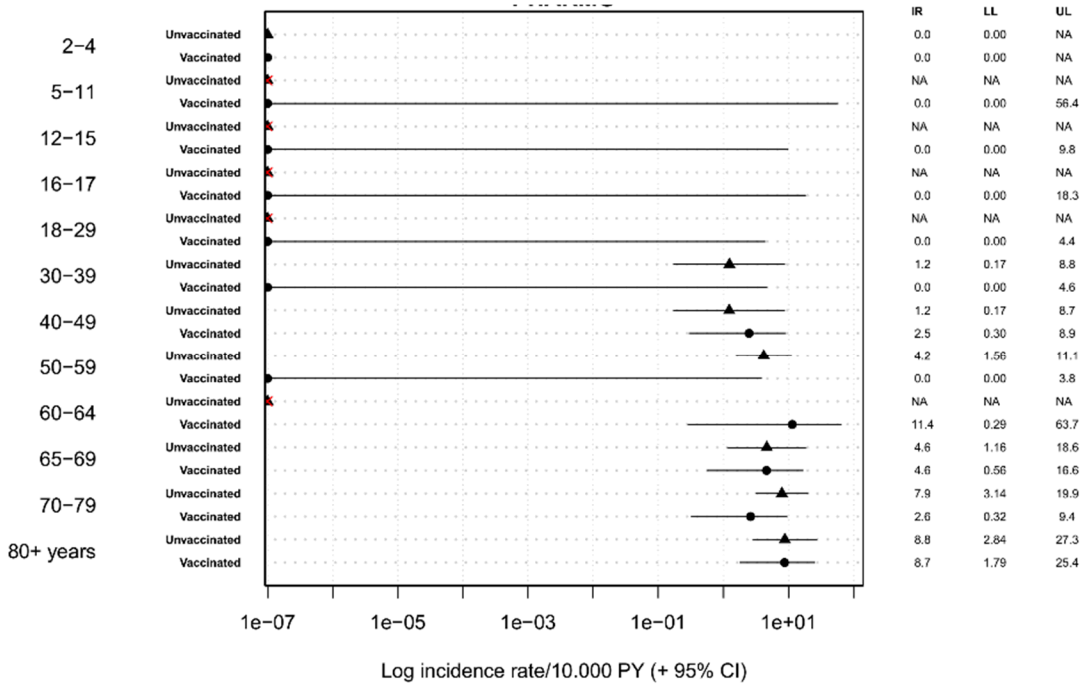


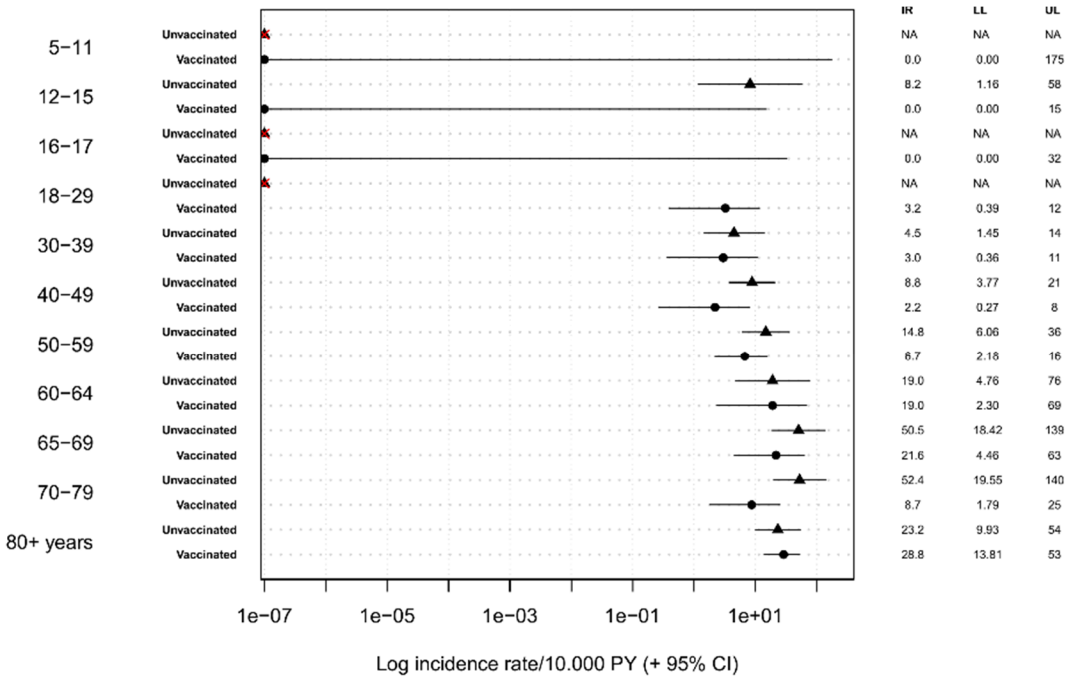
Figure 17. Forest plot showing incidence rates and 95% confidence intervals for (idiopathic) thrombocytopenia among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source and by age groups (risk window: 42 days after dose 1)

PHARMO



EpiChron

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)



SIDIAP

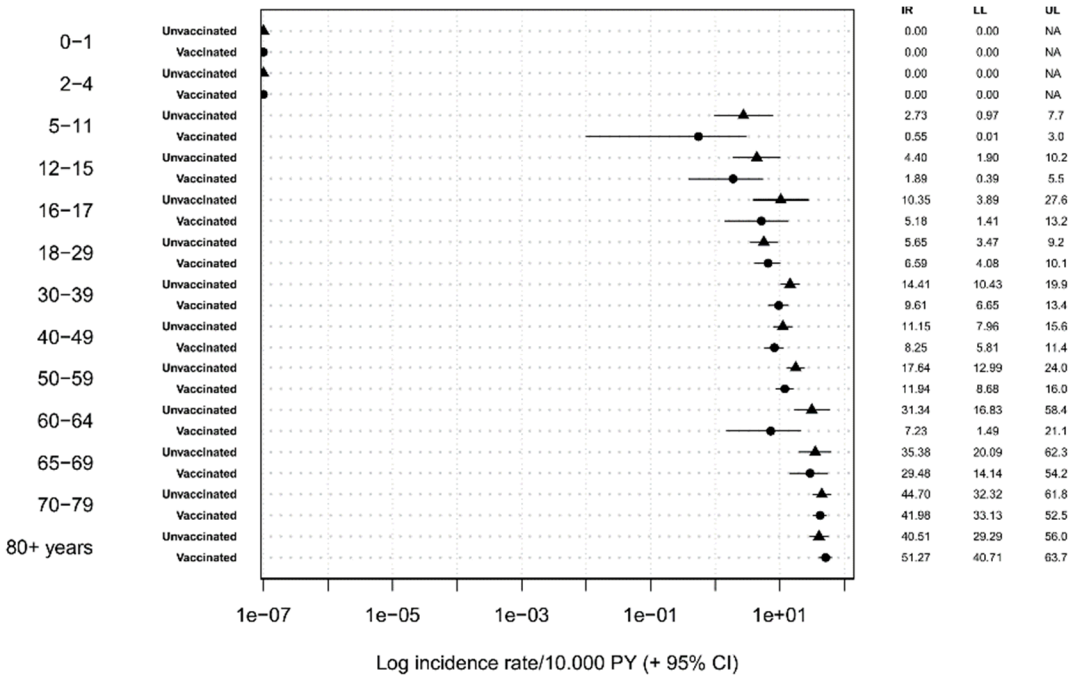


Table 26. Matched and adjusted hazard ratios (HRs) and matched and adjusted risk differences (RDs) per 10,000 person-years and their 95% CIs for (idiopathic) thrombocytopenia among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data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

	Matched HR (95% CI)	Adjusted HR (95% CI)	Matched RD	Adjusted RD
Pedianet	NA	NA	NA	NA
NHR	NA	NA	NA	NA
PHARMO	0.59 (0.27, 1.31)	0.55 (0.25, 1.22)	-0.15	-0.16
EpiChron	0.49 (0.28, 0.85)	0.46 (0.26, 0.78)	-0.82	-0.93
SIDIAP	0.84 (0.71, 1)	0.78 (0.66, 0.93)	-0.25	-0.36

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) was defined as the occurrence of a venous or arterial thrombotic event and thrombocytopenia within 10 days of the occurrence of a thrombotic event. TTS was rarely observed in the vaccinated and unvaccinated cohorts in EpiChron and SIDIAP. The incidence rates were 0.51 per 10,000 person-years (95% CI: 0.01, 2.83) in EpiChron and 0.67 per 10,000 person-years (95% CI: 0.27, 1.39) in SIDIAP in the vaccinated cohorts and 0.29 per 10,000 person-years (95% CI: 0.09, 0.89) in SIDIAP and 0.51 per 10,000 person-years (95% CI: 0.07, 3.61) 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 1.00 (95% CI: 0.056; 15.98) in EpiChron and 2.33 (95% CI: 0.60; 9.02) in SIDIAP. No significant differences were observed in the incidence of TTS between the vaccinated and unvaccinated cohorts in the data sources reporting data.

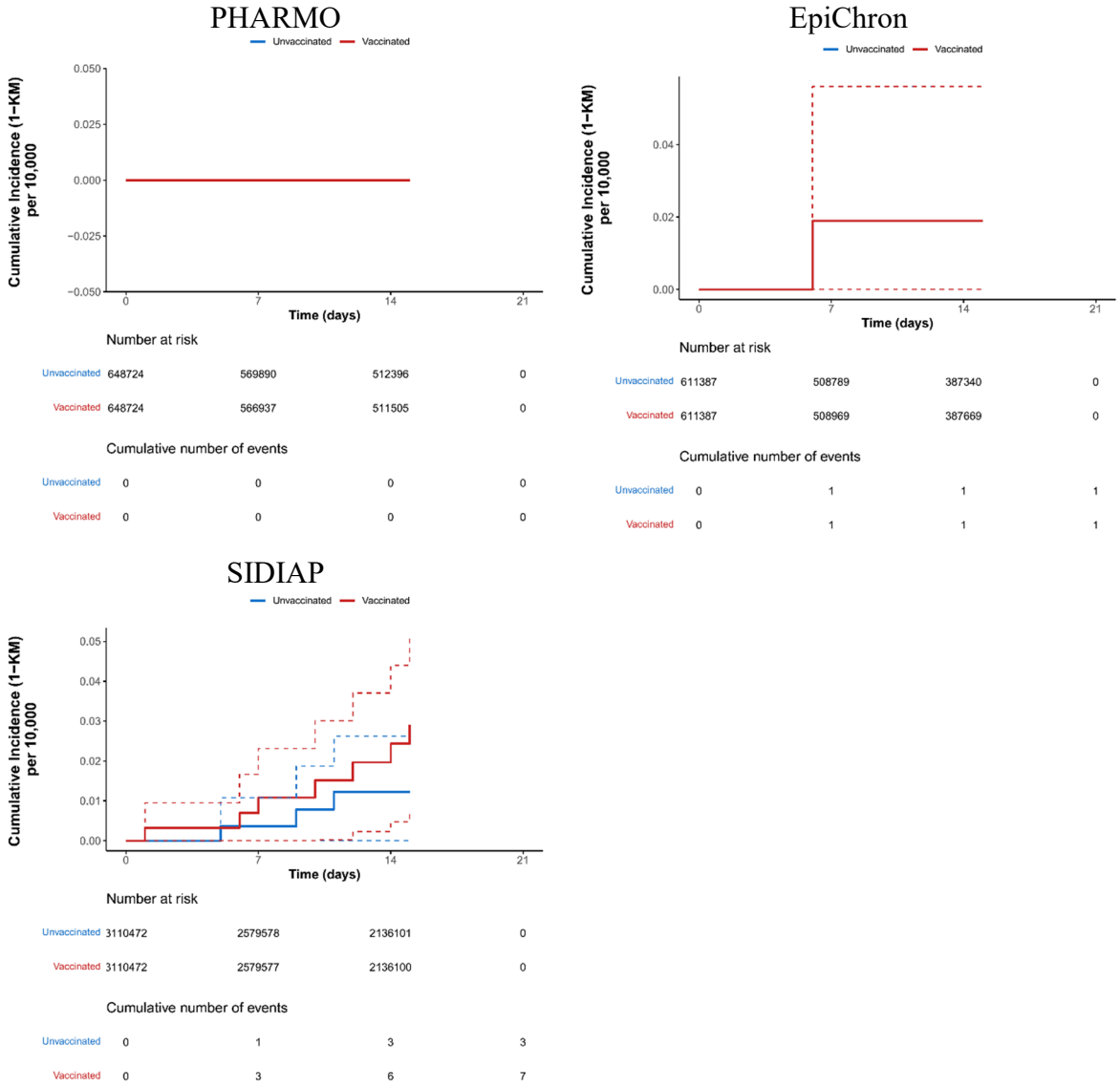
Table 27. Risk estimates (95% CI) per 10,000 person-years (PY) for thrombotic thrombocytopenia syndrome (TTS) among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source (risk window: 15 days after dose 1)

	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)	NA	NA	NA	NA	NA	NA	NA	NA
NHR (Norway)	NA	NA	NA	NA	NA	NA	NA	NA
PHARMO (Netherlands)	0	0 (0, 0)	23,245.29	0 (0, 1.59)	0	0 (0, 0)	23,336.18	NA
EpiChron (Spain)	<5	0.02 (0, 0.06)	19,677.68	0.51 (0.01, 2.83)	<5	0.02 (0, 0.06)	19,669.68	0.51 (0.07, 3.61)
SIDIAP (Spain)	7	0.03 (0.01, 0.05)	104,111.75	0.67 (0.27, 1.39)	<5	0.01 (0, 0.03)	104,111.78	0.29 (0.09, 0.89)

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)

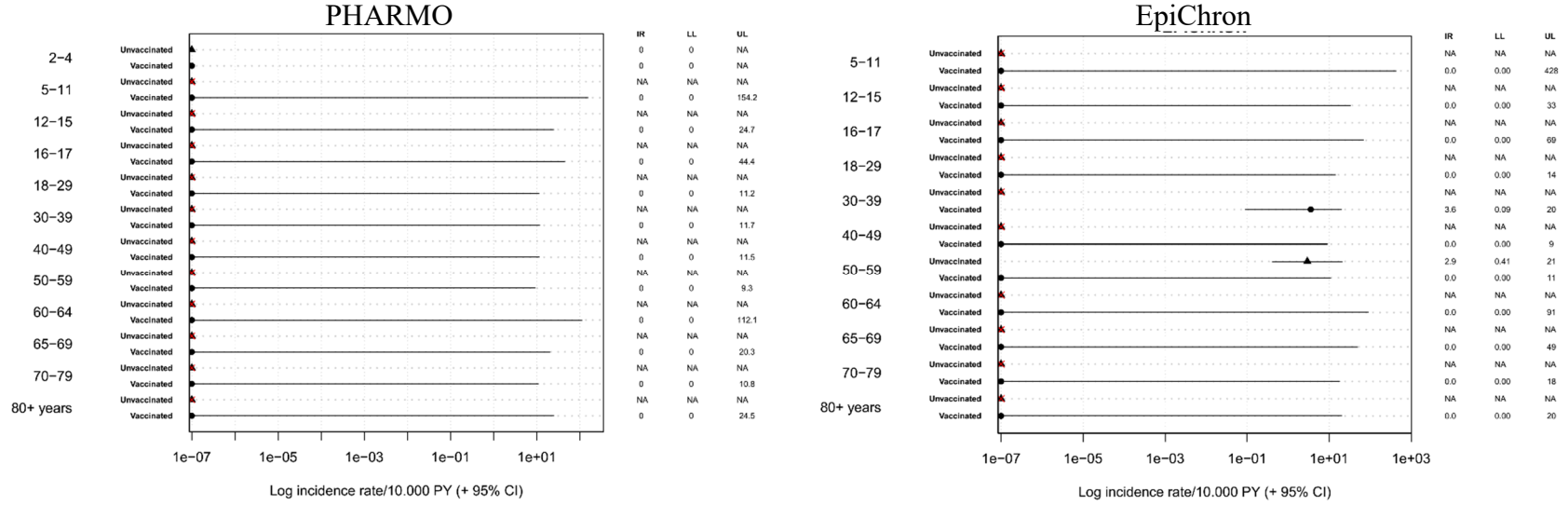


Figure 19. Forest plot showing incidence rates and 95% confidence intervals for thrombotic thrombocytopenia syndrome (TTS) among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source and by age groups (risk window: 15 days after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

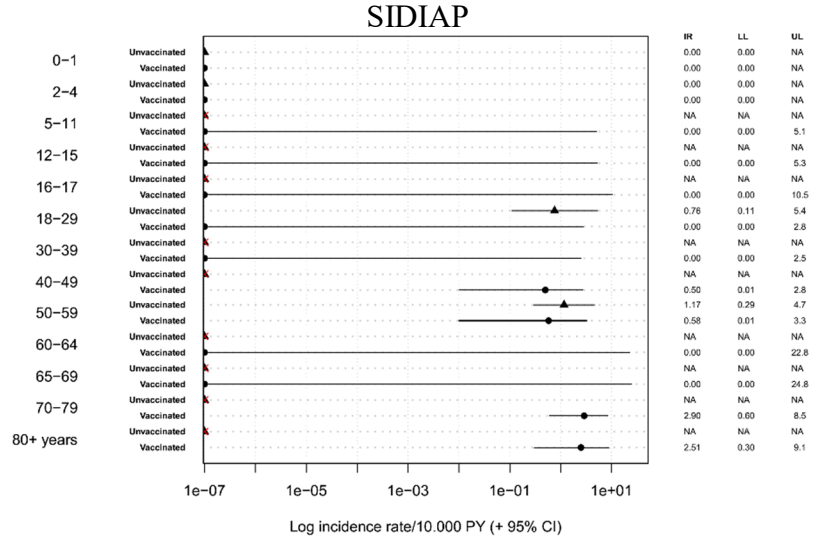


Table 28. Matched and adjusted hazard ratios (HRs) and matched and adjusted risk differences (RDs) per 10,000 person-years and their 95% CIs for thrombotic thrombocytopenia syndrome (TTS) among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals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

	Matched HR (95% CI)	Adjusted HR (95% CI)	Matched RD	Adjusted RD
Pedianet	NA	NA	NA	NA
NHR	NA	NA	NA	NA
PHARMO	NA	NA	NA	NA
EpiChron	1 (0.06, 15.98)	0.81 (0.05, 12.95)	0	0
SIDIAP	2.33 (0.60, 9.02)	1.90 (0.49, 7.40)	0.02	0.01

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

10.3.9. Myositis

Myositis was observed in all the data sources in the vaccinated and unvaccinated cohorts, except in the unvaccinated cohort in Pedianet. The incidence rates in the vaccinated cohorts ranged from 0.26 per 10,000 person-years (95% CI: 0.11, 0.52) in PHARMO to 1.71 per 10,000 person-years (95% CI: 1.46, 1.98) in SIDIAP and in the unvaccinated cohorts, from 0.07 per 10,000 person-years (95% CI: 0.02, 0.29) in PHARMO to 1.80 per 10,000 person-years (95% CI: 1.46, 2.21) in SIDIAP. The incidence was similar in the different age groups. The matched HRs were 0.75 (95% CI: 0.33, 1.67) in NHR, 3.78 (95% CI: 0.80, 17.92) in PHARMO, 1 (95% CI: 0.32, 3.08) in EpiChron, and 0.95 (95% CI: 0.74, 1.23) in SIDIAP. The adjusted HRs were 0.74 (95% CI: 0.33, 1.67) in NHR, 4.41 (95% CI: 0.93, 20.87) in PHARMO, 0.97 (95% CI: 0.32, 2.98) in EpiChron, and 0.85 (95% CI: 0.65, 1.09) in SIDIAP. No differences were observed for the incidence of myositis between the vaccinated and unvaccinated cohorts during the 365-day risk window.

Table 29. Risk estimates (95% CI) per 10,000 person-years (PY) for myositis within 365 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source

	Vaccinated				Unvaccinated			
Data source	**Events (n)**	**Cumulative incidence (95% CI)**	**Person-years (PY)**	**Incidence rate (95% CI)**	**Events (n)**	**Cumulative incidence (95% CI)**	**Person-years (PY)**	**Incidence rate (95% CI)**
Pedianet (Italy)	<5	1.53 (0, 4.54)	6,973.09	1.43 (0.04, 7.99)	0	0 (0, 0)	7,016.93	NA
NHR (Norway)	21	0.15 (0.07, 0.22)	509,606.51	0.41 (0.26, 0.63)	28	0.40 (0, 0.81)	504,460.03	0.56 (0.28, 1.10)
PHARMO (Netherlands)	8	0.23 (0.06, 0.40)	302,869.39	0.26 (0.11, 0.52)	<5	0.06 (0, 0.15)	276,174.06	0.07 (0.02, 0.29)
EpiChron (Spain)	11	0.36 (0.13, 0.59)	199,913.70	0.55 (0.27, 0.98)	11	0.59 (0, 1.19)	198,906.71	0.55 (0.21, 1.44)
SIDIAP (Spain)	173	1.74 (1.46, 2.02)	1,013,712.80	1.71 (1.46, 1.98)	182	1.83 (1.42, 2.23)	1,013,715.12	1.80 (1.46, 2.21)

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 myositis 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

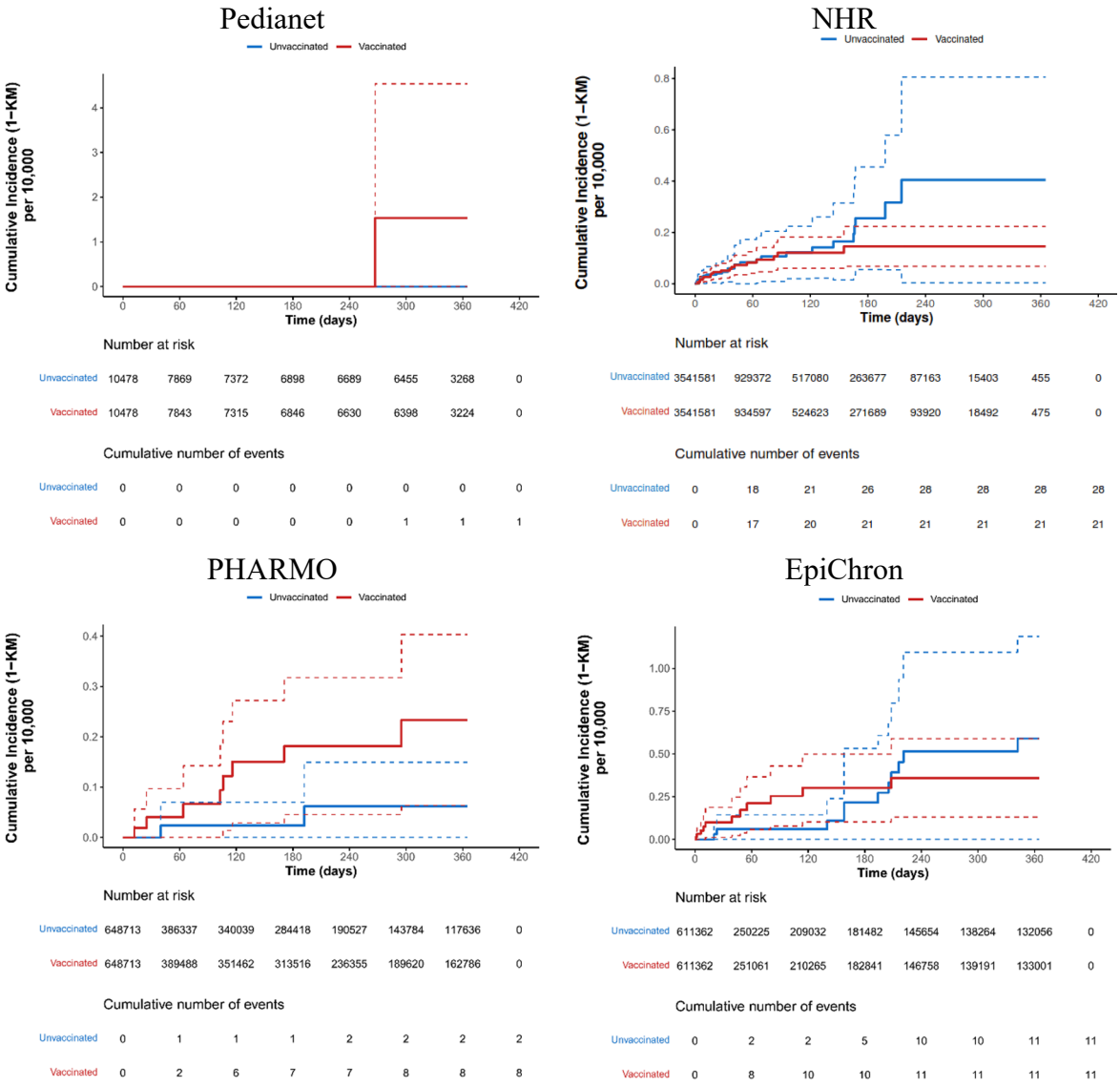
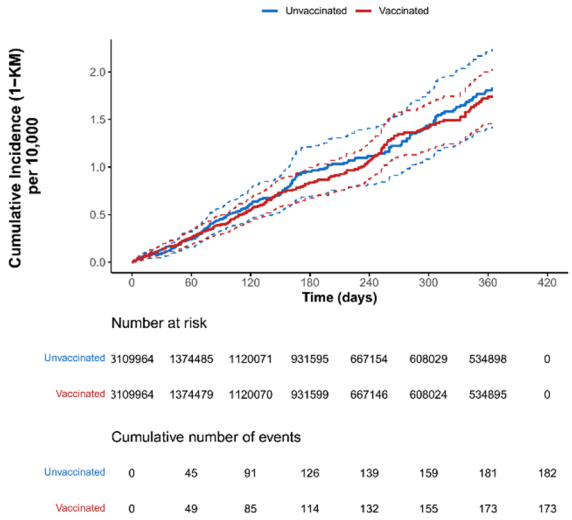


Figure 20. Cumulative incidence of myositis within 365 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source

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

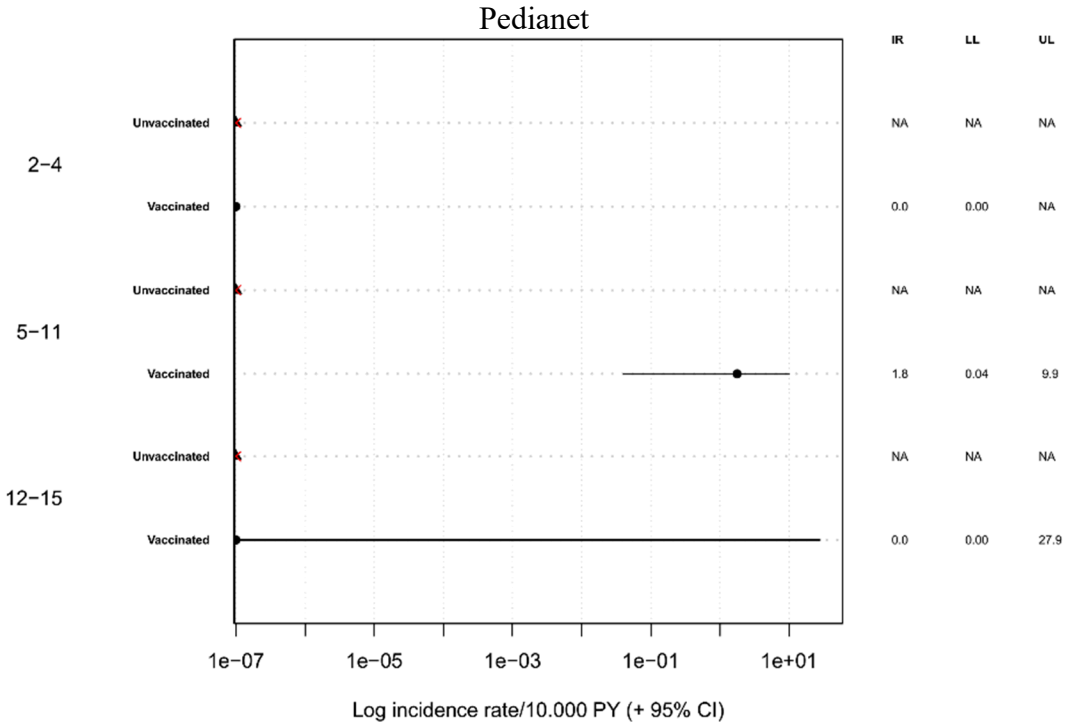


Figure 21. Forest plot showing incidence rates and 95% confidence intervals for myositis within 365 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source and by age groups

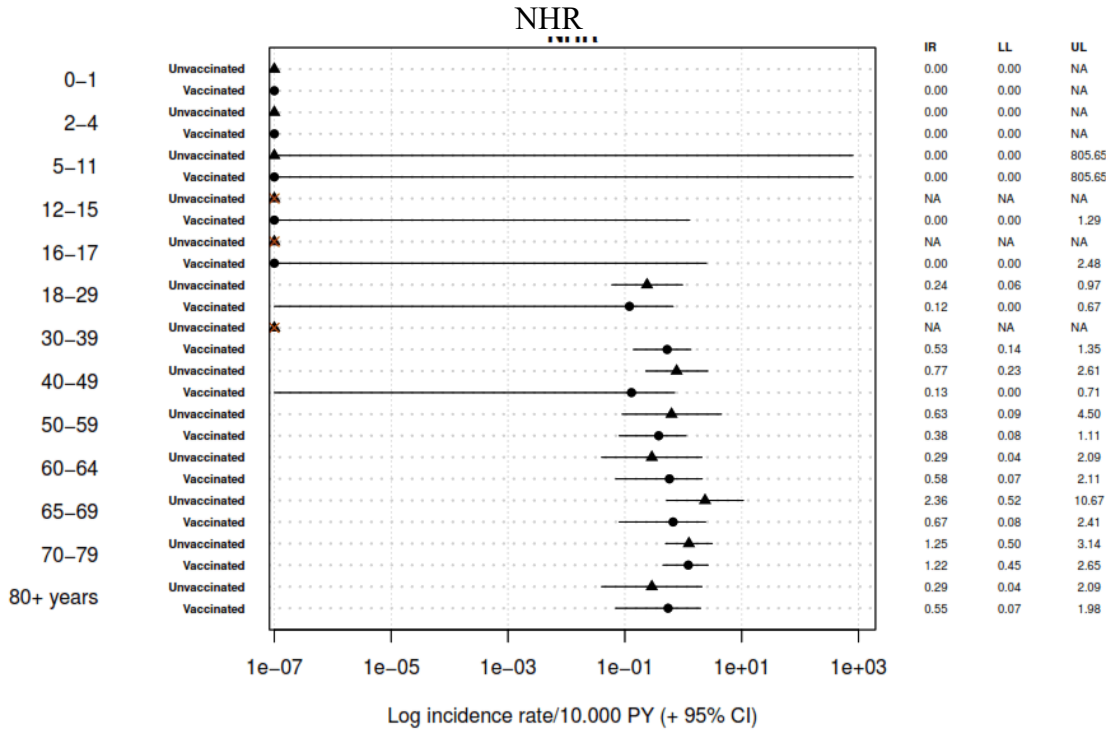


Figure 21. Forest plot showing incidence rates and 95% confidence intervals for myositis within 365 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source and by age groups

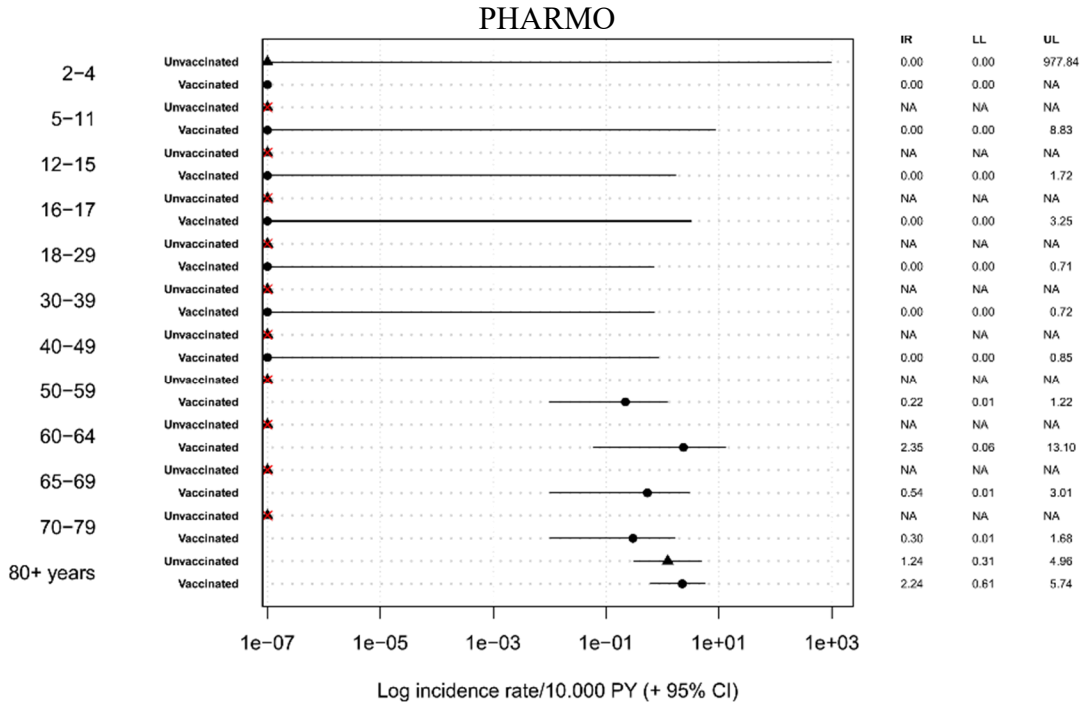


Figure 21. Forest plot showing incidence rates and 95% confidence intervals for myositis within 365 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source and by age groups

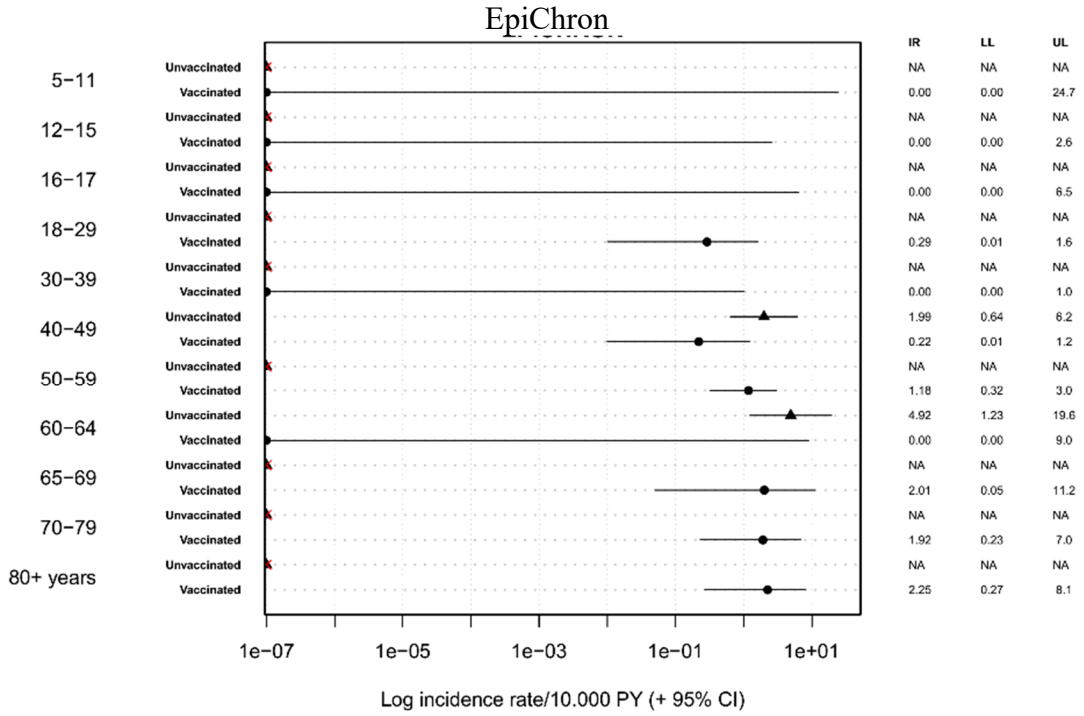


Figure 21. Forest plot showing incidence rates and 95% confidence intervals for myositis within 365 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source and by age groups

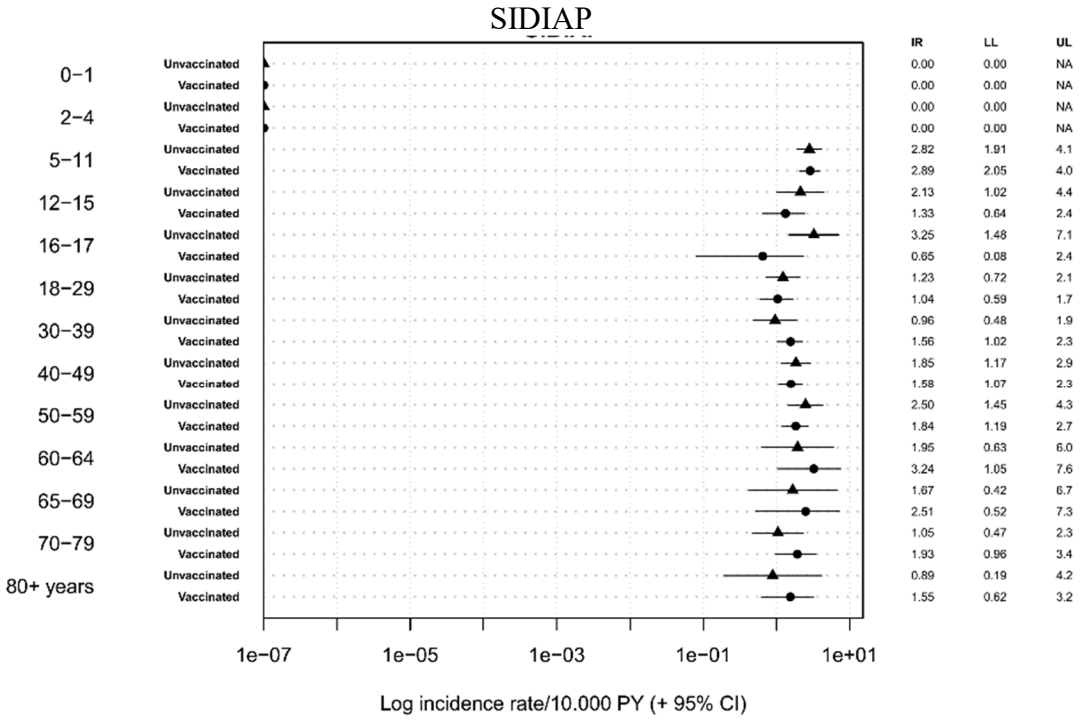


Table 30. Matched and adjusted hazard ratios (HRs) and matched and adjusted risk differences (RDs) per 10,000 person-years and their 95% CIs for myositis within 365 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source

	Matched HR (95% CI)	Adjusted HR (95% CI)	Matched RD	Adjusted RD
Pedianet	NA	NA	1.53	1.58
NHR	0.75 (0.33, 1.67)	0.74 (0.33, 1.67)	-0.26	-0.26
PHARMO	3.78 (0.80, 17.92)	4.41 (0.93, 20.87)	0.17	0.19
EpiChron	1 (0.32, 3.08)	0.97 (0.32, 2.98)	-0.23	-0.24
SIDIAP	0.95 (0.74, 1.23)	0.85 (0.65, 1.09)	-0.09	-0.29

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

10.3.10. Acute cardiovascular injury

Acute cardiovascular injury events (including microangiopathy, heart failure, stress cardiomyopathy, coronary artery disease, arrhythmia) were observed in both the vaccinated and unvaccinated cohorts in all data sources, except Pedianet, which has data only for children. The incidence rates in the vaccinated cohorts ranged from 43.22 per 10,000 person-years (95% CI: 40.90, 45.64) in PHARMO to 131.37 per 10,000 person-years (95% CI: 128.15, 134.65) in NHR and in the unvaccinated cohorts these ranged from 34.79 per 10,000 person-years (95% CI: 31.84, 38.00) in PHARMO to 138.48 per 10,000 person-years (95% CI: 133.23, 143.94) in NHR.

The incidence of acute cardiovascular injury was higher in the older age groups in all data sources, in both the vaccinated and non-vaccinated cohorts during the 365-day risk interval. The matched HRs were 0.95 (95% CI: 0.90, 0.99) in NHR, 1.25 (95% CI: 1.13, 1.39) in PHARMO, 0.96 (95% CI: 0.87, 1.06) in EpiChron, and 0.98 (95% CI: 0.93, 1.04) in SIDIAP. The adjusted HRs were 0.94 (95% CI: 0.90, 0.98) in NHR, 1.20 (95% CI: 1.08, 1.33) in PHARMO, 0.91 (95% CI: 0.82, 1.00) in EpiChron, and 0.93 (95% CI: 0.89, 0.99) in SIDIAP. The upper limits of 95% CIs for the matched and adjusted HRs were all <1, except for the matched HR for SIDIAP, where the upper limit was 0.99.

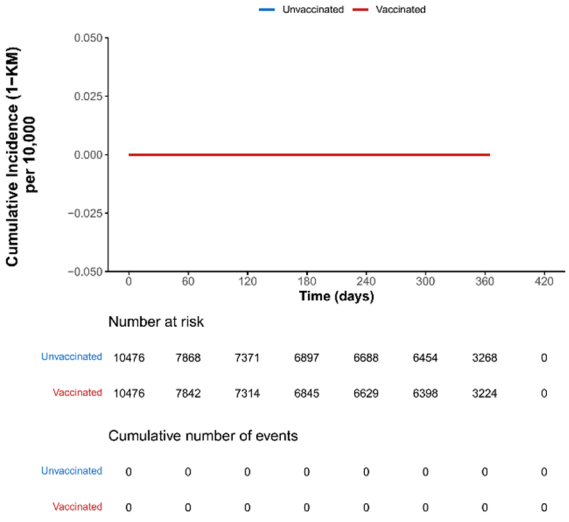
Table 31. Risk estimates (95% CI) per 10,000 person-years (PY) for acute cardiovascular injury among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source (risk window: 365 days after dose 1)

	Vaccinated				Unvaccinated			
Data source	**Events (n)**	**Cumulative incidence (95% CI)**	**Person-years (PY)**	**Incidence rate (95% CI)**	**Events (n)**	**Cumulative incidence (95% CI)**	**Person-years (PY)**	**Incidence rate (95% CI)**
Pedianet (Italy)	0	0 (0, 0)	6,938.50	0 (0, 5.30)	0	0 (0, 0)	6,987.20	
NHR (Norway)	6,309	189.07 (168.85, 209.25)	480,245.80	131.37 (128.15, 134.65)	6,602	219.93 (178.86, 260.82)	476,730.49	138.48 (133.23, 143.94)
PHARMO (Netherlands)	1,298	42.10 (39.70, 44.51)	300,317.30	43.22 (40.90, 45.64)	953	32.30 (29.23, 35.37)	273,962.28	34.79 (31.84, 38)
EpiChron (Spain)	1,326	60.91 (57.42, 64.41)	197,157.25	67.26 (63.68, 70.98)	1,380	60.91 (55.40, 66.42)	196,442.60	70.25 (64.71, 76.27)
SIDIAP (Spain)	4,795	44.27 (42.90, 45.64)	1,003,698.54	47.77 (46.43, 49.15)	4,886	42.94 (40.83, 45.06)	1,003,896.08	48.67 (46.49, 50.96)

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 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)

Pedianet



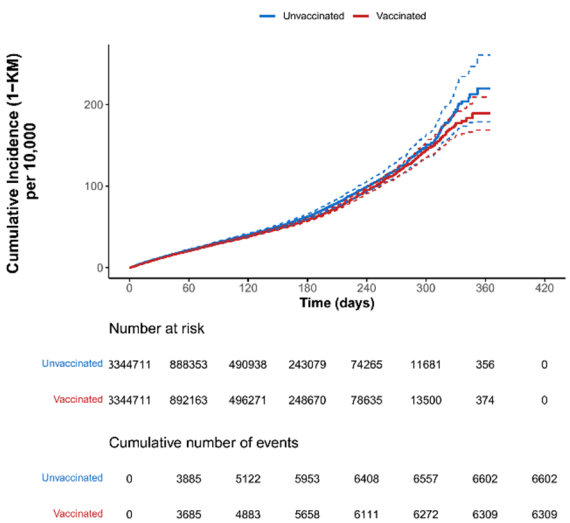
Number at risk

Unvaccinated	10476	7868	7371	6897	6688	6454	3268	0
Vaccinated	10476	7842	7314	6845	6629	6398	3224	0

Cumulative number of events

Unvaccinated	0	0	0	0	0	0	0	0
Vaccinated	0	0	0	0	0	0	0	0

NHR



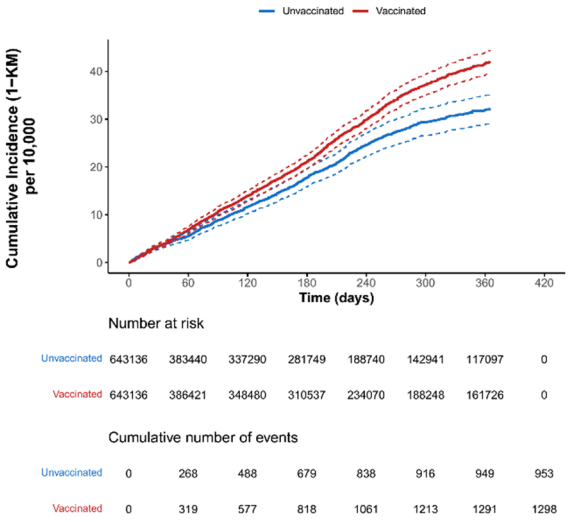
Number at risk

Unvaccinated	3344711	888353	490938	243079	74265	11681	356	0
Vaccinated	3344711	892163	496271	248670	78635	13500	374	0

Cumulative number of events

Unvaccinated	0	3885	5122	5953	6408	6557	6602	6602
Vaccinated	0	3685	4883	5658	6111	6272	6309	6309

PHARMO



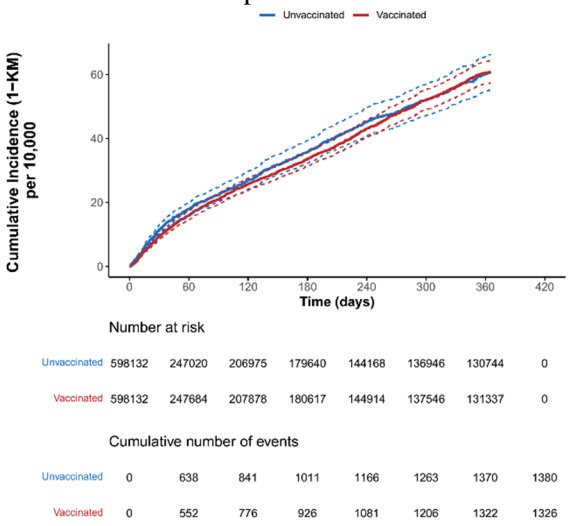
Number at risk

Unvaccinated	643136	383440	337290	281749	188740	142941	117097	0
Vaccinated	643136	386421	348480	310537	234070	188248	161726	0

Cumulative number of events

Unvaccinated	0	268	488	679	838	916	949	953
Vaccinated	0	319	577	818	1061	1213	1291	1298

EpiChron



Number at risk

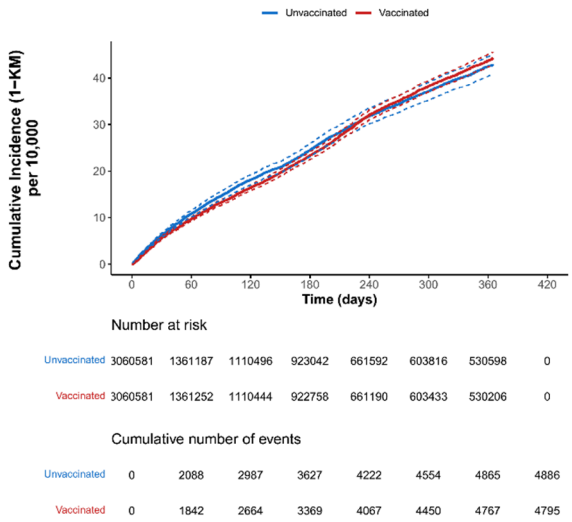
Unvaccinated	598132	247020	206975	179640	144168	136946	130744	0
Vaccinated	598132	247684	207878	180617	144914	137546	131337	0

Cumulative number of events

Unvaccinated	0	638	841	1011	1166	1263	1370	1380
Vaccinated	0	552	776	926	1081	1206	1322	1326

SIDIAP

Figure 22. Cumulative incidence of acute cardiovascular injury among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source (risk window: 365 days after dose 1)



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

Figure 23. Forest plot showing incidence rates and 95% confidence intervals for acute cardiovascular injury among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source and by age groups (risk window: 365 days after dose 1)

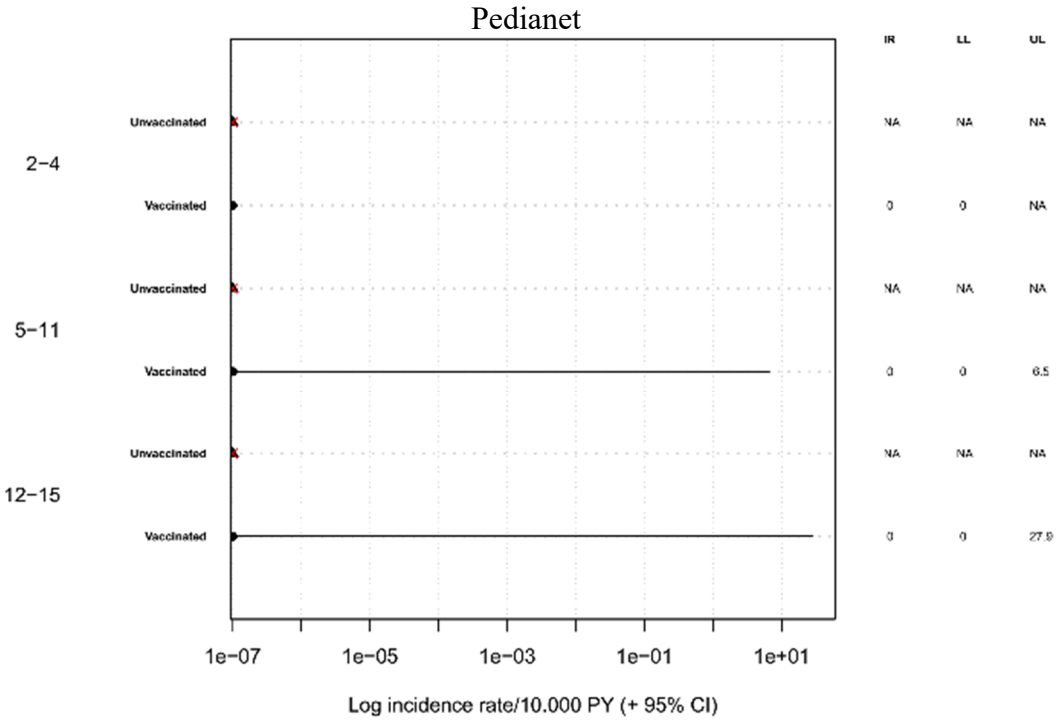


Figure 23. Forest plot showing incidence rates and 95% confidence intervals for acute cardiovascular injury among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source and by age groups (risk window: 365 days after dose 1)

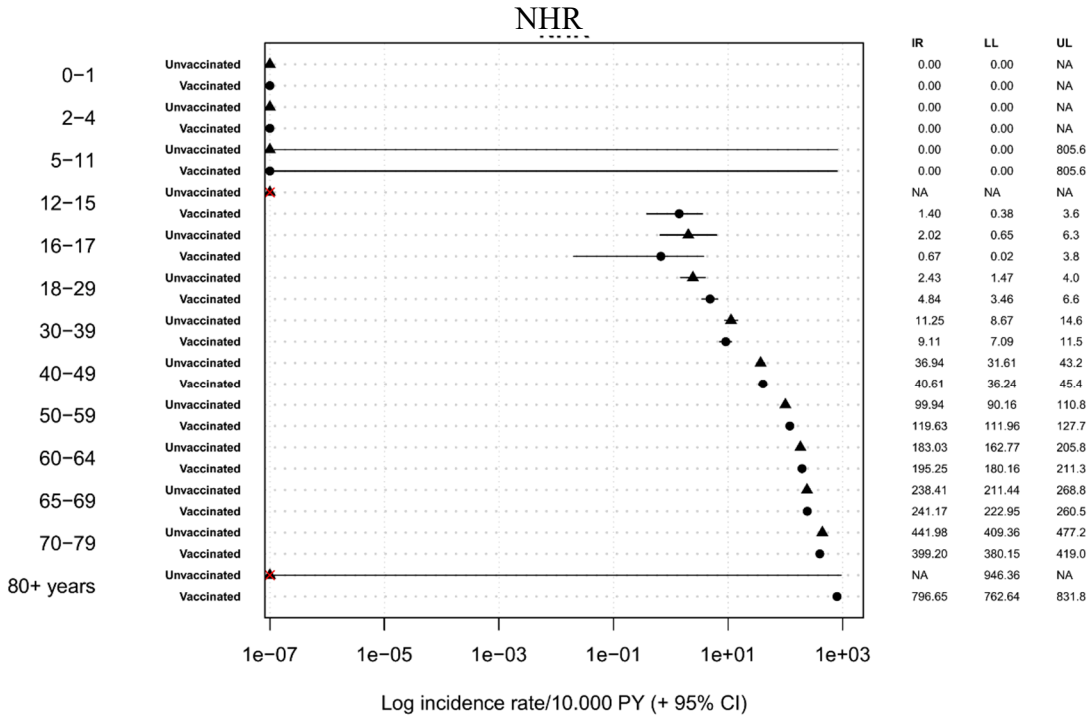


Figure 23. Forest plot showing incidence rates and 95% confidence intervals for acute cardiovascular injury among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source and by age groups (risk window: 365 days after dose 1)

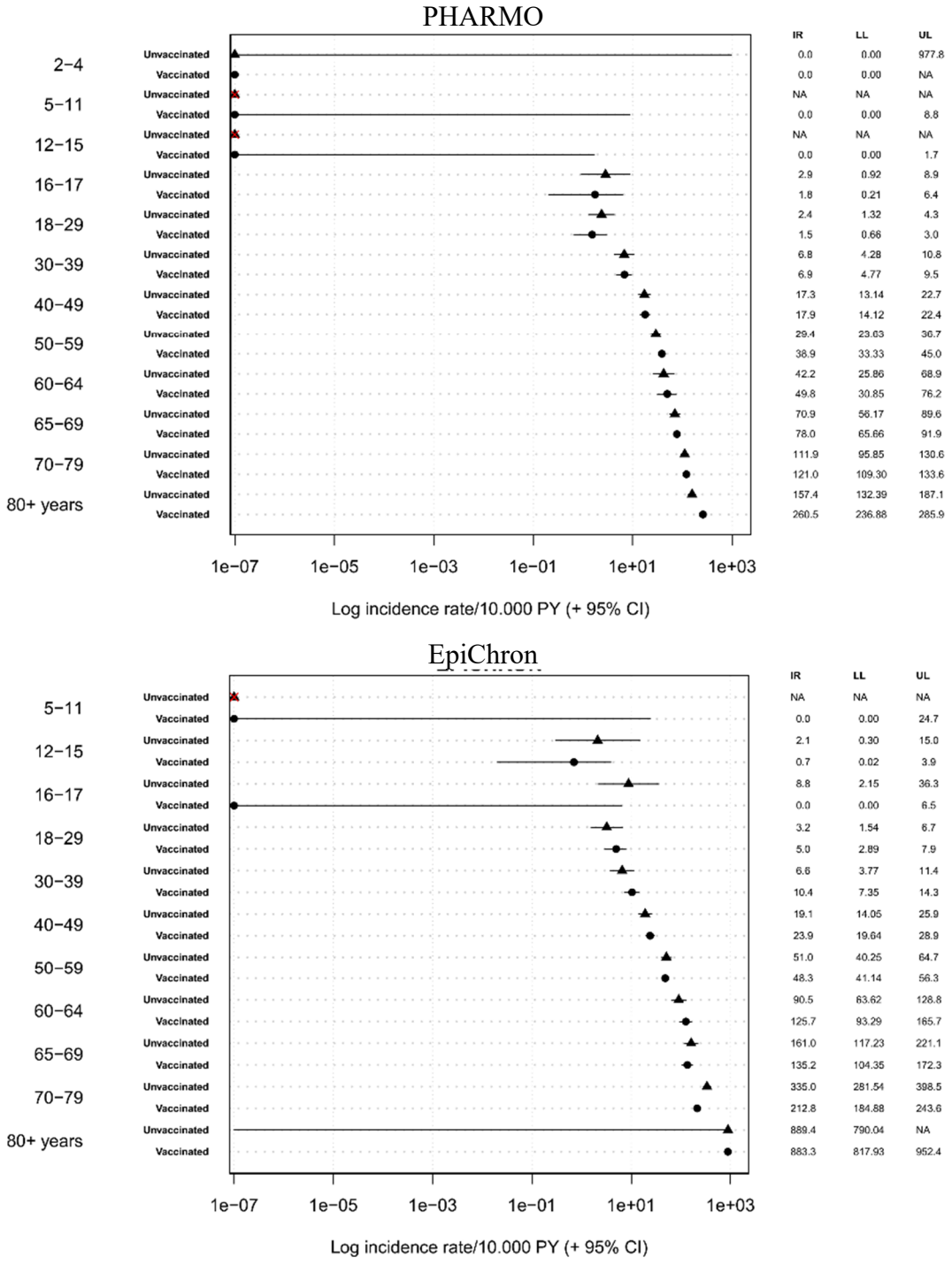


Figure 23. Forest plot showing incidence rates and 95% confidence intervals for acute cardiovascular injury among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source and by age groups (risk window: 365 days after dose 1)

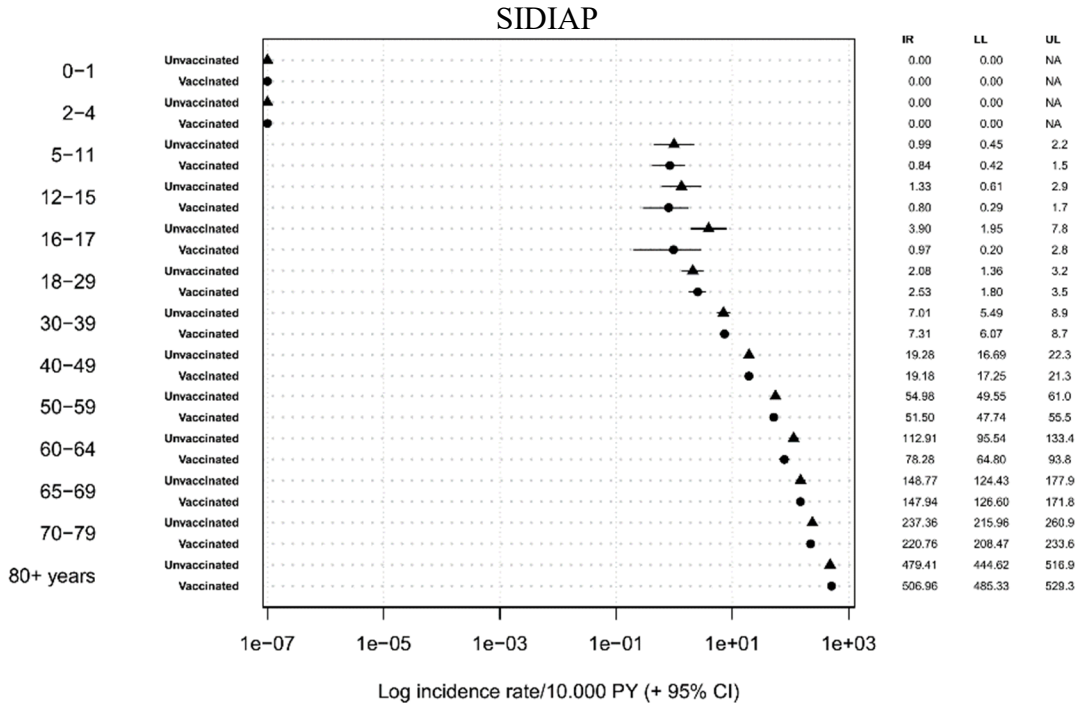


Table 32. Matched and adjusted hazard ratios (HRs) and matched and adjusted risk differences (RDs) per 10,000 person-years and their 95% CIs for acute cardiovascular injury among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source (risk window: 365 days after dose 1)

	Matched HR (95% CI)	Adjusted HR (95% CI)	Matched RD	Adjusted RD
Pedianet	NA	NA	NA	NA
NHR	0.95 (0.90, 0.99)	0.94 (0.90, 0.98)	-30.86	-31.77
PHARMO	1.25 (1.13, 1.39)	1.20 (1.08, 1.33)	9.81	8.41
EpiChron	0.96 (0.87, 1.06)	0.91 (0.82, 1)	0	-4.11
SIDIAP	0.98 (0.93, 1.04)	0.93 (0.89, 0.99)	1.33	-0.68

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

10.3.11. Arrhythmia

Arrhythmia was observed in the vaccinated and unvaccinated cohorts in all data sources. The incidence rates ranged from 24.50 per 10,000 person-years (95% CI: 14.27, 39.23) in Pedianet (children only) to 244.02 per 10,000 person-years (95% CI: 239.55, 248.56) in NHR in the vaccinated cohorts and from 14.31 per 10,000 person-years (95% CI: 7.70, 26.61) in Pedianet to 234.38 per 10,000 person-years (95% CI: 227.58, 241.38) in NHR in the unvaccinated cohorts. The cumulative incidences during the 365-day risk window ranged from 23.95 per 10,000 individuals (95% CI: 12.54, 35.34) in Pedianet to 306.11 per 10,000 person-years (95% CI: 269.85, 342.24) in NHR in the vaccinated cohorts and from 13.90 per 10,000 person-years (95% CI: 5.23, 22.56) in Pedianet to 263.50 per 10,000 person-years (95% CI: 221.64, 305.19) in NHR in the unvaccinated cohorts.

The incidence rates were higher in the older age groups. The matched HRs were 1.71 (95% CI: 0.78, 3.74) in Pedianet, 1.04 (95% CI: 1.01, 1.08) in NHR, 1.36 (95% CI: 1.27, 1.46) in PHARMO, 1.15 (95% CI: 1.06, 1.26) in EpiChron, and 1.07 (95% CI: 1.03, 1.11) in SIDIAP. The adjusted HRs were 1.73 (95% CI: 0.79, 3.78) in Pedianet, 1.04 (95% CI: 1, 1.07) in NHR, 1.28 (95% CI: 1.19, 1.38) in PHARMO, 1.07 (95% CI: 0.98, 1.17) in EpiChron, and 1.02 (95% CI: 0.98, 1.06) in SIDIAP. In NHR, PHARMO, EpiChron and SIDIAP the adjusted HRs were above 1 and the lower limits of the 95% CIs for NHR and PHARMO were >1.

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

	Vaccinated				Unvaccinated			
Data source	**Events (n)**	**Cumulative incidence (95% CI)**	**Person-years (PY)**	**Incidence rate (95% CI)**	**Events (n)**	**Cumulative incidence (95% CI)**	**Person-years (PY)**	**Incidence rate (95% CI)**
Pedianet (Italy)	17	23.95 (12.54, 35.34)	6,938.07	24.50 (14.27, 39.23)	10	13.90 (5.23, 22.56)	6,985.97	14.31 (7.70, 26.61)
NHR (Norway)	11,326	306.11 (269.85, 342.24)	464,140.37	244.02 (239.55, 248.56)	10,805	263.50 (221.64, 305.19)	461,008.02	234.38 (227.58, 241.38)
PHARMO (Netherlands)	2,679	88.49 (84.96, 92.02)	297,554.23	90.03 (86.66, 93.51)	1,800	64.75 (60.44, 69.05)	271,584.58	66.28 (62.34, 70.47)
EpiChron (Spain)	1,804	82.65 (78.59, 86.72)	196,423.61	91.84 (87.65, 96.18)	1,561	68.76 (63.09, 74.42)	195,903.92	79.68 (73.85, 85.97)
SIDIAP (Spain)	10,396	95.80 (93.79, 97.82)	992,555.52	104.74 (102.74, 106.77)	9,727	86.28 (83.33, 89.24)	993,178.45	97.94 (94.90, 101.07)

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 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)

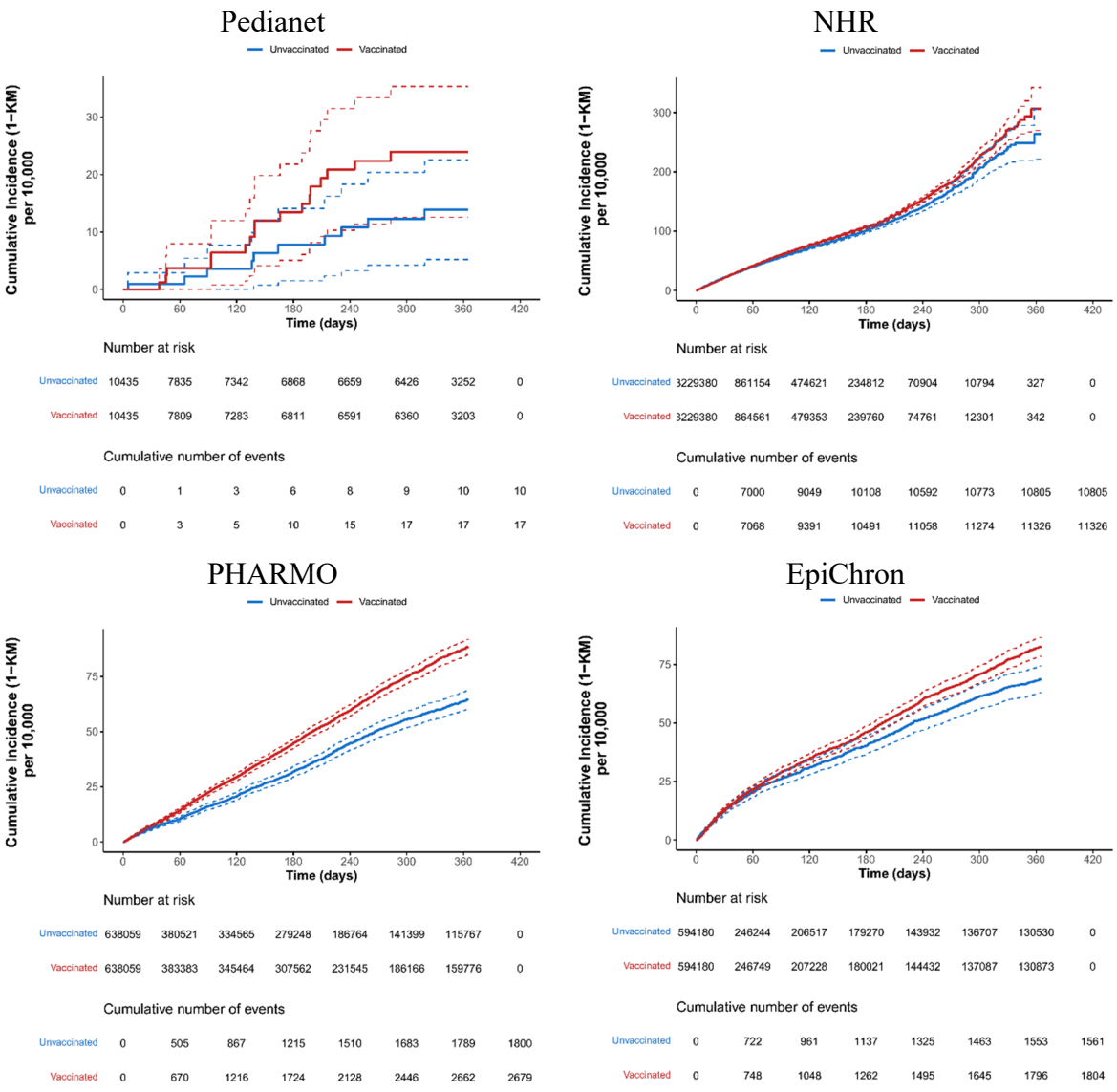
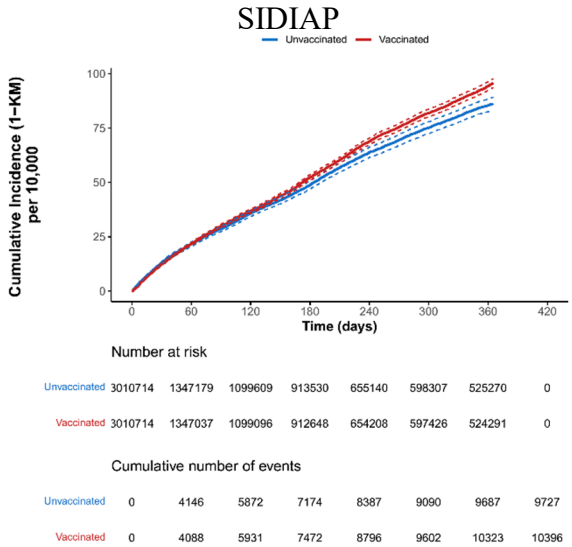


Figure 24. Cumulative incidence of arrhythmia among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source (risk window: 365 days after dose 1)



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

Figure 25. Forest plot showing incidence rates and 95% confidence intervals for arrhythmia among individuals who received atleast 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)

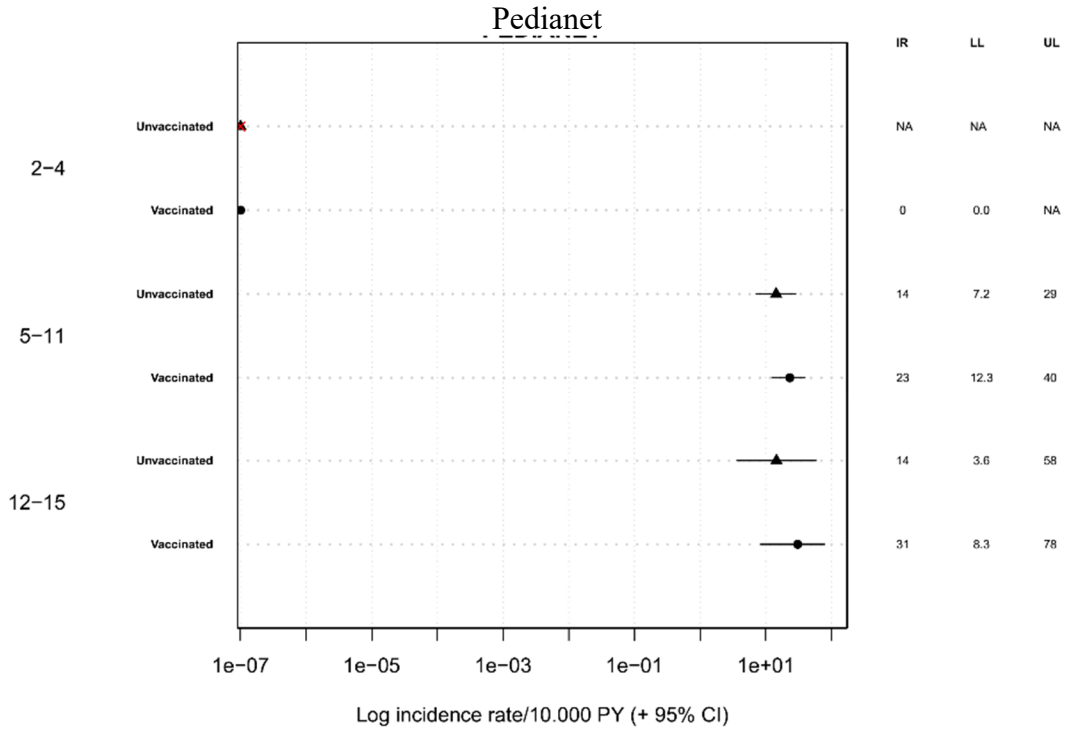


Figure 25. Forest plot showing incidence rates and 95% confidence intervals for arrhythmia among individuals who received atleast one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source and by age groups (risk window: 365 days after dose 1)

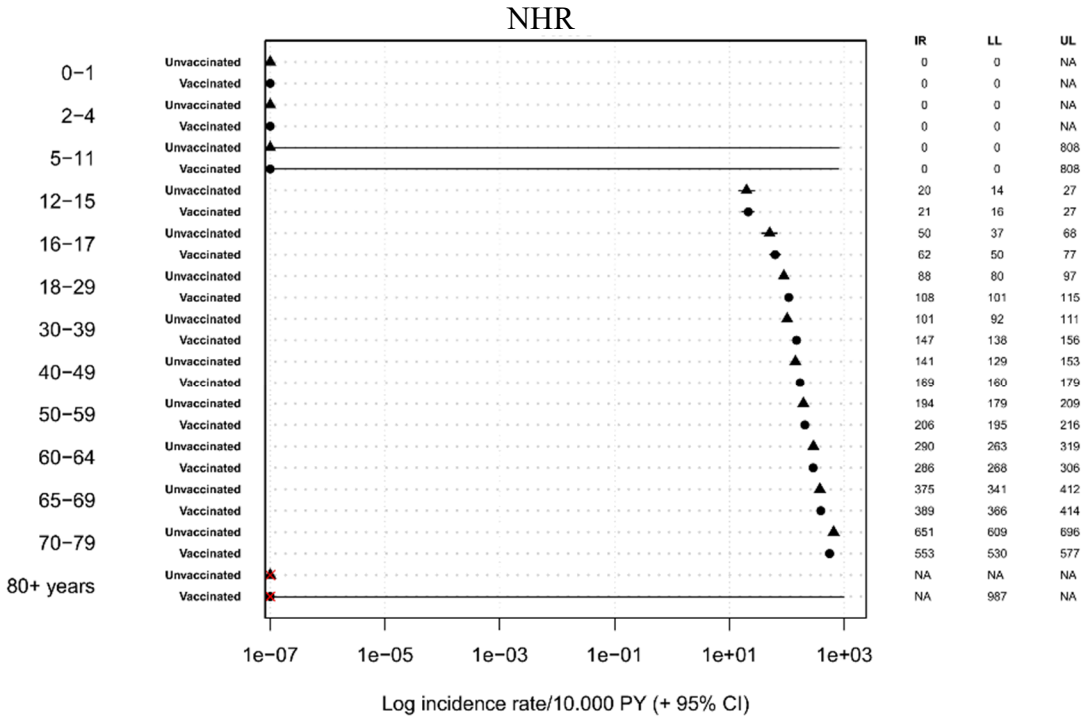


Figure 25. Forest plot showing incidence rates and 95% confidence intervals for arrhythmia among individuals who received atleast one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source and by age groups (risk window: 365 days after dose 1)

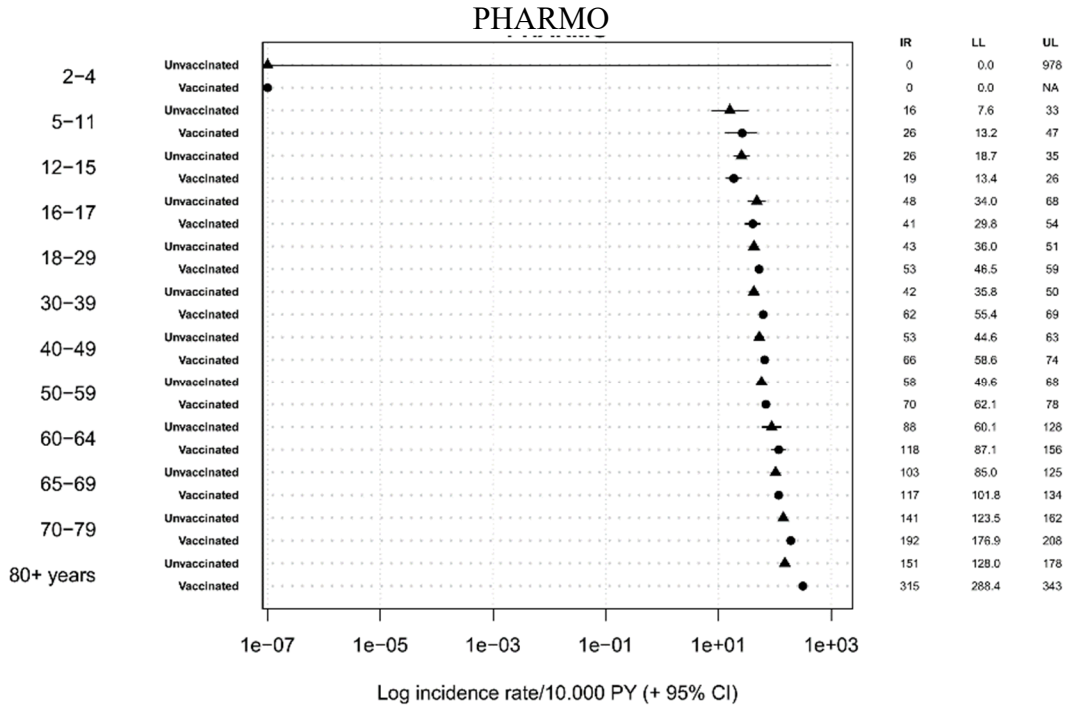


Figure 25. Forest plot showing incidence rates and 95% confidence intervals for arrhythmia among individuals who received atleast one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source and by age groups (risk window: 365 days after dose 1)

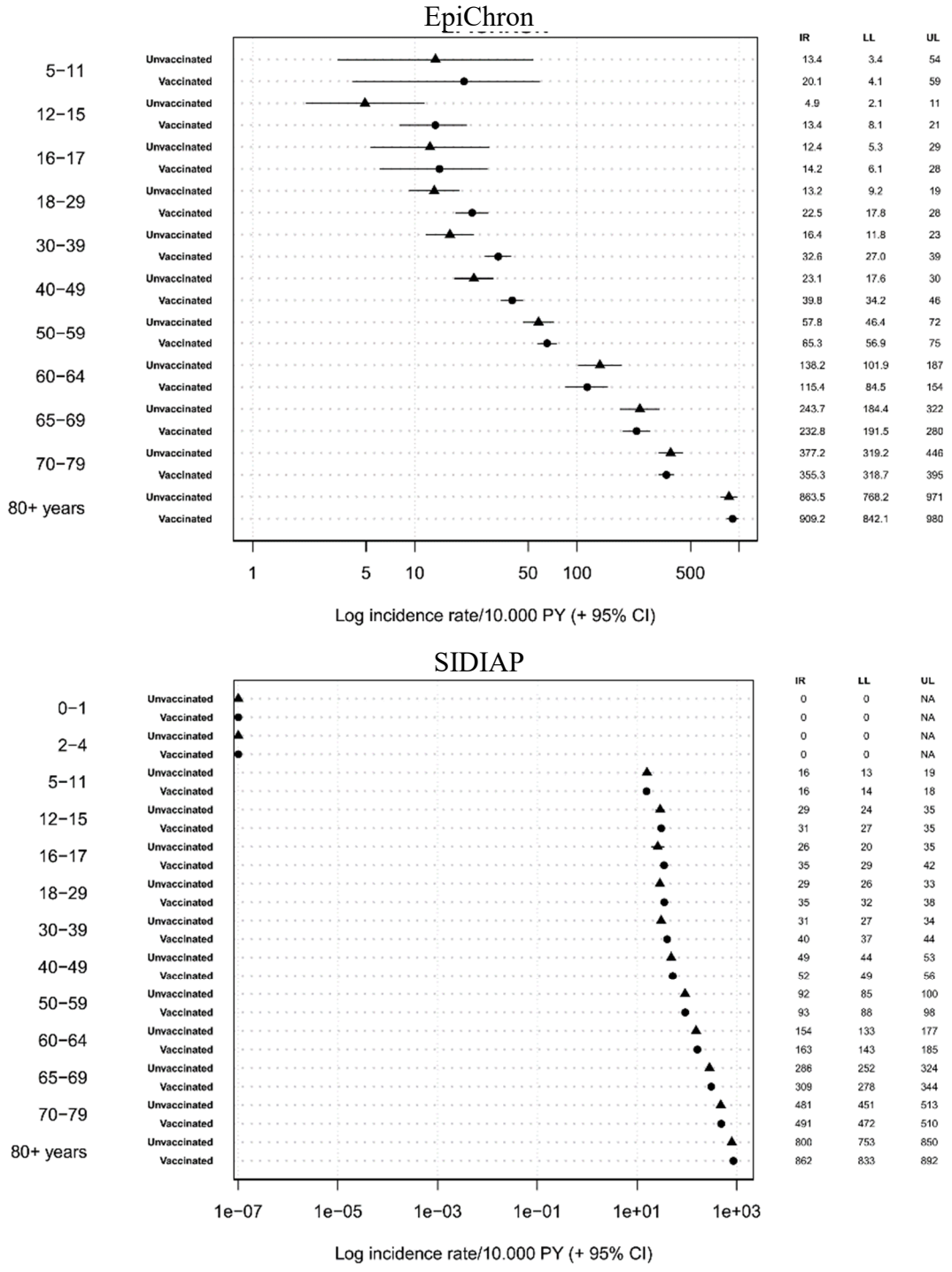


Table 34. Matched and adjusted hazard ratios (HRs) and matched and adjusted risk differences (RDs) per 10,000 person-years and their 95% CIs for arrhythmia among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source (risk window: 365 days after dose 1)

	Matched HR (95% CI)	Adjusted HR (95% CI)	Matched RD	Adjusted RD
Pedianet	1.71 (0.78, 3.74)	1.73 (0.79, 3.78)	10.05	10.05
NHR	1.04 (1.01, 1.08)	1.04 (1, 1.07)	42.61	41.77
PHARMO	1.36 (1.27, 1.46)	1.28 (1.19, 1.38)	23.75	19.56
EpiChron	1.15 (1.06, 1.26)	1.07 (0.98, 1.17)	13.90	7.78
SIDIAP	1.07 (1.03, 1.11)	1.02 (0.98, 1.06)	9.52	5.45

10.3.12. Heart failure

Heart failure was observed in the vaccinated and unvaccinated cohorts in all data sources, except Pedianet. The incidence rates of heart failure ranged from 20.55 per 10,000 person-years (95% CI: 18.96, 22.23) in PHARMO to 62.69 (95% CI: 60.50, 64.93) per 10,000 person-years in NHR in the vaccinated cohorts and from 17.66 per 10,000 person-years (95% CI: 15.58, 20.02) in PHARMO to 77.68 per 10,000 person-years (95% CI: 73.66, 81.92) in NHR in the unvaccinated cohorts. The cumulative incidence of heart failure during the 365-day risk window showed no difference 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 0.80 (95% CI: 0.75, 0.86) in NHR, 1.17 (95% CI: 1.01, 1.36) in PHARMO, 0.92 (95% CI: 0.82, 1.04) in EpiChron, and 0.91 (95% CI: 0.85, 0.98) in SIDIAP. The adjusted HRs were 0.80 (95% CI: 0.75, 0.85) in NHR, 1.13 (95% CI: 0.97, 1.31) in PHARMO, 0.88 (95% CI: 0.78, 0.99) in EpiChron, and 0.87 (95% CI: 0.81, 0.93) in SIDIAP. No differences were observed for the incidence of heart failure between the vaccinated and unvaccinated cohorts during the 365-day risk window.

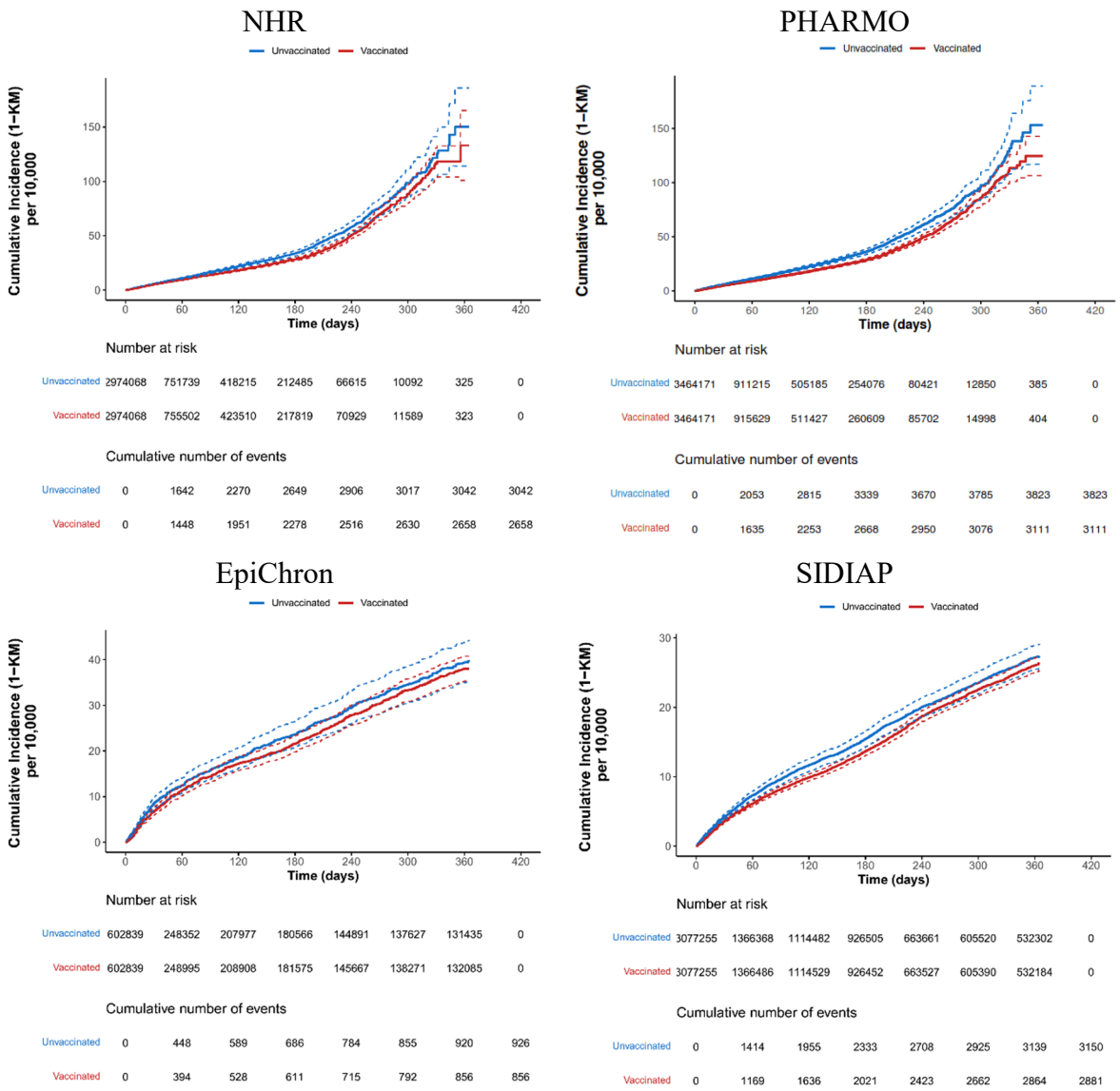
Table 35. Risk estimates (95% CI) per 10,000 person-years (PY) for heart failure among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source (risk window: 365 days after dose 1)

	Vaccinated				Unvaccinated			
Data source	**Events (n)**	**Cumulative incidence (95% CI)**	**Person-years (PY)**	**Incidence rate (95% CI)**	**Events (n)**	**Cumulative incidence (95% CI)**	**Person-years (PY)**	**Incidence rate (95% CI)**
Pedianet (Italy)	NA	NA	NA	NA	NA	NA	NA	NA
NHR (Norway)	3,111	124.56 (106.52, 142.57)	496,275.85	62.69 (60.50, 64.93)	3,823	153.12 (116.88, 189.23)	492,132.94	77.68 (73.66, 81.92)
PHARMO (Netherlands)	620	20.22 (18.55, 21.89)	301,729.37	20.55 (18.96, 22.23)	486	16.18 (13.95, 18.41)	275,206.21	17.66 (15.58, 20.02)
EpiChron (Spain)	856	38.06 (35.33, 40.79)	198,251.66	43.18 (40.33, 46.17)	926	39.86 (35.40, 44.32)	197,511.19	46.88 (42.40, 51.84)
SIDIAP (Spain)	2,881	26.37 (25.31, 27.43)	1,007,618.34	28.59 (27.56, 29.66)	3,150	27.40 (25.65, 29.16)	1,007,644.08	31.26 (29.46, 33.17)

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

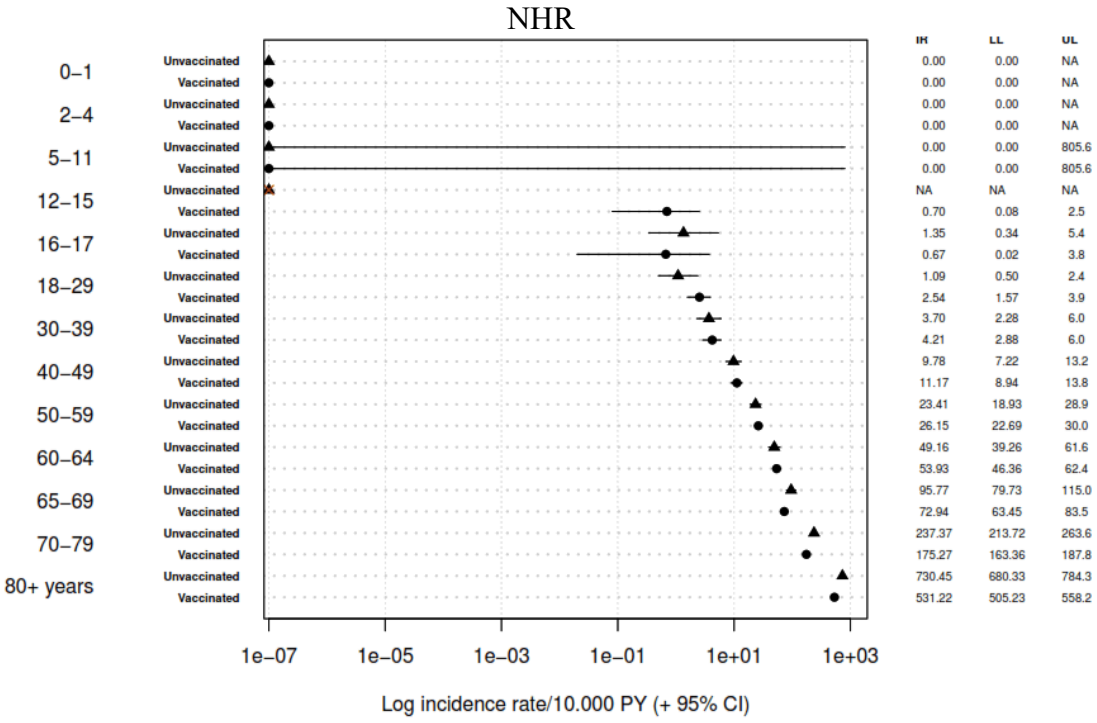


Figure 27. Forest plot showing incidence rates and 95% confidence intervals for heart failure among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source and by age groups (risk window: 365 days after dose 1)

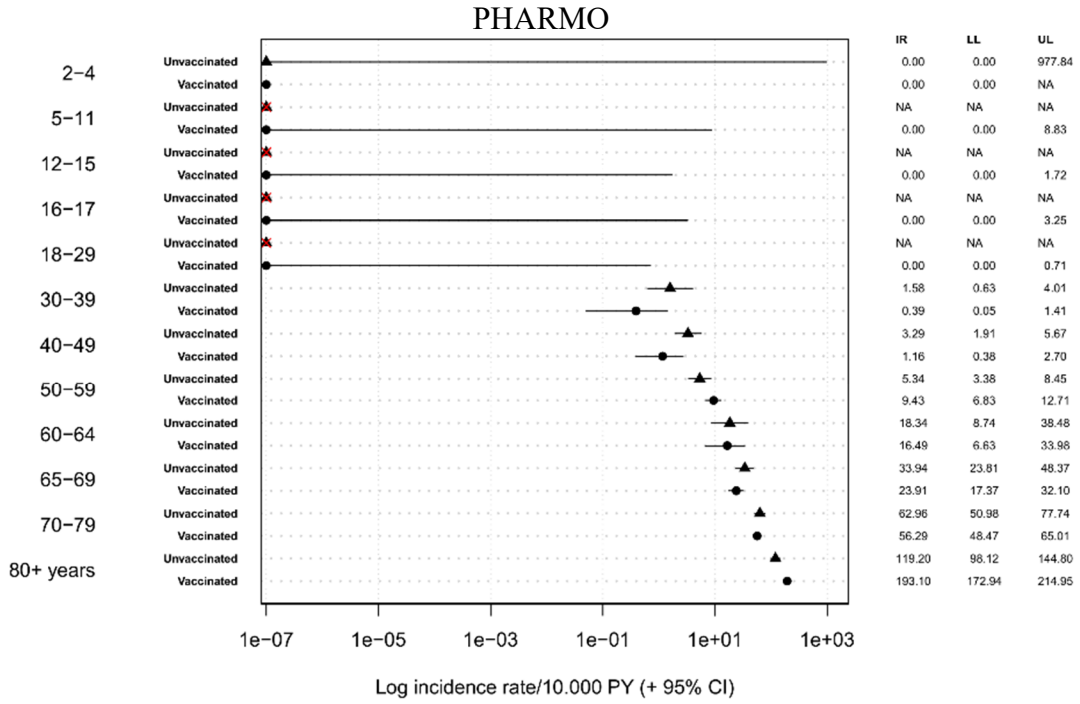


Figure 27. Forest plot showing incidence rates and 95% confidence intervals for heart failure among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source and by age groups (risk window: 365 days after dose 1)

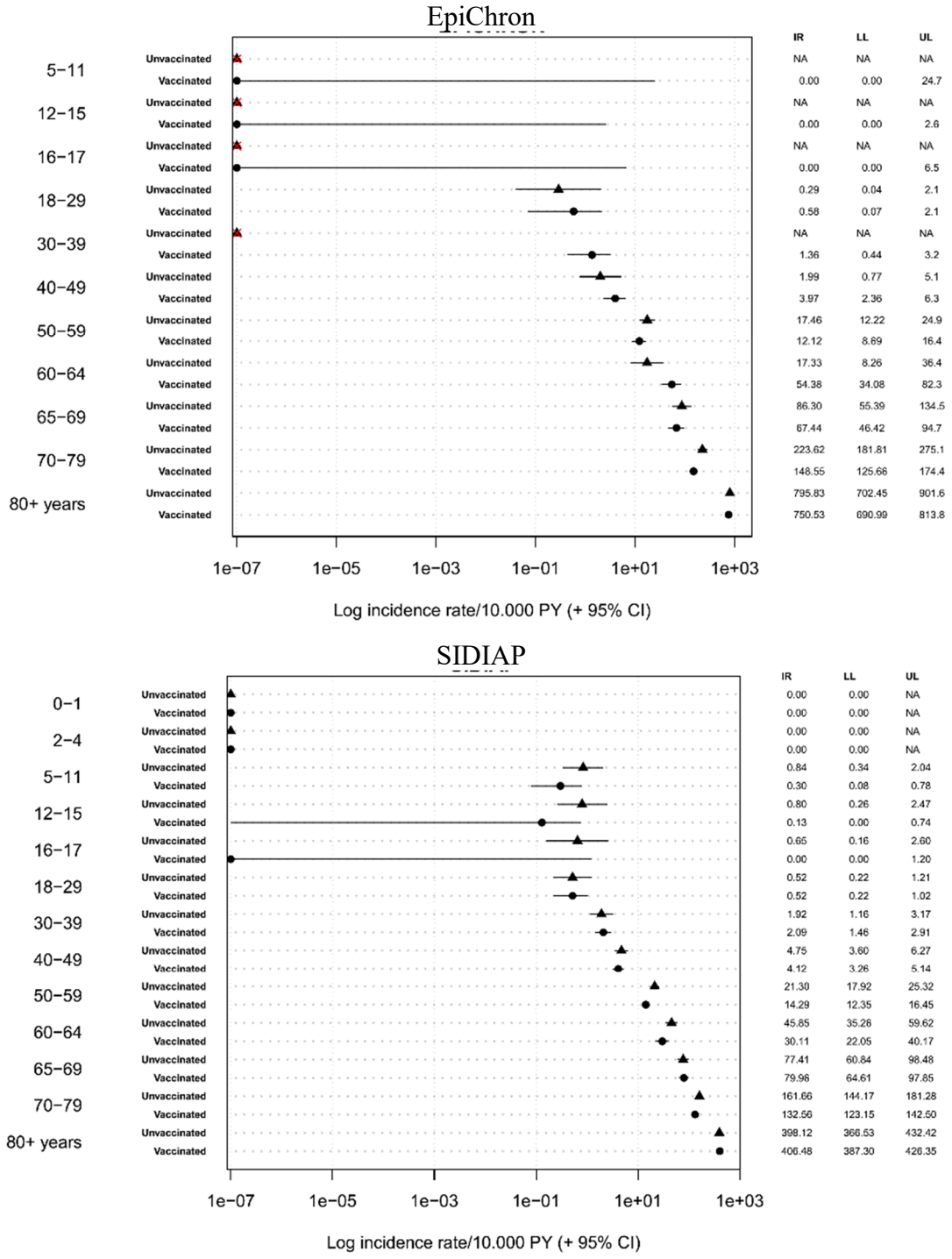


Table 36. Matched and adjusted hazard ratios (HRs) and matched and adjusted risk differences (RDs) per 10,000 person-years and their 95% CIs for heart failure among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source (risk window: 365 days after dose 1)

	Matched HR (95% CI)	Adjusted HR (95% CI)	Matched RD	Adjusted RD
Pedianet	NA	NA	NA	NA
NHR	0.80 (0.75, 0.86)	0.80 (0.75, 0.85)	-28.56	-29.20
PHARMO	1.17 (1.01, 1.36)	1.13 (0.97, 1.31)	4.04	3.51
EpiChron	0.92 (0.82, 1.04)	0.88 (0.78, 0.99)	-1.80	-4.22
SIDIAP	0.91 (0.85, 0.98)	0.87 (0.81, 0.93)	-1.03	-2.43

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

10.3.13. 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 0.17 per 10,000 person-years (95% CI: 0.05, 0.39) in PHARMO to 0.39 per 10,000 person-years (95% CI: 0.28, 0.54) in SIDIAP in the vaccinated cohorts. In the unvaccinated cohorts the incidence rates were: PHARMO 0.11 (95% CI: 0.03, 0.47), EpiChron 0.10 (95% CI: 0.01, 0.71), and SIDIAP 0.25 (95% CI: 0.14, 0.43). 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 1.54 (95% CI: 0.27, 8.90) in PHARMO, 2.98 (95% CI: 0.36, 24.74) in EpiChron, and 1.60 (95% CI: 0.84, 3.03) in SIDIAP. The adjusted HRs were 1.34 (95% CI: 0.23, 7.82) in PHARMO, 3.12 (95% CI: 0.38, 25.82) in EpiChron, and 1.55 (95% CI: 0.82, 2.91) in SIDIAP. No differences were observed for the incidence of stress cardiomyopathy between the vaccinated and unvaccinated cohorts during the 365-day risk window.

Table 37. Risk estimates (95% CI) per 10,000 person-years (PY) for stress cardiomyopathy among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source (risk window: 365 days after dose 1)

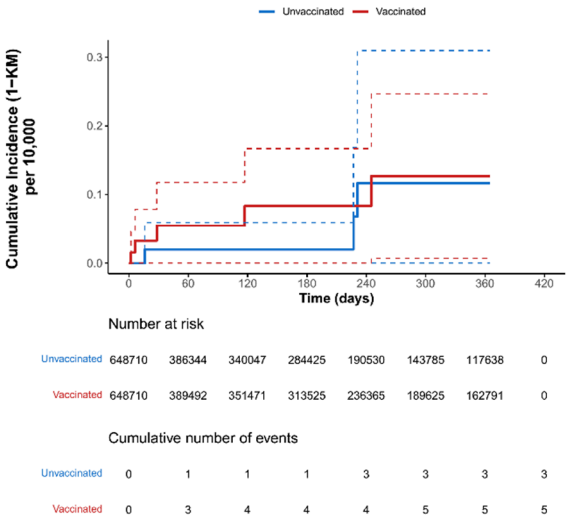
	Vaccinated				Unvaccinated			
Data source	**Events (n)**	**Cumulative incidence (95% CI)**	**Person-years (PY)**	**Incidence rate (95% CI)**	**Events (n)**	**Cumulative incidence (95% CI)**	**Person-years (PY)**	**Incidence rate (95% CI)**
Pedianet (Italy)	NA	NA	NA	NA	NA	NA	NA	NA
NHR (Norway)	NA	NA	NA	NA	NA	NA	NA	NA
PHARMO (Netherlands)	5	0.13 (0.01, 0.25)	302,875.42	0.17 (0.05, 0.39)	<5	0.12 (0, 0.31)	276,178.56	0.11 (0.03, 0.47)
EpiChron (Spain)	6	0.37 (0.07, 0.67)	199,925.09	0.30 (0.11, 0.65)	<5	0.09 (0, 0.26)	198,913.85	0.10 (0.01, 0.71)
SIDIAP (Spain)	40	0.38 (0.25, 0.51)	1,013,957.62	0.39 (0.28, 0.54)	25	0.22 (0.08, 0.36)	1,013,964.44	0.25 (0.14, 0.43)

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 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)

PHARMO



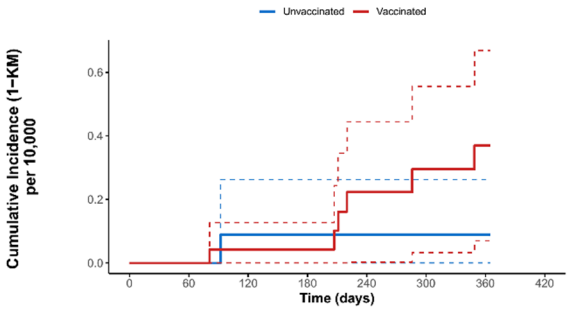
Number at risk

Unvaccinated	648710	386344	340047	284425	190530	143785	117638	0
Vaccinated	648710	389492	351471	313525	236365	189625	162791	0

Cumulative number of events

Unvaccinated	0	1	1	1	3	3	3	3
Vaccinated	0	3	4	4	4	5	5	5

EpiChron



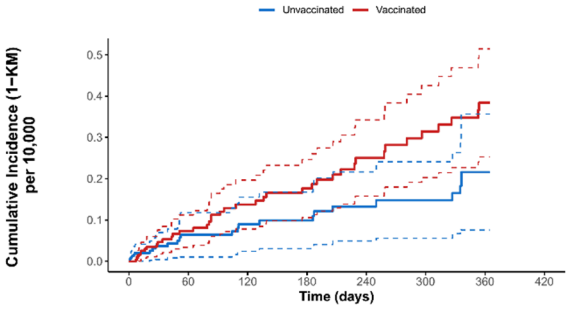
Number at risk

Unvaccinated	611380	250233	209038	181488	145659	138270	132063	0
Vaccinated	611380	251075	210279	182853	146768	139198	133008	0

Cumulative number of events

Unvaccinated	0	0	2	2	2	2	2	2
Vaccinated	0	0	1	1	4	5	6	6

SIDIAP



Number at risk

Unvaccinated	3110464	1374780	1120329	931833	667347	608227	535081	0
Vaccinated	3110464	1374780	1120325	931824	667338	608215	535071	0

Cumulative number of events

Unvaccinated	0	13	16	17	20	21	25	25
Vaccinated	0	14	22	26	32	36	40	40

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

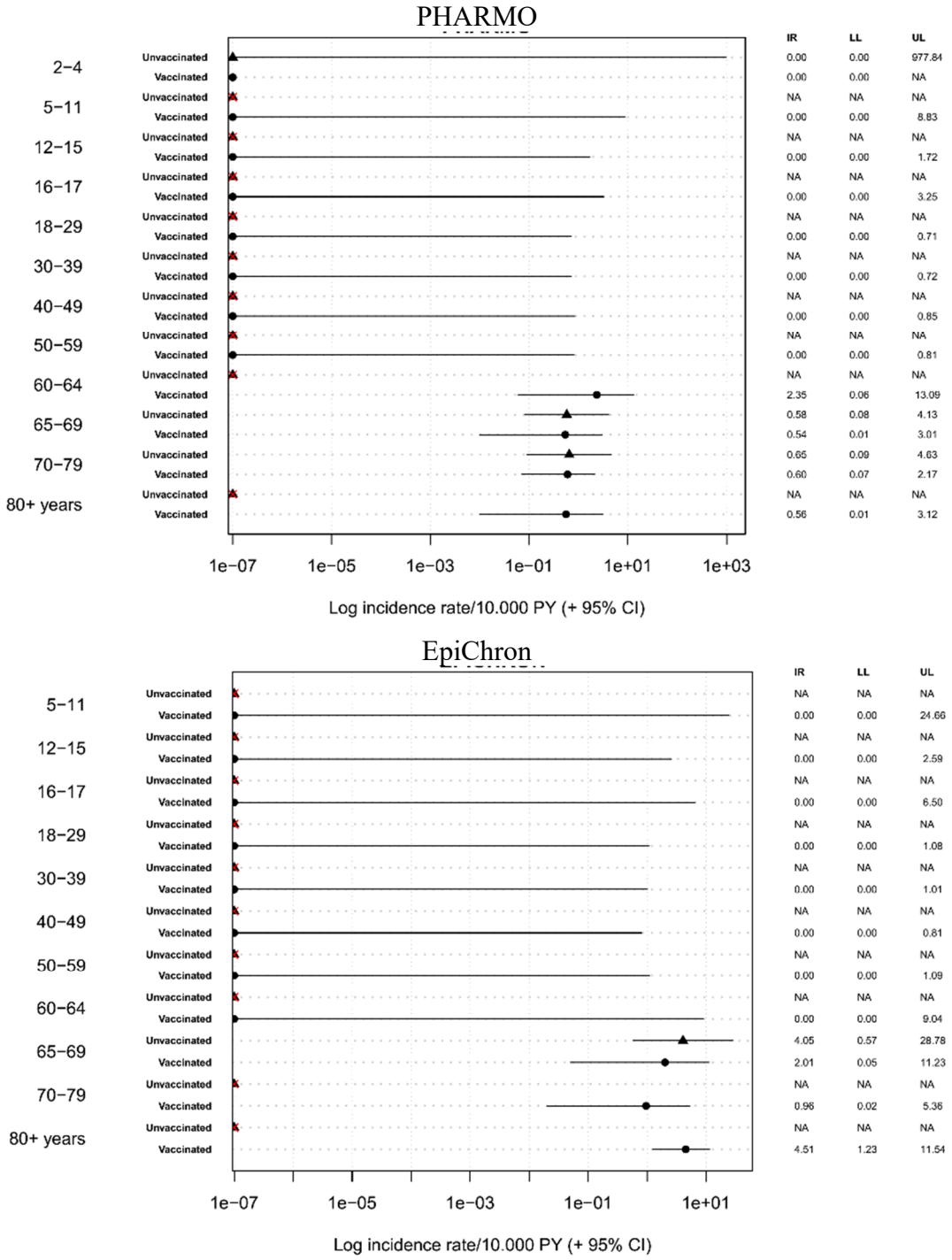


Figure 29. Forest plot showing incidence rates and 95% confidence intervals for stress cardiomyopathy among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source and by age groups (risk window: 365 days after dose 1)

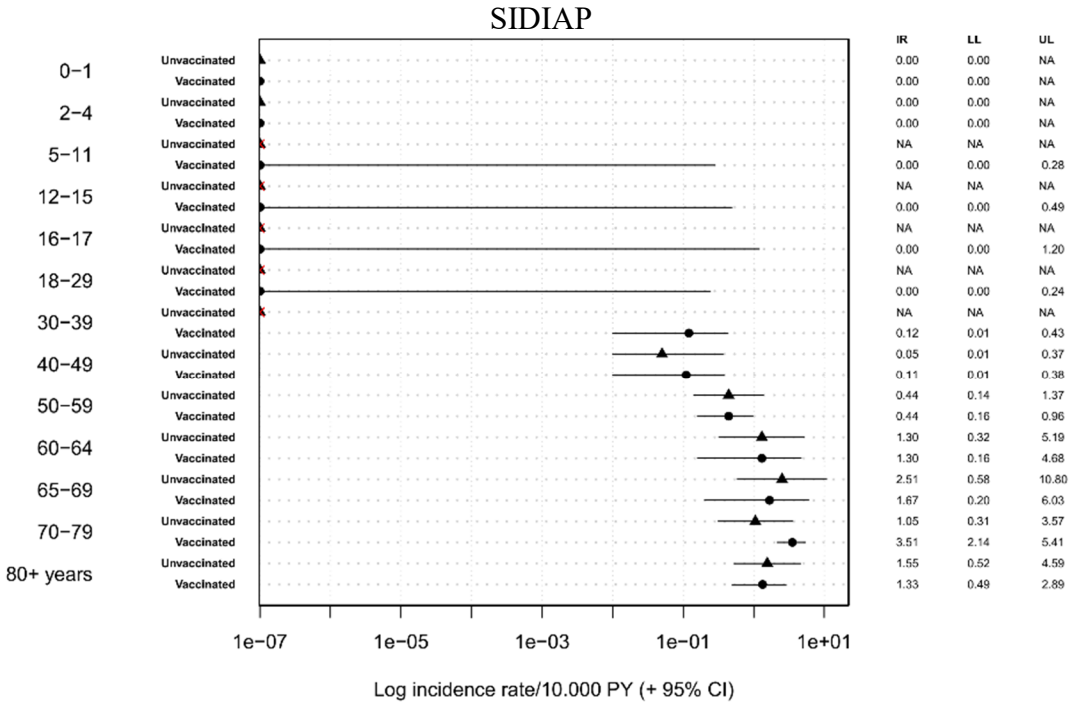


Table 38. Matched and adjusted hazard ratios (HRs) and matched and adjusted risk differences (RDs) per 10,000 person-years and their 95% CIs for stress cardiomyopathy among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source (risk window: 365 days after dose 1)

	Matched HR (95% CI)	Adjusted HR (95% CI)	Matched RD	Adjusted RD
Pedianet	NA	NA	NA	NA
NHR	NA	NA	NA	NA
PHARMO	1.54 (0.27, 8.90)	1.34 (0.23, 7.82)	0.01	-0.01
EpiChron	2.98 (0.36, 24.74)	3.12 (0.38, 25.82)	0.28	0.31
SIDIAP	1.60 (0.84, 3.03)	1.55 (0.82, 2.91)	0.17	0.17

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

10.3.14. 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 16.27 per 10,000 person-years (95% CI: 14.54, 18.14) in EpiChron to 88.86 per 10,000 person-years (95% CI: 86.24, 91.53) in NHR in the vaccinated cohorts and from 13.59 per 10,000 person-years (95% CI: 11.81, 15.65) in PHARMO to 89.17 per 10,000 person-years (95% CI: 84.99, 93.56) in NHR in the unvaccinated cohorts. The incidence of coronary artery disease was higher in higher age groups in all data sources in the vaccinated and unvaccinated cohorts.

The matched HRs of coronary artery disease were 0.99 (95% CI: 0.94, 1.05) in NHR, 1.41 (95% CI: 1.20, 1.66) in PHARMO, 0.89 (95% CI: 0.73, 1.09) in EpiChron, and 1.11 (95% CI: 1.02, 1.22) in SIDIAP. The adjusted HRs were 0,99 (95% CI: 0.94, 1.05) in NHR, 1.36 (95% CI: 1.15, 1.60) in PHARMO, 0.84 (95% CI: 0.69, 1.02) in EpiChron, and 1.06 (95% CI: 0.97, 1.16) in SIDIAP. In NHR and PHARMO the lower limits of the 95% CI for the adjusted HRs were >1.

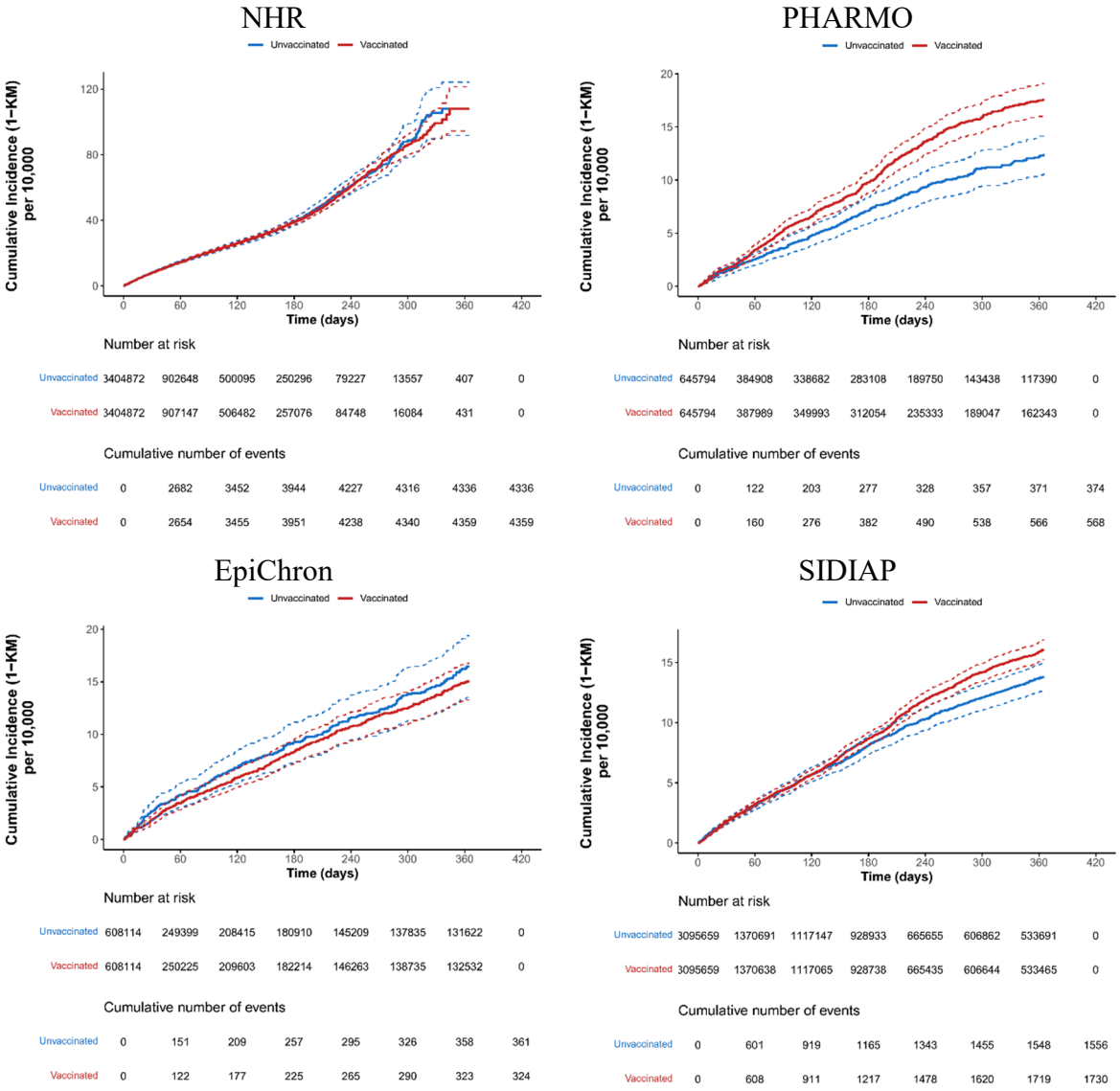
Table 39. Risk estimates (95% CI) per 10,000 person-years (PY) for coronary artery disease among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source (risk window: 365 days after dose 1)

	Vaccinated				Unvaccinated			
Data source	**Events (n)**	**Cumulative incidence (95% CI)**	**Person-years (PY)**	**Incidence rate (95% CI)**	**Events (n)**	**Cumulative incidence (95% CI)**	**Person-years (PY)**	**Incidence rate (95% CI)**
Pedianet (Italy)	NA	NA	NA	NA	NA	NA	NA	NA
NHR (Norway)	4,359	107.99 (94.45, 121.51)	490,570.24	88.86 (86.24, 91.53)	4,336	108.02 (91.70, 124.30)	486,252.24	89.17 (84.99, 93.56)
PHARMO (Netherlands)	568	17.63 (16.11, 19.15)	301,644.62	18.83 (17.31, 20.44)	374	12.47 (10.61, 14.33)	275,101.62	13.59 (11.81, 15.65)
EpiChron (Spain)	324	15.03 (13.29, 16.78)	199,200.73	16.27 (14.54, 18.14)	361	16.46 (13.53, 19.39)	198,229.11	18.21 (15.43, 21.49)
SIDIAP (Spain)	1,730	16.10 (15.28, 16.93)	1,010,742.75	17.12 (16.32, 17.94)	1,556	13.84 (12.69, 14.99)	1,010,887.66	15.39 (14.24, 16.63)

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

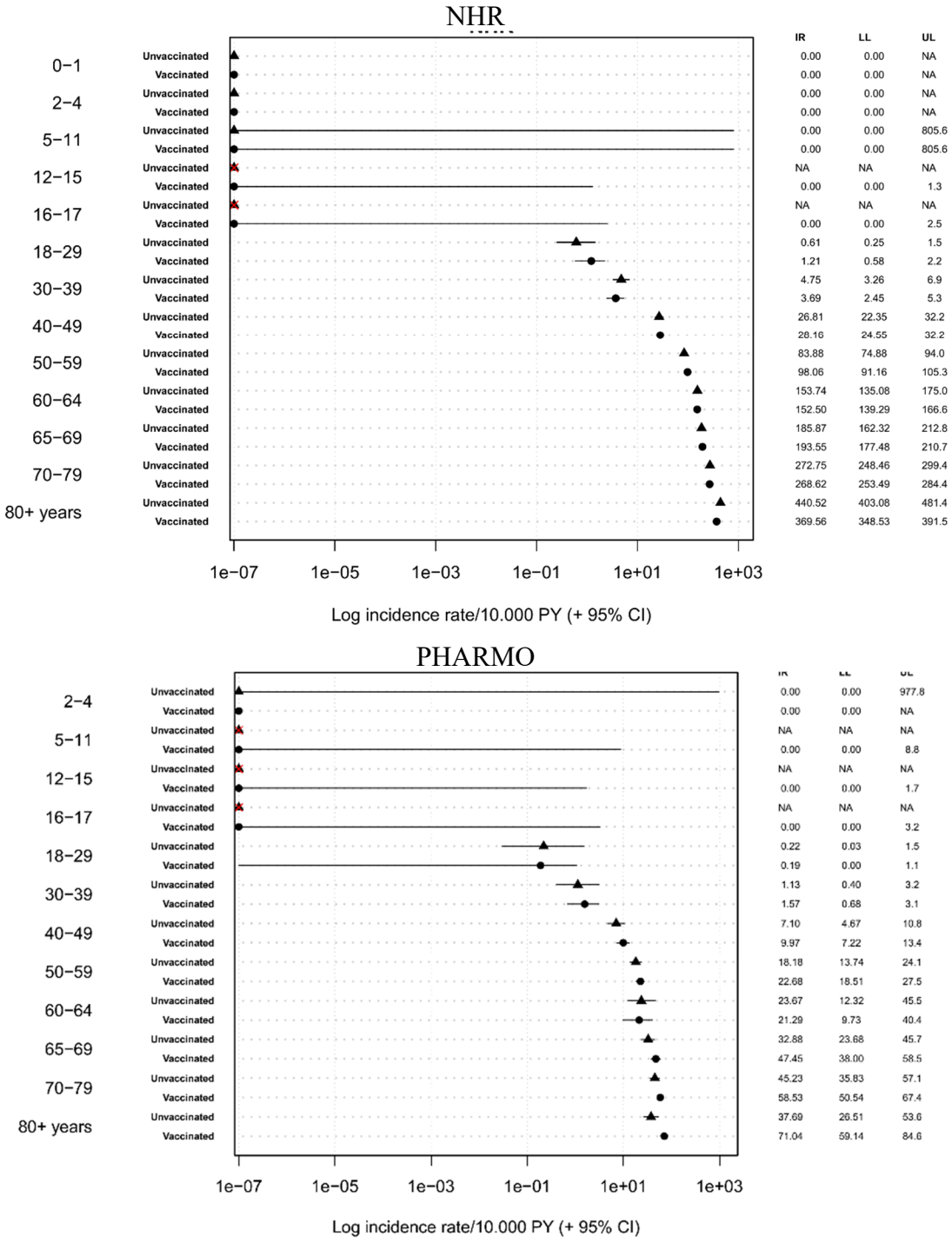


Figure 31. Forest plot showing incidence rates and 95% confidence intervals for coronary artery disease among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source and by age groups (risk window: 365 days after dose 1)

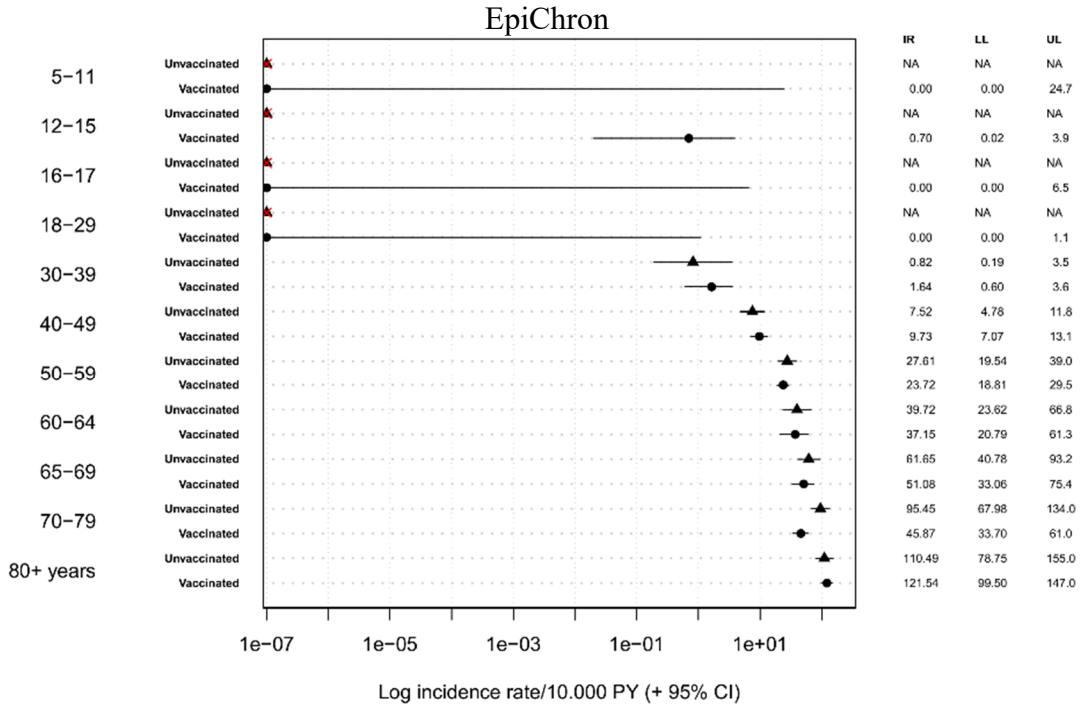


Figure 31. Forest plot showing incidence rates and 95% confidence intervals for coronary artery disease among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source and by age groups (risk window: 365 days after dose 1)

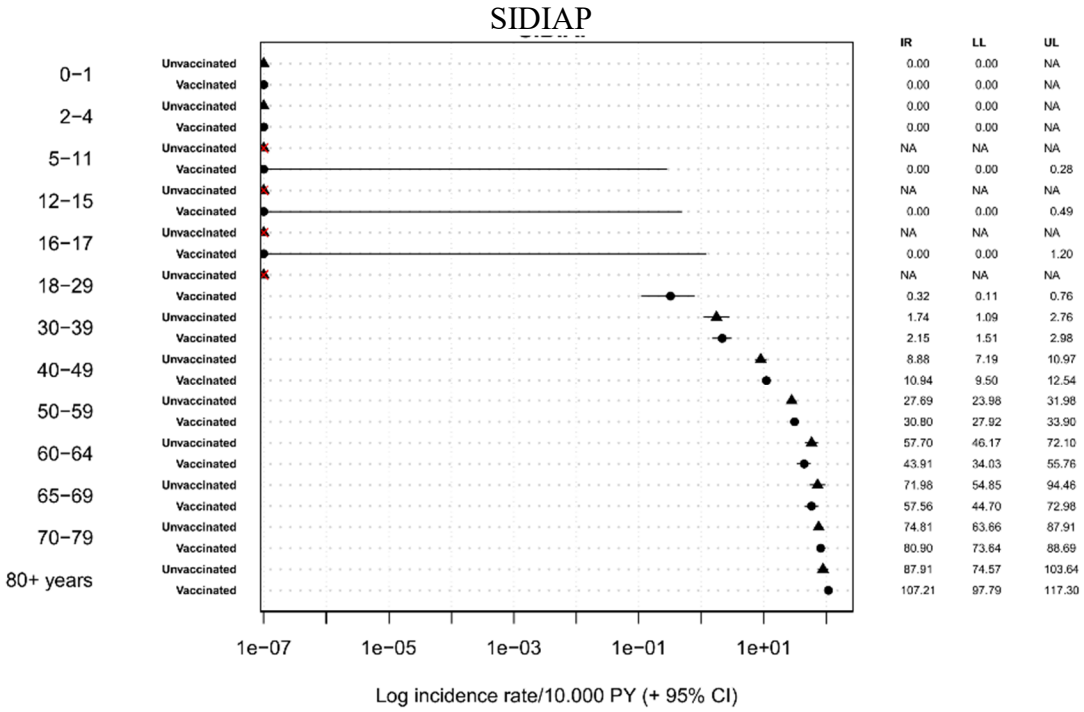


Table 40. Matched and adjusted hazard ratios (HRs) and matched and adjusted risk differences (RDs) per 10,000 person-years and their 95% CIs for coronary artery disease among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source (risk window: 365 days after dose 1)

	Matched HR (95% CI)	Adjusted HR (95% CI)	Matched RD	Adjusted RD
Pedianet	NA	NA	NA	NA
NHR	0.99 (0.94, 1.05)	0.99 (0.94, 1.05)	-0.03	-0.45
PHARMO	1.41 (1.20, 1.66)	1.36 (1.15, 1.60)	5.16	4.67
EpiChron	0.89 (0.73, 1.09)	0.84 (0.69, 1.02)	-1.43	-2.62
SIDIAP	1.11 (1.02, 1.22)	1.06 (0.97, 1.16)	2.26	1.61

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

10.3.15. Myocarditis

Myocarditis events were identified in all data sources, except Pedianet.

During the 7-day risk window after the start of follow-up, the incidence rates ranged from 0.48 per 10,000 person-years (95% CI: 0.10, 1.40) in NHR to 1.72 per 10,000 person-years (95% CI: 0.21, 6.20) in PHARMO in the vaccinated cohorts. In the unvaccinated cohorts these ranged from 0.18 per 10,000 person-years (95% CI: 0.03, 1.30) in SIDIAP to 0.90 per 10,000 person-years (95% CI: 0.30, 2.60) in PHARMO. No events were reported in the vaccinated cohort in SIDIAP or in the unvaccinated cohort in EpiChron and PHARMO 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 1 (95% CI: 0.20, 4.95) in NHR. The adjusted HRs were 1 (95% CI: 0.20, 4.96) in NHR.

During the 14-day risk window after the start of follow-up, the incidence rates ranged from 0.61 per 10,000 person-years (95% CI: 0.22, 1.33) in SIDIAP to 1.07 per 10,000 person-years (95% CI: 0.13, 3.87) in EpiChron in the vaccinated cohorts. In the unvaccinated cohorts these ranged from 0.10 per 10,000 person-years (95% CI: 0.01, 0.72) in SIDIAP to 0.72 per 10,000 person-years (95% CI: 0.36, 1.44) in NHR. 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 1 (95% CI: 0.38, 2.66) in NHR, 2.00 (95% CI: 0.18, 22.05) in EpiChron, and 6.00 (0.72, 49.84) in SIDIAP. The adjusted HRs were 1 (95% CI: 0.38, 2.67) in NHR, 1.88 (95% CI: 0.17, 20.74) in EpiChron, and 6.92 (95% CI: 0.83, 57.71) SIDIAP.

During the 21-day risk window after the start of follow-up, the incidence rates ranged from 0.59 per 10,000 person-years (95% CI: 0.25, 1.15) in SIDIAP to 1.18 per 10,000 person-years (95% CI: 0.24, 3.46) in EpiChron in the vaccinated cohorts. In the unvaccinated cohorts these ranged from 0.22 per 10,000 person-years in (95% CI: 0.07, 0.68) in SIDIAP to 0.73 per 10,000 person-years (95% CI: 0.35, 1.52) in NHR. 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 0.91 (95% CI: 0.35, 2.38) in NHR, 3.00 (95% CI: 0.31, 28.82) in EpiChron, and 2.67 (95% CI: 0.71, 10.05) in SIDIAP. The adjusted HRs were 0.91 (95% CI: 0.35, 2.38) in NHR, 2.82 (95% CI: 0.29, 27.16) in EpiChron, and 2.67 (95% CI: 0.71, 10.05) in SIDIAP.

Table 41. 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

	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)	0	0 (0, 0)	196.19	0 (0, 188.03)	0	0 (0, 0)	196.20	NA
NHR (Norway)	<5	0.01 (0, 0.02)	62,529.36	0.48 (0.10, 1.40)	<5	0.01 (0, 0.02)	62,519	0.48 (0.15, 1.49)
PHARMO (Netherlands)	<5	0.03 (0, 0.08)	11,660.47	1.72 (0.21, 6.20)	0	0 (0, 0)	11,718.92	NA
EpiChron (Spain)	<5	0.02 (0, 0.05)	10,689.36	0.94 (0.02, 5.21)	0	0 (0, 0)	10,687.47	NA
SIDIAP (Spain)	0	0 (0, 0)	54,687.49	0 (0, 0.67)	<5	0 (0, 0.01)	54,687.49	0.18 (0.03, 1.30)

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 42. 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

	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)	0	0 (0, 0)	379.38	0 (0, 97.23)	0	0 (0, 0)	379.40	
NHR (Norway)	8	0.03 (0.01, 0.05)	110,772.05	0.72 (0.31, 1.42)	8	0.03 (0.01, 0.05)	110,732.56	0.72 (0.36, 1.44)
PHARMO (Netherlands)	<5	0.03 (0, 0.08)	21,857.68	0.92 (0.11, 3.31)	0	0 (0, 0)	21,946.57	
EpiChron (Spain)	<5	0.04 (0, 0.10)	18,648.32	1.07 (0.13, 3.87)	<5	0.02 (0, 0.07)	18,641.31	0.54 (0.08, 3.81)
SIDIAP (Spain)	6	0.03 (0.01, 0.05)	98,384.13	0.61 (0.22, 1.33)	<5	0 (0, 0.01)	98,384.15	0.10 (0.01, 0.72)

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

	Vaccinated				Unvaccinated			
Data source	**Events (n)**	**Cumulative incidence (95% CI)**	**Person-years (PY)**	**Incidence rate (95% CI)**	**Events (n)**	**Cumulative incidence (95% CI)**	**Person-years (PY)**	**Incidence rate (95% CI)**
Pedianet (Italy)	0	0 (0, 0)	552.37	0 (0, 66.78)	0	0 (0, 0)	552.42	NA
NHR (Norway)	10	0.04 (0.01, 0.06)	150,558.38	0.66 (0.32, 1.22)	11	0.04 (0.01, 0.08)	150,475.29	0.73 (0.35, 1.52)
PHARMO (Netherlands)	<5	0.06 (0, 0.12)	31,292.31	0.96 (0.20, 2.80)	0	0 (0, 0)	31,386.76	NA
EpiChron (Spain)	<5	0.07 (0, 0.15)	25,375.11	1.18 (0.24, 3.46)	<5	0.02 (0, 0.07)	25,360.33	0.39 (0.06, 2.80)
SIDIAP (Spain)	8	0.04 (0.01, 0.06)	136,511.81	0.59 (0.25, 1.15)	<5	0.01 (0, 0.03)	136,511.91	0.22 (0.07, 0.68)

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 32. 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

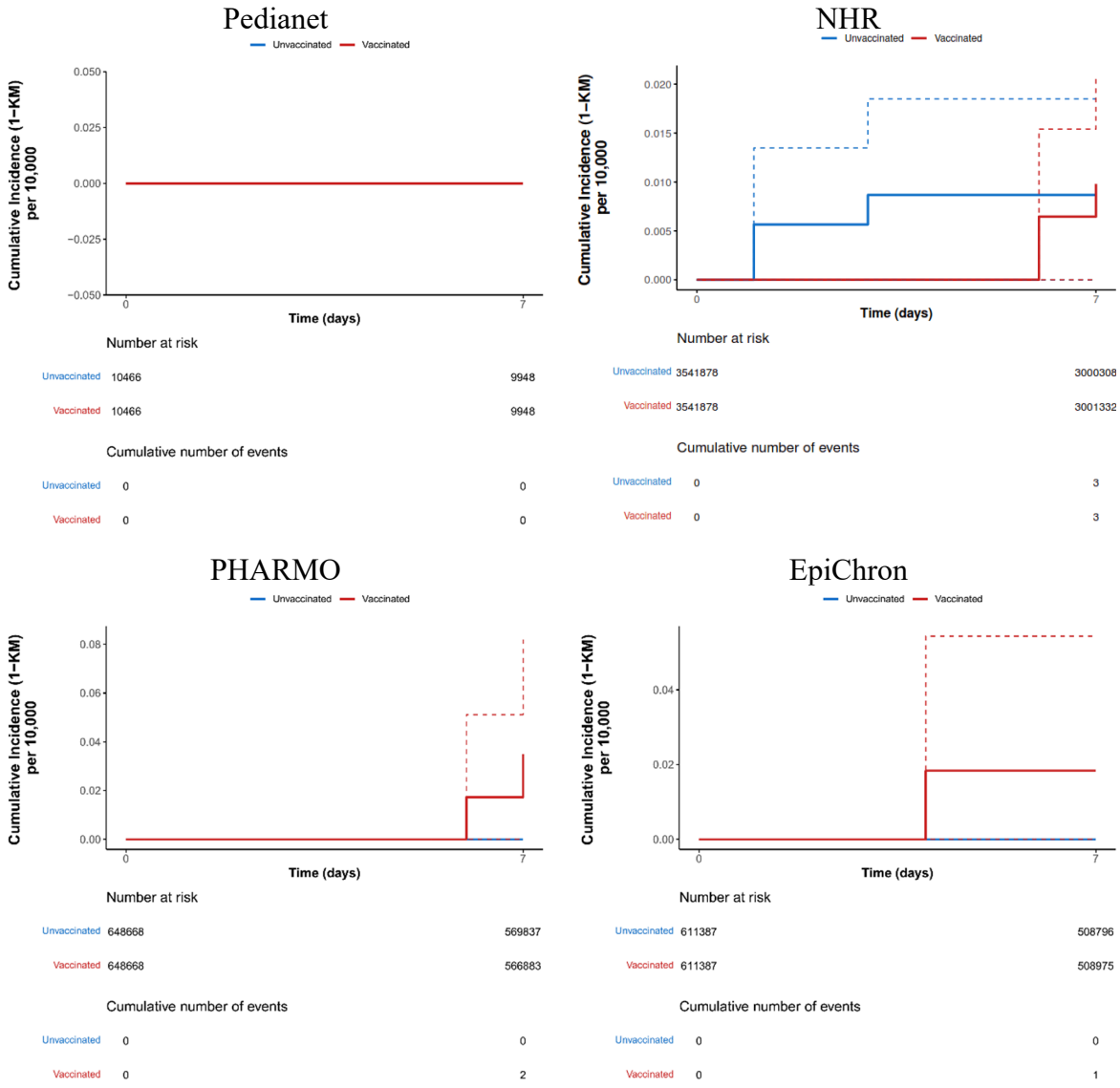
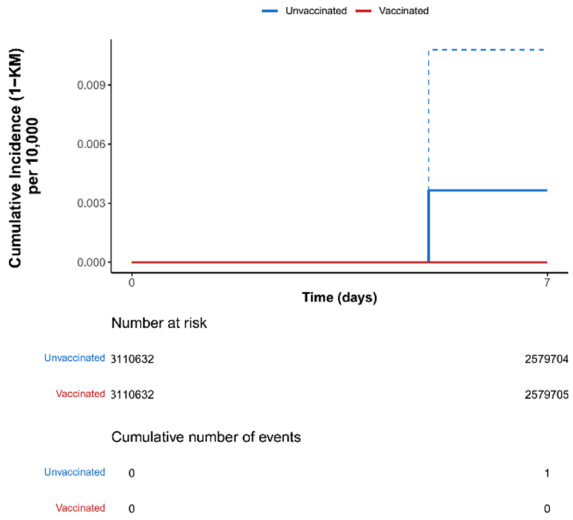


Figure 32. Cumulative incidence of myocarditis within 7 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source

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 33. 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

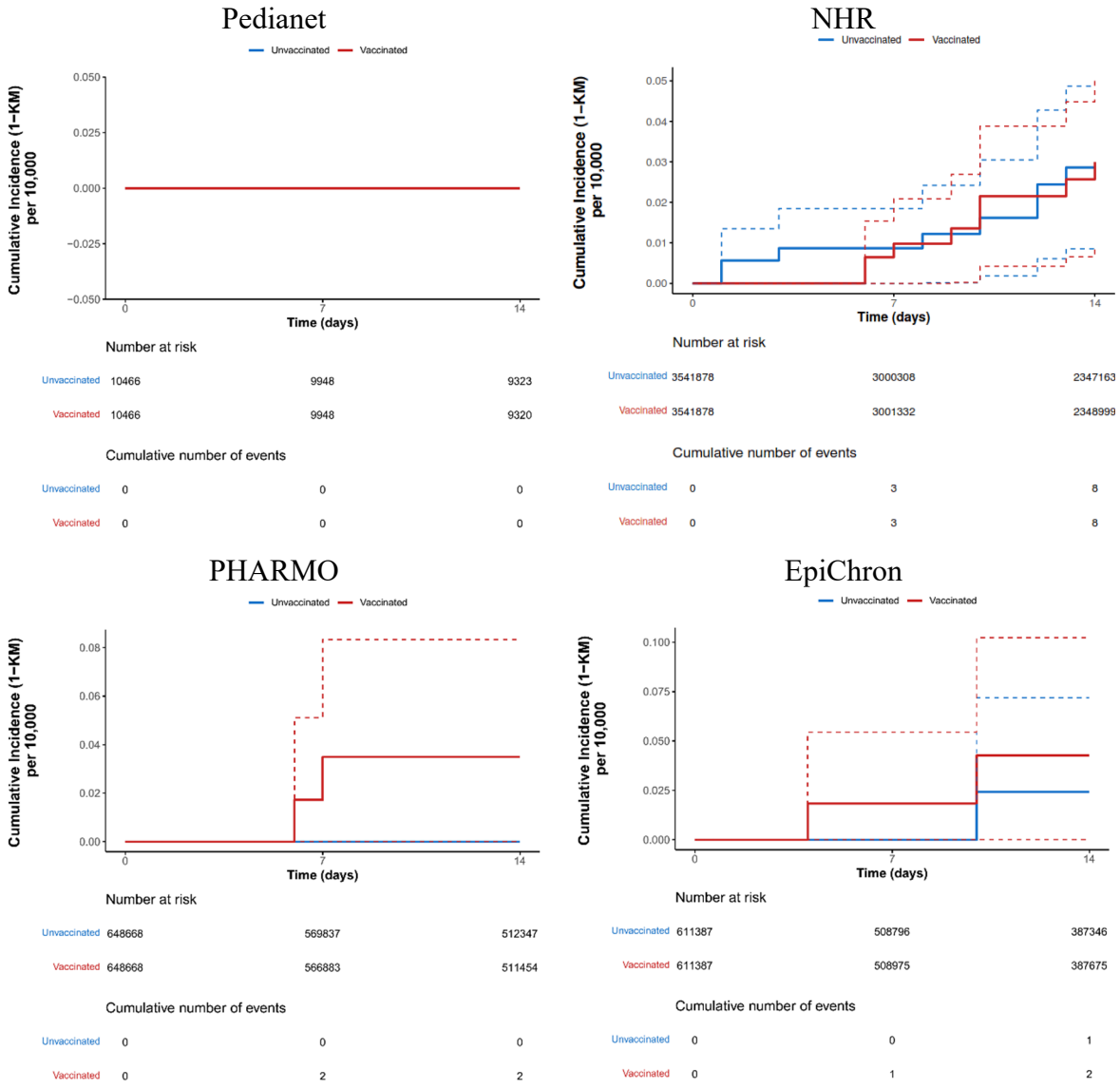
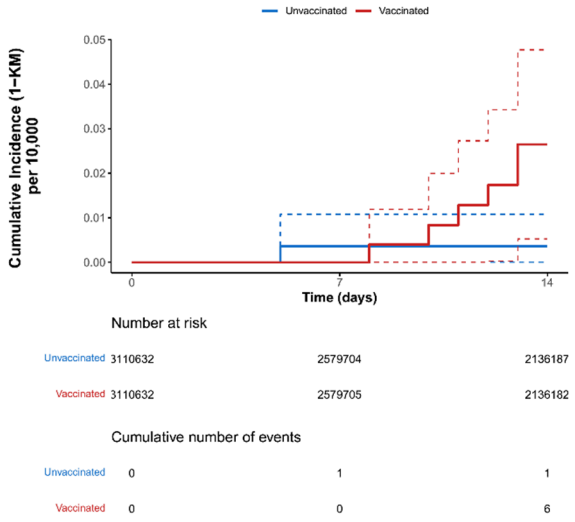


Figure 33. Cumulative incidence of myocarditis within 14 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source

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

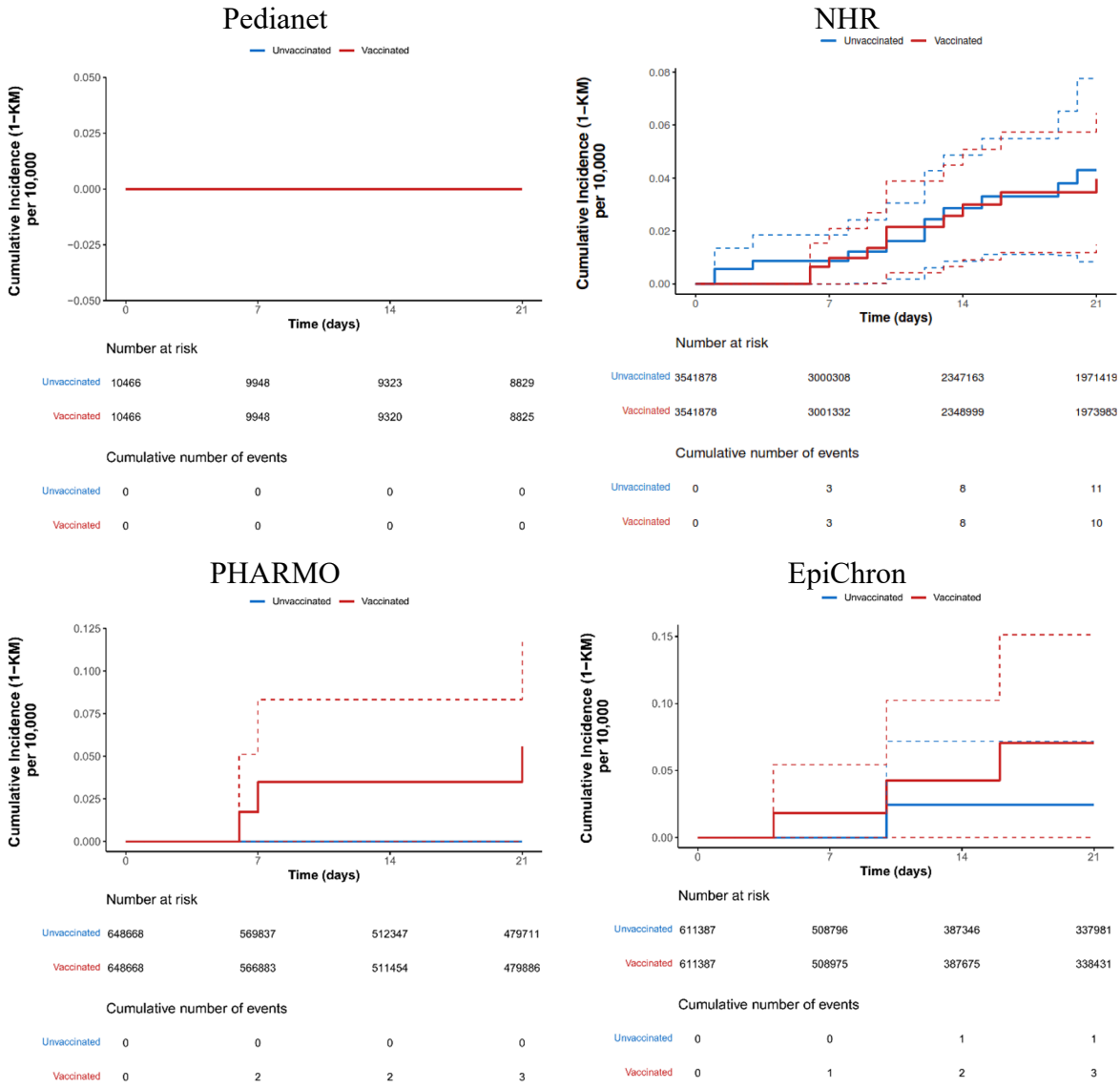
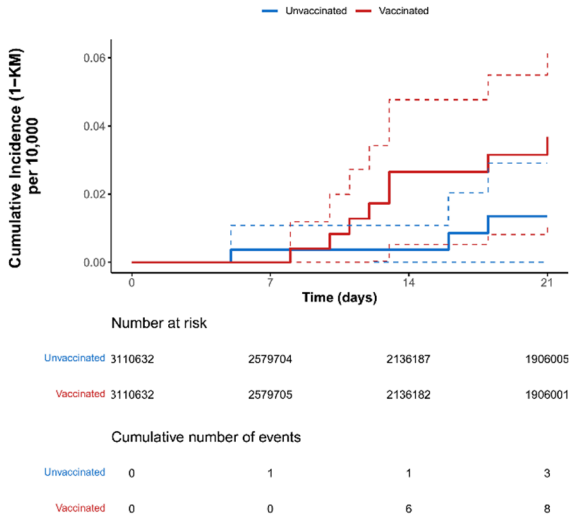


Figure 34. Cumulative incidence of myocarditis within 21 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source

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 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 35. 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

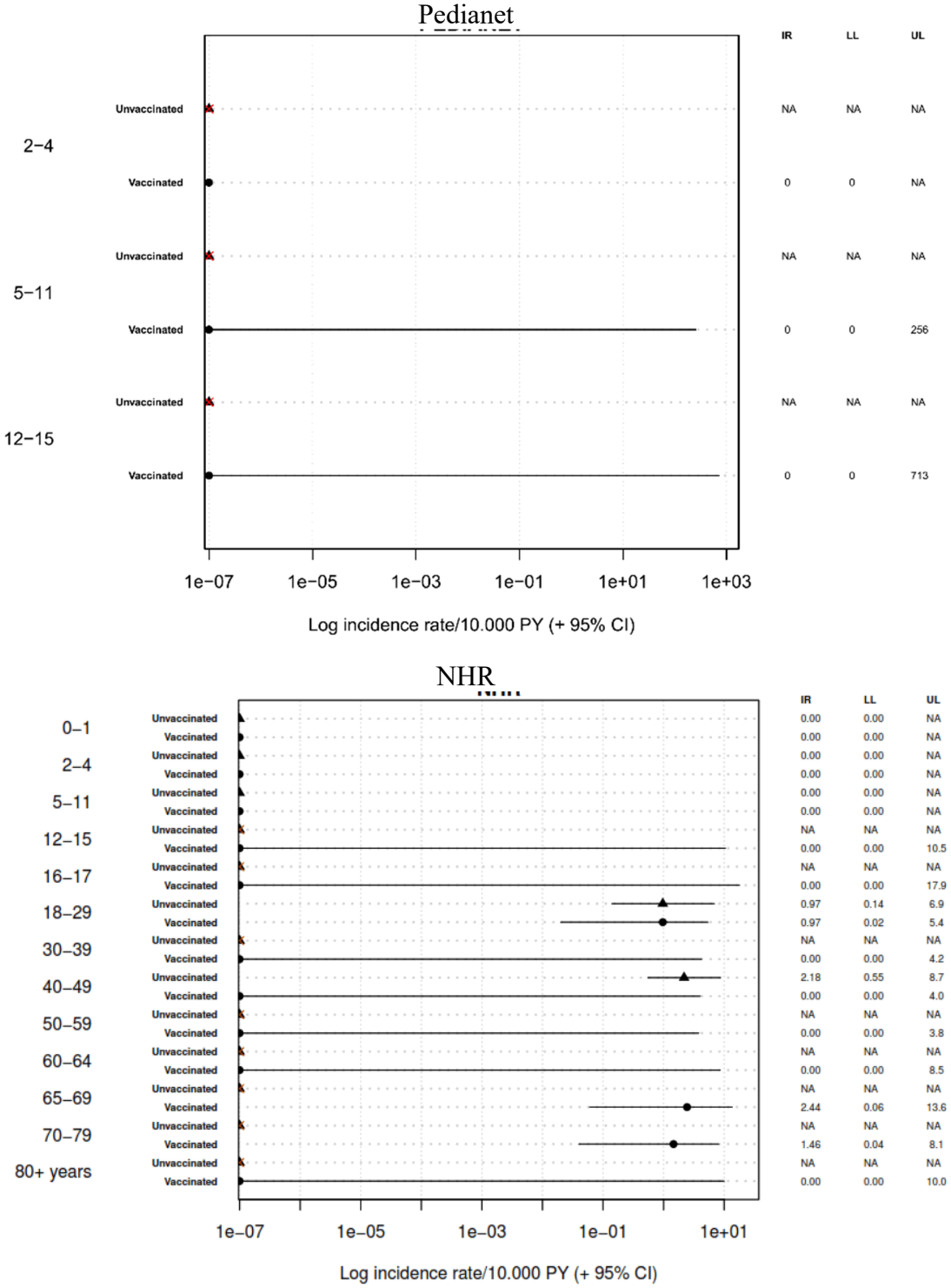


Figure 35. Forest plot showing incidence rates and 95% confidence intervals for myocarditis within 7 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source and by age groups

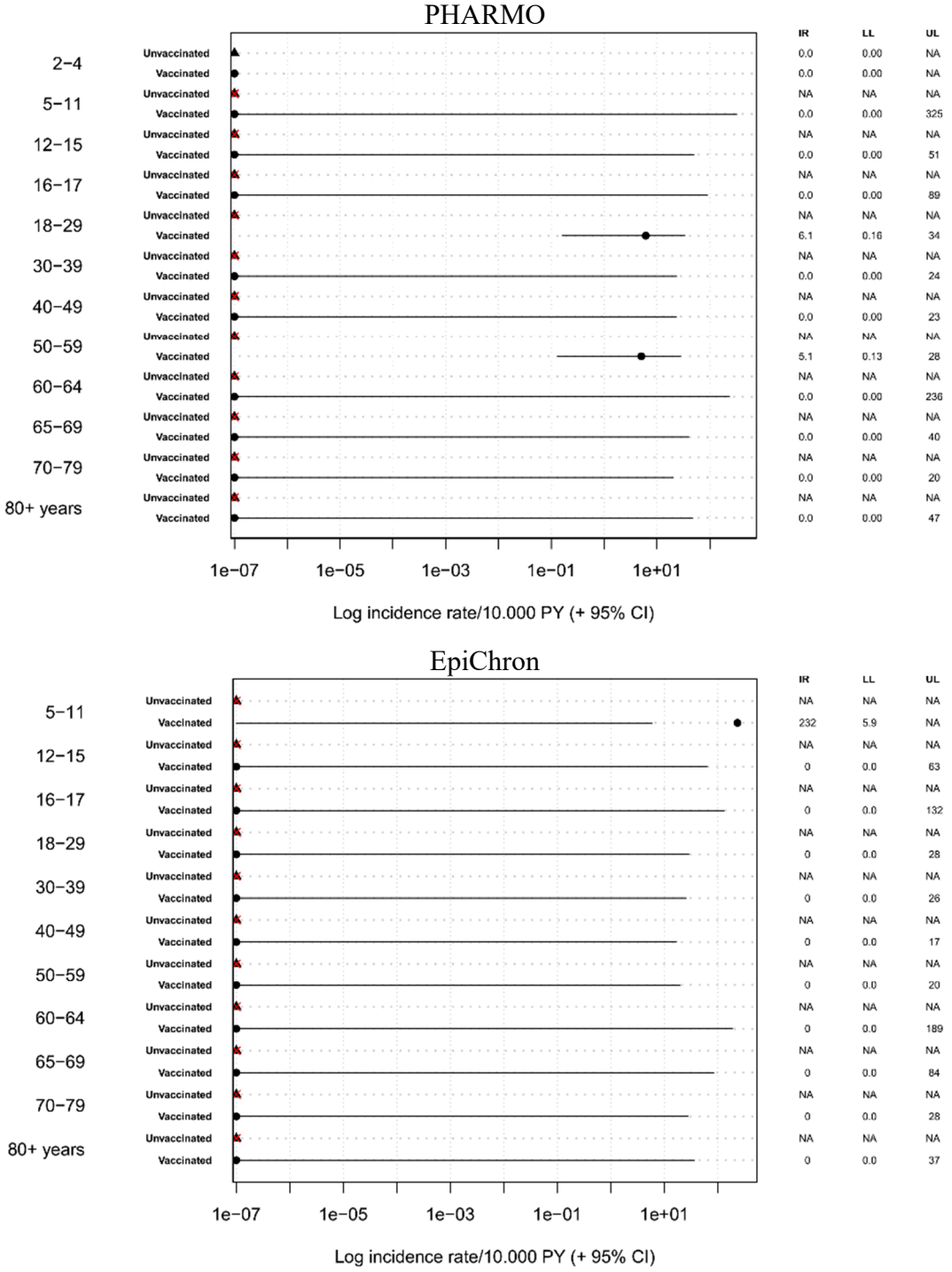


Figure 35. Forest plot showing incidence rates and 95% confidence intervals for myocarditis within 7 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source and by age groups

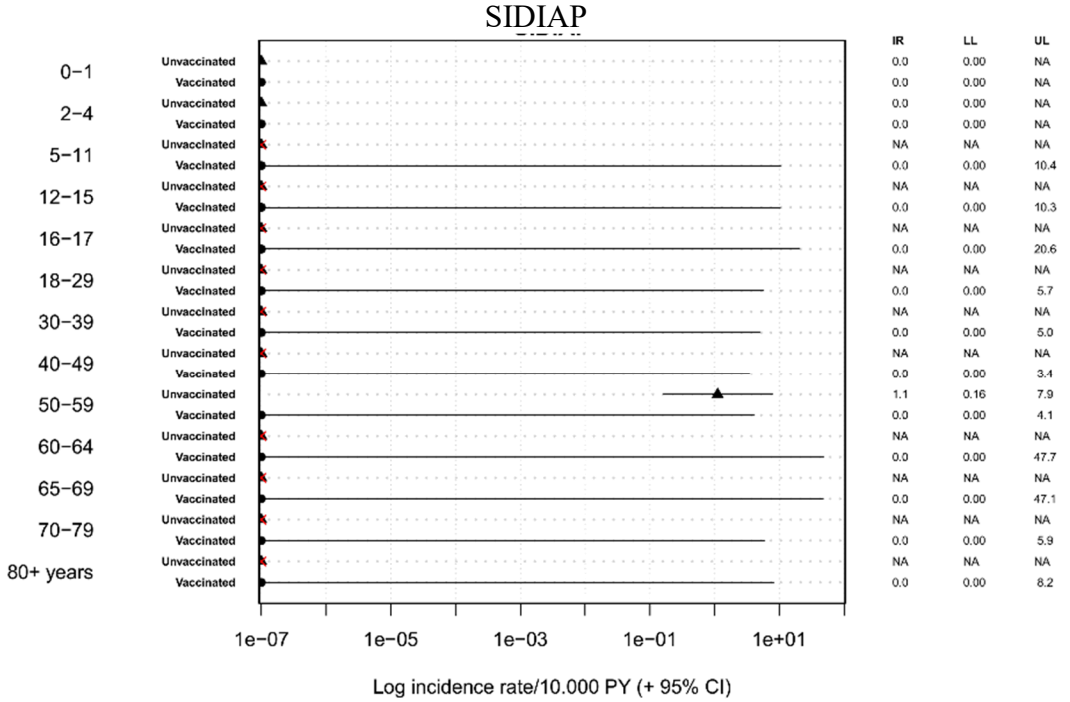


Figure 36. Forest plot showing incidence rates and 95% confidence intervals for myocarditis within 14 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source and by age groups

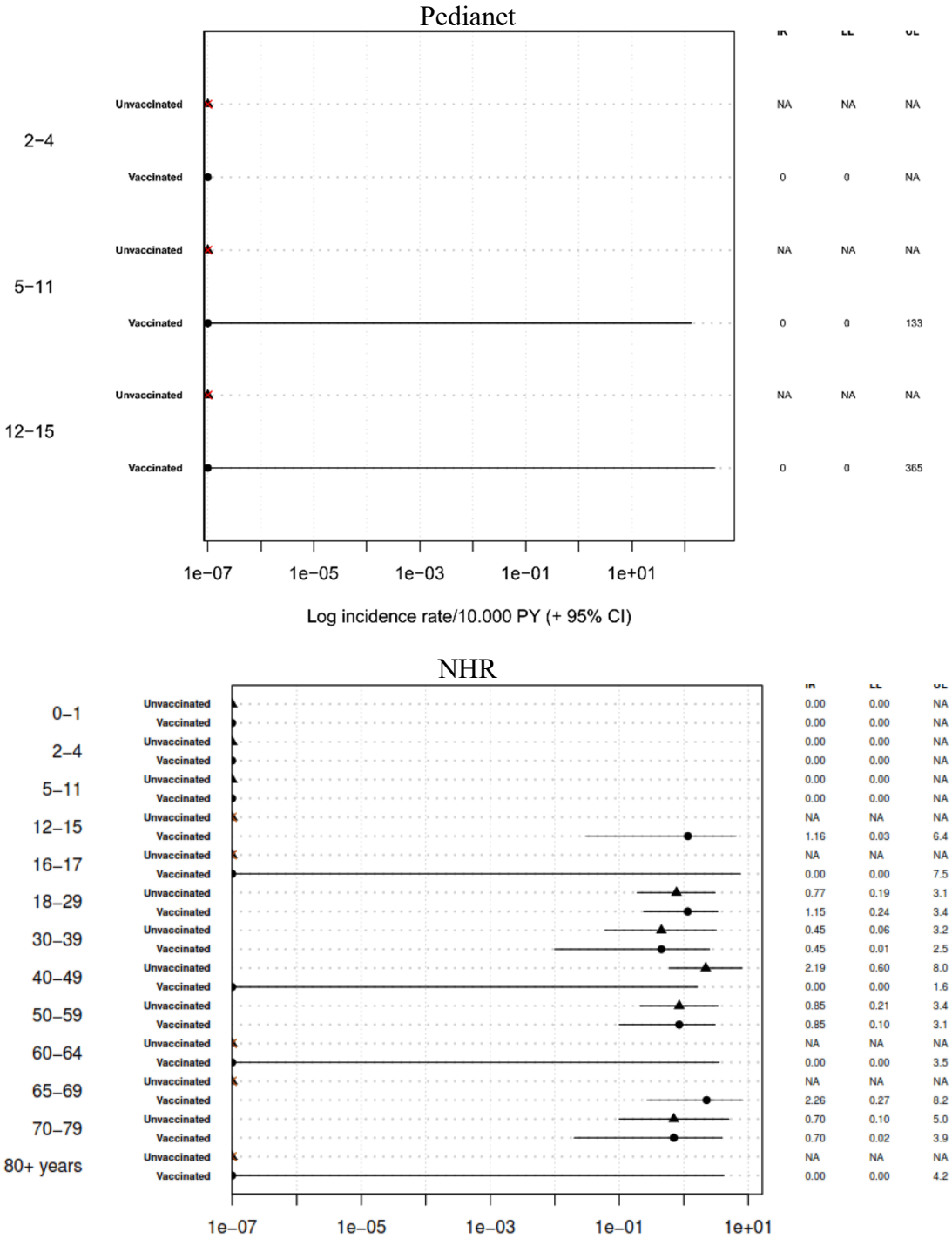


Figure 36. Forest plot showing incidence rates and 95% confidence intervals for myocarditis within 14 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source and by age groups

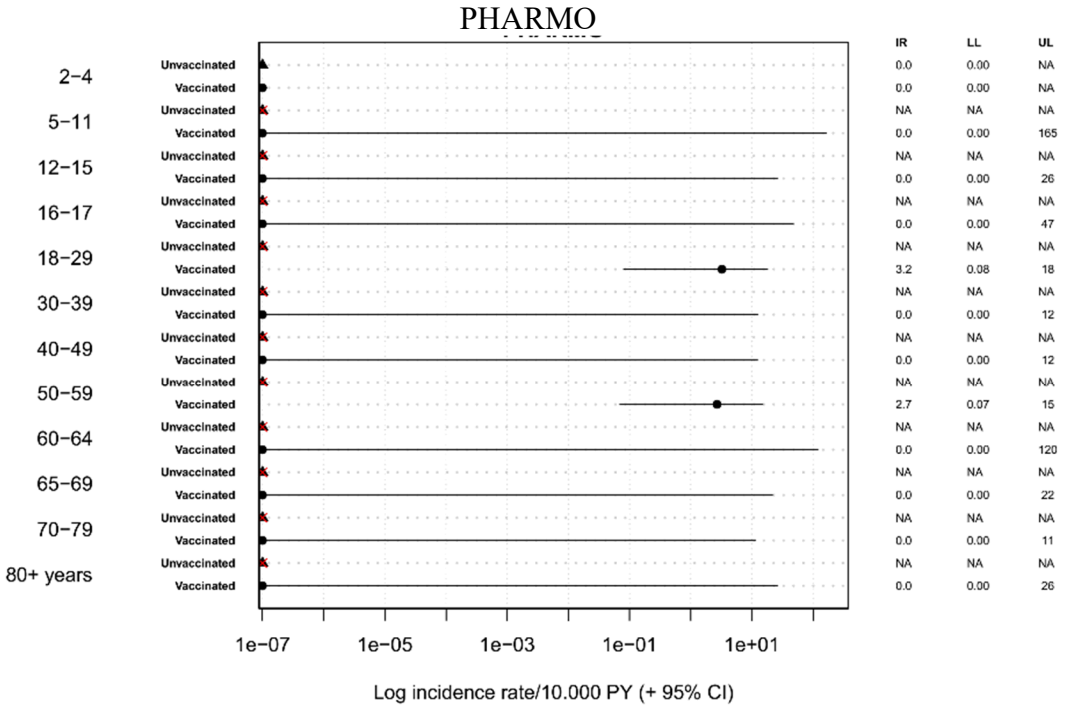


Figure 36. Forest plot showing incidence rates and 95% confidence intervals for myocarditis within 14 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source and by age groups

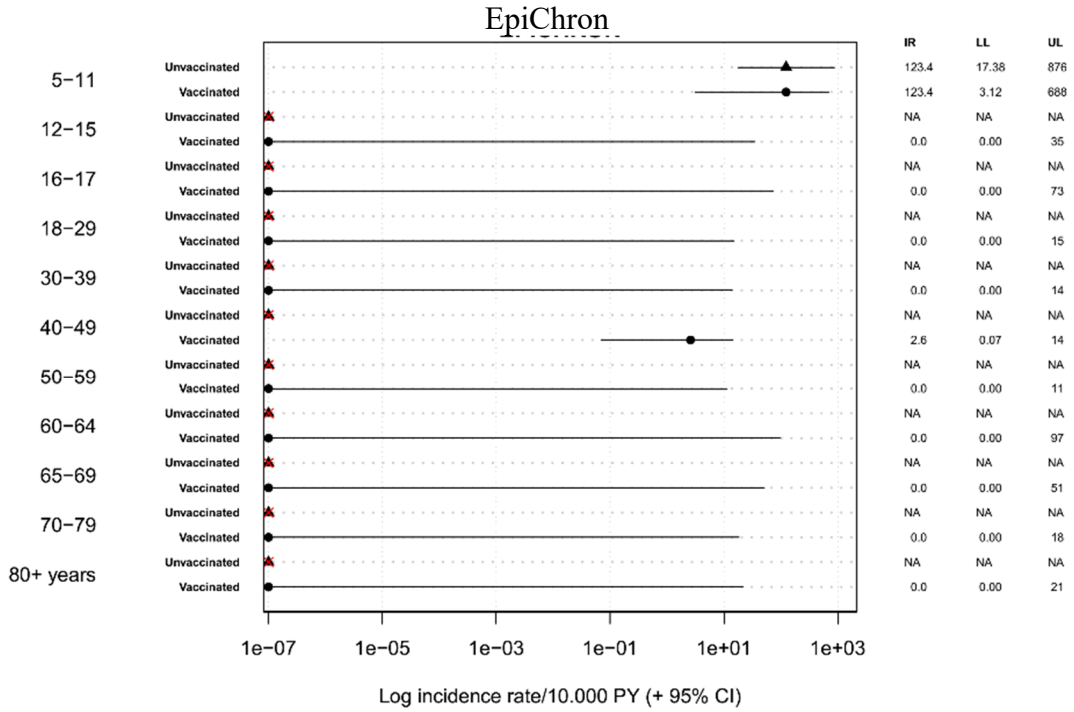


Figure 36. Forest plot showing incidence rates and 95% confidence intervals for myocarditis within 14 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source and by age groups

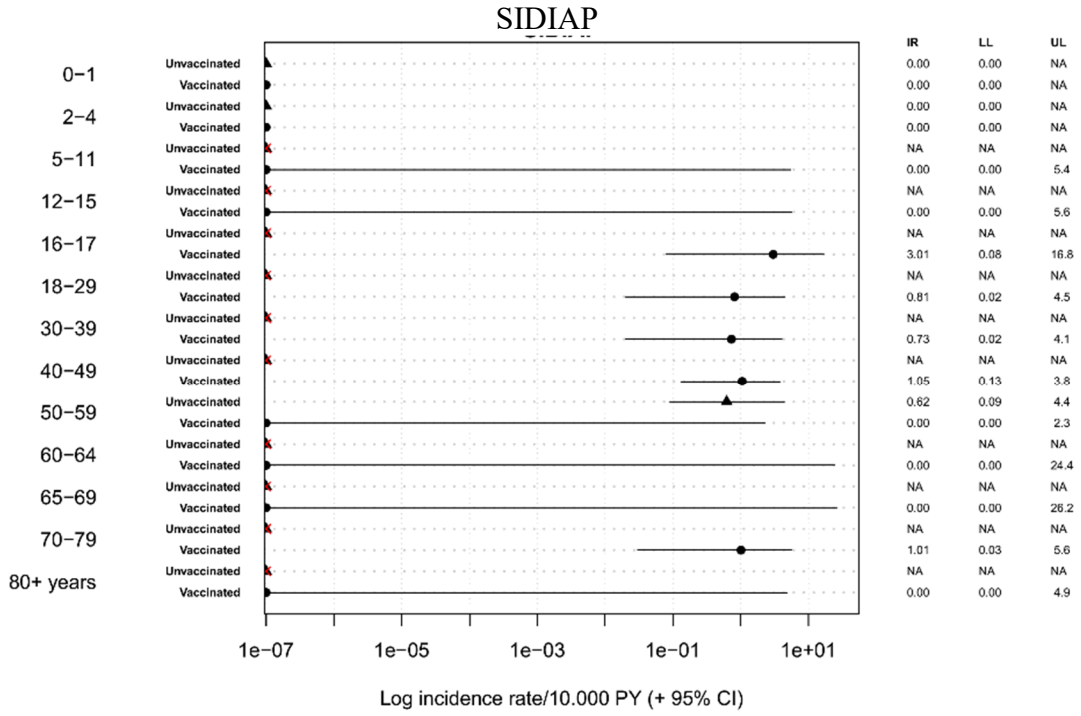


Figure 37. Forest plot showing incidence rates and 95% confidence intervals for myocarditis within 21 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source and by age groups

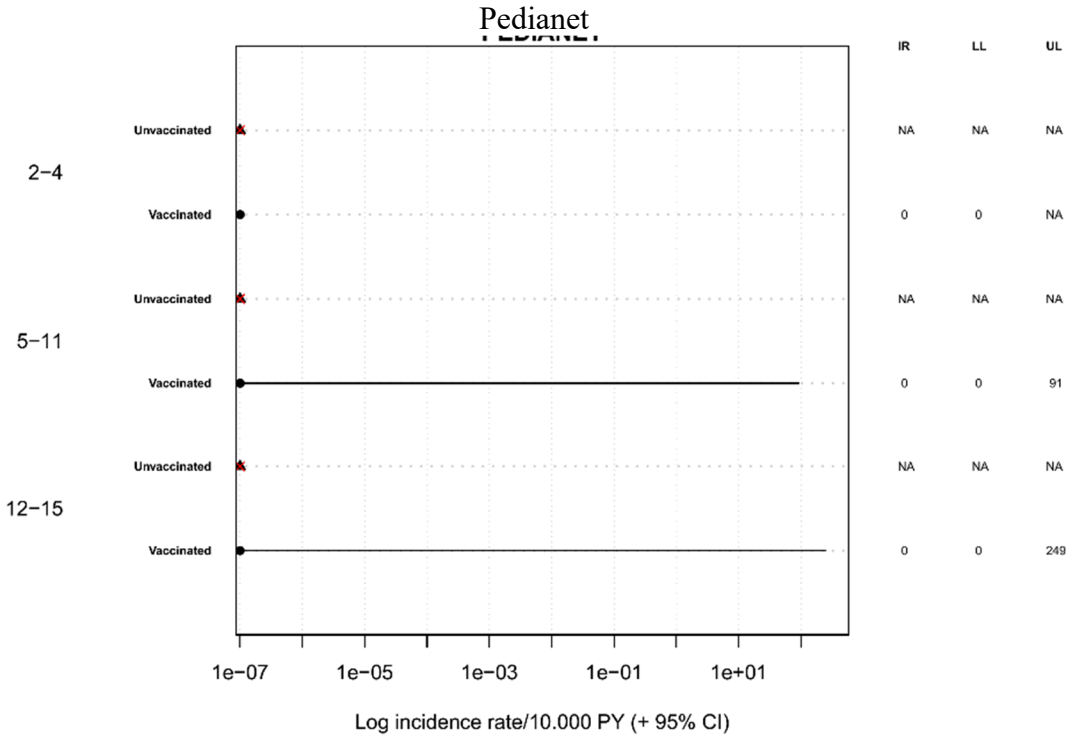


Figure 37. Forest plot showing incidence rates and 95% confidence intervals for myocarditis within 21 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source and by age groups

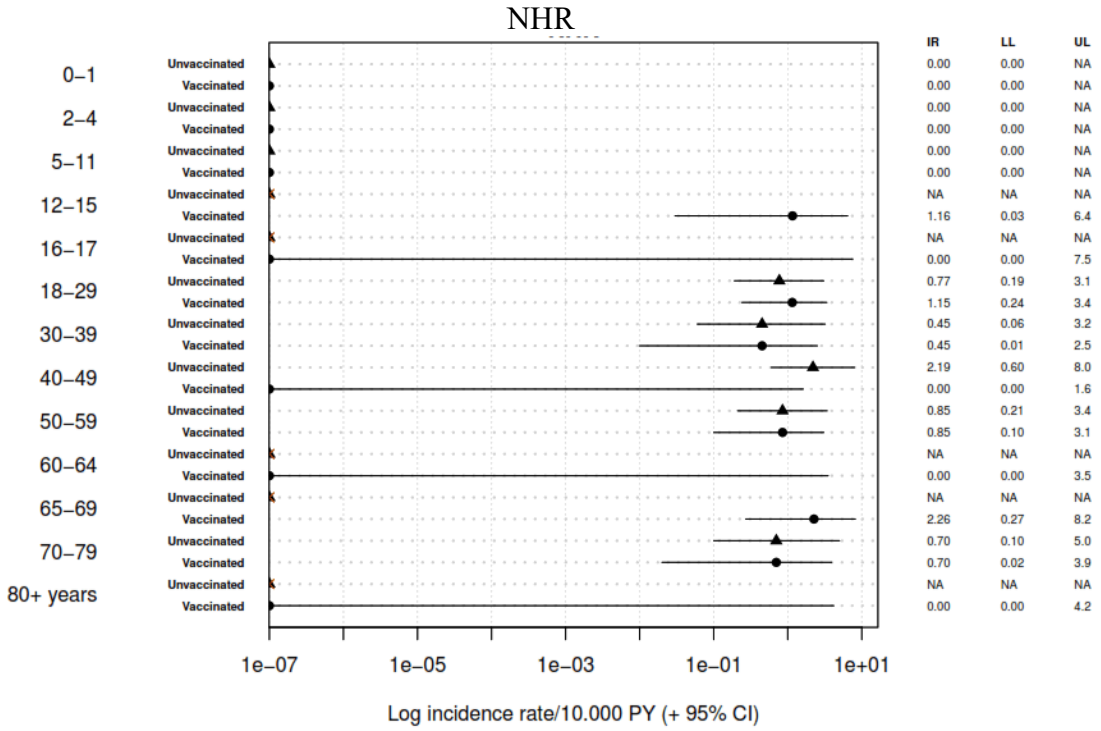


Figure 37. Forest plot showing incidence rates and 95% confidence intervals for myocarditis within 21 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source and by age groups

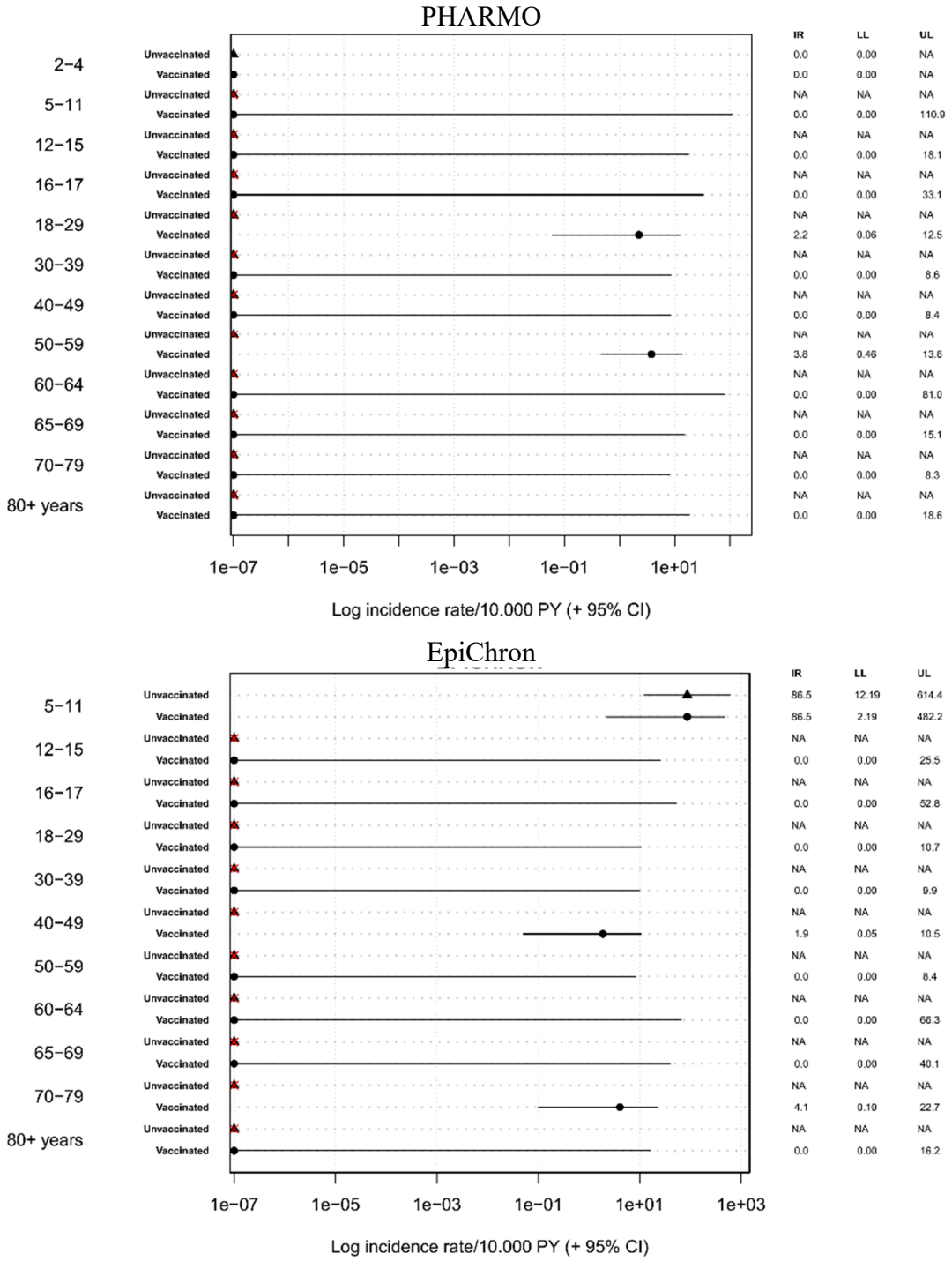


Figure 37. Forest plot showing incidence rates and 95% confidence intervals for myocarditis within 21 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source and by age groups

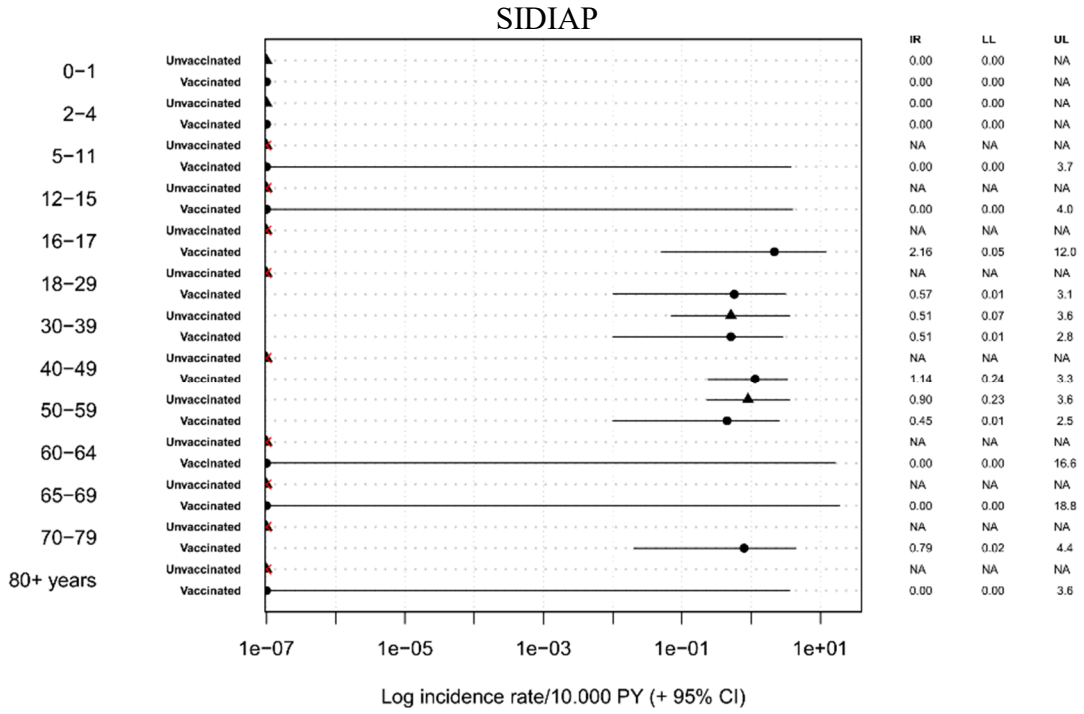


Table 44. Matched and adjusted hazard ratios (HRs) and matched and adjusted risk differences (RDs) per 10,000 person-years and their 95% CIs for myocarditis within 7 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source

	Matched HR (95% CI)	Adjusted HR (95% CI)	Matched RD	Adjusted RD
Pedianet	NA	NA	NA	NA
NHR	1 (0.20, 4.95)	1 (0.20, 4.96)	0	0
PHARMO	NA	NA	0.03	0.03
EpiChron	NA	NA	0.02	0.02
SIDIAP	NA	NA	NA	NA

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

Table 45. Matched and adjusted hazard ratios (HRs) and matched and adjusted risk differences (RDs) per 10,000 person-years and their 95% CIs for myocarditis within 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)	Adjusted HR (95% CI)	Matched RD	Adjusted RD
Pedianet	NA	NA	NA	NA
NHR	1 (0.38, 2.66)	1 (0.38, 2.67)	0	0
PHARMO	NA	NA	0.03	0.03
EpiChron	2 (0.18, 22.05)	1.88 (0.17, 20.74)	0.02	0.02
SIDIAP	6 (0.72, 49.84)	6.92 (0.83, 57.71)	0.02	0.02

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

Table 46. Matched and adjusted hazard ratios (HRs) and matched and adjusted risk differences (RDs) per 10,000 person-years and their 95% CIs for myocarditis within 21 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source

	Matched HR (95% CI)	Adjusted HR (95% CI)	Matched RD	Adjusted RD
Pedianet	NA	NA	NA	NA
NHR	0.91 (0.35, 2.38)	0.91 (0.35, 2.38)	0	0
PHARMO	NA	NA	0.06	0.05
EpiChron	3 (0.31, 28.82)	2.82 (0.29, 27.15)	0.05	0.04
SIDIAP	2.67 (0.71, 10.05)	2.71 (0.71, 10.30)	0.02	0.02

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

10.3.16. Pericarditis

Pericarditis events were identified in all data sources except in PHARMO in the 7-day risk window. In Pedianet no cases were reported in the unvaccinated cohort. The incidence rates ranged from 2.08 per 10,000 person-years (95% CI: 1.11, 3.56) in NHR to 50.94 per 10,000 person-years (95% CI: 1.29, 283.80) in Pedianet in the vaccinated cohorts. In the unvaccinated cohorts these ranged from 4.16 per 10,000 person-years (95% CI: 2.61, 6.62) in NHR to 5.62 per 10,000 person-years (95% CI: 2.00, 15.78) in EpiChron. 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 0.50 (95% CI: 0.24, 1.02) in NHR, 0.83 (95% CI: 0.21, 3.23) in EpiChron, and 1.06 (95% CI: 0.54, 2.10) in SIDIAP for the 7-day risk window. The adjusted HRs were 0.50 (95% CI: 0.24, 1.02) in NHR, 0.93 (95% CI: 0.24, 3.59) in EpiChron, and 0.94 (95% CI: 0.47, 1.87) in SIDIAP.

In the 14-day risk window, pericarditis cases were reported in all data source in the vaccinated cohorts. In the unvaccinated cohorts, no events were reported in Pedianet. The incidence rates ranged from 0.46 per 10,000 person-years (95% CI: 0.01, 2.55) in PHARMO to 4.29 per 10,000 person-years (95% CI: 1.85, 8.46) in EpiChron in the vaccinated cohorts. In the unvaccinated cohorts these ranged from 0.46 per 10,000 person-years (95% CI: 0.06, 3.23) in PHARMO to 4.29 per 10,000 person-years (95% CI: 1.72, 10.74) in EpiChron. In Pedianet the incidence rate in the vaccinated cohort was 26.34 (95% CI: 0.67, 146.77), but this corresponded to <5 events. 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 0.70 (95% CI: 0.40, 1.22) in NHR,.00 (95% CI: 0.06, 16.08) in PHARMO, 1.00 (95% CI: 0.32, 3.15) in EpiChron, and 1.30 (95% CI: 0.75, 2.23) in SIDIAP. The adjusted HRs were 0.70 (95% CI: 0.40, 1.22) in NHR, 1.06 (95% CI: 0.07, 16.96) in PHARMO, 1.04 (95% CI: 0.33, 3.28) in EpiChron, and 1.17 (95% CI: 0.68, 2.04) in SIDIAP.

In the 21-day risk window, pericarditis cases were reported in all data source in the vaccinated cohorts. In the unvaccinated cohorts, no events were reported in Pedianet. The incidence rates ranged from 0.32 per 10,000 person-years (95% CI: 0.01, 1.78) in PHARMO to 2.72 per 10,000 person-years (95% CI: 1.95, 3.70) in NHR in the vaccinated cohorts. In the unvaccinated cohorts these ranged from 0.32 per 10,000 person-years (95% CI: 0.04, 2.26) in PHARMO to 3.16 per 10,000 person-years in EpiChron (95% CI: 1.26, 7.89). In the vaccinated cohort in Pedianet, the incidence rate was 18.09 per 10,000 person-years (95% CI: 0.46, 100.81) (corresponding to <5 events). 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 0.87 (95% CI: 0.51, 1.48) in NHR, 1.00 (95% CI: 0.06, 16.08) in PHARMO, 1.00 (95% CI: 0.32, 3.15) in EpiChron, and 1.25 (95% CI: 0.78, 2.01) in SIDIAP. The adjusted HRs were 0.87 (95% CI: 0.51, 1.48) in NHR, 1.06 (95% CI: 0.07, 16.96) in PHARMO, 1.04 (95% CI: 0.33, 3.28) in EpiChron, and

1.16 (95% CI: 0.71, 1.88) in SIDIAP. The IRs for pericarditis in the first 14-day and first 21-day follow-up periods were similar.

Table 47. 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

	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)	<5	0.98 (0, 2.89)	196.32	50.94 (1.29, 283.80)	0	0 (0, 0)	196.35	
NHR (Norway)	13	0.04 (0.02, 0.06)	62,505.23	2.08 (1.11, 3.56)	26	0.08 (0.04, 0.12)	62,494.78	4.16 (2.61, 6.62)
PHARMO (Netherlands)	0	0 (0, 0)	11,661.13	0 (0, 3.16)	0	0 (0, 0)	11,719.57	
EpiChron (Spain)	5	0.10 (0.01, 0.18)	10,685.80	4.68 (1.52, 10.92)	6	0.11 (0, 0.23)	10,683.89	5.62 (2.00, 15.78)
SIDIAP (Spain)	18	0.06 (0.03, 0.09)	54,662.92	3.29 (1.95, 5.20)	17	0.06 (0.03, 0.09)	54,662.88	3.11 (1.88, 5.14)

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 48. 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

	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)	<5	0.98 (0, 2.89)	379.63	26.34 (0.67, 146.77)	0	0 (0, 0)	379.67	NA
NHR (Norway)	28	0.10 (0.06, 0.14)	110,729.41	2.53 (1.68, 3.65)	40	0.13 (0.08, 0.19)	110,689.66	3.61 (2.38, 5.48)
PHARMO (Netherlands)	<5	0.02 (0, 0.05)	21,858.99	0.46 (0.01, 2.55)	<5	0.02 (0, 0.06)	21,947.84	0.46 (0.06, 3.23)
EpiChron (Spain)	8	0.17 (0.05, 0.29)	18,641.92	4.29 (1.85, 8.46)	8	0.16 (0.01, 0.31)	18,634.86	4.29 (1.72, 10.74)
SIDIAP (Spain)	35	0.14 (0.09, 0.19)	98,340.45	3.56 (2.48, 4.95)	27	0.10 (0.06, 0.15)	98,340.38	2.75 (1.79, 4.22)

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 49. 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

	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)	<5	0.98 (0, 2.89)	552.70	18.09 (0.46, 100.81)	0	0 (0, 0)	552.80	NA
NHR (Norway)	41	0.16 (0.11, 0.21)	150,500.52	2.72 (1.95, 3.70)	47	0.17 (0.09, 0.25)	150,417.02	3.12 (2.03, 4.81)
PHARMO (Netherlands)	<5	0.02 (0, 0.05)	31,294.12	0.32 (0.01, 1.78)	<5	0.02 (0, 0.06)	31,388.51	0.32 (0.04, 2.26)
EpiChron (Spain)	8	0.17 (0.05, 0.29)	25,366.35	3.15 (1.36, 6.21)	8	0.16 (0.01, 0.31)	25,351.53	3.16 (1.26, 7.89)
SIDIAP (Spain)	45	0.19 (0.13, 0.25)	136,451.15	3.30 (2.41, 4.41)	36	0.15 (0.09, 0.20)	136,451.19	2.64 (1.81, 3.85)

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 38. 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

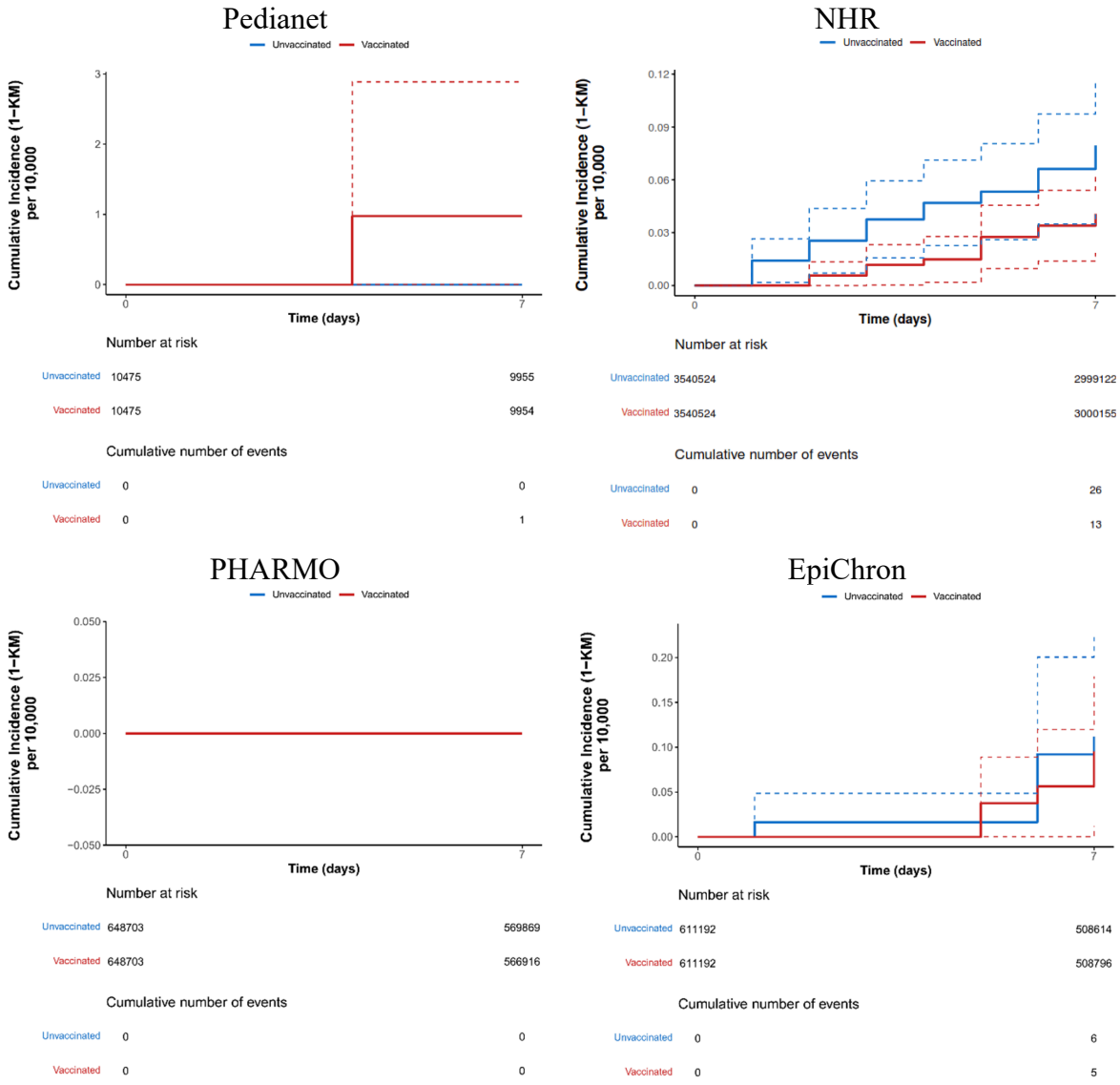
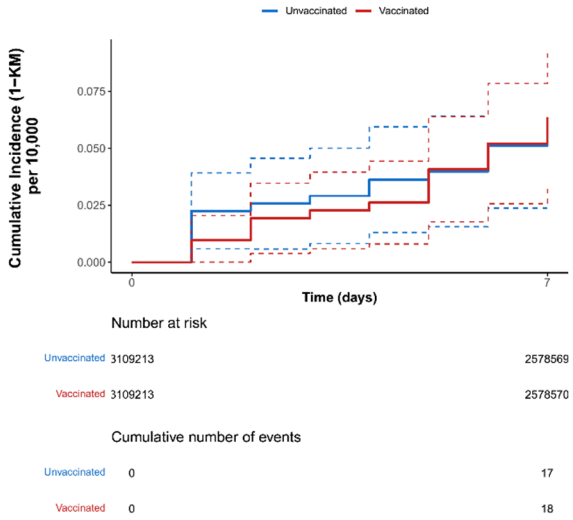


Figure 38. Cumulative incidence of pericarditis within 7 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source

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 39. 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

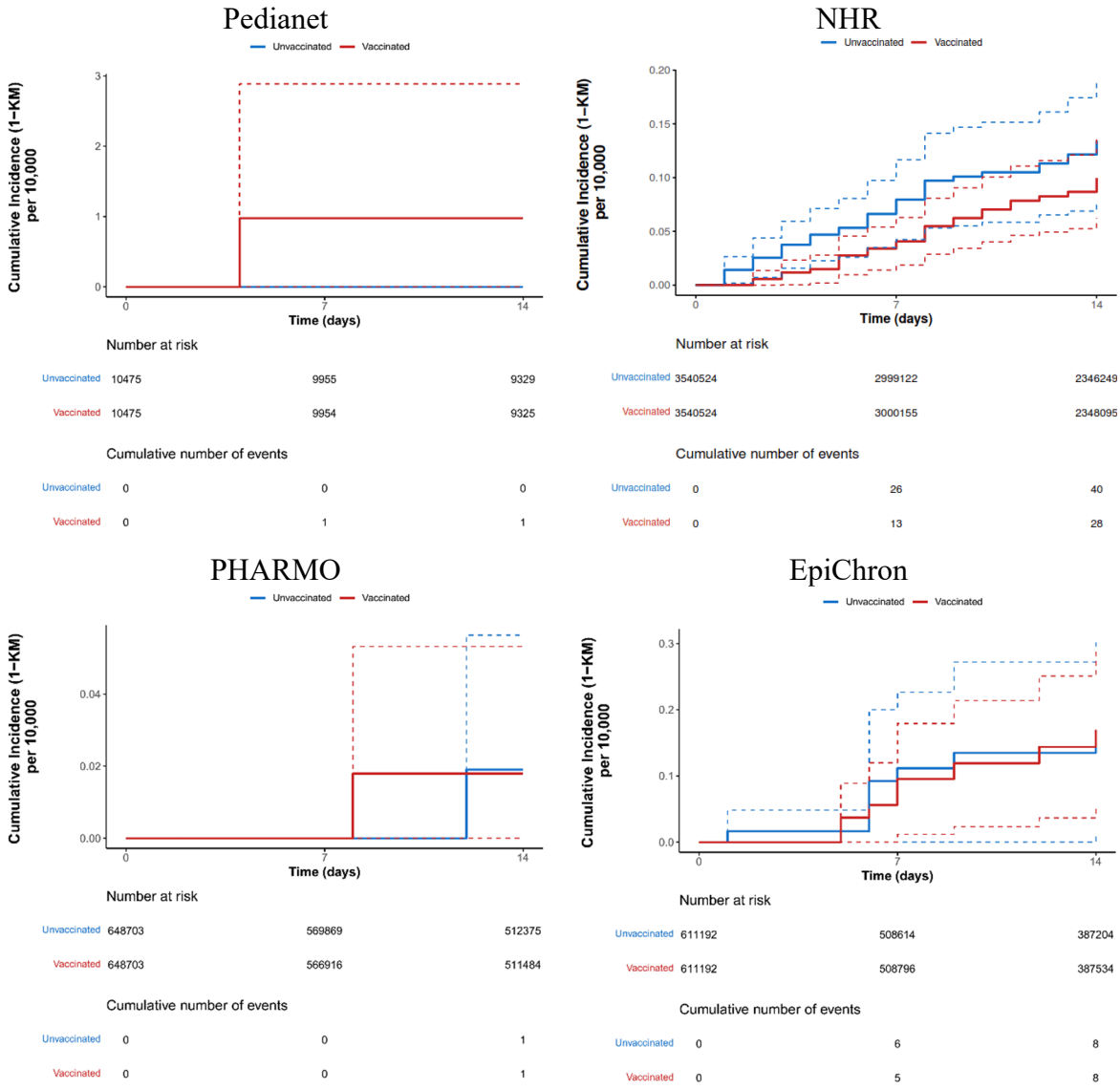
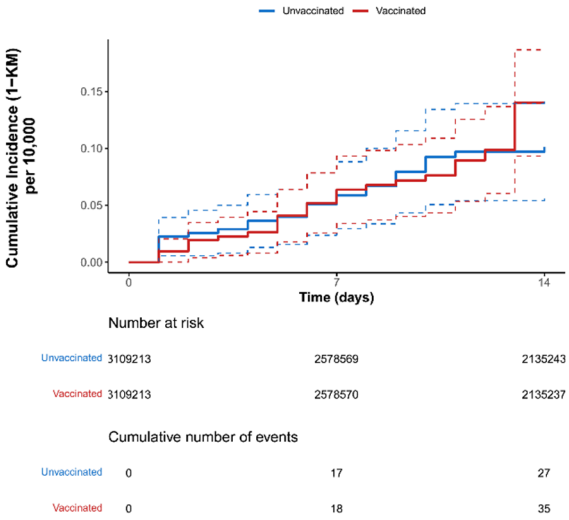


Figure 39. Cumulative incidence of pericarditis within 14 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source

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 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 40. 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

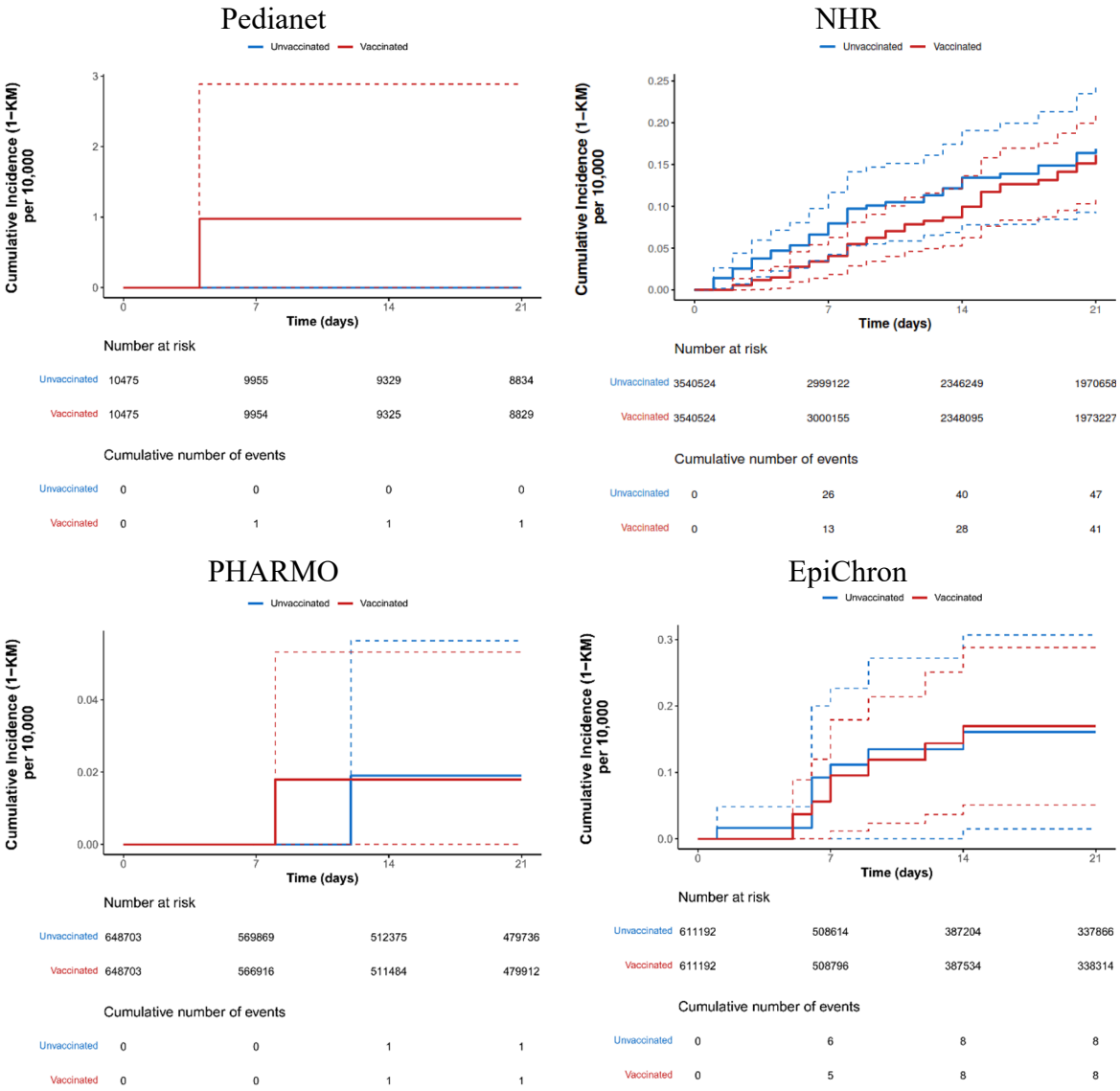
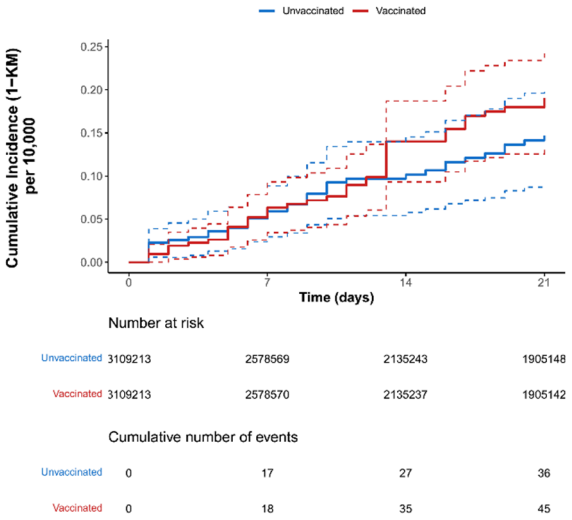


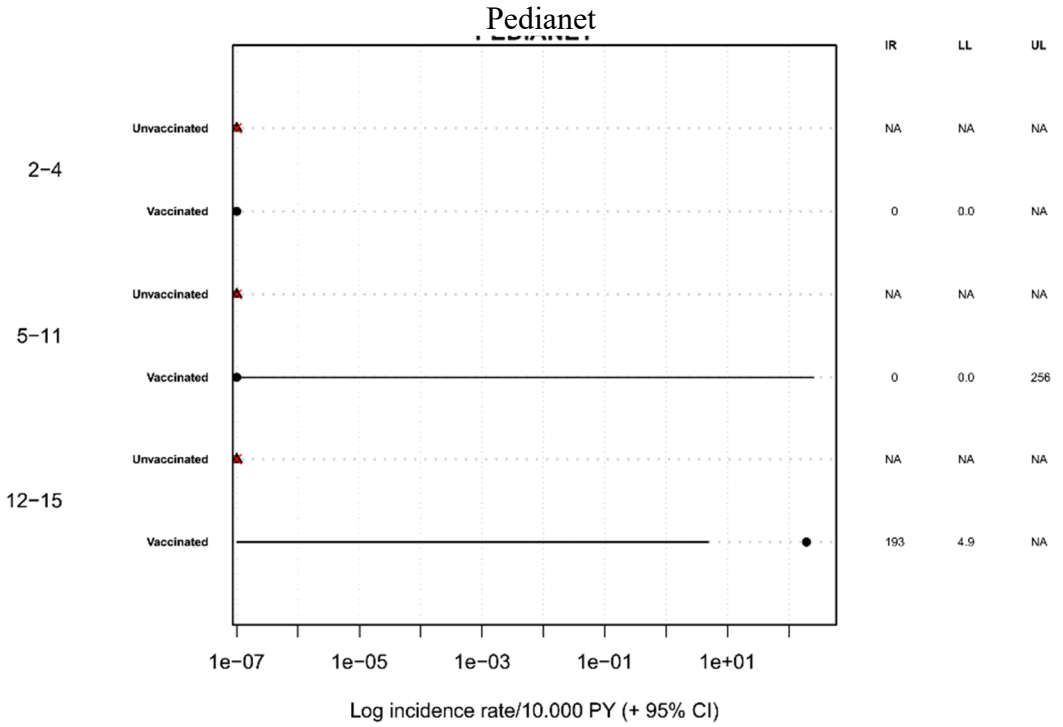
Figure 40. Cumulative incidence of pericarditis within 21 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source

SIDIAP

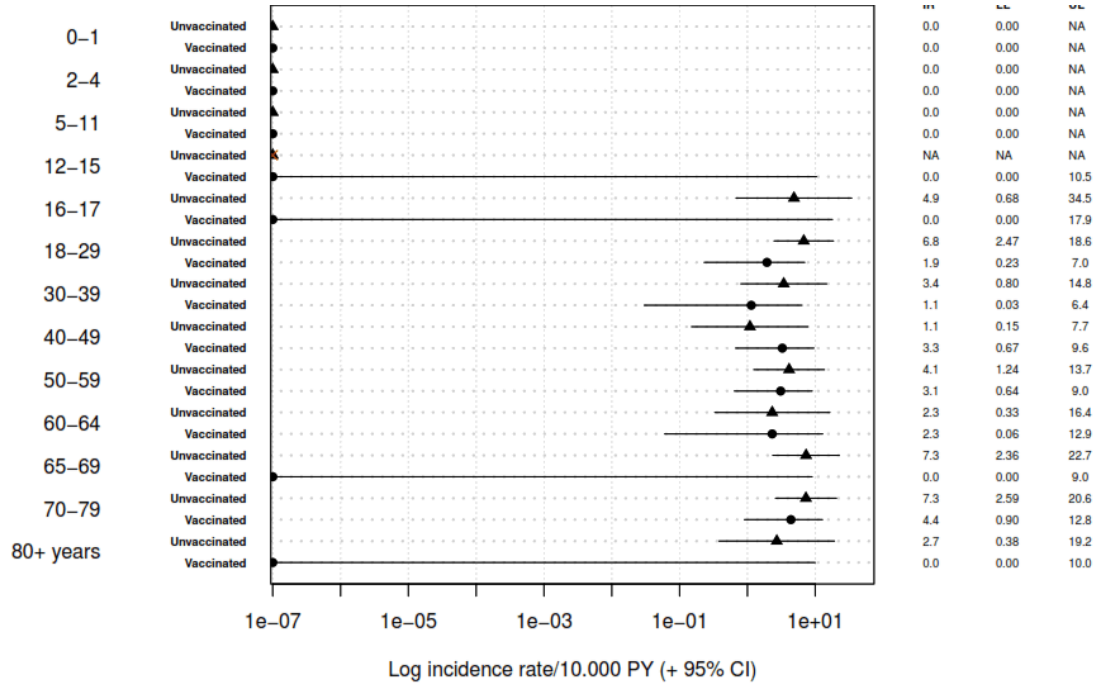


Cumulative incidence curves (1 – Kaplan–Meier risk) starting from the day of administration of the first dose of vaccine. Dotted lines represent 95% confidence intervals. The number at risk at each time point and the cumulative number of events during the 21-day risk window are also shown for each time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

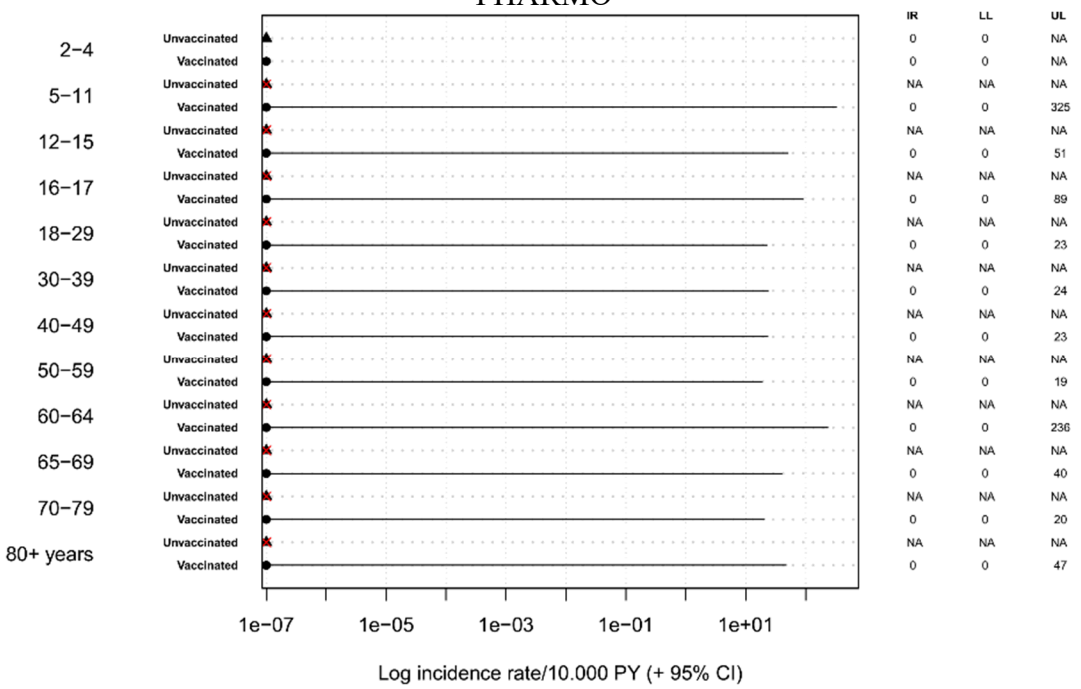
Figure 41. Forest plot showing incidence rates and 95% confidence intervals for pericarditis within 7 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source and by age groups



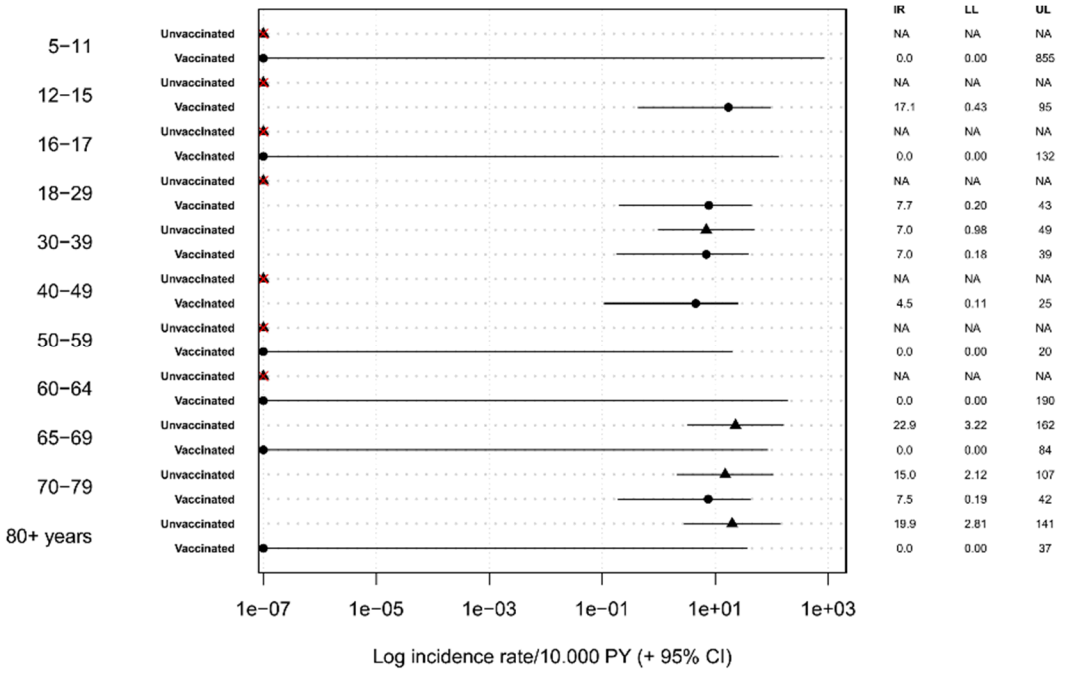
NHR



PHARMO



EpiChron



SIDIAP

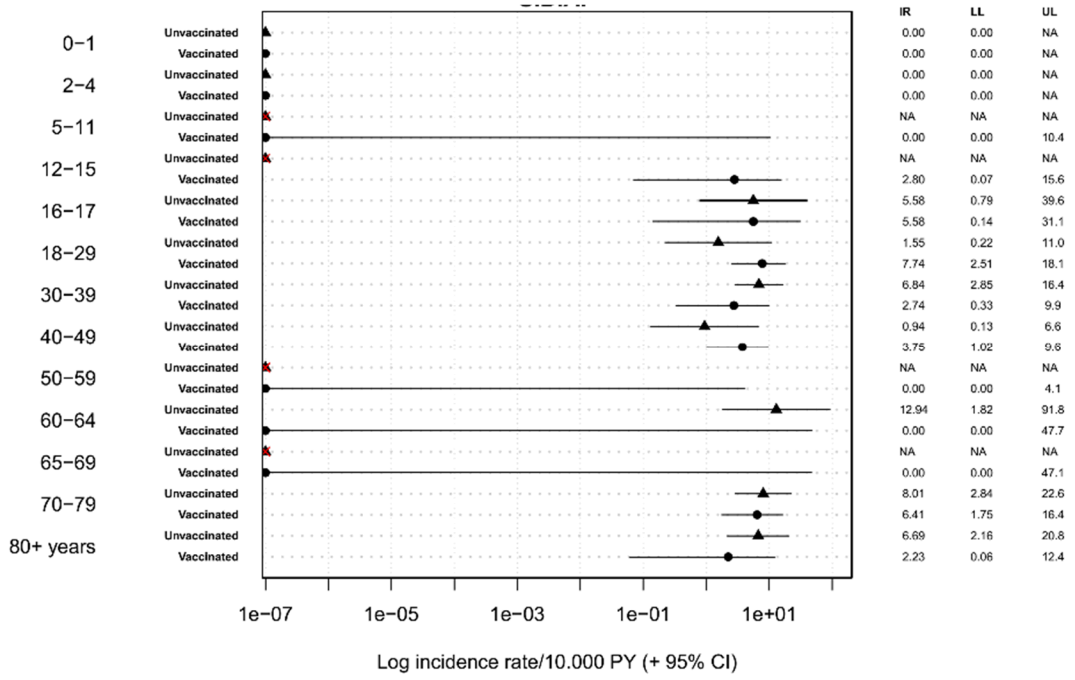


Figure 42. Forest plot showing incidence rates and 95% confidence intervals for pericarditis within 14 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source and by age groups

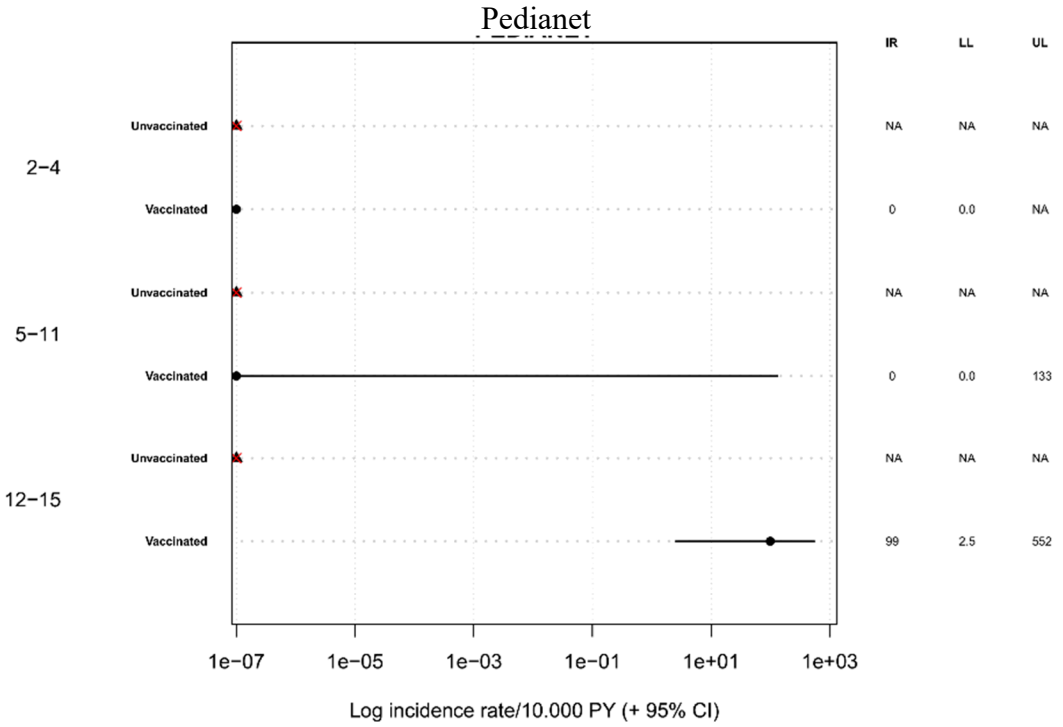


Figure 42. Forest plot showing incidence rates and 95% confidence intervals for pericarditis within 14 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source and by age groups

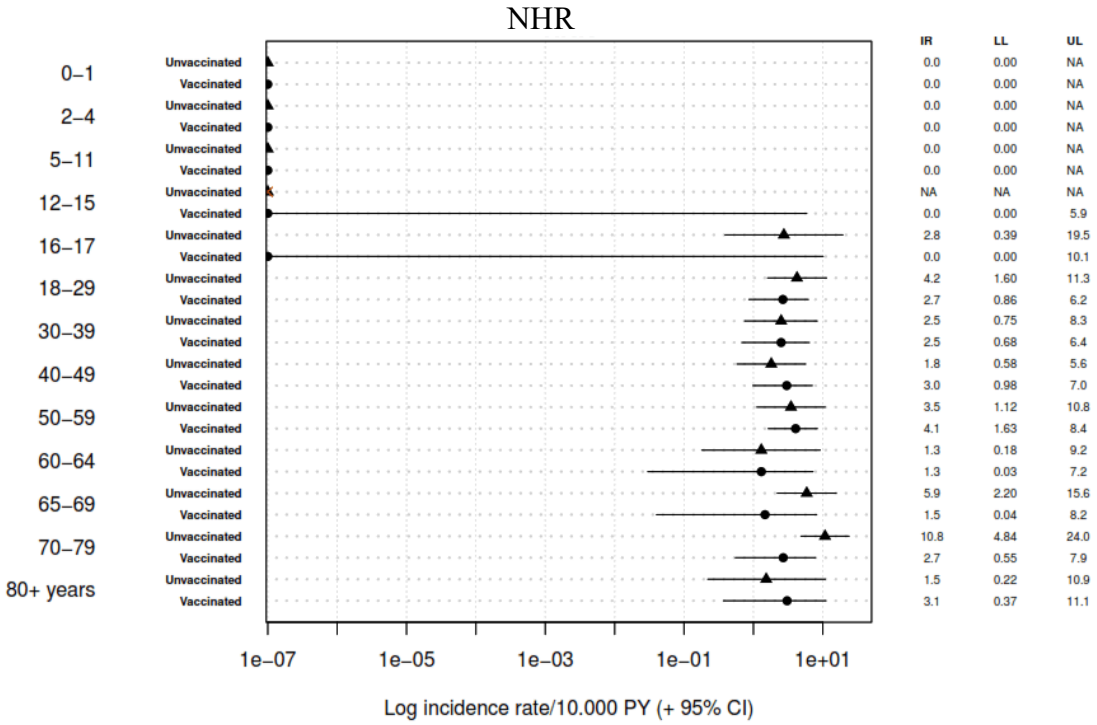


Figure 42. Forest plot showing incidence rates and 95% confidence intervals for pericarditis within 14 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source and by age groups

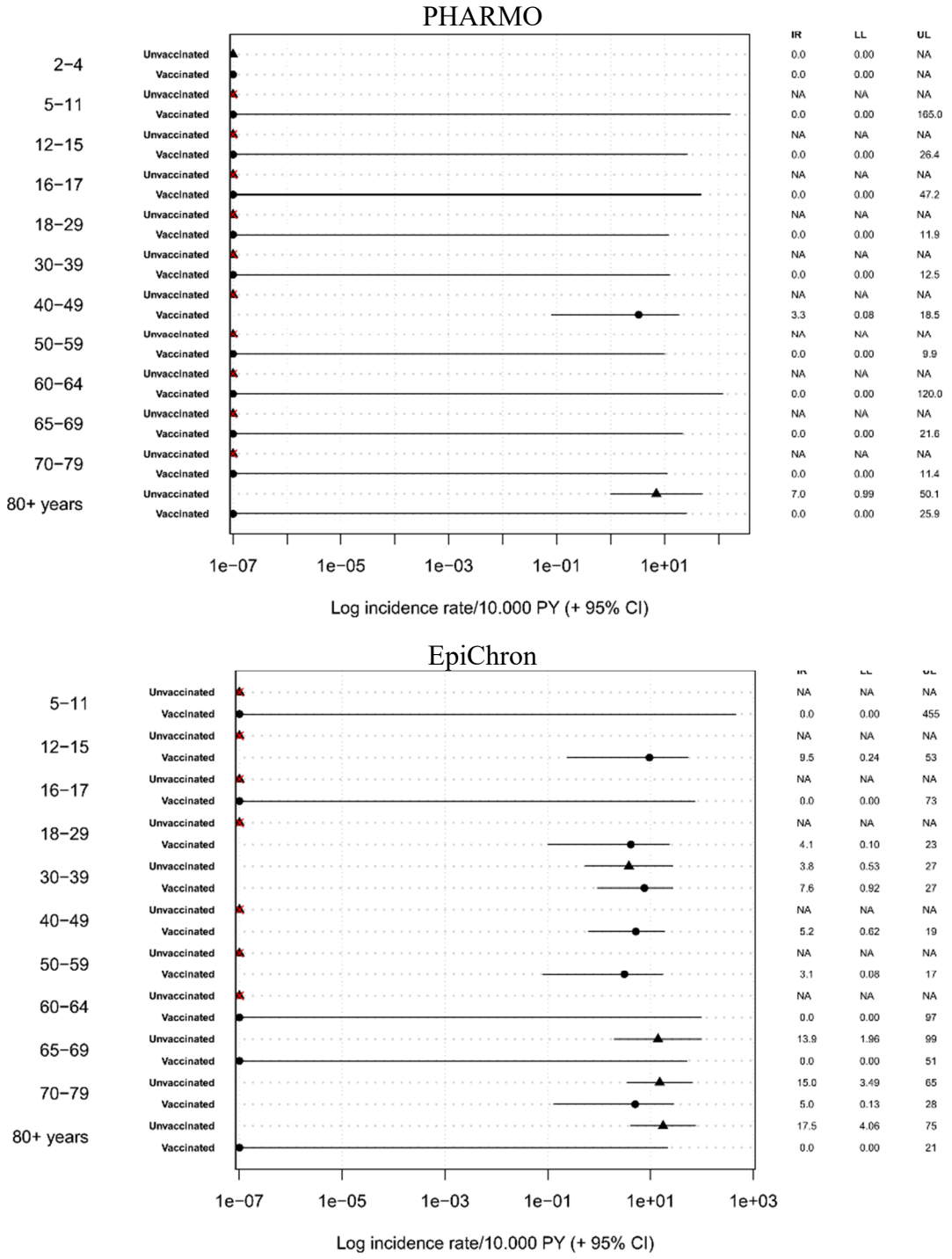


Figure 42. Forest plot showing incidence rates and 95% confidence intervals for pericarditis within 14 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source and by age groups

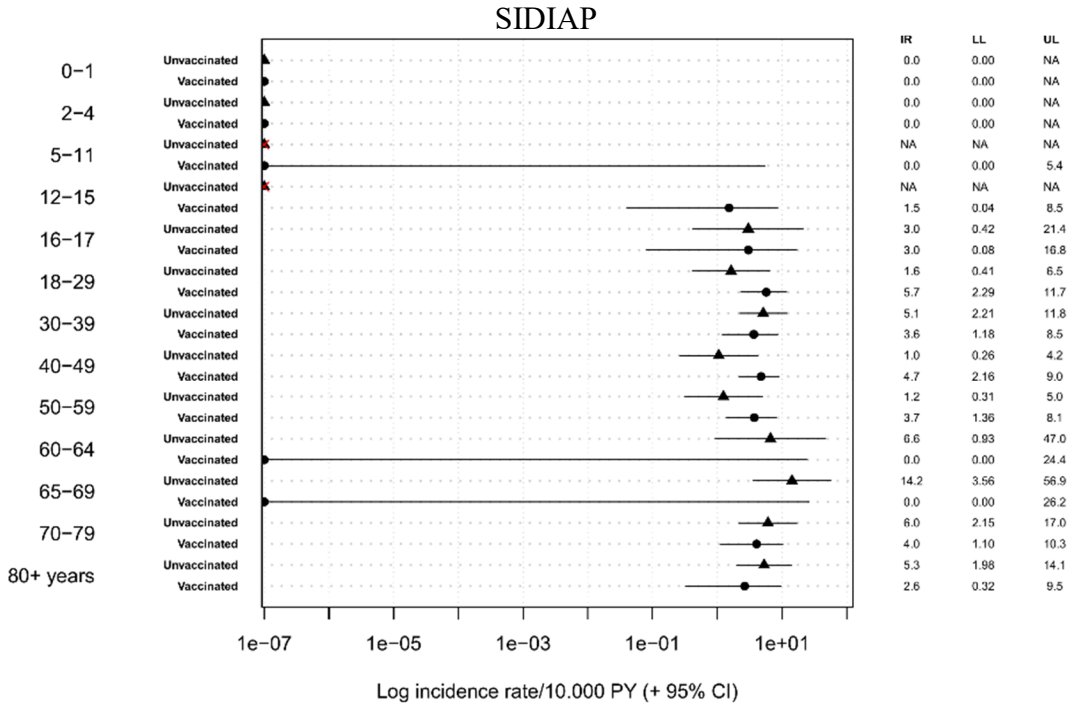


Figure 43. Forest plot showing incidence rates and 95% confidence intervals for pericarditis within 21 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source and by age groups

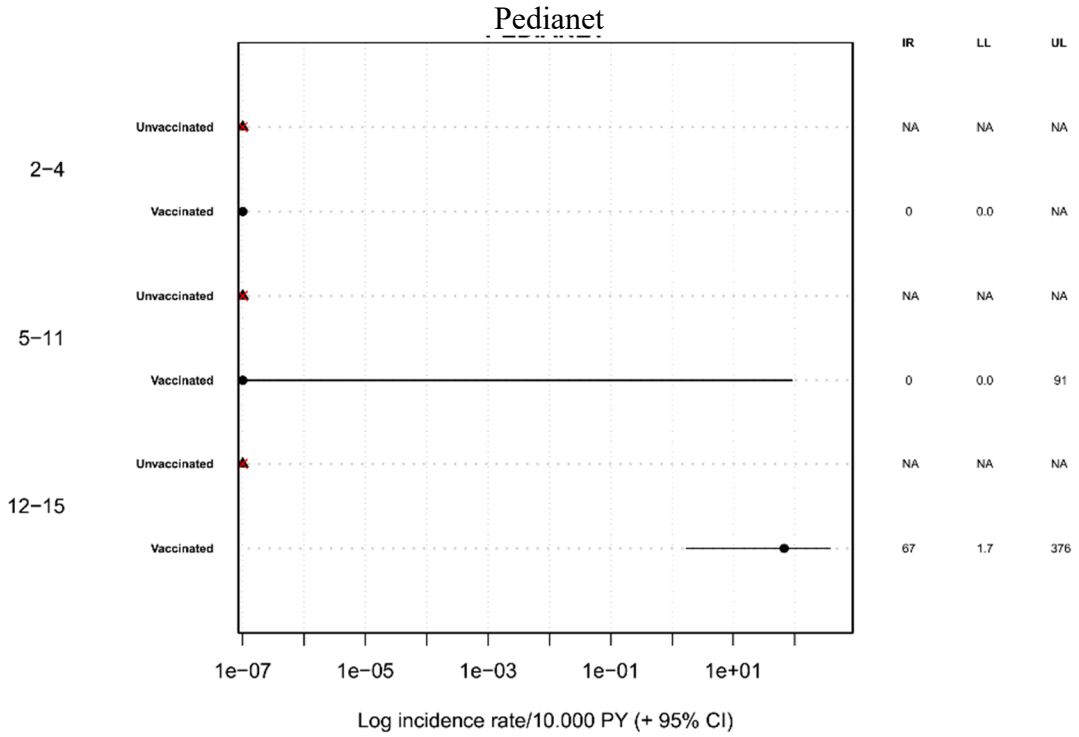


Figure 43. Forest plot showing incidence rates and 95% confidence intervals for pericarditis within 21 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source and by age groups

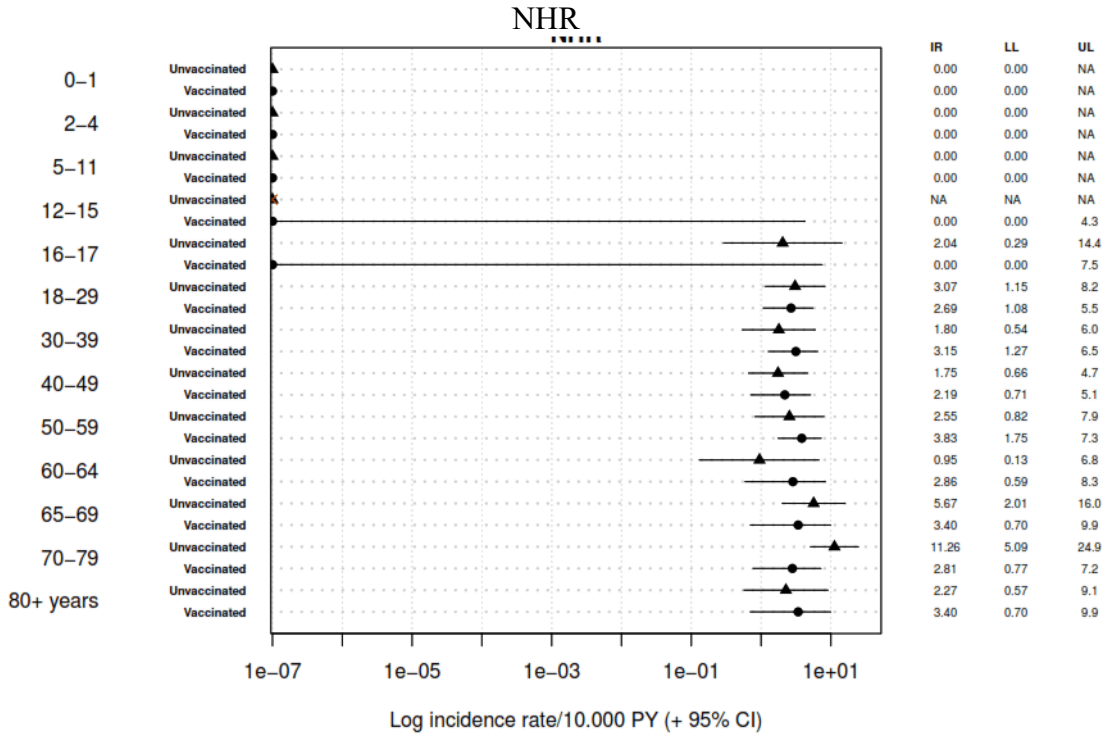


Figure 43. Forest plot showing incidence rates and 95% confidence intervals for pericarditis within 21 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source and by age groups

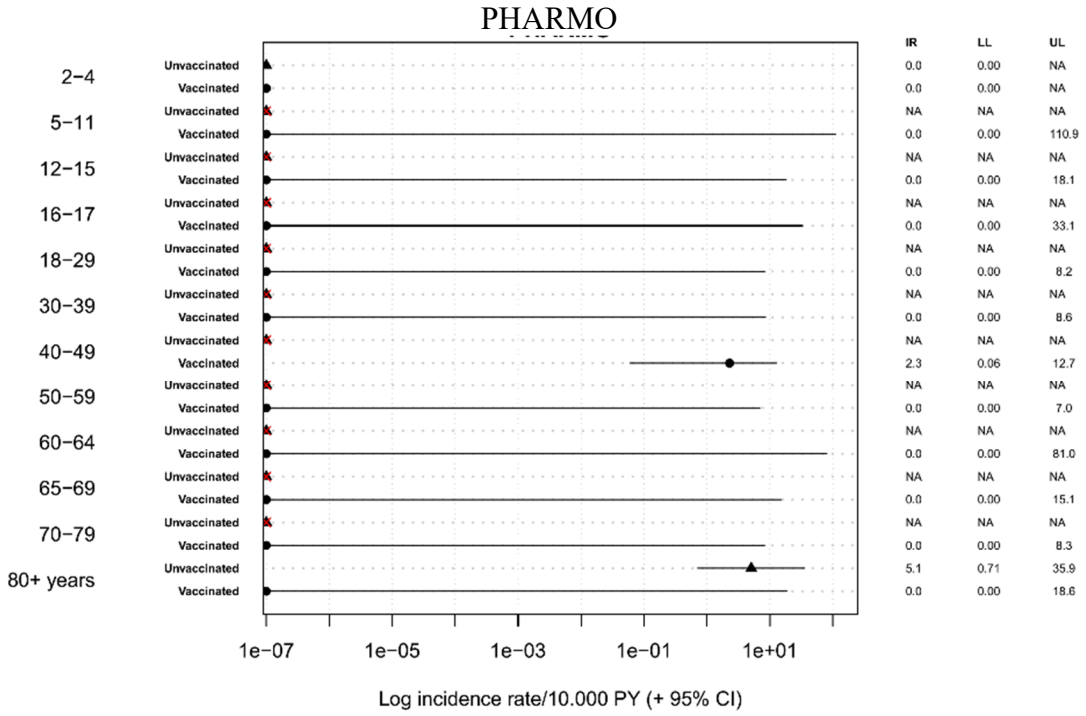
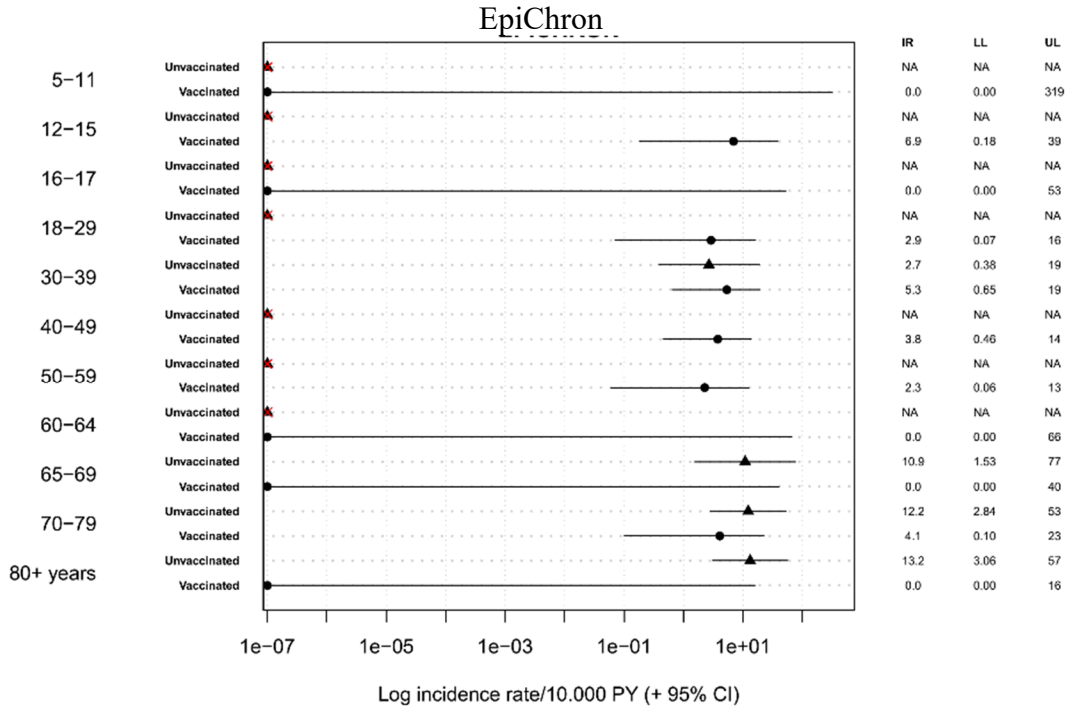


Figure 43. Forest plot showing incidence rates and 95% confidence intervals for pericarditis within 21 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source and by age groups



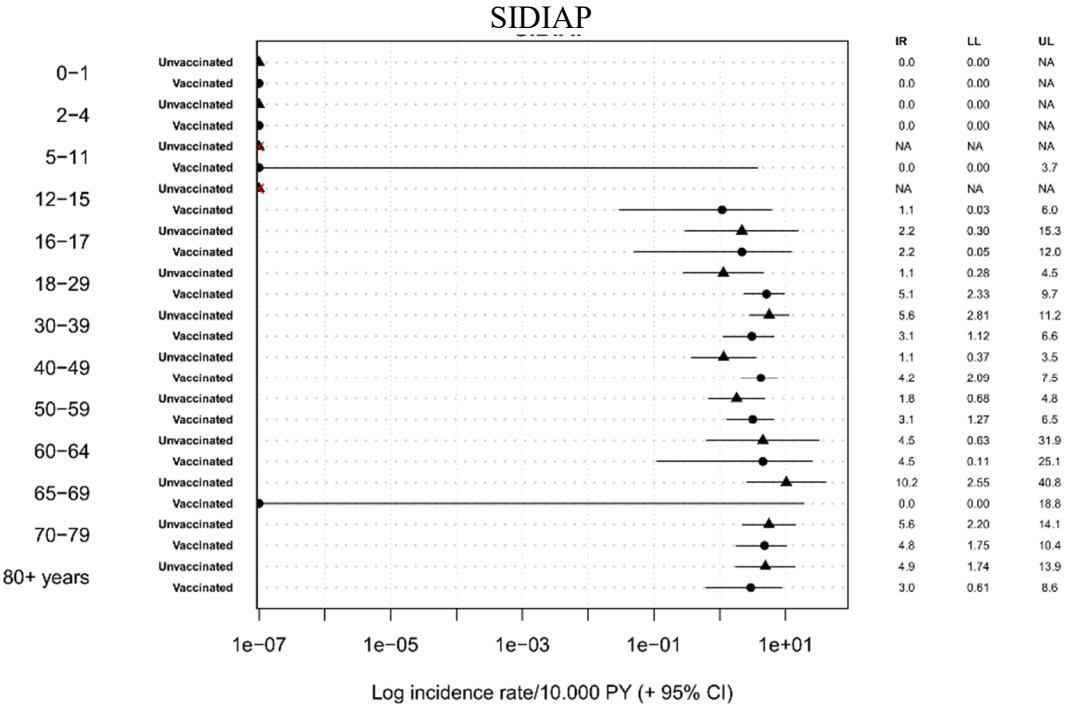


Table 50. Matched hazard ratios (HRs) and matched risk differences (RDs) per 10,000 person-years and their 95% CIs for pericarditis within 7 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source

	Matched HR (95% CI)	Adjusted HR (95% CI)	Matched RD	Adjusted RD
Pedianet	NA	NA	0.98	0.83
NHR	0.50 (0.24, 1.02)	0.50 (0.24, 1.02)	-0.04	-0.04
PHARMO	NA	NA	0	0
EpiChron	0.83 (0.21, 3.23)	0.93 (0.24, 3.59)	-0.02	-0.01
SIDIAP	1.06 (0.54, 2.10)	0.94 (0.47, 1.87)	0	0

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

Table 51. 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)	Adjusted HR (95% CI)	Matched RD	Adjusted RD
Pedianet	NA	NA	0.98	0.83
NHR	0.70 (0.40, 1.22)	0.70 (0.40, 1.22)	-0.03	-0.03
PHARMO	1.00 (0.06, 16.08)	1.06 (0.07, 16.96)	0	0
EpiChron	1.00 (0.32, 3.15)	1.04 (0.33, 3.28)	0.01	0.01
SIDIAP	1.30 (0.75, 2.23)	1.17 (0.68, 2.04)	0.04	0.03

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

Table 52. 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)	Adjusted HR (95% CI)	Matched RD	Adjusted RD
Pedianet	NA	NA	0.98	0.83
NHR	0.87 (0.51, 1.48)	0.87 (0.51, 1.48)	-0.01	-0.01
PHARMO	1 (0.06, 16.08)	1.06 (0.07, 16.96)	0	0
EpiChron	1 (0.32, 3.15)	1.04 (0.33, 3.28)	0.01	0.01
SIDIAP	1.25 (0.78, 2.01)	1.16 (0.71, 1.88)	0.04	0.03

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

10.3.17. 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 3.11 per 10,000 person-years (95% CI: 1.81, 4.98) in SIDIAP to 5.62 per 10,000 person-years (95% CI: 2.06, 12.22) in EpiChron in the vaccinated cohorts and in the unvaccinated cohorts from 3.29 per 10,000 person-years (95% CI: 2.02, 5.36) in SIDIAP to 5.62 per 10,000 person-years (95% CI: 2.00, 15.78) in EpiChron. In Pedianet the incidence rate in the vaccinated cohort was 50.99 (95% CI: 1.29, 284.09), but this corresponded to <5 events. 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 1.00 (95% CI: 0.27; 3.69) in EpiChron and 0.94 (95% CI: 0.48; 1.87) in SIDIAP.

In the 14-day risk window, the incidence rates ranged 1.37 per 10,000 person-years (95% CI 0.28, 4.01) in PHARMO to 5.36 per 10,000 person-years (95% CI: 2.57, 9.87) in EpiChron in the vaccinated cohorts and in the unvaccinated cohorts from 0.46 per 10,000 person-years (95% CI: 0.06, 3.23) in NHR to 4.83 per 10,000 person-years (95% CI: 2.08, 11.23) in EpiChron. In Pedianet the incidence rate in the vaccinated cohort was 26.37, but this corresponded to less than 5 events. 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 3.01 (95% CI: 0.31; 29.01) in PHARMO, 1.11 (95% CI: 0.39; 3.11) in EpiChron and 1.36 (95% CI: 0.80; 2.30) in SIDIAP.

In the 21-day risk window, the incidence rates ranged from 1.28 per 10,000 person-years (95% CI: 0.35, 3.27) in PHARMO to 4.34 per 10,000 person-years (95% CI: 2.16, 7.76) in EpiChron in the vaccinated cohorts and in the unvaccinated cohorts from 0.32 per 10,000 person-years (95% CI: 0.04, 2.26) in PHARMO to 3.72 per 10,000 person-years (95% CI: 1.53, 8.25) in NHR. In the vaccinated cohort in Pedianet, the incidence rate was 18.11 per 10,000 person-years (corresponding to <5 events). 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 4.01 (95% CI: 0.45; 35.93) in PHARMO, 1.22 (95% CI: 0.44; 3.42) in EpiChron and 1.32 (95% CI: 0.83; 2.08) in SIDIAP.

Table 53. 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

	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)	<5	0.98 (0, 2.89)	196.12	50.99 (1.29, 284.09)	0	0 (0, 0)	196.15	NA
NHR (Norway)	16	0.05 (0.03, 0.08)	62,497.22	2.56 (1.46, 4.16)	29	0.09 (0.05, 0.13)	62,486.74	4.64 (3.01, 7.15)
PHARMO (Netherlands)	<5	0.03 (0, 0.08)	11,659.99	1.72 (0.21, 6.20)	0	0 (0, 0)	11,718.43	NA
EpiChron (Spain)	6	0.11 (0.02, 0.21)	10,685.09	5.62 (2.06, 12.22)	6	0.11 (0, 0.23)	10,683.18	5.62 (2, 15.78)
SIDIAP (Spain)	17	0.06 (0.03, 0.09)	54,659.25	3.11 (1.81, 4.98)	18	0.06 (0.03, 0.09)	54,659.20	3.29 (2.02, 5.36)

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 54. 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)	<5	0.98 (0, 2.89)	379.26	26.37 (0.67, 146.91)	0	0 (0, 0)	379.30	NA
NHR (Norway)	36	0.13 (0.09, 0.17)	110,714.80	3.25 (2.28, 4.50)	46	0.15 (0.10, 0.21)	110,675.01	4.16 (2.85, 6.06)
PHARMO (Netherlands)	<5	0.05 (0, 0.11)	21,856.77	1.37 (0.28, 4.01)	<5	0.02 (0, 0.06)	21,945.67	0.46 (0.06, 3.23)
EpiChron (Spain)	10	0.21 (0.08, 0.34)	18,640.69	5.36 (2.57, 9.87)	9	0.19 (0.03, 0.34)	18,633.66	4.83 (2.08, 11.23)
SIDIAP (Spain)	38	0.15 (0.10, 0.20)	98,333.71	3.86 (2.73, 5.30)	28	0.11 (0.06, 0.15)	98,333.62	2.85 (1.87, 4.33)

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 55. 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

	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)	<5	0.98 (0, 2.89)	552.19	18.11 (0.46, 100.90)	0	0 (0, 0)	552.29	NA
NHR (Norway)	50	0.20 (0.14, 0.25)	150,480.16	3.32 (2.47, 4.38)	56	0.20 (0.12, 0.29)	150,396.65	3.72 (2.53, 5.48)
PHARMO (Netherlands)	<5	0.07 (0, 0.15)	31,290.98	1.28 (0.35, 3.27)	<5	0.02 (0, 0.06)	31,385.43	0.32 (0.04, 2.26)
EpiChron (Spain)	11	0.24 (0.10, 0.38)	25,364.68	4.34 (2.16, 7.76)	9	0.19 (0.03, 0.34)	25,349.90	3.55 (1.53, 8.25)
SIDIAP (Spain)	50	0.21 (0.15, 0.28)	136,441.69	3.66 (2.72, 4.83)	38	0.16 (0.10, 0.21)	136,441.74	2.79 (1.93, 4.01)

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 44. 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

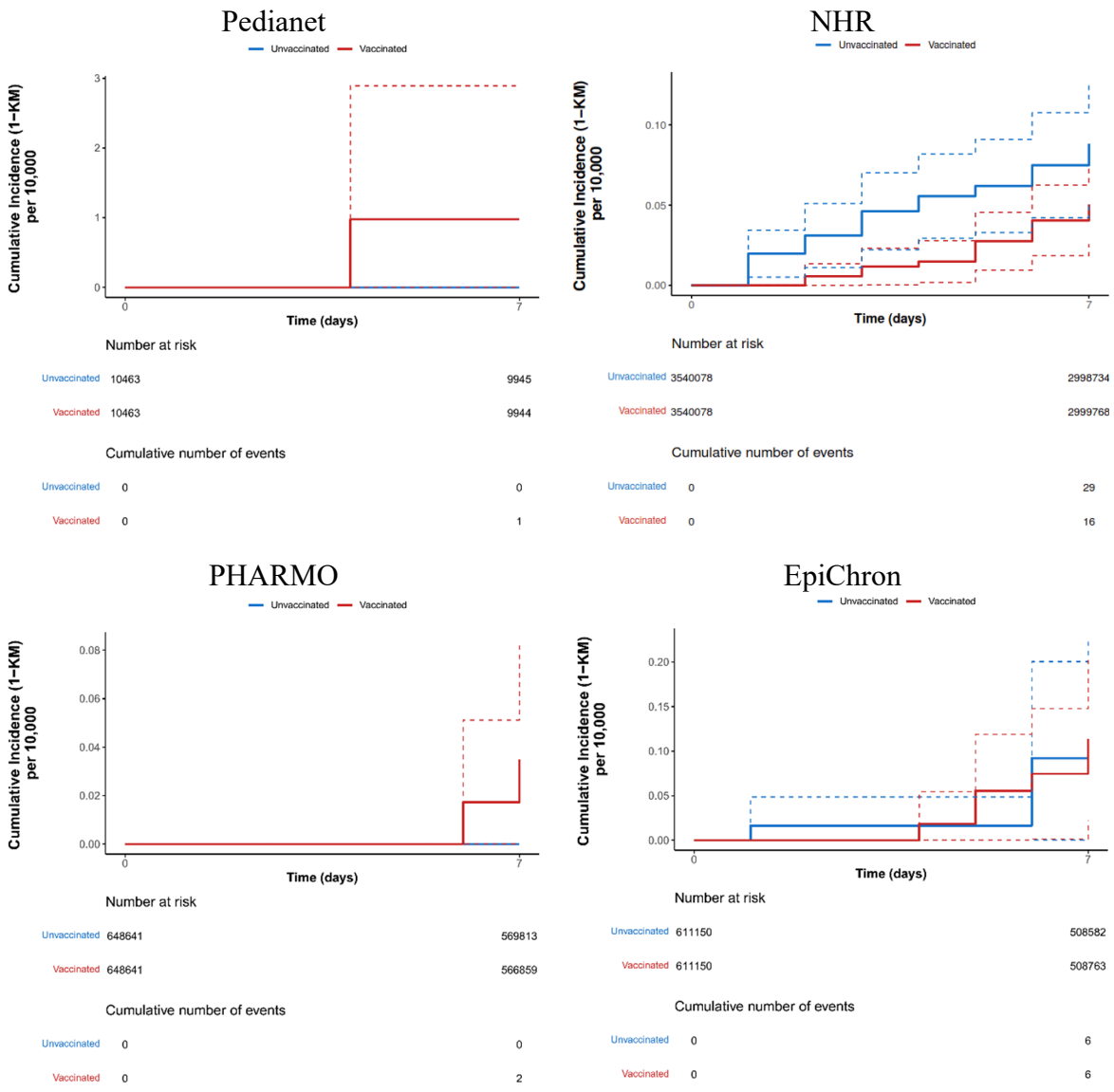
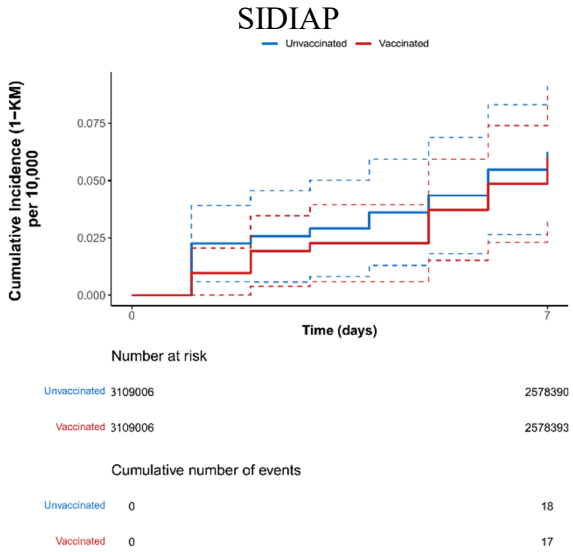


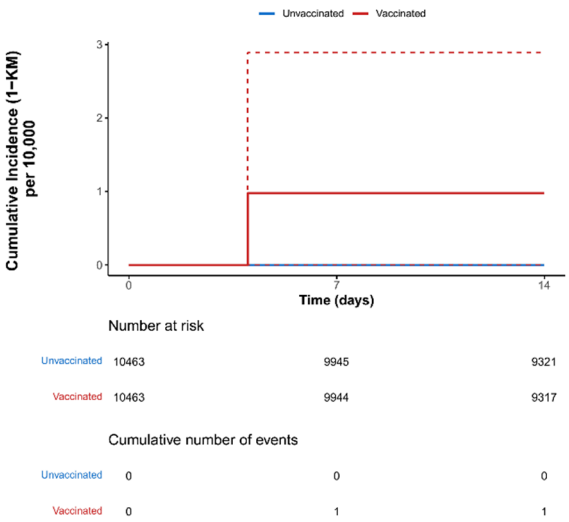
Figure 44. Cumulative incidence of myocarditis/pericarditis within 7 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source



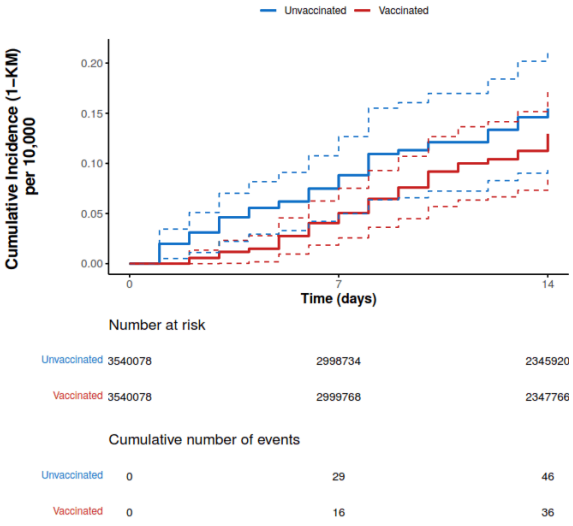
Cumulative incidence curves (1 – Kaplan–Meier risk) starting from the day of administration of the first dose of vaccine. Dotted lines represent 95% confidence intervals. The number at risk at each time point and the cumulative number of events during the 7-day risk window are also shown for each time point. The numerical data correspond to the days indicated by the tick marks on the x-axis.

Figure 45. 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

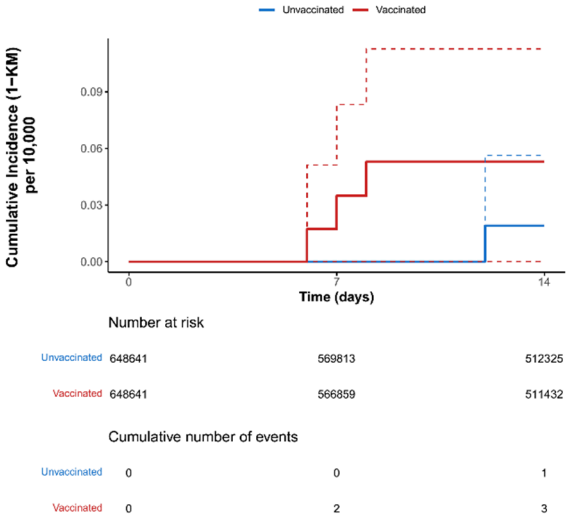
Pedianet



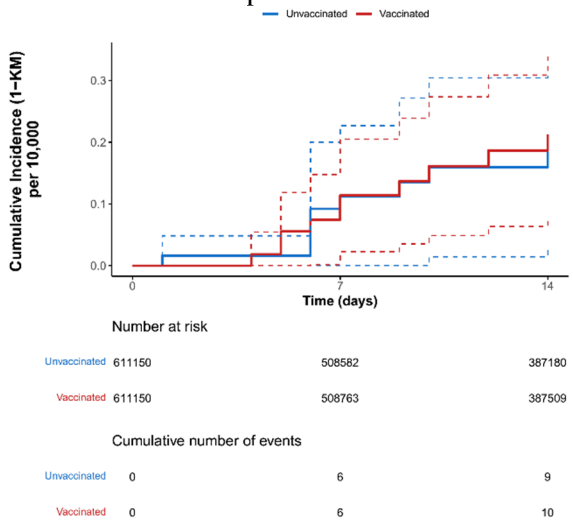
NHR



PHARMO

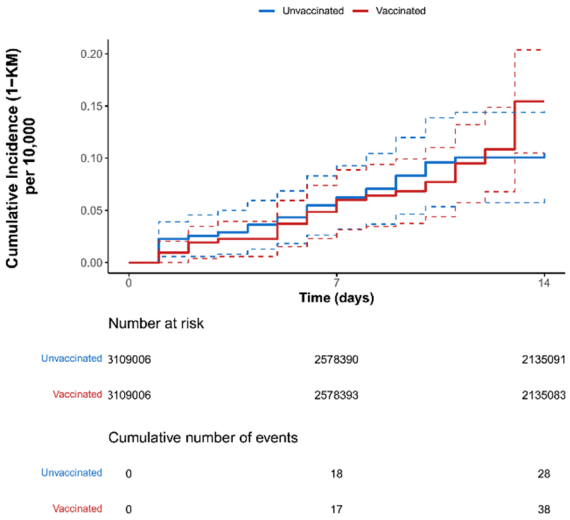


EpiChron



SIDIAP

Figure 45. 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 46. 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

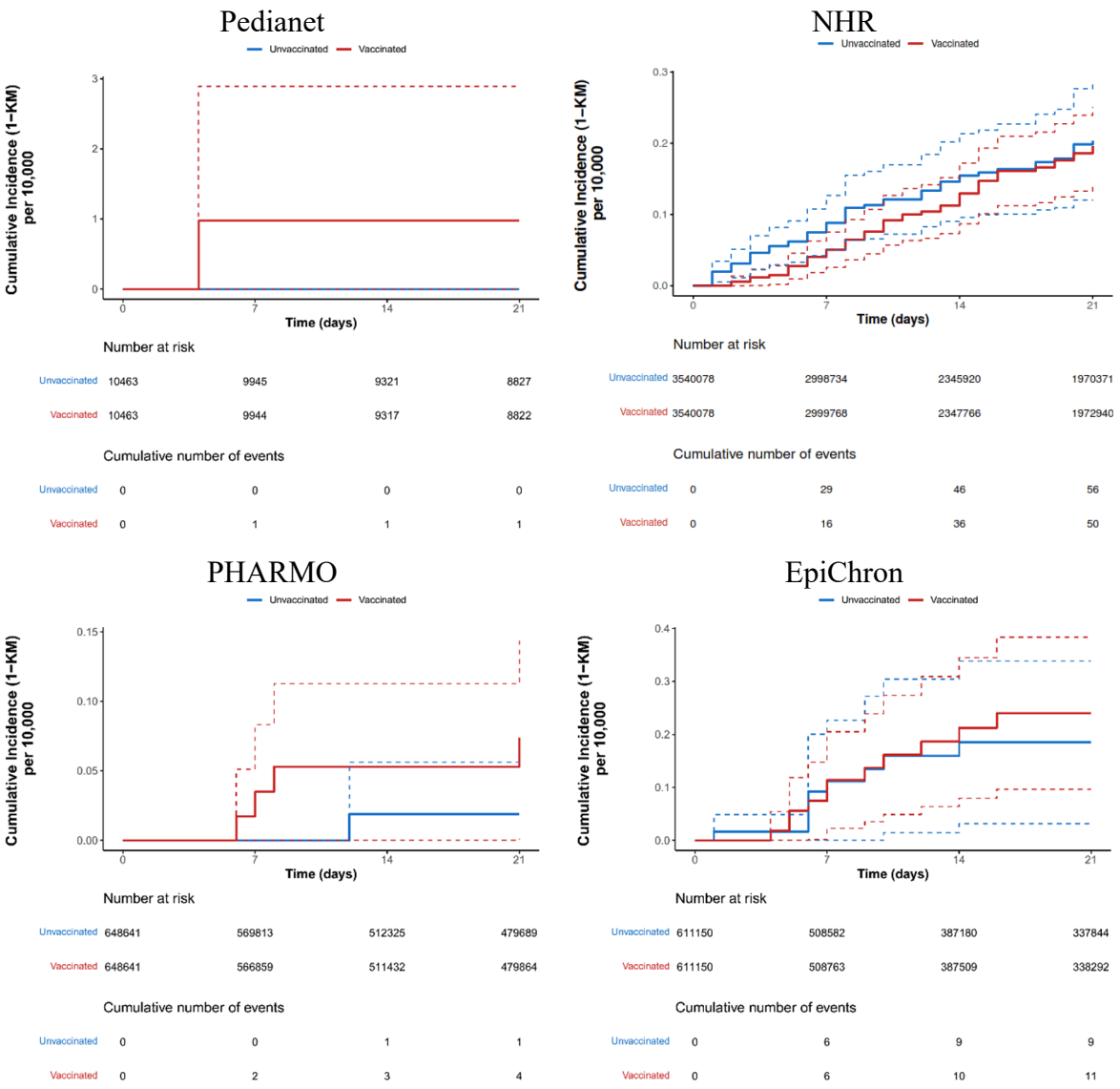
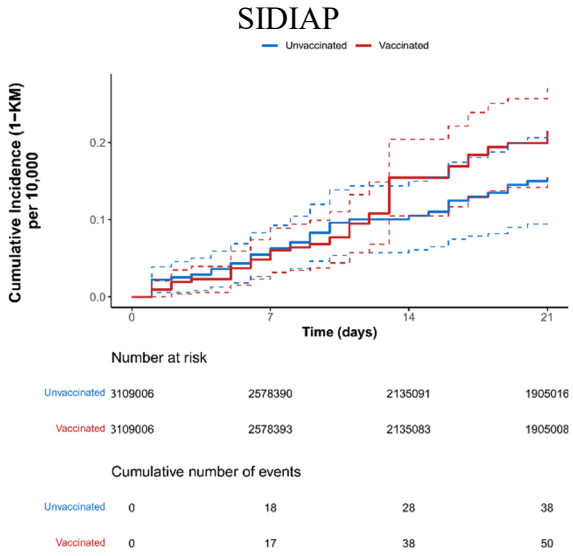


Figure 46. Cumulative incidence of myocarditis/pericarditis within 21 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source



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 47. 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

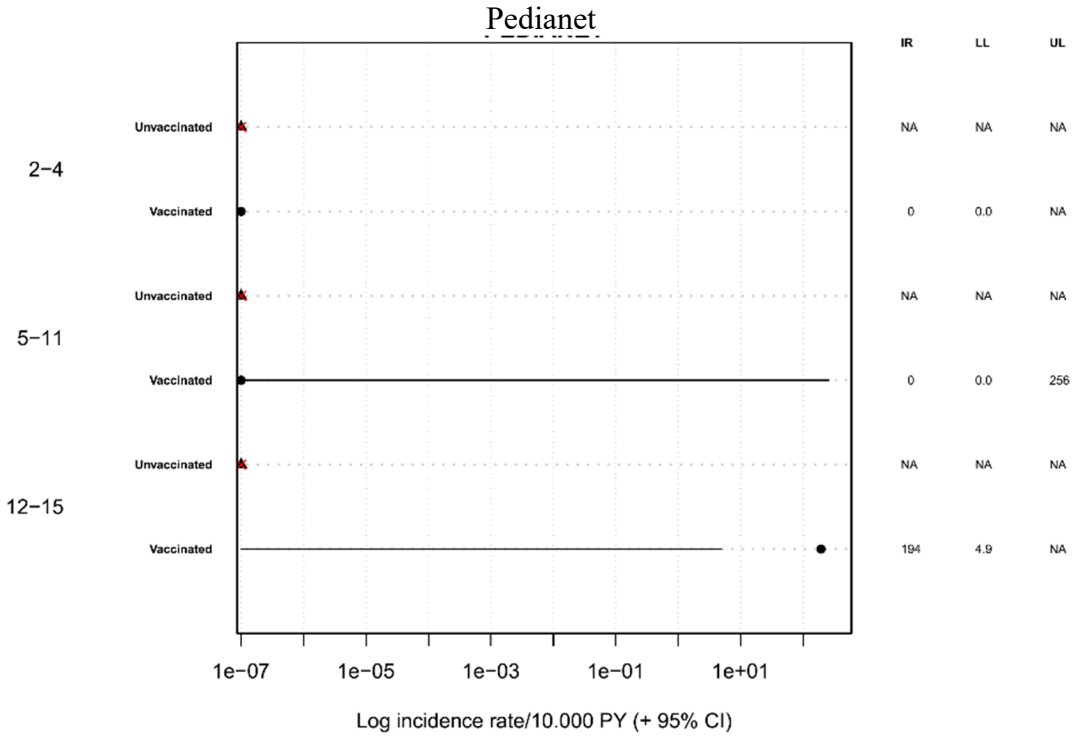


Figure 47. Forest plot showing incidence rates and 95% confidence intervals for myocarditis or pericarditis within 7 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source and by age groups

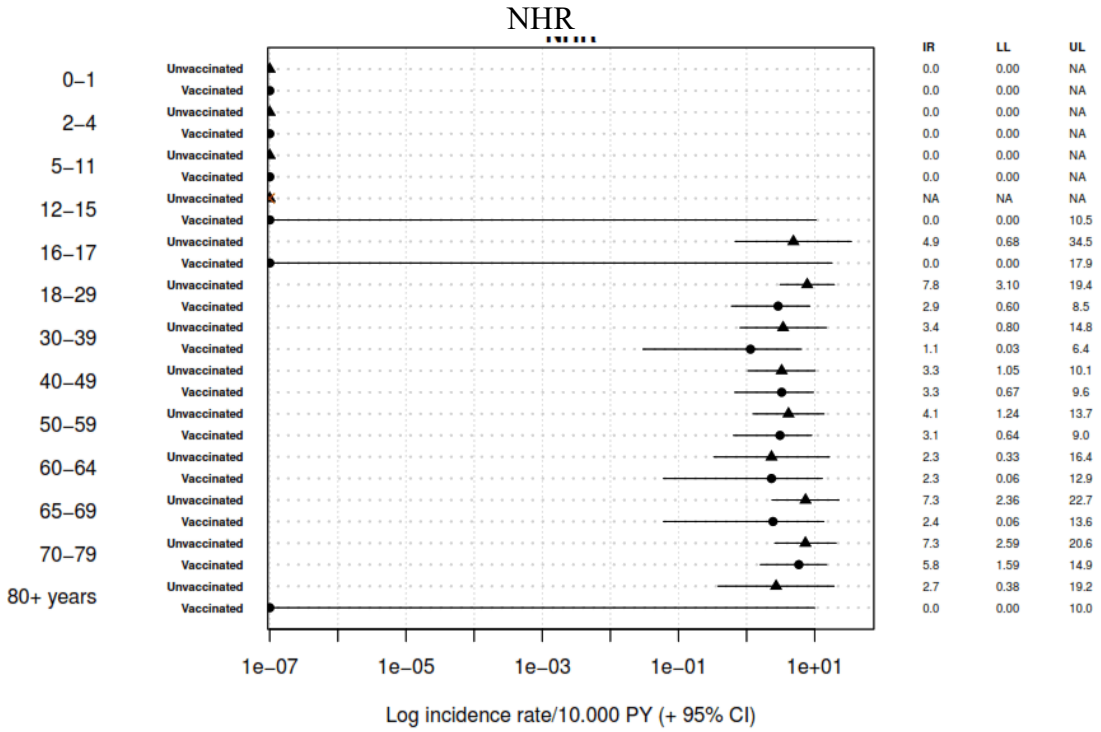


Figure 47. Forest plot showing incidence rates and 95% confidence intervals for myocarditis or pericarditis within 7 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source and by age groups

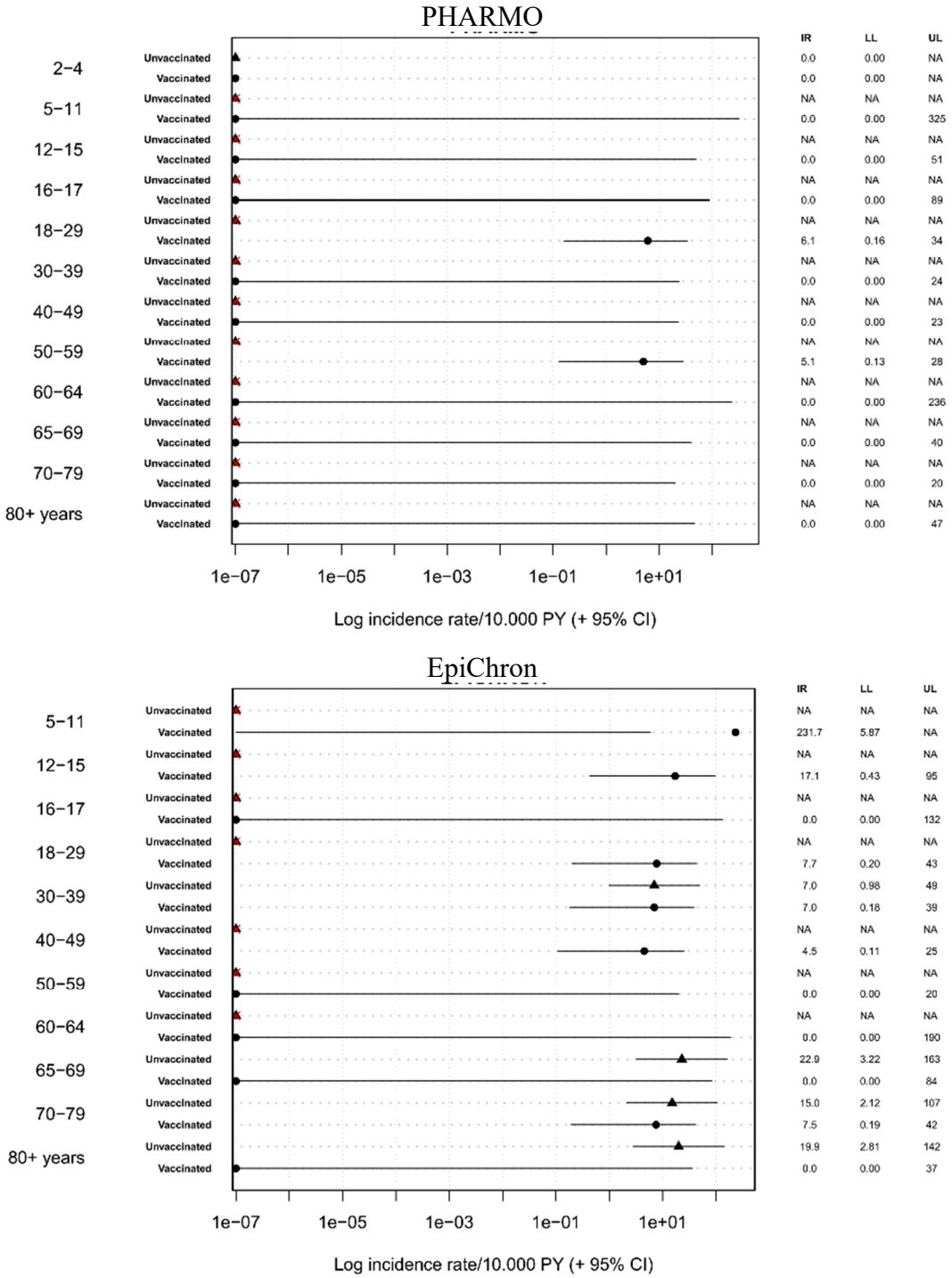


Figure 47. Forest plot showing incidence rates and 95% confidence intervals for myocarditis or pericarditis within 7 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source and by age groups

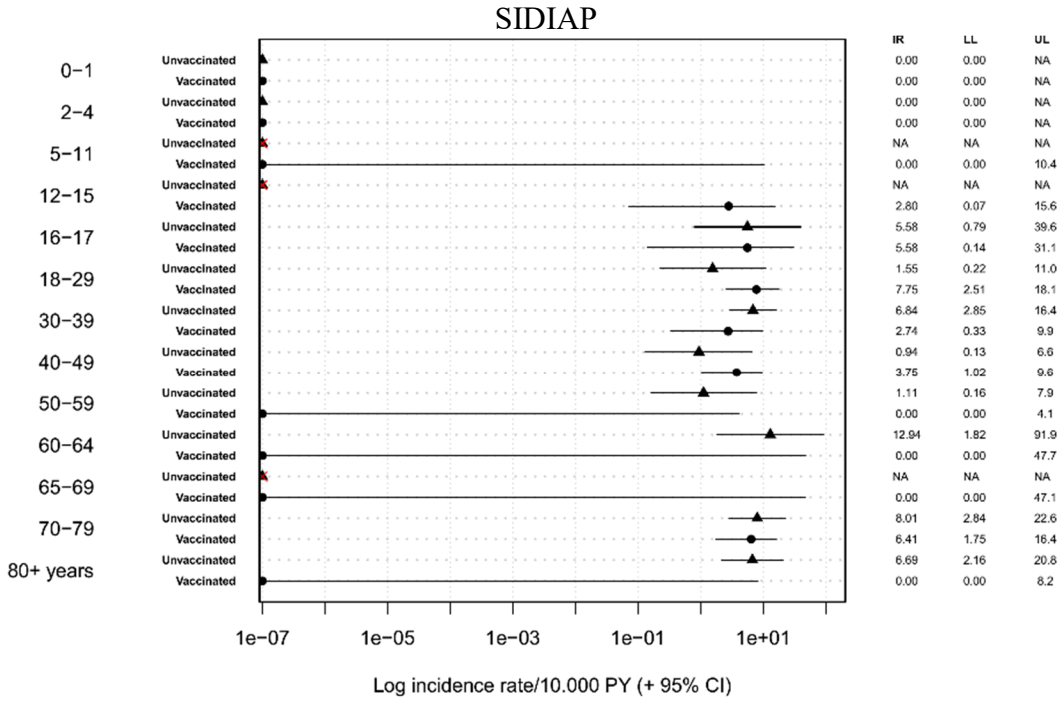


Figure 48. Forest plot showing incidence rates and 95% confidence intervals for myocarditis or pericarditis within 14 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source and by age groups

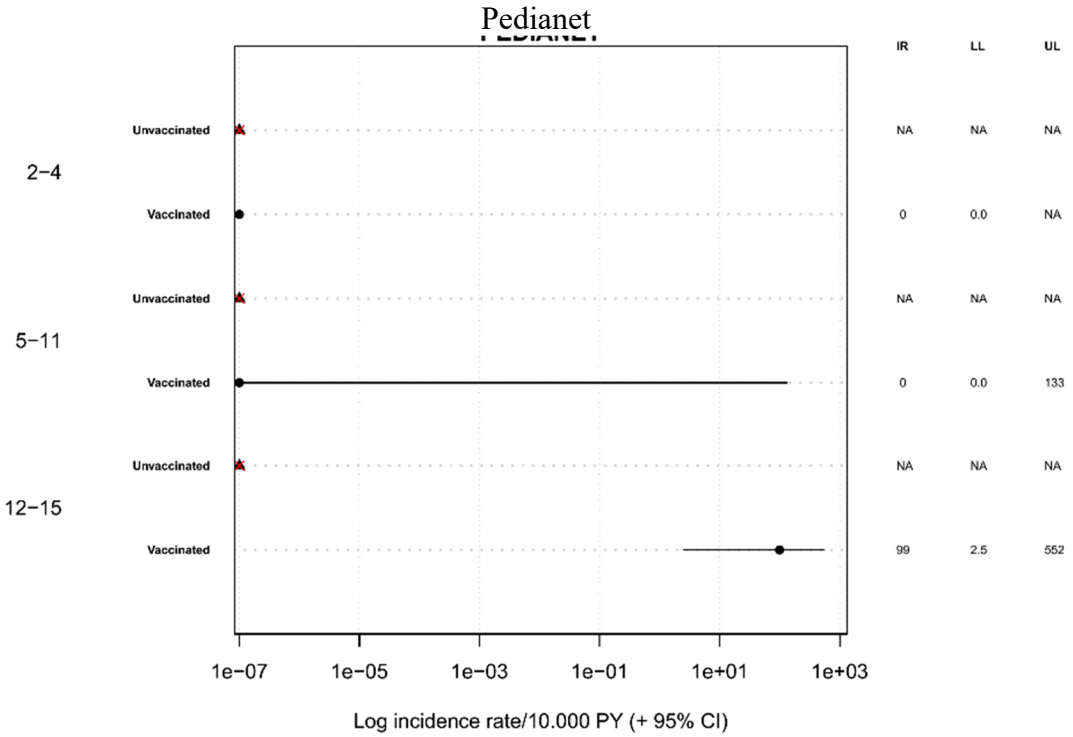


Figure 48. Forest plot showing incidence rates and 95% confidence intervals for myocarditis or pericarditis within 14 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source and by age groups

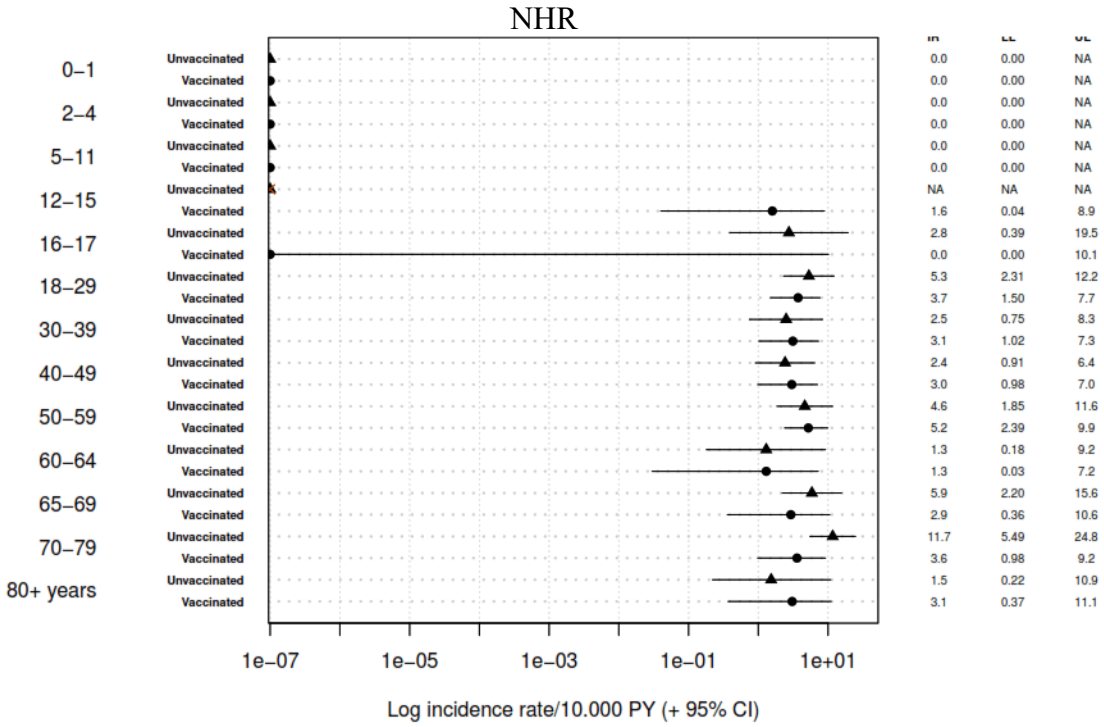


Figure 48. Forest plot showing incidence rates and 95% confidence intervals for myocarditis or pericarditis within 14 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source and by age groups

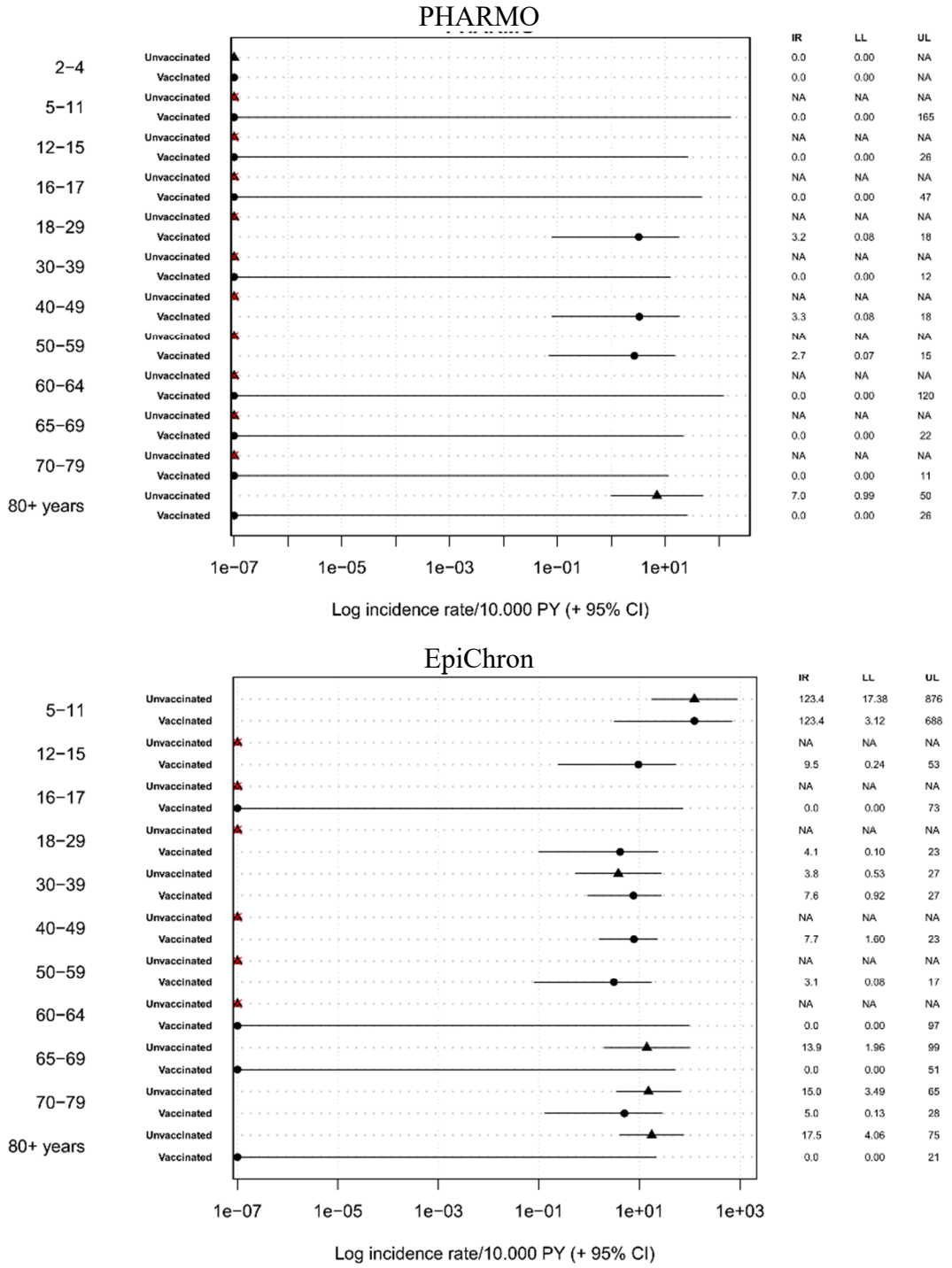


Figure 48. Forest plot showing incidence rates and 95% confidence intervals for myocarditis or pericarditis within 14 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source and by age groups

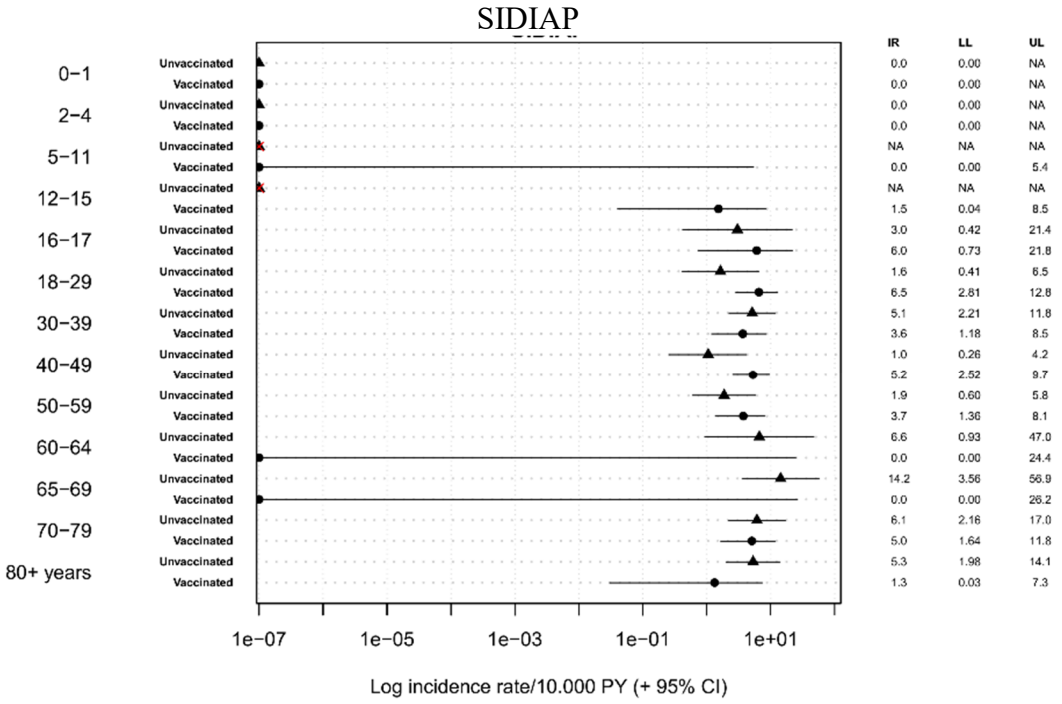


Figure 49. Forest plot showing incidence rates and 95% confidence intervals for myocarditis or pericarditis within 21 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source and by age groups

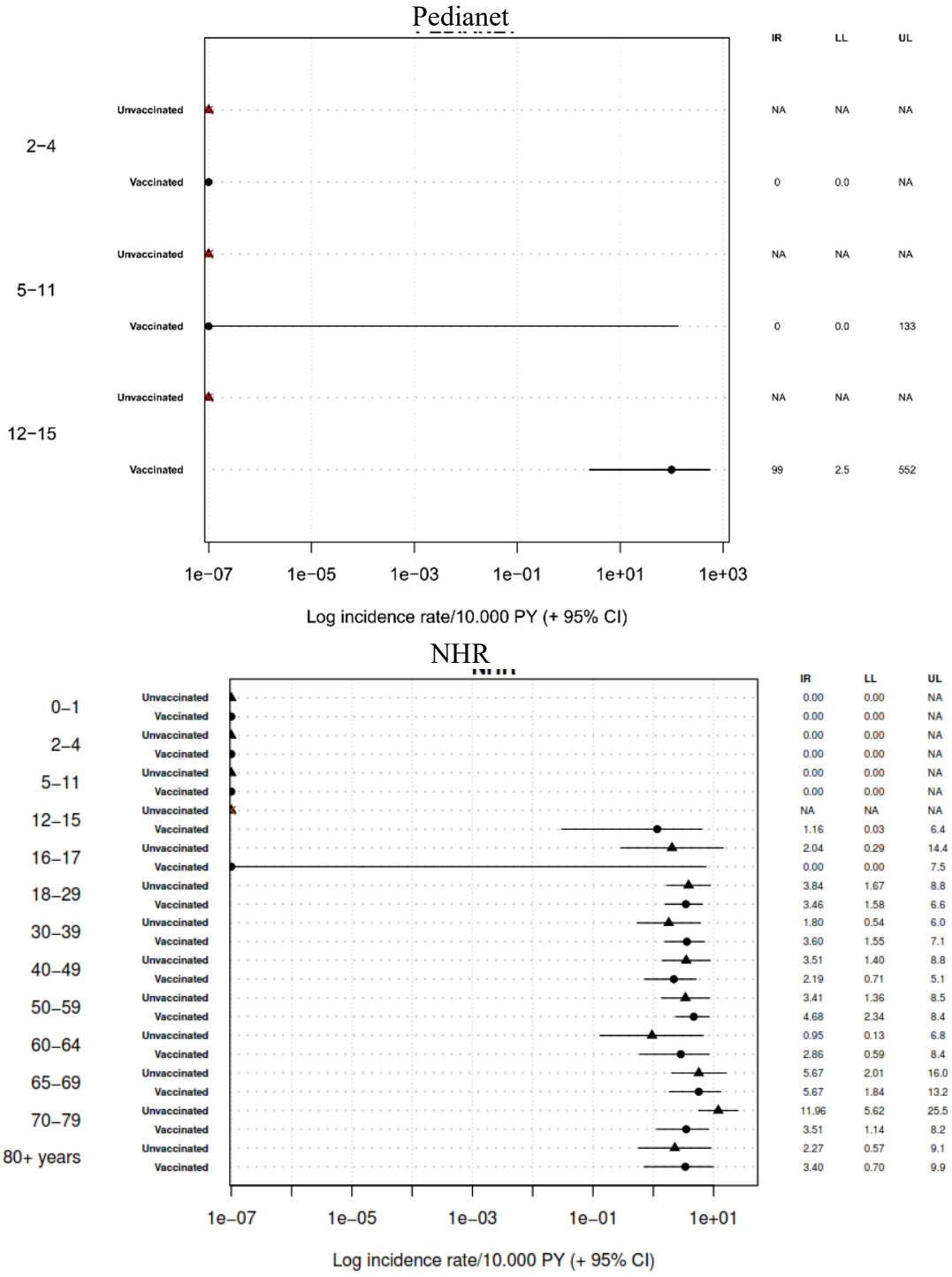


Figure 49. Forest plot showing incidence rates and 95% confidence intervals for myocarditis or pericarditis within 21 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source and by age groups

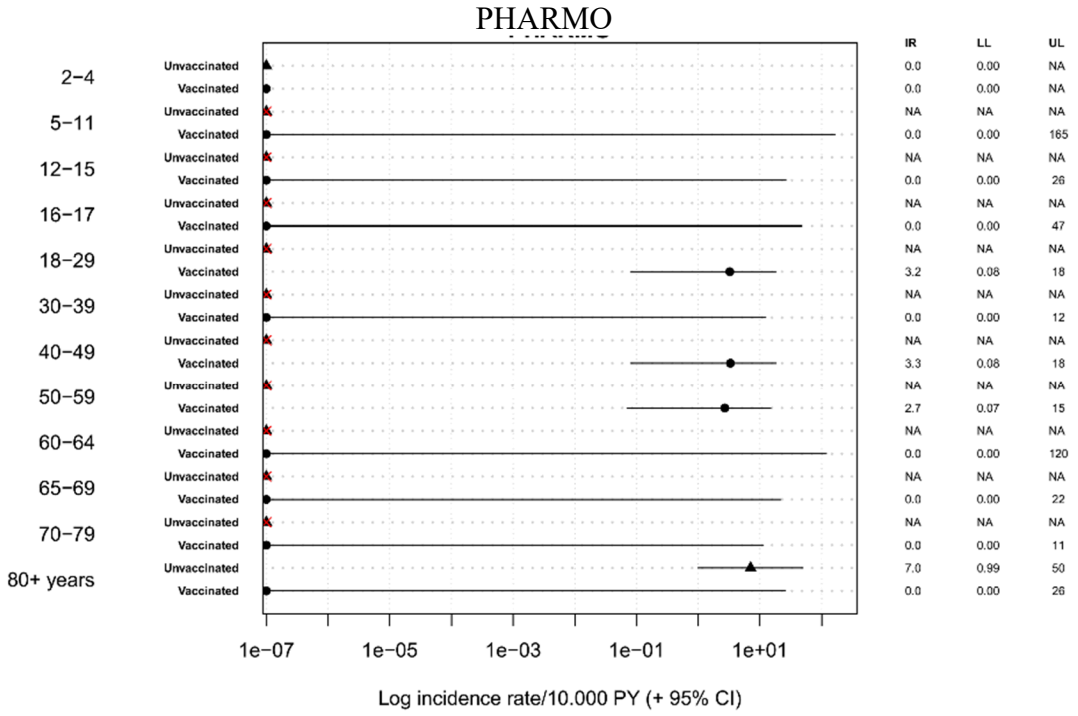


Figure 49. Forest plot showing incidence rates and 95% confidence intervals for myocarditis or pericarditis within 21 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source and by age groups

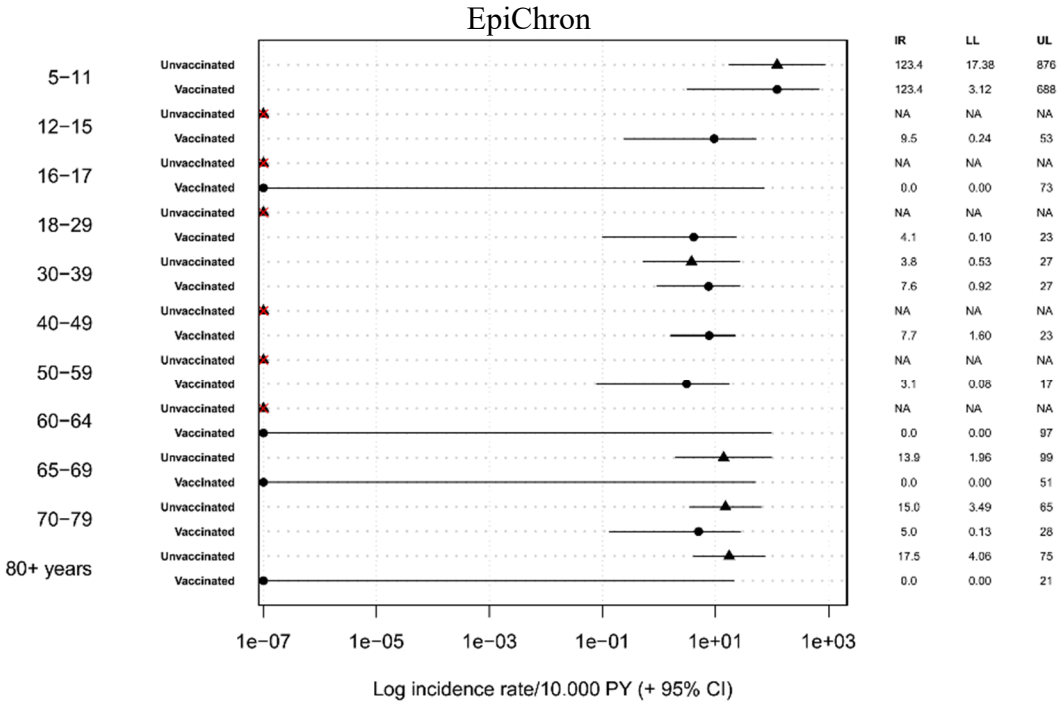


Figure 49. Forest plot showing incidence rates and 95% confidence intervals for myocarditis or pericarditis within 21 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source and by age groups

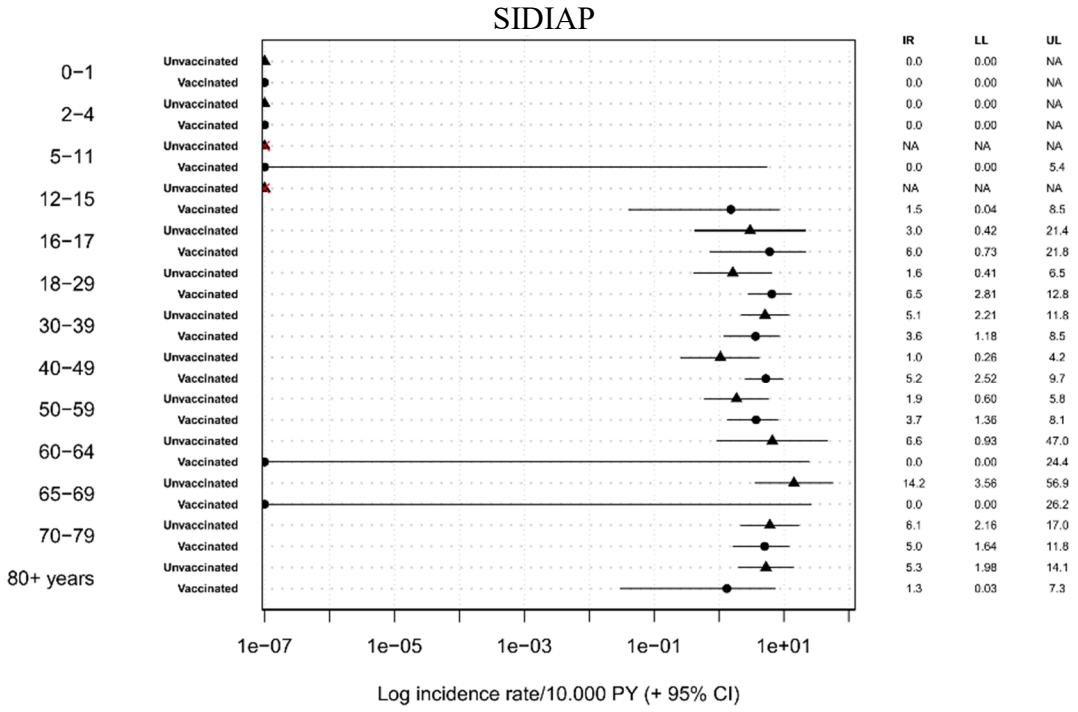


Table 56. Matched and adjusted hazard ratios (HRs) and matched and adjusted risk differences (RDs) per 10,000 person-years and their 95% CIs for myocarditis or pericarditis within 7 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source

	Matched HR (95% CI)	Adjusted HR (95% CI)	Matched RD	Adjusted RD
Pedianet	NA	NA	0.98	0.83
NHR	0.55 (0.29, 1.06)	0.55 (0.29, 1.06)	-0.04	-0.04
PHARMO	NA	NA	0.03	0.03
EpiChron	1 (0.27, 3.69)	1.10 (0.30, 4.05)	0	0.01
SIDIAP	0.94 (0.48, 1.87)	0.85 (0.43, 1.68)	0	-0.01

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

Table 57. Matched and adjusted hazard ratios (HRs) and matched and adjusted 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)	Adjusted HR (95% CI)	Matched RD	Adjusted RD
Pedianet	NA	NA	0.98	0.83
NHR	0.78 (0.48, 1.29)	0.78 (0.48, 1.29)	-0.03	-0.03
PHARMO	3.01 (0.31, 29.01)	2.74 (0.28, 26.51)	0.03	0.03
EpiChron	1.11 (0.39, 3.16)	1.14 (0.40, 3.24)	0.03	0.03
SIDIAP	1.36 (0.80, 2.30)	1.24 (0.73, 2.13)	0.05	0.04

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

Table 58. Matched and adjusted hazard ratios (HRs) and matched and adjusted 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)	Adjusted HR (95% CI)	Matched RD	Adjusted RD
Pedianet	NA	NA	0.98	0.83
NHR	0.89 (0.55, 1.44)	0.89 (0.55, 1.44)	-0.01	-0.01
PHARMO	4.01 (0.45, 35.93)	3.58 (0.40, 32.16)	0.05	0.05
EpiChron	1.22 (0.44, 3.42)	1.25 (0.45, 3.51)	0.05	0.06
SIDIAP	1.32 (0.83, 2.08)	1.23 (0.77, 1.95)	0.06	0.05

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

10.3.18. Coagulation disorders (thromboembolism, haemorrhage)

Coagulation disorders were identified in all data sources, except Pedianet. The incidence rates ranged from 19.70 per 10,000 person-years (95% CI: 15.60, 24.55) in PHARMO to 71.69 per 10,000 person-years (95% CI: 62.59, 81.74) in EpiChron in the vaccinated cohorts. In the unvaccinated cohorts these ranged from 17.17 per 10,000 person-years (95% CI: 13.01, 22.64) in PHARMO to 88.79 per 10,000 person-years (95% CI: 74.55, 105.75) in EpiChron. The cumulative incidence was less than 7 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 HRs for coagulation disorders were 0.85 (95% CI: 0.77, 0.94) in NHR, 1.15 (95% CI: 0.81, 1.63) in PHARMO, 0.81 (95% CI: 0.65, 1.00) in EpiChron, and 0.74 (95% CI: 0.66, 0.83) in SIDIAP. The adjusted HRs were 0.87 (95% CI: 0.79, 0.96) in NHR, 1.07 (95% CI: 0.75, 1.53) in PHARMO, 0.78 (95% CI: 0.63, 0.97) in EpiChron, and 0.69 (95% CI: 0.61, 0.77) in SIDIAP. No differences were observed for the incidence of coagulation disorders between the vaccinated and unvaccinated cohorts during the 28-day risk window.

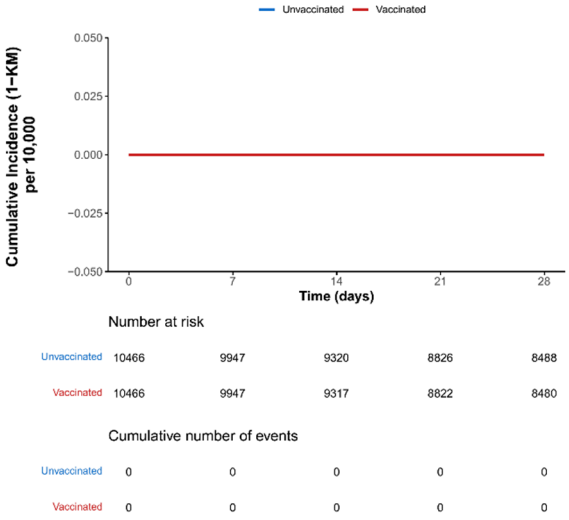
Table 59. Risk estimates (95% CI) per 10,000 person-years (PY) for coagulation disorders (thromboembolism, haemorrhage) within 28 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source

	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)	0	0 (0, 0)	717.37	0 (0, 51.42)	0	0 (0, 0)	717.55	NA
NHR (Norway)	1,102	4.62 (4.34, 4.90)	182,204.70	60.48 (56.96, 64.16)	1,263	5.19 (4.81, 5.58)	182,069.27	69.37 (64.50, 74.61)
PHARMO (Netherlands)	79	1.50 (1.16, 1.83)	40,098.50	19.70 (15.60, 24.55)	69	1.29 (0.94, 1.65)	40,197.95	17.17 (13.01, 22.64)
EpiChron (Spain)	223	5.48 (4.74, 6.21)	31,107.06	71.69 (62.59, 81.74)	276	6.89 (5.65, 8.13)	31,084.01	88.79 (74.55, 105.75)
SIDIAP (Spain)	688	3.12 (2.89, 3.36)	169,702.74	40.54 (37.57, 43.69)	928	4.12 (3.76, 4.48)	169,691.20	54.69 (50.18, 59.60)

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 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

Pedianet



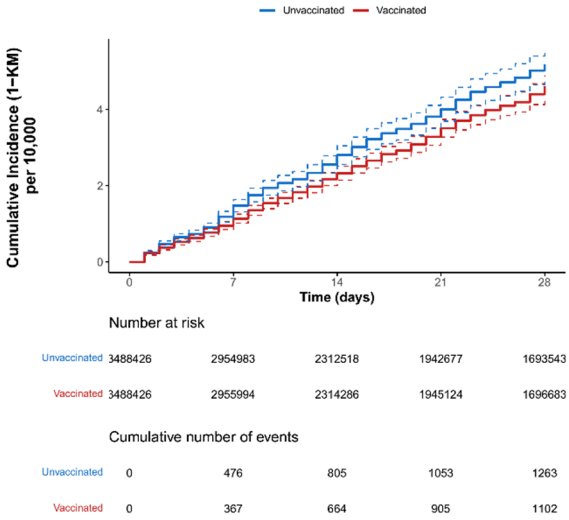
Number at risk

Unvaccinated	10466	9947	9320	8826	8488
Vaccinated	10466	9947	9317	8822	8480

Cumulative number of events

Unvaccinated	0	0	0	0	0
Vaccinated	0	0	0	0	0

NHR



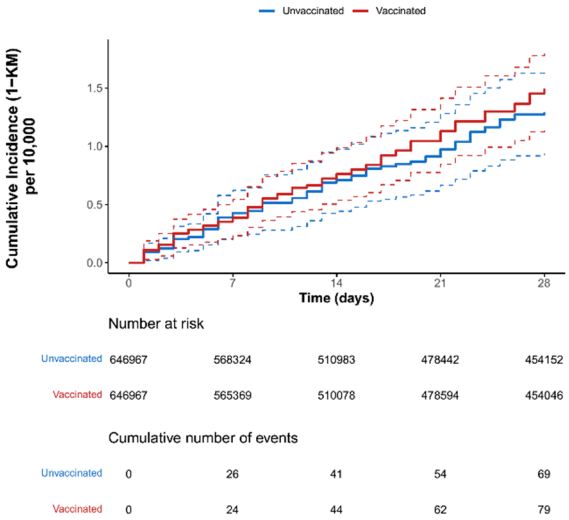
Number at risk

Unvaccinated	3488426	2954983	2312518	1942677	1693543
Vaccinated	3488426	2955994	2314286	1945124	1696683

Cumulative number of events

Unvaccinated	0	476	805	1053	1263
Vaccinated	0	367	664	905	1102

PHARMO



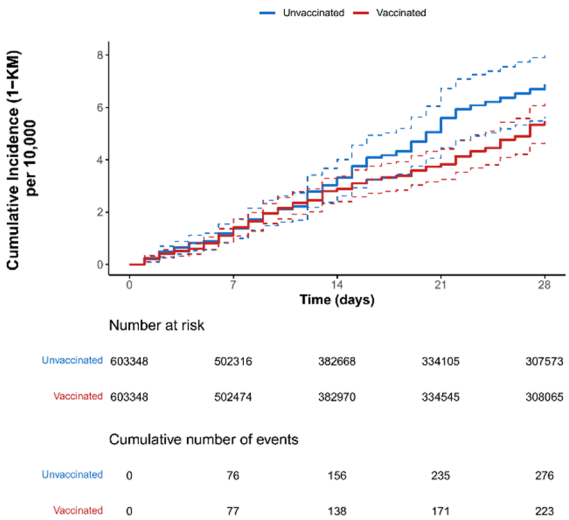
Number at risk

Unvaccinated	646967	568324	510983	478442	454152
Vaccinated	646967	565369	510078	478594	454046

Cumulative number of events

Unvaccinated	0	26	41	54	69
Vaccinated	0	24	44	62	79

EpiChron



Number at risk

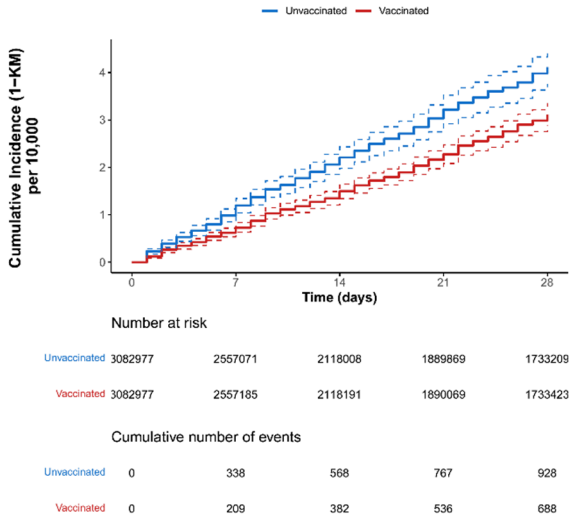
Unvaccinated	603348	502316	382668	334105	307573
Vaccinated	603348	502474	382970	334545	308065

Cumulative number of events

Unvaccinated	0	76	156	235	276
Vaccinated	0	77	138	171	223

SIDIAP

Figure 50. 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 51. 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

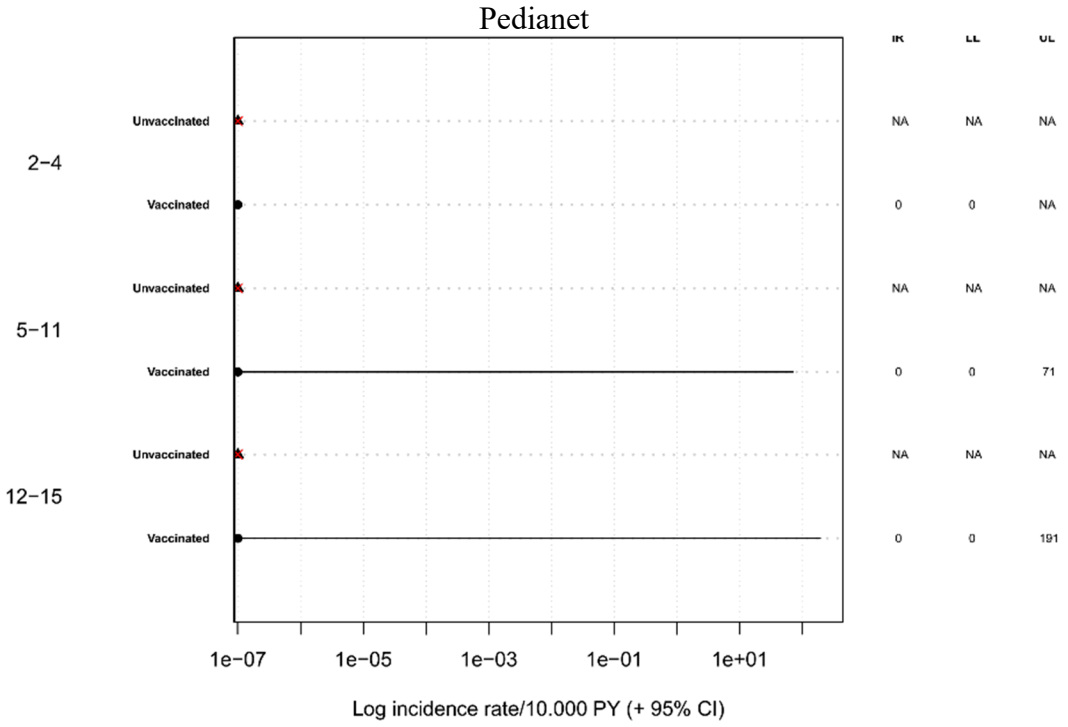


Figure 51. Forest plot showing incidence rates and 95% confidence intervals for coagulation disorders (thromboembolism, haemorrhage) within 28 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source and by age groups

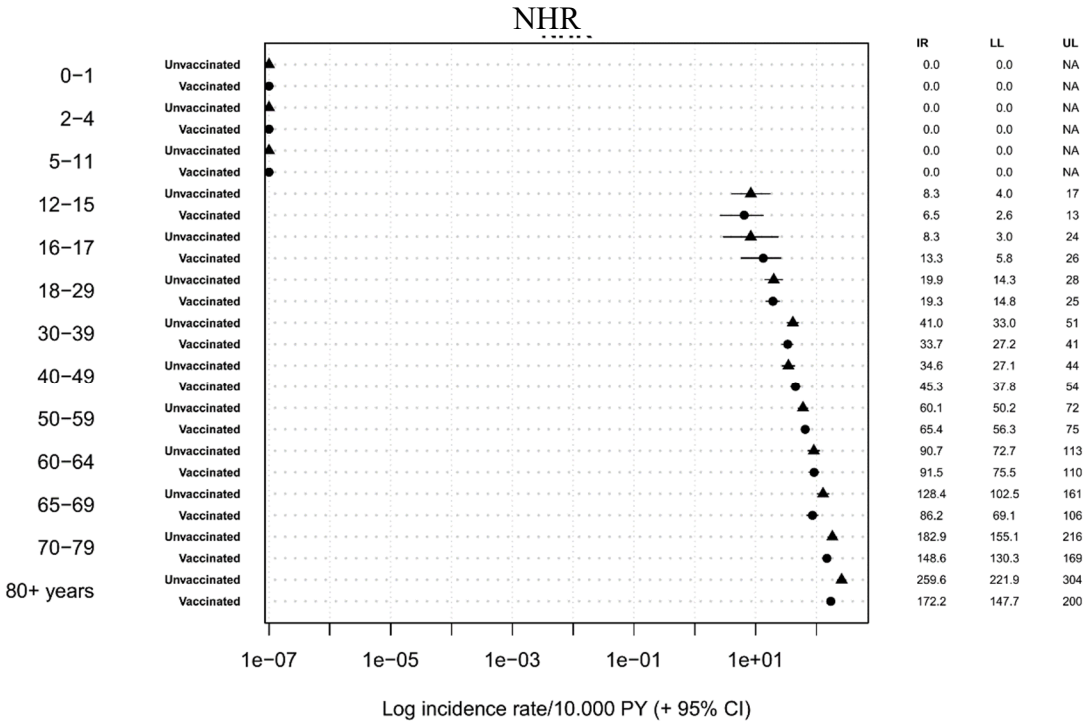
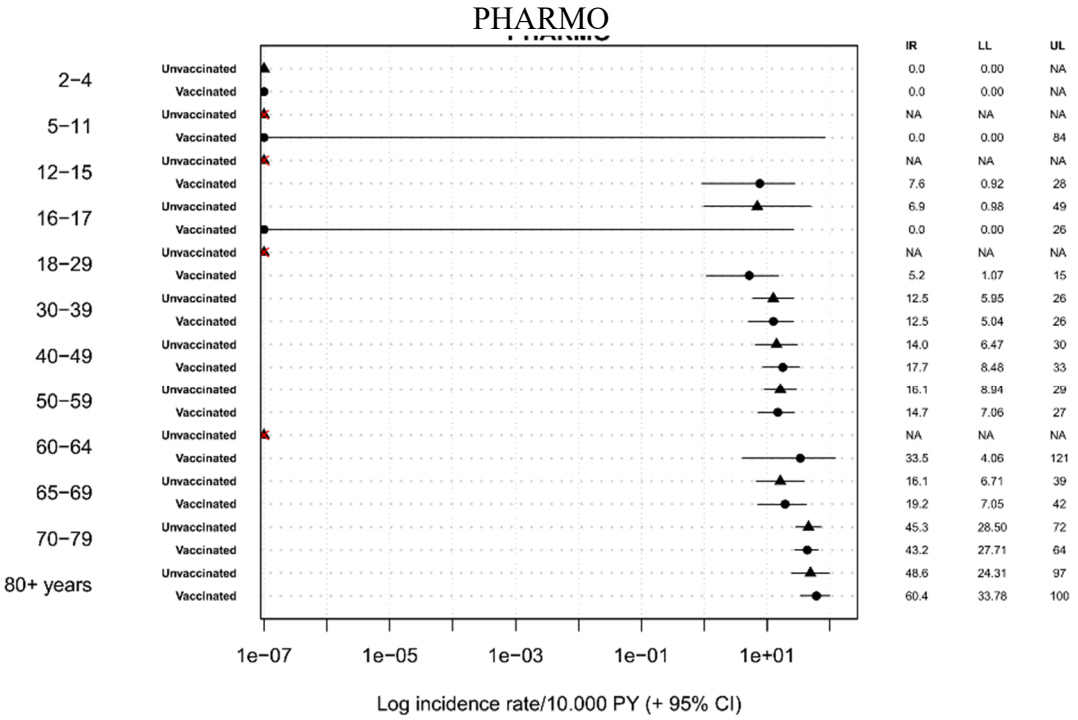


Figure 51. Forest plot showing incidence rates and 95% confidence intervals for coagulation disorders (thromboembolism, haemorrhage) within 28 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source and by age groups



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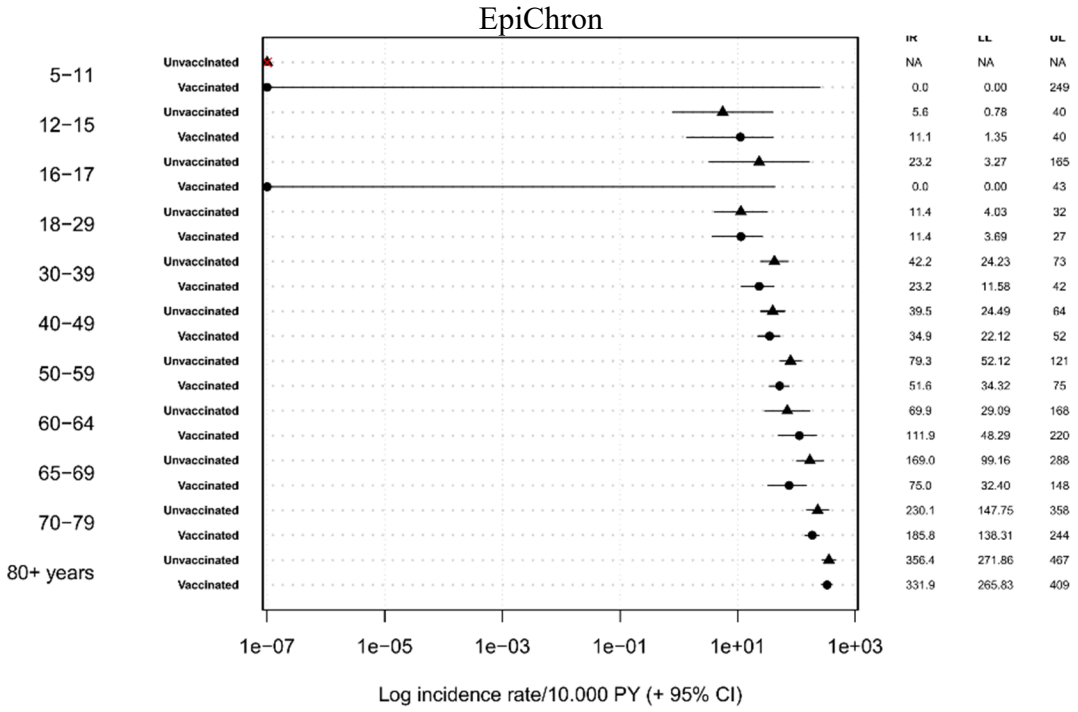

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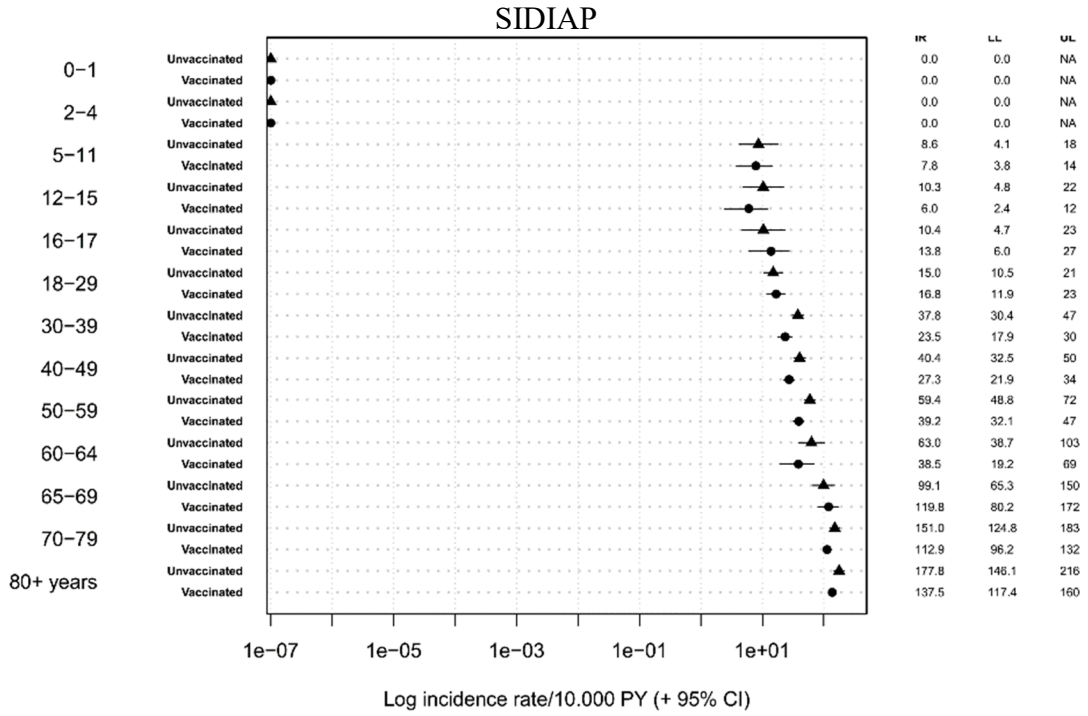


Table 60. Matched and adjusted hazard ratios (HRs) and matched and adjusted risk differences (RDs) per 10,000 person-years and their 95% CIs for coagulation disorders (thromboembolism, haemorrhage) within 28 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech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

	Matched HR (95% CI)	Adjusted HR (95% CI)	Matched RD	Adjusted RD
Pedianet	NA	NA	0	0
NHR	0.87 (0.79, 0.96)	0.87 (0.79, 0.95)	-0.57	-0.59
PHARMO	1.15 (0.81, 1.63)	1.07 (0.75, 1.53)	0.20	0.11
EpiChron	0.81 (0.65, 1)	0.78 (0.63, 0.97)	-1.41	-1.66
SIDIAP	0.74 (0.66, 0.83)	0.69 (0.61, 0.77)	-1	-1.26

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

10.3.19. Single organ cutaneous vasculitis

Single organ cutaneous vasculitis, which was a very rare event within the 28-day risk window, was identified in both cohorts in EpiChron and SIDIAP and in the unvaccinated cohort only in PHARMO, with <5 events. The incidence rates ranged from 0.29 per 10,000 person-years (95% CI: 0.09, 0.68) in SIDAP to 8.58 per 10,000 person-years (95% CI: 5.66, 12.49) in EpiChron in the vaccinated cohorts. In the unvaccinated cohorts these ranged from 0.25 per 10,000 person-years (95% CI: 0.03, 1.76) in PHARMO to 6.68 per 10,000 person-years (95% CI: 3.85, 11.60) in EpiChron. The cumulative incidence was below 1 per 10,000 individuals in both cohorts in both data sources. The incidence was similar in the different age groups.

The matched adjusted HRs were 1.28 (95% CI: 0.66, 2.48) in EpiChron, and 0.45 (95% CI: 0.14, 1.51) in SIDIAP. The adjusted HRs were 1.19 (95% CI: 0.62, 2.31) in EpiChron, and 0.44 (95% CI: 0.13, 1.48) in SIDIAP. No differences were observed for the incidence of single organ cutaneous vasculitis between the vaccinated and unvaccinated cohorts during the 28-day risk window.

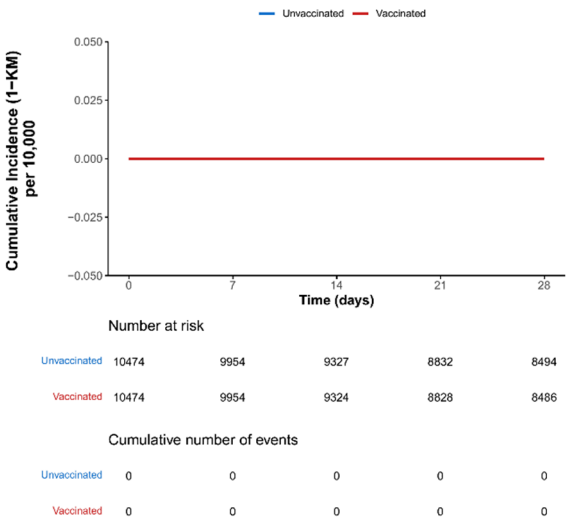
Table 61. Risk estimates (95% CI) per 10,000 person-years (PY) for single organ cutaneous vasculitis within 28 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source

	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)	0	0 (0, 0)	717.88	0 (0, 51.39)	0	0 (0, 0)	718.06	NA
NHR (Norway)	0	0 (0, 0)	184,974.64	0 (0, 0.20)	0	0 (0, 0)	184,834	NA
PHARMO (Netherlands)	0	0 (0, 0)	40,209.35	0 (0, 0.92)	<5	0.02 (0, 0.06)	40,307.66	0.25 (0.03, 1.76)
EpiChron (Spain)	27	0.67 (0.41, 0.93)	31,461.26	8.58 (5.66, 12.49)	21	0.51 (0.21, 0.81)	31,437.39	6.68 (3.85, 11.60)
SIDIAP (Spain)	5	0.02 (0, 0.04)	171,160.93	0.29 (0.09, 0.68)	11	0.06 (0.01, 0.10)	171,160.79	0.64 (0.28, 1.45)

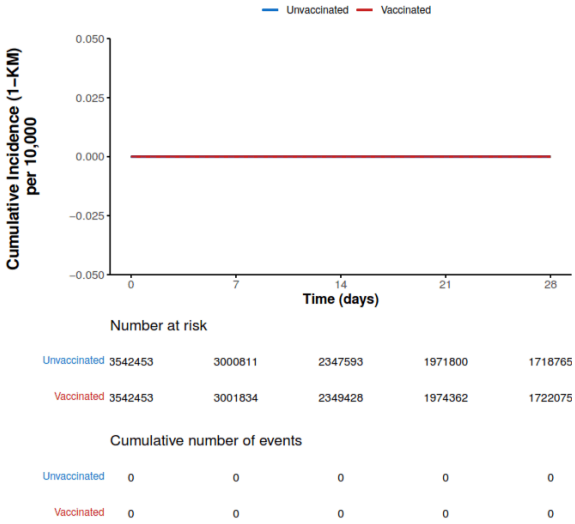
Note: Estimation of confidence intervals differs between vaccinated and unvaccinated, since the unvaccinated estimate is a GEE estimates (to account for individuals who were matched to more than one vaccinated individual). When NA (not-assessable) is listed for the 1-KM it means that there is no estimate 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 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

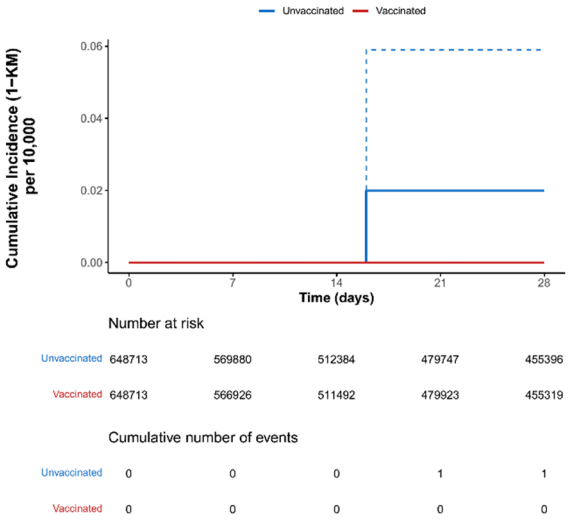
Pedianet



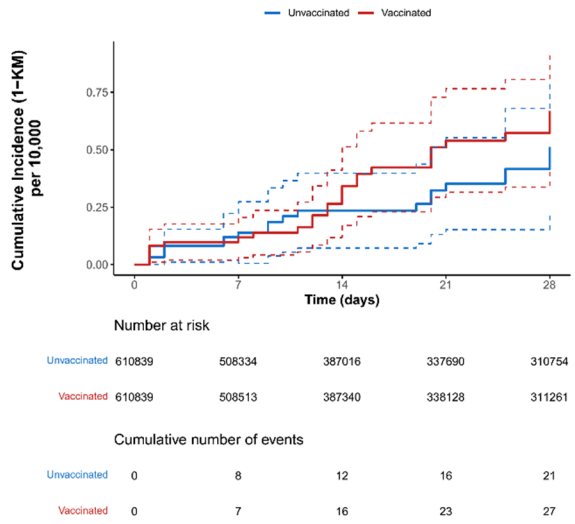
NHR



PHARMO

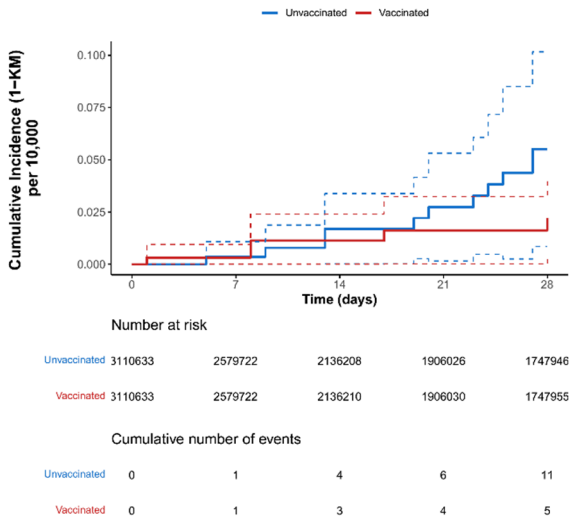


EpiChron



SIDIAP

Figure 52. 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 53. 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

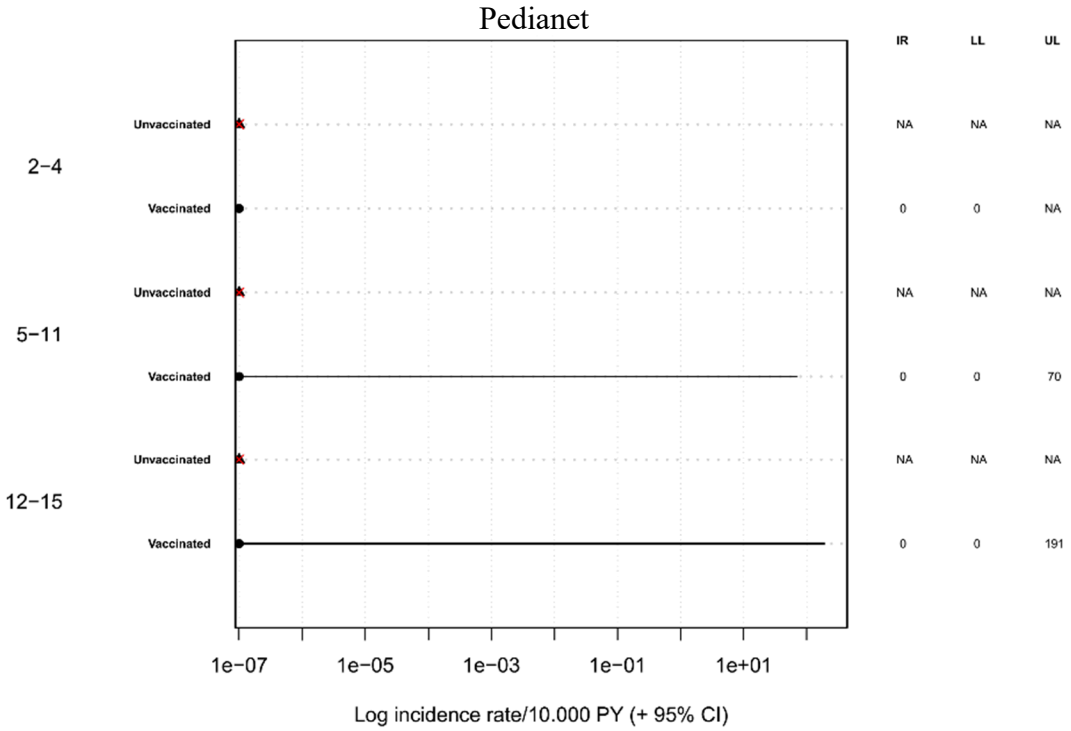


Figure 53. Forest plot showing incidence rates and 95% confidence intervals for single organ cutaneous vasculitis within 28 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source and by age groups

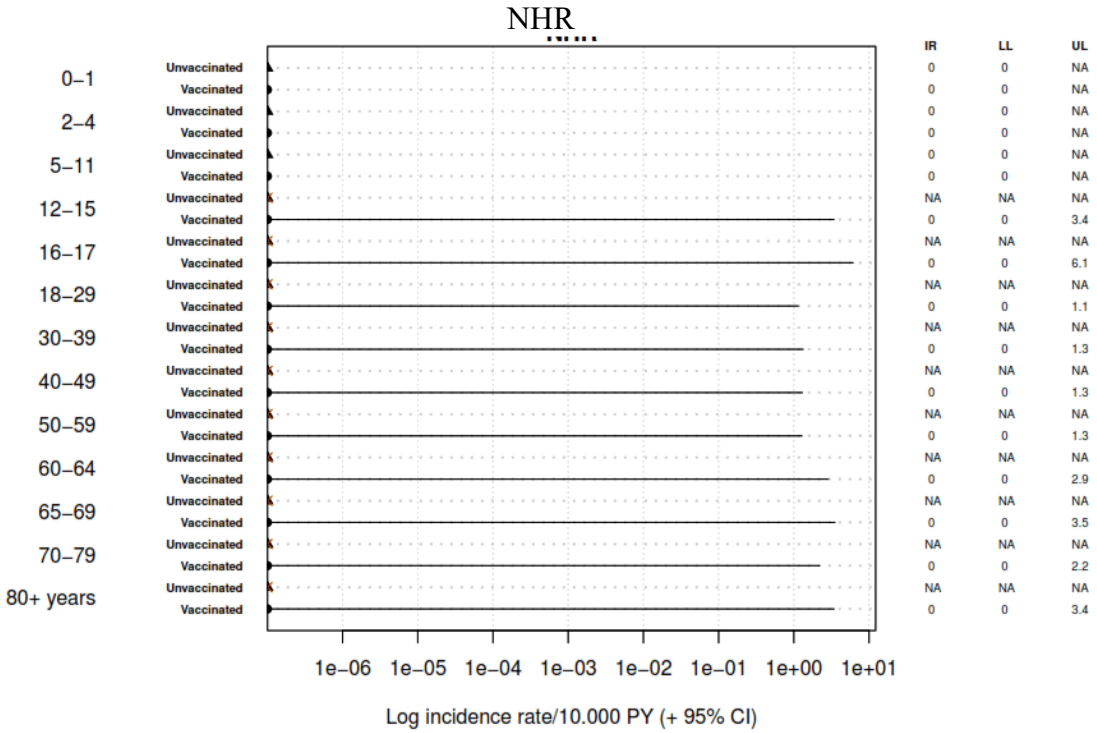


Figure 53. Forest plot showing incidence rates and 95% confidence intervals for single organ cutaneous vasculitis within 28 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source and by age groups

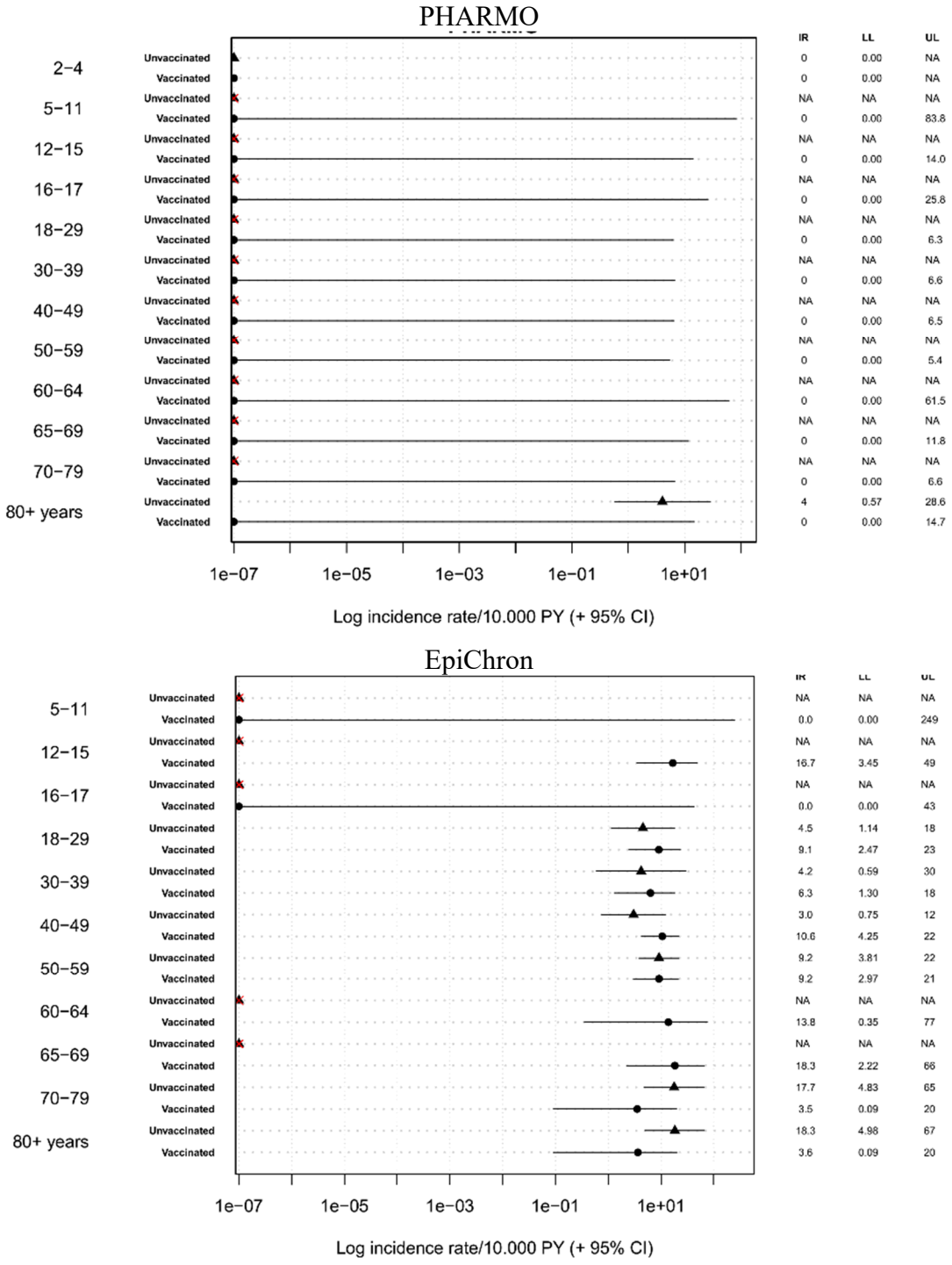


Figure 53. Forest plot showing incidence rates and 95% confidence intervals for single organ cutaneous vasculitis within 28 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source and by age groups

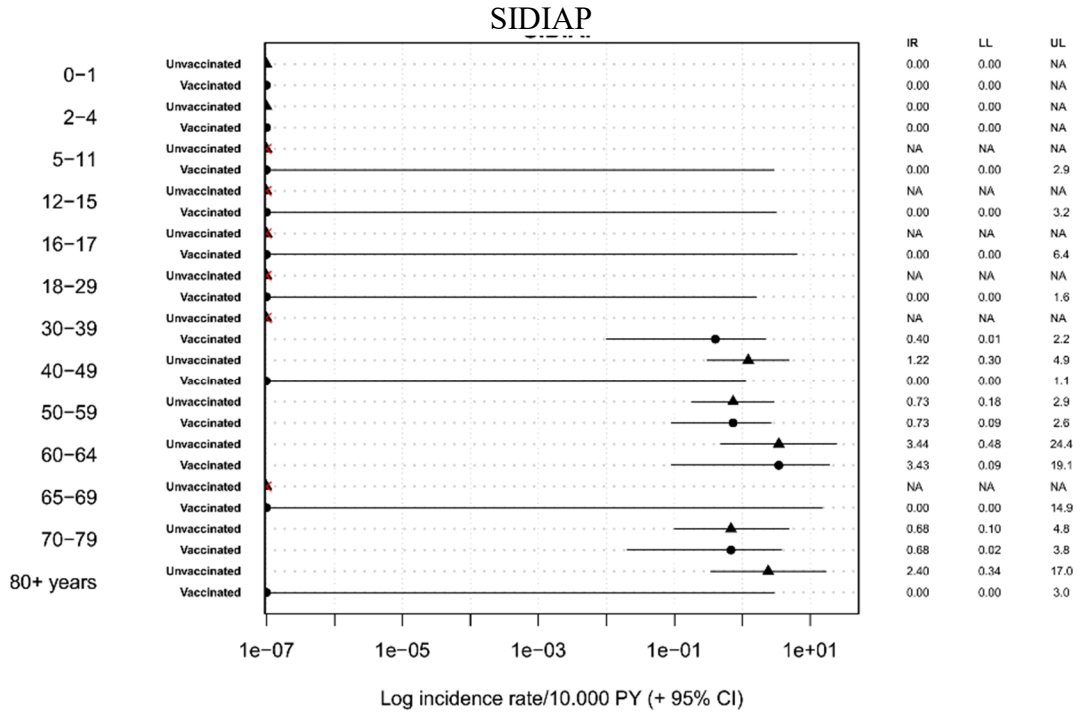


Table 62. Matched and adjusted hazard ratios (HRs) and matched and adjusted risk differences (RDs) per 10,000 person-years and their 95% CIs for single organ cutaneous vasculitis within 28 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source

	Matched HR (95% CI)	Adjusted HR (95% CI)	Matched RD	Adjusted RD
Pedianet	NA	NA	NA	NA
NHR	NA	NA	NA	NA
PHARMO	NA	NA	-0.02	-0.02
EpiChron	1.28 (0.66, 2.48)	1.19 (0.62, 2.31)	0.16	0.11
SIDIAP	0.45 (0.14, 1.51)	0.44 (0.13, 1.48)	-0.03	-0.03

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

10.3.20. Acute liver injury

Acute liver injury events were identified in all data sources except Pedianet. The incidence rates ranged from 0.20 per 10,000 person-years (95% CI: 0.07, 0.43) in PHARMO to 3.65 per 10,000 person-years (95% CI: 2.86, 4.59) in EpiChron in the vaccinated cohorts. In the unvaccinated cohorts these ranged from 0.62 per 10,000 person-years (95% CI: 0.32, 1.17) in PHARMO and 3.27 per 10,000 person-years (95% CI: 2.29, 4.66) in EpiChron. The cumulative incidence during the 365-day risk window was below 3.6 per 10,000 individuals in the vaccinated cohorts and below 3 per 10,000 individuals in the unvaccinated cohorts. The incidence was similar in the different age groups.

The matched HRs for acute liver injury were 0.97 (95% CI: 0.59, 1.60) in NHR, 0.33 (95% CI: 0.12, 0.91) in PHARMO, 1.12 (95% CI: 0.73, 1.71) in EpiChron, and 0.72 (95% CI: 0.54, 0.94) in SIDIAP. The adjusted HRs were 0.97 (95% CI: 0.59, 1.59) in NHR, 0.32 (95% CI: 0.11, 0.88) in PHARMO, 1.05 (95% CI: 0.69, 1.61) in EpiChron, and 0.63 (95% CI: 0.48, 0.83) in SIDIAP. No differences were observed for the incidence of acute liver injury between the vaccinated and unvaccinated cohorts during the 365-day risk window.

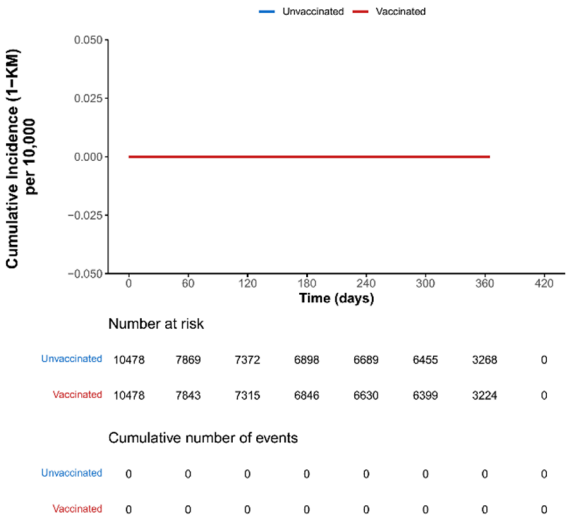
Table 63. Risk estimates (95% CI) per 10,000 person-years (PY) for acute liver injury within 365 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source

	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)	0	0 (0, 0)	6,973.34	0 (0, 5.29)	0	0 (0, 0)	7,016.93	NA
NHR (Norway)	63	1.49 (0.58, 2.40)	509,579.51	1.24 (0.95, 1.58)	64	1.31 (0.14, 2.47)	504,442.91	1.27 (0.83, 1.95)
PHARMO (Netherlands)	6	0.18 (0.03, 0.32)	302,872.61	0.20 (0.07, 0.43)	17	0.56 (0.21, 0.90)	276,168.62	0.62 (0.32, 1.17)
EpiChron (Spain)	73	3.57 (2.70, 4.43)	199,816.84	3.65 (2.86, 4.59)	65	2.88 (1.76, 4)	198,823.42	3.27 (2.29, 4.66)
SIDIAP (Spain)	133	1.35 (1.10, 1.60)	1,013,728.74	1.31 (1.10, 1.55)	186	1.61 (1.24, 1.97)	1,013,713.03	1.83 (1.48, 2.28)

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 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

Pedianet



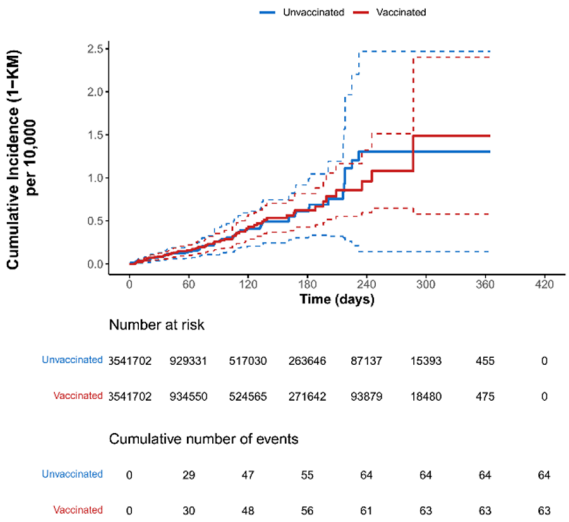
Number at risk

Unvaccinated	10478	7869	7372	6898	6689	6455	3268	0
Vaccinated	10478	7843	7315	6846	6630	6399	3224	0

Cumulative number of events

Unvaccinated	0	0	0	0	0	0	0	0
Vaccinated	0	0	0	0	0	0	0	0

NHR



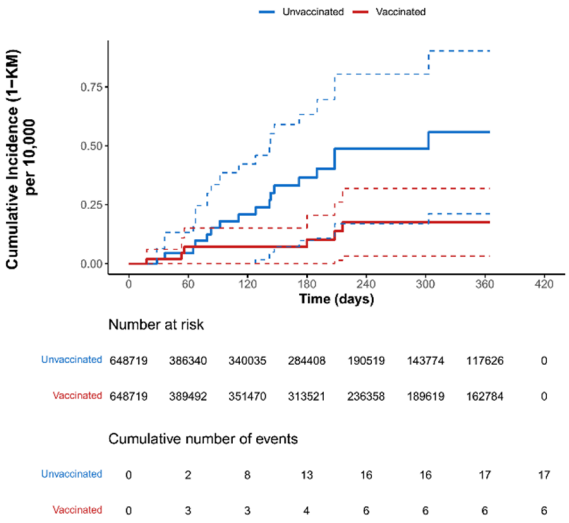
Number at risk

Unvaccinated	3541702	929331	517030	263646	87137	15393	455	0
Vaccinated	3541702	934550	524565	271642	93879	18480	475	0

Cumulative number of events

Unvaccinated	0	29	47	55	64	64	64	64
Vaccinated	0	30	48	56	61	63	63	63

PHARMO



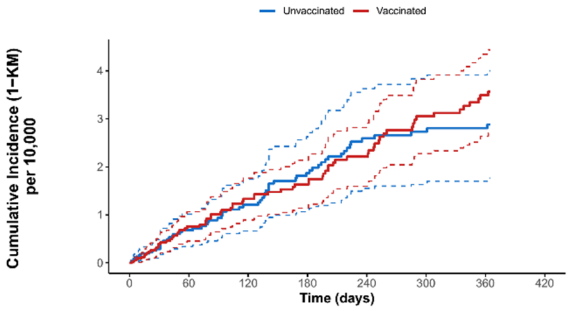
Number at risk

Unvaccinated	648719	386340	340035	284408	190519	143774	117626	0
Vaccinated	648719	389492	351470	313521	236358	189619	162784	0

Cumulative number of events

Unvaccinated	0	2	8	13	16	16	17	17
Vaccinated	0	3	3	4	6	6	6	6

EpiChron



Number at risk

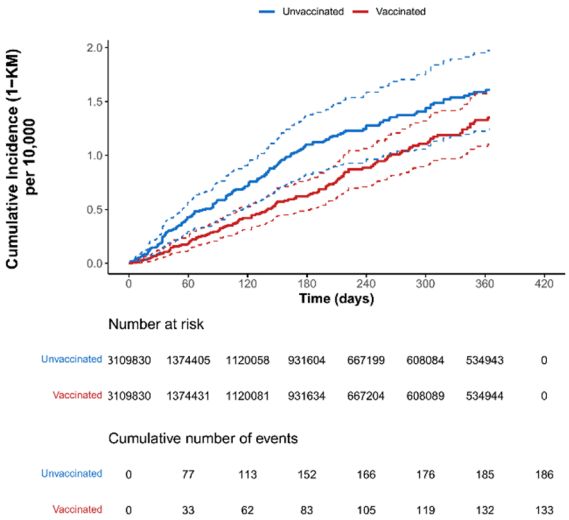
Unvaccinated	611060	250103	208950	181421	145603	138213	132008	0
Vaccinated	611060	250934	210175	182762	146693	139118	132927	0

Cumulative number of events

Unvaccinated	0	24	36	49	61	63	64	65
Vaccinated	0	25	38	44	54	66	72	73

Figure 54. 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

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 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 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

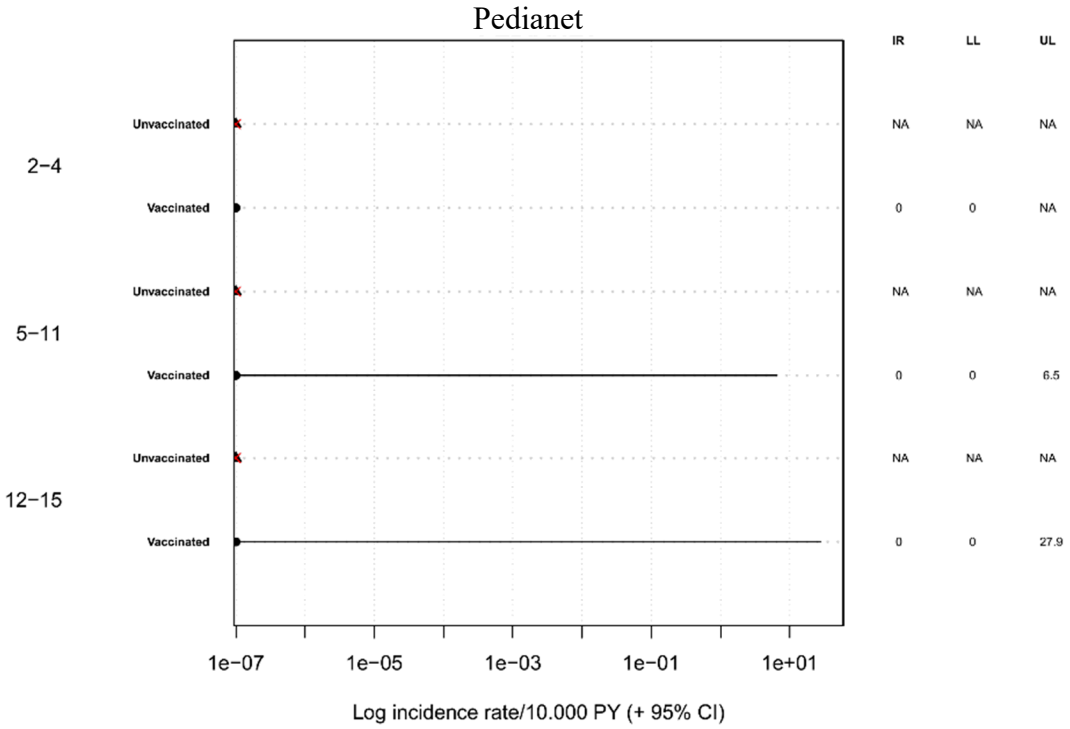


Figure 55. Forest plot showing incidence rates and 95% confidence intervals for acute liver injury within 365 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source and by age groups

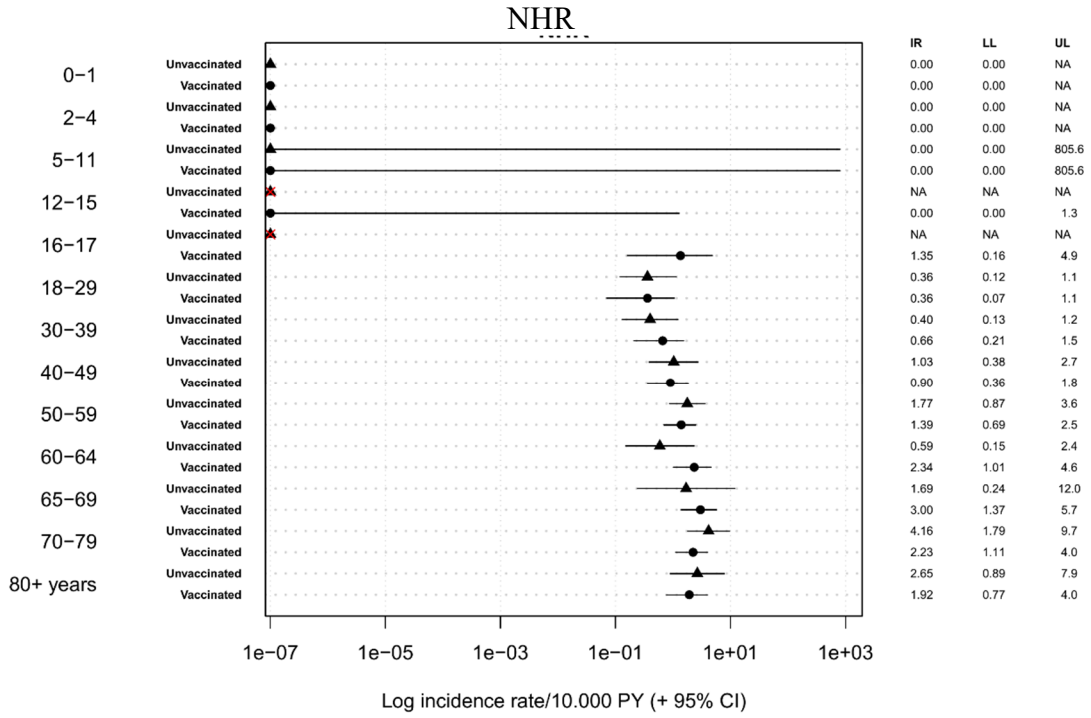


Figure 55. Forest plot showing incidence rates and 95% confidence intervals for acute liver injury within 365 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source and by age groups

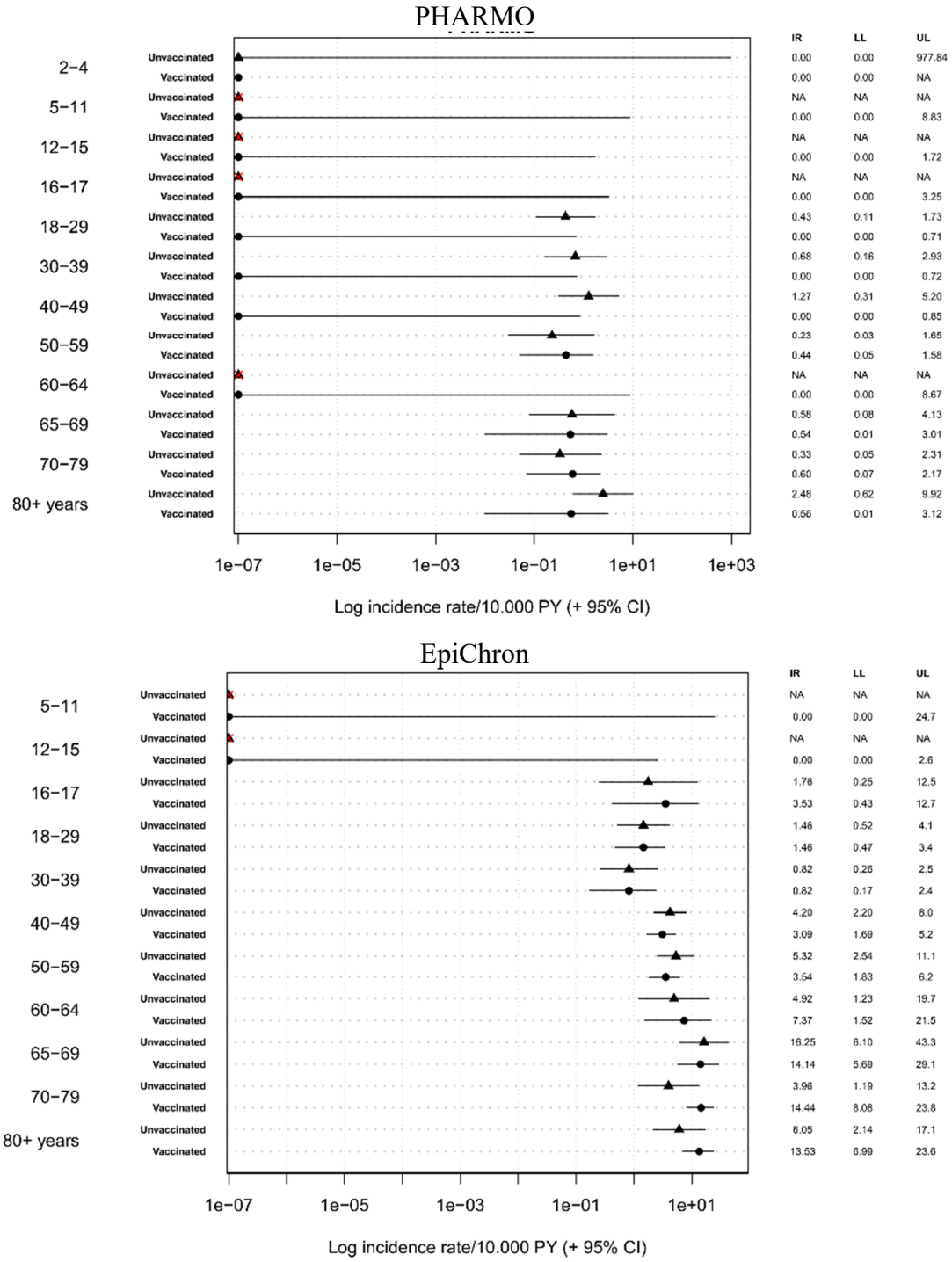


Figure 55. Forest plot showing incidence rates and 95% confidence intervals for acute liver injury within 365 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source and by age groups

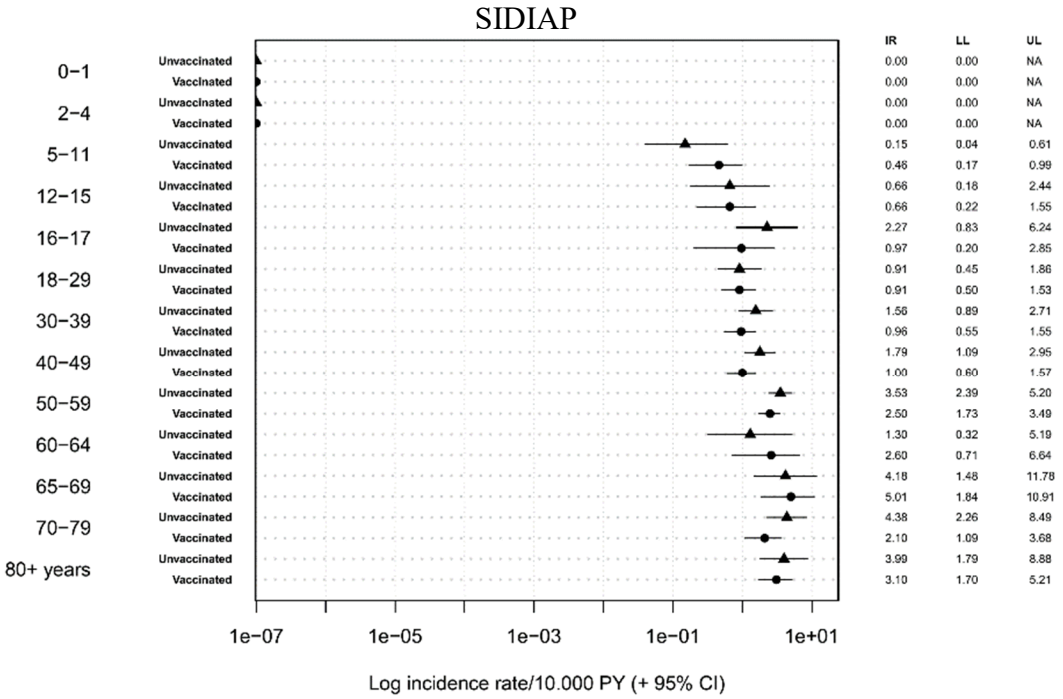


Table 64. Matched and adjusted hazard ratios (HRs) and matched and adjusted risk differences (RDs) per 10,000 person-years and their 95% CIs for acute liver injury within 365 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source

	Matched HR (95% CI)	Adjusted HR (95% CI)	Matched RD	Adjusted RD
Pedianet	NA	NA	NA	NA
NHR	0.97 (0.59, 1.60)	0.97 (0.59, 1.59)	0.18	0.18
PHARMO	0.33 (0.12, 0.91)	0.32 (0.11, 0.88)	-0.38	-0.39
EpiChron	1.12 (0.73, 1.71)	1.05 (0.69, 1.61)	0.69	0.54
SIDIAP	0.72 (0.54, 0.94)	0.63 (0.48, 0.83)	-0.26	-0.44

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 kidney injury

Acute kidney injury events within 365 days after the start of follow-up were identified in all data sources, except in Pedianet. The incidence rates ranged from 0.24 per 10,000 person-years (95% CI: 0, 0.41) in NHR to 33.93 per 10,000 person-years (95% CI: 31.42, 36.59) in EpiChron in the vaccinated cohorts. In the unvaccinated cohorts these ranged from 0.95 per 10,000 person-years (95% CI: 0.56, 1.62) in NHR to 35.21 per 10,000 person-years (95% CI: 33.44, 37.07) in SIDIAP. The cumulative incidence during the 365-day risk window was below 30.88 per 10,000 individuals in the vaccinated cohorts and below 35.21 per 10,000 individuals 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 0.24 (95% CI: 0.11, 0.52) in NHR, 0.97 (95% CI: 0.76, 1.22) in PHARMO, 0.96 (95% CI: 0.84, 1.11) in EpiChron, and 0.88 (95% CI: 0.82, 0.93) in SIDIAP. The adjusted HRs were 0.24 (95% CI: 0.11, 0.52) in NHR, 0.96 (95% CI: 0.76, 1.22) in PHARMO, 0.90 (95% CI: 0.78, 1.04) in EpiChron, and 0.81 (95% CI: 0.76, 0.86) in SIDIAP. No differences were observed for the incidence of acute kidney injury between the vaccinated and unvaccinated cohorts during the 365-day risk window.

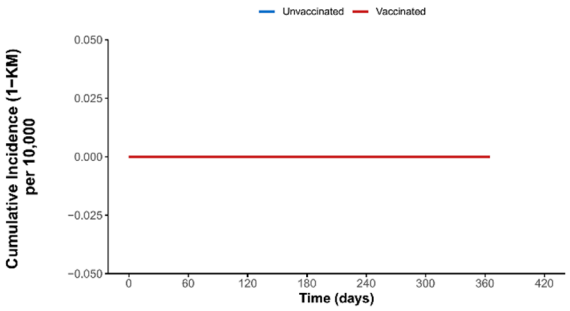
Table 65. Risk estimates (95% CI) per 10,000 person-years (PY) for acute kidney injury within 365 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source

	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)	0	0 (0, 0)	6,973.34	0 (0, 5.29)	0	0 (0, 0)	7,016.93	NA
NHR (Norway)	12	2.90 (0, 6.93)	509,718.47	0.24 (0.12, 0.41)	48	3.05 (0, 6.85)	504,569.80	0.95 (0.56, 1.62)
PHARMO (Netherlands)	196	5.81 (4.97, 6.65)	302,470.42	6.48 (5.60, 7.45)	191	5.87 (4.66, 7.08)	275,841.87	6.92 (5.73, 8.37)
EpiChron (Spain)	675	30.88 (28.39, 33.37)	198,949.76	33.93 (31.42, 36.59)	697	30.78 (26.72, 34.83)	198,081.13	35.19 (31.20, 39.68)
SIDIAP (Spain)	3,108	29.90 (28.75, 31.05)	1,006,639.08	30.88 (29.80, 31.98)	3,544	31.65 (29.91, 33.38)	1,006,608.91	35.21 (33.44, 37.07)

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 56. 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

Pedianet



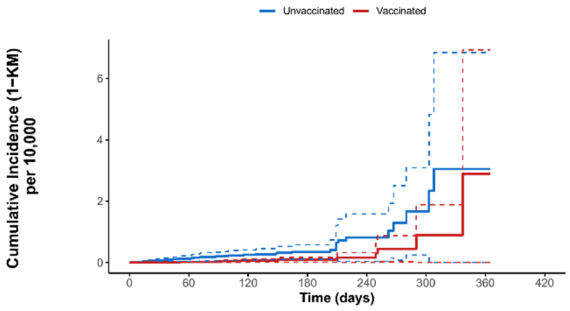
Number at risk

Unvaccinated	10478	7869	7372	6898	6689	6455	3268	0
Vaccinated	10478	7843	7315	6846	6630	6399	3224	0

Cumulative number of events

Unvaccinated	0	0	0	0	0	0	0	0
Vaccinated	0	0	0	0	0	0	0	0

NHR



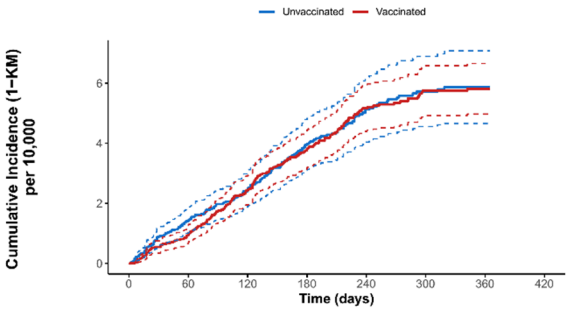
Number at risk

Unvaccinated	3542453	929559	517162	263732	87183	15404	455	0
Vaccinated	3542453	934790	524709	271748	93942	18494	475	0

Cumulative number of events

Unvaccinated	0	24	33	37	43	46	48	48
Vaccinated	0	3	6	7	8	11	12	12

PHARMO



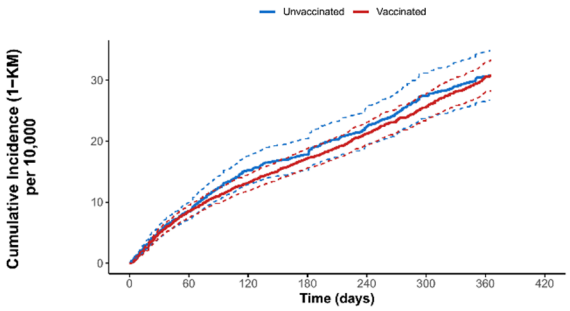
Number at risk

Unvaccinated	647979	385898	339619	283993	190231	143668	117592	0
Vaccinated	647979	389022	351000	313047	235960	189386	162629	0

Cumulative number of events

Unvaccinated	0	68	106	153	179	189	191	191
Vaccinated	0	47	100	146	183	195	196	196

EpiChron



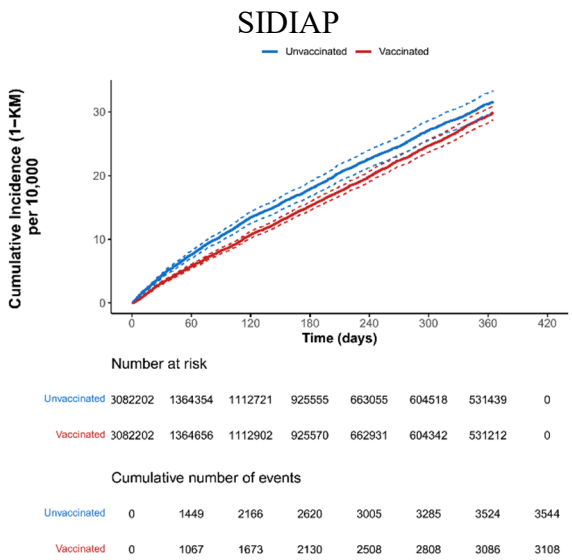
Number at risk

Unvaccinated	607156	249053	208327	180917	145195	137835	131654	0
Vaccinated	607156	249824	209438	182090	146106	138592	132387	0

Cumulative number of events

Unvaccinated	0	301	455	505	582	652	695	697
Vaccinated	0	290	397	476	542	604	671	675

Figure 56. 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 57. 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

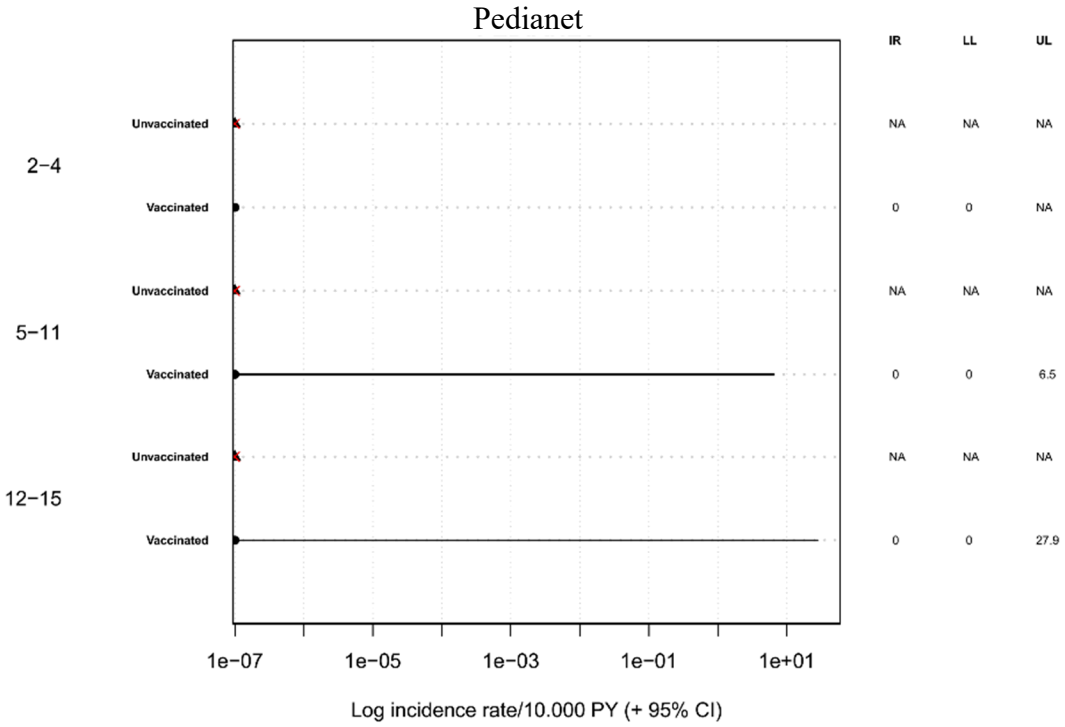


Figure 57. Forest plot showing incidence rates and 95% confidence intervals for acute kidney injury within 365 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source and by age groups

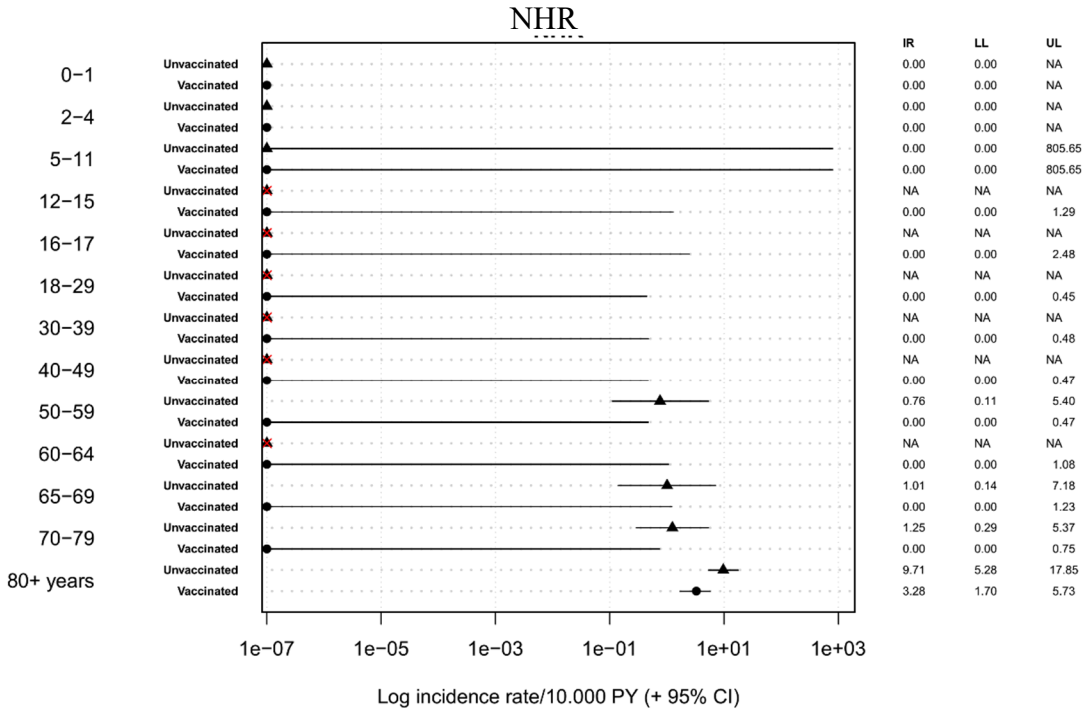


Figure 57. Forest plot showing incidence rates and 95% confidence intervals for acute kidney injury within 365 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source and by age groups

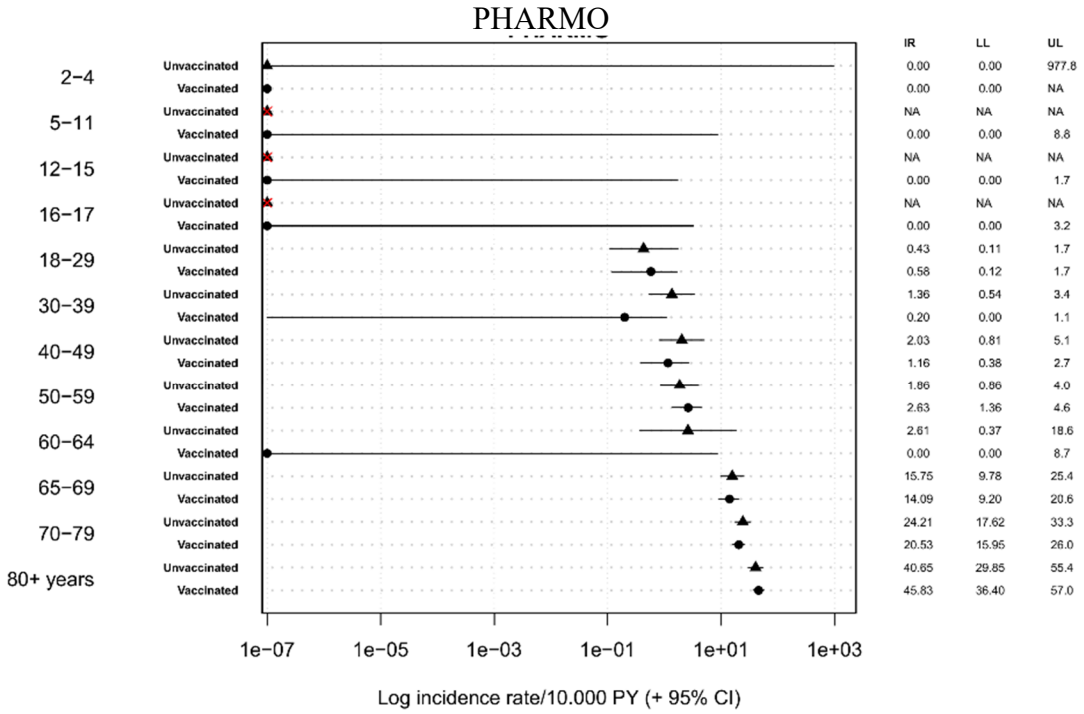


Figure 57. Forest plot showing incidence rates and 95% confidence intervals for acute kidney injury within 365 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source and by age groups

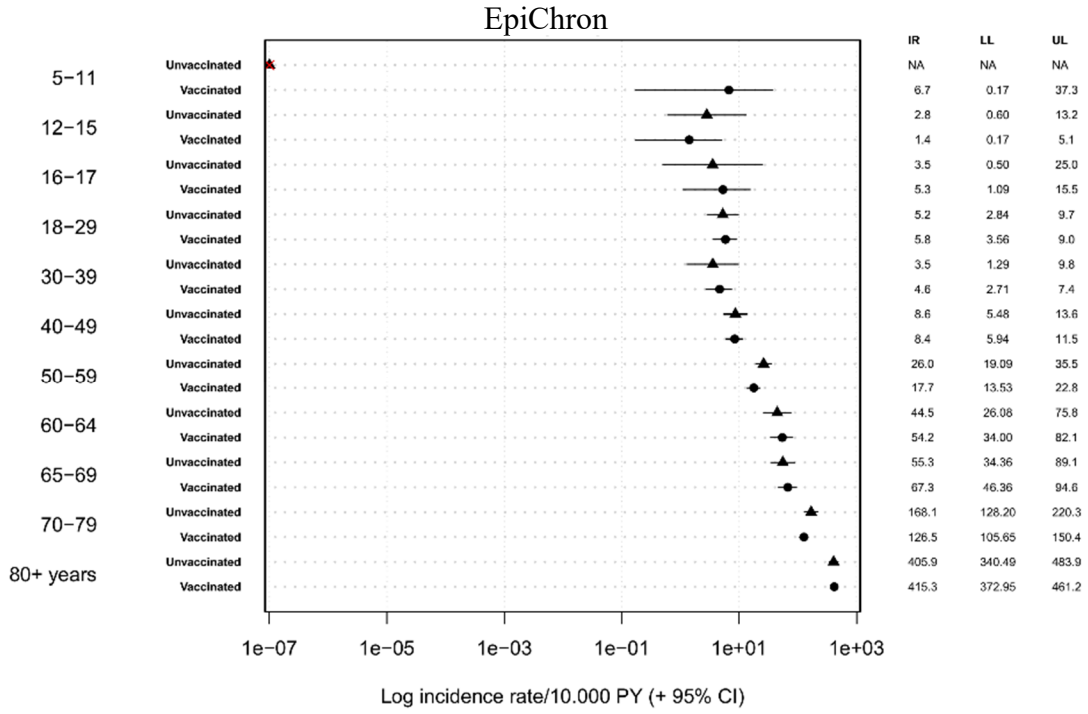


Figure 57. Forest plot showing incidence rates and 95% confidence intervals for acute kidney injury within 365 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source and by age groups

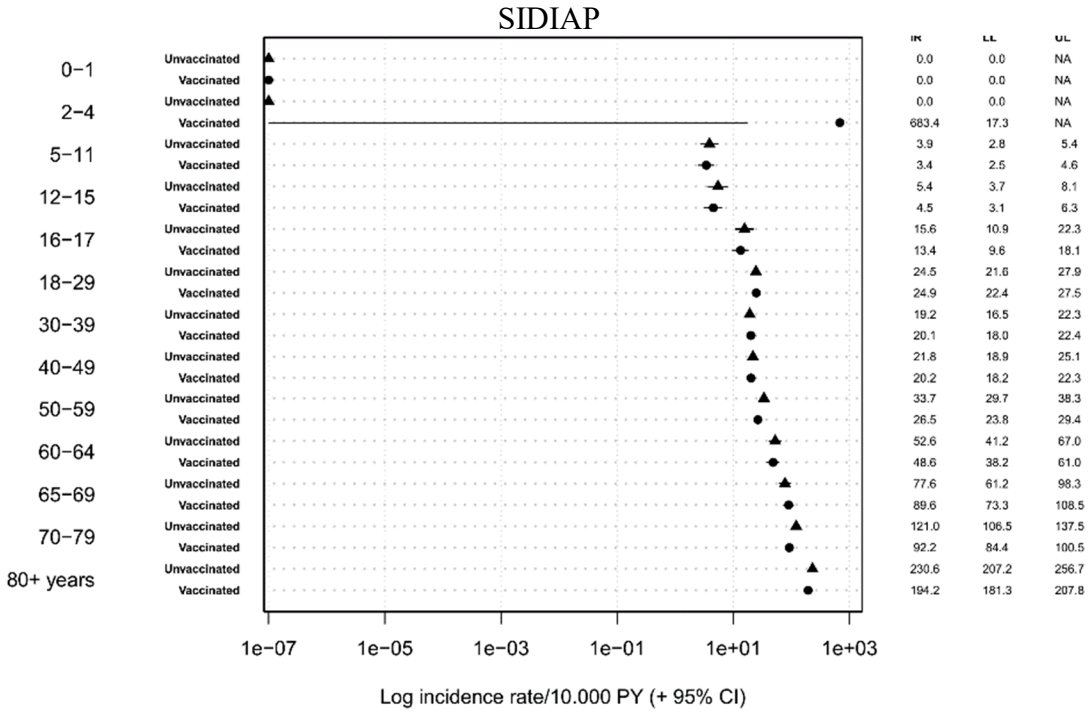


Table 66. Matched and adjusted hazard ratios (HRs) and matched and adjusted risk differences (RDs) per 10,000 person-years and their 95% CIs for acute kidney injury within 365 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source

	Matched HR (95% CI)	Adjusted HR (95% CI)	Matched RD	Adjusted RD
Pedianet	NA	NA	NA	NA
NHR	0.24 (0.11, 0.53)	0.24 (0.11, 0.52)	-0.16	-0.18
PHARMO	0.97 (0.76, 1.22)	0.96 (0.76, 1.22)	-0.06	-0.03
EpiChron	0.96 (0.84, 1.11)	0.90 (0.78, 1.04)	0.11	-2.31
SIDIAP	0.88 (0.82, 0.93)	0.81 (0.76, 0.86)	-1.75	-4.17

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

10.3.22. Acute pancreatitis

Acute pancreatitis events were identified in all data sources except Pedianet. The incidence rates ranged from 0.16 per 10,000 person-years (95% CI: 0.07, 0.31) in NHR to 5.06 per 10,000 person-years (95% CI: 4.12, 6.15) in EpiChron in the vaccinated cohorts. In the unvaccinated cohorts these ranged from 0.16 per 10,000 person-years (95% CI: 0.06, 0.40) in NHR to 4.72 per 10,000 person-years (95% CI: 4.12, 5.40) in SIDIAP. The cumulative incidence during the 365-day risk window was less than 5 per 10,000 individuals in the vaccinated cohorts and less than 4.8 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.

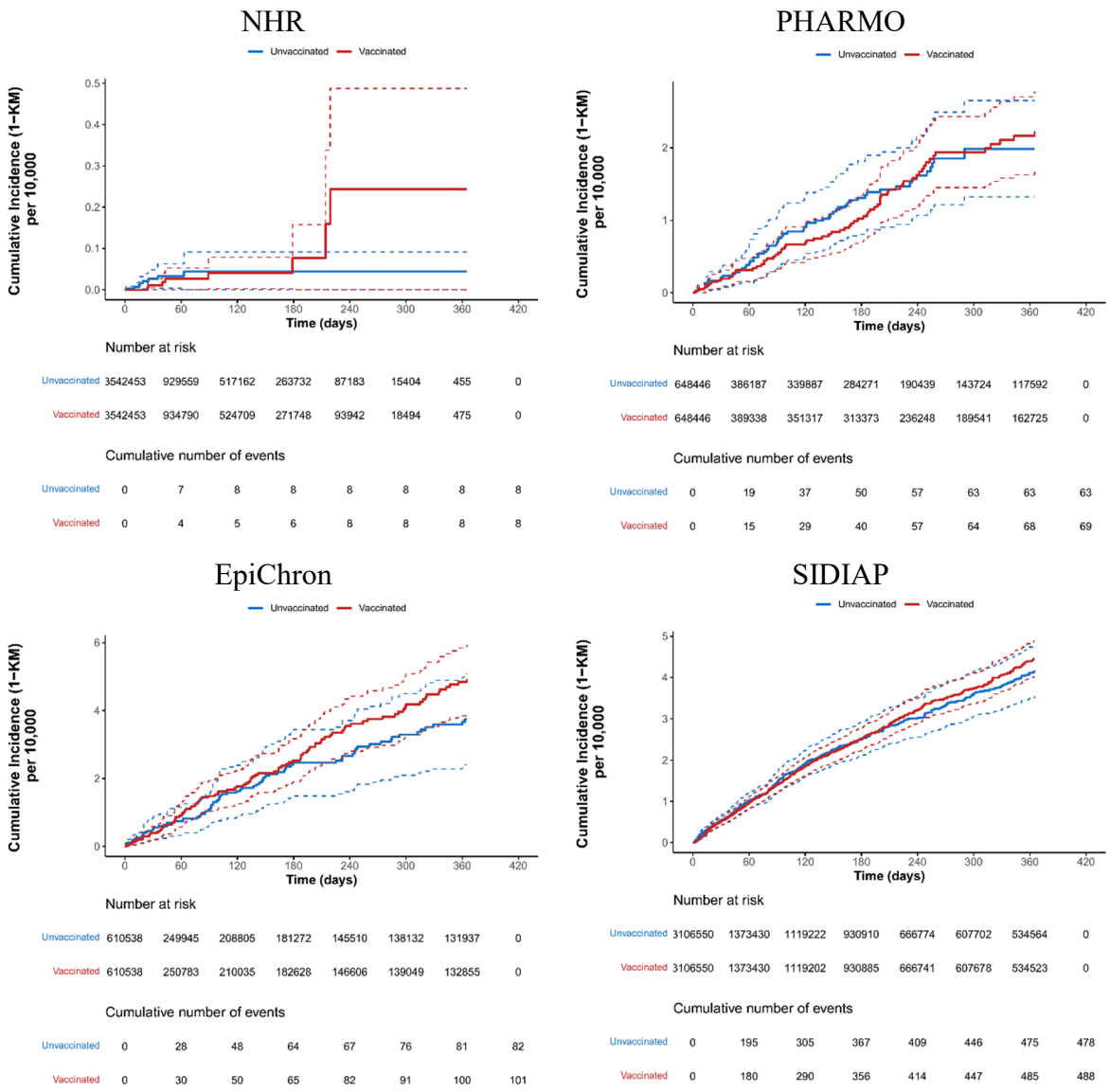
The matched unadjusted HRs were 0.99 (95% CI: 0.31, 3.10) in NHR, 1.01 (95% CI: 0.68, 1.51) in PHARMO, 1.23 (95% CI: 0.83, 1.80) in EpiChron, and 1.02 (95% CI: 0.87, 1.20) in SIDIAP. The adjusted HRs were 0.98 (95% CI: 0.31, 3.08) in NHR, 0.96 (95% CI: 0.64, 1.43) in PHARMO, 1.14 (95% CI: 0.77, 1.68) in EpiChron, and 0.95 (95% CI: 0.80, 1.11) in SIDIAP. No differences were observed for the incidence of acute pancreatitis between the vaccinated and unvaccinated cohorts during the 365-day risk window.

Table 67. 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

	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)	NA	NA	NA	NA	NA	NA	NA	NA
NHR (Norway)	8	0.24 (0, 0.49)	509,718.47	0.16 (0.07, 0.31)	8	0.04 (0, 0.09)	504,569.80	0.16 (0.06, 0.40)
PHARMO (Netherlands)	69	2.23 (1.68, 2.78)	302,741.63	2.28 (1.77, 2.88)	63	1.99 (1.32, 2.65)	276,052.96	2.28 (1.64, 3.17)
EpiChron (Spain)	101	4.92 (3.91, 5.93)	199,687.29	5.06 (4.12, 6.15)	82	3.74 (2.40, 5.08)	198,686.38	4.13 (2.95, 5.78)
SIDIAP (Spain)	488	4.45 (4.02, 4.88)	1,012,933.93	4.82 (4.40, 5.26)	478	4.17 (3.54, 4.81)	1,012,954.85	4.72 (4.12, 5.40)

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 58. 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 59. 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

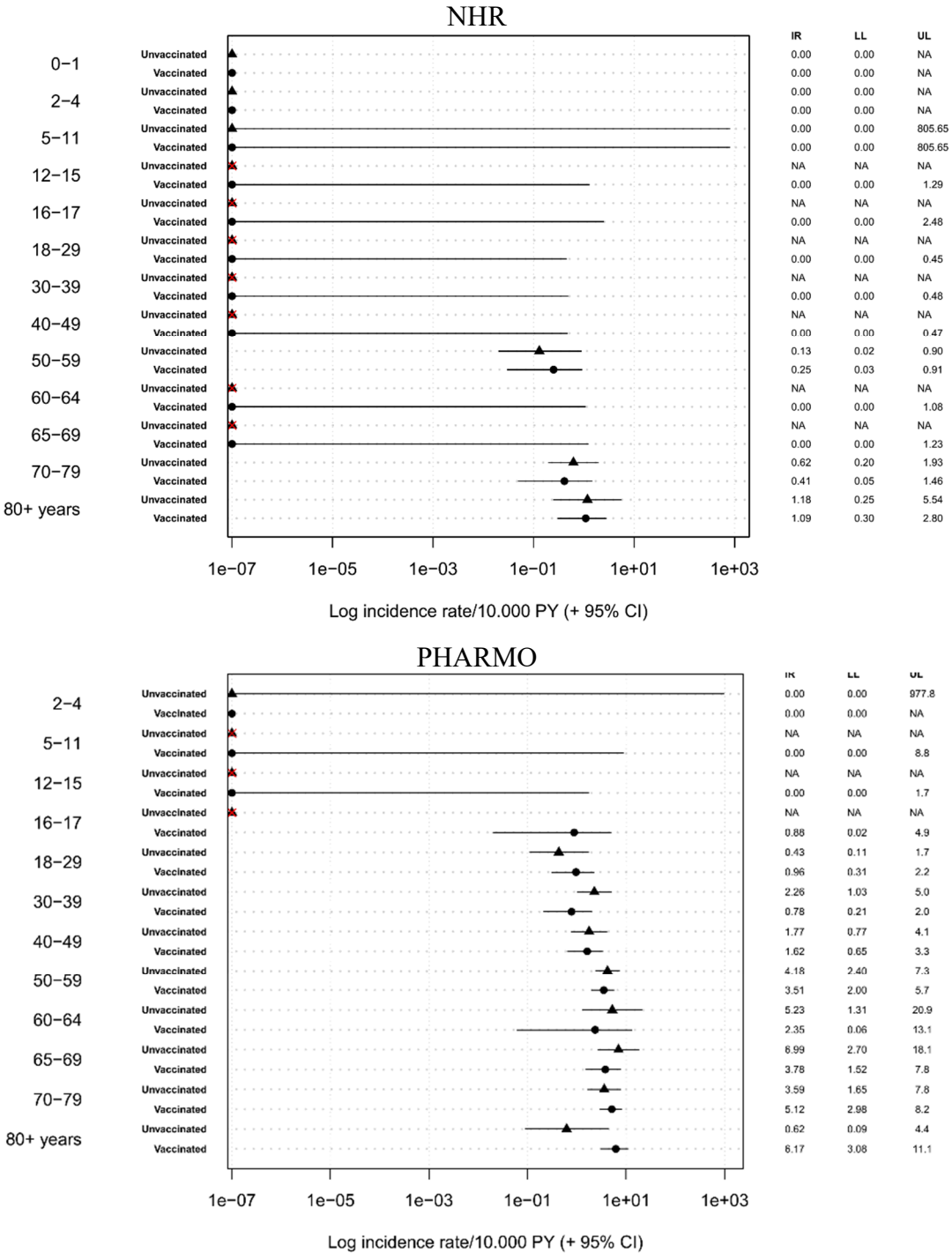


Figure 59. Forest plot showing incidence rates and 95% confidence intervals for acute pancreatitis within 365 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source and by age groups

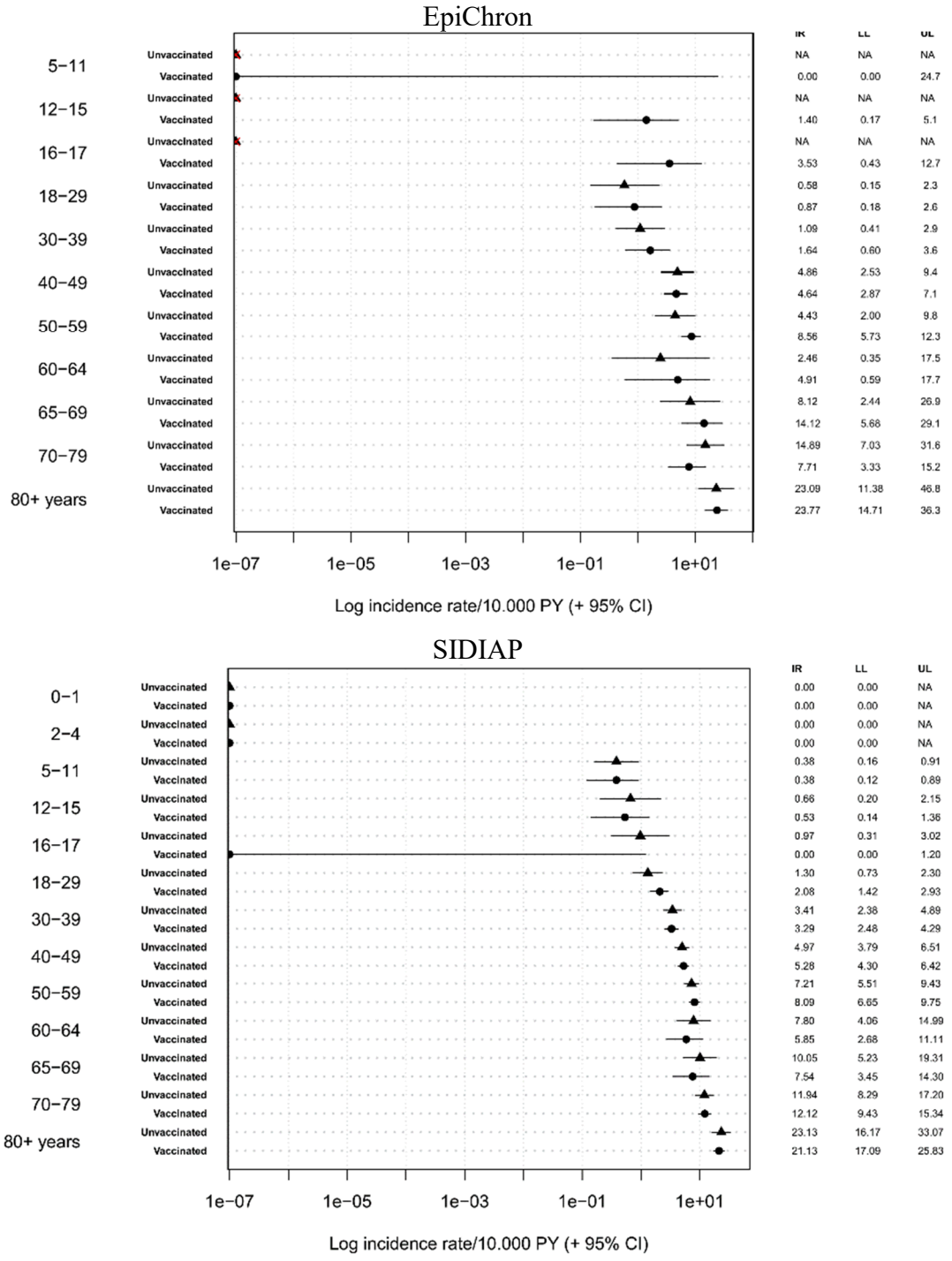


Table 68. Matched and adjusted hazard ratios (HRs) and matched and adjusted risk differences (RDs) per 10,000 person-years and their 95% CIs for acute pancreatitis within 365 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source

	Matched HR (95% CI)	Adjusted HR (95% CI)	Matched RD	Adjusted RD
Pedianet	NA	NA	NA	NA
NHR	0.99 (0.31, 3.10)	0.98 (0.31, 3.08)	0.20	0.20
PHARMO	1.01 (0.68, 1.51)	0.96 (0.64, 1.43)	0.24	0.12
EpiChron	1.23 (0.83, 1.80)	1.14 (0.77, 1.68)	1.18	0.86
SIDIAP	1.02 (0.87, 1.20)	0.95 (0.80, 1.11)	0.28	-0.05

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

10.3.23. Rhabdomyolysis

Rhabdomyolysis events were reported in all data sources except Pedianet. The incidence rates ranged from 0.02 per 10,000 person-years (95% CI: 0, 0.11) in NHR to 1.70 per 10,000 person-years (95% CI: 1.18, 2.38) in EpiChron in the vaccinated cohorts. In the unvaccinated cohorts the incidence rates ranged from 0.07 per 10,000 person-years (95% CI: 0.01, 0.51) in PHARMO to 2.39 per 10,000 person-years (95% CI: 1.92, 2.96) in SIDIAP. The cumulative incidence was below 1.7 per 10,000 individuals in the vaccinated cohorts and 2.2 in the unvaccinated cohorts. The incidence of rhabdomyolysis was higher in older age groups.

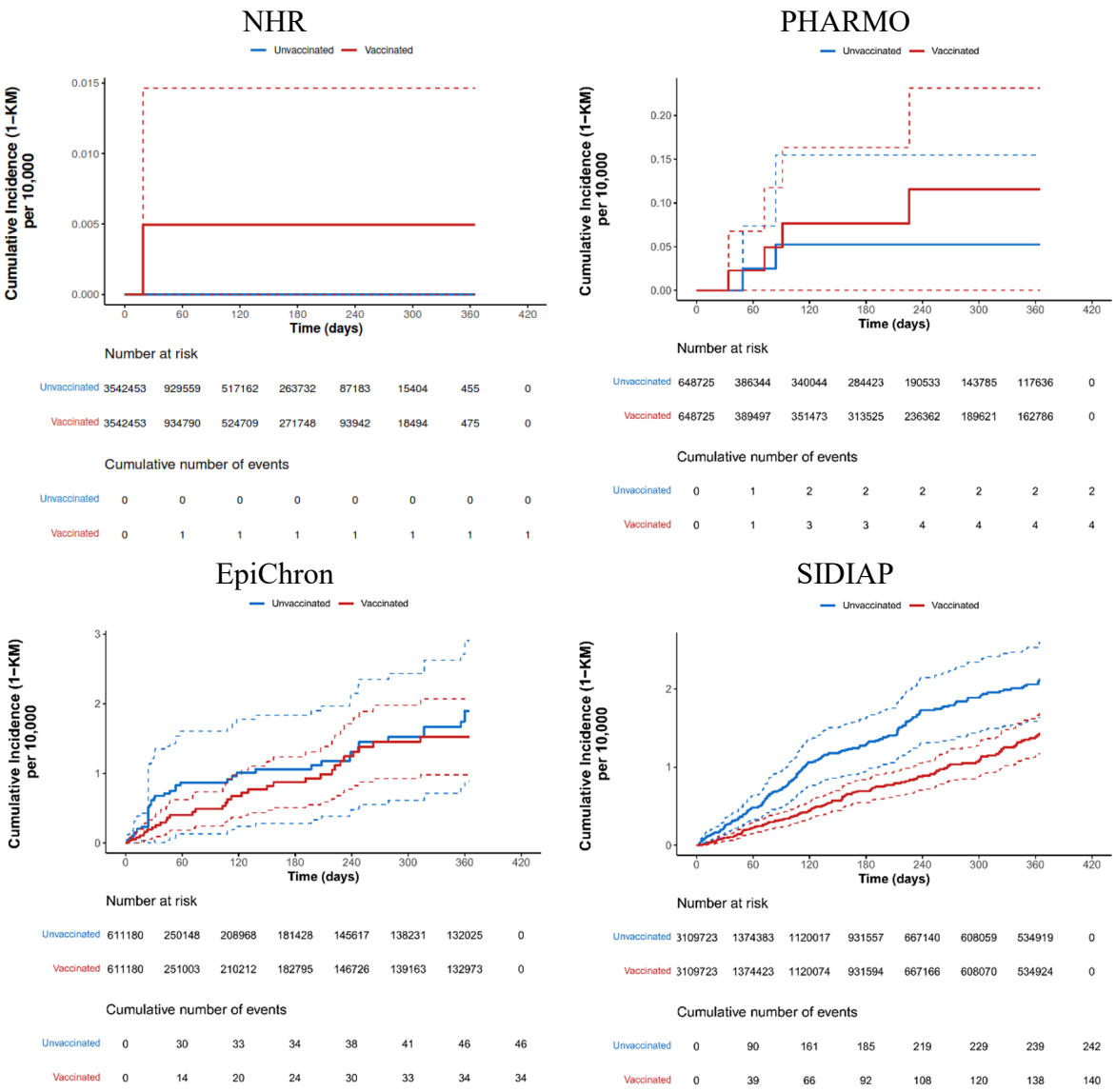
The matched HRs were 1.92 (95% CI: 0.22, 16.86) in PHARMO, 0.74 (95% CI: 0.38, 1.42) in EpiChron and 0.58 (95% CI: 0.44, 0.76) in SIDIAP. The adjusted HRs were 1.88 (95% CI: 0.21, 16,58), 0.69 (95% CI: 0.35, 1.34) in EpiChron and 0.57 (95% CI: 0.43, 0.74) in SIDIAP. No differences were observed for the incidence of rhabdomyolysis between the vaccinated and unvaccinated cohorts during the 365-day risk window.

Table 69. 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)

	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)	NA	NA	NA	NA	NA	NA	NA	NA
NHR (Norway)	<5	0 (0, 0.01)	509,718.47	0.02 (0, 0.11)	0	0 (0, 0)	504,569.80	NA
PHARMO (Netherlands)	<5	0.12 (0, 0.23)	302,876.02	0.13 (0.04, 0.34)	<5	0.05 (0, 0.15)	276,179	0.07 (0.01, 0.51)
EpiChron (Spain)	34	1.53 (0.98, 2.07)	199,864.01	1.70 (1.18, 2.38)	46	1.90 (0.89, 2.91)	198,848.14	2.31 (1.31, 4.08)
SIDIAP (Spain)	140	1.43 (1.17, 1.68)	1,013,702.35	1.38 (1.16, 1.63)	242	2.12 (1.64, 2.59)	1,013,674.15	2.39 (1.92, 2.96)

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 60. 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.

Figure 61. 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)

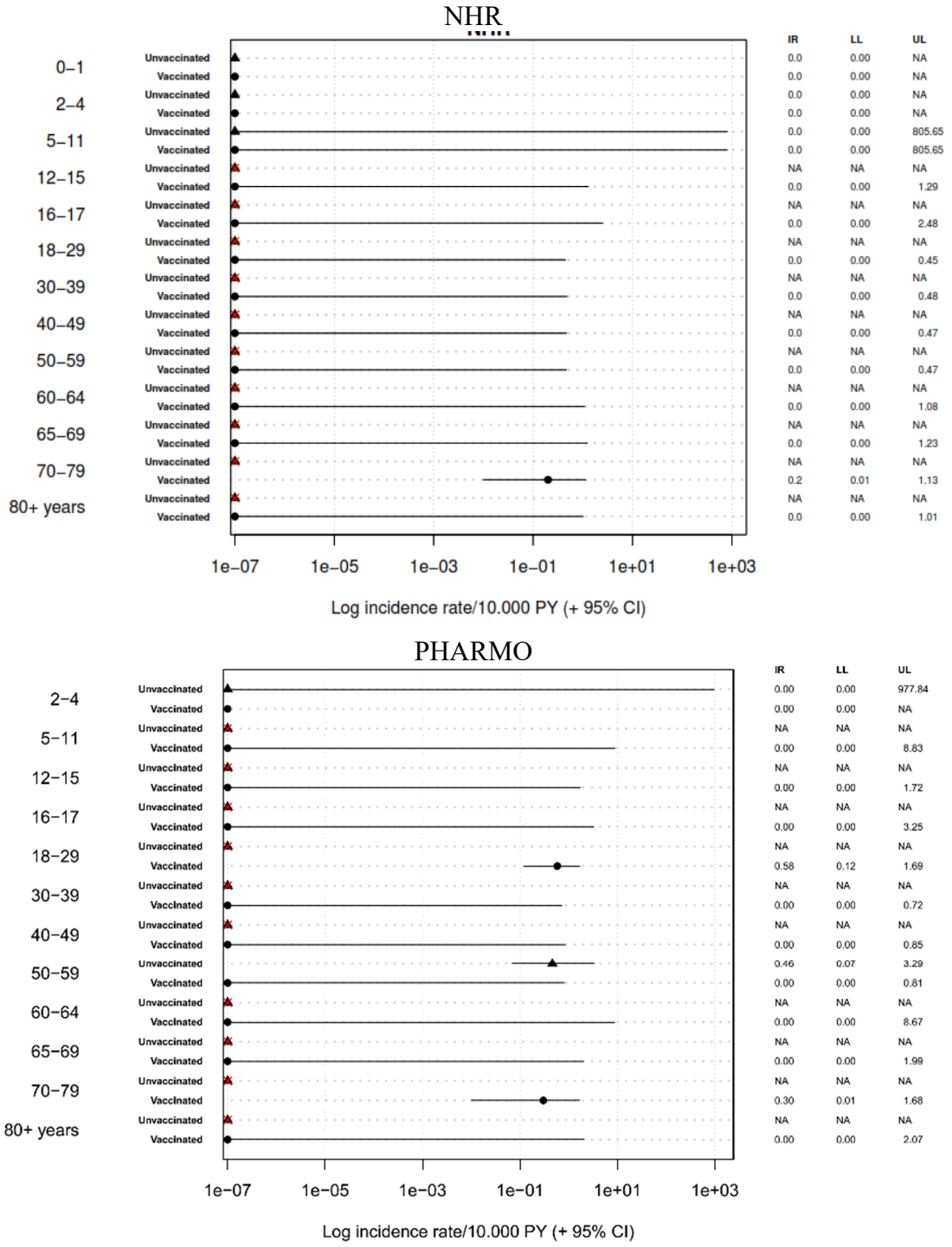


Figure 61. Forest plot showing incidence rates and 95% confidence intervals for rhabdomyolysis among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source and by age groups (risk window: 365 days after dose 1)

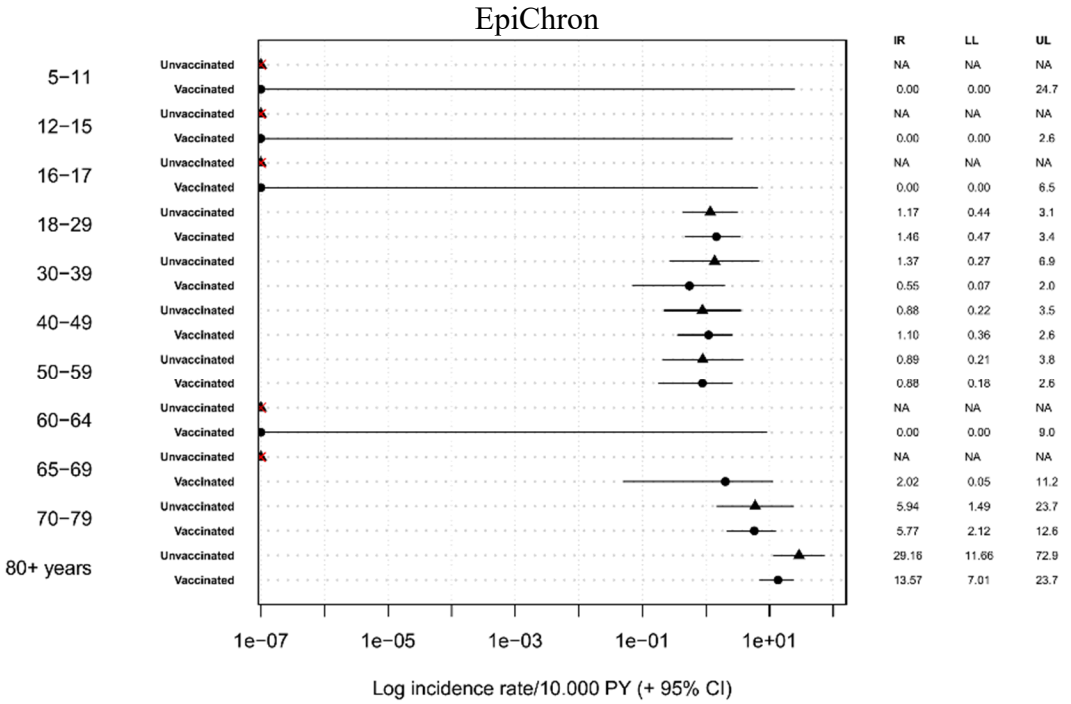


Figure 61. Forest plot showing incidence rates and 95% confidence intervals for rhabdomyolysis among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source and by age groups (risk window: 365 days after dose 1)

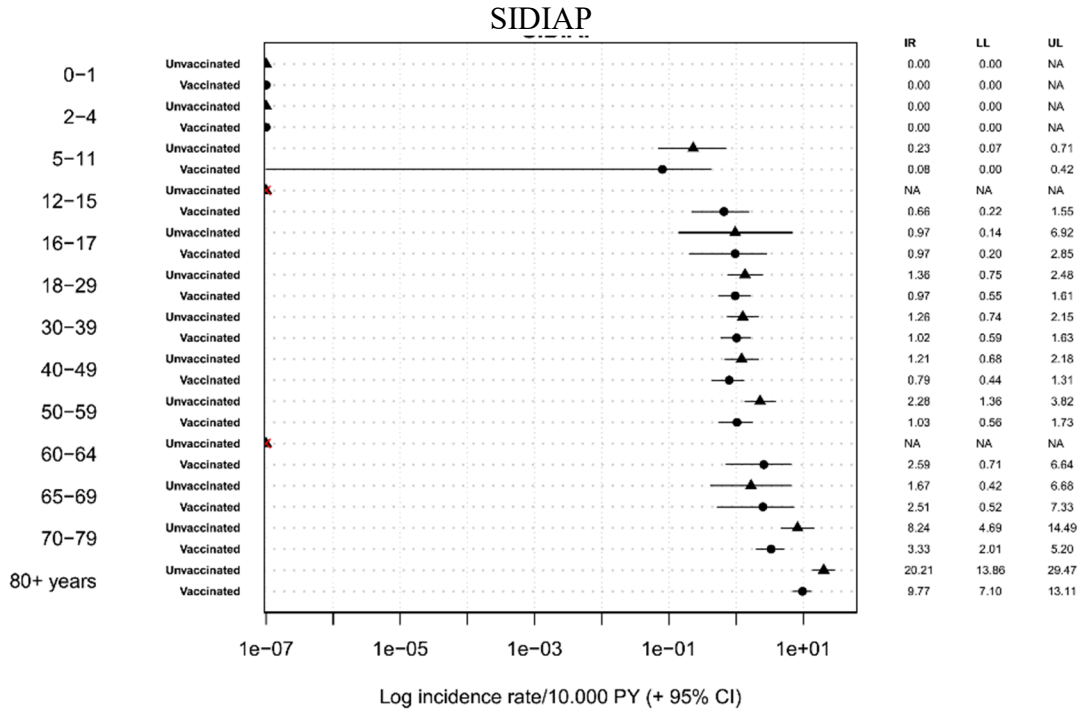


Table 70. Matched and adjusted hazard ratios (HRs) and matched and adjusted risk differences (RDs) per 10,000 person-years and their 95% CIs for rhabdomyolysis among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source (risk window: 365 days after dose 1)

	Matched HR (95% CI)	Adjusted HR (95% CI)	Matched RD	Adjusted RD
Pedianet	NA	NA	NA	NA
NHR	NA	NA	NA	NA
PHARMO	1.92 (0.22, 16.86)	1.88 (0.21, 16.58)	0.06	0.06
EpiChron	0.74 (0.38, 1.42)	0.69 (0.35, 1.34)	-0.37	-0.48
SIDIAP	0.58 (0.44, 0.76)	0.57 (0.43, 0.74)	-0.69	-0.72

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

10.3.24. Generalised convulsions

Generalised convulsion events were identified in all data sources, except Pedianet and in the vaccinated cohort in NHR. The incidence rates ranged from 1.23 per 10,000 person-years (95% CI: 0.50, 2.54) in PHARMO to 2.11 per 10,000 person-years (95% CI: 0.97, 4.01) in EpiChron in the vaccinated cohorts. In the unvaccinated cohorts these ranged from 0.20 per 10,000 person-years (95% CI: 0.10, 0.70) in NHR to 2.63 per 10,000 person-years (95% CI: 1.27, 5.45) in PHARMO. The cumulative incidence was below 1 per 10,000 individuals in both cohorts in all data sources. The incidence was similar in the different age groups.

The matched HRs were 0.47 (95% CI: 0.17, 1.32) in PHARMO, 0.90 (95% CI: 0.32, 2.49) in EpiChron, and 1.00 (95% CI: 0.57, 1.75) in SIDIAP. The adjusted HRs were 0.44 (95% CI: 0.16, 1.26) in PHARMO, 0.93 (95% CI: 0.33, 2.58) in EpiChron, and 0.90 (95% CI: 0.51, 1.57) in SIDIAP. No differences were observed for the incidence of generalised convulsions between the vaccinated and unvaccinated cohorts during the 42-day risk window.

Table 71. 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

	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)	0	0 (0, 0)	1,033.80	0 (0, 35.68)	0	0 (0, 0)	1,034.37	NA
NHR (Norway)	0	0 (0, 0)	240,790.32	0 (0, 0.15)	<5	0 (0, 0.01)	240,499.36	0.04 (0.01, 0.30)
PHARMO (Netherlands)	7	0.16 (0.04, 0.28)	56,847.09	1.23 (0.50, 2.54)	15	0.31 (0.07, 0.54)	56,946.88	2.63 (1.27, 5.45)
EpiChron (Spain)	9	0.25 (0.08, 0.42)	42,598.42	2.11 (0.97, 4.01)	10	0.27 (0.05, 0.48)	42,550.65	2.35 (1.07, 5.15)
SIDIAP (Spain)	31	0.16 (0.10, 0.22)	233,072.80	1.33 (0.90, 1.89)	31	0.15 (0.09, 0.22)	233,072.48	1.33 (0.86, 2.05)

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 62. 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

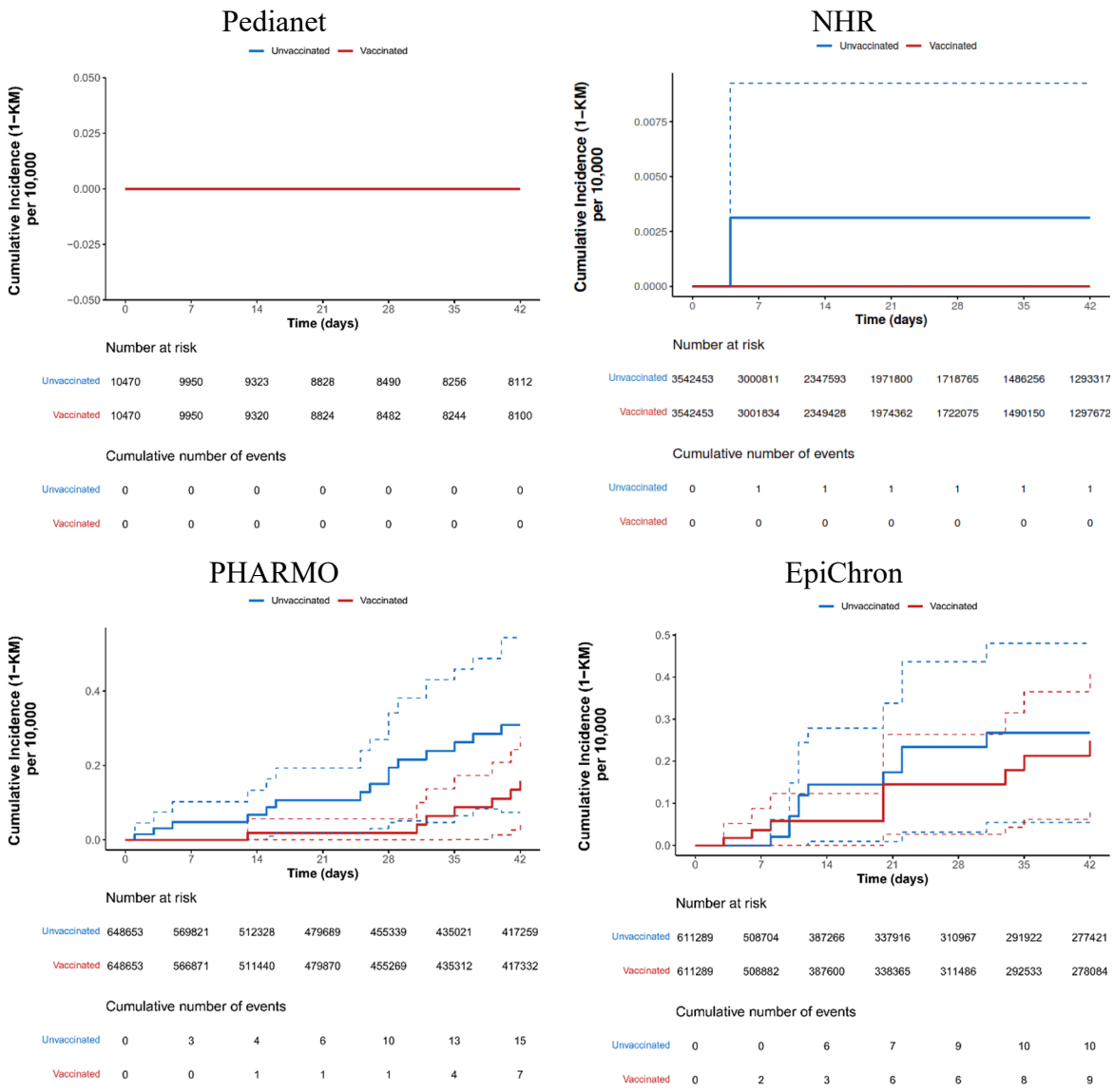
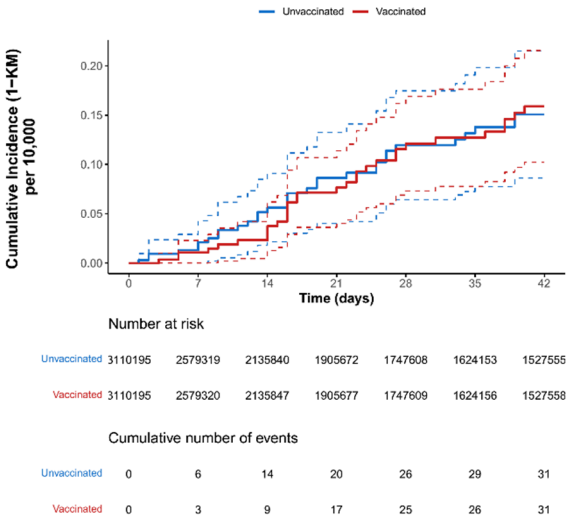


Figure 62. Cumulative incidence of generalised convulsions within 42 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source

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 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 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

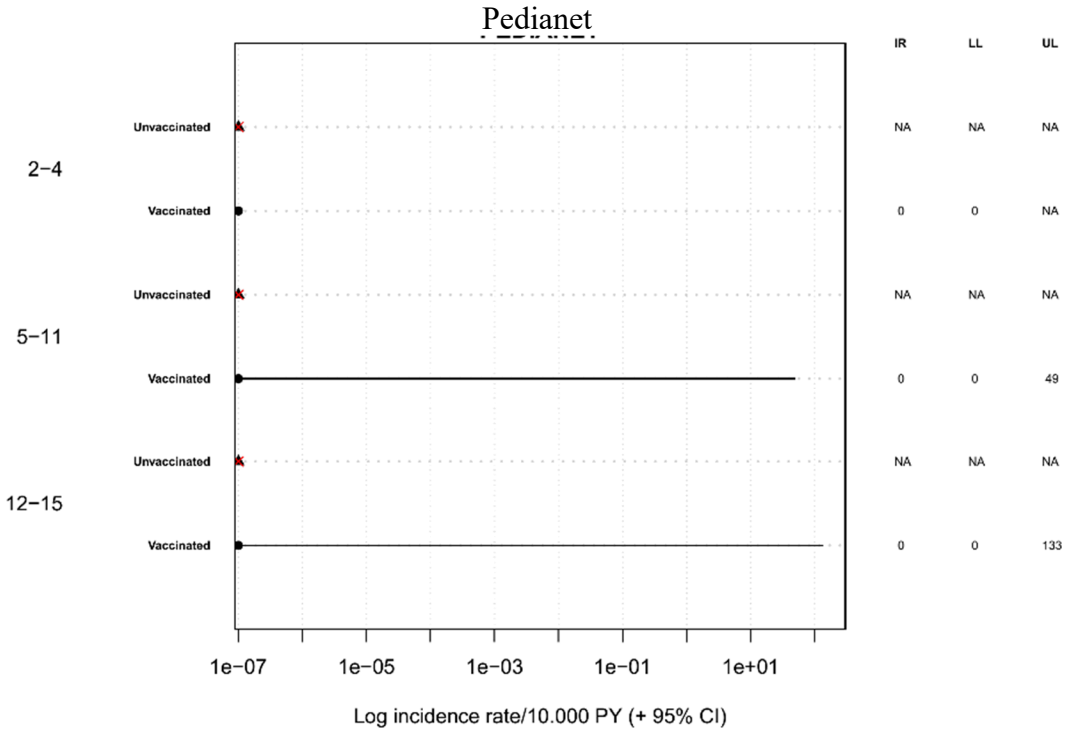


Figure 63. Forest plot showing incidence rates and 95% confidence intervals for generalised convulsions within 42 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source and by age groups

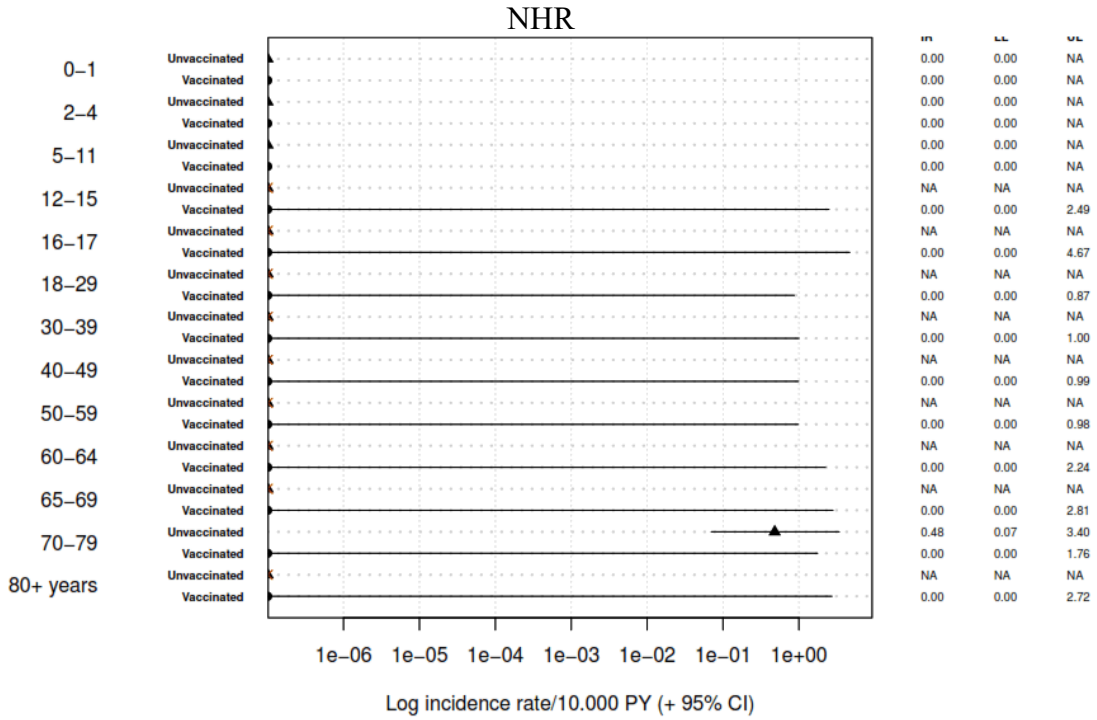


Figure 63. Forest plot showing incidence rates and 95% confidence intervals for generalised convulsions within 42 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source and by age groups

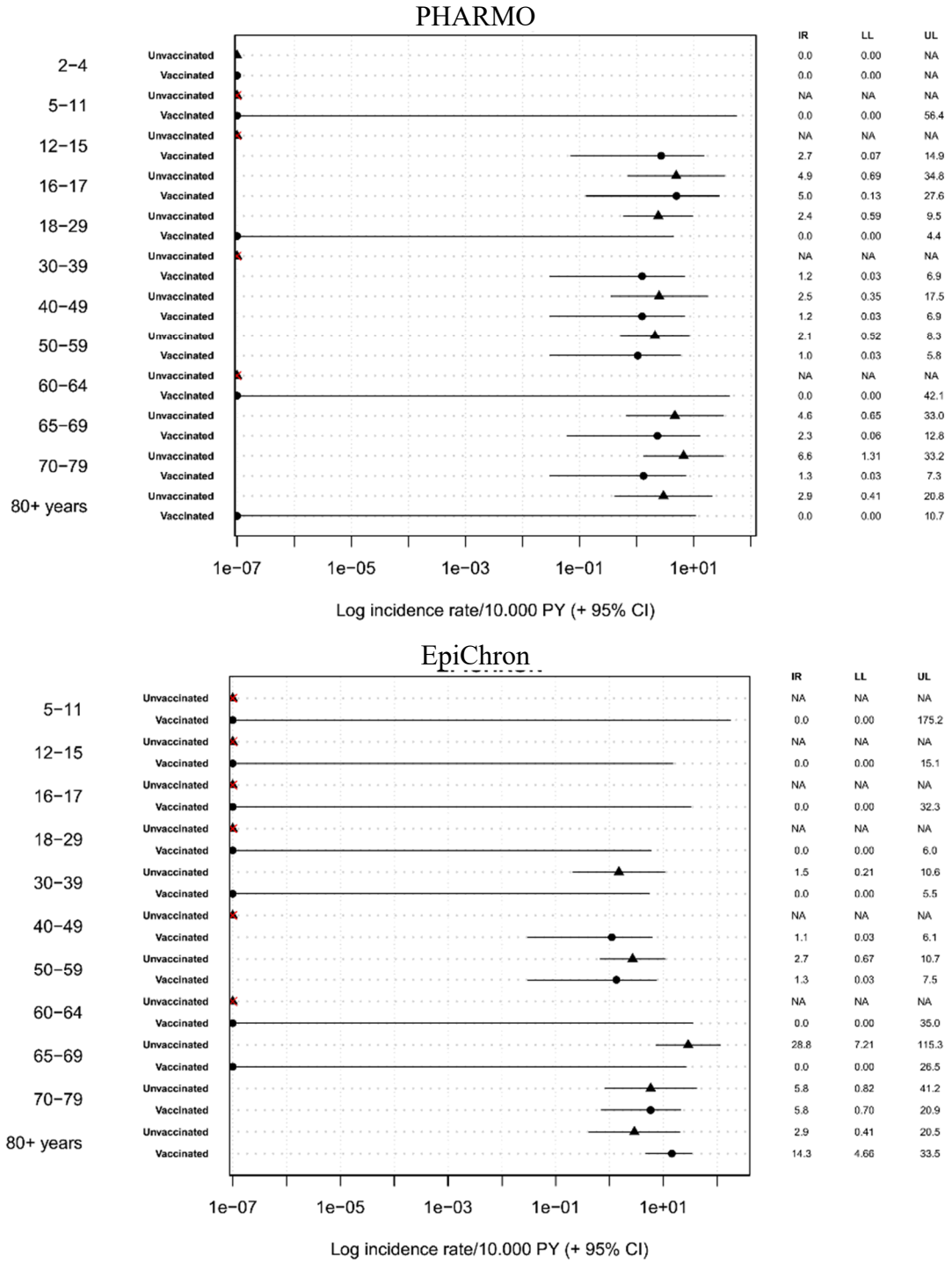


Figure 63. Forest plot showing incidence rates and 95% confidence intervals for generalised convulsions within 42 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source and by age groups

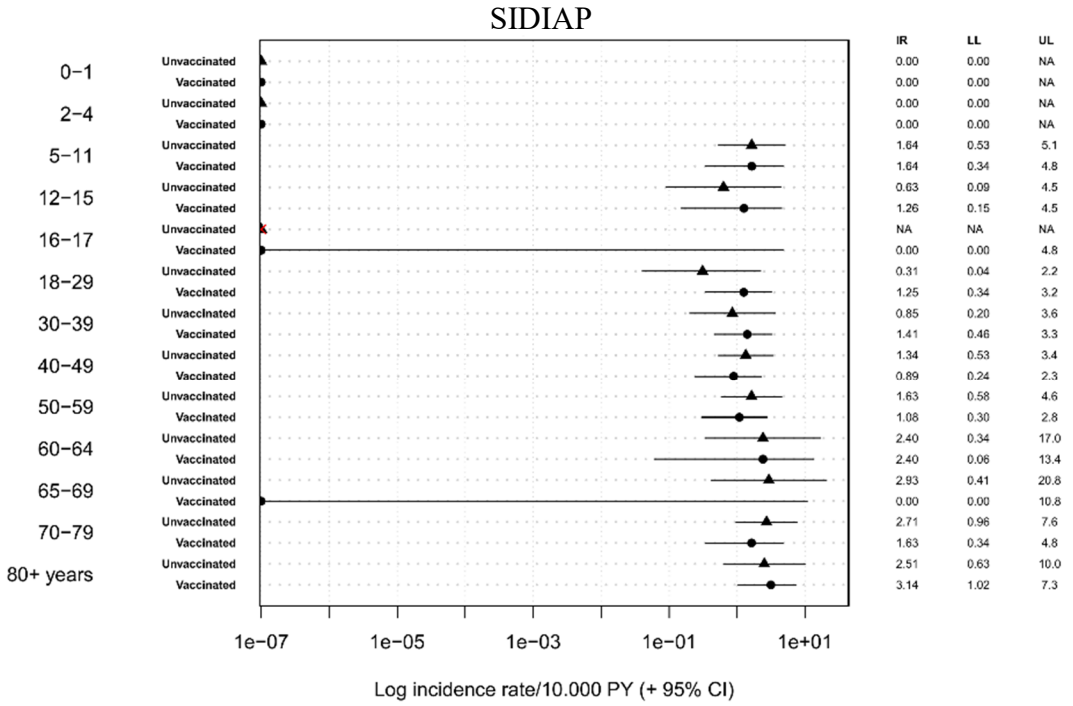


Table 72. Matched and adjusted hazard ratios (HRs) and matched and adjusted risk differences (RDs) per 10,000 person-years and their 95% CIs for generalised convulsions within 42 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source

	Matched HR (95% CI)	Adjusted HR (95% CI)	Matched RD	Adjusted RD
Pedianet	NA	NA	NA	NA
NHR	NA	NA	0	0
PHARMO	0.47 (0.17, 1.32)	0.44 (0.16, 1.26)	-0.15	-0.16
EpiChron	0.90 (0.32, 2.49)	0.93 (0.33, 2.58)	-0.02	-0.01
SIDIAP	1 (0.57, 1.75)	0.90 (0.51, 1.57)	0.01	-0.01

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

10.3.25. Meningoencephalitis

Meningoencephalitis was a rare event in all data sources, with no events identified in Pedianet. The incidence rates ranged from 0.35 per 10,000 person-years (95% CI: 0.04, 1.27) in PHARMO to 1.79 per 10,000 person-years (95% CI: 1.29, 2.41) in NHR in the vaccinated cohorts. In the unvaccinated cohorts these ranged from 1.05 per 10,000 person-years (95% CI: 0.37, 2.96) in PHARMO and 2.37 per 10,000 person-years (95% CI: 1.63, 3.45) in NHR. The cumulative incidence was below 1.00 per 10,000 individuals in both cohorts in all data sources. The incidence was similar in the different age groups.

The matched HRs were 0.75 (95% CI: 0.47, 1.21) in NHR, 1.00 (95% CI: 0.16, 6.37) in PHARMO, 0.40 (95% CI: 0.08, 2.06) in EpiChron, and 0.95 (95% CI: 0.44, 2.04) in SIDIAP. The adjusted HRs were 0.75 (95% CI: 0.47, 1.21) in NHR, 0.36 (95% CI: 0.06, 2.07) in PHARMO, 0.52 (95% CI: 0.11, 2.41) in EpiChron, and 0.67 (95% CI: 0.34, 1.33) in SIDIAP. No differences were observed for the incidence of meningoencephalitis between the vaccinated and unvaccinated cohorts during the 42-day risk window.

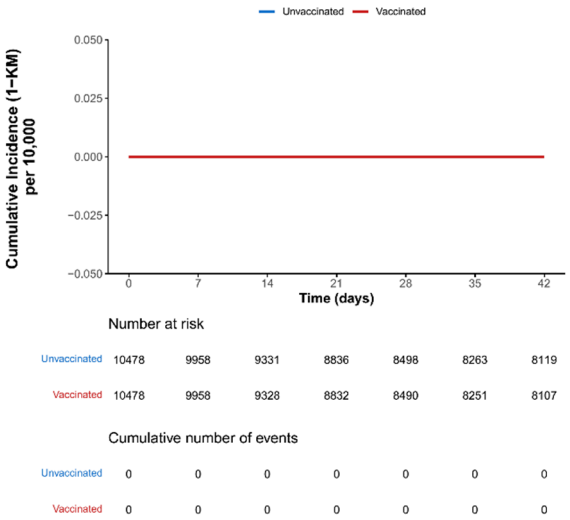
Table 73. Risk estimates (95% CI) per 10,000 person-years (PY) for meningoencephalitis within 42 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source

	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)	0	0 (0, 0)	1,034.69	0 (0, 35.65)	0	0 (0, 0)	1,035.25	NA
NHR (Norway)	43	0.19 (0.13, 0.25)	240,646.34	1.79 (1.29, 2.41)	57	0.26 (0.16, 0.37)	240,355.59	2.37 (1.63, 3.45)
PHARMO (Netherlands)	<5	0.04 (0, 0.08)	56,851.11	0.35 (0.04, 1.27)	6	0.13 (0, 0.26)	56,951.50	1.05 (0.37, 2.96)
EpiChron (Spain)	<5	0.10 (0, 0.21)	42,602.74	0.70 (0.15, 2.06)	5	0.12 (0, 0.24)	42,555.15	1.17 (0.42, 3.31)
SIDIAP (Spain)	18	0.10 (0.05, 0.14)	233,085.07	0.77 (0.46, 1.22)	25	0.13 (0.07, 0.19)	233,084.32	1.07 (0.66, 1.75)

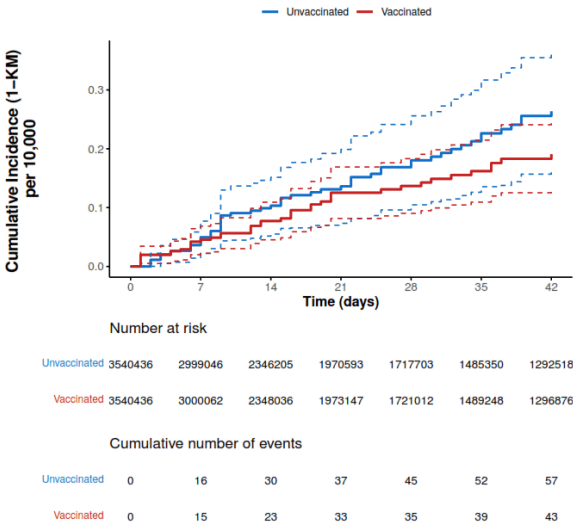
Note: Estimation of confidence intervals differs between vaccinated and unvaccinated, since the unvaccinated estimate is a GEE estimates (to account for individuals who were matched to more than one vaccinated individual). When NA (not-assessable) is listed for the 1-KM it means that there is no estimate 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 64. 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

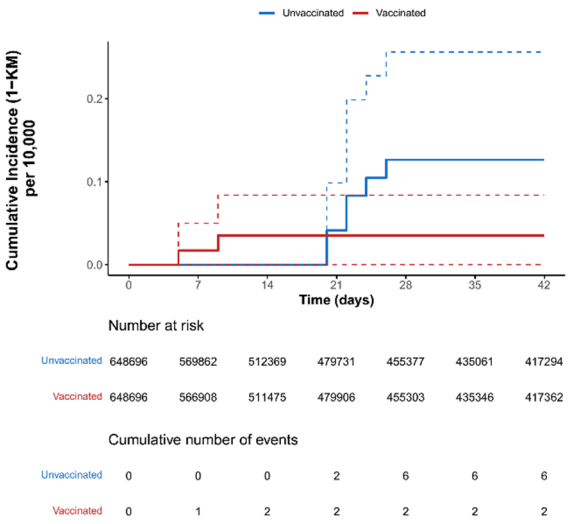
Pedianet



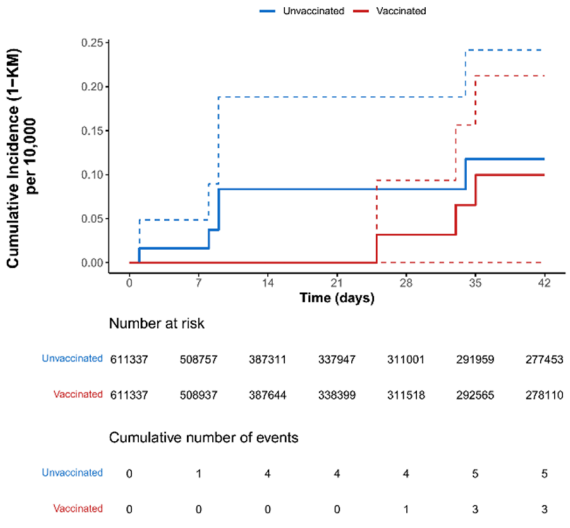
NHR



PHARMO

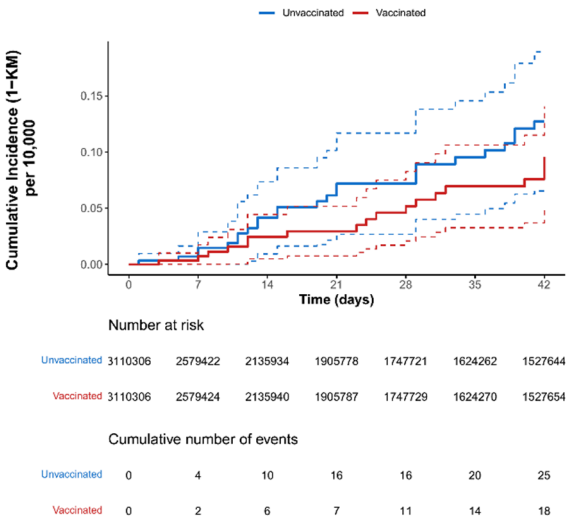


EpiChron



SIDIAP

Figure 64. 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 65. 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

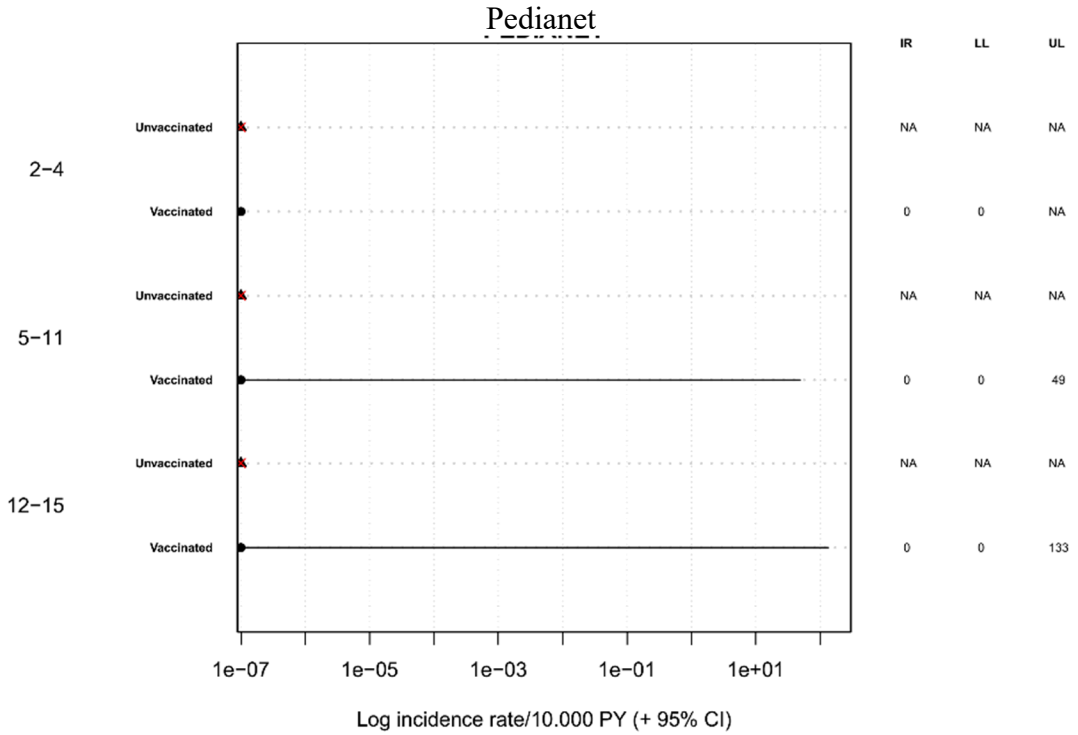


Figure 65. Forest plot showing incidence rates and 95% confidence intervals for meningoencephalitis within 42 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source and by age groups

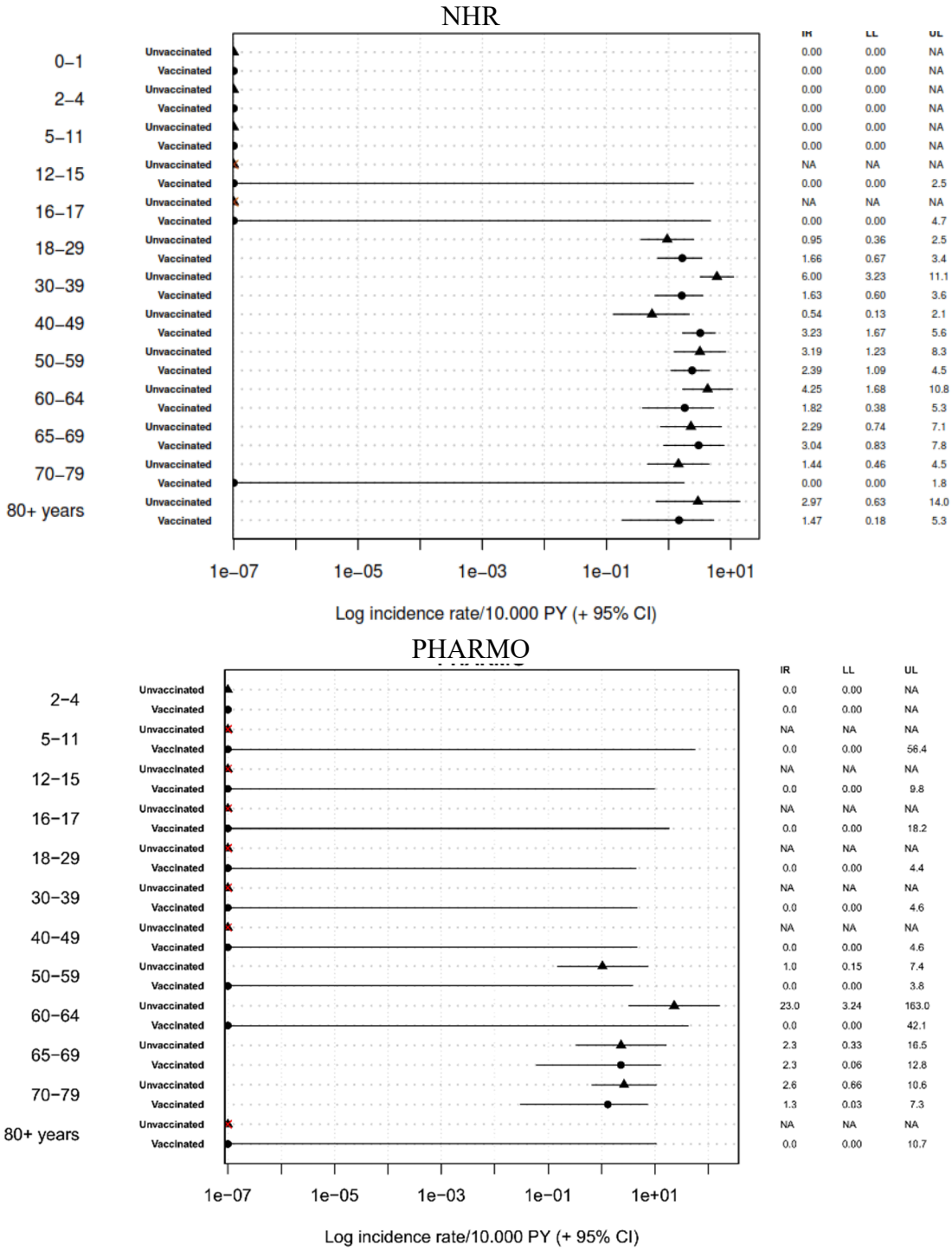


Figure 65. Forest plot showing incidence rates and 95% confidence intervals for meningoencephalitis within 42 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source and by age groups

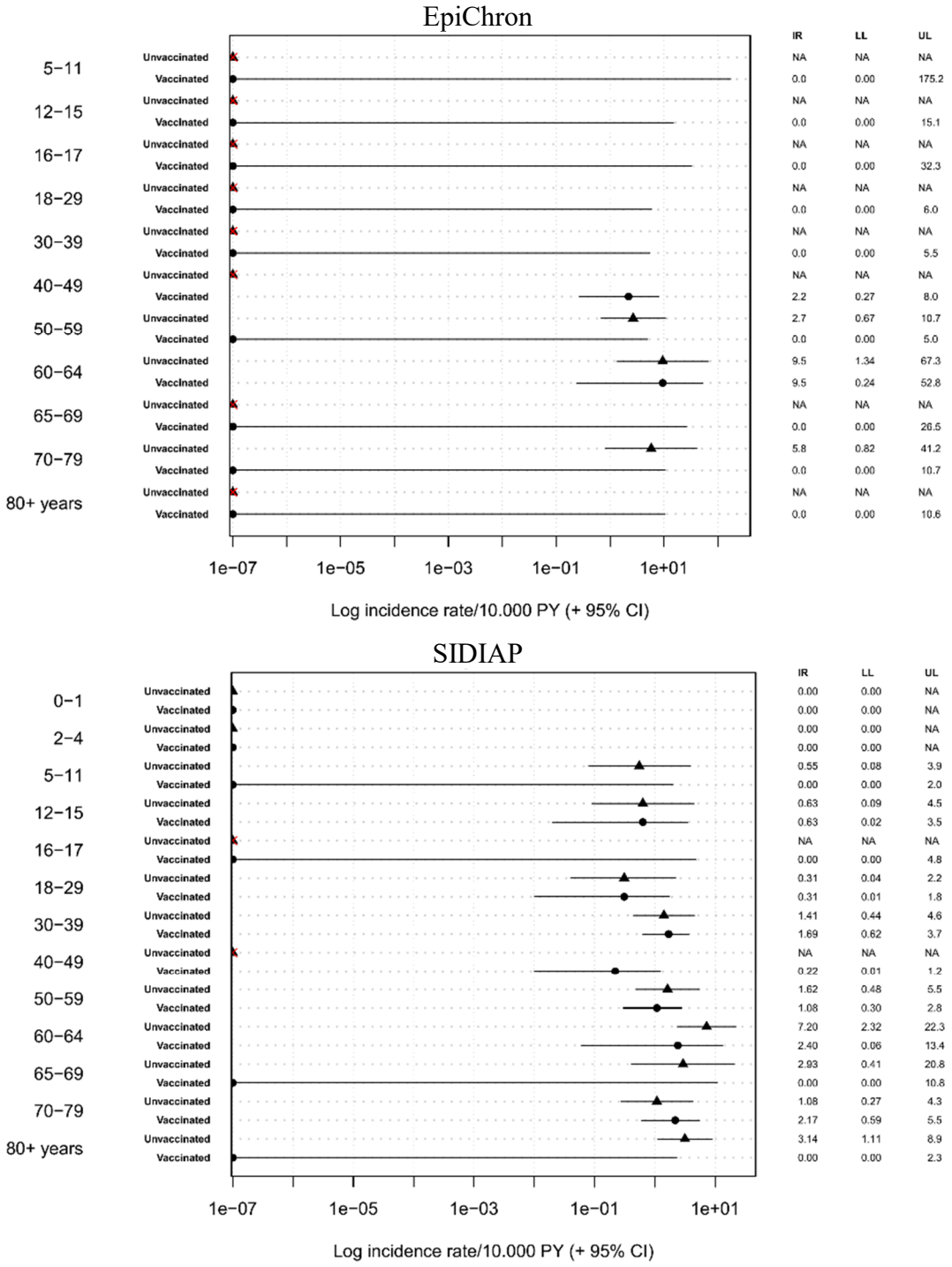


Table 74. Matched and adjusted hazard ratios (HRs) and matched and adjusted risk differences (RDs) per 10,000 person-years and their 95% CIs for meningoencephalitis within 42 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source

	Matched HR (95% CI)	Adjusted HR (95% CI)	Matched RD	Adjusted RD
Pedianet	NA	NA	NA	NA
NHR	0.75 (0.47, 1.21)	0.75 (0.47, 1.21)	-0.07	-0.07
PHARMO	0.33 (0.06, 1.88)	0.36 (0.06, 2.07)	-0.09	-0.08
EpiChron	0.60 (0.13, 2.78)	0.52 (0.11, 2.41)	-0.02	-0.03
SIDIAP	0.72 (0.37, 1.41)	0.67 (0.34, 1.33)	-0.03	-0.04

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

10.3.26. Transverse myelitis

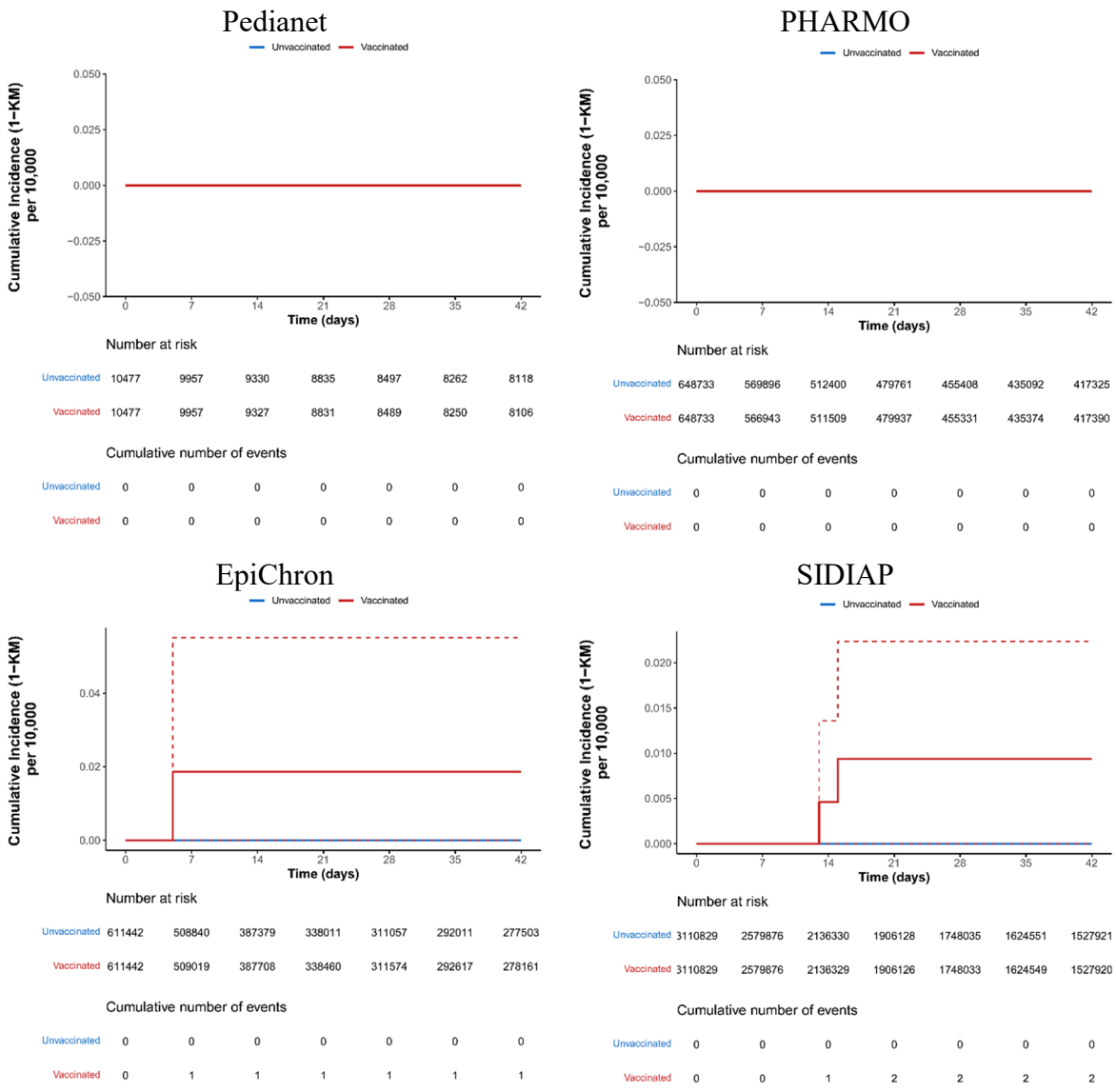
Transverse myelitis within 42 days after start of follow-up was a very rare event identified in EpiChron and SIDIAP, with <5 events in each of the data sources. The incidence rates are less than 1.00 per 10,000 person-years in the vaccinated and unvaccinated cohorts in all data sources. Due to the low 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 transverse myelitis within the 42-day risk window, between the vaccinated and unvaccinated cohorts.

Table 75. 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

	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)	0	0 (0, 0)	1,034.58	0 (0, 35.66)	0	0 (0, 0)	1,035.14	NA
NHR (Norway)	NA	NA	NA	NA	NA	NA	NA	NA
PHARMO (Netherlands)	0	0 (0, 0)	56,854.70	0 (0, 0.65)	0	0 (0, 0)	56,955.13	NA
EpiChron (Spain)	<5	0.02 (0, 0.06)	42,610.11	0.23 (0.01, 1.31)	0	0 (0, 0)	42,562.64	NA
SIDIAP (Spain)	<5	0.01 (0, 0.02)	233,125.85	0.09 (0.01, 0.31)	0	0 (0, 0)	233,125.98	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+).
LL: lower limit of 95% CI; UL: upper lower limit of 95% CI.

Figure 66. 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 67. 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

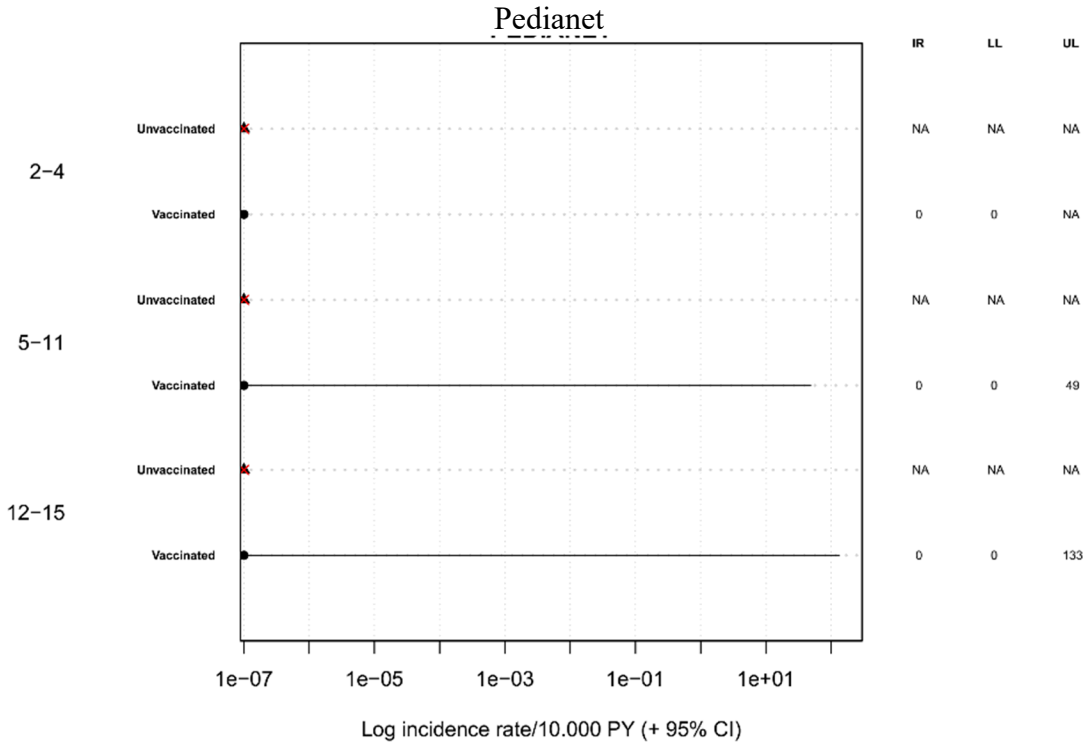


Figure 67. Forest plot showing incidence rates and 95% confidence intervals for transverse myelitis within 42 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source and by age groups

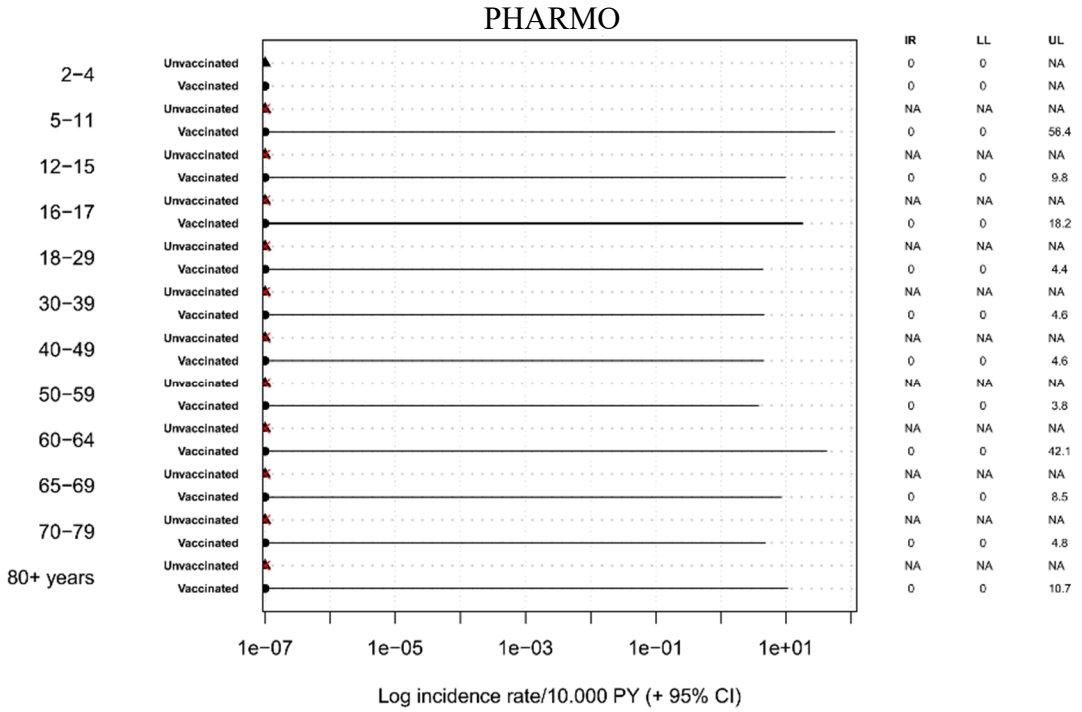


Figure 67. Forest plot showing incidence rates and 95% confidence intervals for transverse myelitis within 42 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source and by age groups

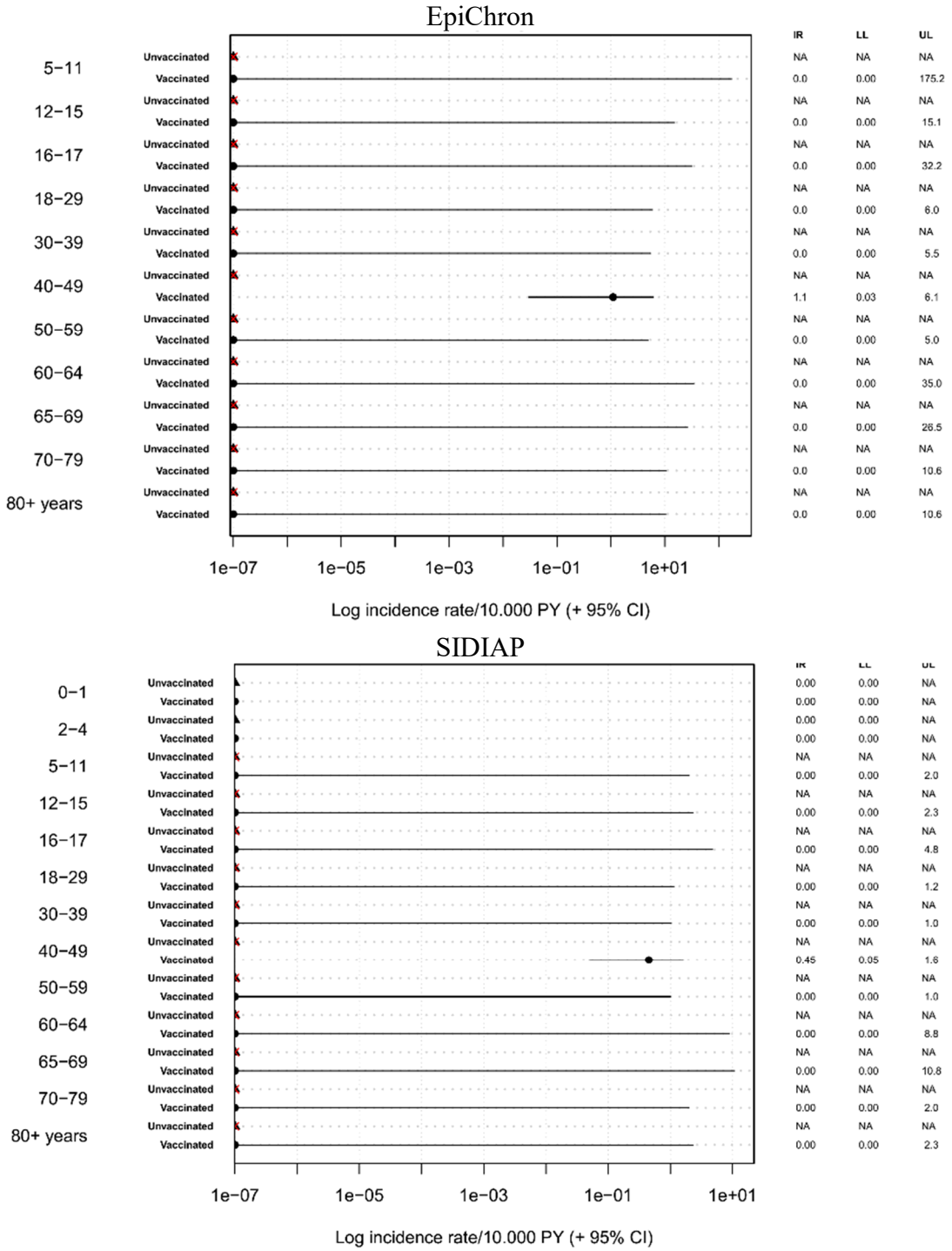


Table 76. Matched and adjusted hazard ratios (HRs) and matched and adjusted risk differences (RDs) per 10,000 person-years and their 95% CIs for transverse myelitis within 42 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source

	Matched HR (95% CI)	Adjusted HR (95% CI)	Matched RD	Adjusted RD
Pedianet	NA	NA	NA	NA
NHR	NA	NA	NA	NA
PHARMO	NA	NA	0	0
EpiChron	NA	NA	0.02	0.02
SIDIAP	NA	NA	0.01	0.01

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

10.3.27. Bell's palsy

Bell's palsy events were identified in all data sources, except the vaccinated cohort in Pedianet. The incidence rates ranged from 4.22 per 10,000 person-years (95% CI: 2.71, 6.28) in PHARMO to 7.09 per 10,000 person-years (95% CI: 6.05, 8.26) in SIDIAP in the vaccinated cohorts. In the unvaccinated cohorts these ranged from 1.23 per 10,000 person-years (95% CI: 0.53, 2.85) in PHARMO to 9.66 per 10,000 person-years (95% CI: 1.36, 68.60) in Pedianet. The cumulative incidence was below 1.00 per 10,000 individuals in both cohorts in all data sources except Pedianet where it was 1.2 in the unvaccinated cohort but based on <5 cases. The incidence was similar in the different age groups.

The matched HRs were 1.01 (95% CI: 0.76, 1.35) in NHR, 3.44 (1.39, 8.50) in PHARMO, 0.93 (0.42, 2.08) in EpiChron, and 0.94 (0.74, 1.19) in SIDIAP. The adjusted HRs were 1.01 (95% CI: 0.76, 1.35) in NHR, 3.08 (1.24, 7.62) in PHARMO, 0.89 (0.40, 2.00) in EpiChron, and 0.91 (0.71, 1.16) in SIDIAP. In PHARMO the lower limits of the 95% CIs for the HRs were above 1 in the matched and adjusted results. In PHARMO the lower limits of the 95% CIs for the HRs were above 1 in both cohorts.

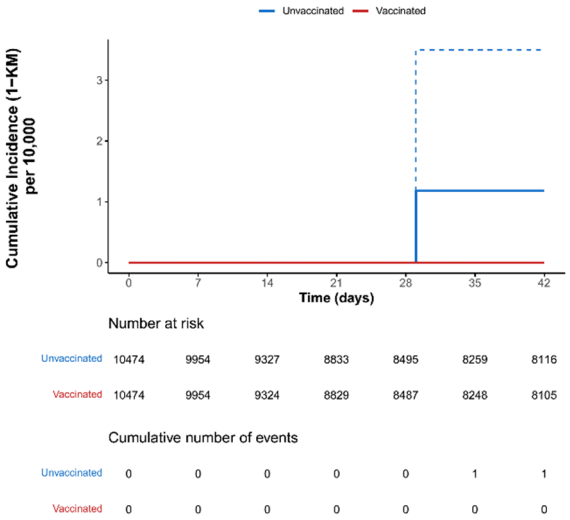
Table 77. Risk estimates (95% CI) per 10,000 person-years (PY) for Bell's palsy within 42 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source

	Vaccinated				Unvaccinated			
Data source	**Events (n)**	**Cumulative incidence (95% CI)**	**Person-years (PY)**	**Incidence rate (95% CI)**	**Events (n)**	**Cumulative incidence (95% CI)**	**Person-years (PY)**	**Incidence rate (95% CI)**
Pedianet (Italy)	0	0 (0, 0)	1,034.32	0 (0, 35.66)	<5	1.18 (0, 3.50)	1,034.85	9.66 (1.36, 68.60)
NHR (Norway)	130	0.62 (0.51, 0.74)	240,470.01	5.41 (4.52, 6.42)	128	0.61 (0.46, 0.75)	240,180.32	5.33 (4.21, 6.74)
PHARMO (Netherlands)	24	0.47 (0.28, 0.65)	56,826.96	4.22 (2.71, 6.28)	7	0.13 (0.02, 0.25)	56,928.70	1.23 (0.53, 2.85)
EpiChron (Spain)	29	0.84 (0.53, 1.15)	42,567.49	6.81 (4.56, 9.78)	31	0.93 (0.23, 1.63)	42,520.49	7.29 (3.58, 14.87)
SIDIAP (Spain)	165	0.80 (0.68, 0.93)	232,746.49	7.09 (6.05, 8.26)	176	0.85 (0.69, 1.01)	232,745.62	7.56 (6.24, 9.16)

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 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

Pedianet



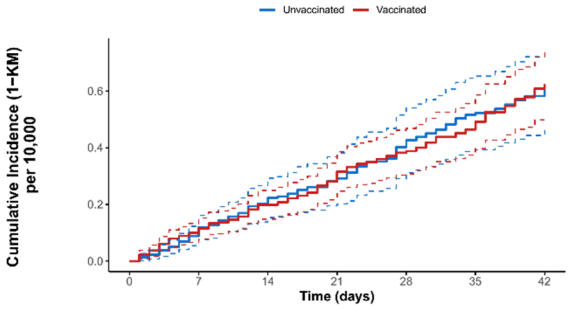
Number at risk

	0	7	14	21	28	35	42
Unvaccinated	10474	9954	9327	8833	8495	8259	8116
Vaccinated	10474	9954	9324	8829	8487	8248	8105

Cumulative number of events

	0	7	14	21	28	35	42
Unvaccinated	0	0	0	0	0	1	1
Vaccinated	0	0	0	0	0	0	0

NHR



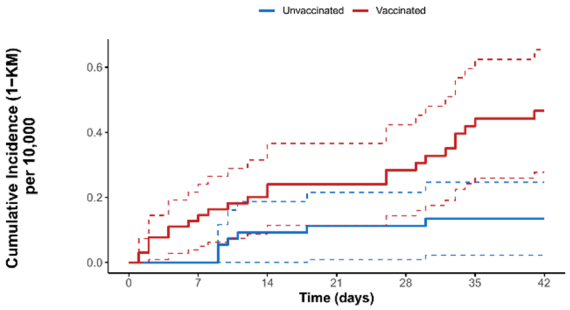
Number at risk

	0	7	14	21	28	35	42
Unvaccinated	3537917	2996882	2344439	1969135	1716452	1484263	1291614
Vaccinated	3537917	2997895	2346263	1971683	1719750	1488149	1295942

Cumulative number of events

	0	7	14	21	28	35	42
Unvaccinated	0	38	64	78	102	117	128
Vaccinated	0	38	59	83	96	112	130

PHARMO



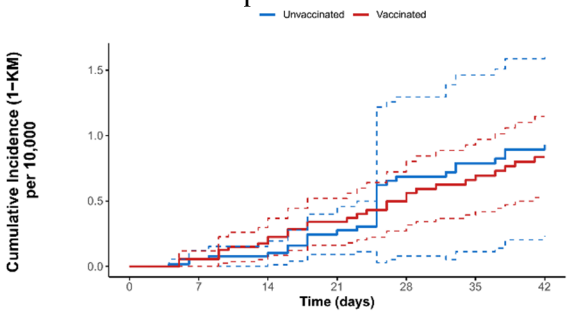
Number at risk

	0	7	14	21	28	35	42
Unvaccinated	648430	569633	512160	479536	455197	434891	417132
Vaccinated	648430	566670	511260	479702	455108	435156	417179

Cumulative number of events

	0	7	14	21	28	35	42
Unvaccinated	0	0	5	6	6	7	7
Vaccinated	0	9	14	14	16	23	24

EpiChron



Number at risk

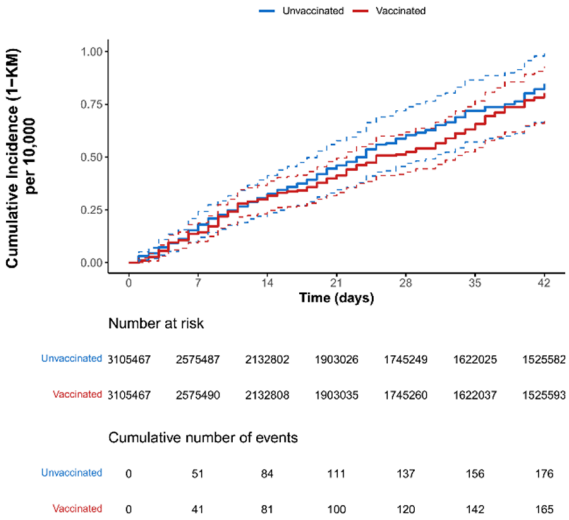
	0	7	14	21	28	35	42
Unvaccinated	610855	508351	386999	337673	310736	291714	277218
Vaccinated	610855	508526	387320	338115	311252	292318	277872

Cumulative number of events

	0	7	14	21	28	35	42
Unvaccinated	0	3	5	11	24	27	31
Vaccinated	0	3	10	14	21	25	29

Figure 68. 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

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

Figure 69. Forest plot showing incidence rates and 95% confidence intervals for Bell's palsy within 42 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source and by age groups

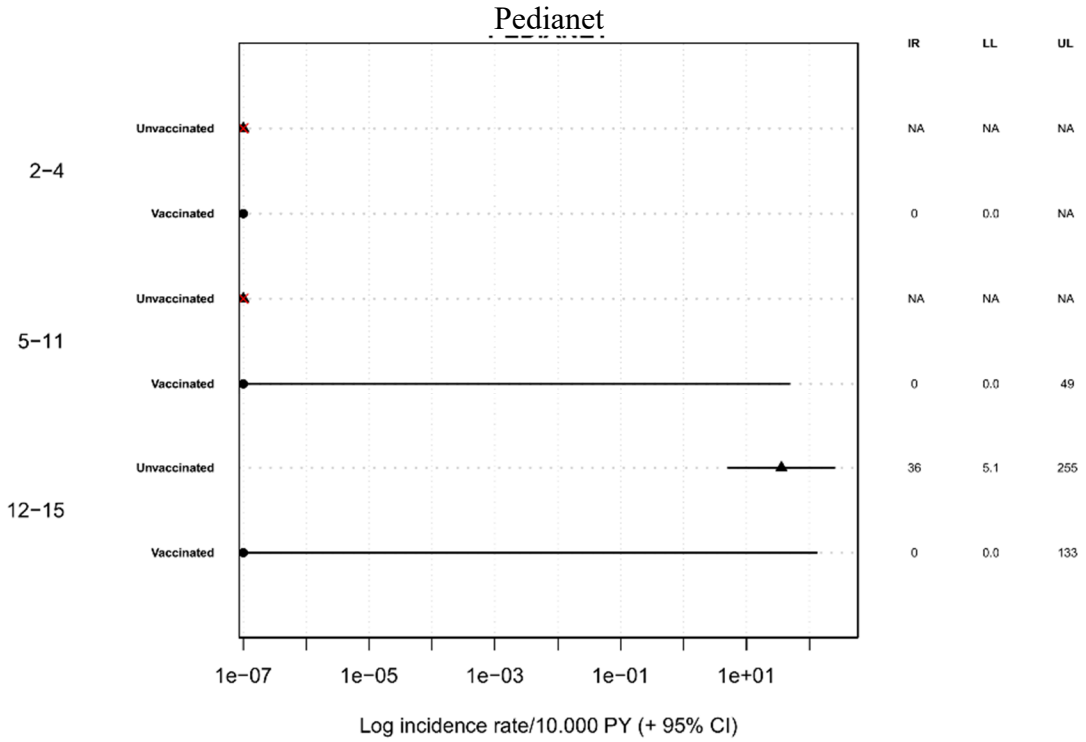


Figure 69. Forest plot showing incidence rates and 95% confidence intervals for Bell's palsy within 42 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source and by age groups

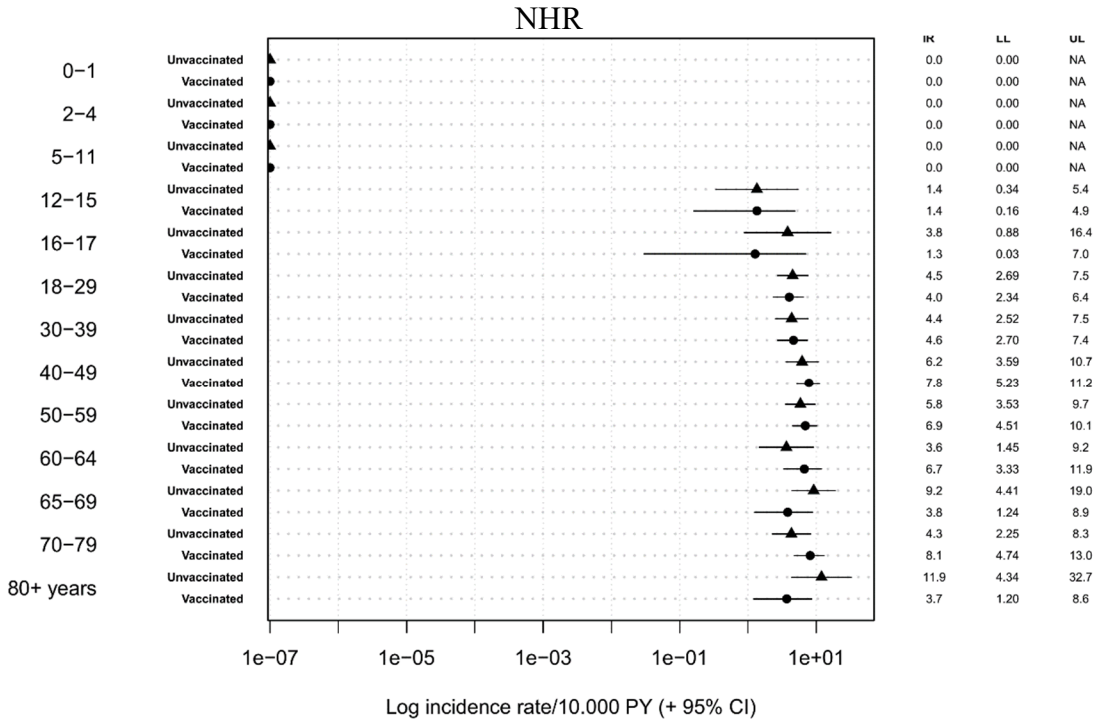


Figure 69. Forest plot showing incidence rates and 95% confidence intervals for Bell's palsy within 42 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source and by age groups

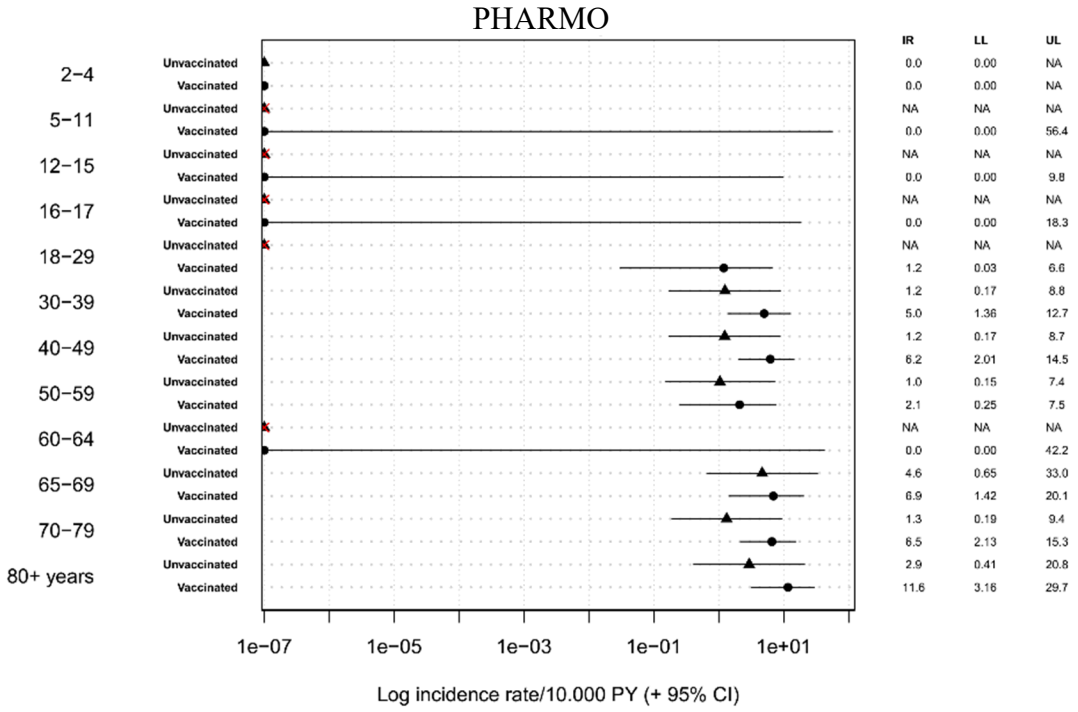
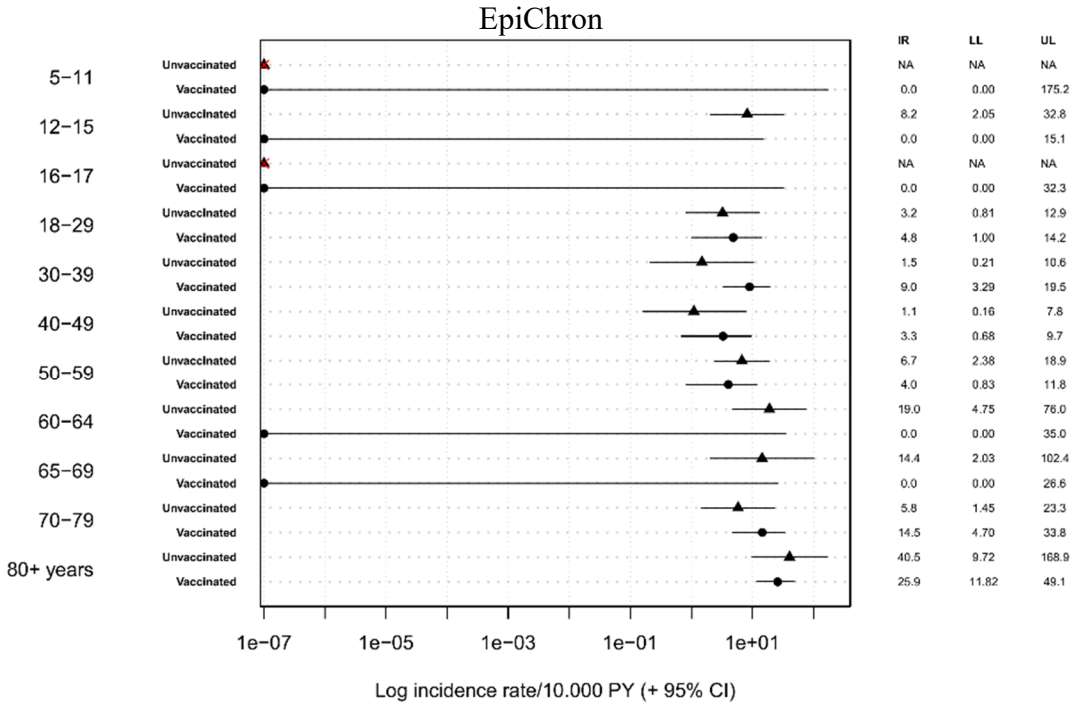


Figure 69. Forest plot showing incidence rates and 95% confidence intervals for Bell's palsy within 42 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source and by age groups



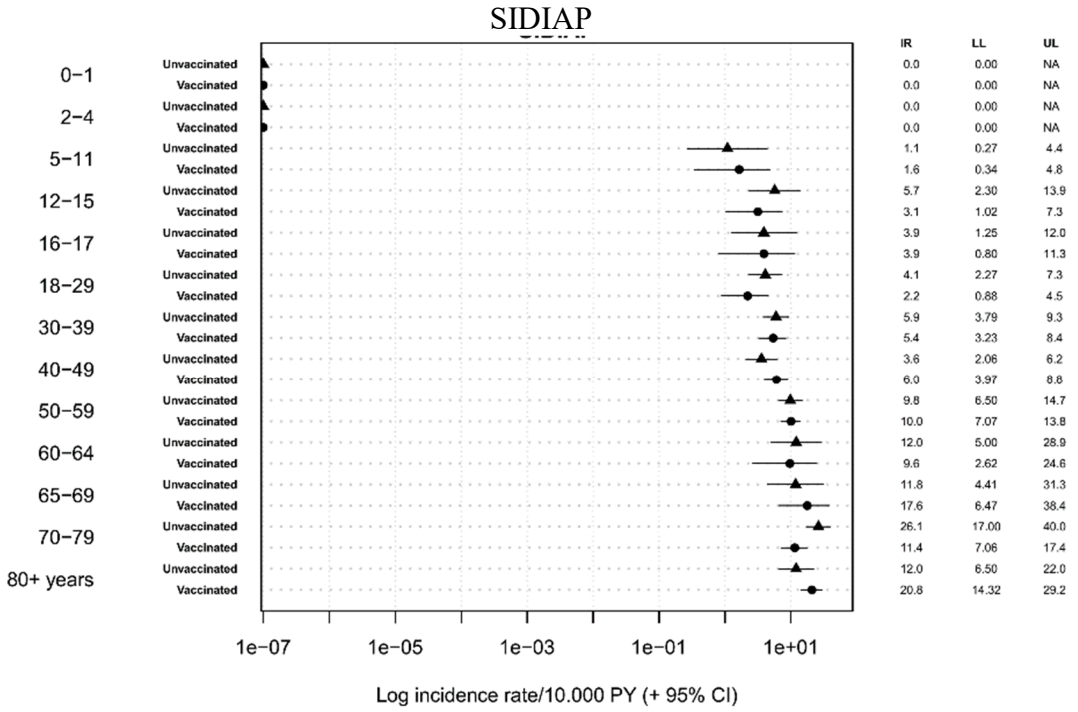


Table 78. Matched and adjusted hazard ratios (HRs) and matched and adjusted risk differences (RDs) per 10,000 person-years and their 95% CIs for Bells Palsy within 42 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source

	Matched HR (95% CI)	Adjusted HR (95% CI)	Matched RD	Adjusted RD
Pedianet	NA	NA	-1.18	-1.19
NHR	1.01 (0.76, 1.35)	1.01 (0.76, 1.35)	0.02	0.02
PHARMO	3.44 (1.39, 8.50)	3.08 (1.24, 7.62)	0.33	0.30
EpiChron	0.93 (0.42, 2.08)	0.89 (0.40, 2.00)	-0.09	-0.13
SIDIAP	0.94 (0.74, 1.19)	0.91 (0.71, 1.16)	-0.04	-0.07

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

10.3.28. Acute respiratory distress syndrome

Acute respiratory distress syndrome events were identified in all data sources except Pedianet. The incidence rates ranged from 0.43 per 10,000 person-years (95% CI: 0.23, 0.73) in PHARMO to 1.35 per 10,000 person-years (95% CI: 0.89, 1.97) in EpiChron in the vaccinated cohorts. In the unvaccinated cohorts these ranged from 0.36 per 10,000 person-years (95% CI: 0.17, 0.79) in PHARMO to 8.55 per 10,000 person-years (95% CI: 6.69, 10.93) in EpiChron. The cumulative incidence was below 1.80 per 10,000 individuals in the vaccinated cohorts and below 8 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.

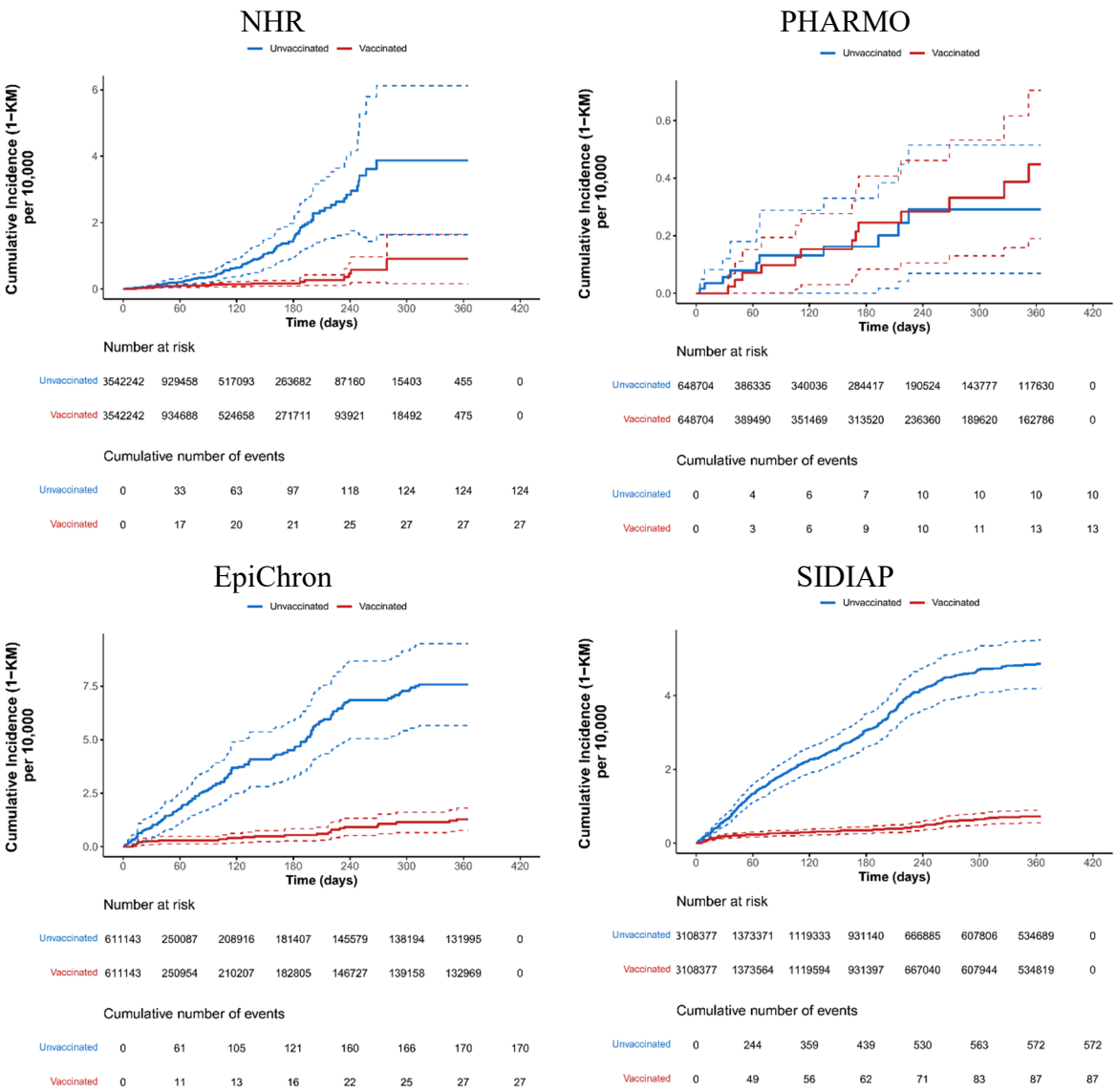
The matched HRs were 0.21 (95% CI: 0.13, 0.35) in NHR, 1.20 (95% CI: 0.47, 3.07) in PHARMO, 0.16 (95% CI: 0.10, 0.25) in EpiChron, and 0.15 (95% CI: 0.12, 0.19) in SIDIAP. The adjusted HRs were 0.21 (95% CI: 0.13, 0.35) in NHR, 1.23 (95% CI: 0.48, 3.12) in PHARMO, 0.14 (95% CI: 0.09, 0.23) in EpiChron, and 0.14 (95% CI: 0.11, 0.18) in SIDIAP. No differences were observed for the incidence of acute respiratory distress syndrome within the 365-day risk window, between the vaccinated and unvaccinated cohorts.

Table 79. 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)

	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)	NA	NA	NA	NA	NA	NA	NA	NA
NHR (Norway)	27	0.90 (0.16, 1.65)	509,669.14	0.53 (0.35, 0.77)	124	3.88 (1.64, 6.12)	504,514.79	2.46 (1.77, 3.41)
PHARMO (Netherlands)	13	0.45 (0.19, 0.71)	302,872.11	0.43 (0.23, 0.73)	10	0.29 (0.07, 0.52)	276,170.19	0.36 (0.17, 0.79)
EpiChron (Spain)	27	1.28 (0.76, 1.80)	199,852.18	1.35 (0.89, 1.97)	170	7.58 (5.67, 9.49)	198,806.73	8.55 (6.69, 10.93)
SIDIAP (Spain)	87	0.72 (0.55, 0.90)	1,013,293.91	0.86 (0.69, 1.06)	572	4.86 (4.20, 5.51)	1,013,115.63	5.65 (4.98, 6.40)

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 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 71. 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)

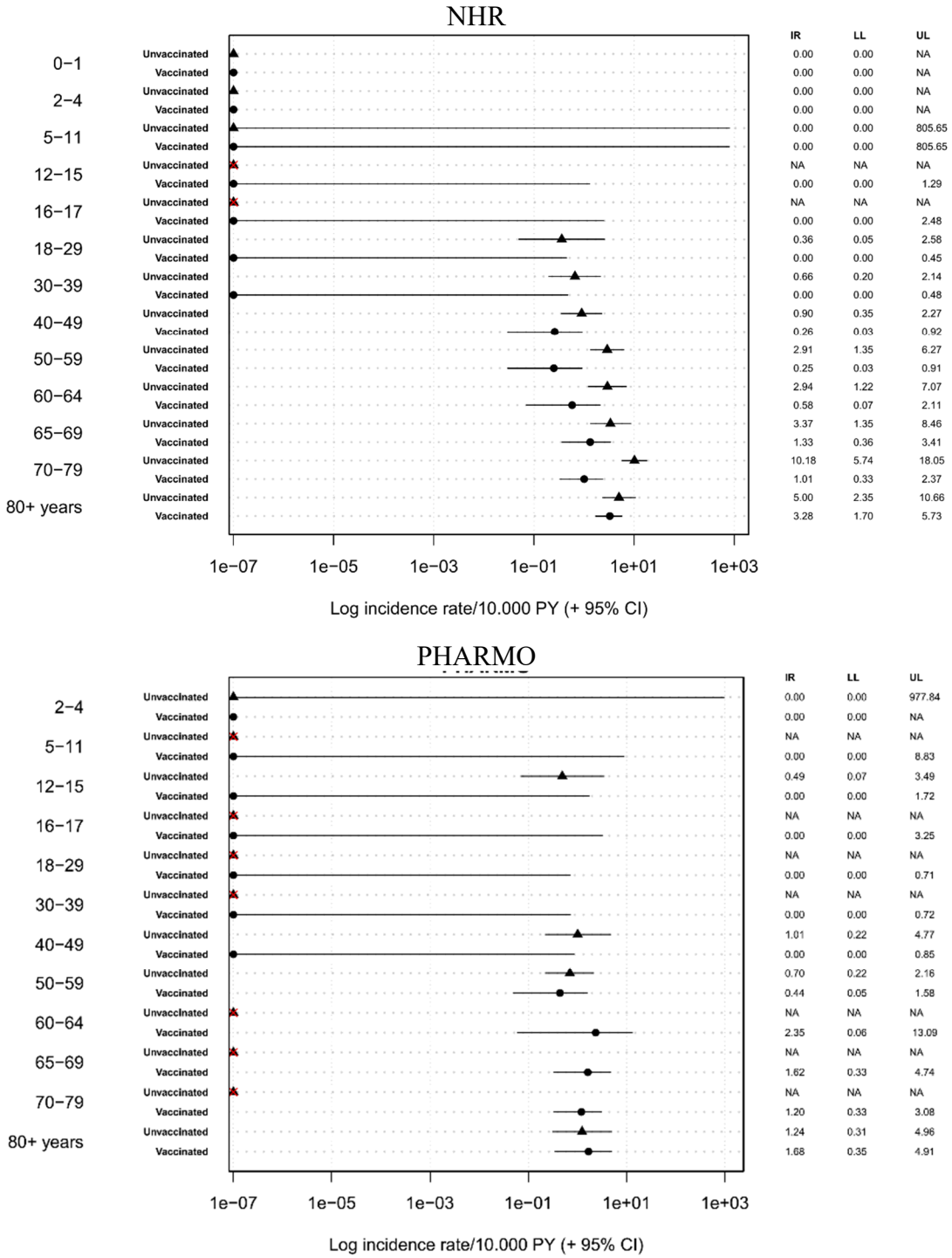


Figure 71. Forest plot showing incidence rates and 95% confidence intervals for acute respiratory distress syndrome among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source and by age groups (risk window: 365 days after dose 1)

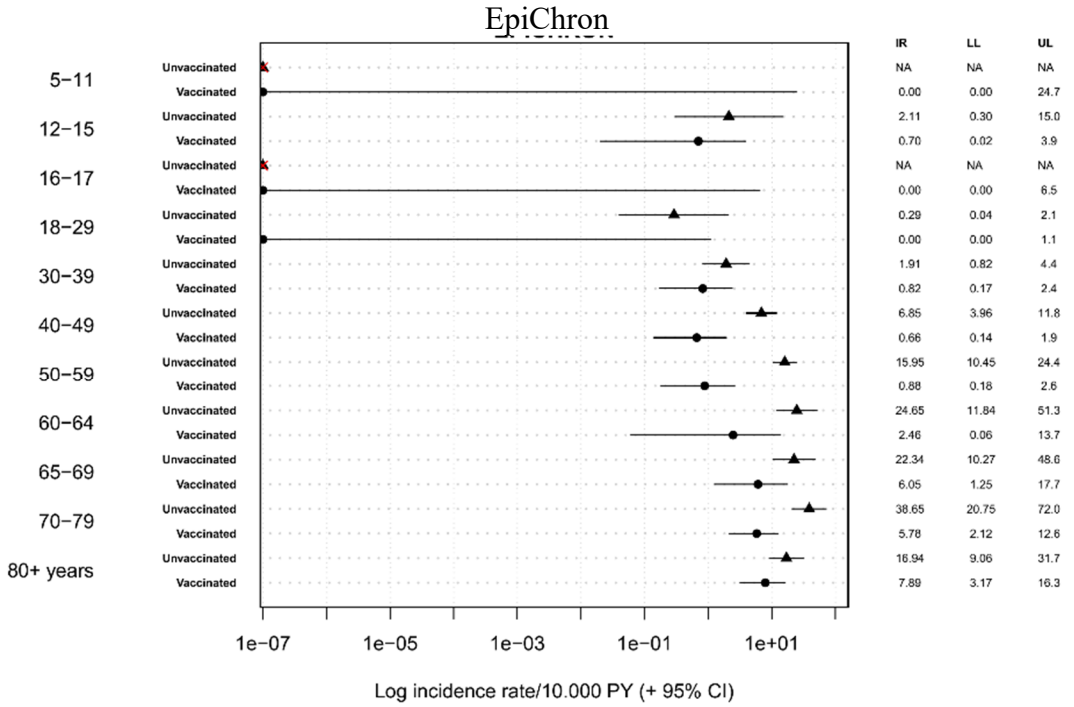


Figure 71. Forest plot showing incidence rates and 95% confidence intervals for acute respiratory distress syndrome among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source and by age groups (risk window: 365 days after dose 1)

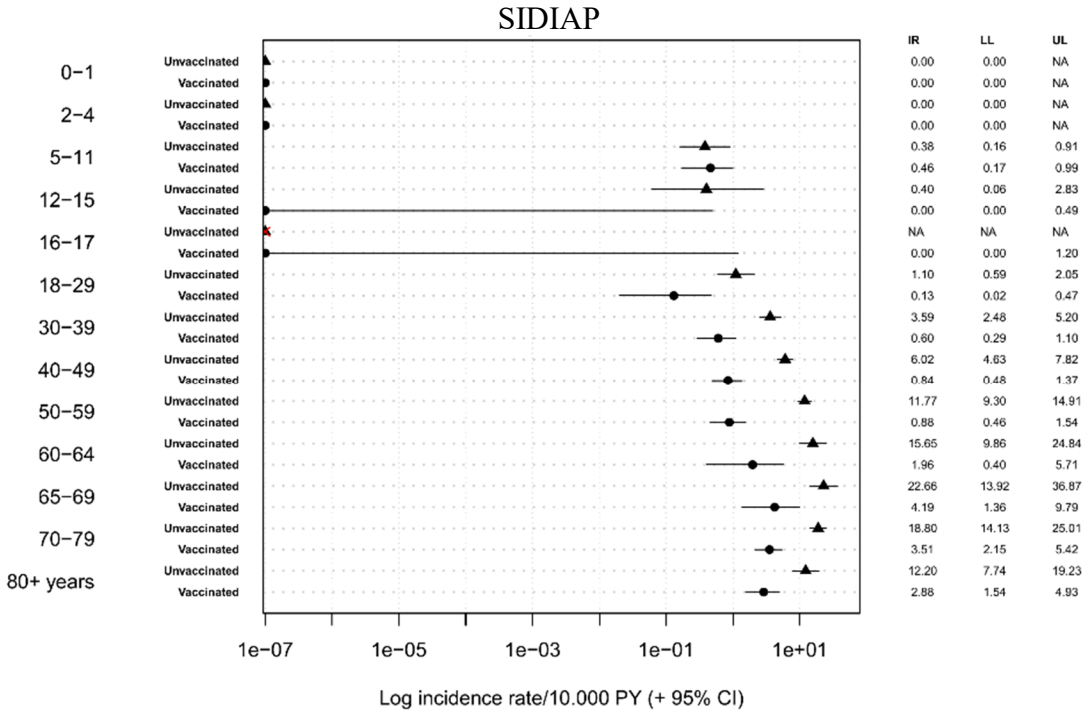


Table 80. Matched and adjusted hazard ratios (HRs) and matched and adjusted risk differences (RDs) per 10,000 person-years and their 95% CIs for acute respiratory distress syndrome among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source (risk window: 365 days after dose 1)

	Matched HR (95% CI)	Adjusted HR (95% CI)	Matched RD	Adjusted RD
Pedianet	NA	NA	NA	NA
NHR	0.21 (0.13, 0.35)	0.21 (0.13, 0.35)	-2.97	-2.98
PHARMO	1.20 (0.47, 3.07)	1.23 (0.48, 3.12)	0.16	0.16
EpiChron	0.16 (0.10, 0.25)	0.14 (0.09, 0.23)	-6.30	-6.95
SIDIAP	0.15 (0.12, 0.19)	0.14 (0.11, 0.18)	-4.13	-4.30

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

10.3.29. Erythema multiforme

Erythema multiforme events were rare and were identified in PHARMO, EpiChron and SIDIAP. The incidence rates ranged from 0.53 per 10,000 person-years (95% CI: 0.11, 1.54) in PHARMO to 1.17 per 10,000 person-years (95% CI: 0.38, 2.74) in EpiChron in the vaccinated cohorts. In the unvaccinated cohorts these were 0.47 per 10,000 person-years (95% CI: 0.24, 0.94) in SIDIAP and 0.70 per 10,000 person-years (95% CI: 0.10, 5.00) in EpiChron. The cumulative incidence was less than 1.00 per 10,000 individuals in both cohorts in the three data sources. There was a trend to higher incidences in the younger age groups, but the number of events was low.

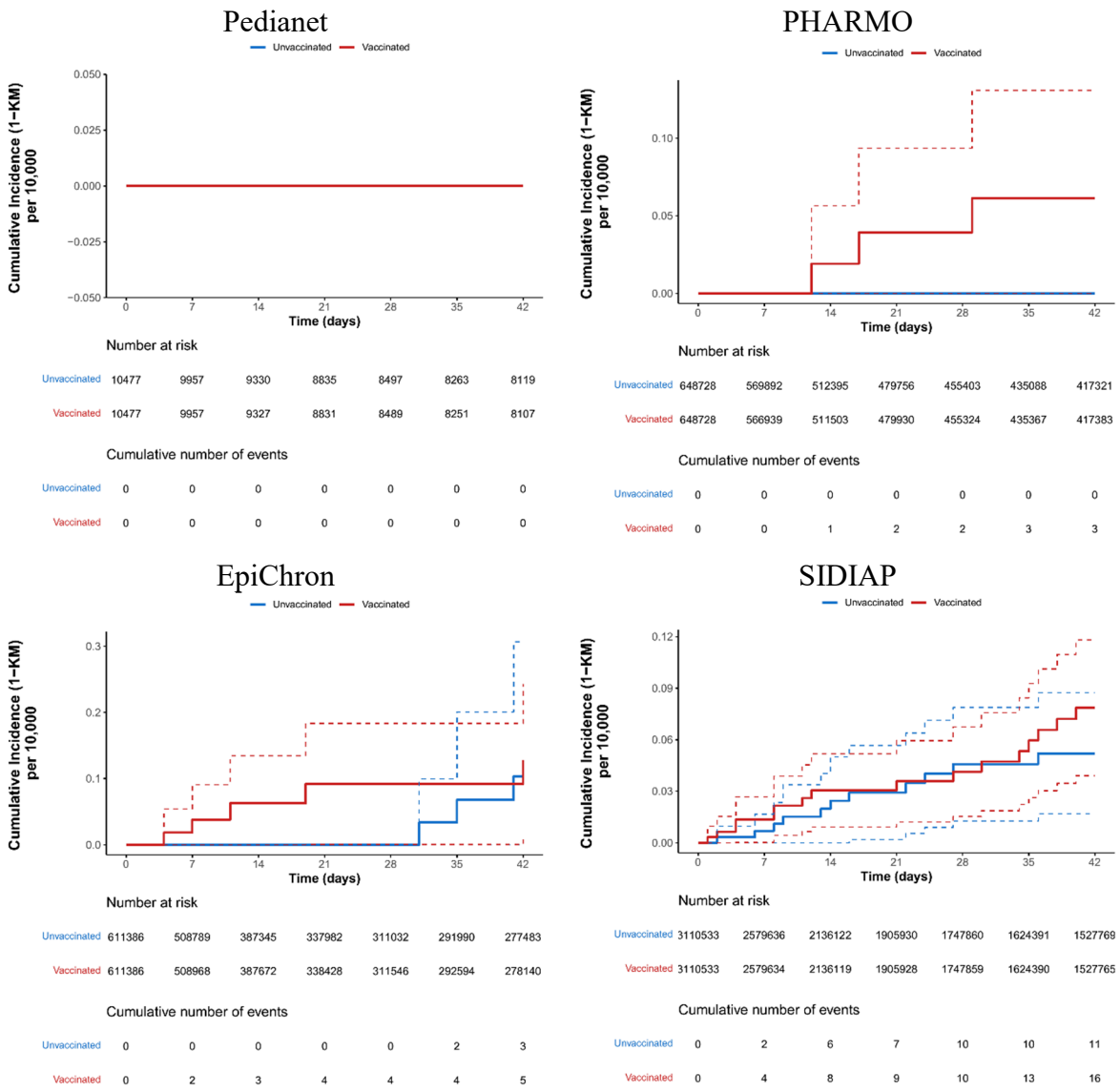
The matched HRs were 1.66 (95% CI: 0.19, 14.25) in EpiChron and 1.45 (95% CI: 0.62, 3.39) in SIDIAP. The adjusted HRs were 1.69 (95% CI: 0.20, 14.71) in EpiChron and 1.25 (95% CI: 0.53, 2.93) in SIDIAP. No differences were observed for the incidence of erythema multiforme within the 42-day risk window, between the vaccinated and unvaccinated cohorts.

Table 81. 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

	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)	0	0 (0, 0)	1,034.61	0 (0, 35.65)	0	0 (0, 0)	1,035.18	NA
NHR (Norway)	NA	NA	NA	NA	NA	NA	NA	NA
PHARMO (Netherlands)	<5	0.06 (0, 0.13)	56,854	0.53 (0.11, 1.54)	0	0 (0, 0)	56,954.61	NA
EpiChron (Spain)	5	0.13 (0.01, 0.24)	42,606.26	1.17 (0.38, 2.74)	<5	0.10 (0, 0.31)	42,558.99	0.70 (0.10, 5)
SIDIAP (Spain)	16	0.08 (0.04, 0.12)	233,102.90	0.69 (0.39, 1.11)	11	0.05 (0.02, 0.09)	233,103.13	0.47 (0.24, 0.94)

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 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 73. 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

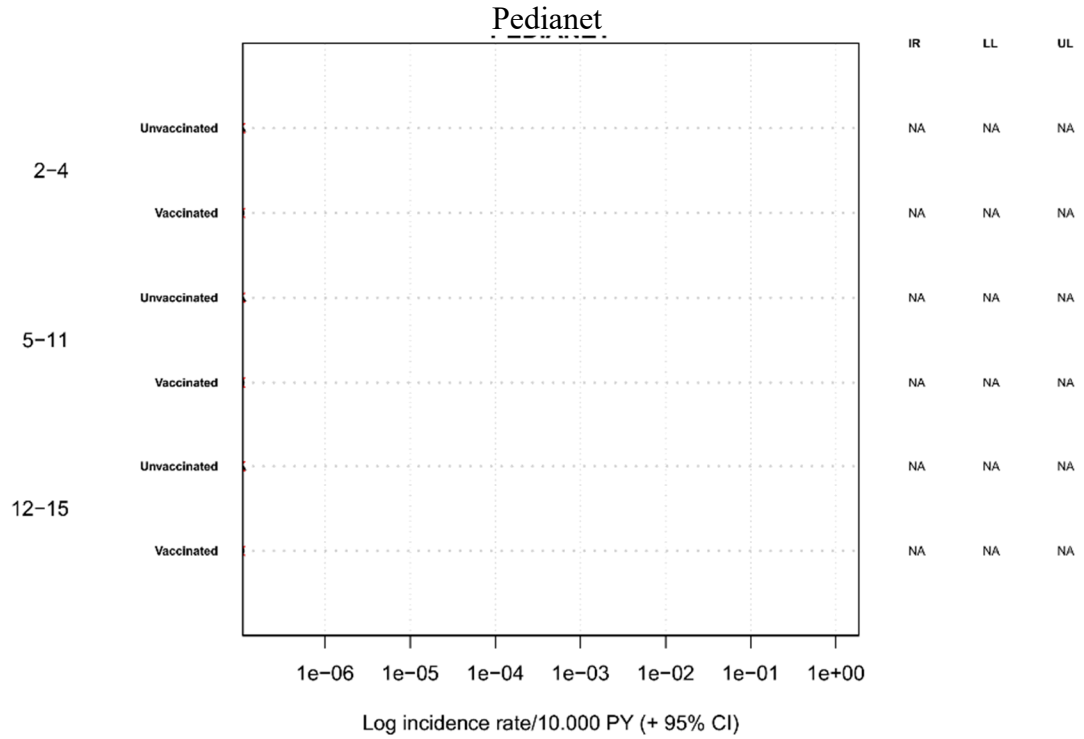


Figure 73. Forest plot showing incidence rates and 95% confidence intervals for erythema multiforme within 42 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source and by age groups

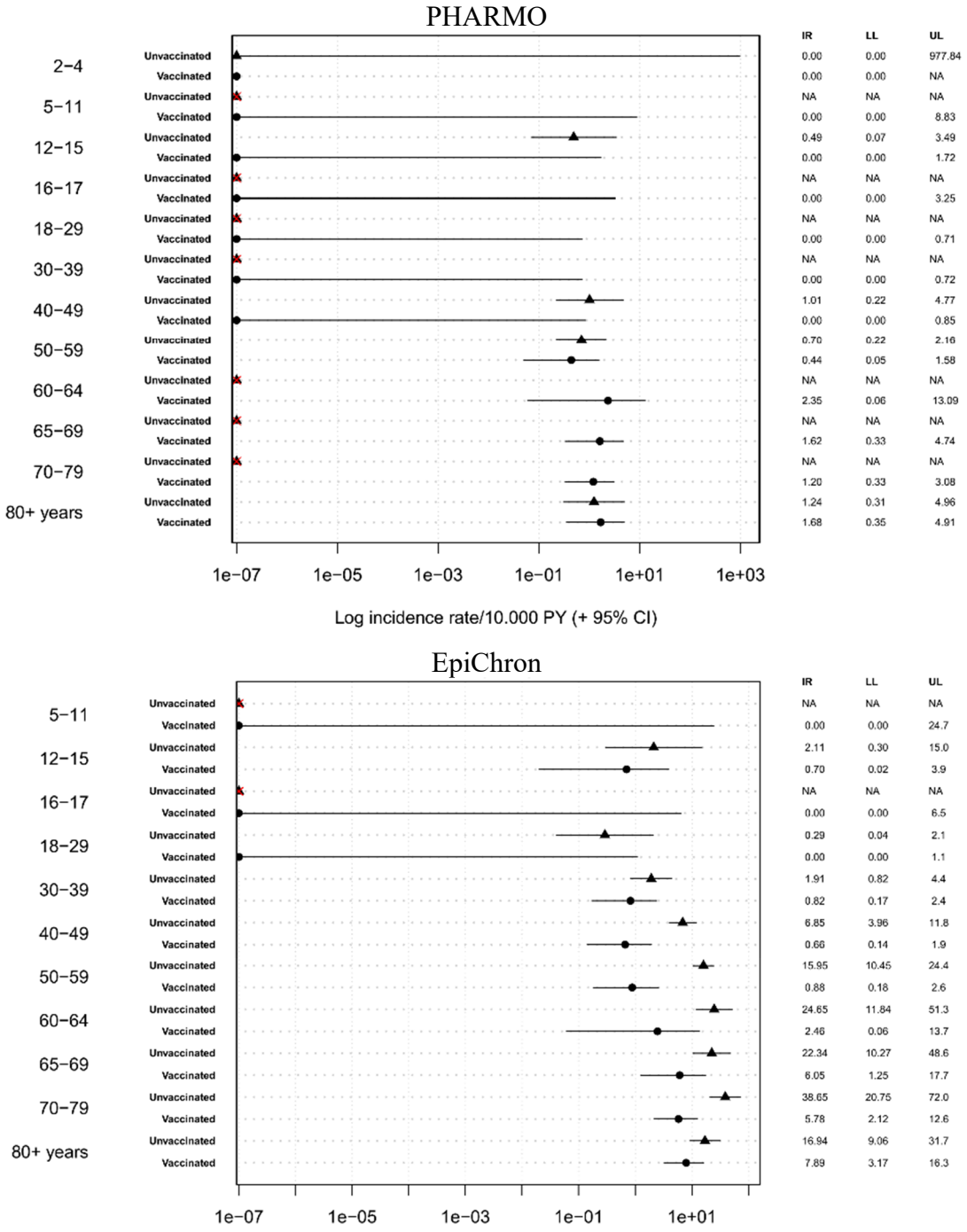


Figure 73. Forest plot showing incidence rates and 95% confidence intervals for erythema multiforme within 42 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source and by age groups

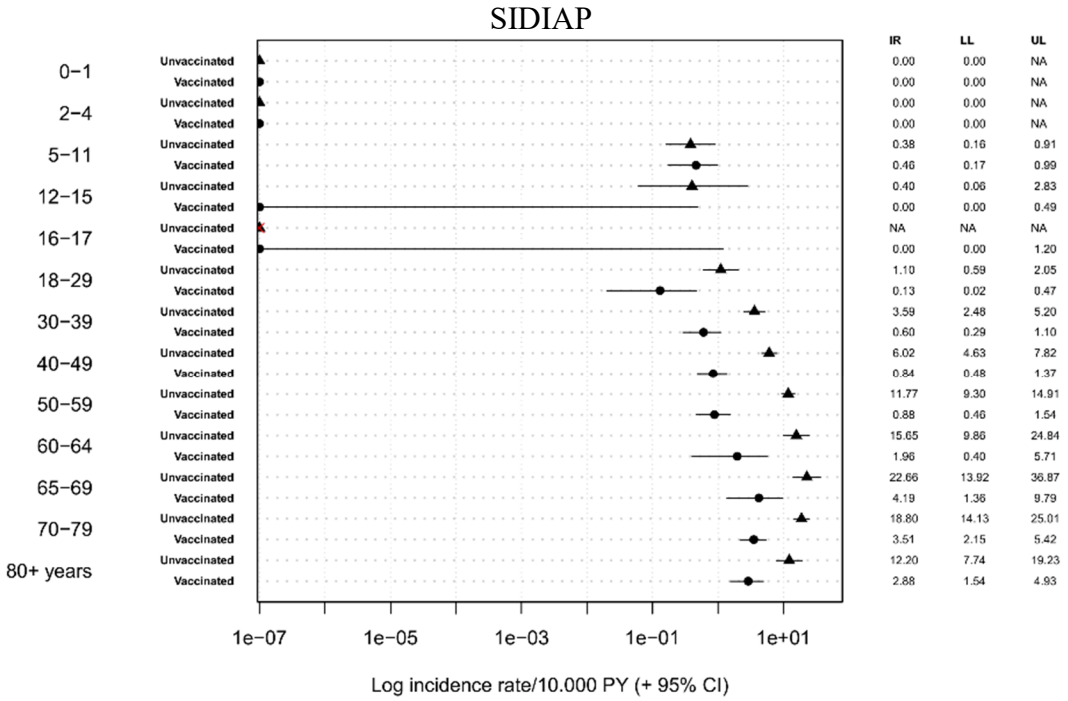


Table 82. Matched and adjusted hazard ratios (HRs) and matched and adjusted risk differences (RDs) per 10,000 person-years and their 95% CIs for erythema multiforme within 42 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source

	Matched HR (95% CI)	Adjusted HR (95% CI)	Matched RD	Adjusted RD
Pedianet	NA	NA	NA	NA
NHR	NA	NA	NA	NA
PHARMO	NA	NA	0.06	0.07
EpiChron	1.66 (0.19, 14.25)	1.69 (0.20, 14.71)	0.02	0.02
SIDIAP	1.45 (0.62, 3.39)	1.25 (0.53, 2.93)	0.03	0.02

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

10.3.30. Chilblain-like lesions

Chilblain-like lesions were identified in all data sources except NHR. The incidence rates ranged from 1.41 per 10,000 person-years (95% CI: 0.52, 3.07) in EpiChron to 19.34 (per 10,000 person-years (95% CI: 2.34, 69.87) in Pedianet in the vaccinated cohorts. In the unvaccinated cohorts these range from 1.18 per 10,000 person-years (95% CI: 0.49, 2.82) in EpiChron to 3.16 per 10,000 person-years (95% CI: 1.78, 5.63) in PHARMO. The cumulative incidences during the 42-day risk window were less than 1.3 per 10,000 individuals in the vaccinated cohorts, except in Pedianet, with a cumulative incidence of 2.22 (95% CI: 0, 5.32) and less than 0.50 per 10,000 individuals in the unvaccinated cohorts. The incidence was similar in the different age groups.

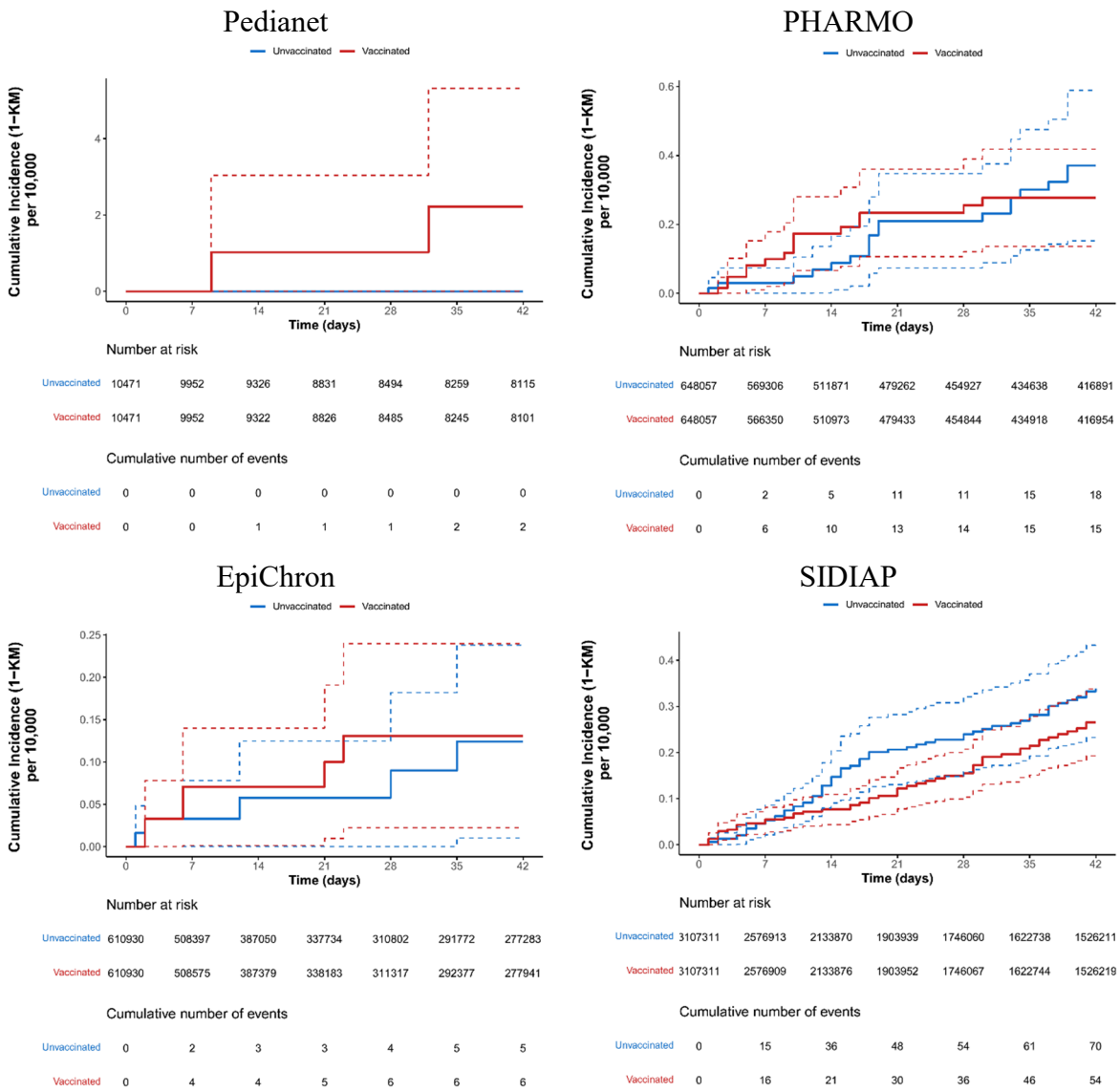
The matched unadjusted HRs were 0.60 (95% CI: 0.28, 1.30) in PHARMO, 0.36 (95% CI: 0.13, 0.99) in EpiChron, and 0.58 (95% CI: 0.40, 0.85) in SIDIAP. The adjusted HRs were 0.54 (95% CI: 0.25, 1.16) in PHARMO, 0.31 (95% CI: 0.11, 0.87) in EpiChron, and 0.57 (95% CI: 0.39, 0.83) in SIDIAP. No differences were observed for the incidence of chilblain-like lesions within the 42-day risk window, between the vaccinated and unvaccinated cohorts.

Table 83. 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

	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)	<5	2.22 (0, 5.32)	1,034.02	19.34 (2.34, 69.87)	0	0 (0, 0)	1,034.69	NA
NHR (Norway)	NA	NA	NA	NA	NA	NA	NA	NA
PHARMO (Netherlands)	15	0.28 (0.14, 0.42)	56,794.93	2.64 (1.48, 4.36)	18	0.37 (0.15, 0.59)	56,895.87	3.16 (1.78, 5.63)
EpiChron (Spain)	6	0.13 (0.02, 0.24)	42,574.64	1.41 (0.52, 3.07)	5	0.12 (0.01, 0.24)	42,527.23	1.18 (0.49, 2.82)
SIDIAP (Spain)	54	0.27 (0.19, 0.34)	232,861.28	2.32 (1.74, 3.03)	70	0.34 (0.24, 0.44)	232,860.69	3.01 (2.23, 4.05)

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 74. 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 75. 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

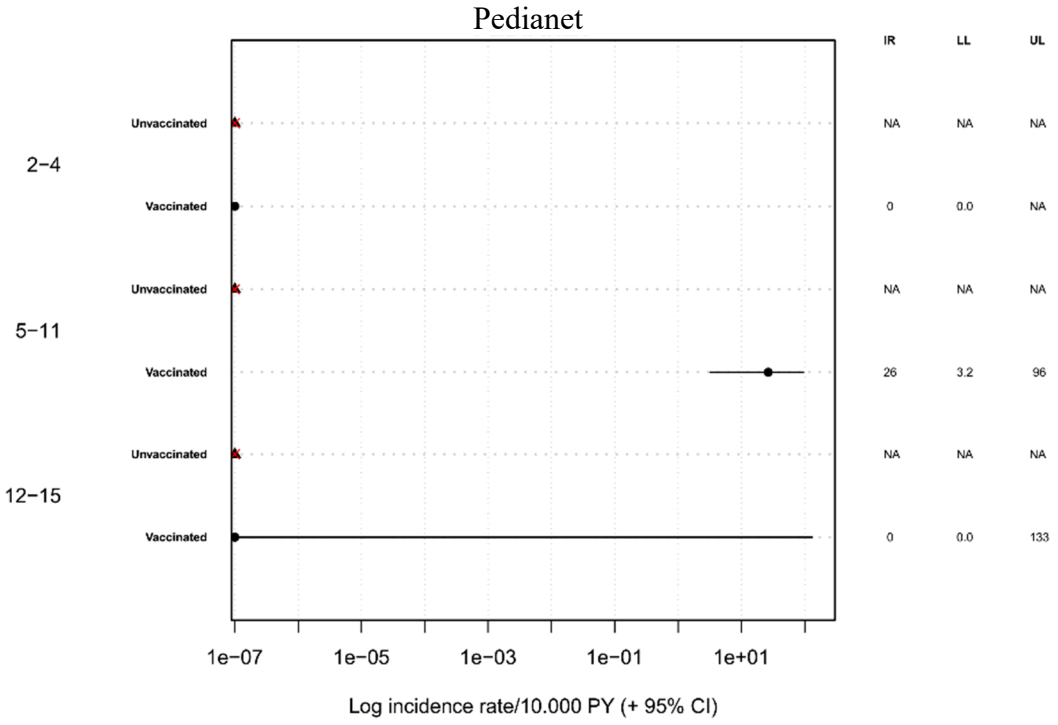


Figure 75. Forest plot showing incidence rates and 95% confidence intervals for chilblain-like lesions within 42 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source and by age groups

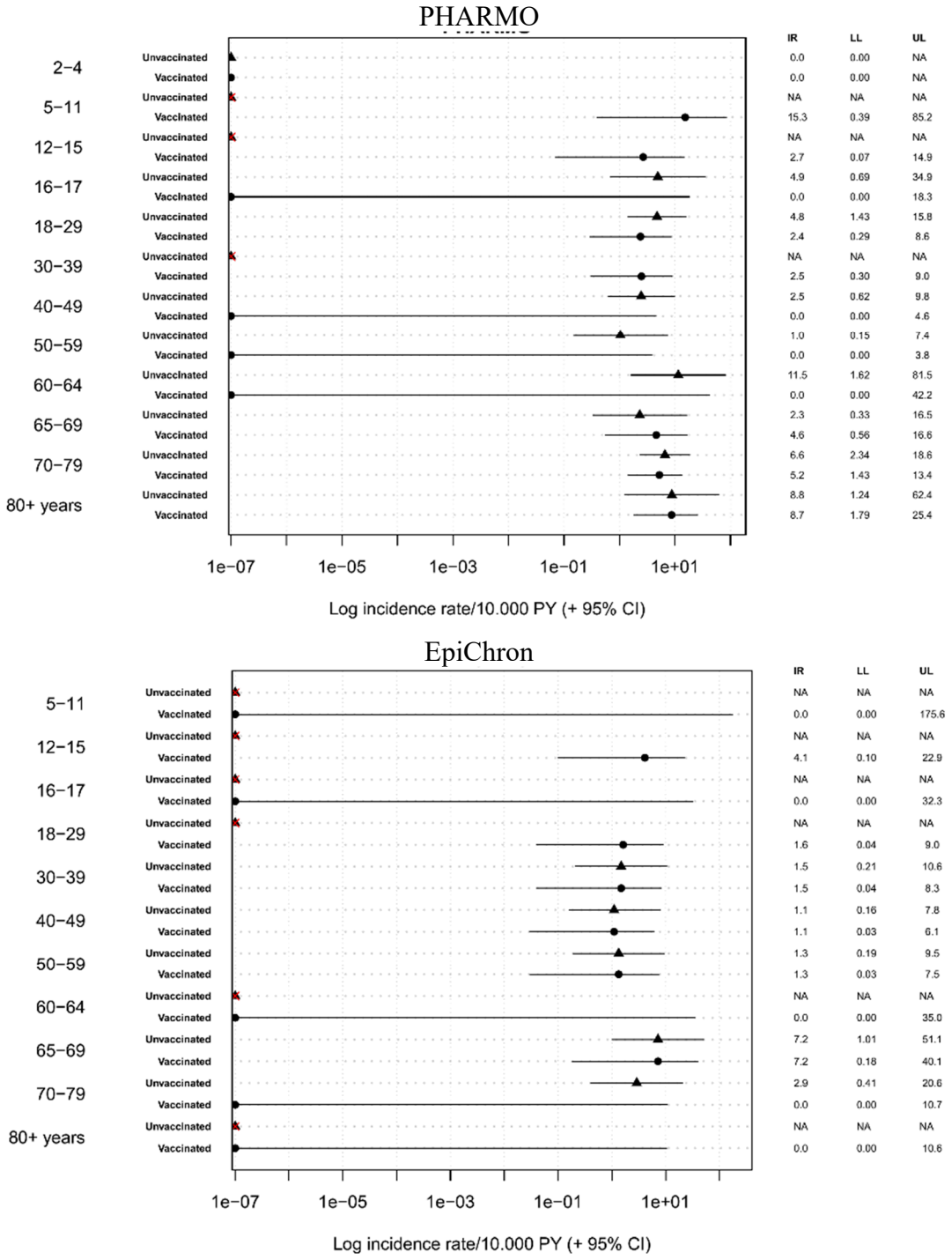


Figure 75. Forest plot showing incidence rates and 95% confidence intervals for chilblain-like lesions within 42 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source and by age groups

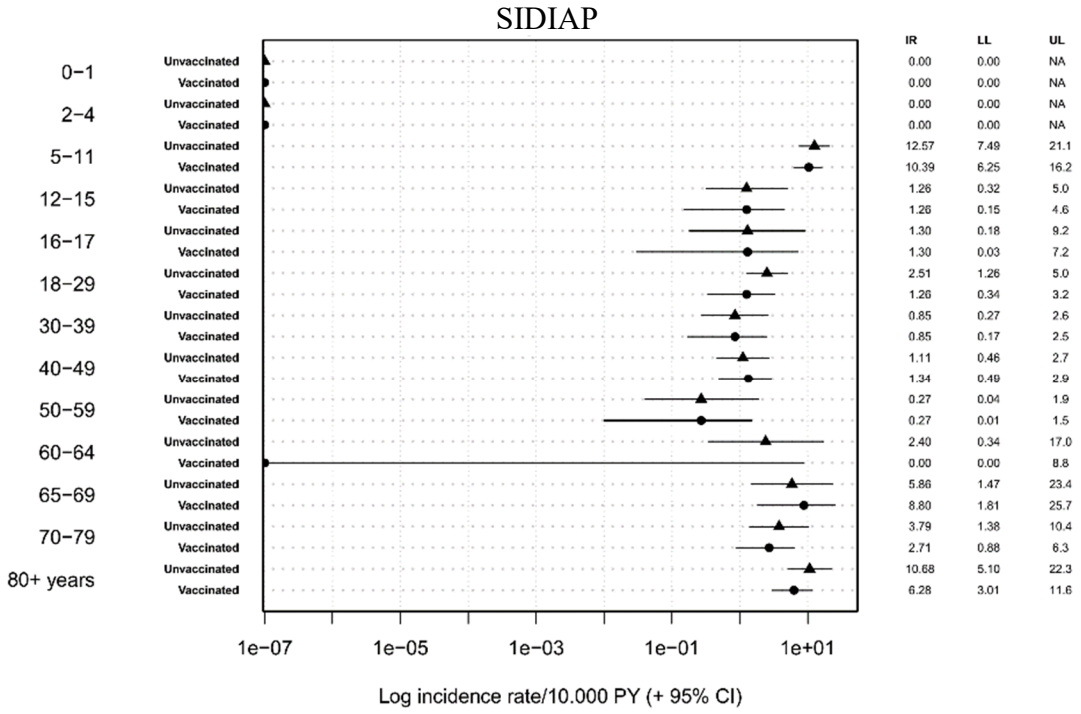


Table 84. Matched and adjusted hazard ratios (HRs) and matched and adjusted risk differences (RDs) per 10,000 person-years and their 95% CIs for chilblain-like lesions within 42 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source

	Matched HR (95% CI)	Adjusted HR (95% CI)	Matched RD	Adjusted RD
Pedianet	NA	NA	2.22	2.26
NHR	NA	NA	NA	NA
PHARMO	0.84 (0.39, 1.80)	0.77 (0.36, 1.66)	-0.09	-0.12
EpiChron	1.20 (0.37, 3.93)	1.13 (0.34, 3.75)	0.01	0
SIDIAP	0.77 (0.52, 1.15)	0.77 (0.52, 1.14)	-0.07	-0.07

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

10.3.31. Secondary amenorrhea

Secondary amenorrhea events were identified in EpiChron and SIDIAP. The incidence rates, which were assessed only in females in age groups considered to be of child-bearing potential, were 0.16 per 10,000 person-years (95% CI: 0.02, 0.57) in EpiChron and 28.62 per 10,000 person-years (95% CI: 27.36, 29.93) in SIDIAP in the vaccinated cohorts. In the unvaccinated cohorts the incidence rates were 0.40 per 10,000 person-years (95% CI: 0.17, 0.9) in EpiChron and 25.42 per 10,000 person-years (95% CI: 23.86, 27.08) in SIDIAP. In Pedianet below 5 events were found in the vaccinated and unvaccinated. The cumulative incidence varied between below 0.1 in EpiChron and below 13 in SIDIAP per 10,000 individuals in the vaccinated cohorts and unvaccinated cohorts. Age patterns reflected occurrence of menstrual problems in women in child-bearing age.

The matched HRs HRs were 0.40 (95% CI: 0.08, 2.05) in EpiChron and 1.13 (95% CI: 1.04, 1.22) in SIDIAP. The adjusted HRs were 0.34 (95% CI: 0.07, 1.76) in EpiChron and 1.07 (95% CI: 0.99, 1.16) in SIDIAP. No significant differences were observed in the incidence of secondary amenorrhea between the vaccinated and unvaccinated cohorts in the data sources in the adjusted analyses.

Table 85. 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

	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)	<5	2.40 (0, 5.74)	3,883.14	5.15 (0.62, 18.61)	<5	1.40 (0, 4.13)	3,902.53	2.56 (0.36, 18.19)
NHR (Norway)	0	0 (0, 0)	478,587.41	0 (0, 0.08)	0	0 (0, 0)	475,619.82	NA
PHARMO (Netherlands)	0	0 (0, 0)	194,644.81	0 (0, 0.19)	0	0 (0, 0)	190,301.36	NA
EpiChron (Spain)	<5	0.09 (0, 0.20)	126,586.30	0.16 (0.02, 0.57)	5	0.20 (0.02, 0.38)	126,100.75	0.40 (0.17, 0.95)
SIDIAP (Spain)	1,939	14.61 (13.93, 15.28)	677,440.40	28.62 (27.36, 29.93)	1,722	12.60 (11.77, 13.44)	677,491.12	25.42 (23.86, 27.08)

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 76. 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

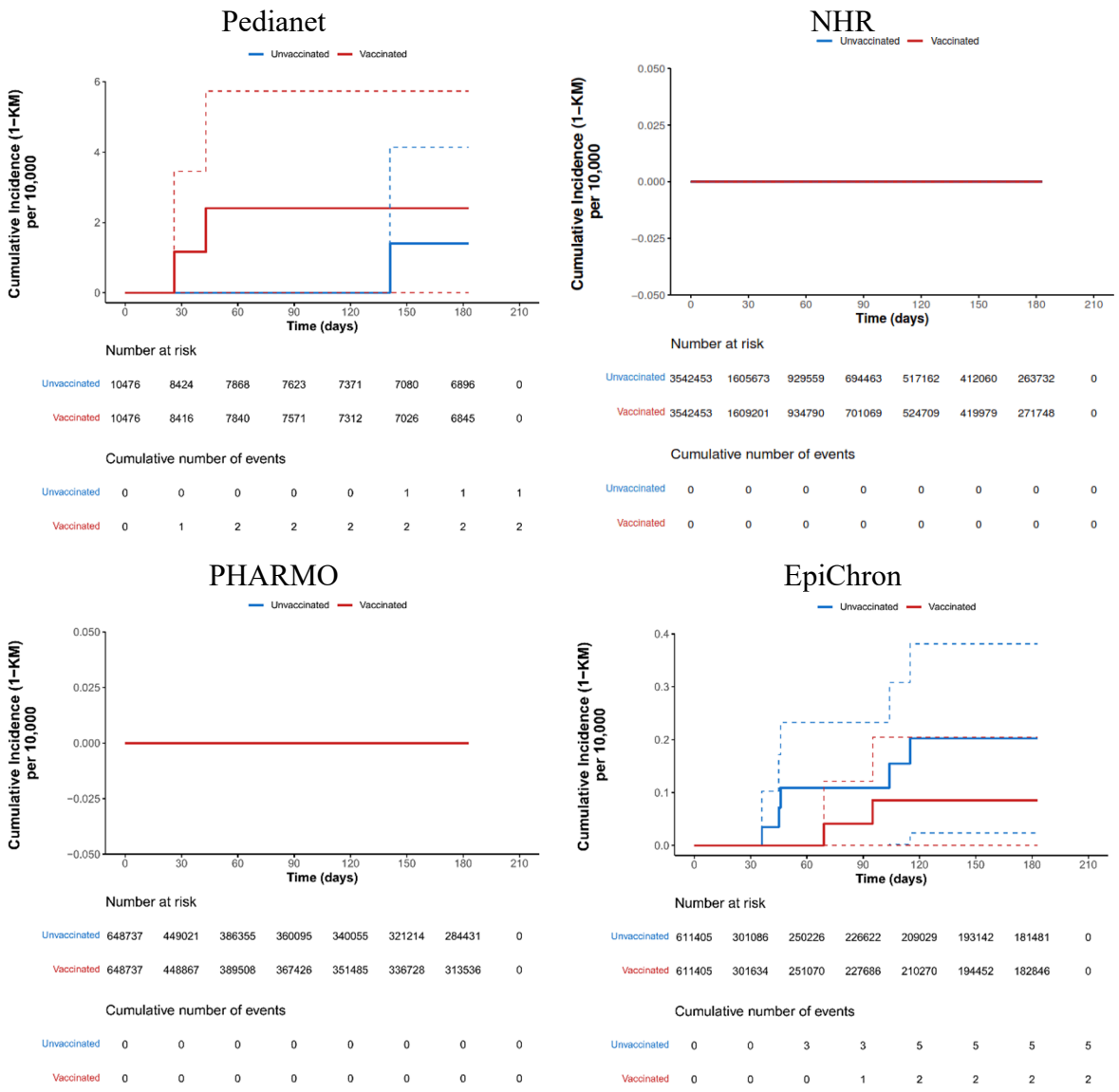
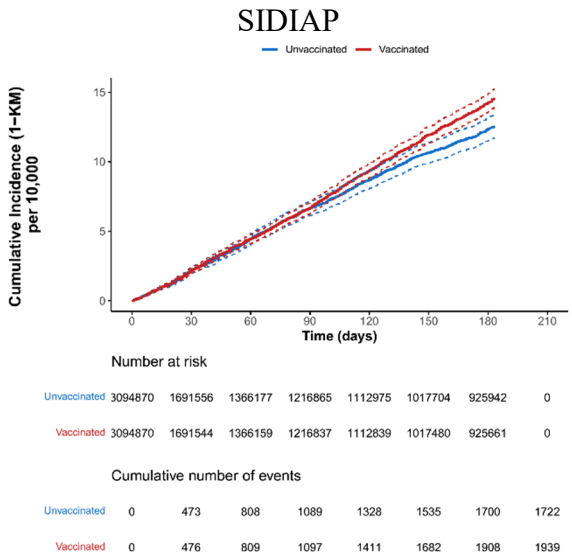


Figure 76. Cumulative incidence of secondary amenorrhea within 183 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source



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 77. 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

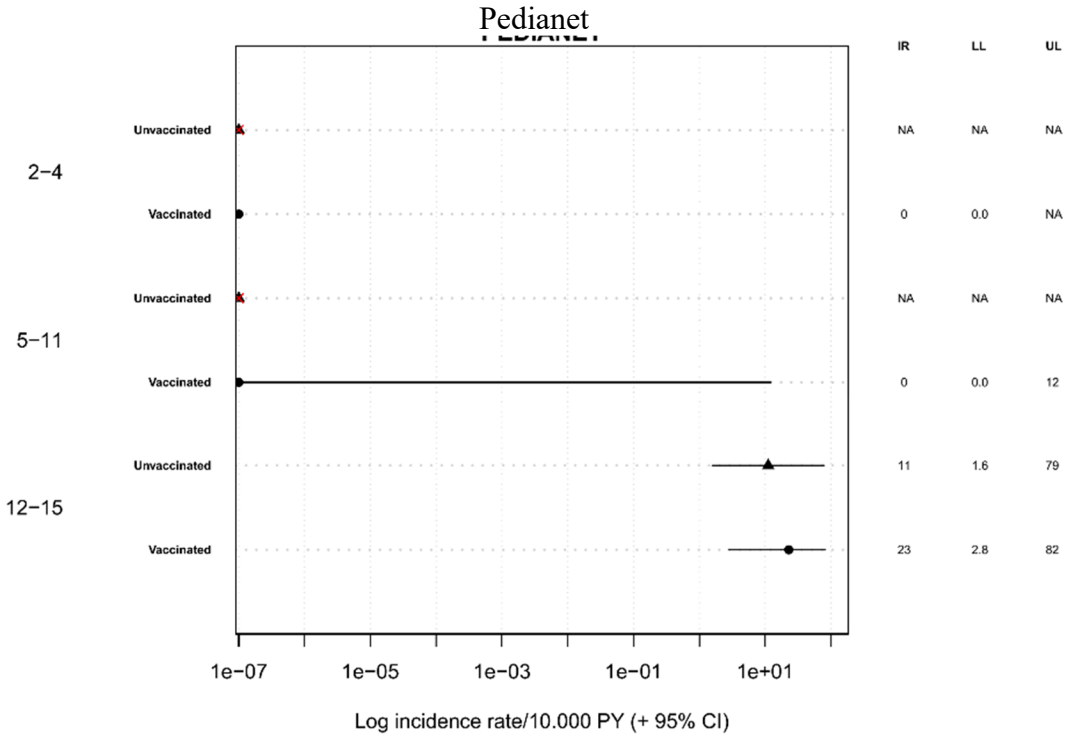


Figure 77. Forest plot showing incidence rates and 95% confidence intervals for secondary amenorrhea within 183 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source and by age groups

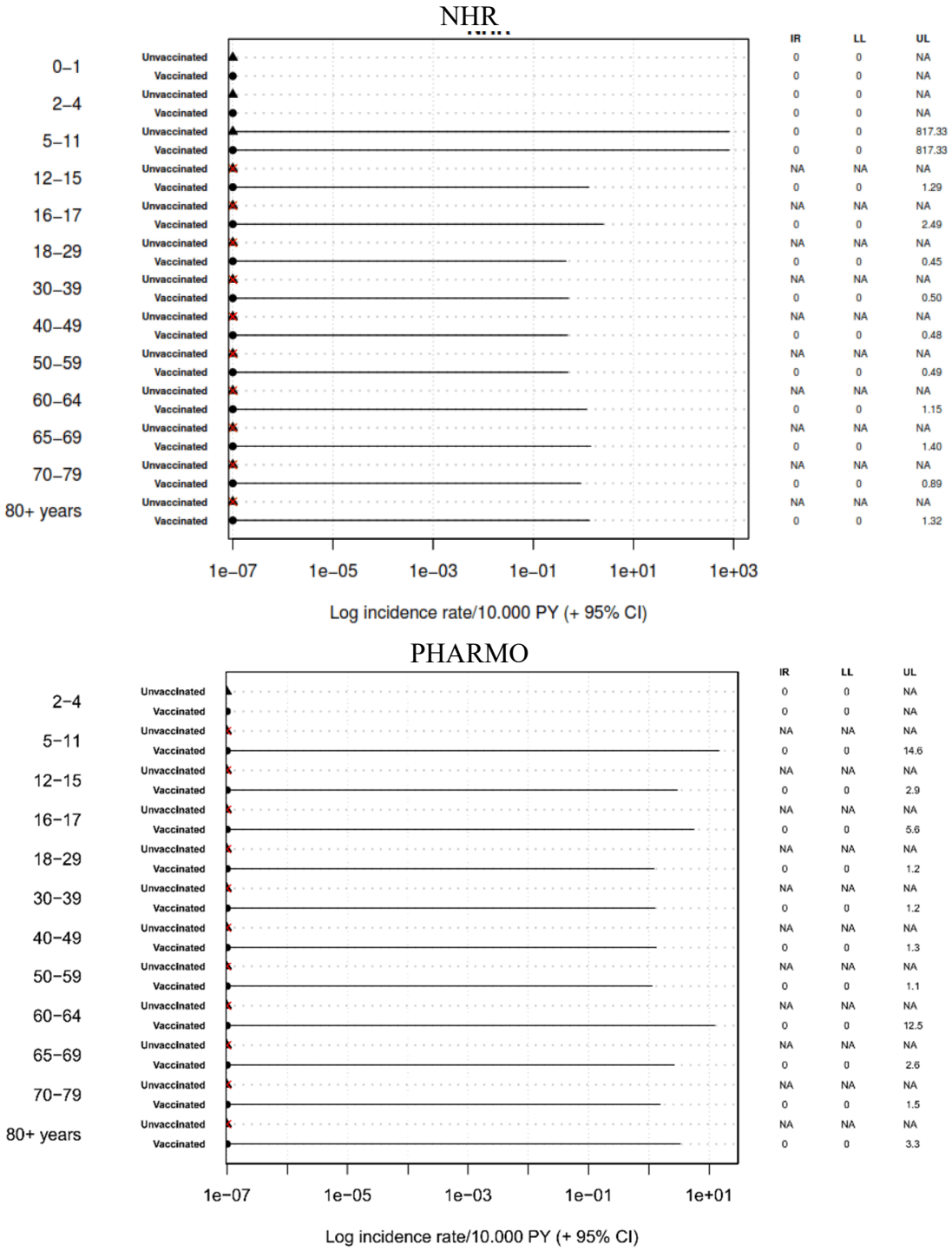


Figure 77. Forest plot showing incidence rates and 95% confidence intervals for secondary amenorrhea within 183 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source and by age groups

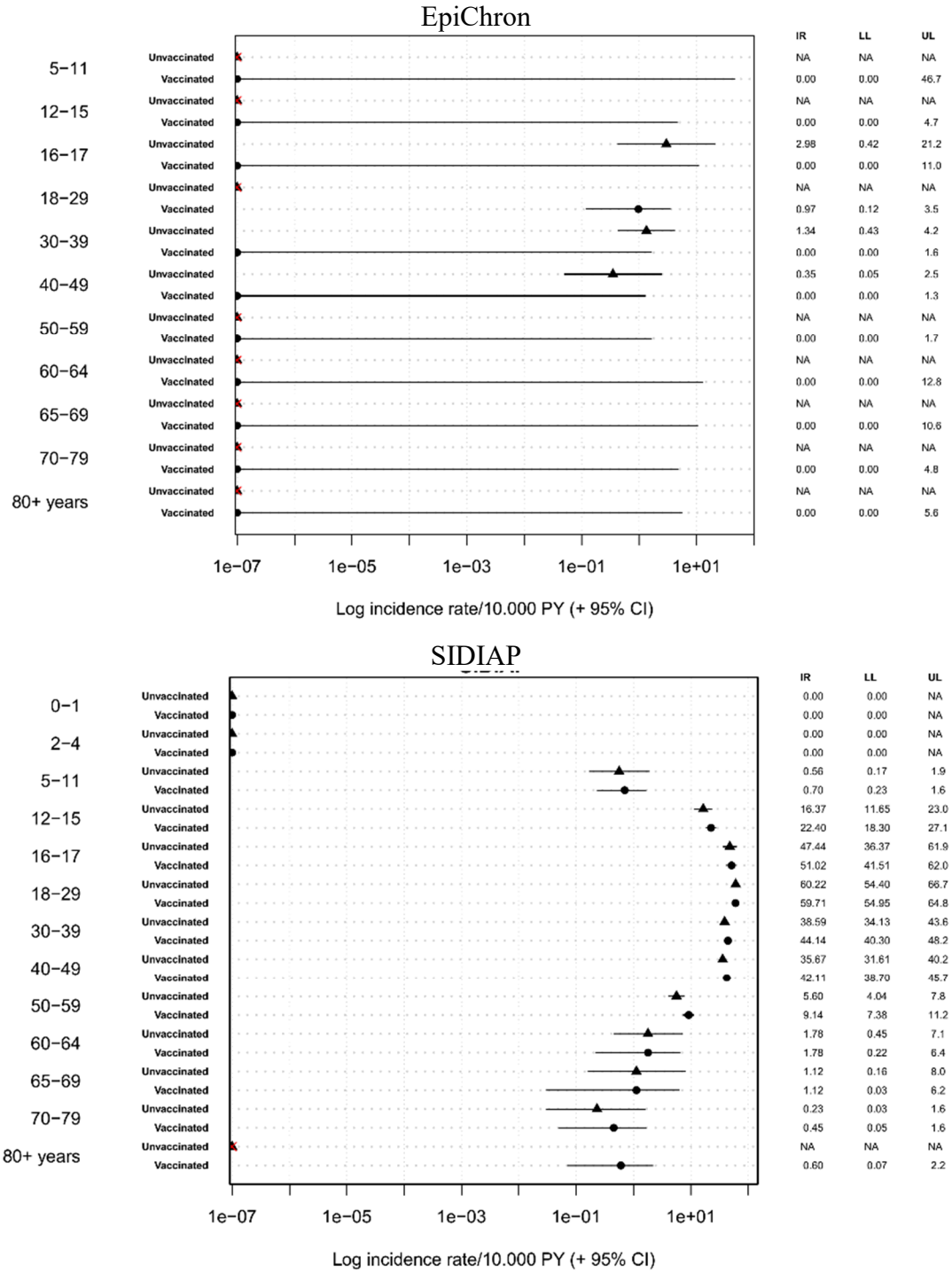


Table 86. Matched hazard ratios (HRs) and matched risk differences (RDs) per 10,000 person-years and their 95% CIs for secondary amenorrhea within 183 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source

	Matched HR (95% CI)	Adjusted HR (95% CI)	Matched RD	Adjusted RD
Pedianet	2.01 (0.18, 22.06)	1.78 (0.16, 19.84)	1.01	0.76
NHR	NA	NA	NA	NA
PHARMO	NA	NA	NA	NA
EpiChron	0.40 (0.08, 2.05)	0.34 (0.07, 1.76)	-0.12	-0.14
SIDIAP	1.13 (1.04, 1.22)	1.07 (0.99, 1.16)	2	1.29

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

10.3.32. Hypermenorrhea

Hypermenrrohea events were identified in Pedianet, PHARMO, EpiChron, and SIDIAP. The incidence rates, which were assessed only in females in age groups considered to be of child-bearing potential, were 47.17 per 10,000 person-years (95% CI: 45.55, 48.84) in SIDIAP and 66.96 per 10,000 person-years (95% CI: 62.50, 71.65) in EpiChron in the vaccinated cohorts. In the unvaccinated cohorts the incidence rates were 40.39 per 10,000 person-years (95% CI: 38.40, 42.50) in SIDIAP and 43.58 per 10,000 person-years (95% CI: 38.95, 48.77) in EpiChron. In PHARMO, incidence rates were below 1 with very few cases identified in both cohorts. The cumulative incidence was below 46.00 per 10,000 individuals in the vaccinated cohorts and unvaccinated cohorts. Age patterns were reflecting occurrence of menstrual problems in women in child-bearing age. However, a few cases have been identified in SIDIAP and EpiChron among children, therefore identification of hypermenorrhea will be assessed further in both data sources.

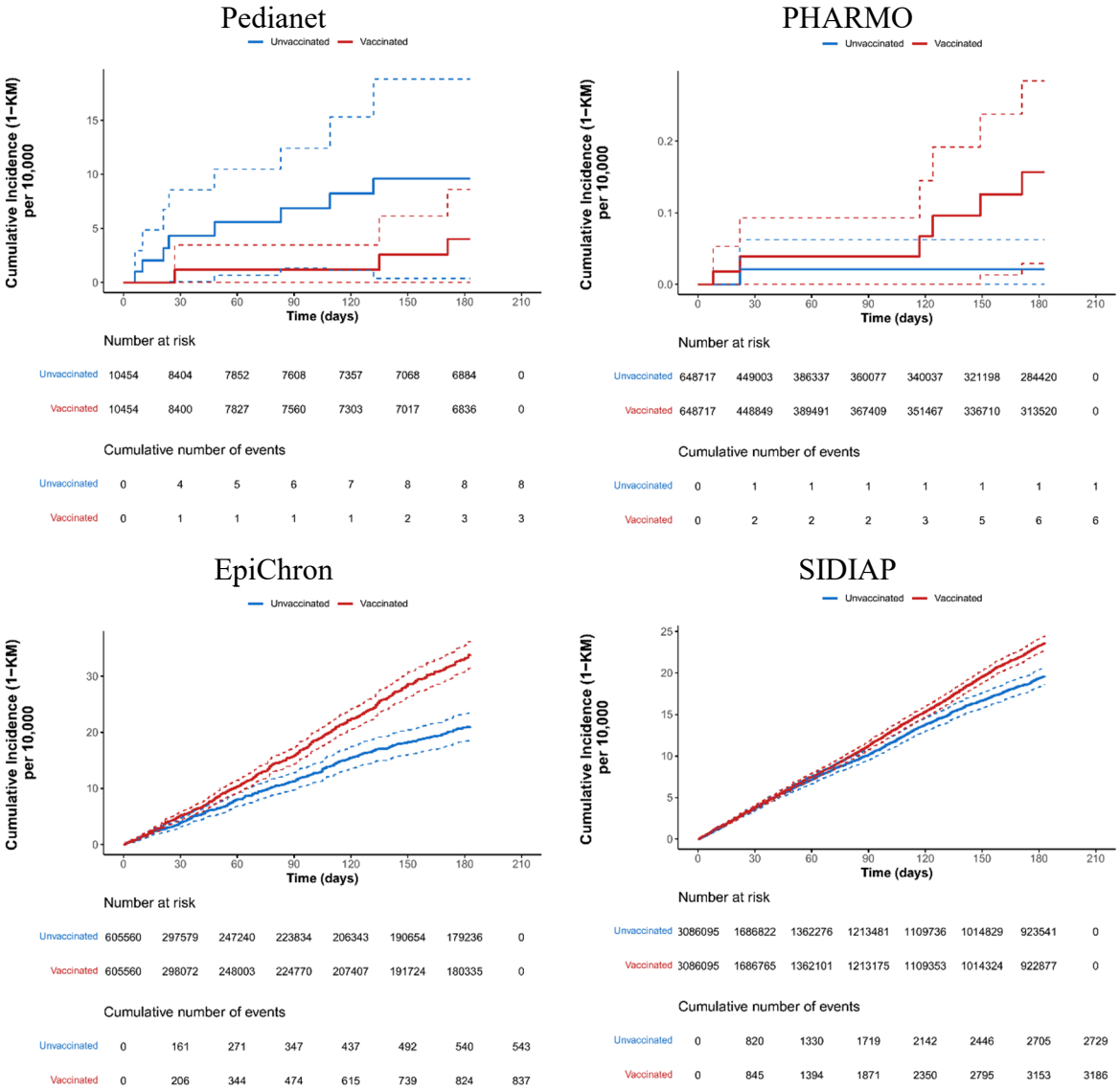
The matched HRs were 0.38 (95% CI: 0.09, 1.61) in Pedianet, 5.84 (95% CI: 0.71, 48.15) in PHARMO, 1.54 (95% CI: 1.35, 1.75) in EpiChron, and 1.17 (95% CI: 1.10, 1.24) in SIDIAP. The adjusted HRs were 0.33 (95% CI: 0.08, 1.42) in Pedianet, 6.62 (95% CI: 0.80, 54.62), 6.62 (95% CI: 0.80, 54.62) in PHARMO, 1.38 (95% CI: 1.21, 1.57) in EpiChron, and 1.09 (95% CI: 1.03, 1.16) in SIDIAP.

Table 87. Risk estimates (95% CI) per 10,000 person-years (PY) for hypermenorrhea within 183 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source

	Vaccinated				Unvaccinated			
Data source	**Events (n)**	**Cumulative incidence (95% CI)**	**Person-years (PY)**	**Incidence rate (95% CI)**	**Events (n)**	**Cumulative incidence (95% CI)**	**Person-years (PY)**	**Incidence rate (95% CI)**
Pedianet (Italy)	<5	4.03 (0, 8.60)	3,877.11	7.74 (1.60, 22.61)	8	9.60 (0.38, 18.81)	3,894.89	20.54 (8.21, 51.37)
NHR (Norway)	NA	NA	NA	NA	NA	NA	NA	NA
PHARMO (Netherlands)	6	0.16 (0.03, 0.28)	194,636.06	0.31 (0.11, 0.67)	<5	0.02 (0, 0.06)	190,292.80	0.05 (0.01, 0.37)
EpiChron (Spain)	837	33.91 (31.55, 36.28)	125,007.67	66.96 (62.50, 71.65)	543	21.03 (18.57, 23.50)	124,591.32	43.58 (38.95, 48.77)
SIDIAP (Spain)	3,186	23.65 (22.80, 24.51)	675,430.90	47.17 (45.55, 48.84)	2,729	19.64 (18.59, 20.68)	675,580.88	40.39 (38.40, 42.50)

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



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

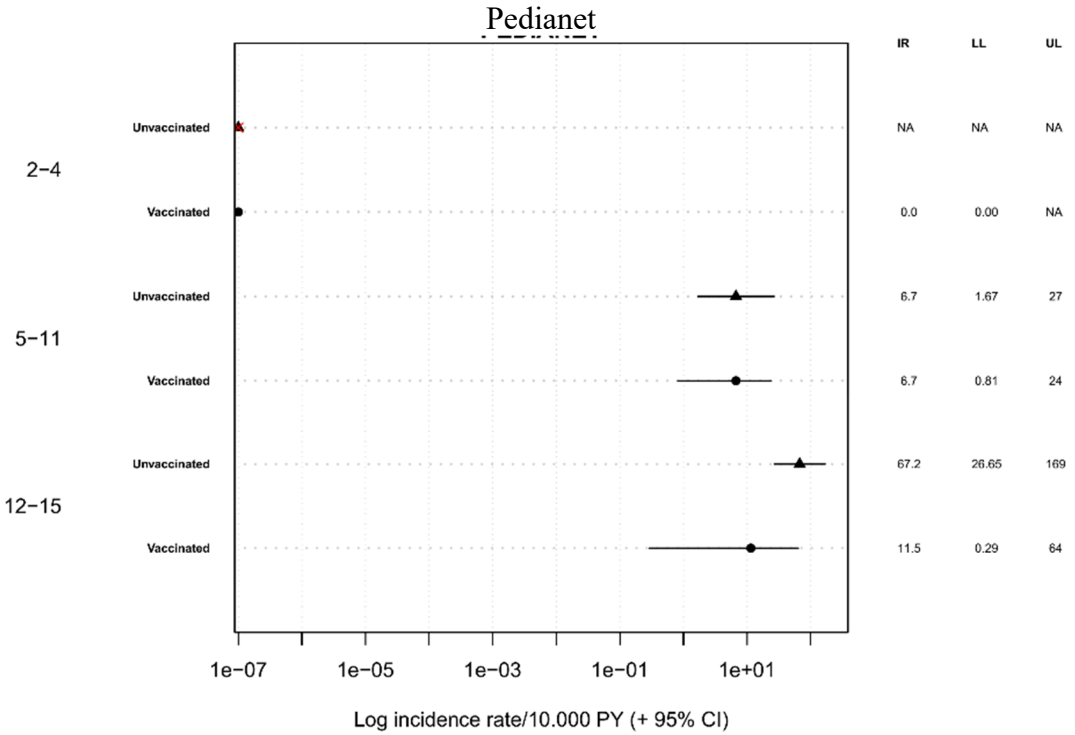


Figure 79. Forest plot showing incidence rates and 95% confidence intervals for hypermenorrhea within 183 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source and by age groups

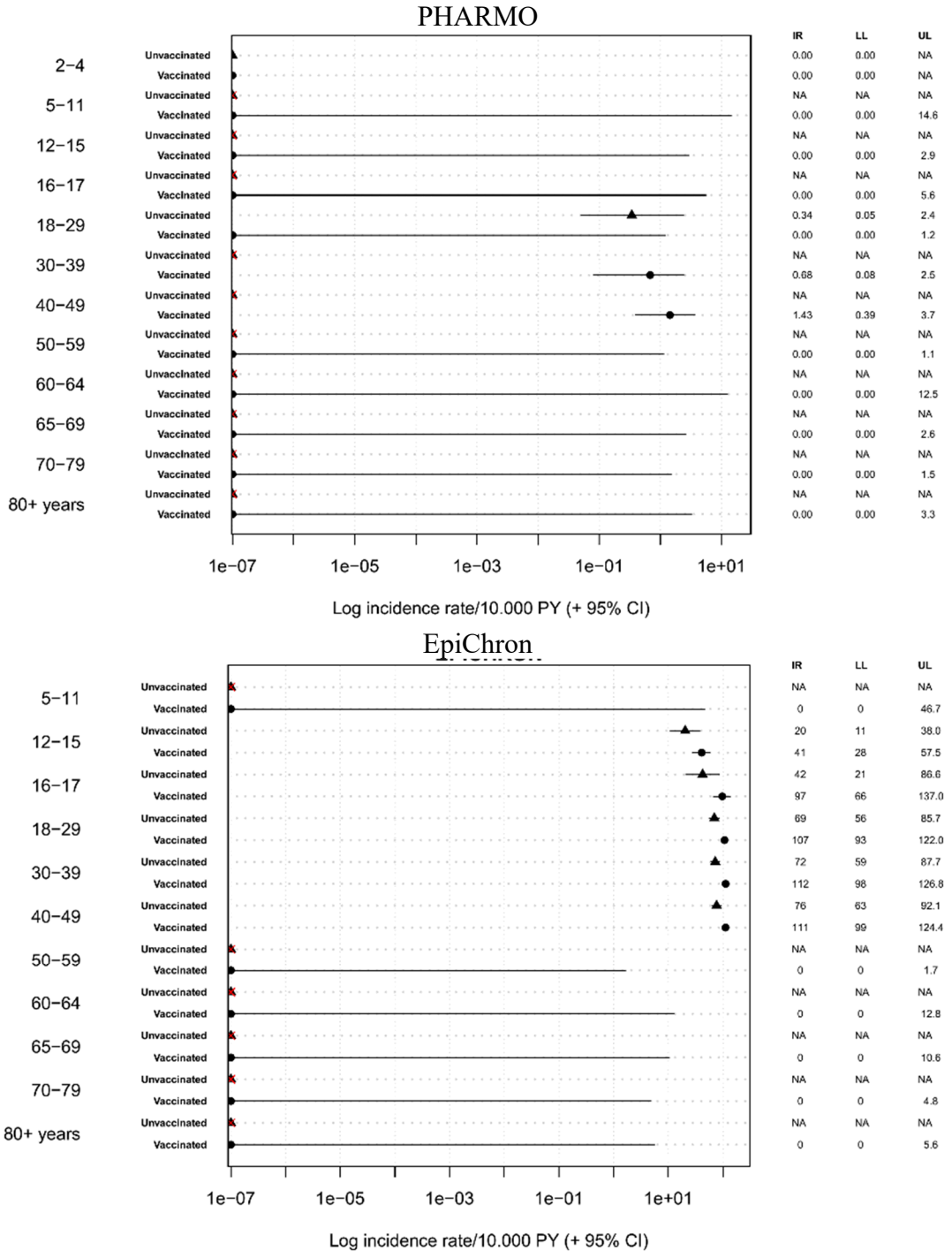


Figure 79. Forest plot showing incidence rates and 95% confidence intervals for hypermenorrhea within 183 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source and by age groups

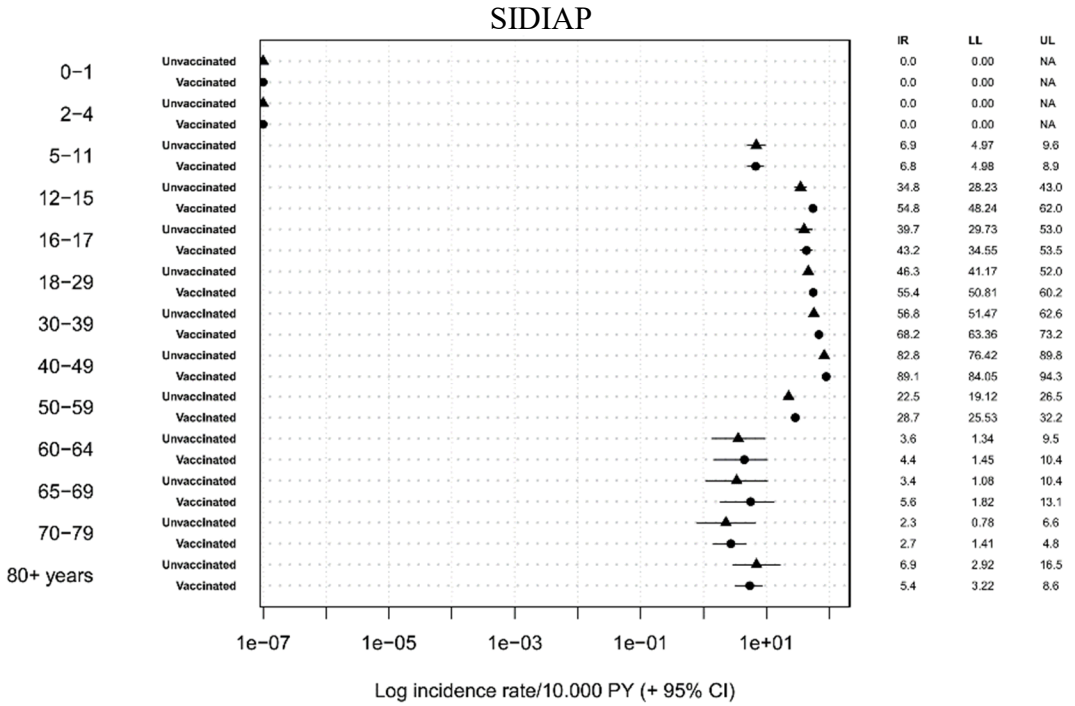


Table 88. Matched and adjusted hazard ratios (HRs) and matched and adjusted risk differences (RDs) per 10,000 person-years and their 95% CIs for hypermenorrhea within 183 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source

	Matched HR (95% CI)	Adjusted HR (95% CI)	Matched RD	Adjusted RD
Pedianet	0.38 (0.09, 1.61)	0.33 (0.08, 1.42)	-5.57	-6.45
NHR	NA	NA	NA	NA
PHARMO	5.84 (0.71, 48.15)	6.62 (0.80, 54.62)	0.14	0.14
EpiChron	1.54 (1.35, 1.75)	1.38 (1.21, 1.57)	12.88	9.86
SIDIAP	1.17 (1.10, 1.24)	1.09 (1.03, 1.16)	4.02	2.58

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

10.3.33. Anosmia, ageusia

Anosmia, ageusia events were identified in all data sources except in the unvaccinated cohort in Pedianet. The incidence rates ranged from 4.12 per 10,000 person-years (95% CI: 3.35, 5.01) in NHR to 19.31 per 10,000 person-years (95% CI: 15.36, 23.97) in EpiChron in the vaccinated cohorts. In the unvaccinated cohorts these ranged from 3.69 per 10,000 person-years (95% CI: 2.31, 5.809 in PHARMO to 15.09 per 10,000 person-years (95% CI: 11.29, 20.18) in EpiChron. The cumulative incidence was less than 2.2 per 10,000 individuals in the vaccinated cohorts and less than 1.90 per 10,000 individuals in the unvaccinated cohorts in all data sources. The incidence was similar in the different age groups.

The matched HRs for anosmia, ageusia were 0.91 (95% CI: 0.67, 1.24) in NHR, 1.38 (95% CI: 0.77, 2.50) in PHARMO, 1.28 (95% CI: 0.89, 1.83) in EpiChron, and 0.76 (95% CI: 0.61, 0.94) in SIDIAP. The adjusted HRs were 0.92 (95% CI: 0.67, 1.24) in NHR, 1.26 (95% CI: 0.70, 2.29) in PHARMO, 1.20 (95% CI: 0.83, 1.72) in EpiChron, and 0.72 (95% CI: 0.58, 0.90) in SIDIAP. No differences were observed for the incidence of anosmia/ ageusia within the 42-day risk window, between the vaccinated and unvaccinated cohorts.

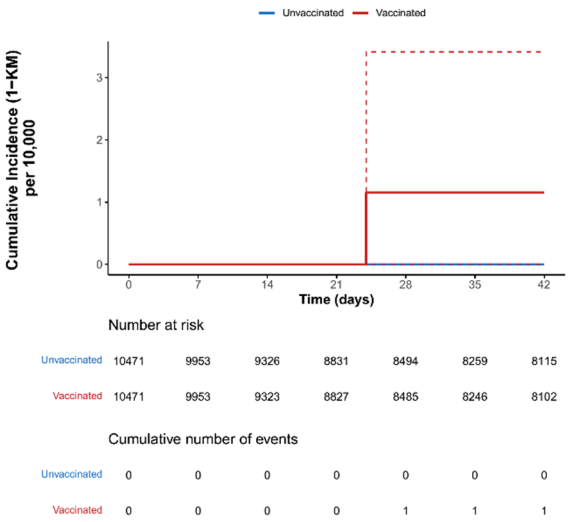
Table 89. Risk estimates (95% CI) per 10,000 person-years (PY) for anosmia, ageusia within 42 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source

	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)	<5	1.15 (0, 3.41)	1,034.10	9.67 (0.24, 53.88)	0	0 (0, 0)	1,034.71	NA
NHR (Norway)	99	0.45 (0.36, 0.54)	240,524.70	4.12 (3.35, 5.01)	108	0.52 (0.39, 0.65)	240,233.91	4.50 (3.54, 5.70)
PHARMO (Netherlands)	29	0.59 (0.37, 0.80)	56,803.13	5.11 (3.42, 7.33)	21	0.43 (0.23, 0.63)	56,903.72	3.69 (2.31, 5.89)
EpiChron (Spain)	82	2.14 (1.67, 2.62)	42,459.04	19.31 (15.36, 23.97)	64	1.85 (1.29, 2.40)	42,413.39	15.09 (11.29, 20.18)
SIDIAP (Spain)	185	0.90 (0.77, 1.03)	232,735.24	7.95 (6.84, 9.18)	245	1.21 (1.01, 1.41)	232,732.28	10.53 (8.94, 12.39)

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 80. 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

Pedianet



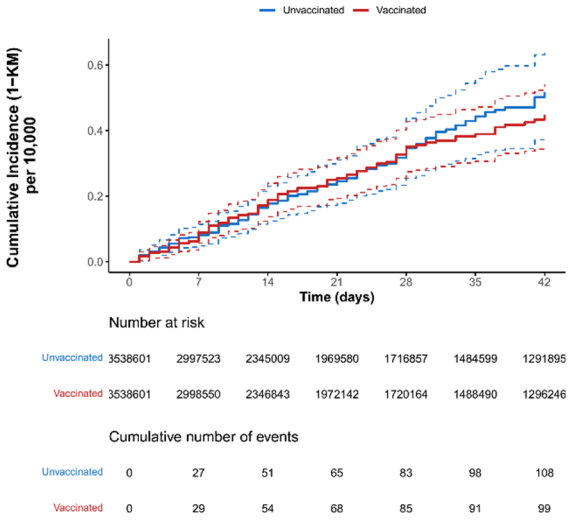
Number at risk

	0	7	14	21	28	35	42
Unvaccinated	10471	9953	9326	8831	8494	8259	8115
Vaccinated	10471	9953	9323	8827	8485	8246	8102

Cumulative number of events

	0	7	14	21	28	35	42
Unvaccinated	0	0	0	0	0	0	0
Vaccinated	0	0	0	0	1	1	1

NHR



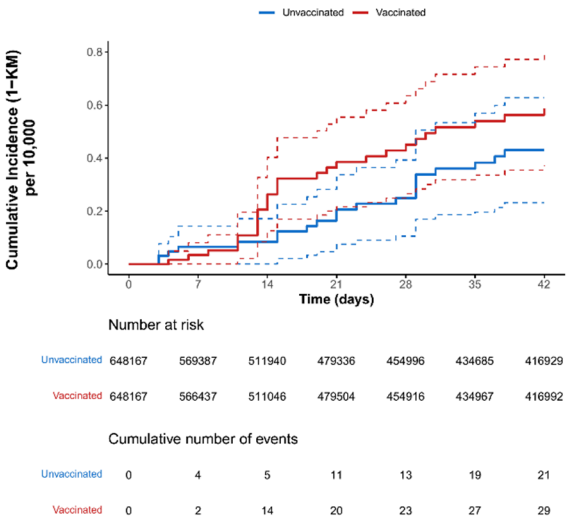
Number at risk

	0	7	14	21	28	35	42
Unvaccinated	3538601	2997523	2345009	1969580	1716857	1484599	1291895
Vaccinated	3538601	2998550	2346843	1972142	1720164	1488490	1296246

Cumulative number of events

	0	7	14	21	28	35	42
Unvaccinated	0	27	51	65	83	98	108
Vaccinated	0	29	54	68	85	91	99

PHARMO



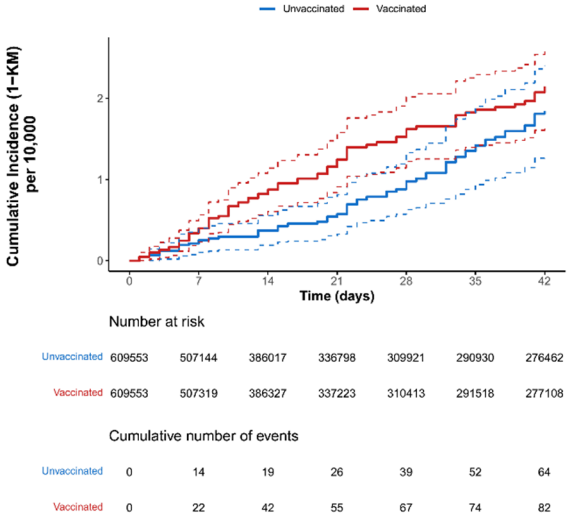
Number at risk

	0	7	14	21	28	35	42
Unvaccinated	648167	569387	511940	479336	454996	434685	416929
Vaccinated	648167	566437	511046	479504	454916	434967	416992

Cumulative number of events

	0	7	14	21	28	35	42
Unvaccinated	0	4	5	11	13	19	21
Vaccinated	0	2	14	20	23	27	29

EpiChron



Number at risk

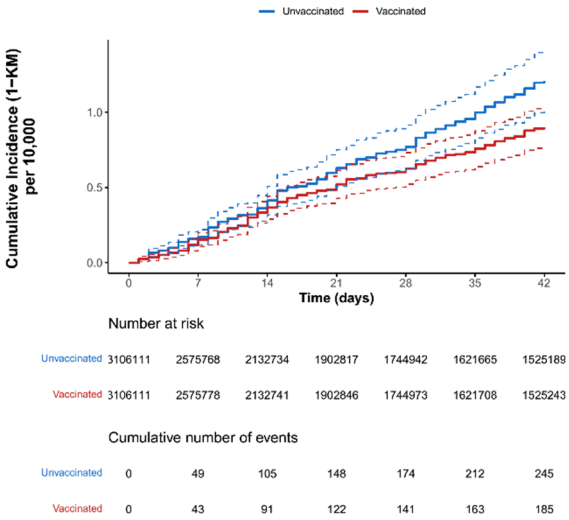
	0	7	14	21	28	35	42
Unvaccinated	609553	507144	386017	336798	309921	290930	276462
Vaccinated	609553	507319	386327	337223	310413	291518	277108

Cumulative number of events

	0	7	14	21	28	35	42
Unvaccinated	0	14	19	26	39	52	64
Vaccinated	0	22	42	55	67	74	82

Figure 80. 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

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 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 81. 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

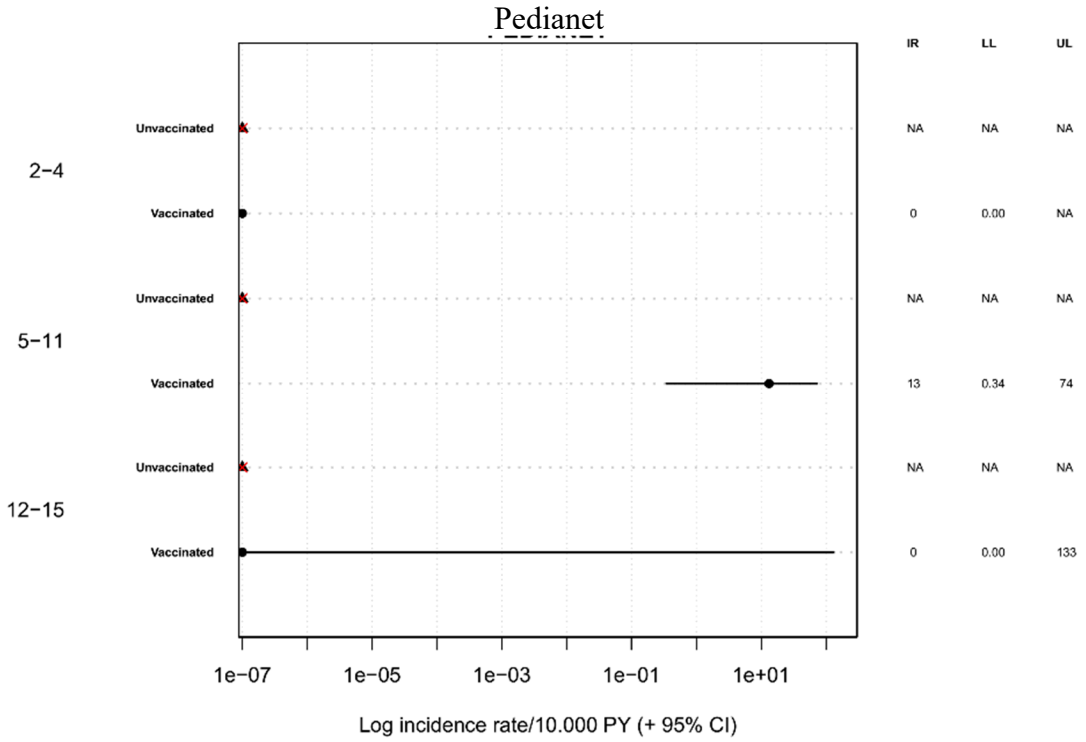


Figure 81. Forest plot showing incidence rates and 95% confidence intervals for anosmia, ageusia within 42 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source and by age groups

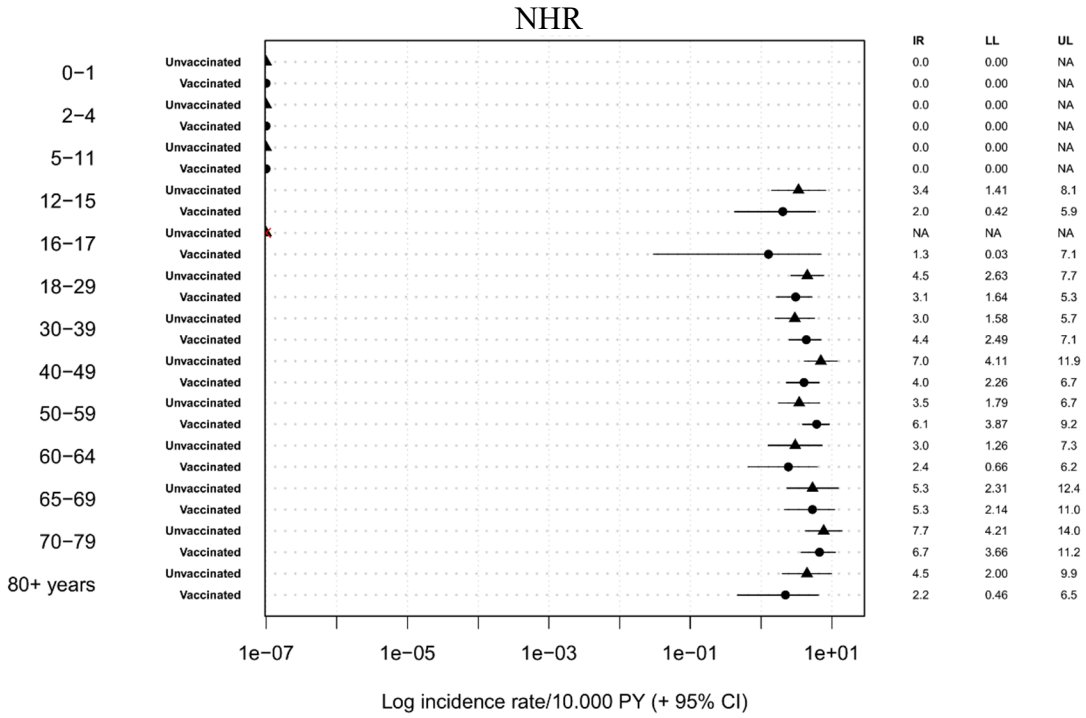


Figure 81. Forest plot showing incidence rates and 95% confidence intervals for anosmia, ageusia within 42 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source and by age groups

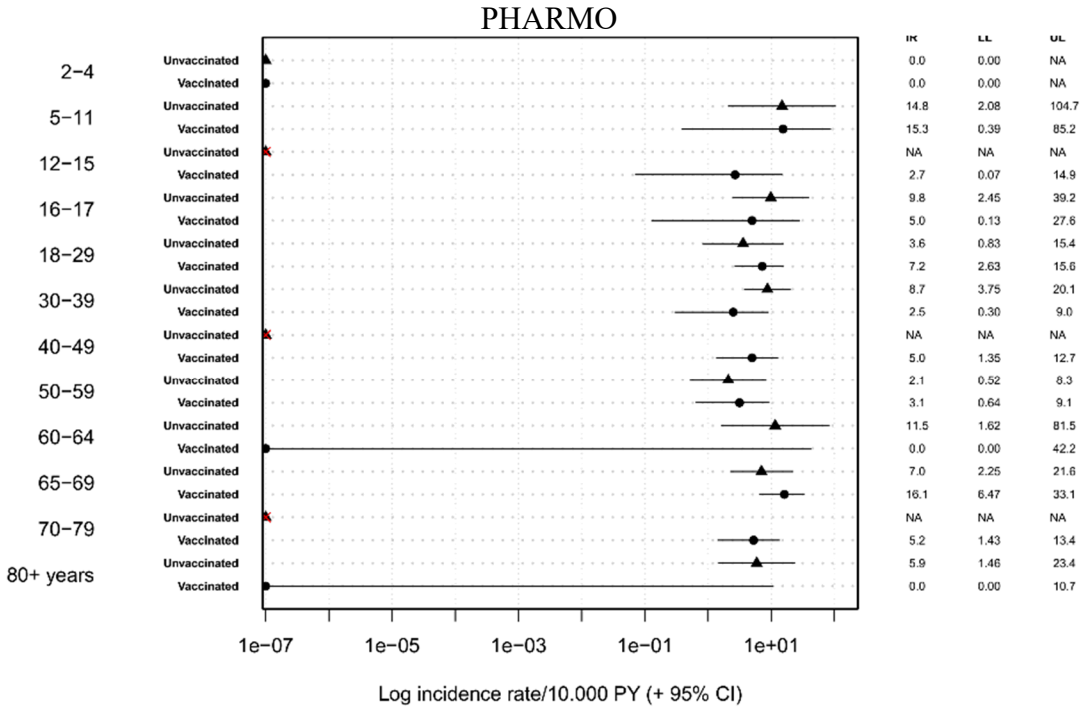


Figure 81. Forest plot showing incidence rates and 95% confidence intervals for anosmia, ageusia within 42 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source and by age groups

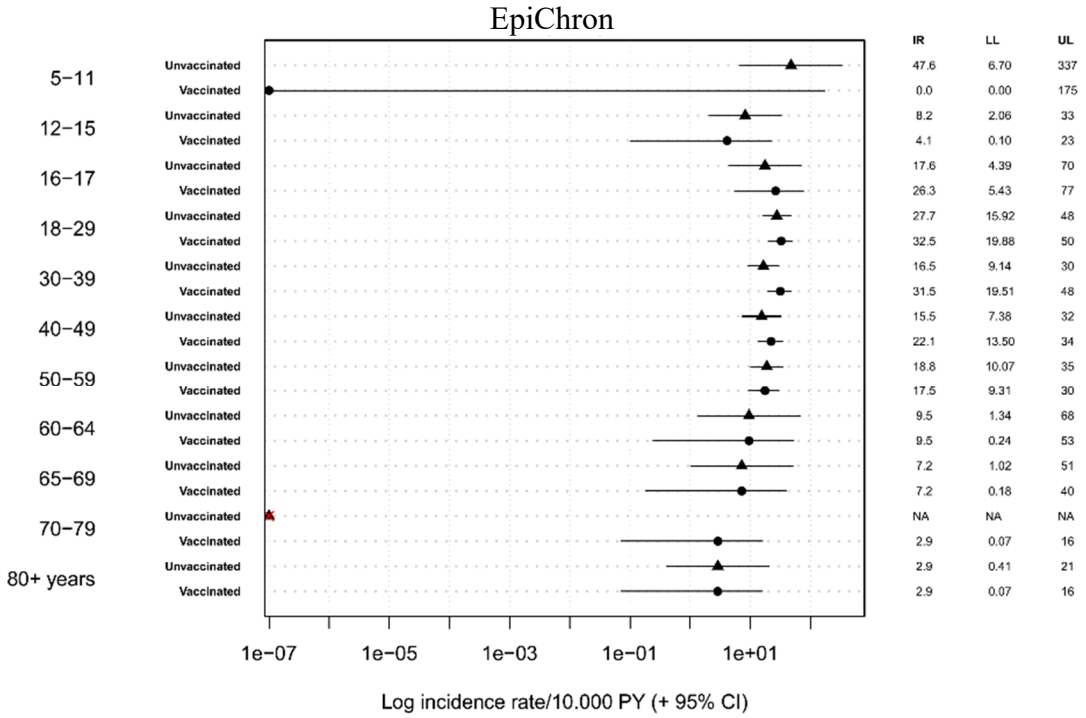


Figure 81. Forest plot showing incidence rates and 95% confidence intervals for anosmia, ageusia within 42 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source and by age groups

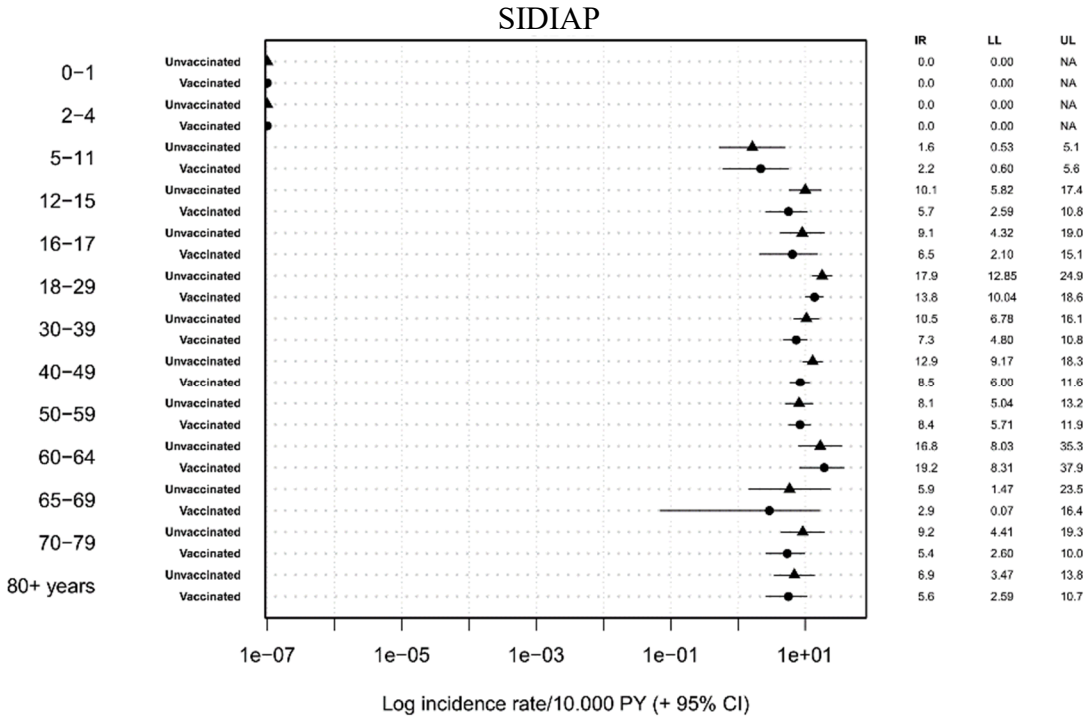


Table 90. Matched and adjusted hazard ratios (HRs) and matched and adjusted risk differences (RDs) per 10,000 person-years and their 95% CIs for anosmia, ageusia within 42 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source

	Matched HR (95% CI)	Adjusted HR (95% CI)	Matched RD	Adjusted RD
Pedianet	NA	NA	1.15	1.16
NHR	0.92 (0.67, 1.24)	0.92 (0.67, 1.24)	-0.07	-0.07
PHARMO	1.38 (0.77, 2.50)	1.26 (0.70, 2.29)	0.16	0.11
EpiChron	1.28 (0.89, 1.83)	1.20 (0.83, 1.72)	0.30	0.15
SIDIAP	0.76 (0.61, 0.94)	0.72 (0.58, 0.90)	-0.31	-0.36

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

10.3.34. Anaphylaxis

Anaphylaxis events were reported in Pedianet, PHARMO, EpiChron, and SIDIAP. The prevalence rate was highest in EpiChron with 2.21 (95% CI: 1.87, 2.62). The prevalence rates were very low in SIDIAP and PHARMO as only very few events were reported. The prevalence was similar in the different age groups.

The matched HR was 5.32 (95% CI: 3.37, 8.39) in EpiChron. The adjusted HRs were 5.06 (95% CI: 3.20, 8.00) in EpiChron. The lower limits of the 95% CIs for the matched and adjusted HRs were above 1.

Table 91. 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

	Vaccinated		Unvaccinated	
Data source	**Events (n)**	**Prevalence rate (95% CI)**	**Events (n)**	**Prevalence rate (95% CI)**
Pedianet (Italy)	0	0 (0, 3.67)	<5	0.96 (0.13, 6.79)
NHR (Norway)	NA	NA	NA	NA
PHARMO (Netherlands)	<5	0.02 (0, 0.09)	0	NA
EpiChron (Spain)	133	2.21 (1.87, 2.62)	25	0.42 (0.27, 0.63)
SIDIAP (Spain)	6	0.02 (0.01, 0.04)	0	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+).

Figure 82. 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

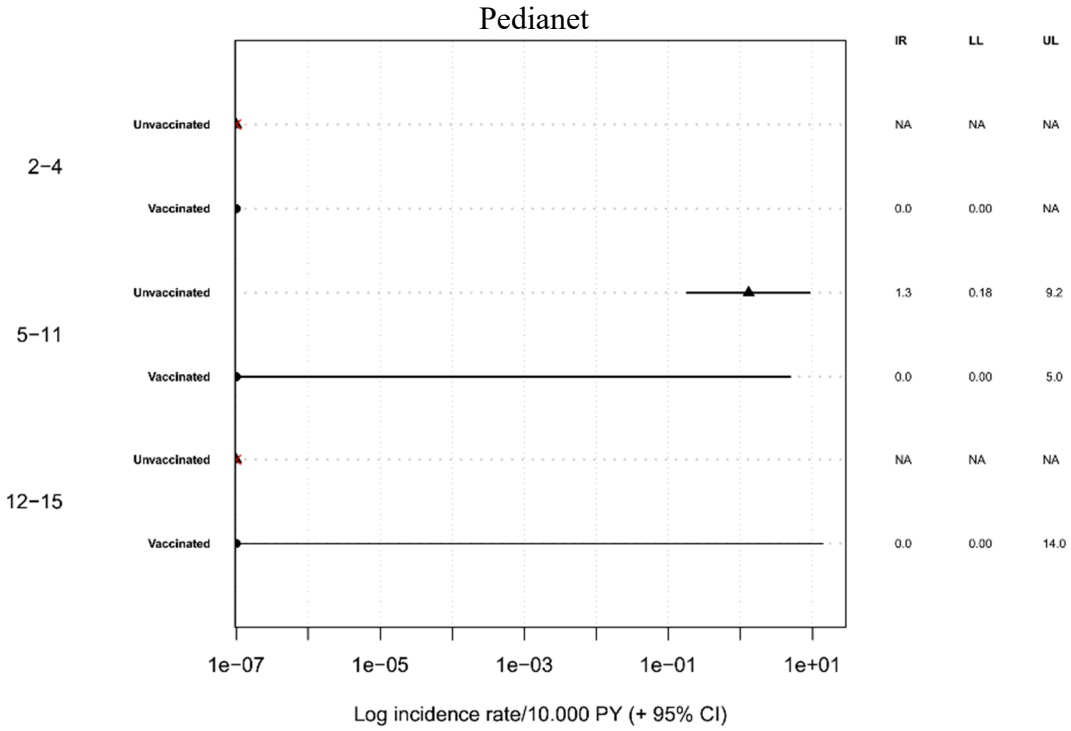


Figure 82. Forest plot showing prevalence rates and 95% confidence intervals for anaphylaxis within 1 day after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source and by age groups

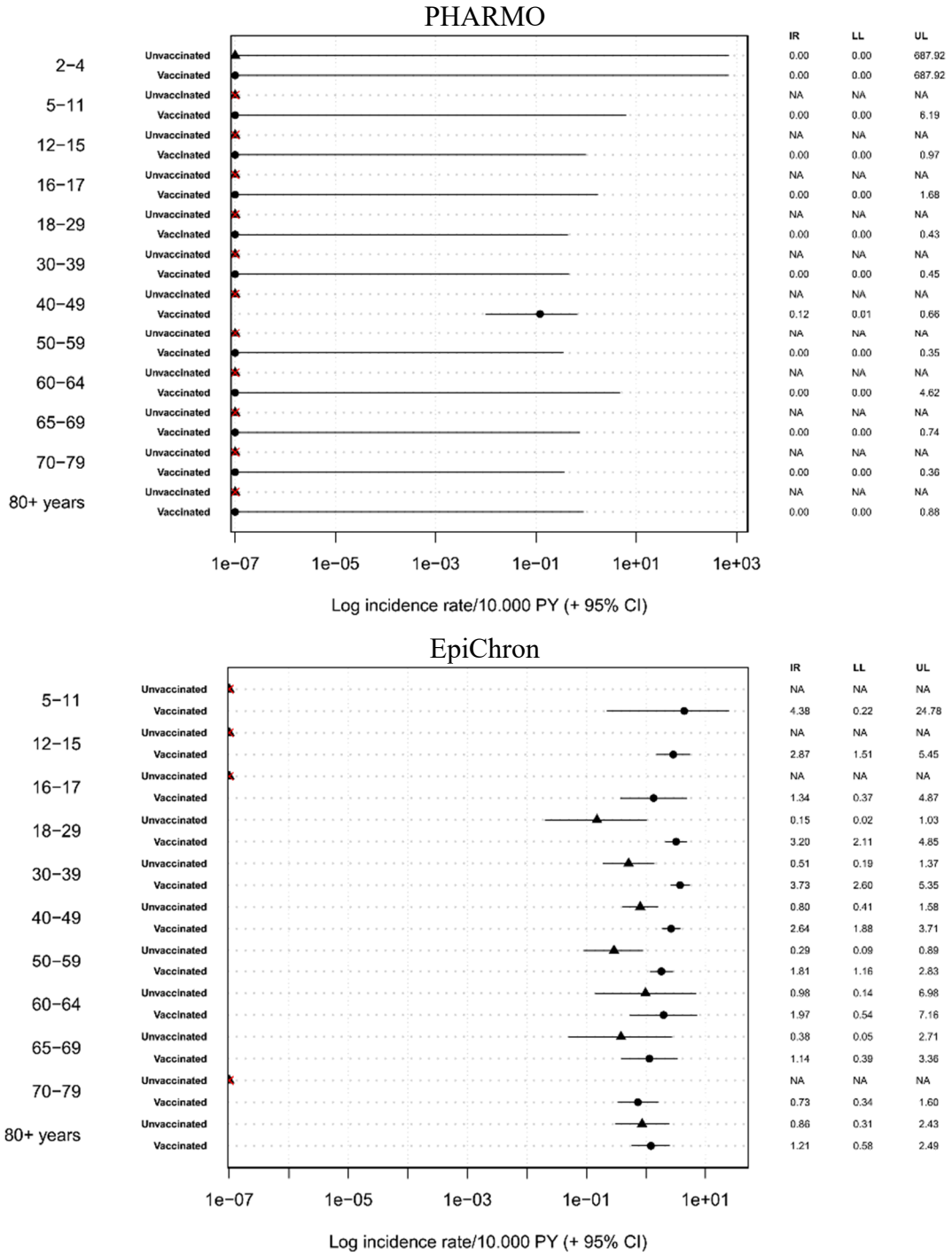


Figure 82. Forest plot showing prevalence rates and 95% confidence intervals for anaphylaxis within 1 day after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source and by age groups

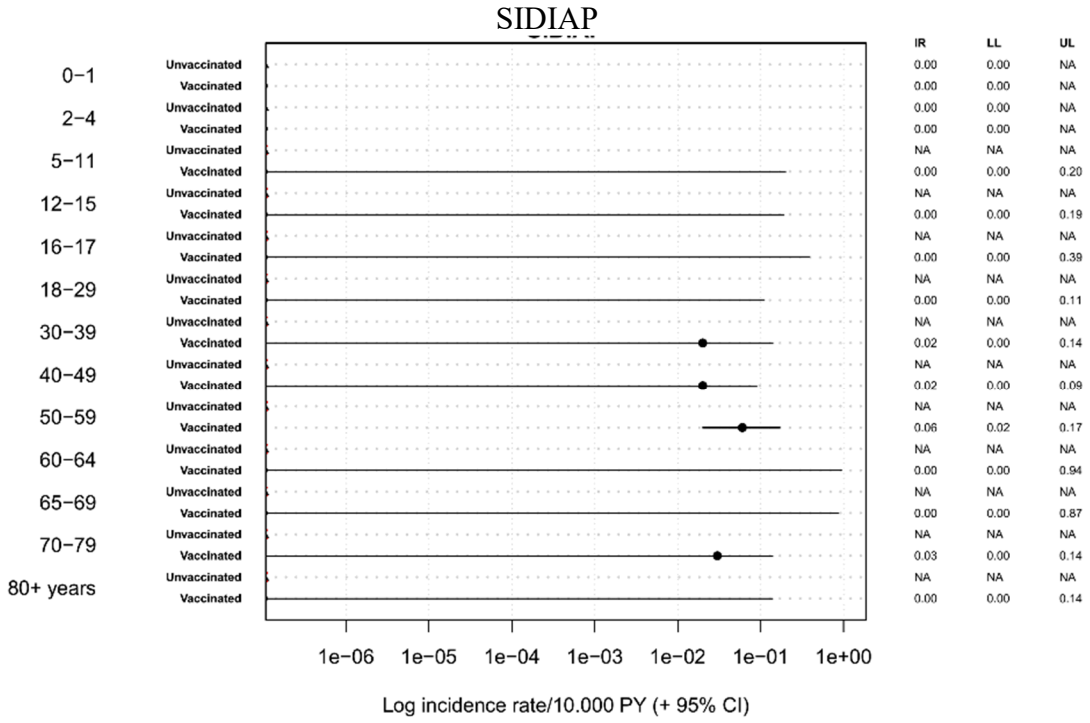


Table 92. Matched hazard ratios (HRs) and matched risk differences (RDs) per 10,000 person-years and their 95% CIs for anaphylaxis within 1 day after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source

	Matched HR (95% CI)	Adjusted HR (95% CI)	Matched RD	Adjusted RD
Pedianet	NA	NA	NA	NA
NHR	NA	NA	NA	NA
PHARMO	NA	NA	NA	NA
EpiChron	5.32 (3.37, 8.39)	5.06 (3.20, 8.00)	NA	NA
SIDIAP	NA	NA	NA	NA

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

10.3.35. Multisystem inflammatory syndrome

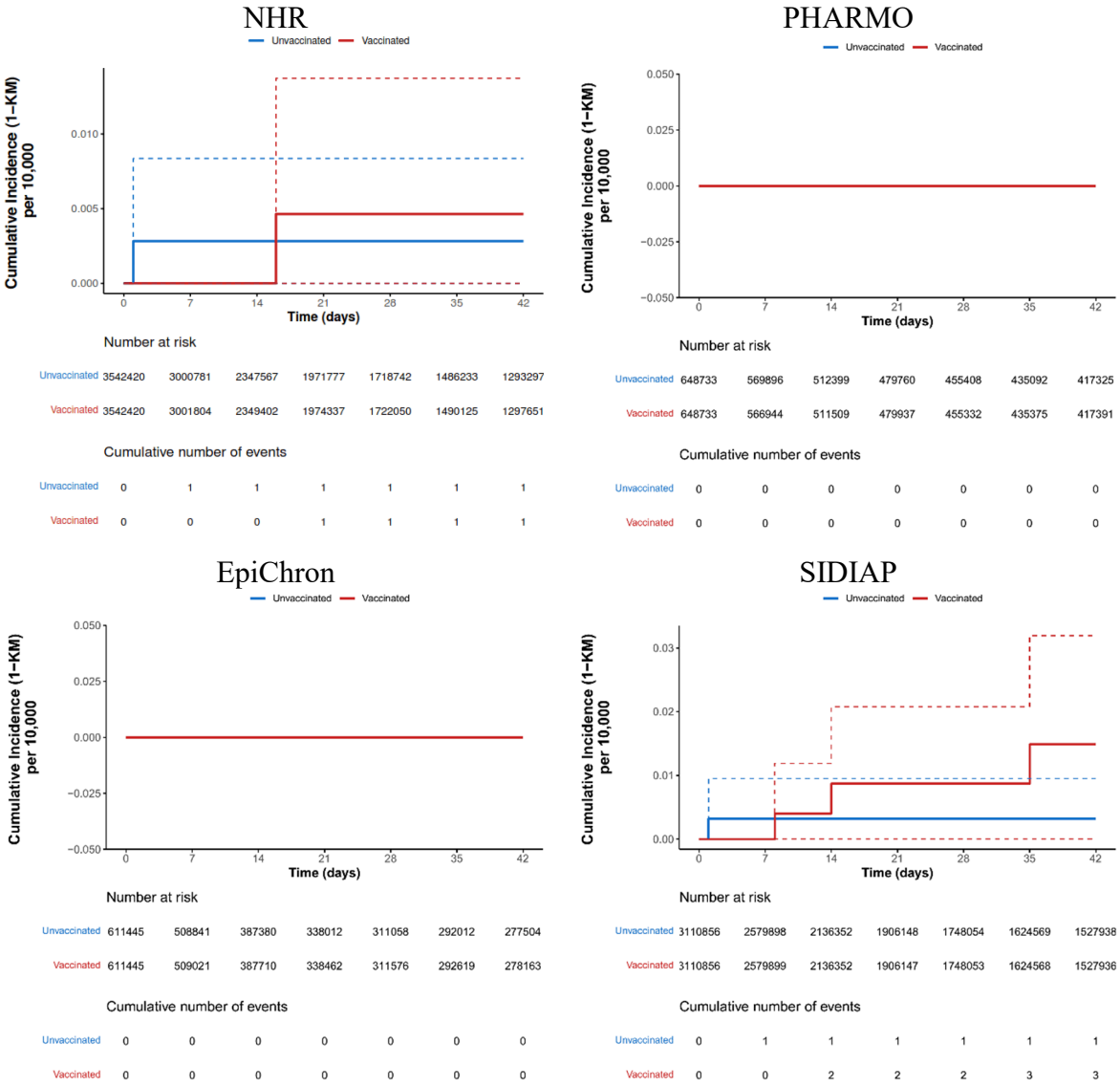
Multisystem inflammatory syndrome events were rare very rare and were only detected in NHR and SIDIAP. In the vaccinated cohorts, the incidence rates were 0.04 per 10,000 person-years (95% CI: 0, 0.23) in NHR and 0.13 per 10,000 person-years (95% CI: 0.03, 0.38) in SIDIAP. In the unvaccinated cohorts these were 0.04 per 10,000 person-years (95% CI: 0.01, 0.30) in NHR and 0.04 per 10,000 person-years (95% CI: 0.01, 0.30) in SIDIAP. The number of cases were <5 and the cumulative incidence was 0.01 per 10,000 individuals. The matched HRs were 1.00 (95% CI: 0.06, 15.97) and 3.00 (95% CI: 0.31, 28.84) in NHR and SIDIAP, respectively. The adjusted HRs were 1.00 (95% CI: 0.06, 15.93) and 2.99 (95% CI: 0.31, 28.79) in NHR and SIDIAP, respectively. No differences were observed for the incidence of multisystem inflammatory syndrome within the 42-day risk window, between the vaccinated and unvaccinated cohorts.

Table 93. 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

	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)	NA	NA	NA	NA	NA	NA	NA	NA
NHR (Norway)	<5	0 (0, 0.01)	240,787.30	0.04 (0, 0.23)	<5	0 (0, 0.01)	240,496.47	0.04 (0.01, 0.30)
PHARMO (Netherlands)	0	0 (0, 0)	56,854.78	0 (0, 0.65)	0	0 (0, 0)	56,955.10	NA
EpiChron (Spain)	0	0 (0, 0)	42,610.35	0 (0, 0.87)	0	0 (0, 0)	42,562.78	NA
SIDIAP (Spain)	<5	0.01 (0, 0.03)	233,128.24	0.13 (0.03, 0.38)	<5	0 (0, 0.01)	233,128.31	0.04 (0.01, 0.30)

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 83. 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.

Figure 84. 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

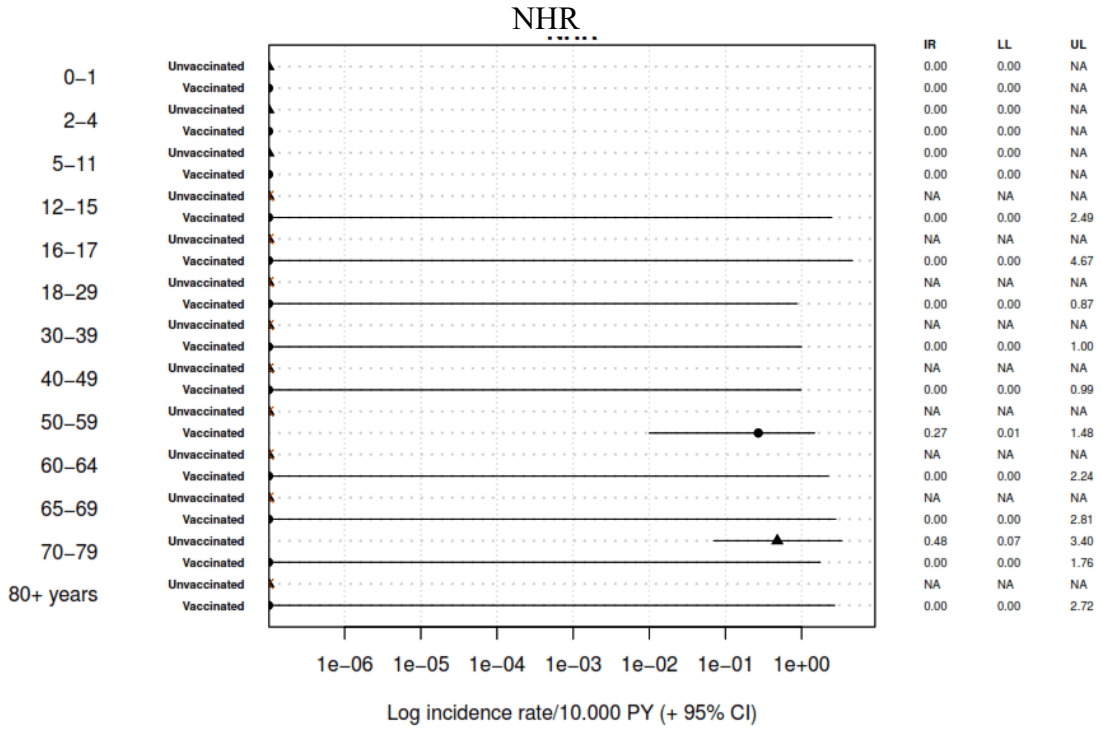


Figure 84. Forest plot showing incidence rates and 95% confidence intervals for multisystem inflammatory syndrome within 42 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source and by age groups

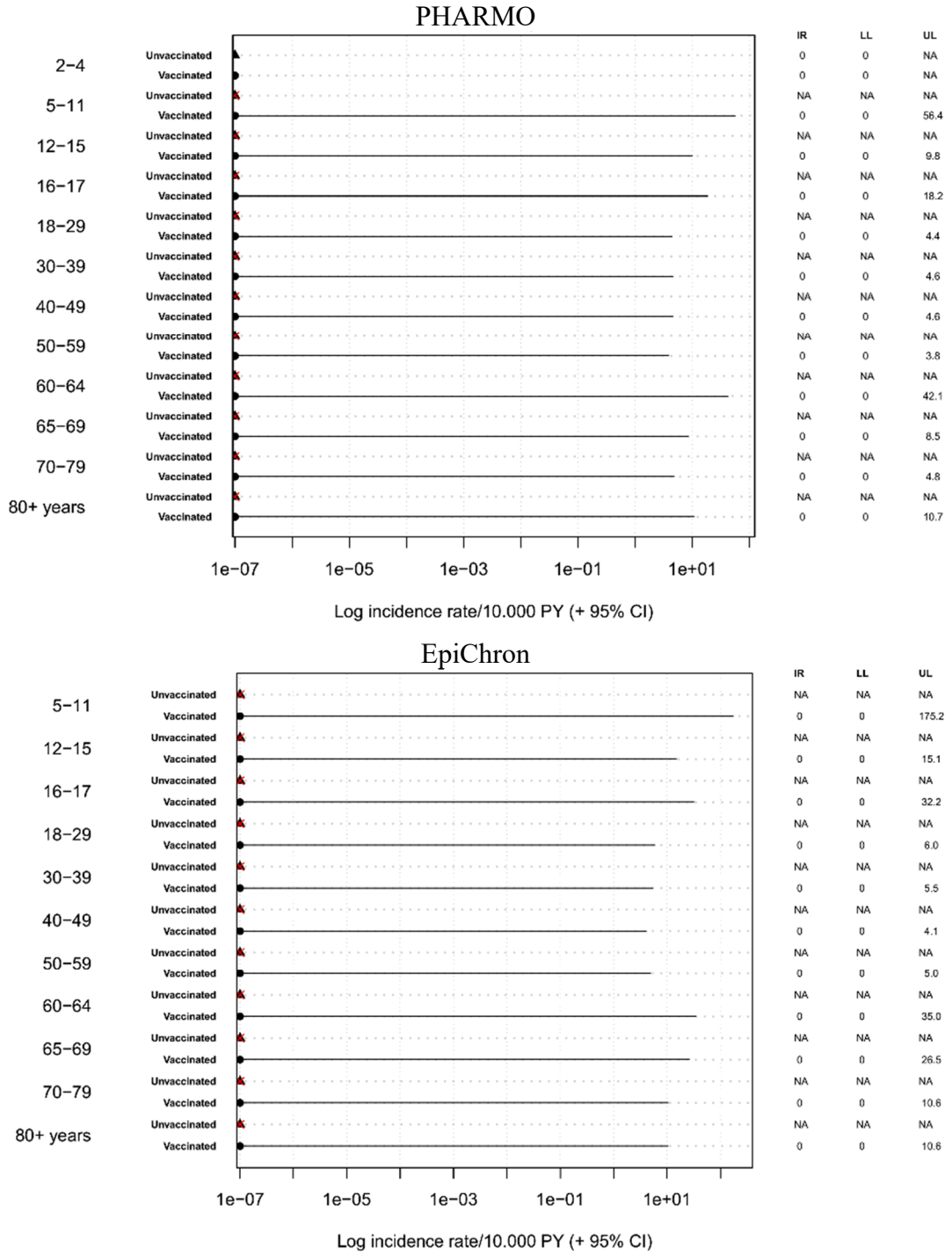


Figure 84. Forest plot showing incidence rates and 95% confidence intervals for multisystem inflammatory syndrome within 42 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source and by age groups

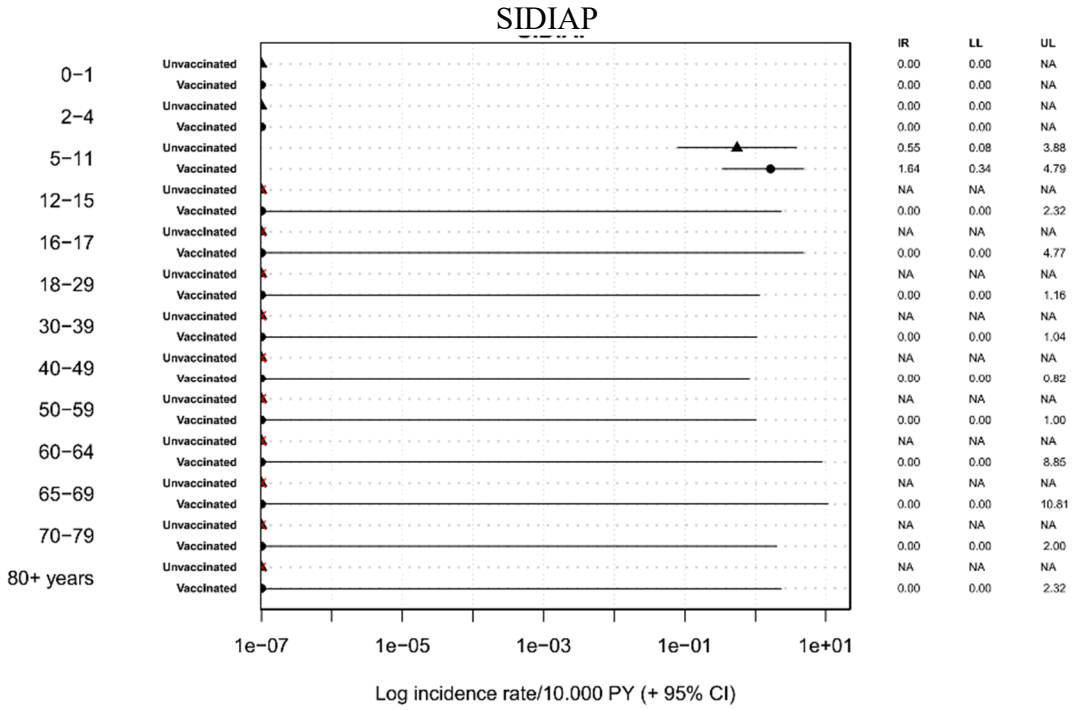


Table 94. Matched and adjusted hazard ratios (HRs) and matched and adjusted risk differences (RDs) per 10,000 person-years and their 95% CIs for multisystem inflammatory syndrome within 42 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source

	Matched HR (95% CI)	Adjusted HR (95% CI)	Matched RD	Adjusted RD
Pedianet	NA	NA	NA	NA
NHR	1.00 (0.06, 15.97)	1.00 (0.06, 15.93)	0	0
PHARMO	NA	NA	NA	NA
EpiChron	NA	NA	NA	NA
SIDIAP	3.00 (0.31, 28.84)	2.99 (0.31, 28.79)	0.01	0.01

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

10.3.36. Death (any cause)

Deaths (any cause) were identified in all data sources. In Pedianet and SIDIAP <5 deaths were reported in the vaccinated cohorts and in the unvaccinated cohorts <5 deaths were reported in SIDIAP and none in Pedianet. In the other data sources the incidence rates ranged from 39.09 per 10,000 person-years (95% CI: 36.90, 41.38) in PHARMO to 111.10 per 10,000 person-years (95% CI: 108.23, 114.03) in NHR in the vaccinated cohorts. In the unvaccinated cohorts these ranged from 68.25 per 10,000 person-years (95% CI: 63.99, 72.79) in PHARMO to 226.15 per 10,000 person-years (95% CI: 218.69, 233.87) in NHR. The cumulative incidences in the vaccinated cohorts ranged from 38.76 per 10,000 individuals (95% CI: 36.41, 41.11) in PHARMO to 643.87 per 10,000 individuals (95% CI: 564.03, 723.04) in NHR in the vaccinated cohorts. In the unvaccinated cohorts these ranged from 54.36 per 10,000 individuals (95% CI: 50.74, 57.97) in PHARMO to 828.77 per 10,000 individuals (95% CI: 722.62, 933.70) in NHR. The incidences of death (any cause) were highest in the oldest age groups.

The matched HRs were 0.48 (95% CI: 0.46, 0.50) in NHR, 0.59 (95% CI: 0.54, 0.65) in PHARMO, 0.61 (95% CI: 0.56, 0.66) in EpiChron, and 0.50 (95% CI: 0.05, 5.51) in SIDIAP. The adjusted HRs were 0.48 (95% CI: 0.46, 0.50) in NHR, 0.56 (95% CI: 0.51, 0.60) in PHARMO, 0.59 (95% CI: 0.54, 0.64) in EpiChron, and 0.38 (95% CI: 0.03, 4.24) in SIDIAP. In all data sources except SIDIAP vaccination showed a protective effect for death.

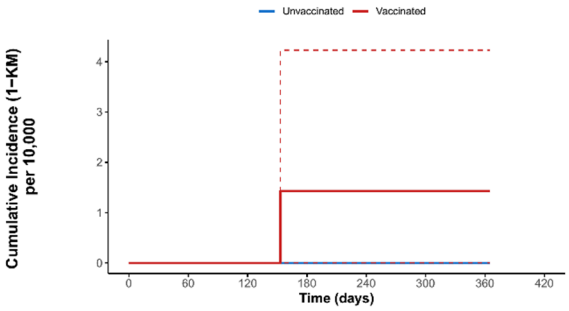
Table 95. Risk estimates (95% CI) per 10,000 person-years (PY) for death (any cause) among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source (risk window: 365 days after dose 1)

	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)	<5	1.43 (0, 4.23)	6,973.34	1.43 (0.04, 7.99)	0	0 (0, 0)	7,016.93	NA
NHR (Norway)	5,663	643.87 (564.03, 723.04)	509,718.47	111.10 (108.23, 114.03)	11,411	828.77 (722.62, 933.70)	504,569.80	226.15 (218.69, 233.87)
PHARMO (Netherlands)	1,184	38.76 (36.41, 41.11)	302,886.54	39.09 (36.90, 41.38)	1,885	54.36 (50.74, 57.97)	276,186.13	68.25 (63.99, 72.79)
EpiChron (Spain)	1,449	67.58 (63.89, 71.26)	199,937.57	72.47 (68.79, 76.30)	2,365	100.14 (92.95, 107.33)	198,926.03	118.89 (111.25, 127.05)
SIDIAP (Spain)	<5	0.01 (0, 0.03)	1,014,031.92	0.01 (0, 0.05)	<5	0.03 (0, 0.07)	1,014,031.92	0.02 (0, 0.08)

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 85. 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)

Pedianet



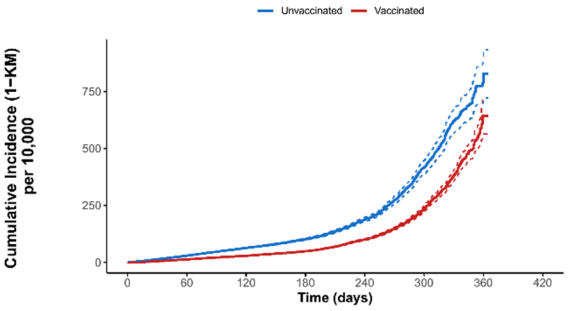
Number at risk

	0	60	120	180	240	300	360	420
Unvaccinated	10478	7869	7372	6898	6689	6455	3268	0
Vaccinated	10478	7843	7315	6846	6630	6399	3224	0

Cumulative number of events

	0	60	120	180	240	300	360	420
Unvaccinated	0	0	0	0	0	0	0	0
Vaccinated	0	0	0	1	1	1	1	1

NHR



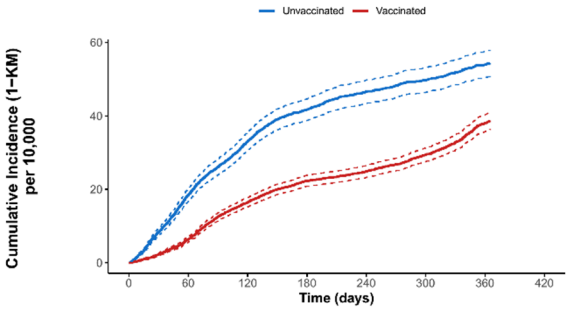
Number at risk

	0	60	120	180	240	300	360	420
Unvaccinated	3542453	929559	517162	263732	87183	15404	455	0
Vaccinated	3542453	934790	524709	271748	93942	18494	475	0

Cumulative number of events

	0	60	120	180	240	300	360	420
Unvaccinated	0	5286	7646	9175	10324	11107	11411	11411
Vaccinated	0	2226	3333	4138	4856	5377	5663	5663

PHARMO



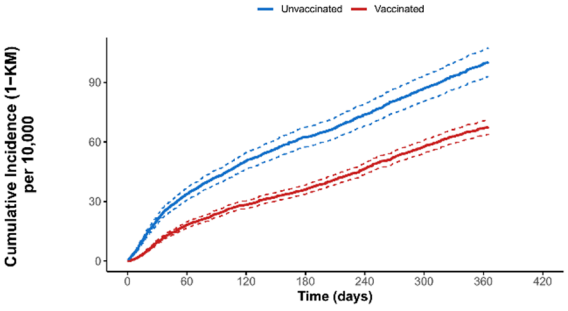
Number at risk

	0	60	120	180	240	300	360	420
Unvaccinated	648737	386355	340055	284431	190537	143788	117639	0
Vaccinated	648737	389508	351485	313536	236372	189630	162795	0

Cumulative number of events

	0	60	120	180	240	300	360	420
Unvaccinated	0	849	1380	1655	1774	1825	1880	1885
Vaccinated	0	288	661	856	928	1022	1173	1184

EpiChron



Number at risk

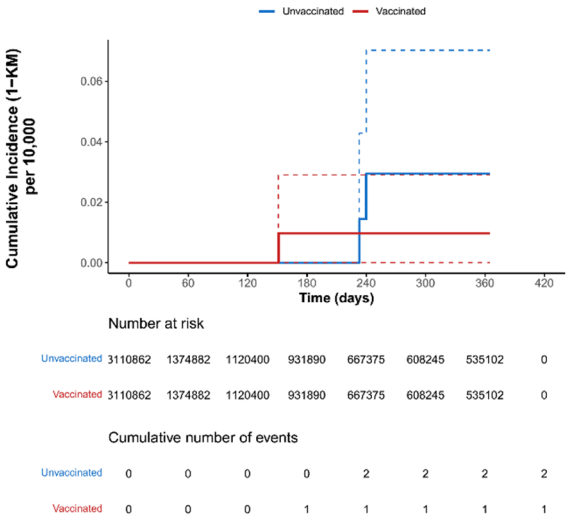
	0	60	120	180	240	300	360	420
Unvaccinated	611445	250251	209047	181497	145667	138277	132070	0
Vaccinated	611445	251093	210287	182861	146777	139207	133016	0

Cumulative number of events

	0	60	120	180	240	300	360	420
Unvaccinated	0	1199	1582	1812	2000	2186	2358	2365
Vaccinated	0	599	829	979	1155	1315	1441	1449

Figure 85. 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)

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 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 86. 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)

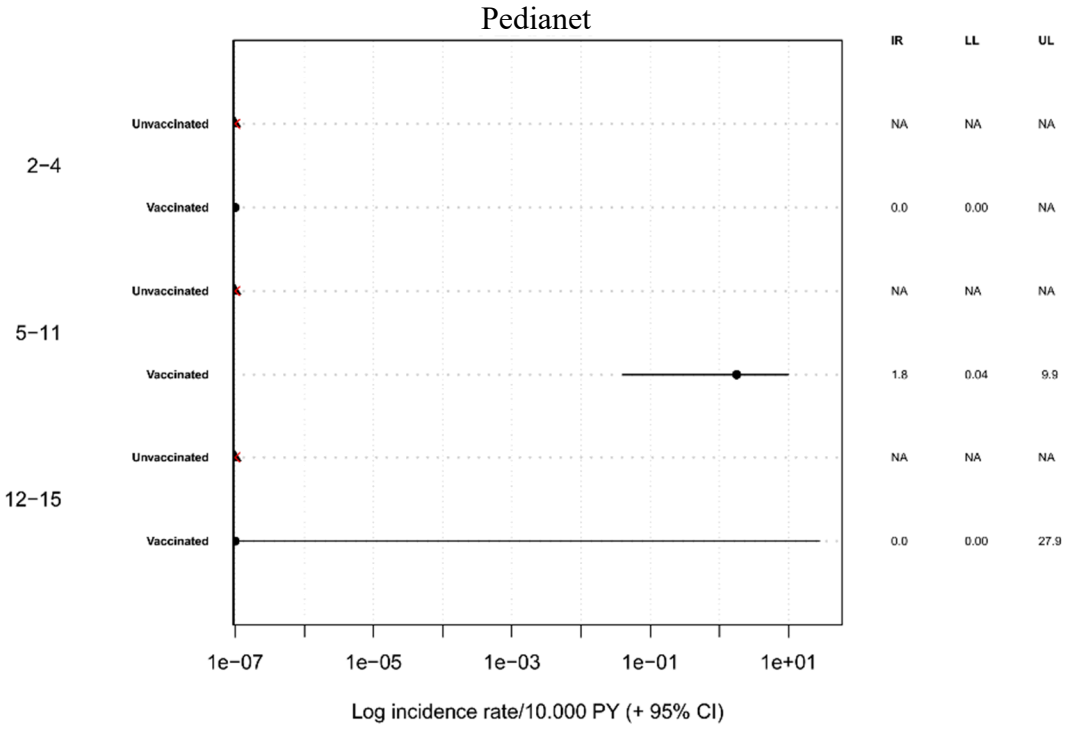


Figure 86. Forest plot showing incidence rates and 95% confidence intervals for death (any cause) among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source and by age groups (risk window: 365 days after dose 1)

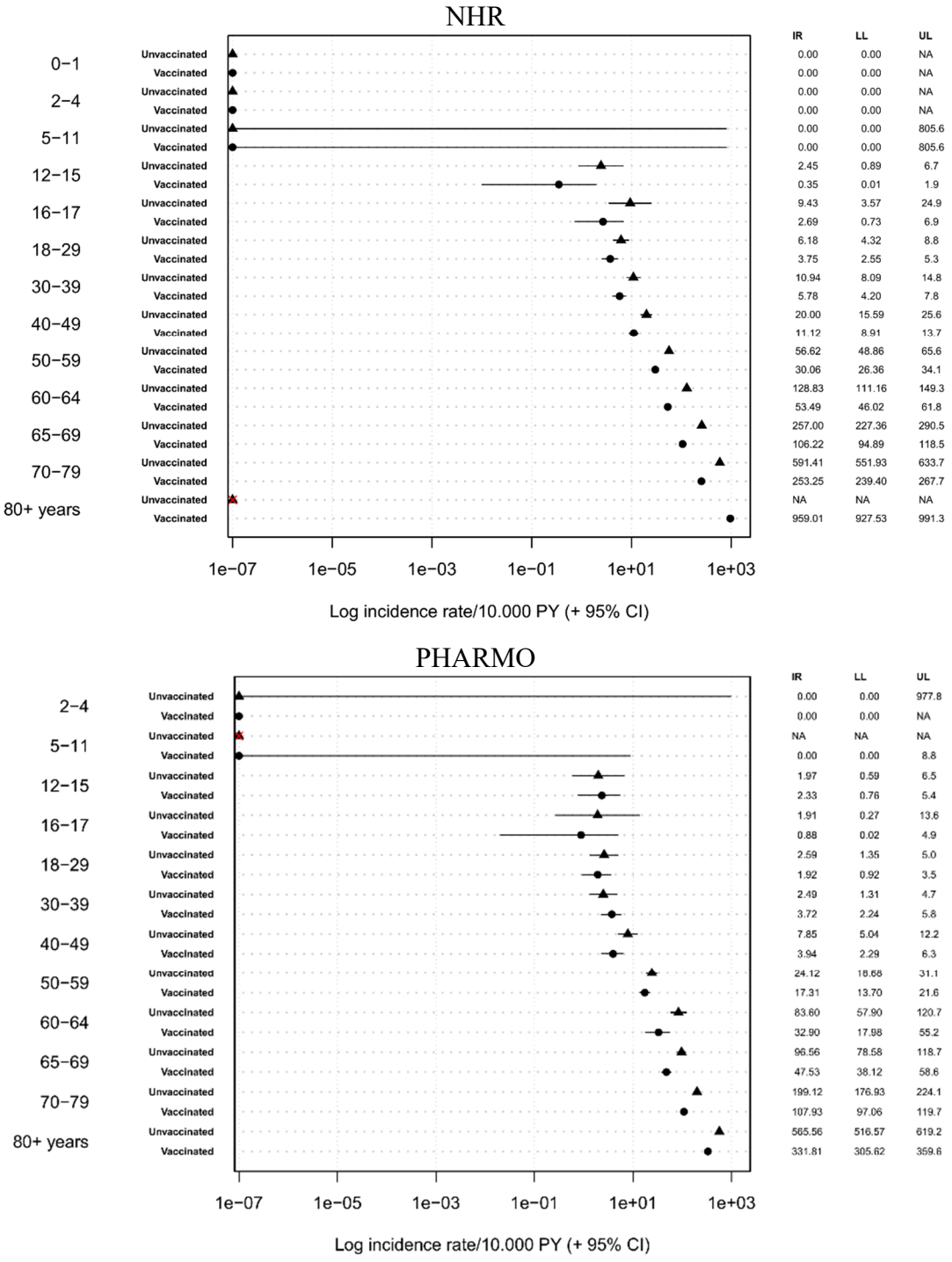


Figure 86. Forest plot showing incidence rates and 95% confidence intervals for death (any cause) among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source and by age groups (risk window: 365 days after dose 1)

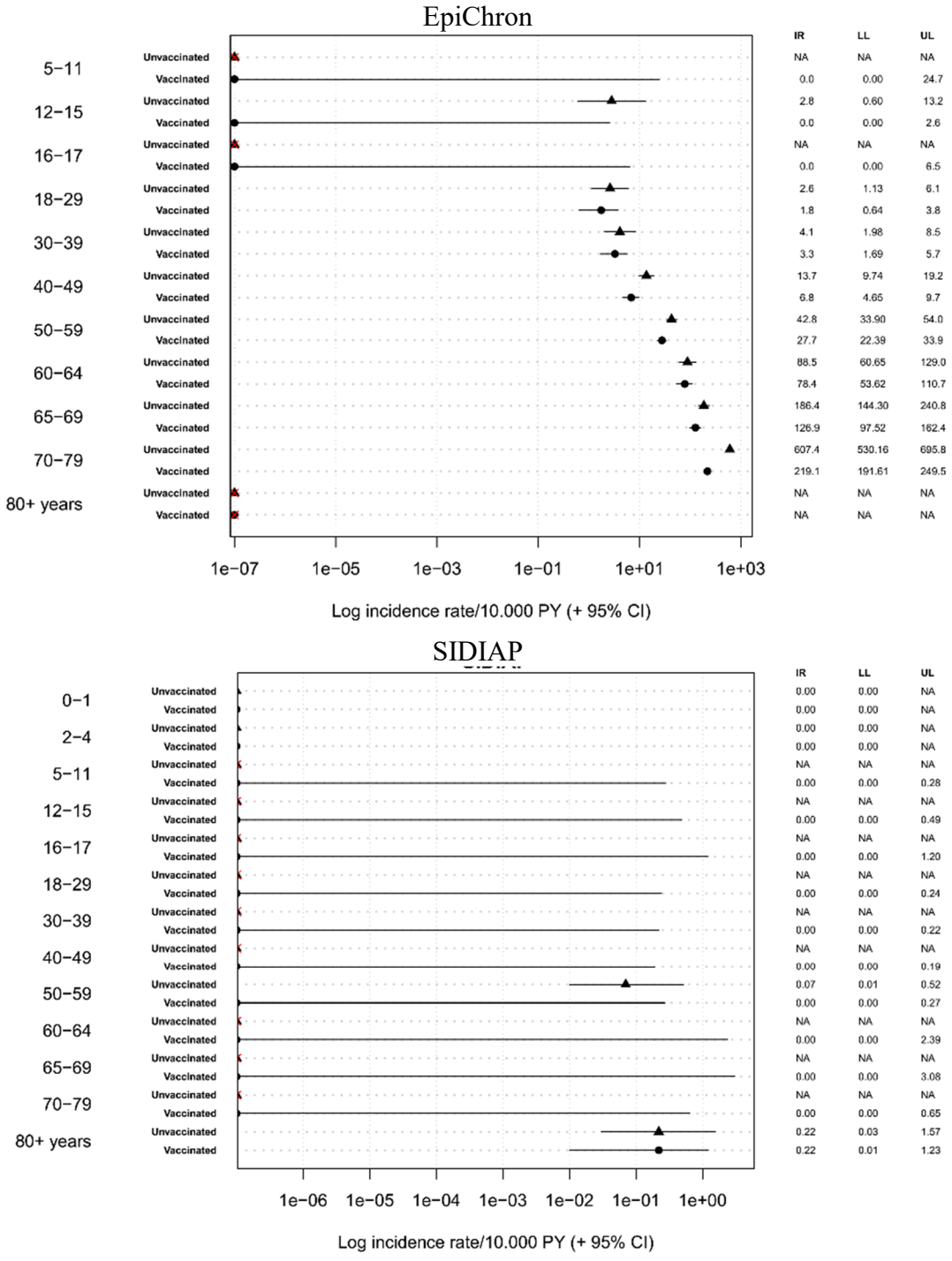


Table 96. Matched and adjusted hazard ratios (HRs) and matched and adjusted risk differences (RDs) per 10,000 person-years and their 95% CIs for death (any cause) among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source (risk window: 365 days after dose 1)

	Matched HR (95% CI)	Adjusted HR (95% CI)	Matched RD	Adjusted RD
Pedianet	NA	NA	1.43	1.44
NHR	0.48 (0.46, 0.50)	0.48 (0.46, 0.50)	-184.90	-187.54
PHARMO	0.59 (0.54, 0.65)	0.56 (0.51, 0.60)	-15.60	-18.61
EpiChron	0.61 (0.56, 0.66)	0.59 (0.54, 0.64)	-32.57	-37.34
SIDIAP	0.50 (0.05, 5.51)	0.38 (0.03, 4.24)	-0.02	-0.03

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

10.3.37. Subacute thyroiditis

Subacute thyroiditis events within the 365-day risk window were reported in EpiChron and SIDIAP only. The incidence rates were 0.03 per 10,000 person-years (95% CI: 0.01, 0.09) and 0.05 per 10,000 person-years (95% CI: 0, 0.28) in the vaccinated cohorts in SIDIAP and EpiChron, respectively. In the unvaccinated cohorts the rates were 0.05 per 10,000 person-years (95% CI: 0.01, 0.36) in EpiChron and were 0.01 per 10,000 person-years (95% CI: 0, 0.7) in SIDIAP. The cumulative incidence during the 42-day risk window was less than 0.10 per 10,000 individuals in the vaccinated and unvaccinated cohorts. The incidence of acute thyroiditis was highest in older age groups in both the vaccinated and unvaccinated cohorts.

The matched HRs were 1.00 (95% CI: 0.06, 15.94) in EpiChron and 3.00 (95% CI: 0.31, 28.84) in SIDIAP. The adjusted HRs were 0.91 (95% CI: 0.06, 14.33) in EpiChron and 2.70 (95% CI: 0.28, 26.18) in SIDIAP. No differences were observed for the incidence of subacute thyroiditis between the vaccinated and unvaccinated cohorts.

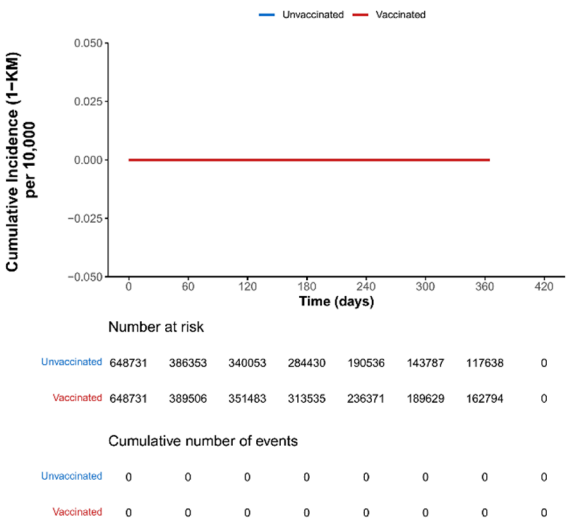
Table 97. Risk estimates (95% CI) per 10,000 person-years (PY) for subacute thyroiditis among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source (risk window: 365 days after dose 1)

	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)	NA	NA	NA	NA	NA	NA	NA	NA
NHR (Norway)	NA	NA	NA	NA	NA	NA	NA	NA
PHARMO (Netherlands)	0	0 (0, 0)	303,530.40	0 (0, 0.10)	0	0 (0, 0)	276,977.90	NA
EpiChron (Spain)	<5	0.04 (0, 0.11)	199,932.96	0.05 (0, 0.28)	<5	0.03 (0, 0.08)	198,921.63	0.05 (0.01, 0.36)
SIDIAP (Spain)	<5	0.02 (0, 0.05)	1,014,026.62	0.03 (0.01, 0.09)	<5	0.01 (0, 0.04)	1,014,027.70	0.01 (0, 0.07)

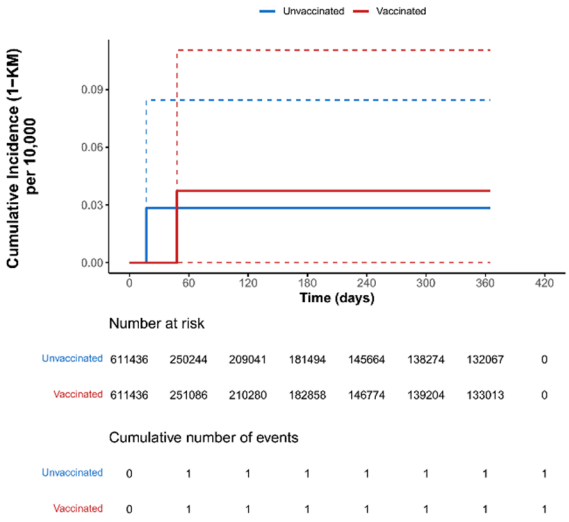
Note: Estimation of confidence intervals differs between vaccinated and unvaccinated, since the unvaccinated estimate is a GEE estimates (to account for individuals who were matched to more than one vaccinated individual). When NA (not-assessable) is listed for the 1-KM it means that there is no estimate 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 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

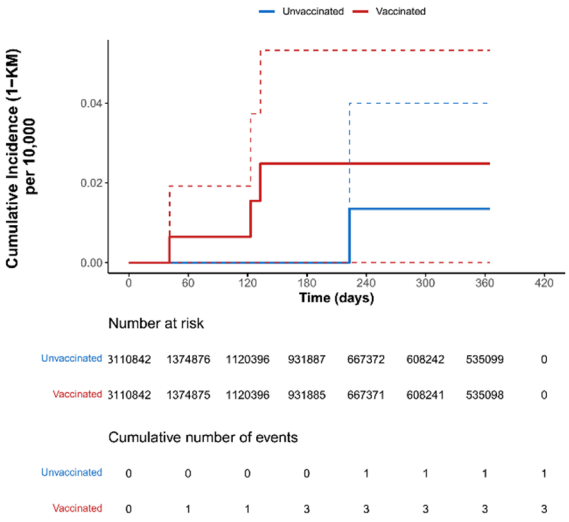
PHARMO



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 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 88. 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

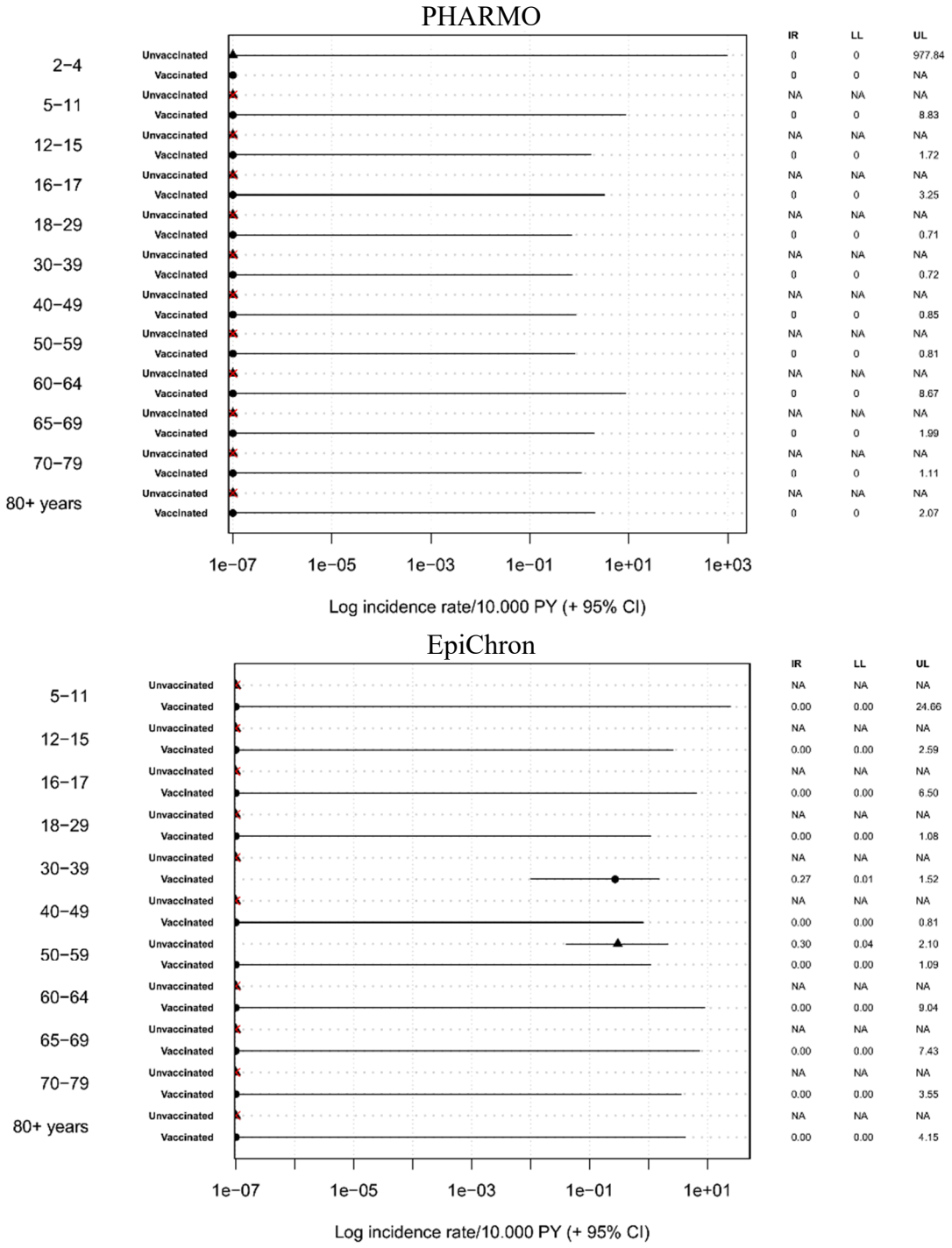


Figure 88. Forest plot showing incidence rates and 95% confidence intervals for subacute thyroiditis within 365 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source and by age groups

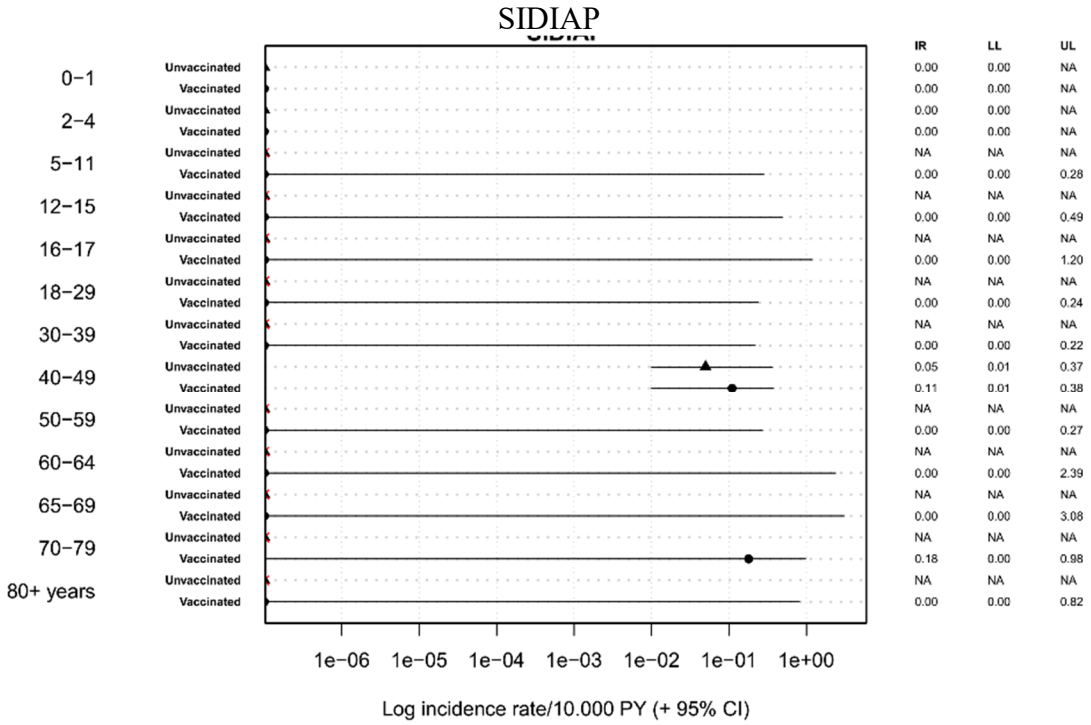


Table 98. Matched and adjusted hazard ratios (HRs) and matched and adjusted risk differences (RDs) per 10,000 person-years and their 95% CIs for subacute thyroiditis within 365 days after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source

	Matched HR (95% CI)	Adjusted HR (95% CI)	Matched RD	Adjusted RD
Pedianet	NA	NA	NA	NA
NHR	NA	NA	NA	NA
PHARMO	NA	NA	NA	NA
EpiChron	1 (0.06, 15.94)	0.91 (0.06, 14.33)	0.01	0.01
SIDIAP	3 (0.31, 28.84)	2.70 (0.28, 26.18)	0.01	0.01

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

10.3.38. 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 2.12 per 10,000 person-years (95% CI: 1.74, 2.56) in NHR and 0.07 per 10,000 person-years (95% CI: 0.01, 0.24) in PHARMO, with no events in EpiChron. The incidence rates in the unvaccinated cohorts were 3.59 per 10,000 person-years (95% CI: 2.76, 4.66) in NHR, 0.05 per 10,000 person-years (95% CI: 0.01, 0.36) in EpiChron, and 0.07 per 10,000 person-years (95% CI: 0.02, 0.29) in PHARMO. In NHR the cumulative incidences were 15.81 per 10,000 individuals (95% CI: 0, 36.25) in the vaccinated cohort and 14.44 per 10,000 person-years (95% CI: 5.32, 23.56) in NHR in the unvaccinated cohort, and less than 0.20 per 10,000 individuals in the vaccinated and unvaccinated cohorts in PHARMO and EpiChron.

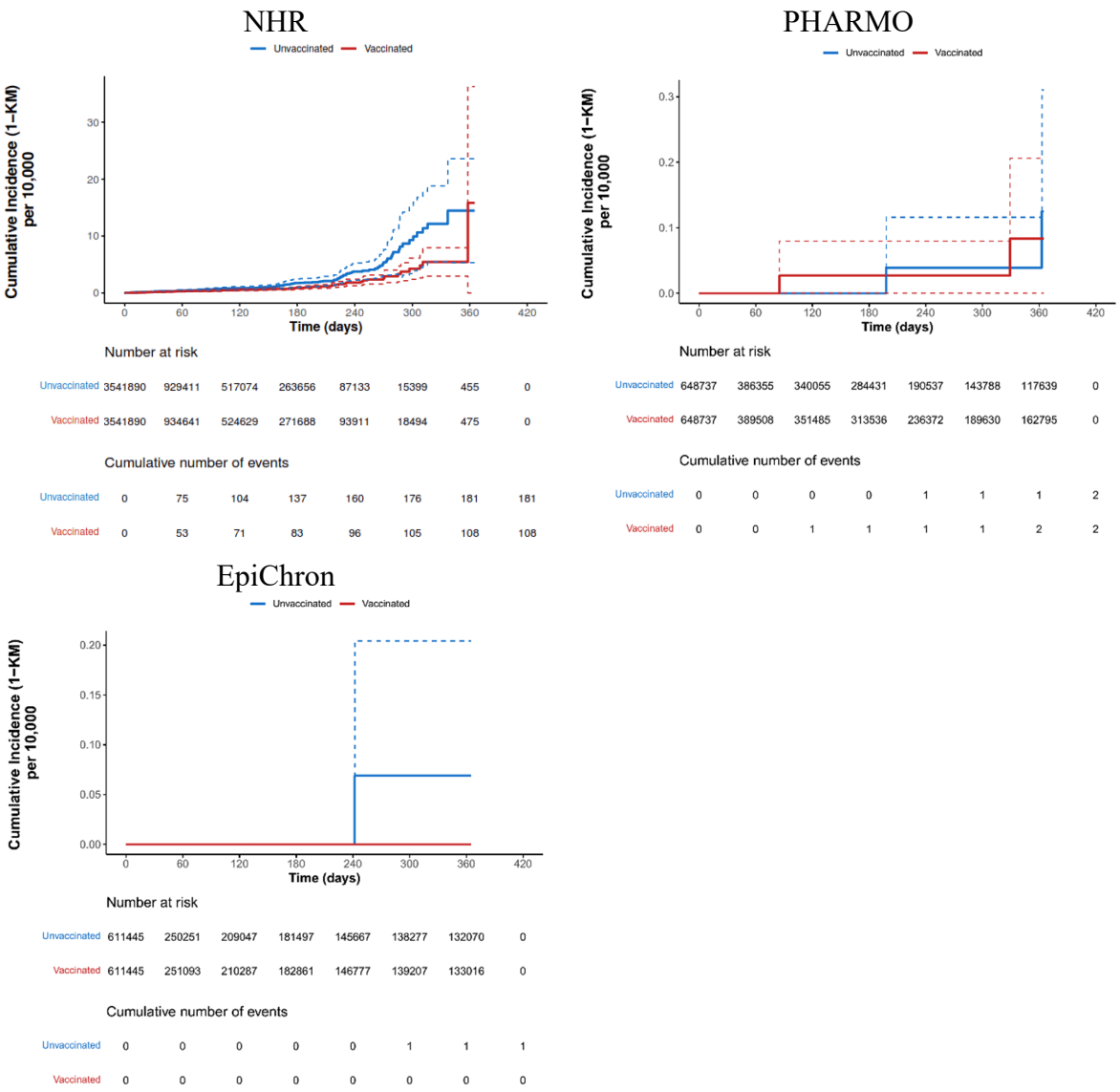
The matched HRs were 0.58 (95% CI: 0.42, 0.80) in NHR, and 0.82 (95% CI: 0.11, 6.12) in PHARMO. The adjusted HRs were 0.58 (95% CI: 0.42, 0.80) in NHR, and 0.71 (95% CI: 0.09, 5.31) in PHARMO. No differences were observed for the incidence of sudden death within the 365-day risk window, between the vaccinated and unvaccinated cohorts.

Table 99. 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)

	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)	NA	NA	NA	NA	NA	NA	NA	NA
NHR (Norway)	108	15.81 (0, 36.25)	509,635.58	2.12 (1.74, 2.56)	181	14.44 (5.32, 23.56)	504,480.23	3.59 (2.76, 4.66)
PHARMO (Netherlands)	<5	0.08 (0, 0.21)	302,886.53	0.07 (0.01, 0.24)	<5	0.13 (0, 0.31)	276,186.13	0.07 (0.02, 0.29)
EpiChron (Spain)	0	0 (0, 0)	199,937.57	0 (0, 0.18)	<5	0.07 (0, 0.20)	198,926.03	0.05 (0.01, 0.36)
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+).

Figure 89. 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)



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 90. 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)

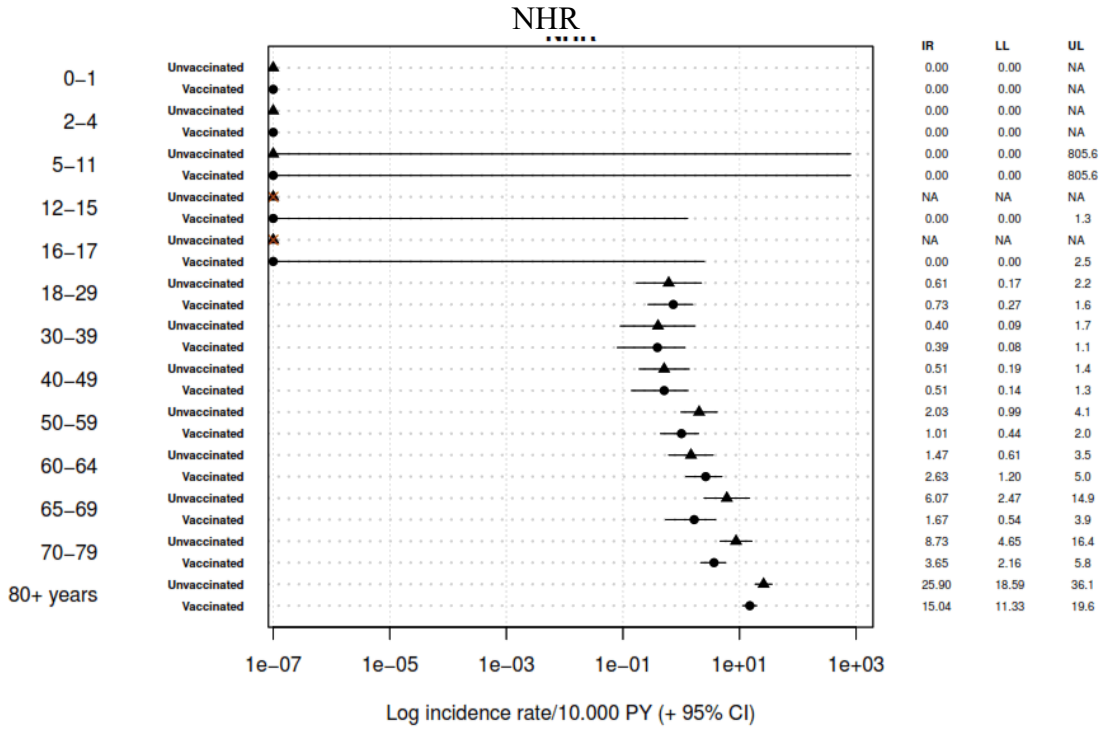


Figure 90. Forest plot showing incidence rates and 95% confidence intervals for sudden death among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source and by age groups (risk window: 365 days after dose 1)

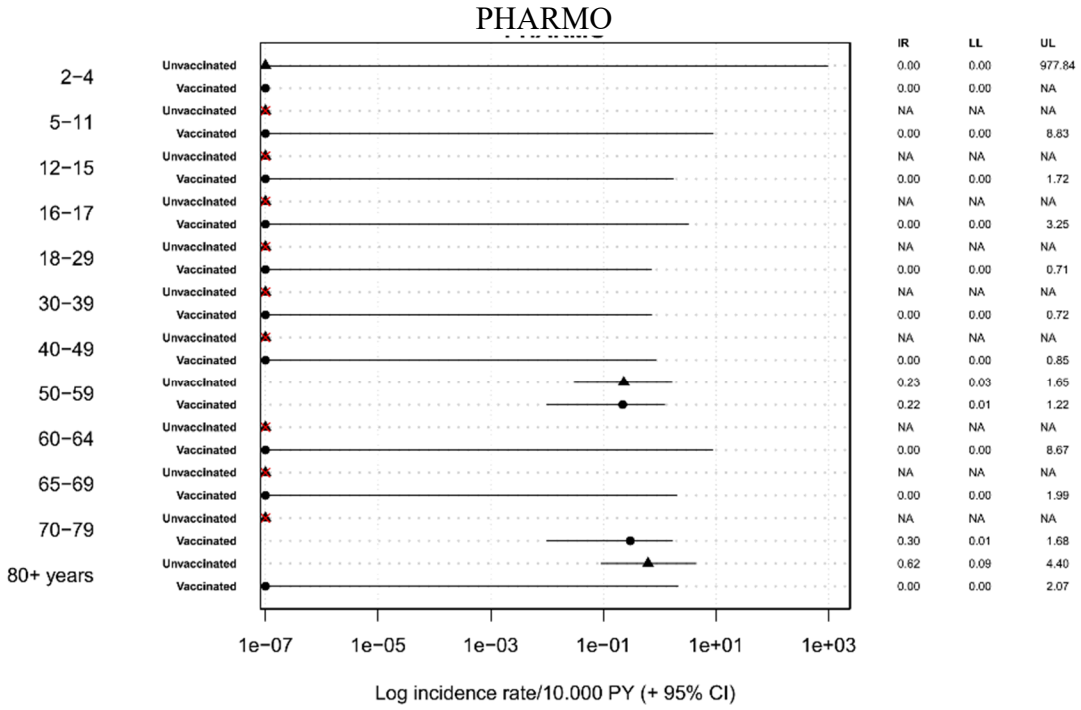


Figure 90. Forest plot showing incidence rates and 95% confidence intervals for sudden death among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source and by age groups (risk window: 365 days after dose 1)

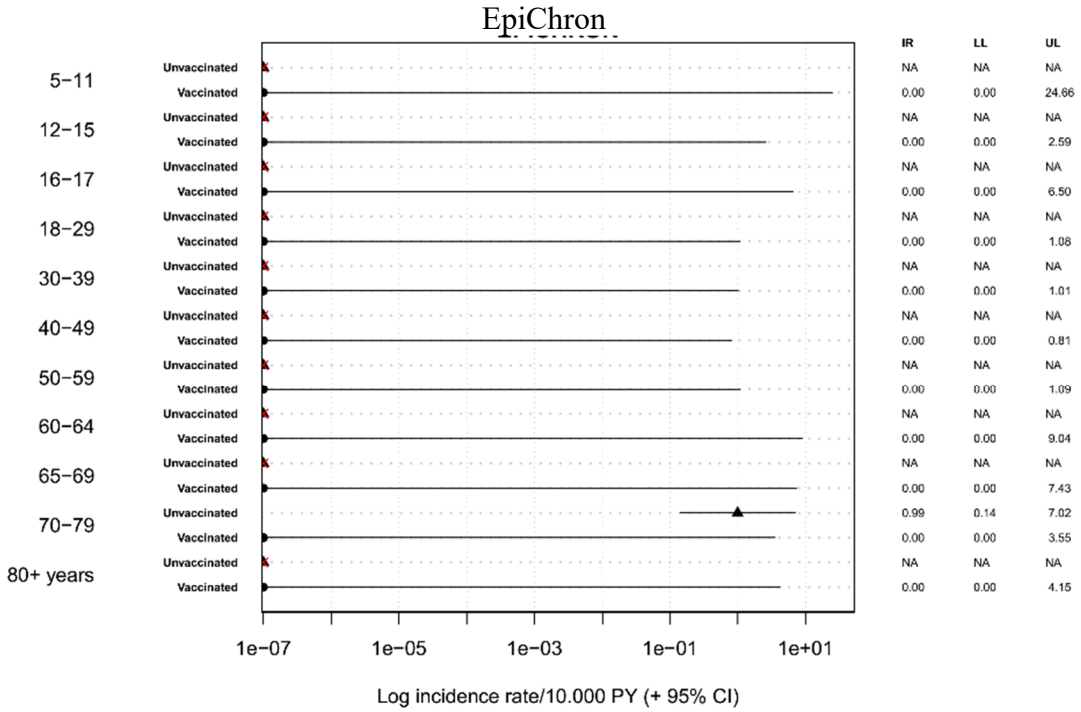


Table 100. Matched hazard ratios (HRs) and matched risk differences (RDs) per 10,000 person-years and their 95% CIs for sudden death among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source (risk window: 365 days after dose 1)

	Matched HR (95% CI)	Adjusted HR (95% CI)	Matched RD	Adjusted RD
Pedianet	NA	NA	NA	NA
NHR	0.58 (0.42, 0.80)	0.58 (0.42, 0.80)	1.37	1.36
PHARMO	0.82 (0.11, 6.12)	0.71 (0.09, 5.31)	-0.04	-0.06
EpiChron	NA	NA	-0.07	-0.08
SIDIAP	NA	NA	NA	NA

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

10.3.39. Severe COVID-19

Severe COVID-19 disease was defined as hospitalised COVID-19 or death due to COVID-19 infection and was identified in all data sources. The incidence rates ranged from 0.94 per 10,000 person-years (95% CI: 0.66, 1.31) in PHARMO to 131.34 per 10,000 person-years (95% CI: 126.93, 135.87) in EpiChron in the vaccinated cohorts. In the unvaccinated cohorts these ranged from 1.73 per 10,000 person-years (95% CI: 1.50, 2.90) in PHARMO to 199.07 per 10,000 person-years (95% CI: 190.68, 207.84) in EpiChron. The cumulative incidences ranged from 0.79 per 10,000 individuals (95% CI: 0.44, 1.15) in PHARMO to 150.38 per 10,000 person-years (95% CI: 144.72, 156.04) in EpiChron in the vaccinated cohorts and from 1.71 per 10,000 person-years (95% CI: 1.12, 2.30) in PHARMO to 226.17 per 10,000 person-years (95% CI: 215.61, 236.72) in EpiChron in the unvaccinated cohorts. The incidence of severe COVID-19 was highest in the older age groups, in both the unvaccinated and vaccinated cohorts.

The matched unadjusted HRs were 0.73 (95% CI: 0.51, 1.00) in Pedianet, 0.19 (95% CI: 0.17, 0.21) in NHR, 0.55 (95% CI: 0.35, 0.85) in PHARMO, 0.66 (95% CI: 0.62, 0.70) in EpiChron, and 0.36 (95% CI: 0.34, 0.38) in SIDIAP. The adjusted HRs 0.73 (95% CI: 0.51, 1.05) in Pedianet, 0.19 (95% CI: 0.17, 0.21) in NHR, 0.52 (95% CI: 0.33, 0.81) in PHARMO, 0.59 (95% CI: 0.56, 0.63) in EpiChron, and 0.34 (95% CI: 0.32, 0.36) in SIDIAP. All HRs and the upper limits of the 95% CIs were below 1 in all data sources except in Pedianet where the upper limit of the 95% CI was 1.05.

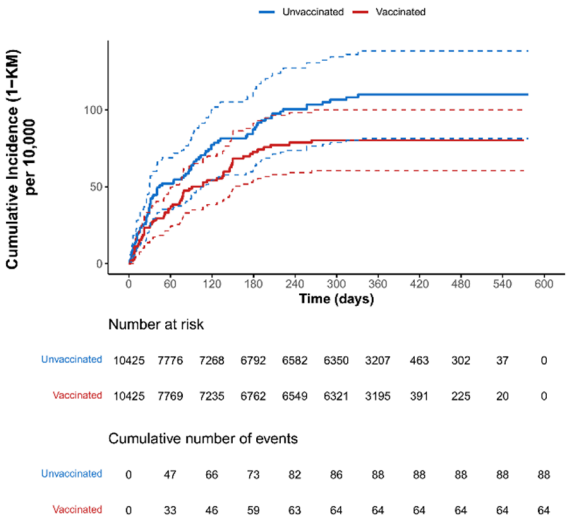
Table 101. Risk estimates (95% CI) per 10,000 person-years (PY) for severe COVID-19 within any time after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source

	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)	64	80.25 (60.48, 99.98)	7,069.41	90.53 (69.72, 115.61)	88	109.91 (81.37, 138.36)	7,120.54	123.59 (95.60, 159.77)
NHR (Norway)	528	30.66 (24.84, 36.48)	508,651.59	10.38 (9.51, 11.30)	2,669	216.47 (172.66, 260.08)	503,154.26	53.05 (49.70, 56.61)
PHARMO (Netherlands)	35	0.79 (0.44, 1.15)	370,492.79	0.94 (0.66, 1.31)	56	1.71 (1.12, 2.30)	323,540.48	1.73 (1.27, 2.36)
EpiChron (Spain)	3,346	150.38 (144.72, 156.04)	254,752.48	131.34 (126.93, 135.87)	5,026	226.17 (215.61, 236.72)	252,469.37	199.07 (190.68, 207.84)
SIDIAP (Spain)	2,967	26.81 (25.71, 27.90)	1,197,941.10	24.77 (23.88, 25.68)	8,196	73.18 (70.50, 75.87)	1,195,115.85	68.58 (66.31, 70.93)

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 91. Cumulative incidence of severe COVID-19 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

Pedianet



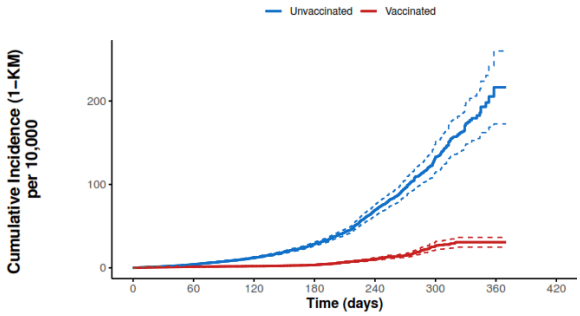
Number at risk

Unvaccinated	10425	7776	7268	6792	6582	6350	3207	463	302	37	0
Vaccinated	10425	7769	7235	6762	6549	6321	3195	391	225	20	0

Cumulative number of events

Unvaccinated	0	47	66	73	82	86	88	88	88	88	88
Vaccinated	0	33	46	59	63	64	64	64	64	64	64

NHR



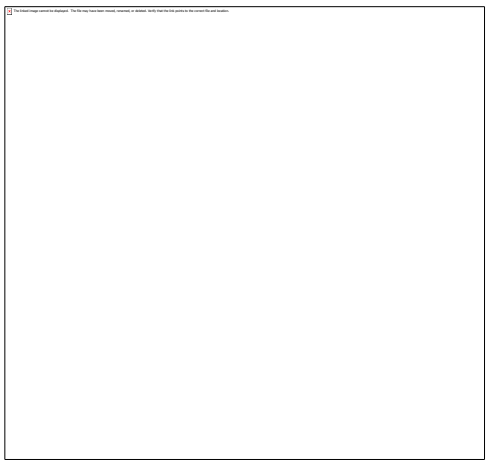
Number at risk

Unvaccinated	3537633	926830	515272	262485	86585	15297	446	0
Vaccinated	3537633	932450	523522	271205	93706	18431	470	0

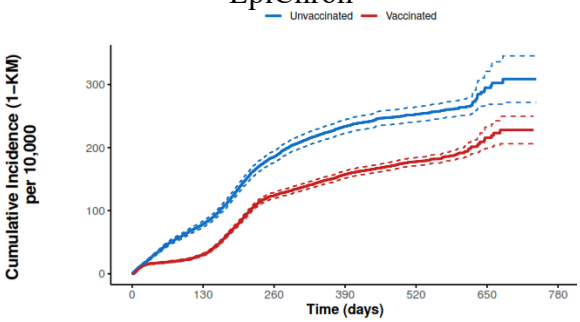
Cumulative number of events

Unvaccinated	0	675	1230	1859	2384	2612	2669	2669
Vaccinated	0	260	308	363	466	522	528	528

PHARMO



EpiChron



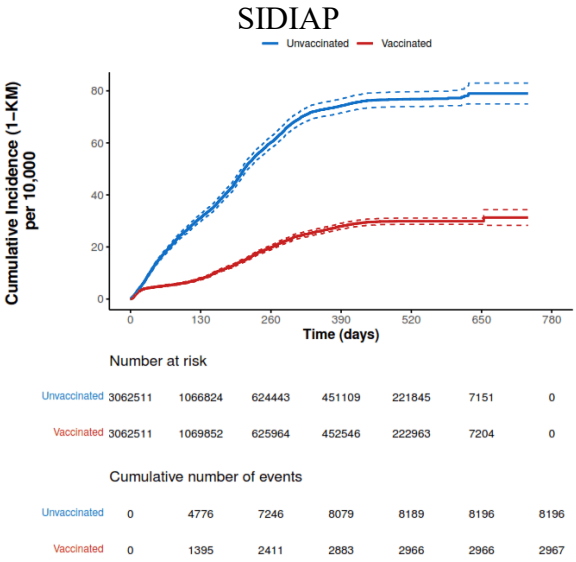
Number at risk

Unvaccinated	600768	199054	137640	124477	82908	2680	0
Vaccinated	600768	201191	138848	125646	84028	2830	0

Cumulative number of events

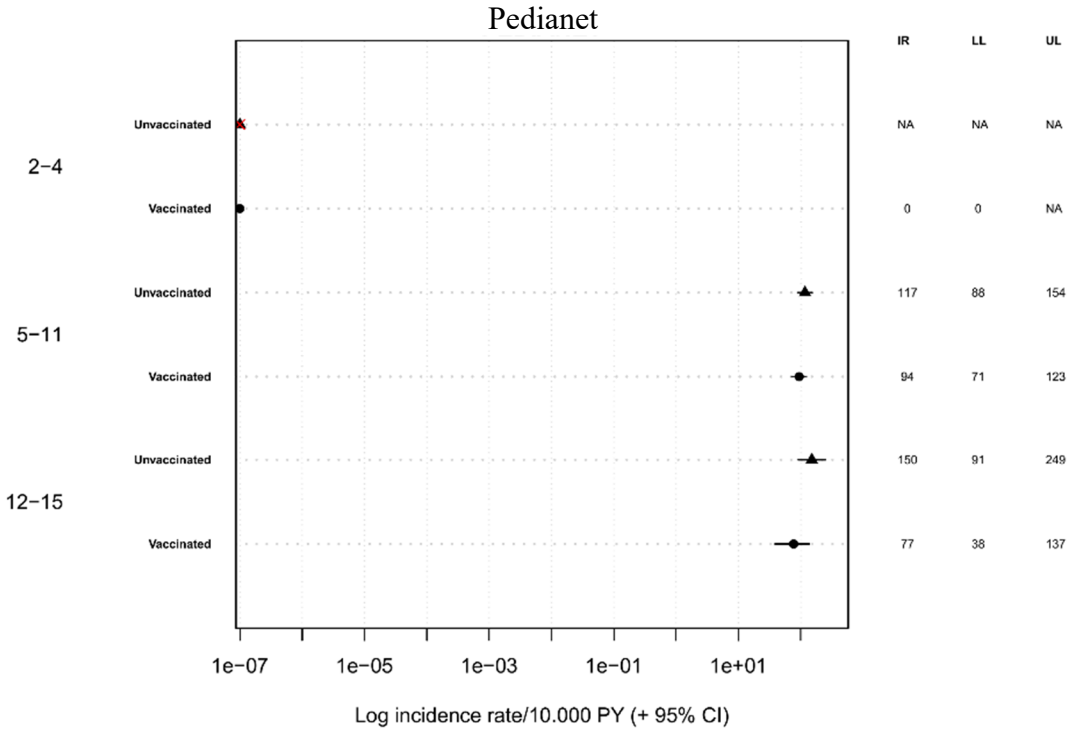
Unvaccinated	0	2263	4091	4744	4970	5023	5026
Vaccinated	0	977	2597	3044	3286	3343	3346

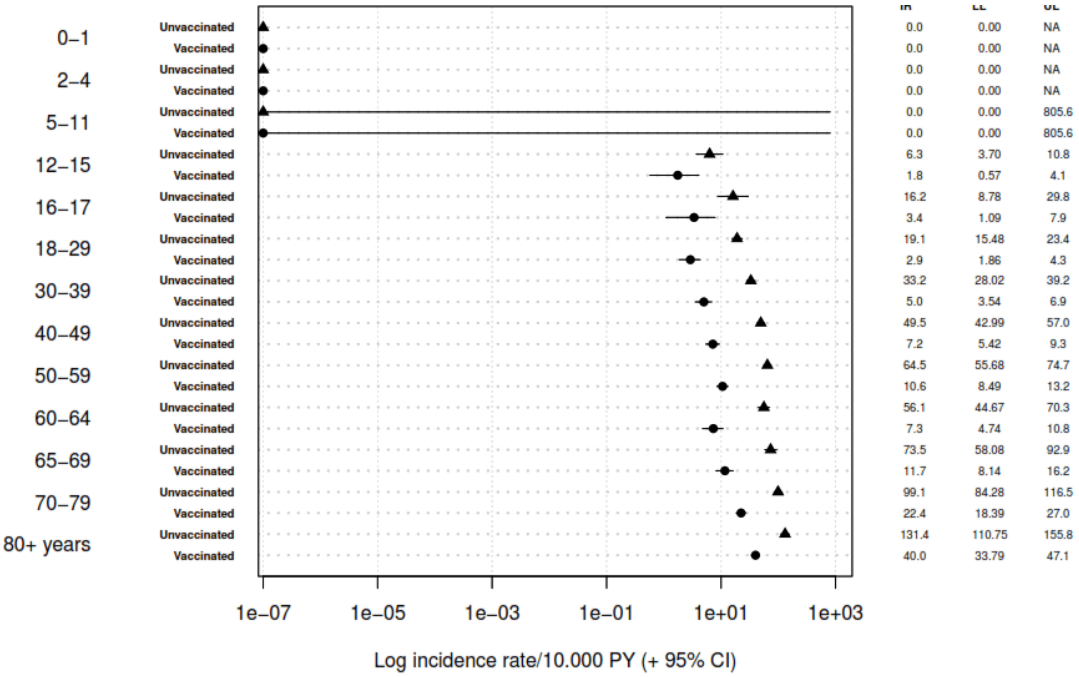
Figure 91. Cumulative incidence of severe COVID-19 within any time after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source



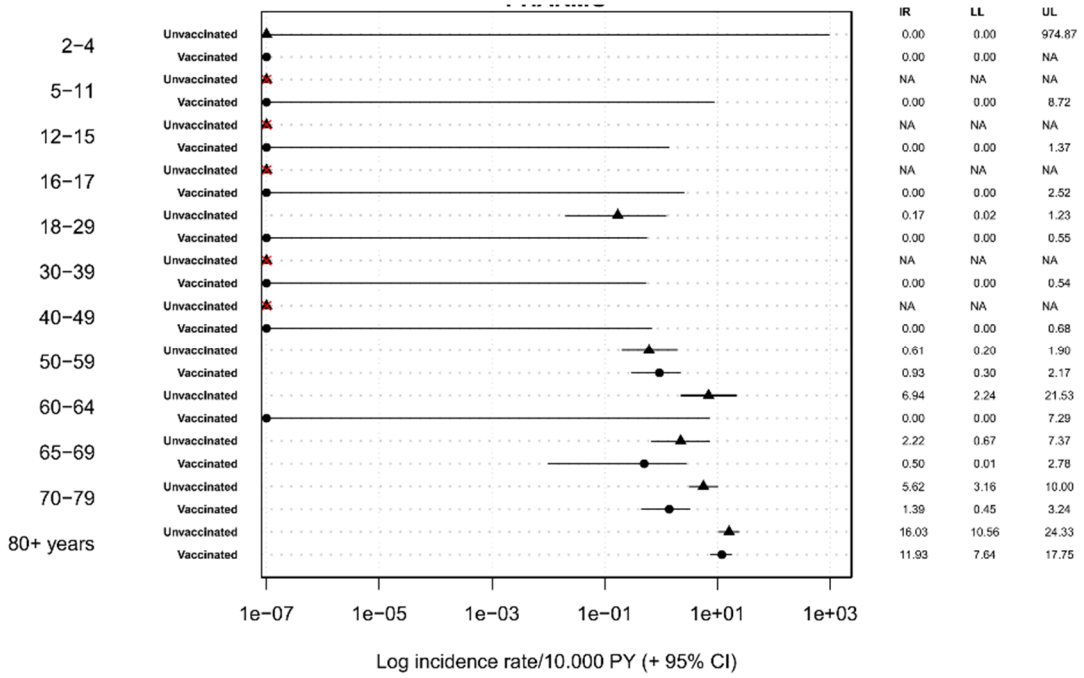
Cumulative incidence curves (1 – Kaplan–Meier risk) starting from the day of administration of the first dose of vaccine. Dotted lines represent 95% confidence intervals. The number at risk at each time point and the cumulative number of events within any time after start of follow-up are also shown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

Figure 92. Forest plot showing incidence rates and 95% confidence intervals for severe COVID-19 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

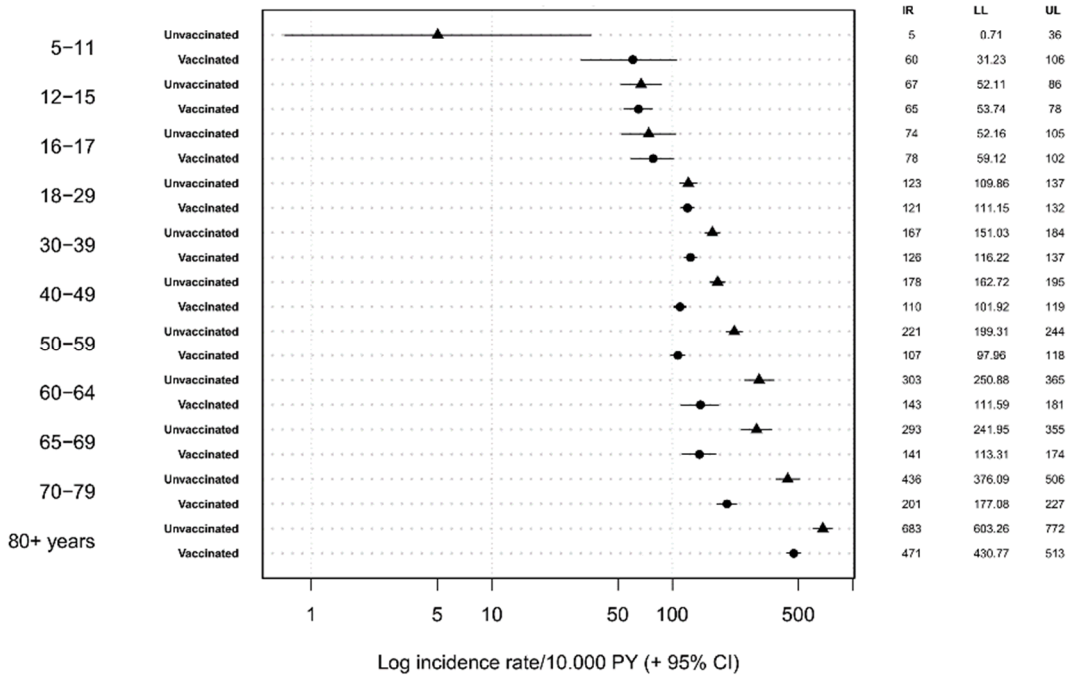




PHARMO



EpiChron



SIDIAP

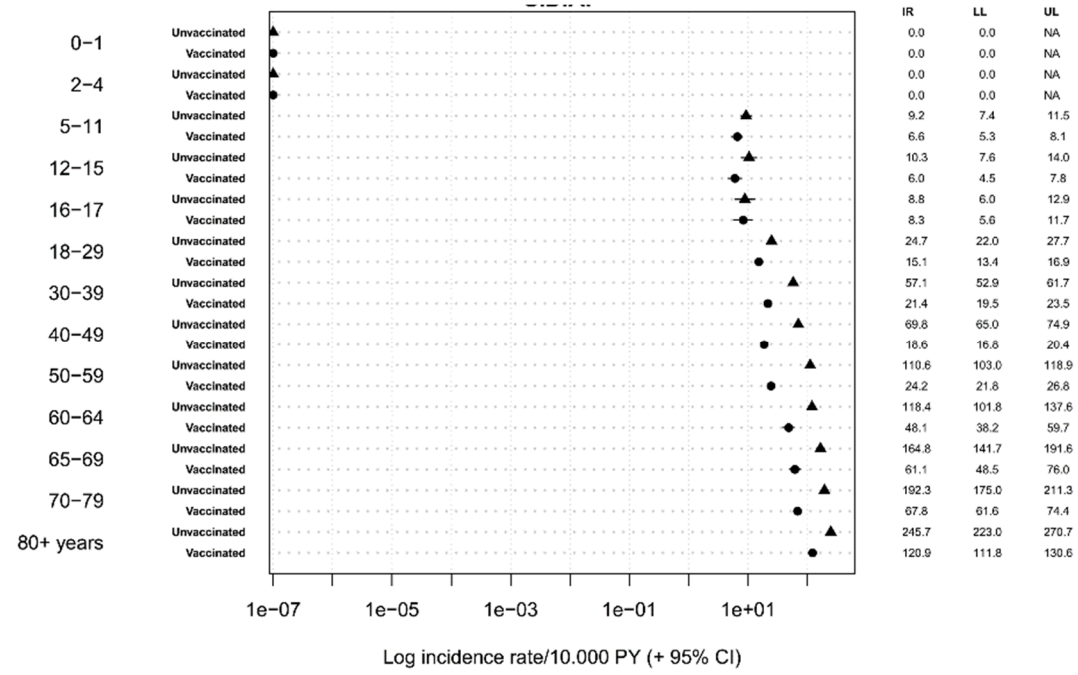


Table 102. Matched and adjusted hazard ratios (HRs) and matched and adjusted risk differences (RDs) per 10,000 person-years and their 95% CIs for severe COVID-19 within any time after start of follow-up after start of follow-up among individuals who received at least one dose of Pfizer-BioNTech COVID-19 vaccine and matched unvaccinated individuals by data source

	Matched HR (95% CI)	Adjusted HR (95% CI)	Matched RD	Adjusted RD
Pedianet	0.73 (0.51, 1.04)	0.73 (0.51, 1.05)	-29.66	-29.75
NHR	0.19 (0.17, 0.21)	0.19 (0.17, 0.21)	-185.81	-185.94
PHARMO	0.55 (0.35, 0.85)	0.51 (0.33, 0.81)	-0.92	-1
EpiChron	0.66 (0.62, 0.70)	0.59 (0.56, 0.63)	-75.79	-100.67
SIDIAP	0.36 (0.34, 0.38)	0.34 (0.32, 0.36)	-46.38	-50.15

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

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 fourth interim report provides updated results on the estimated incidence rates (IRs) and hazard ratios (HRs) for the 38 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. Results are reported for two recently added AESIs, i.e., myositis and hypermenorrhea.

These results are based on data from five data sources in four countries; Pedianet in Italy, PHARMO in the Netherlands, NHR in Norway and EpiChron and SIDIAP in Spain. No data from the UK (CRPD) were included as explained in Section 11.1.1, below. No new data from ARS (IT) could be extracted and analysed for this fourth interim report because of national and regional reassessment of their ability to provide public data for PASS.

In this report we included data up to 31 December 2022 from Pedianet, and GP data from PHARMO, SIDIAP and EpiChron. Only data up to 31 December 2021 were available from NHR, as the data for 2022 will only be made available by the Norwegian Health Record Database in Q2 2023 due to their lag time policy of annual data base update. In addition, hospital data are available from PHARMO up until 31 December 2021 for the first time. The period covered in the analysed data included months when participants could receive up to four doses of the Pfizer-BioNTech COVID-19 vaccine, which was implemented in many countries in late 2022. Hence, data for individuals who had received a third and fourth (booster) dose of the Pfizer-BioNTech COVID-19 vaccine have also been included.

In this fourth interim report, we have used all matching criteria and verified the balance between the matched vaccinated and unvaccinated cohorts. Matching on pregnancy status (except in PHARMO, because no pregnancy linkage is currently available and Pedianet which is a paediatric database only) was done using a pregnancy algorithm developed by the ConcePTION project.[16] We used a negative control outcome, i.e., COVID-19 disease in the first 12 days after time zero which is compatible with the absence of relevant baseline residual confounding. Because the use of this negative control outcome assumes that the confounders for COVID-19 disease are equally relevant for all AESIs, effect estimates were additionally adjusted via IPT weighting, since similar estimates with and without IPT weighting would support this assumption. This was what we observed, thus matching achieved comparable cohorts.

These results should still be considered as interim results from a long-term safety surveillance study. For this fourth data extraction we included extraction, transformation and harmonisation of outcomes and some covariates. Some limitations from prior reports have been identified and some issues have been corrected, such as the inclusion of IPT adjusted results, improved algorithms to clean the vaccination information, refined and more specific disease code lists, and performance of matching based on all matching variables including socio-economic status. We will continue to work on resolving issues for interim report 5.

11.1.1. Important information on data sources

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

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

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

- There was a quality issue with the CPRD data availability that was disclosed in January 2023, and required re-extraction of data which showed results differing from published incidence rates. This may be due to incorrect reading of the data from study scripts which is under investigation. Delay was caused by the need to adhere to an extensive pre-matching procedure before data of matched patient IDs could be requested by the DAP from CPRD. However, a new updated data release from CPRD became available in July/August 2023, and the analyses with these new data are being prepared for next interim report.

In the other data sources, data for events can 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.[17]

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

The results from NHR in this interim report were based the same data that were used for the third interim report.because the new data instance was only made available by the Norwegian Health Record Database in Q2 2023 due to their lag time policy of annual data base update, which was too late to be included in the analyses reported here. Thus, data from all the requested data sources has not been included, in particular, hospitalisation data were not yet

available. Hence the results for the events for this interim report are based on outpatient data only.

The data in this fourth interim report from PHARMO were extracted from GP records up until 31 December 2022 and, for the first time, from hospital records up until 31 December 2021. The coding system used in the PHARMO GP databases is ICPC, which is not as granular as ICD coding, and therefore free text identification of AESIs was conducted. Although substantial efforts to improve the free text identification and to improve the ETL script for variables and AESIs have been made, the rates and number of events still tend to be lower than in other data sources. The identification algorithms will continue to be refined and validated for the fifth interim report.

The EpiChron data source included diagnosis codes from general practitioners and from hospital discharges up to 31 December 2022 for this fourth interim report.

The SIDIAP data source included data from general practitioner and hospital discharge records up to 31 December 2022 for this 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 in this fourth report was 8,139,228. A total of 6,704,064 (82.4%) individuals received a second dose of the Pfizer-BioNTech COVID-19 vaccine. The second dose was mainly administered within six weeks after the first dose; 16.5% 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 (29.62%), where the COVID-19 vaccination campaign prioritised the administration of first doses to a large percentage of the population, before administering 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 from 2.74% in Pedianet to 16.34% in PHARMO. In Pedianet more vaccinated and unvaccinated matched controls have been included in this interim report 4 compared with interim report 2 because the matching algorithm was improved and had a more logical definition of the geographic region and socioeconomic status.

A total of 25,290 pregnant women received a first dose of the Pfizer-BioNTech COVID-19 vaccine and satisfied the inclusion criteria. Among these women 7,555 (29.87%) received the dose during their first trimester of pregnancy and 8,851 (35.00%) in their second trimester.

Overall, 1,959,413 individuals had a recorded third dose of the Pfizer vaccine which is 24.07% of those who received a 1st dose. The mean age of these individuals was higher than those who had received at least a first dose (except in PHARMO), reflecting the targeted roll out of booster doses to elderly individuals first. The interval between the second and third

doses varied between data sources with the median interval ranging from 21 weeks in Pedianet to 31 weeks in SIDIAP.

At the time of database lock, 324,290 (3.98%) individuals had received a fourth dose of the Pfizer-BioNTech COVID-19 vaccine. The highest uptake rate of this fourth dose was in SIDIAP (8.1%) and the lowest in NHR (0.01%). The low number in NHR is related to their earlier database lock, with data available only up to the end of 2021.

11.1.3. Matched cohorts

In this fourth 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 by the Centers for Disease Control and Prevention (CDC) and socio-economic status.

From a total of 8,139,228 individuals who received a first dose of the Pfizer-BioNTech COVID-19 vaccine, 7,427,102 (91.3%) 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 varied from 0.8 months in NHR to 11.3 months in Pedianet. Censoring of follow-up was mostly due to unvaccinated individuals being vaccinated with a COVID-19 vaccine, which also resulted in the censoring of the matched vaccinated individual.

The median age of vaccinated individuals was highest in PHARMO (49 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 aged under 5 years captured. We assessed lifestyle factors, healthcare use, prevalence of comorbidity and comorbidity summary scores, as well as the use of comedications and vaccines prior to time zero. Information on long-term care facility residency and healthcare worker or essential worker status could not be identified in the data sources. The lifestyle indicators (i.e., smoking status and BMI), which were available from PHARMO, EpiChron and SIDIAP, and the healthcare use indicators, showed a similar distribution between the vaccinated and unvaccinated cohorts. This should be interpreted cautiously because of the high percentage of missing data for these variables.

PHARMO and SIDIAP had missing data on other vaccines, 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 individuals and 8 million unvaccinated individuals in the study, which, in the pooled analysis that is planned for the final report, would be sufficient to detect a risk ratio of 3 for Guillain-Barré syndrome (incidence rate of 1 in 100,000 person-years and a risk window of 42 days), assuming a two-sided alpha of 0.95 and a power of 80%.

The data and results from this fourth interim report are better compared with those in the first three interim reports in terms of size, follow-up and harmonisation of AESIs, as well as the inclusion of many covariates for the first time, and more detailed matching on pre-specified covariates.

11.1.4. Incidence rates and hazard ratios for AESIs

Since the analyses in interim report 3, the AESIs code lists have been re-reviewed by clinical epidemiologists within VAC4EU, and tags for specific and sensitive codes were assessed per descendant code, instead of at the concept level. This may have led to changes in some of the event rates.

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, PHARMO, EpiChron and SIDIAP the differences for the incidences were less than 1 per 1,000 individuals. In Pedianet the difference for the incidences of COVID-19 in the first 12 days was 2 per 1,000 cases but this is not suggestive of confounding. Consequently, we considered that the matching process achieved the required balance between the cohorts. Regardless of the negative control results, the analyses were performed in the matched cohorts with PS adjustments to assess the effect of control of confounding.

AESIs with long time window (365 days)

The cumulative incidence curves for a series of cardiovascular and metabolic AESIs with 365-day risk window in specific databases (PHARMO) showed differences in risk between the vaccinated and unvaccinated cohorts that occurred after day 100. This was observed for acute cardiovascular injury, arrhythmia, and coronary artery disease. This finding, which was observed in other data sources for these outcomes in previous analyses, is thought to be due to differential ascertainment of exposure or outcomes with long term follow-up and will be investigated in detail, as was previously done for the other data sources. 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

Guillain-Barré syndrome events were observed in three of the five data sources. In SIDIAP events occurred in both the vaccinated and unvaccinated cohorts and in PHARMO and EpiChron these occurred only in the unvaccinated cohort. The IRs were 0.3 per 10,000 person-years (95% CI: 0.15, 0.68) in SIDIAP in the vaccinated cohort and were 0.30 per 10,000 person-years (95% CI: 0.13, 0.70) in SIDIAP and 0.47 per 10,000 person-years (95% CI: 0.12; 1.88) in EpiChron in the unvaccinated cohorts. The cumulative incidence was below 0.1 per 10,000 individuals in both cohorts in all three data sources. Due to the absence of events in the vaccinated cohorts in Pedianet, NHR, PHARMO, and EpiChron, age-related effects on incidence were only observed in SIDIAP, with a trend for increased incidence at older age groups. The matched HR for Guillain-Barré syndrome in SIDIAP was 1.14 (95% CI: 0.38, 3.40) and the adjusted HR was 1.11 (95% CI: 0.37, 3.31). No differences were observed for the incidence of Guillain-Barré syndrome between the vaccinated and unvaccinated cohorts.

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.[17]

Acute disseminated encephalomyelitis

Less than five cases were observed in the vaccinated cohort in SIDIAP, therefore, the incidence of acute disseminated encephalomyelitis was very low, 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

Narcolepsy was a rare event, only observed in SIDIAP with an incidence rate of 0.13 (95% CI: 0.03, 0.38) per 10,000 person-years in the vaccinated cohort and 0.21 (95% CI: 0.08, 0.61) per 10,000 person-years in the unvaccinated cohort. This 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

There are,o specific codes for acute aseptic arthritis, 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 21.18 per 10,000 person-years (95% CI: 17.56, 25.33) in PHARMO to 60.57 per 10,000 person-years (95% CI: 57.48, 63.79) in NHR in the vaccinated cohorts and from 18.15 per 10,000 person-years (95% CI: 14.59, 22.56) in PHARMO to 58.37 per 10,000 person-years (95% CI: 23.17, 147.01) in Pedianet in the unvaccinated cohorts. 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. No differences were observed for the incidence of acute aseptic arthritis between the vaccinated and unvaccinated cohorts during the 42 days risk window, all matched and adjusted HRs were around 1 with narrow 95% CIs that included 1.

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, except Pedianet. The IRs in the vaccinated cohorts ranged from 1.16 per 10,000 person-years (95% CI: 0.81, 1.61) in PHARMO to 6.30 per 10,000 person-years (95% CI: 5.62, 7.04) in NHR and from 1.09 per 10,000 person-years (95% CI: 0.70, 1.70) in PHRAMO to 5.26 per 10,000 person-years (95% CI: 4.39, 6.31) in NHR in the unvaccinated cohorts. The incidence was similar in the different age groups. The matched HRs were 1.19 (95% CI: 0.97, 1.48) in NHR, 1.08 (95% CI: 0.62, 1.85) in PHARMO, 0.69 (95% CI: 0.43, 1.09) in EpiChron, and 1.00 (95% CI: 0.84, 1.20) in SIDIAP. The adjusted HR were 1.19 (95% CI: 0.97, 1.48) in NHR, 1.06 (95% CI: 0.62, 1.84) in PHARMO, 0.70 (95% CI: 0.44, 1.11) in EpiChron, and 0.97 (95% CI: 0.81, 1.16) 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.[18,19] For the fifth interim report, we will create an algorithm with insulin medication as an inclusion criterion, and presence of non-insulin glucose-lowering agents as an exclusion criterion.

(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 ranged from 1.76 per 10,000 person-years (95% CI: 0.84, 3.24) in PHARMO to 13.55 per 10,000 person-years (95% CI: 12.09, 15.13) in SIDIAP and in the unvaccinated cohorts from 2.99 per 10,000 person-years (95% CI: 1.81, 4.94) in PHARMO to 16.13 per 10,000 person-years (95% CI: 14.14, 18.40) in SIDIAP. The cumulative incidence (1-KM)

per 10,000 individuals over the 365-day risk window and was less than 1.8 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 0.59 (95% CI: 0.27, 1.31) in PHARMO, 0.49 (95% CI: 0.28, 0.85) in EpiChron, and 0.84 (95% CI: 0.71, 1) in SIDIAP. The adjusted HRs were 0.55 (0.25, 1.22) in PHARMO, 0.46 (0.26, 0.78) in EpiChron, and 0.78 (0.66, 0.93) 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 findings in this fourth 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. Pedianet, PHARMO, EpiChron and SIDIAP 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 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 0.51 per 10,000 person-years (95% CI: 0.01, 2.83) in EpiChron and 0.67 per 10,000 person-years (95% CI: 0.27, 1.39) in SIDIAP in the vaccinated cohorts and 0.29 per 10,000 person-years (95% CI: 0.09, 0.89) in SIDIAP and 0.51 per 10,000 person-years (95% CI: 0.07, 3.61) 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 1.00 (95% CI: 0.056; 15.98) in EpiChron and 2.33 (95% CI: 0.60; 9.02) in SIDIAP. No significant differences were observed in the incidence of TTS between the vaccinated and unvaccinated cohorts in the data sources reporting data.

Myositis

This is the first time we have included myositis in our analyses. Myositis events were observed in both the vaccinated and unvaccinated cohorts in all data sources, except in the Pedianet unvaccinated cohort (only children). The incidence rates in the vaccinated cohorts ranged 0.26 per 10,000 person-years (95% CI: 0.11, 0.52) in PHARMO to 1.71 per 10,000 person-years (95% CI: 1.46, 1.98) in SIDIAP and in the unvaccinated cohorts, from 0.07 per 10,000 person-years (95% CI: 0.02, 0.29) in PHARMO to 1.80 per 10,000 person-years (95% CI: 1.46, 2.21) in SIDIAP. The incidence was similar in the different age groups. The matched HRs were 0.75 (95% CI: 0.33, 1.67) in NHR, 3.78 (95% CI: 0.80, 17.92) in PHARMO, 1 (95% CI: 0.32, 3.08) in EpiChron, and 0.95 (95% CI: 0.74, 1.23) in SIDIAP. The adjusted HRs were 0.74 (95% CI: 0.33, 1.67) in NHR, 4.41 (95% CI: 0.93, 20.87) in PHARMO, 0.97 (95% CI: 0.32, 2.98) in EpiChron, and 0.85 (95% CI: 0.65, 1.09) in SIDIAP.

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

Acute cardiovascular injury

Acute cardiovascular injury events were observed in both the vaccinated and unvaccinated cohorts in all data sources, except in Pedianet, which only has data for children. The incidence rates in the vaccinated cohorts ranged from 43.22 per 10,000 person-years (95% CI: 40.90, 45.64) in PHARMO to 131.37 per 10,000 person-years (95% CI: 128.15, 134.65) in NHR. In the unvaccinated cohorts these ranged from 34.79 per 10,000 person-years (95% CI: 31.84, 38) in PHARMO to 138.48 per 10,000 person-years (95% CI: 133.23, 143.94) in NHR.

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 in both the vaccinated and unvaccinated cohorts during the 365-day risk interval. The matched HRs were 0.95 (95% CI: 0.90, 0.99) in NHR, 1.25 (95% CI: 1.13, 1.39) in PHARMO, 0.91 (95% CI: 0.82, 1) in EpiChron, and 0.93 (95% CI: 0.89, 0.99) in SIDIAP. The adjusted HRs were 0.94 (95% CI: 0.90, 0.98) in NHR, 1.20 (95% CI: 1.08, 1.33) in PHARMO, 0.91 (95% CI: 0.82, 1) in EpiChron, and 0.93 (95% CI: 0.89, 0.99) in SIDIAP. The 95% CIs for the matched and adjusted HRs included 1 in EpiChron and SIDIAP. In NHR the upper limit of the 95% CI was <1 for both the matched and adjusted HRs. In PHARMO the lower limit of the 95% CI was >1 for both the matched and adjusted HRs.

The cumulative incidence curves show that the differentiation in risk of acute cardiovascular injury between vaccinated and non-vaccinated occurred after day 100 in PHARMO. As mentioned above this finding was observed only in PHARMO but not in the other sources participating in this study. This 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 was also analysed separately.

Arrhythmia was observed in the vaccinated and unvaccinated cohorts in all data sources. The incidence rates in the vaccinated cohorts ranged from 24.50 per 10,000 person-years (95% CI: 14.27, 39.23) in Pedianet (children only) to 244.02 per 10,000 person-years (95% CI: 239.55, 248.56) in NHR. In the unvaccinated cohorts these ranged from 14.31 per 10,000 person-years (95% CI: 7.70, 26.61) in Pedianet to 234.38 per 10,000 person-years (95% CI: 227.58, 241.38) in NHR. These rates were comparable to those reported in ACCESS. The rates reported here and those reported in ACCESS showed a strong age relationship. Rates in PHARMO showed the impact of having both primary care and hospital data.

The cumulative incidences during the 365-day risk window ranged from 23.95 per 10,000 individuals (95% CI: 12.54, 35.34) in Pedianet to 306.11 per 10,000 person-years (95% CI: 269.85, 342.24) in NHR in the vaccinated cohorts and from 13.90 per 10,000 person-years (95% CI: 5.23, 22.56) in Pedianet to 263.50 per 10,000 person-years (95% CI: 221.64, 305.19) in NHR in the unvaccinated cohorts.

The incidence rates were higher in older age groups. The matched HRs were 1.71 (95% CI: 0.78, 3.74) in Pedianet, 1.04 (95% CI: 1.01, 1.08) in NHR, 1.36 (95% CI: 1.27, 1.46) in PHARMO, 1.15 (95% CI: 1.06, 1.26) in EpiChron, and 1.07 (95% CI: 1.03, 1.11) in SIDIAP. The adjusted HRs were 1.73 (95% CI: 0.79, 3.78) in Pedianet, 1.04 (95% CI: 1, 1.07) in NHR, 1.28 (95% CI: 1.19, 1.38) in PHARMO, 1.07 (95% CI: 0.98, 1.117) in EpiChron, and 1.02 (95% CI: 0.98, 1.06) in SIDIAP.

Discussion on arrhythmia AESI (reply to EMA/FDA request)

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

In all data sources except NHR, adjustment (PS control of confounding) resulted in a lowering of the HRs. Hence, it could be that there is residual confounding which may contribute to the lower adjusted estimates. Also, it could be that health-seeking behaviour related to this diagnosis event is responsible for the finding as arrhythmia is not always a severe event and heathy individuals interested in vaccination would be more likely to consult and therefore have arrhythmia diagnosed (i.e., a healthy vaccinee effect).

In interim report 3 we observed a higher cumulative incidence rate for arrhythmia in the SIDIAP vaccinated cohort compared with that in the unvaccinated cohort which was not seen in interim report 4. Possible explanations for the differences in results between interim reports 3 and 4 include changes in the matching algorithms, which included matching on socio-economic status in interim report 4, differences in the diagnostic codes used to identify outcomes, which also affect the number of eligible individuals, improvements in the COVID-19 vaccination identification (i.e., inclusion of a cleaning algorithm deleting vaccinations that occurred within 14 days after dose 1 and 90 days after dose 2). Additionally, differences in the follow-up could contribute, since in this interim report 4 the follow-up is longer, so the impact of immortal-time bias present would be diluted.

In the current analysis we see the largest differences in PHARMO, where we have some difficulties defining vaccination that is leading to small differences in incidence of CV AESIs with long time windows. We continue our diagnostics of the database as in the past we have experienced that improvement in vaccination detection procedures reduces the differences.

We have discussed these results with the SAB, who agreed with our interpretation and stated that very little evidence of an increased risk in the other data sources which is suggestive that something is going on in PHARMO, as can be seen in other outcomes. If the problem remains after diagnostic attempts to solve the exposure definition problems in PHARMO, it

could be possible to model some constructive bias analysis to correct this in the final analyses.

Heart failure

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

The incidence rates of heart failure in the vaccinated cohorts ranged from 20.55 per 10,000 person-years (95% CI: 18.96, 22.23) in PHARMO to 62.69 (95% CI: 60.50, 64.93) per 10,000 person-years in NHR. In the unvaccinated cohorts these ranged from 17.66 per 10,000 person-years (95% CI: 15.58, 20.02) in PHARMO to 77.68 per 10,000 person-years (95% CI: 73.66, 81.92) in NHR. The matched HRs were 0.80 (95% CI: 0.75, 0.86) in NHR, 1.17 (95% CI: 1.01, 1.36) in PHARMO, 0.92 (95% CI: 0.82, 1.04) in EpiChron, and 0.91 (95% CI: 0.85, 0.98) in SIDIAP. The adjusted HRs were 0.80 (95% CI: 0.75, 0.85) in NHR, 1.13 (95% CI: 0.97, 1.31) in PHARMO, 0.88 (95% CI: 0.78, 0.99) in EpiChron, and 0.87 (95% CI: 0.81, 0.93) in SIDIAP. All 95% CIs included 1. No differences were observed for the incidence of heart failure between the vaccinated and unvaccinated cohorts during the 365-day risk window.

Stress cardiomyopathy

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

Stress cardiomyopathy was a rare event in the three data sources in which events were identified, i.e., PHARMO, EpiChron, and SIDIAP. The incidence rates of stress cardiomyopathy in the vaccinated cohorts were 0.17 per 10,000 person-years (95% CI: 0.05, 0.39) in PHARMO to 0.39 per 10,000 person-years (95% CI: 0.28, 0.54) in SIDIAP. In the unvaccinated cohorts these were PHARMO 0.11 (95% CI: 0.03, 0.47), EpiChron 0.10 (95% CI: 0.01, 0.71), and SIDIAP 0.25 (95% CI: 0.14, 0.43). The cumulative incidence during the 365-day risk window was less than 1 per 10,000 individuals 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 1.54 (95% CI: 0.27, 8.90) in PHARMO, 2.98 (95% CI: 0.36, 24.74) in EpiChron, and 1.60 (95% CI: 0.84, 3.03) in SIDIAP. The adjusted HRs were 1.34 (95% CI: 0.23, 7.82) in PHARMO, 3.12 (95% CI: 0.38, 25.82) in EpiChron, and 1.55 (95% CI: 0.82, 2.91) in SIDIAP. No differences were observed for the incidence of stress cardiomyopathy between the vaccinated and unvaccinated cohorts during the 365-day risk window. 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 ranged from 16.27 per 10,000 person-years (95% CI: 14.54, 18.14) in EpiChron to 88.86 per 10,000 person-years (95% CI: 86.24, 91.53) in NHR. In the unvaccinated cohorts they ranged from 13.59 per 10,000 person-years (95% CI: 11.81, 15.65) in PHARMO to 83.3 per 10,000 person-years (95% CI: 79.1, 87.7) in NHR. The incidence of coronary artery disease was higher in higher age groups in all data sources in both the vaccinated and unvaccinated cohorts.

The matched HRs for coronary artery disease were 0.99 (95% CI: 0.94, 1.05)in NHR, 1.41 (95% CI: 1.20, 1.66) in PHARMO, 0.89 (95% CI: 0.73, 1.09) in EpiChron, and 1.11 (95% CI: 1.02, 1.22) in SIDIAP. The adjusted HRs were 0,99 (95% CI: 0.94, 1.05) in NHR, 1.36 (95% CI: 1.15, 1.60) in PHARMO, 0.84 (95% CI: 0.69, 1.02) in EpiChron, and 1.06 (95% CI: 0.97, 1.16) in SIDIAP. In NHR and PHARMO the lower limit of the 95% CI for the adjusted HRs was >1.

Myocarditis

Myocarditis events were identified in all data sources, except Pedianet.

For the 7-day risk window after the start of follow-up, the incidence rates ranged from 0.48 per 10,000 person-years (95% CI: 0.10, 1.40) in NHR to 1.72 per 10,000 person-years (95% CI: 0.21, 6.20) in PHARMO in the vaccinated cohorts. In the unvaccinated cohorts these ranged from 0.18 per 10,000 person-years (95% CI: 0.03, 1.30) in SIDIAP to 0.90 per 10,000 person-years (95% CI: 0.30, 2.60) in PHARMO. No events were reported in the vaccinated cohort in SIDIAP or in the unvaccinated cohort in EpiChron and PHARMO 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 1.00 (95% CI: 0.20, 4.95) in NHR. The adjusted HRs were 1.00 (95% CI: 0.20, 4.96) in NHR.

During the 14-day risk window after the start of follow-up, in the vaccinated cohorts the incidence rates ranged from 0.61 per 10,000 person-years (95% CI: 0.22, 1.33) in SIDIAP to 1.07 per 10,000 person-years (95% CI: 0.13, 3.87) in EpiChron. In the unvaccinated cohorts these ranged from 0.10 per 10,000 person-years (95% CI: 0.01, 0.72) in SIDIAP to 0.72 per 10,000 person-years (95% CI: 0.36, 1.44) in NHR. The cumulative incidence during the 14-day risk window was below 1.0 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 1.00 (95% CI: 0.38, 2.66) in NHR, 2.00 (95% CI: 0.18, 22.05) in EpiChron, and 6.00 (0.72, 49.84) in SIDIAP. The adjusted HRs were 1.00 (95% CI: 0.38, 2.67) in NHR, 1.88 (95% CI: 0.17, 20.74) in EpiChron, and 6.92 (95% CI: 0.83, 57.71) SIDIAP.

During the 21-day risk window after the start of follow-up, in the vaccinated cohorts the incidence rates ranged from 0.59 per 10,000 person-years (95% CI: 0.25, 1.15) in SIDIAP to 1.18 per 10,000 person-years (95% CI: 0.24, 3.46) in EpiChron. In the unvaccinated cohorts these ranged from 0.22 per 10,000 person-years in (95% CI: 0.07, 0.68) in SIDIAP to 0.73 per 10,000 person-years (95% CI: 0.35, 1.52) in NHR. 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 0.91 (95% CI: 0.35, 2.38) in NHR, 3.00 (95% CI: 0.31, 28.82) in EpiChron, and 2.67 (95% CI: 0.71, 10.05) in SIDIAP. The adjusted HRs were 0.91 (95% CI: 0.35, 2.38) in NHR, 2.82 (95% CI: 0.29, 27.16) in EpiChron, and 2.67 (95% CI: 0.71, 10.05) in SIDIAP. 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 COVID-19 mRNA vaccines in several studies in young adults,[20] 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

In the 7-day risk window, pericarditis events were identified in all data sources except in PHARMO. In Pedianet no cases were reported in the unvaccinated cohort. The incidence rates in the vaccinated cohorts ranged from 2.08 per 10,000 person-years (95% CI: 1.11, 3.56) in NHR to 50.94 per 10,000 person-years (95% CI: 1.29, 283.80) in Pedianet. In the unvaccinated cohorts these ranged from 4.16 per 10,000 person-years (95% CI: 2.61, 6.62) in NHR to 5.62 per 10,000 person-years (95% CI: 2.00, 15.78) in EpiChron. The cumulative incidence was below 1.0 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 0.50 (95% CI: 0.24, 1.02) in NHR, 0.83 (95% CI: 0.21, 3.23) in EpiChron, and 1.06 (95% CI: 0.54, 2.10) in SIDIAP for the 7-day risk window. The adjusted HRs were 0.50 (95% CI: 0.24, 1.02) in NHR, 0.93 (95% CI: 0.24, 3.59) in EpiChron, and 0.94 (95% CI: 0.47, 1.87) in SIDIAP.

In the 14-day risk window, pericarditis events were reported in all data source in the vaccinated cohorts. In the unvaccinated cohorts, no events were reported in Pedianet. The incidence rates ranged from 0.46 per 10,000 person-years (95% CI: 0.01, 2.55) in PHARMO to 4.29 per 10,000 person-years (95% CI: 1.85, 8.46) in EpiChron in the vaccinated cohorts. In the unvaccinated cohorts these ranged from 0.46 per 10,000 person-years (95% CI: 0.06, 3.23) in PHARMO to 4.29 per 10,000 person-years (95% CI: 1.72, 10.74) in EpiChron. In Pedianet the incidence rate in the vaccinated cohort was 26.34 (95% CI: 0.67, 146.77), but this corresponded to <5 events. The cumulative incidence was below 1.0 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 0.70 (95% CI: 0.40, 1.22) in NHR, 1.00 (95% CI: 0.06, 16.08) in PHARMO, 1.00 (95% CI: 0.32, 3.15) in EpiChron, and 1.30 (95%

CI: 0.75, 2.23) in SIDIAP. The adjusted HRs were 0.70 (95% CI: 0.40, 1.22) in NHR, 1.06 (95% CI: 0.07, 16.96) in PHARMO, 1.04 (95% CI: 0.33, 3.28) in EpiChron, and 1.17 (95% CI: 0.68, 2.04) in SIDIAP. All 95% CIs included 1.

In the 21-day risk window, pericarditis cases events were reported in all data source in the vaccinated cohorts. In the unvaccinated cohorts, no events were reported in Pedianet. The incidence rates ranged from 0.32 per 10,000 person-years (95% CI: 0.01, 1.78) in PHARMO to 2.72 per 10,000 person-years (95% CI: 1.95, 3.70) in NHR in the vaccinated cohorts. In the unvaccinated cohorts these ranged from 0.32 per 10,000 person-years (95% CI: 0.04, 2.26) in PHARMO to 3.16 per 10,000 person-years in EpiChron (95% CI: 1.26, 7.89). In the vaccinated cohort in Pedianet, the incidence rate was 18.09 per 10,000 person-years (95% CI: 0.46, 100.81) (corresponding to <5 events). The cumulative incidence was below 1.0 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 0.87 (95% CI: 0.51, 1.48) in NHR, 1.00 (95% CI: 0.06, 16.08) in PHARMO, 1.00 (95% CI: 0.32, 3.15) in EpiChron, and 1.25 (95% CI: 0.78, 2.01) in SIDIAP. The adjusted HRs were 0.87 (95% CI: 0.51, 1.48) in NHR, 1.06 (95% CI: 0.07, 16.96) in PHARMO, 1.04 (95% CI: 0.33, 3.28) in EpiChron, and 1.16 (95% CI: 0.71, 1.88) in SIDIAP. The IRs for pericarditis in the first 14-day and first 21-day follow-up periods were similar.

Myocarditis or pericarditis

Myocarditis or pericarditis events were identified in all data sources except NHR.

In the 7-day risk window, the incidence rates ranged from 3.11 per 10,000 person-years (95% CI 1.81, 4.98) in SIDIAP to 5.62 per 10,000 person-years (95% CI 2.06, 12.22) in EpiChron in the vaccinated cohorts and from 3.29 per 10,000 person-years (95% CI 2.02, 5.36) in SIDIAP to 5.62 per 10,000 person-years (95% CI 2.00, 15.78) in EpiChron in the unvaccinated cohorts. In Pedianet the incidence rate in the vaccinated cohort was 50.99 (95% CI: 1.29, 284.09), but this corresponded to <5 events. 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 1.00 (95% CI: 0.27; 3.69) in EpiChron and 0.94 (95% CI: 0.48; 1.87) in SIDIAP.

In the 14-day risk window, the incidence rates ranged 1.37 per 10,000 person-years (95% CI 0.28, 4.01) in PHARMO to 5.36 per 10,000 person-years (95% CI 2.57, 9.87) in EpiChron in the vaccinated cohorts and from 0.46 per 10,000 person-years (95% CI 0.06, 3.23) in NHR to 4.83 per 10,000 person-years (95% CI 2.08, 11.23) in EpiChron in the unvaccinated cohorts. In Pedianet the incidence rate in the vaccinated cohort was 26.37, but this corresponded to less than 5 events. 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 3.01 (95%

CI: 0.31; 29.01) in PHARMO, 1.11 (95% CI: 0.39; 3.11) in EpiChron and 1.36 (95% CI: 0.80; 2.30) in SIDIAP.

In the 21-day risk window, the incidence rates ranged from 1.28 per 10,000 person-years (95% CI 0.35, 3.27) in PHARMO to 4.34 per 10,000 person-years (95% CI 2.16, 7.76) in EpiChron in the vaccinated cohorts and from 0.32 per 10,000 person-years (95% CI 0.04, 2.26) in PHARMO to 3.72 per 10,000 person-years (95% CI 2.53, 5.48) in NHR in the unvaccinated cohorts. In the vaccinated cohort in Pedianet, the incidence rate was 18.11 per 10,000 person-years (corresponding to less than five events). 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 4.01 (95% CI: 0.45; 35.93) in PHARMO, 1.22 (95% CI: 0.44; 3.42) in EpiChron and 1.32 (95% CI: 0.83; 2.08) in SIDIAP.

Coagulation disorders

Coagulation disorders were identified in all data sources, except Pedianet.

The incidence rates in the vaccinated cohorts ranged from 19.70 per 10,000 person-years (95% CI: 15.60, 24.55) in PHARMO to 71.69 per 10,000 person-years (95% CI: 62.59, 81.74) in EpiChron. In the unvaccinated cohorts these ranged from 17.17 per 10,000 person-years (95% CI: 13.01, 22.64) in PHARMO to 88.79 per 10,000 person-years (95% CI: 74.55, 105.75) in EpiChron. The cumulative incidence was less than 7.0 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 HRs for coagulation disorders were 0.87 (95% CI: 0.79, 0.96) in NHR, 1.15 (95% CI: 0.81, 1.63) in PHARMO, 0.81 (95% CI: 0.65, 1.00) in EpiChron, and 0.74 (95% CI: 0.66, 0.83) in SIDIAP. The adjusted HRs were 0.87 (95% CI: 0.79, 0.95) in NHR, 1.07 (95% CI: 0.75, 1.53) in PHARMO, 0.78 (95% CI: 0.63, 0.97) in EpiChron, and 0.69 (95% CI: 0.61, 0.77) in SIDIAP.

No differences were observed for the incidence of coagulation disorders between the vaccinated and unvaccinated cohorts during the 28-day risk window.

Single organ cutaneous vasculitis

Single organ cutaneous vasculitis within the 28-day risk window was a rare event and was identified in EpiChron and SIDIAP in both cohorts and in PHARMO with <5 events in the unvaccinated cohort only. The incidence rates in the vaccinated cohorts were from 0.29 per 10,000 person-years (95% CI: 0.09, 0.68) in SIDAP to 8.58 per 10,000 person-years (95% CI: 5.66, 12.49) in EpiChron. In the unvaccinated cohorts these ranged from 0.25 per 10,000

person-years (95% CI: 0.03, 1.76) in PHARMO to 6.68 per 10,000 person-years (95% CI: 3.85, 11.60) in EpiChron. The cumulative incidence was below 1.0 per 10,000 individuals in both cohorts in both data sources. The incidence was similar in the different age groups. The matched adjusted HRs were 1.28 (95% CI: 0.66, 2.48) in EpiChron, and 0.45 (95% CI: 0.14, 1.51) in SIDIAP. The adjusted HRs were 1.19 (95% CI: 0.62, 2.31) in EpiChron, and 0.44 (95% CI: 0.13, 1.48) in SIDIAP. No differences were observed for the incidence of single organ cutaneous vasculitis between the vaccinated and unvaccinated cohorts during the 28-day risk window.

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 all data sources except Pedianet. The incidence rates in the vaccinated cohorts ranged from 0.20 per 10,000 person-years (95% CI: 0.07, 0.43) in PHARMO to 3.65 per 10,000 person-years (95% CI: 2.86, 4.59) in EpiChron. In the unvaccinated cohorts they ranged 0.62 per 10,000 person-years (95% CI: 0.32, 1.17) in PHARMO and 3.27 per 10,000 person-years (95% CI: 2.29, 4.66) in EpiChron. The cumulative incidence during the 365-day risk window was below 3.6 per 10,000 individuals in the vaccinated cohorts and below 3.0 per 10,000 individuals in the unvaccinated cohorts. The incidence was similar in the different age groups.

The matched HRs for acute liver injury were 0.97 (95% CI: 0.59, 1.60) in NHR, 0.33 (95% CI: 0.12, 0.91) in PHARMO, 1.12 (95% CI: 0.73, 1.71) in EpiChron, and 0.72 (95% CI: 0.54, 0.94) in SIDIAP. The adjusted HRs were 0.97 (95% CI: 0.59, 1.59) in NHR, 0.32 (95% CI: 0.11, 0.88) in PHARMO, 1.05 (95% CI: 0.69, 1.61) in EpiChron, and 0.63 (95% CI: 0.48, 0.83) in SIDIAP. All 95% CIs included 1. No differences were observed for the incidence of acute liver injury between the vaccinated and unvaccinated cohorts during the 365-day risk window.

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 in all data sources, except Pedianet. The incidence rates in the vaccinated cohorts ranged from from 0.24 per 10,000 person-years (95% CI: 0.12, 0.41) in NHR to 33.93 per 10,000 person-years (95% CI: 31.42, 36.59) in EpiChron. In the unvaccinated cohorts these ranged from 0.95 per 10,000 person-years (95% CI: 0.56, 1.62) in NHR to 35.21 per 10,000 person-years (95% CI: 33.44, 37.07) in SIDIAP. The cumulative incidence during the 365-day risk

window was below 30.88 per 10,000 individuals in the vaccinated cohorts and below 35.21 per 10,000 individuals 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 0.24 (95% CI: 0.11, 0.53) in NHR, 0.97 (95% CI: 0.76, 1.22) in PHARMO, 0.96 (95% CI: 0.84, 1.11) in EpiChron, and 0.88 (95% CI: 0.82, 0.93) in SIDIAP. The adjusted HRs were 0.24 (95% CI: 0.11, 0.52) in NHR, 0.96 (95% CI: 0.76, 1.22) in PHARMO, 0.90 (95% CI: 0.78, 1.04) in EpiChron, and 0.81 (95% CI: 0.76, 0.86) in SIDIAP. No differences were observed for the incidence of acute kidney injury between the vaccinated and unvaccinated cohorts during the 365-day risk window.

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 were 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 ranged from 0.16 per 10,000 person-years (95% CI: 0.07, 0.31) in NHR to 5.06 per 10,000 person-years (95% CI: 4.12, 6.15) in EpiChron. In the unvaccinated cohorts these ranged from 0.16 per 10,000 person-years (95% CI: 0.06, 0.40) in NHR to 4.72 per 10,000 person-years (95% CI: 4.12, 5.40) in SIDIAP. The cumulative incidence during the 365-day risk window was less than 5.0 per 10,000 individuals in the vaccinated cohorts and less than 4.8 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 0.99 (95% CI: 0.31, 3.10) in NHR, 1.01 (95% CI: 0.68, 1.51) in PHARMO, 1.23 (95% CI: 0.83, 1.80) in EpiChron, and 1.02 (95% CI: 0.87, 1.20) in SIDIAP. The adjusted HRs were 0.98 (95% CI: 0.31, 3.08) in NHR, 0.96 (95% CI: 0.64, 1.43) in PHARMO, 1.14 (95% CI: 0.77, 1.68) in EpiChron, and 0.95 (95% CI: 0.80, 1.11) in SIDIAP. No differences were observed for the incidence of acute pancreatitis between the vaccinated and unvaccinated cohorts during the 365-day risk window.

IRs for acute pancreatitis were not reported in ACCESS.

Rhabdomyolysis

Rhabdomyolysis events were reported in all data sources except Pedianet. The incidence rates in the vaccinated cohorts ranged from 0.02 per 10,000 person-years (95% CI: 0, 0.11) in NHR to 1.70 per 10,000 person-years (95% CI: 1.18, 2.38) in EpiChron. In the unvaccinated cohorts the incidence rates were 0.07 per 10,000 person-years (95% CI: 0.01, 0.51) in PHARMO to 2.39 per 10,000 person-years (95% CI: 1.92, 2.96) in SIDIAP. The cumulative incidence was below 1.7 per 10,000 individuals in the vaccinated cohorts and 2.2 per 10,000

individuals in the unvaccinated cohorts. The incidence of rhabdomyolysis was higher in older age groups.

The matched HRs were 1.92 (95% CI: 0.22, 16.86) in PHARMO, 0.74 (95% CI: 0.38, 1.42) in EpiChron and 0.58 (95% CI: 0.44, 0.76) in SIDIAP. The adjusted HRs were 1.88 (95% CI: 0.21, 16,58), 0.69 (95% CI: 0.35, 1.34) in EpiChron and 0.57 (95% CI: 0.43, 0.74) in SIDIAP. No differences were observed for the incidence of rhabdomyolysis between the vaccinated and unvaccinated cohorts during the 365-day risk window.

ACCESS has not reported IRs for rhabdomyolysis.

Generalised convulsion

Generalised convulsion events were identified in all data sources, except in both cohorts in Pedianet, and in the vaccinated cohort in NHR. The incidence rates in the vaccinated cohorts ranged from 1.23 per 10,000 person-years (95% CI: 0.50, 2.54) in PHARMO to 2.11 per 10,000 person-years (95% CI: 0.97, 4.01) in EpiChron. In the unvaccinated cohorts these ranged from 0.04 per 10,000 person-years (95% CI: 0.01, 0.30) in NHR to 2.63 per 10,000 person-years (95% CI: 1.27, 5.45) in PHARMO. The cumulative incidence was below 1 per 10,000 individuals in both cohorts in all data sources. The incidence was similar in the different age groups.

The matched HRs were 0.47 (95% CI: 0.17, 1.32) in PHARMO, 0.90 (95% CI: 0.32, 2.49) in EpiChron, and 1.00 (95% CI: 0.57, 1.75) in SIDIAP. The adjusted HRs were 0.44 (95% CI: 0.16, 1.26) in PHARMO, 0.93 (95% CI: 0.33, 2.58) in EpiChron, and 0.90 (95% CI: 0.51, 1.57) in SIDIAP. No differences were observed for the incidence of generalised convulsions between the vaccinated and unvaccinated cohorts during the 42-day risk window.

ACCESS reported IRs for generalised convulsion per 100,000 for the years 2017–2020 for PHARMO, ARS, Pedinaet, and SIDIAP that ranged 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. The incidence rates in the vaccinated cohorts ranged from 0.35 per 10,000 person-years (95% CI: 0.04, 1.27) in PHARMO to 1.79 per 10,000 person-years (95% CI: 1.29, 2.41) in NHR. In the unvaccinated cohorts the incidence rates ranged from 1.05 per 10,000 person-years (95% CI: 0.37, 2.96) in PHARMO and 2.37 per 10,000 person-years (95% CI: 1.63, 3.45) in NHR. The cumulative incidence was below 1.0 per 10,000 individuals in both cohorts in all data sources. The incidence was similar in the different age groups.

The matched HRs were 0.75 (95% CI: 0.47, 1.21) in NHR, 0.33 (95% CI: 0.06, 1.88) in PHARMO, 0.60 (95% CI: 0.13, 2.78) in EpiChron, and 0.72 (95% CI: 0.37, 1.41) in SIDIAP. The adjusted HRs were 0.75 (95% CI: 0.47, 1.21) in NHR, 0.36 (95% CI: 0.06, 2.07) in

PHARMO, 0.52 (95% CI: 0.11, 2.41) in EpiChron, and 0.67 (95% CI: 0.34, 1.33) in SIDIAP. No differences were observed for the incidence of meningoencephalitis between the vaccinated and unvaccinated cohorts during the 42-day risk window.

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

Transverse myelitis

Transverse myelitis within 42 days after the start of follow-up was a rare event observed in EpiChron and SIDIAP, with <5 events in each of the data sources. The incidence rates are less than 1.0 per 10,000 person-years in the vaccinated and unvaccinated. 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 transverse myelitis within the 42-day risk window, between the vaccinated and unvaccinated cohorts.

ACCESS reported IRs for transverse myelitis 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 both cohorts in all data sources, except Pedianet where events were only identified in the unvaccinated cohort. The incidence rates in the vaccinated cohorts ranged from 4.22 per 10,000 person-years (95% CI: 2.71, 6.28) in PHARMO to 7.09 per 10,000 person-years (95% CI: 6.05, 8.26) in SIDIAP. In the unvaccinated cohorts these ranged from 1.23 per 10,000 person-years (95% CI: 0.53, 2.85) in PHARMO to 9.66 per 10,000 person-years (95% CI: 1.36, 68.60) in Pedianet. The cumulative incidence was below 1.0 per 10,000 individuals in both cohorts in all data sources except Pedianet where it was 1.2 per 10,000 individuals in the unvaccinated cohort but based on <5 cases. The incidence was similar in the different age groups.

The matched HRs were 1.01 (95% CI: 0.76, 1.35) in NHR, 3.44 (1.39, 8.50) in PHARMO, 0.93 (0.42, 2.08) in EpiChron, and 0.94 (0.74, 1.19) in SIDIAP. The adjusted HRs 1.01 (95% CI: 0.76, 1.35) in NHR, 3.08 (1.24, 7.62) in PHARMO, 0.89 (0.40, 2.00) in EpiChron, and 0.91 (0.71, 1.16) in SIDIAP. In PHARMO the lower limits of the 95% CIs for the HRs were above 1 in the matched and adjusted results.

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 ranged from 0.43 per 10,000 person-years (95% CI: 0.23, 0.73) in PHARMO to 1.35 per 10,000 person-years (95% CI:

0.89, 1.97) in EpiChron. In the unvaccinated cohorts these ranged from 0.36 per 10,000 person-years (95% CI: 0.17, 0.79) in PHARMO to 8.55 per 10,000 person-years (95% CI: 6.69, 10.93) in EpiChron. The cumulative incidence was below 1.8 per 10,000 individuals in the vaccinated cohorts and below 8.2 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 0.21 (95% CI: 0.13, 0.35) in NHR, 1.20 (95% CI: 0.47, 3.07) in PHARMO, 0.16 (95% CI: 0.10, 0.25) in EpiChron, and 0.15 (95% CI: 0.12, 0.19) in SIDIAP. The adjusted HRs were 0.21 (95% CI: 0.13, 0.35) in NHR, 1.23 (95% CI: 0.48, 3.12) in PHARMO, 0.14 (95% CI: 0.09, 0.23) in EpiChron, and 0.14 (95% CI: 0.11, 0.18) in SIDIAP. The upper limits of the 95% CIs were <1 in all data sources, except for PHARMO where they were >1, but based on fewer events. This is suggestive of protective effects of vaccination. No differences were observed for the incidence of acute respiratory distress syndrome within the 365-day risk window, between the vaccinated and unvaccinated cohorts.

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 rare and were identified in both cohorts in PHARMO, EpiChron and SIDIAP. The incidence rates in the vaccinated cohorts ranged from 0.53 per 10,000 person-years (95% CI: 0.11, 1.54) in PHARMO to 1.17 per 10,000 person-years (95% CI: 0.38, 2.74) in EpiChron. In the unvaccinated cohorts they were 0.47 per 10,000 person-years (95% CI: 0.24, 0.94) in SIDIAP and 0.70 per 10,000 person-years (95% CI: 0.10, 5) in EpiChron. The cumulative incidence was less than 1.0 per 10,000 individuals in the three data sources. The incidence tended to be higher in the younger age groups, but the number of events was low. The matched HRs were 1.66 (95% CI: 0.19, 14.25) in EpiChron and 1.45 (95% CI: 0.62, 3.39) in SIDIAP. The adjusted HRs were 1.69 (95% CI: 0.20, 14.71) in EpiChron and 1.25 (95% CI: 0.53, 2.93) in SIDIAP. No differences were observed for the incidence of erythema multiforme within the 42-day risk window, between the vaccinated and unvaccinated cohorts.

ACCESS reported IRs for erythema multiforme syndrome per 100,000 for the years 2017–2020 of 6.0 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 ranged from 1.41 per 10,000 person-years (95% CI: 0.52, 3.07) in EpiChron to 19.34 (per 10,000 person-years (95% CI: 2.34, 69.87) in Pedianet. In the unvaccinated cohorts they ranged from 1.18 per 10,000 person-years (95% CI: 0.49, 2.82) in

EpiChron to 3.16 per 10,000 person-years (95% CI: 1.78, 5.63) in PHARMO. The cumulative incidences during the 42-day risk window were less than 1.3 per 10,000 individuals in the vaccinated cohorts, except in Pedianet with a cumulative incidence of 2.22 (95% CI: 0, 5.32) and less than 0.50 per 10,000 individuals in the unvaccinated cohorts. The incidence was similar in the different age groups. The matched HRs were 0.84 (95% CI: 0.39, 1.80) in PHARMO, 1.20 (95% CI: 0.37, 3.93) in EpiChron, and 0.77 (95% CI: 0.52, 1.15) in SIDIAP. The adjusted HRs were 0.77 (95% CI: 0.36, 1.66) in PHARMO, 1.13 (95% CI: 0.34, 3.75) in EpiChron, and 0.77 (95% CI: 0.52, 1.14) in SIDIAP. No differences were observed for the incidence of chilblain-like lesions within the 42-day risk window, between the vaccinated and unvaccinated cohorts.

ACCESS reported IRs for chilblain-like lesions per 100,000 individuals for the years 2017–2020 for PHARMO, ARS, Pedianet, and SIDIAP from 0.04 per 100,000 individuals (ARS) to 15.97 per 100,000 individuals (SIDIAP). These estimates depended on GP diagnoses.

Secondary amenorrhea

Secondary amenorrhea events were identified in EpiChron, and SIDIAP. The incidence rates were assessed only in females in age groups considered to be of child-bearing potential and in the vaccinated cohorts these were Pedianet, EpiChron, and SIDIAP. The incidence rates were assessed only in females in age groups considered to be of child-bearing potential and in the vaccinated cohorts these were 0.16 per 10,000 person-years (95% CI: 0.02, 0.57) in EpiChron and 28.62 per 10,000 person-years (95% CI: 27.36, 29.93) in SIDIAP. In the unvaccinated cohorts the incidence rates were 0.40 per 10,000 person-years (95% CI: 0.17, 0.9) in EpiChron and 25.42 per 10,000 person-years (95% CI: 23.86, 27.08) in SIDIAP. The cumulative incidence varied between below 0.1 in EpiChron and below 13 in SIDIAP per 10,000 individuals in the vaccinated and unvaccinated cohorts. Age patterns reflected the occurrence of menstrual problems in women in child-bearing age. The matched HRs were 0.40 (95% CI: 0.08, 2.05) in EpiChron and 1.13 (95% CI: 1.04, 1.22) in SIDIAP. The adjusted HRs were 0.34 (95% CI: 0.07, 1.76) in EpiChron and 1.07 (95% CI: 0.99, 1.16) in SIDIAP.

Codes were reviewed and the exclusion of codes that were potentially too sensitive has resulted in more specific disease code spectrum. This allowed secondary amenorrhea to identify more closely. Therefore, rates and case numbers have changed since the previous interim report.

Hypermenorrhea

Hypermenrrohea events were identified in Pedianet, PHARMO, EpiChron, and SIDIAP. The incidence rates were assessed only in females in age groups considered to be of child-bearing potential and in the vaccinated cohorts these were 47.17 per 10,000 person-years (95% CI: 45.55, 48.84) in SIDIAP and 66.96 per 10,000 person-years (95% CI: 62.50, 71.65) in EpiChron. The incidence rates in the unvaccinated cohorts were 39.3 per 10,000 person-years (95% CI: 37.4, 41.4) in SIDIAP and 60.7 per 10,000 person-years (95% CI: 55.1, 67) in EpiChron. In PHARMO, the incidence rates were below 1 with very few cases identified in

both cohorts. In Pedianet there were <5 cases in the vaccinated cohort and 8 cases in the unvaccinated cohort. The cumulative incidence was below 34 per 10,000 individuals in the vaccinated cohorts and below 22 per 10,000 individuals in the unvaccinated cohorts. Age patterns reflected the occurrence of menstrual problems in women in child-bearing age. However, a few events were identified in SIDIAP and EpiChron among children, therefore the identification of hypermenorrhea will be reassessed in both data sources in the next interim report, as these data cleaning and validation steps will be undertaken by the DAPs as part of the next data extraction.

The matched HRs were 0.38 (95% CI: 0.09, 1.61) in Pedianet, 5.84 (95% CI: 0.71, 48.15) in PHARMO, 1.54 (95% CI: 1.35, 1.75) in EpiChron, and 1.17 (95% CI: 1.10, 1.24) in SIDIAP. The adjusted HRs were 0.33 (95% CI: 0.08, 1.42) in Pedianet, 6.62 (95% CI: 0.80, 54.62) I PHARMO, 6.62 (95% CI: 0.80, 54.62) in PHARMO, 1.38 (95% CI: 1.21, 1.57) in EpiChron, and 1.09 (95% CI: 1.03, 1.16) in SIDIAP.

For hypermenorrhea, a higher incidence of the event in the vaccinated cohorts compared with the unvaccinated cohorts was observed in some data sources. These results suggest a potential association between Pfizer-BioNTech COVID-19 vaccine use and hypermenorrhea, which will be further investigated. Two recent systematic reviews suggest that menstrual problems have been observed following COVID-19 vaccination but further longitudinal studies are needed to confirm the causal relationship between COVID-19 vaccination and menstrual irregularities.[21,22] However, as with secondary amenorrhea, it is possible that extraneous codes for this outcome were included, as there are some cases of this event among children and women over 50 years of age. However, the definition used was very specific, with very few codes per dictionary. For instance, only one ICD10 code -N92.1 (Excessive and frequent menstruation with irregular cycle) was used for hypermenorrhea. Further evaluation of this AESI will be undertaken in subsequent IRs and the final report.

Anosmia, ageusia

Anosmia, ageusia events were identified in both cohorts in all data sources except in the unvaccinated cohort in Pedianet. The incidence rates in the vaccinated cohorts ranged from 3.80 per 10,000 person-years (95% CI: 3.00, 4.70) in NHR to 19.31 per 10,000 person-years (95% CI: 15.36, 23.97) in EpiChron. In the unvaccinated cohorts these ranged from 4.30 per 10,000 person-years (95% CI: 3.20, 5.80) in PHARMO to 15.09 per 10,000 person-years (95% CI: 11.29, 20.18) in EpiChron. The cumulative incidence was less than 2.2 per 10,000 individuals in the vaccinated cohorts and less than 1.90 per 10,000 individuals in the unvaccinated cohorts in all data sources. The incidence was similar in the different age groups.

The matched HRs for anosmia, ageusia were 0.92 (95% CI: 0.67, 1.24) in NHR, 1.38 (95% CI: 0.77, 2.50) in PHARMO, 1.28 (95% CI: 0.89, 1.83) in EpiChron, and 0.76 (95% CI: 0.61, 0.94) in SIDIAP. The adjusted HRs were 0.92 (95% CI: 0.67, 1.24) in NHR, 1.26 (95% CI: 0.70, 2.29) in PHARMO, 1.20 (95% CI: 0.83, 1.72) in EpiChron, and 0.72 (95% CI: 0.58, 0.90) in SIDIAP. No differences were observed for the incidence of anosmia/ ageusia within the 42-day risk window, between the vaccinated and unvaccinated cohorts.

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

Anaphylaxis

Anaphylaxis events were reported in Pedianet, PHARMO, EpiChron, and SIDIAP. The prevalence rate was highest in EpiChron with 2.21 (95% CI: 1.87, 2.62). Prevalence In PHARMO and SIDIAP there were only a few events identified, and therefore, the prevalence rates were low. The prevalence was similar in the different age groups. The matched HR was 5.32 (95% CI: 3.37, 8.39) and the adjusted HR was 5.06 (95% CI: 3.20, 8.00) in EpiChron. The lower limits of the 95% CIs for the matched and adjusted HRs were above 1. This is under investigation at the data source.

Multisystem inflammatory syndrome

Multisystem inflammatory syndrome events were rare and <5 events were detected in bother cohorts for NHR and SIDIAP. In the vaccinated cohorts the incidence rates were 0.04 per 10,000 person-years (95% CI: 0, 0.23) in NHR and 0.13 per 10,000 person-years (95% CI: 0.03, 0.38) in SIDIAP. In the unvaccinated cohorts these were 0.04 per 10,000 person-years (95% CI: 0.01, 0.30) in NHR and 0.04 per 10,000 person-years (95% CI: 0.01, 0.30) in SIDIAP.

The matched HRs were 1.00 (95% CI: 0.06, 15.97) in NHR and 3.00 (95% CI: 0.31, 28.84). The adjusted HRs were 1.00 (95% CI: 0.06, 15.93) in NHR and 2.99 (95% CI: 0.31, 28.79) in SIDIAP. No differences were observed for the incidence of multisystem inflammatory syndrome within the 42-day risk window, between the vaccinated and unvaccinated cohorts.

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

Death (any cause)

Deaths (any cause) were identified in all data sources. The incidence rates ranged from 39.09 per 10,000 person-years (95% CI: 36.90, 41.38) in PHARMO to 111.10 per 10,000 person-years (95% CI: 108.23, 114.03) in NHR in the vaccinated cohorts. In the unvaccinated cohorts these ranged from 68.25 per 10,000 person-years (95% CI: 63.99, 72.79) in PHARMO to 226.15 per 10,000 person-years (95% CI: 218.69, 233.87) in NHR. The cumulative incidences in the vaccinated cohorts ranged from 38.76 per 10,000 individuals (95% CI: 36.41, 41.11) in PHARMO to 726.00 per 10,000 individuals (95% CI: 621.20, 829.70) in NHR in the vaccinated cohorts. In the unvaccinated cohorts these ranged from 54.36 per 10,000 individuals (95% CI: 50.74, 57.97) in PHARMO to 784.20 per 10,000 individuals (95% CI: 680.30, 886.90) in NHR. The incidences of death (any cause) were highest in the oldest age groups.

The matched HRs were 0.48 (95% CI: 0.46, 0.50) in NHR, 0.59 (95% CI: 0.54, 0.65) in PHARMO, 0.61 (95% CI: 0.56, 0.66) in EpiChron, and 0.50 (95% CI: 0.05, 5.51) in SIDIAP. The adjusted HRs were 0.48 (95% CI: 0.46, 0.50) in NHR, 0.56 (95% CI: 0.51, 0.60) in PHARMO, 0.59 (95% CI: 0.54, 0.64) in EpiChron, and 0.38 (95% CI: 0.03, 4.24) in SIDIAP. In all data sources except SIDIAP the vaccination shows a protective effect for death.

Subacute thyroiditis

Subacute thyroiditis events within the 365-day risk window were reported in EpiChron and SIDIAP only. The incidence rate was 0.03 per 10,000 person-years (95% CI: 0.01, 0.09) in SIDIAP and 0.05 per 10,000 person-years (95% CI: 0, 0.28) in the vaccinated cohort. In the unvaccinated cohorts the rates were 0.05 per 10,000 person-years (95% CI: 0.01, 0.36) in EpiChron and were 0.01 per 10,000 person-years (95% CI: 0, 0.7) in SIDIAP. The cumulative incidence during the 42-day risk window was less than 0.05 per 10,000 individuals in the vaccinated and unvaccinated cohorts.

The matched HR was 1 (95% CI: 0.06, 15.94) in EpiChron and 3 (95% CI: 0.31, 28.84) in SIDIAP. The adjusted HR was 0.91 (95% CI: 0.06, 14.33) in EpiChron and 2.70 (95% CI: 0.28, 26.18) in SIDIAP. No differences between the vaccinated and unvaccinated cohorts were observed for the incidence of subacute thyroiditis within the 365-day risk window.

ACCESS has not reported IRs for subacute thyroiditis.

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 2.12 per 10,000 person-years (95% CI: 1.74, 2.56) in NHR and 0.07 per 10,000 person-years (95% CI: 0.01, 0.24) in PHARMO, with no events in EpiChron. The incidence rates in the unvaccinated cohorts were 3.59 per 10,000 person-years (95% CI: 2.76, 4.66) in NHR, 0.05 per 10,000 person-years (95% CI: 0.01, 0.36) in EpiChron, and 0.07 per 10,000 person-years (95% CI: 0.02, 0.29) in PHARMO. The cumulative incidence in the vaccinated cohort in NHR was 15.81 per 10,000 individuals (95% CI: 0, 36.25), and in the unvaccinated cohort in NHR this was 14.44 per 10,000 person-years (95% CI: 5.32, 23.56). In PHARMO and EpiChron the cumulative incidence and less than 1.00 per 10,000 individuals in the vaccinated and unvaccinated cohorts.

The matched HRs were 0.58 (95% CI: 0.42, 0.80) in NHR, and 0.82 (95% CI: 0.11, 6.12) in PHARMO. The adjusted HRs were 0.58 (95% CI: 0.42, 0.80) in NHR, and 0.71 (95% CI: 0.09, 5.31) in PHARMO. No differences were observed for the incidence of sudden death within the 365-day risk window, between the vaccinated and unvaccinated cohorts.

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

Severe COVID-19

Severe COVID-19 disease, defined as hospitalised COVID-19 events or patients that died due to COVID-19 infection, was identified in all data sources. The incidence rates in the vaccinated cohorts ranged from 0.94 per 10,000 person-years (95% CI: 0.66, 1.31) in PHARMO to 131.34 per 10,000 person-years (95% CI: 126.93, 135.87) in EpiChron. In the unvaccinated cohorts these ranged from 1.73 per 10,000 person-years (95% CI: 1.50, 2.90) in PHARMO to 199.07 per 10,000 person-years (95% CI: 190.68, 207.84) in EpiChron. The cumulative incidences ranged from 0.79 per 10,000 individuals (95% CI: 0.44, 1.15) in PHARMO to 150.38 per 10,000 person-years (95% CI: 144.72, 156.04) in EpiChron in the vaccinated cohorts and from 1.71 per 10,000 person-years (95% CI: 1.12, 2.30) in PHARMO to 226.17 per 10,000 person-years (95% CI: 215.61, 236.72) in EpiChron in the unvaccinated cohorts. The incidence of severe COVID-19 was highest in the older age groups, in both the unvaccinated and vaccinated cohorts.

The matched HRs were 0.73 (95% CI: 0.51, 1.00) in Pedianet, 0.19 (95% CI: 0.17, 0.21) in NHR, 0.55 (95% CI: 0.35, 0.85) in PHARMO, 0.66 (95% CI: 0.62, 0.70) in EpiChron, and 0.36 (95% CI: 0.34, 0.38) in SIDIAP. The adjusted HRs 0.73 (95% CI: 0.51, 1.05) in Pedianet, 0.19 (95% CI: 0.17, 0.21) in NHR, 0.52 (95% CI: 0.33, 0.81) in PHARMO, 0.59 (95% CI: 0.56, 0.63) in EpiChron, and 0.34 (95% CI: 0.32, 0.36) in SIDIAP. In Pedianet the upper limits of the 95% CIs for the matched and adjusted HRs were 1.03 and 1.04, respectively.

11.2. Limitations

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

In the contributing data sources, data for events originated from different data bases (GP, emergency visits, hospital discharge data bases) which could have an impact on the estimates for the incidence rates as shown in a recent study.[17]

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

In PHARMO, data on COVID-19 vaccinations were entered in the GP medical record through various routes, including directly by the GPs who administered the vaccine or through the public health vaccination register if an individual was vaccinated by the public health institute. When GPs vaccinate, the Pfizer-BioNTech COVID-19 vaccine could not be

used because of the cold chain requirements, 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 plans to have linkage with the vaccination register established.

Data from NHR were available up to the end of 2021. Data for 2022 are expected to be available later in 2023 for inclusion in the fifth interim report. Since the third interim report, NHR have updated previously missing COVID-19 vaccine brand information. Additionally, some hospital event information was included, in addition to the existing primary care data. However, events were not identified with full ICD10 codes. Full ICD10 codes will be available with the new data extraction later in 2023 and will be included in the fifth interim report.

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

In SIDIAP the results for death (any cause) are under investigation; this will be corrected in the next draft.

Definition of AESIs

AESIs were identified through diagnostic codes, which can be tagged as narrow (specific) and possible (sensitive). In this fourth 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. The NHR results are 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.

11.3. Interpretation

These analyses were performed on data from more than 8 million individuals who had received at least one dose of the Pfizer-BioNTech COVID-19 vaccine (vaccinated cohorts) and from an equal number of matched unvaccinated individuals (unvaccinated cohorts). The matching was successful, both in terms of the identification of an appropriately matched pair as well as minimised confounding. In this IR #4, follow-up has been extended which had an impact, especially for AESIs with longer risk windows.

11.4. Generalisability

The distribution of age and sex of the source populations closely resembles the national statistics of each country. The study population for this IR #4 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 fourth interim report describe the characteristics and incidence rates for the 38 AESIs in more than 8 million vaccinated individuals and 8 million matched unvaccinated controls.

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. In this fourth interim report, the incidence rates of hypermenorrhea were reported to be higher in the vaccinated cohorts that in the unvaccinated cohorts in most of the data source. This is under investigation. Additionally, long term follow-up for some event rates introduced challenges that will need further exploration and refinement in the future IRs and the final report.

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15. LIST OF SOURCE TABLES AND FIGURES

Not applicable.

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