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Table of Contents

List of Tables

List of Figures

Rapid Safety Assessment of SARS-CoV-2 vaccines in EU Member States using electronic health care data sources.

1 Executive Summary/Abstract

1.1 Title

Rapid Safety Assessment of SARS-CoV-2 vaccines in EU Member States using electronic health care data sources.

1.2 Keywords

Safety; databases; COVID-19; vaccines; adverse events of special interest, methods

1.3 Rationale and objectives

1.3.1 Rationale

To complement spontaneous reporting systems for signal detection (routine pharmacovigilance) and other initial safety monitoring activities such as pharmaco-epidemiological studies conducted or planned by different stakeholders, the Agency procured several safety monitoring studies through its framework contracts.

In January 2021 the Agency launched a new tender for safety monitoring of COVID-19 vaccines in the EU. The EU PE & PV and the VAC4EU network received and implemented the tender, which had two objectives, the first was to implement a prospective cohort monitoring in more than 10 countries and the second was signal strengthening. This executive summary is focusing on the second objective which was to conduct signal strengthening activities for potential safety concerns emerging from active surveillance electronic health data.
Based on the technical specifications signal strengthening meant the collection of additional information to further characterise the incidence of the safety concern in comparison to its expected incidence in non- vaccinated populations or suitable comparator populations. This activity should provide additional evidence supporting signal management and regulatory decision-making on the need for a full signal evaluation. The safety concerns for which signal strengthening should be performed could be identified by the Agency, other regulatory authorities, or the consortium itself.

1.3.2 Objectives

The request for signal strengthening capacity was translated into two objectives:

1) To create and assess readiness of electronic health record data sources for rapid evaluation of safety signals by

- Providing an overview of the methods for identification of COVID-19 vaccine exposure in the data sources
- Monitoring the number of individuals exposed to any COVID-19 vaccine and to compare this to COVID-19 vaccine exposure (benchmark: ECDC vaccine tracker)[1]
- Generation of updated background rates for AESIs

[1] ECDC vaccine tracker: https://vaccinetracker.ecdc.europa.eu/public/extensions/COVID-19/vaccine-tracker.html#uptake-tab

2) To conduct rapid safety assessment studies using electronic healthcare records and support EMA safety assessments.
Moreover, it was planned that this should allow for specific subgroup analyses:

- immunocompromised persons
- persons with the presence of co-morbidities elevating the risk of serious COVID-19
- persons with a history of diagnosed COVID-19 disease
- pregnant women
- age groups
- patients with a prior history (ever) of that event more than a year before.

1.4 Methods

1.4.1 Setting

Nine well known European electronic health record (EHR) data sources in Norway, UK, Italy, the Netherlands, and Spain were included (all listed in ENCePP Database Register). The data access providers were members of the EU PE&PV and VAC4EU networks, willing to participate, had access to potential fit for purpose data and had transformed their data already in the ConcePTION CDM for prior studies. From the ACCESS study, which was also conducted by the same consortium it was clear that University Aarhus (Denmark) and University Bordeaux (France) could not get rapid access to required data and that GePARD (DE) did not have access to COVID-19 vaccination data.

1.4.2 Study design

Study designs differed for the two different objectives:

1. Readiness: a retrospective cohort design using data from 2019 to latest data availability
2. Rapid assessment studies: a comparative cohort study and a self-controlled risk interval study;

1.4.3 Subjects and study size

Readiness: Study subjects comprised all subjects in the source population of the participating data sources who were in follow-up for at least 365 days during the study period (January 1, 2019, for readiness study) or were born into the cohort during the study period, and for whom vaccination data could be obtained/linked.
Rapid assessment: For self- controlled designs we included only subjects with the outcome of interest and a covid-19 vaccination. For the cohort study, vaccinated subjects and matched comparators were included.

1.4.4 Data sources

For the implementation of the readiness study, 10 electronic health care databases in Northern, Southern and Western Europe showed interest to participate. The data sources and the data access providers that were included are:

Italy

- ARS Toscana (Agenzia Regionale di Sanità della Toscana)
- Pedianet (Societa Servizi Informatici)

- Caserta local health database (INSPIRE srl)
- Lazio Regional data source (Pharmacoepidemiology Unit Lazio Region)

The Netherlands

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

The United Kingdom

- CPRD: Clinical Practice Research Datalink (University Utrecht)

Norway

- The Norwegian health registers (University of Oslo)

Spain

- SIDIAP: Sistema d'Informació per el Desenvolupament de la Investigació en Atenció Primària (IDIAP Jordi Gol)
- BIFAP: Base de Datos para la Investigación Farmacoepidemiológica en Atención Primaria: (Spanish Medicines Agency)
- VID, Valencia health system Integrated Database (FISABIO)

Lazio regional data could not be accessed due to changes in data access rules.

For actual rapid assessment studies, choices for data sources were made based on:

- Availability of fit for purpose data
- Sample size and resources
- Ability to commit to timelines.

1.4.5 Variables

- Person-time: birth and death dates as well as periods of observation.
- Events: dates of medical and/or procedure and/or prescription/dispensing codes to identify AESI, COVID-19, and at-risk medical conditions. The following events were extracted as AESI or potential negative control.

Table ES1. AESI and Negative Control events list.

Event	SCRI	cohort	Naïve period to estimate new onset	Primary Risk period*
Multisystem inflammatory syndrome	✓	✓	365 days	28 days
Acute respiratory distress syndrome	✓	✓	365 days	28 days
Acute cardiovascular injury	✓	✓	365 days	
Microangiopathy	✓	✓	365 days	28 days
Acute CAD	✓	✓	365 days	28 days
Arrhythmia	✓	✓	365 days	28 days
Myocarditis	✓	✓	365 days	28 days
Pericarditis	✓	✓	365 days	28 days
Coagulation disorders, including deep vein thrombosis, pulmonary embolus, cerebrovascular stroke, limb ischaemia, haemorrhagic disease				
VTE (DVT & PE & Splanchnic)	✓	✓	365 days	28 days
CVST	✓	✓	365 days	28 days
Arterial thrombosis (AMI /Ischemic stroke)	✓	✓	365 days	28 days
TTS (VTE, arterial thrombosis, or CVST with thrombocytopenia in 10 days)	✓	✓	365 days	28 days

Event	SCRI	cohort	Naïve period to estimate new onset	Primary Risk period*
Hemorrhagic stroke	✓	✓	365 days	28 days
DIC	✓	✓	365 days	28 days
Generalised convulsion	✓	✓	365 days	14 days
Guillain Barré Syndrome	✓	✓	365 days	42 days
Diabetes (type 1)		✓	365 days	180 days
Acute kidney injury		✓	365 days	180 days
Acute liver injury		✓	365 days	180 days
Anosmia, ageusia	✓	✓	365 days	28 days
Chilblain-like lesions	✓	✓	365 days	28 days
Single organ cutaneous vasculitis	✓	✓	365 days	28 days
Erythema multiforme	✓	✓	365 days	7 days
Anaphylaxis	✓	✓	30 days	2 days
Death (any cause)** (postvaccination control window)	✓	✓	365 days	7 days
Sudden death (by codes)** (postvaccination control window)	✓	✓	365 days	7 days
Meningoencephalitis	✓	✓	365 days	28 days
Acute disseminated encephalomyelitis (ADEM)	✓	✓	365 days	28 days
Narcolepsy		✓	365 days	180 days
Thrombocytopenia	✓	✓	365 days	28 days
Transverse myelitis	✓	✓	365 days	28 days
Bells' palsy	✓	✓	365 days	28 days
Haemophagocytic lymphohistiocytosis	✓	✓	365 days	180 days
Kawasaki's disease	✓	✓	365 days	28 days
Pancreatitis	✓	✓	365 days	28 days
Rhabdomyolysis	✓	✓	365 days	28 days
SCARs	✓	✓	365 days	28 days
Sensorineural hearing loss		✓	365 days	180 days
Thyroiditis		✓	365 days	180 days
Negative control events				
Gout	✓	✓	365 days	28 days
Otitis externa	✓	✓	365 days	28 days
Trigeminal neuralgia	✓	✓	365 days	28 days
Acute kidney injury	✓	✓	365 days	28 days
Anaphylaxis (not drug-induced)	✓	✓	365 days	28 days
C. difficile infection	✓	✓	365 days	28 days
Conjunctivitis	✓	✓	365 days	28 days
COVID-19 within 12 days after vaccination	✓	✓	365 days	28 days
Diverticulitis	✓	✓	365 days	28 days
Fractures	✓	✓	365 days	28 days
Gall stones	✓	✓	365 days	28 days
Influenza	✓		365 days	28 days
Liver cirrhosis	✓	✓	365 days	28 days
Organic (secondary) psychosis	✓	✓	365 days	28 days
Osteoarthritis	✓	✓	365 days	28 days
Osteomyelitis	✓	✓	365 days	28 days
Reactive arthritis	✓	✓	365 days	28 days
Renovascular disease	✓	✓	365 days	28 days
Sjögren's syndrome	✓	✓	365 days	28 days
Urinary tract infections	✓	✓	365 days	28 days
Valvular heart disease (non-congenital, not rheumatic)	✓	✓	365 days	28 days

- Vaccines: COVID-19 vaccines approved for use by EMA during the study period (Monovalent Pfizer, Moderna, AstraZeneca, Janssen, Novavax).

Specifically, vaccination data were obtained in the following manner

Exposure to COVID-19 vaccines was based on available recorded prescription, dispensing, or administration of the COVID-19 vaccines. The main exposure of interest for the rapid assessment studies was the receipt of COVID-19 vaccine(s).

- ARS Toscana (IT): ARS identified vaccines from the regional immunization register using the national product code, including batch number.
- Pedianet (IT): Information on COVID-19 vaccine was obtained from the regional immunization register and included the date of immunization, type of vaccine, vaccine batches, dose.
- Caserta LHU database (IT): Caserta LHU record linkage database contains information from all claims databases (e.g. hospitalizations, drug dispensing, etc.) of Caserta province catchment area (around 1 million population). Those claims data could be linked to the local immunization registry which includes name and batch of the vaccine; manufacturing company; dose; administration route; administration location (eg, general practice); date of administration.
- PHARMO (NL): Data on vaccination were obtained from PHARMO's GP database. Information on vaccines include ATC code, brand, and date of administration/recording. Several COVID-19 vaccines have been administered through other routes and information was provided to GP with different lag times.
- CPRD (UK): The CPRD contains information recorded by National Health Service (NHS) primary care general practitioners (GPs); and information on the administration of COVID-19 vaccines to individuals is available. This includes, alongside an encrypted unique patient identifier; the name of the vaccine; manufacturing company; dose; and date
- Norwegian health registers (NO): The national, electronic immunization register (SYSVAK) was used. In SYSVAK, the following data are registered: individual personal identifier, vaccine name and Anatomical Therapeutic Chemical (ATC) code, vaccine batch number, date of vaccination, reason for vaccination as health care professional versus risk-group patient, and the center where the vaccine was administered.
- SIDIAP (ES): SIDIAP has available information on the administration of COVID-19 vaccines to individuals linked to a unique and anonymous identifier. The information originated from electronic medical records. For each patient, SIDIAP had date and center of administration, dose, brand, reasons for vaccination (eg, risk group), and other information related to vaccination.
- BIFAP (ES): BIFAP (Base de Datos para la Investigación Farmacoepidemiológica en Atencion Primaria), a computerized database of medical records of primary care (www.bifap.aemps.es) is a non-profit research project funded by the Spanish Agency for Medicines and Medical Devices (AEMPS). Data on vaccination with COVID-19 vaccines were obtained from the COVID-19 vaccination registries in the participating regions and linked to the primary care medical records in BIFAP. Date of vaccination, brand, batch, and dose are registered.
- FISABIO (ES): Data on vaccine exposure were obtained from the Vaccine Information System (VIS), which includes information on vaccine type, manufacturer, batch number, number of doses, location and administration date.

- Medicines: proxies for co-morbidities or associated with AESIs.
- Covariates (medicines or conditions for subgroup analyses)

- Cancer diagnosis or cancer medicines (L01A*, L01B*, L01C*, L01D*, L01X*, L02A*, L02B*, L03*, L04*)
- Chronic kidney disease diagnosis (exclusion criterium for assessment for acute kidney injury)
- Chronic liver disease diagnosis (cirrhosis, non-alcoholic fatty liver disease, alcoholic liver disease, autoimmune hepatitis)
- Chronic respiratory disease diagnosis (chronic obstructive pulmonary disease, bronchiectasis, asthma, interstitial lung disease, cystic fibrosis) or drug proxies (R03*, R07A*)
- Cardio/Cerebrovascular disease (CVD) diagnosis (stroke, transient ischemic attack (TIA), aneurysm, and vascular malformation, coronary artery disease, heart failure or cardiomyopathies) or drug proxies for such disease (C01*, C03*, C07*, C08*, C09*, B01AC*)
- Obesity diagnoses or anti-obesity medicines as proxy (A08AB*, A08AA*)
- Down syndrome diagnoses
- Mental health disease (depression, dementia, and schizophrenia spectrum disorders) or drug proxies (N05A*, N06A*, N06D*)
- Sickle cell disease diagnosis or drug proxies (L01XX05, B06AX01)
- Diabetes (type 1 or 2) or diabetes medicines as proxy (A10B*, A10A*)
- Human immunodeficiency virus diagnoses or drug proxies (J05AE*, J05AR*, J05AF*, J05AG*)
- Immunosuppressants: Use of corticosteroids or other immunosuppressive medications (H02*, L04*)

COVID-19 History

- COVID-19 infection: Covid-19 Dx diagnosis code or positive test further classified by severity:
- Level 1: any recorded COVID-19 diagnosis or positive test
- Level 2: hospitalization for COVID-19 (COVID-19 diagnosis in primary/secondary discharge diagnosis)
- Level 3: ICU admission in those with COVID-19 related admission
- Level 4: death during hospitalization for COVID-19 (any cause)

Prior history of events

- prior VTE (deep venous thromboembolism, Pulmonary embolism, splanchnic) or drug proxies (B01AB*)
- History of anaphylaxis diagnosis or use of injectable epinephrine (C01CA24)
- History of allergic reactions

Comedication that may be associated with any of the AESI, assessed at start of follow-up and at time zero (prescription/dispensing 90 days prior)

- Antithrombotic agents (B01A*)
- Sex hormones (G03*) year prior
- Antibiotics (J01*)
- Antiviral medications (J05*)
- Lipid lowering drugs (C10*)
- Vaccines (J07 not J07BX03)

1.4.6 Data management

This study was conducted in a distributed manner using a common protocol, the ConcePTION common data model (CDM), and a common distributed analytics program. The data pipeline has been developing from the EU-ADR project and was further improved in the IMI-ConcePTION project[] and used in multiple EMA-tendered and VAC4EU studies. The ConcePTION CDM has been described by Thurin et al, 2022.[2]

1.4.7 Statistical analysis

Detailed methodology for summary and statistical analyses of data collected in this study are documented in the statistical analysis plan that was delivered to EMA. All analyses were conducted using R version R-4.0.3 or higher (Foundation for Statistical Computing, Vienna, Austria;[1] or SAS version 9.3 software or higher (Cary, North Carolina, USA; SAS Institute, Inc.).

1.5 Results

1.5.1 Readiness (Objective 1)

During the readiness phase, all Data Access Providers (DAP) requested approvals to participate in the studies specified in the CVM readiness and rapid assessment protocol (including all potential AESI). The *Extraction, Transformation, and Load* (ETL) design document was updated based on required data. Required data was ETL'ed into the ConcePTION CDM. To assess the quality of the data, level 1-3 quality checks were conducted. These quality checks were reported in the interim report and comprise assessment of completeness, correctness, plausibility of the data, and accuracy. They were conducted for each data instance, and some data sources conducted these multiple times when data was refreshed (e.g. for updated rapid assessments for myocarditis).
Nine data sources from Italy (ARS, Pedianet, Caserta), Spain (BIFAP, VID, SIDIAP), Netherlands (PHARMO), UK (CPRD) and Norway (national registers) completed this phase. The regional database from Lazio (Italy) could not participate because of administrative issues and data access rules.
The study population at January 1, 2019 included in the readiness assessment comprised a total of 52,306,672 subjects persons, CPRD and BIFAP contributed the largest populations. Data sources had completed data instances with information up until end of 2021 or June 2022.

Population characteristics

ARS has a relatively old population (8.4% is above 80 years of age) whereas the PEDIANET population is very young since it only captures children 0-14 years of age. The rest of the data sources all had median ages of 40 years of age, with a slightly higher prevalence of women in all data sources. This reflects the national populations. The most prevalent co-morbidity at baseline (1/1/2020) was a history of cardio/cerebrovascular disease (28% in ARS and lower in others). Based on the population shapes (level 3 quality checks) the population gender/age trees were similar to national data, and date of birth and gender were available. Some DAPs censored data instances to earlier dates than the extraction dates, to ensure that all databanks would have had the time to be updated.

[2] Thurin, N.H., et al (2022). From Inception to ConcePTION: Genesis of a Network to Support Better Monitoring and Communication of Medication Safety During Pregnancy and Breastfeeding. Clin. Pharmacol. Ther., 111: 321-331.

COVID-19 vaccinations data

Covid-19 vaccination data was available in each of the data sources, and timing of recording as well as uptake percentage was comparable with data from the COVID-19 vaccine tracker at ECDC. The PHARMO data source saw some delays since it was based on GP data, and GPs received the data from the national health agency with delay. All data sources were considered fit 'for' purpose to study COVID-19 vaccination uptake.

In general, more than 70% of persons received Pfizer vaccine in each data source except in UK, followed by Moderna, AstraZeneca and Janssen. In UK the pattern was different, AstraZeneca had a much higher percentage of first dose (48%), Pfizer was first dose for 49% of population, and Janssen vaccine was not used. In Norway, mostly Pfizer and Moderna were used and no Janssen.

For those starting with Pfizer vaccine dose 1, more than 80% had a homologous second Pfizer dose, in Pedianet second dose was lower, in Norway second dose was frequently Moderna (16.25%). Median distance to second dose differed between regions from 21-63 days (UK) and was much longer when there was a heterologous second dose. In most countries, those vaccinated first with Moderna vaccine had a homologous second dose, in NL-PHARMO and Norway second dose was also frequently Pfizer (14.7% and 12.95% respectively), median distance to second dose was usually 28 days, but there was variation across regions. In persons with AstraZeneca dose 1 a large proportion had a homologous second dose, except in Norway, where 97% used either Pfizer or Moderna as a second dose. Median distance to second dose was between 75-80 days. Boosters after Janssen vaccine were infrequently a Janssen vaccine, the majority had a booster with an mRNA platform vaccine (Pfizer or Moderna).

Strong channeling of different vaccines to certain age groups was observed, which within country could even change per region. Due to the age channeling: Pfizer to very old, and children, AstraZeneca mostly between 50-69 and Moderna distributed, prevalence of co-morbidity was highest in AstraZeneca 1st dose users on a population level.

AESIs

Age and gender standardized and age-specific incidence rates of AESIs were created for 2019, and 2020 prior to COVID-19 disease, as well as post-COVID-19 disease until vaccination, rates were benchmarked with published data from the ACCESS project[3] and the rates by Li et al.[4], Gubernot et al.[5], mainly (see annex 1). Based on the type of event data that the DAP can access and the setting in which these events are assessed (e.g. in primary care, outpatient specialist and or discharge/emergency) as well as the vocabularies of diagnostic codes, the rates differed, as was described already by Willame et al.[2] The methodological assessment on misclassification shows the impact of the differences of event provenance in studies and this should be considered in the choice of data sources when conducting safety evaluation studies.

[3] Willame C, Dodd C, Durán CE, Elbers R, Gini R, Bartolini C, et al. Background rates of 41 adverse events of special interest for COVID-19 vaccines in 10 European healthcare databases - an ACCESS cohort study. Vaccine. 2023 Jan 4;41(1):251-262. doi: 10.1016/j.vaccine.2022.11.031

[4] Li X, Ostropolets A, Makadia R, Shoaibi A, Rao G, Sena AG, et al. Characterising the background incidence rates of adverse events of special interest for covid-19 vaccines in eight countries: multinational network cohort study. BMJ. 2021 Jun 14;373:n1435. doi: 10.1136/bmj.n1435.

[5] Gubernot D, Jazwa A, Niu M, Baumblatt J, Gee J, Moro P, et al. U.S. Population-Based background incidence rates of medical conditions for use in safety assessment of COVID-19 vaccines. Vaccine. 2021 Jun 23;39(28):3666-3677. doi: 10.1016/j.vaccine.2021.05.016.

Table ES2. AESI list and comparison with ACCESS literature, impact of COVID-19 pandemic and lock down, and heterogeneity by provenance.

AESI	Comparison ACCESS and literature	Effect of lock down	Effect of COVID-19 infection	Heterogeneity by provenance and impact on fitness for purpose
CAD	Consistent	Consistent absolute decrease of 20-40/100,000 PY	1.5-3 fold increase after infection	Underestimation in GP only or hosp. only highest when hosp & outpatient & GP. Norwegian data overestimate due to lack of precise codes, Caserta data instance not fit for purpose.
ADEM	Consistently very low (<0.6/100,000)	Not visible, but very rare event	Increased rate after COVID-19	Small data sources do not observe, and neither those with ICPC coding. Hospital data required to identify the event. Caserta data instance not fit for purpose.
ARDS	Lower rates than in ACCESS due to retagging of codes	Lowering of rates	5-800 fold increase	Extreme effect of having hospital data, only data sources with hospital are fit for purpose. Caserta data instance should not be used.
AKI	consistent	Decrease of rates	2-10 fold increase	Underestimation in GP only or hosp. only highest when hosp & outpatient & GP. Norwegian, Caserta and PHARMO instances not fit for purpose.
ALI	consistent	Decrease of rates	2-10 fold increase	No adequate data in Pedianet, Caserta and PHARMO instances. Rest of source fit for purpose. Best to have GP & hospital data
Anaphylaxis	consistent	Decrease of rates	1.5-2 fold increase	No adequate data in the data instance from Norway, more specific ICD10 codes are required. GP data is required. Caserta data instance not fit for purpose.
Anosmia, ageusia	consistent	Increase of rates (maybe undetected COVID-19	10-100 fold increase	Hospital data alone are not fit for purpose. GP data are required. Caserta data instance should not be used.
Arrhythmia	consistent	Decrease of rates	2-5 fold increase	All provenances add sensitivity. Caserta data instance not fit for purpose.
Arterial thrombosis	Not done in ACCESS	Decrease of rates	2-5 fold increase	GP data alone underestimate, inclusion of hospital data doubles the rate
Bell's Palsy	Not done in ACCESS, but consistent with literature	Small decrease	1.5 fold increase	Caserta and PHARMO data instance not fit for purpose
Chilblain-like lesions	consistent	Small increase	2-5 fold increase	Data from hospital alone not adequate, GP data are required. Instances from Caserta, Norway are not fit for purpose
Coagulation disorders	Not done as aggregate in ACCESS	decrease	2-10 fold increase	PHARMO, Caserta instance not fit for purpose, hospital & GP data required
Cerebral Venous Sinus Thrombosis (CVST)	consistent	Not much impact	2-5 fold increase	PHARMO, Caserta instance not fit for purpose, hospital & GP data required
Diabetes type 1	higher	Not much impact	2-10 fold increase	Homogeneous across data sources based on medicines algorithm
Disseminated Intravascular Coagulation (DIC)	consistent	Small decrease	5-20 fold increase	GP data alone not fit for purpose for this event. CASERTA data instance not fit for purpose
Death (any cause)	consistent	Small increase	>10 fold increase	Homogeneous patterns, CASERTA data instance not fit for purpose
Erythema multiforme	consistent	decrease	No real impact	GP data alone not fit for purpose for this event. CASERTA data instance not fit for purpose
Generalized convulsion	Lower (due to exclusion of febrile)	No impact	No big change	PHARMO , Caserta, and Norwegian instance not fit for purpose
Guillain Barré Syndrome (GBS)	consistent	decrease	substantial increase	PHARMO, Norwegian and Caserta instances not fit for purpose
Haemophagocytic lymphohistiocytosis	Not measured in ACCESS	decrease	2-5-fold increase	Hospital data are required, Caserta, Norwegian, PHARMO instance not fit for purpose
Kawasaki´s disease	consistent	No impact	>10 fold (may be MIS)	Caserta, Norwegian and PHARMO instance not fit for purpose

AESI	Comparison ACCESS and literature	Effect of lock down	Effect of COVID-19 infection	Heterogeneity by provenance and impact on fitness for purpose
(Meningo) encephalitis	Slightly higher	Decrease in rates	2-5-fold higher	Norwegian data very high. Caserta instance not fit for purpose
Microangiopathy	consistent	Decrease	2-10 fold higher	Data instance from Caserta, CPRD and BIFAP not fit for purpose for this event
Multisystem inflammatory syndrome (MIS)	Lower, since kawasaki was not included anymore	Did not exist as code	Strong increase	ICD9 and ICPC codes do not exist for this condition. Only ICD10 and SNOMED codes. To study MIS & KD should be combined
Myocarditis	consistent	decrease	10-200 fold increase	GP only data underestimate by 50%. PHARMO data not fit for purpose due to lack of specific ICPC
Narcolepsy	consistent	decrease	No increase	Hospital only data underestimate. Data instance of PHARMO, Caserta and Norway not fit for purpose for this event
Pancreatitis	Not measured in ACCESS	Slight decrease	increase	PHARMO, Caserta and Norway not fit for purpose for this event. SIDIAP requires inspection
Pericarditis	consistent	No major impact	1.5-5 fold increase	PHARMO, Caserta data not fit for purpose for this event
Rhabdomyolysis	Not measured in ACCESS	decrease	10-fold increase	PHARMO, Norwegian, Pedianet, Caserta data instances not fit for purpose. Hospital data required
Severe cutaneous adverse reactions to drugs (SCARs)	Not measured in ACCESS	decrease	Up to tenfold increase	ARS, Caserta, PHARMO and Norwegian data sources not fit for purpose for this event. Hospital data required.
Sensorineural hearing loss	Not measured in ACCESS	decrease	2-fold increase	Caserta and ARS data instances not fit for purpose, GP data is required
Single organ cutaneous vasculitis (SOCV)	Decrease due to reclassification of narrow codes	decrease	3-5 fold increase	PHARMO, Caserta, ARS, Pedianet and Norwegian data instances not fit for purpose
Stroke haemorrhagic	Lower	decrease	3-4 fold increase	Hospital data are required. Caserta, Pedianet, Norwegian data not fit for purpose. GP only underestimates
Sudden death	Not measured in ACCESS	No observable impact	Strong increase	Cause of death not able to be detected in many data sources. Only ARS, BIFAP and Norway
Thrombocytopenia	Higher than in ACCESS	decrease	2-10 fold increase	Caserta, Norwegian, PHARMO data instances not fit for purpose
TTS	Consistent	No major impact	10-fold increase	Caserta not fit for purpose, hospital data required
Thyroiditis (autoimmune)	Not measured in ACCESS	decrease	4-fold Increase	Norwegian, ARS, PHARMO, Caserta data not fit for purpose, GP & Hospital data are required
Transverse myelitis	consistent	decrease	5-10 fold increase	Norwegian, PHARMO, Caserta and Pedianet instances not fit for purpose.
VTE	consistent	decrease	2-10 fold increase	Both GP & Hospital data are required, otherwise underestimation, Norwegian data overestimate. Caserta data not fit for purpose

1.5.2 Conduct of electronic healthcare records-based rapid assessment studies (Objective 2)

During the 2-year phase of the project, EMA requested 3 rapid evaluation studies to address emerging safety concerns under review by PRAC or research questions important to support regulatory decision-making.

Multi-inflammatory syndrome (MIS)

The request from EMA was to generate incidence rates (IRs) for MIS stratified by COVID-19 and pre-post-vaccination. The analysed study population included more than 6 million persons, with 650,731 children aged between 0 and 17 years old. Since MIS is a condition related to COVID-19 disease, MIS codes were created only at the end of 2020. ARS-IT could not identify MIS codes as this data source makes use of ICD9 codes, which are not updated

anymore. In the absence of MIS codes, KD-like disease codes were used by the Italian colleagues due to the reported association between MIS and KD in children. Rates of KD were highest in 0-11 years old individuals, both in males and females, with only one case of MIS effectively occurring after the COVID-19 pandemic, in 2021. An increment of the KD-like disease cases in 0-11 years old children was also observed in 2020, during the COVID-19 pandemic. KD and MIS rates were both very low. No cases of KD & MIS in children post-vaccination were observed, also because very few vaccinated children were present on the April and May 2021 data extractions of BIFAP and ARS, respectively.
For this final report updated Kawasaki and MIS specific incidence rates were calculated. Kawasaki disease rates increased more than 10-fold after COVID-19 diagnosis, and MIS also increased very much, but could only be observed in Norwegian data after COVID-19, which have issues with specificity of the codes.

COVID-19 severity in children

The EMA Pediatric Committee (PDCO) requested an estimation of the incidence rates of serious COVID-19 in children, Data were initially presented to the PDCO in July 2022, and a final report delivered on May 8, 2023. Results have been updated for this final report, including data from Norway since it has fit-for-purpose for this study.
Four COVID-19 severity levels were considered (diagnosis, hospitalization, intensive care unit admission, and death after COVID-19*).* Non hospitalized COVID-19 disease was considered non-severe, and severe disease was hospitalization, ICU or death.

The total study population comprised 6,719,867 under 18 years old individuals (51% women) across the 7 data sources. Median age ranged from 6-10 years old. The at-risk of severe COVID-19 disease population comprised 445,174 (6.6%) children and adolescents with comorbidities. Vaccine uptake in children and adolescents (mostly Comirnaty) was mainly from July 2021 and September 2021 in Italy and Spain, respectively, whereas in Norway in September 2021 for adolescents. In children and adolescents without risk factors, the highest incidence rates of non-severe COVID-19 across data sources varied between 27 to 143 cases/100 PY in December 2021 and January 2022. Rates were much lower (0 to 1/100 PY) for severe COVID-19 infection. Incidence rates of severe COVID-19 were higher among children and adolescents with at-risk conditions for a severe disease. Overall, mortality cases were almost zero across all databases and cohorts.

Myocarditis and pericarditis

EMA requested to evaluate the signal of COVID-19 vaccines and myocarditis/pericarditis at the end of September 2021. Study results were first reported to EMA and PRAC in November 2021, updates with additional data sources and more follow-up were conducted and results have been published in a peer-reviewed journal in April 2022.[6] From these analyses emerged an increased risk of myocarditis in people below 30 years old after Pfizer doses 1 and 2 and Moderna dose 2. We could not exclude from these results an association between myocarditis risk and AstraZeneca dose 2. Pericarditis was not associated with vaccination.

To include longer follow-up and data sources, an update of the SCRI myocarditis was again presented to PRAC in January 2023. In this report (May 2023), we include a re-analysis taking account larger data instances from data partners and small methodological adjustments. Key primary results from the May 2023 analysis with fit for purpose data sources confirmed

[6] Bots SH, Riera-Arnau J, Belitser SV, Messina D, Aragón M, et al. Myocarditis and pericarditis associated with SARS-CoV-2 vaccines: A population-based descriptive cohort and a nested self-controlled risk interval study using electronic health care data from four European countries. Front Pharmacol. 2022 Nov 24;13:1038043. doi: 10.3389/fphar.2022.1038043.

what had been found before: Pfizer dose 2 and Moderna dose 2 were associated with an increased risk of myocarditis in persons below 30 years of age, and not for a booster Pfizer dose, but it persisted when the third dose was Moderna. Analyses by week rather than 28 days, showed that elevations of risk occurred.

Exclusion of subjects with COVID-19 during follow-up resulted in an increase of the IRR (not stratified by age) for second dose of Pfizer, Moderna and AstraZeneca, which were all significantly elevated. After exclusion of persons with COVID-19 disease, third doses were not associated with significant elevation anymore. The negative control sensitivity analysis showed estimates around 1 and an effect towards the 1 when persons with COVID-19 were excluded.

1.6 Discussion

The CVM EHR data studies had several objectives, first to create readiness of data sources and assess whether data sources were fit 'for' purpose. All 9 data sources were fit for purpose as regards population and COVID-19 vaccinations, but depending on the AESI would not be fit to participate in evaluation studies due to misclassification of the AESI.
Misclassification depended on the type of databanks that were available in the data sources (primary care, emergency room visits, outpatient specialist and hospitalization), meanings of codes (primary discharge vs. secondary discharge diagnoses) as well as the use of narrow (specific) codes and/or broad codes (sensitive). Most fit for all types of events were data sources that could link GP data to hospital data (e.g. SIDIAP, BIFAP, FISABIO, Norway). A review of the existing literature on the PPV of these events showed a range of false positive rates and an impact on the RR which would lead to bias towards the null in case of non-differential misclassification and different directions when there would be differential misclassification in comparative studies.
Confounding may have impacted the results of the evaluation study on COVID-19 vaccines and myocarditis which the EMA requested. We showed considerable channeling of certain COVID-19 vaccines towards specific age groups , which could confound comparative studies. The self-controlled designs automatically adjust for time-fixed confounding factors but are still sensitive to time-varying confounding. COVID-19 disease was a strong time varying confounder that needed to be controlled for (adjustment, restriction) Post vaccination follow-up data are not rapidly available during a vaccination campaign because of time lags, and multiple vaccine doses, among other reasons. Design choices such as pre-vaccination control or post-vaccination control period needed to be made. It was shown that using a pre-vaccination control period did not overestimate the effect but rather yielded a more conservative estimate. The SCRI design was less susceptible to time varying confounding than the SCCS design.

1.7 Conclusion

The CVM EHR studies showed that several data sources are ready to evaluate COVID-19 vaccine-AESI associations, but data sources are not always fit for each type of event. Depending on the health care setting where such events are diagnosed and treated, and the provenance of the databanks, a data instance may or may not be fit.
Misclassification of the outcome may have a large impact on the absolute and relative estimates and only the 'fit' data should be used. Because of the large channeling of the different vaccines, the designs chosen (SCRI) dealt best with time stable and time varying confounding. Using this design, we were able to estimate the associations between COVID-19

vaccines and myocarditis repeatedly. For myocarditis we showed significant associations between the second dose of mRNA platform vaccines and myocarditis. When we excluded patients diagnosed with COVID-19, the relative risks increased and also showed a significant association for the AstraZeneca vaccine. Other associations can be studied using this design with fit for purpose data sources for the AESI.

2 List of abbreviations

ACCESS	vACCine covid-19 monitoring readinESS
ADVANCE	Accelerated Development of VAccine beNefit-risk Collaboration in Europe
AESI	Adverse Event of Special Interest
ARDS	Acute respiratory distress requiring ventilation
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass Index
CDC	Centers for Disease Control and Prevention
CDM	Common Data Model
CI	Confidence interval
DAP	Data Access Provider
DRE	Digital Research Environment
ECDC	European Centre for Disease Prevention and Control
EMA	European Medicines Agency
EHR	Electronic Health Records
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance.
ETL	Extract, Transform, and Load
EU PAS	The European Union electronic Register of Post-Authorisation Studies
GDPR	General Data Protection Regulation
GP	General Practitioner
GPP	Good Participatory Practice
HIV	Human Immunodeficiency Virus
ICD	International Classification of Diseases
ICMJE	International Committee of Medical Journal Editors
ICU	Intensive Care Unit
MIS-C	Multisystem Inflammatory Syndrome in children
mRNA	messenger Ribonucleic acid
NHS	National Health Service
QC	Quality Control
RNA	Ribonucleic acid
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SPEAC	Safety Platform for Emergency vACcines
VAC4EU	Vaccine monitoring Collaboration for Europe

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4 Milestones

Start of project	6 Apr 2021
D1 Study plan	6 May 2021
D2 Study protocol(s)	7 Jun 2021
Study start	7 July 2021
Multi-Inflammatory Syndrome associated to COVID-19 vaccines	
EMA's Study Request	10 September 2021
Study results	2 November 2021
Update of Study results	8 May 2023
COVID-19 severity in children	
EMA's Study Request	8 March 2022
Study results	21 July 2022
COVID-19 severity in children – request of update including risk factors analyses	
EMA's Study Request	13 September 2022
Study results	8 May 2022
Myocarditis and Pericarditis association with COVID-19 vaccines	
EMA's Study Request	22 September 2023
Study results	21 October 2021
Update of Study results 1	22 April 2022
Update of Study results 2	5 January 2023
Update of Study results 3	8 May 2022
D4.1 Interim study report + D3 monthly interim statistical report 7 &SAP	8 Apr 2022
D4.2 Final study report	8 May 2023
D5 Manuscript	8 May 2023
D4.2 Final study report update (missing covariate data added and correction of VID data instance)	August 10, 2023

5 Rationale and background

To complement spontaneous reporting systems for signal detection (routine pharmacovigilance) and other initial safety monitoring activities such as pharmaco-epidemiological studies conducted or planned by different stakeholders, the Agency procured several safety monitoring studies through its framework contracts.

In January 2021 the Agency launched a new tender for safety monitoring of COVID-19 vaccines in the EU. The EU PE & PV and the VAC4EU network received and implemented the tender, which had two objectives, the first was to implement a prospective cohort monitoring in more than 10 countries and the second was signal strengthening. This executive summary is focusing on the second objective which was to conduct signal strengthening activities for potential safety concerns emerging from active surveillance electronic health data.
Based on the technical specifications signal strengthening meant the collection of additional information to further characterise the incidence of the safety concern in comparison to its expected incidence in non- vaccinated populations or suitable comparator populations. This activity should provide additional evidence supporting signal management and regulatory decision-making on the need for a full signal evaluation. The safety concerns for which signal strengthening should be performed could be identified by the Agency, other regulatory authorities, or the consortium itself.

6 Goal and objectives

The request for signal strengthening capacity was translated into three objectives:

1) To create and assess readiness of electronic health record data sources for rapid evaluation of safety signals
by

- Providing an overview of the methods for identification of COVID-19 vaccine exposure in the data sources
- Monitoring the number of individuals exposed to any COVID-19 vaccine and to compare this to COVID-19 vaccine exposure (benchmark: ECDC vaccine tracker)[7]
- Generation of updated background rates for AESIs

2) To conduct rapid safety assessment studies using electronic healthcare records and support EMA safety assessments.
Moreover, it was planned that this should allow for specific subgroup analyses:

- immunocompromised persons
- persons with the presence of co-morbidities elevating the risk of serious COVID-19
- persons with a history of diagnosed COVID-19 disease
- pregnant women
- age groups
- patients with a prior history (ever) of that event more than a year before.

[7] ECDC vaccine tracker: https://vaccinetracker.ecdc.europa.eu/public/extensions/COVID-19/vaccine-tracker.html#uptake-tab

The following VAC4EU and/or EU PE&PV research network data access providers were invited to participate in the readiness, rapid assessment studies, and in-depth analyses:

Table 1. Participating data access providers and data sources

Country	Data Access Provider	Name Data source	Experience ConcePTION CDM v2.2	AESI experience	Active population	Type of data source
NL	PHARMO	PHARMO	Yes	Yes (ACCESS)	6 million	Record linkage
ES	AEMPS	BIFAP	Yes	Yes (ACCESS)	10 million	GP & Hospital medical records
ES	IDIAPJGol	SIDIAP	Yes	Yes (ACCESS)	5.8 million	Record linkage
ES	FISABIO	VID	Yes	Yes (ACCESS)	5 million	Record linkage
IT	SoSeTe	PEDIANET	Yes	Yes (ACCESS)	0.5 million	Pediatric medical record
IT	ARS Toscana	ARS data	Yes	Yes (ACCESS)	3.6 million	Record linkage
IT	PEPI	Regional data Lazio	No	No		Record linkage
IT	INSPIRE srl	Caserta data	No	No	1 million	Record linkage
UK	Utrecht University	CPRD/HES GOLD	Yes	Yes (ACCESS)	16 million	GP & Hospital medical record
NO	University Oslo	Norwegian	Yes	No	5 million	Record linkage

7 Amendments and updates to the protocols

NA

8 Research methods

8.1 Study Design

8.1.1 Readiness phase

The primary design for the readiness phase was a cohort study including all subjects with at least one day of follow-up after January 1, 2019, and at least 365 days of availability prior to that date, unless the date of birth occurred was during 2019-2021. No further in- or exclusion criteria were required.
In the readiness phase, data sources:

- Prepared the ETL design for the transformation of local data into the ConcePTION CDM (CCDM).[8]
- Ran level 1-3 quality checks (INSIGHT) and additional readiness assessment script (vaccine uptake, characteristics of vaccinated, incidence rates of AESI in 2019 and 2020) on data required for all AESI and covariates, aiming at investigating the completeness (level 1), the logic of the converted data (level 2), and subsequently whether the data was fit for purpose, especially as regards vaccine and events data (level 3 and additional readiness script).

8.1.2 Rapid assessment studies primary design

A general protocol was created (EUPAS42467)[9] to be ready for rapid assessment of safety concerns of any of the AESI. The design comprised a retrospective observational study using EHR databases. Eligible individuals would be included in the study from the start of vaccination campaigns: 1 December 2020, and the observation period ended at the last date of data availability in each database.
The primary study design for acute events (events expected to occur within 60 days of vaccination) was a self-controlled risk interval (SCRI) design and for non-acute events (events expected to occur or be diagnosed with delay, within 180 days) a cohort design with contemporary exposed (vaccinated) comparators. Acute events could also be studied using the cohort design to address uncertainties around risk windows and limitations of the SCRI design.

Self-controlled Risk Interval Design

The SCRI design compared the risk of the event of interest in post-vaccination risk windows to a pre-vaccination control window within the same individual. We used a pre-vaccination control window to allow for rapid hypothesis testing, since data lag times may occur, we did not want to wait too long after introduction of COVID-19 vaccines to be able to analyze. The SCRI design included only individuals who received at least one dose of a COVID-19 vaccine during the study period and who experience the specific event in the control period or after vaccination (starting date of vaccination). Study subjects enter the study at the time of the start of the control window, which starts 90 days (as a default) before the date of vaccination with a COVID-19 vaccine. The SCRI design compared the risk of each outcome

[8] Thurin NH, Pajouheshnia R, Roberto G, et al. From inception to ConcePTION: genesis of a network to support better monitoring and communication of medication safety during pregnancy and breastfeeding. Clin Pharmacol Ther 2022;111(1):321–31.
[9] Sturkenboom, MCJM Covid-Vaccine-Monitor Rapid Safety Assessment of SARS-CoV-2 vaccines in EU Member States using electronic health care datasources. 42634 (encepp.eu)

during the risk window following dose 1 or dose 2 with the self-matched control interval, used to assess the baseline risk of the outcome. The control period was 60 days long and was followed by a 30-day pre-exposure buffer period, to account for healthy vaccinee effect and potential temporary event-dependency of the exposure, the length of the pre-exposure period may be adapted based on the assessment of the methods by WP4 and the specific event of interest. Cases with an event in either the risk or control window contributed to the estimation of the incidence rate ratio of interest. If an event occurs in the pre-exposure period, it was kept in the study to enable sensitivity analyses.
The risk window post-vaccination started at day 1 and was divided into dose-specific risk intervals following each dose of the COVID-19 vaccine, except for anaphylaxis for which the risk interval would start at day 0. If a second dose is given within the risk interval of the first dose, the period of follow-up for the first dose will be censored. Sensitivity analyses will be conducted that include day 0 in the risk interval.

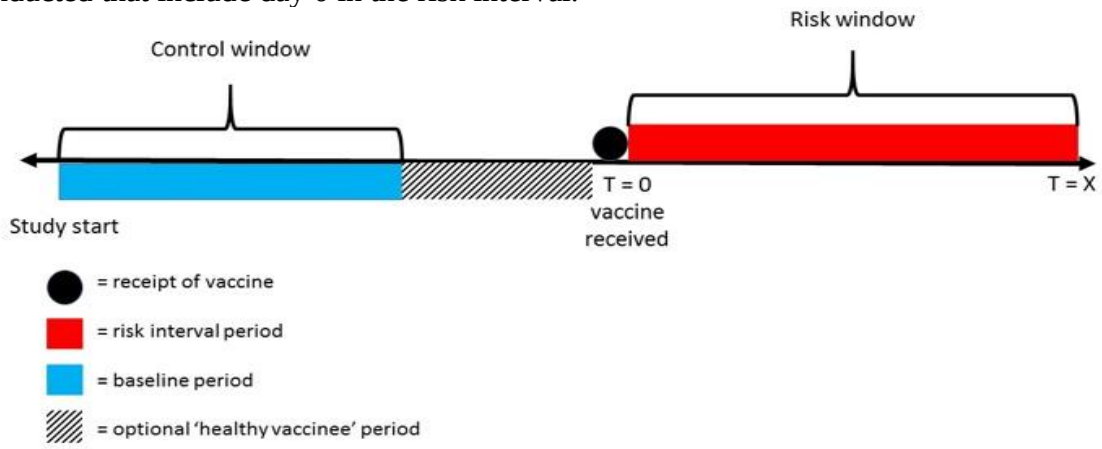

Figure 1: Self-Controlled Risk Interval Design

Cohort design for rapid assessment

A retrospective cohort design was used to estimate the rate of non-acute events of interest after receipt of COVID-19 vaccination dose and compare this incidence primarily with that occurring in a COVID-19 vaccinated matched comparator group.

- *Exposed cohort (index cohort)***:** individuals who have received at least one dose of a specific COVID-19 vaccine.

- *Concurrently exposed cohort (reference cohort):* individuals that have been vaccinated with another type of COVID-19 vaccine.
  In this retrospective cohort design, time zero (cohort entry) was defined as the time at which the exposure status was assigned, when selection criteria are applied, and when study outcomes start to be counted. Time zero (i.e., recipients of the vaccine) is the day the specific COVID-19 vaccination (index cohort) was received for anaphylaxis and date of vaccination +1 for other events of interest.

- *Concurrently unexposed cohort (reference cohort)***:** individuals who have not received a COVID-19 on or before time zero.

8.2 Setting

For the implementation of the readiness study, 10 electronic health care databases in Northern, Southern and Western Europe showed interest to participate. The data sources that were included are:

Italy
- ARS Toscana (Agenzia Regionale di Sanità della Toscana)
- Pedianet (Societa Servizi Informatici)
- Caserta local health database (INSPIRE srl)
- Lazio Regional data source (Pharmacoepidemiology Unit Lazio Region)

The Netherlands
- PHARMO Database Network (PHARMO Institute for Drug Outcomes Research) (NL)

The United Kingdom
- CPRD (Clinical Practice Research Datalink)

Norway
- The Norwegian health registers

Spain
- SIDIAP (Sistema d'Informació per el Desenvolupament de la Investigació en Atenció Primària)
- BIFAP (Base de Datos para la Investigación Farmacoepidemiológica en Atención Primaria)
- FISABIO (VID, Valencia health system Integrated Database)

Further information on the data sources used in this study can be found in the methods section. All but one data source participated in the readiness phase. Lazio regional data could not be accessed due to changes in data access rules.

For actual rapid assessment studies, choices have been made based on:
- Availability of fit for purpose data
- Sample size and resources
- Ability to commit to timelines.

8.2.1 Study population

The source population comprised all individuals registered in each of the participating healthcare data sources.

8.2.2 Study Duration and Follow-up

Readiness

For the readiness phase study, the study period started on 1 January 2019 and ended on the last data update. Subjects were followed from 1 January 2019 until the earliest of the following dates: death, end of data availability, subject exit, or the completion of the period. If persons have multiple periods within the same data source, we only used the period in which the first COVID-19 vaccine was provided as active follow-up.

Rapid hypothesis testing (rapid assessment) study
For the SCRI, the study period started on 1 September 2020 and lasted until the end of the study period. For the cohort study the study period started on December 1st, 2020.

SCRI: Follow-up ended at the earliest of the following: censoring at death, end of data availability, subject exited the database or recommended end date.

Cohort: The cohort design follow-up ended at occurrence of the outcome, or censoring at death, end of data availability, subject exited the database or recommended end date (as per DAP decision, based on an assessment of the validity of the data). For unvaccinated groups, individuals were censored when they received a COVID-19 vaccine dose.

8.2.3 Inclusion Criteria

Readiness study
For the readiness study, the person was included if there was at least one day of follow-up and the person had at least 12 months of data in the data source at the start of follow-up or is born during 2019-2020.

SCRI Design
For analyses of outcomes assessed with the SCRI design, the following criteria needed to be met.

- Received at least one dose of COVID-19 vaccine during the study period.
- Experienced the specific outcome of interest during the predefined observation period.
- Had at least 12 months of data/registration in the data sources at study entry (except when born during study period)

Cohort design
To be included in the cohort design individuals were required to meet all the following inclusion criteria:

- At time zero, being in the underlying population of the data source for at least 12 months; or, being born in the previous 12 months in the underlying population.
- No history of vaccination with a COVID-19 vaccine before time zero

8.2.4 Exclusion Criteria

For the readiness study, there were no exclusion criteria.
Individuals were excluded from the hypothesis testing studies if:

- They had a recorded diagnosis for the specific event in the 365 days prior to cohort /SCRI entry (time zero). Upon investigation of one event, we do not exclude any history or prevalence of other groups of events (AESIs).
- They had a contra-indication for one of the COVID-19 vaccines.

8.3 Variables

8.3.1 Exposure Assessment

Exposure to COVID-19 vaccines was based on available recorded prescription, dispensing, or administration of the COVID-19 vaccines. The main exposure of interest for the rapid assessment studies was the receipt of COVID-19 vaccine(s).

- ARS Toscana (IT): ARS identified vaccines from the regional immunization register using the national product code, including batch number.
- Pedianet (IT): Information on COVID-19 vaccine included the date of immunization, type of vaccine, vaccine batches, dose.
- PHARMO (NL): Data on vaccination were obtained from PHARMO's GP database. Information on vaccines include ATC code, brand, and date of administration/recording. Several COVID-19 vaccines have been administered through other routes and information was provided to GP with different lag times.
- Caserta LHU database (IT): Caserta LHU record linkage database contains information from all claims databases (e.g. hospitalizations, drug dispensing, etc.) of Caserta province catchment area (around 1 million population). Those claims data could be linked to the local immunization registry which includes name and batch of the vaccine; manufacturing company; dose; administration route; administration location (eg, general practice); date of administration.
- CPRD (UK): The CPRD contains information recorded by National Health Service (NHS) primary care general practitioners (GPs); and information on the administration of COVID-19 vaccines to individuals is available. This includes, alongside an encrypted unique patient identifier; the name of the vaccine; manufacturing company; dose; and date
- Norwegian health registers (NO): The national, electronic immunization register (SYSVAK) was established in 1995 and records an individual's vaccination status and vaccination coverage in Norway. All vaccinations are subject to notification to SYSVAK and are registered without obtaining patient consent. This applies to all COVID-19 vaccines. In SYSVAK, the following data are registered: individual personal identifier, vaccine name and Anatomical Therapeutic Chemical (ATC) code, vaccine batch number, date of vaccination, reason for vaccination as health care professional versus risk-group patient, and the center where the vaccine was administered.
- SIDIAP (ES): SIDIAP has available information on the administration of COVID-19 vaccines to individuals linked to a unique and anonymous identifier. The information originated from electronic medical records. For each patient, SIDIAP had date and center of administration, dose, brand, reasons for vaccination (eg, risk group), and other information related to vaccination.
- BIFAP (ES): BIFAP (Base de Datos para la Investigación Farmacoepidemiológica en Atencion Primaria), a computerized database of medical records of primary care (www.bifap.aemps.es) is a non-profit research project funded by the Spanish Agency for Medicines and Medical Devices (AEMPS). Data on vaccination with COVID-19 vaccines were obtained from the COVID-19 vaccination registries in the participating regions and linked to the primary care medical records in BIFAP. Date of vaccination, brand, batch, and dose are registered.
- FISABIO (ES): Data on vaccine exposure were obtained from the Vaccine Information System (VIS), which includes information on vaccine type, manufacturer, batch number, number of doses, location and administration date.

The vaccination strategies for the different exposure groups are defined as follows:

- Subjects who receive a first dose of a specific COVID-19 vaccine are classified as exposed to D1 for that specific vaccine (if brand is unknown, it will be unknown). Subsequent doses were counted based on chronological order. A minimum of 14 days was required between dose 1 and 2, and a minimum of 60 days between dose 2 and 3.

- In the SCRI design subjects who receive a second, third or fourth dose of COVID-19 vaccine will only contribute time to the prior dose/brand risk window and move into the risk window of the next dose for a COVID-19 vaccine, by brand for both the cohort as well as the SCRI design, once this occurs.

In the cohort study the vaccination strategy for the matched reference cohort(s) was defined at time zero based on the dose 1 as:

- Pfizer
- Moderna
- Janssen
- AstraZeneca
- Novavax
- Unknown

For the SCRI design, person-time in the risk interval have been considered *exposed* while person-time in the control interval was considered *unexposed*. Risk intervals are specific to the outcome of interest and listed in Table 2.

8.3.2 Study Outcomes

AESIs assessed in this study are listed below (Table **2**). Definitions and code lists are based on those created for the ACCESS project. Code lists were verified and updated through VAC4EU by two independent clinical assessors following Brighton Collaboration definitions[10] and agreement reached within an *ad hoc* code list working group. Each code was tagged as narrow (specific) or broad (sensitive). Only narrow codes were used.
The codelist is provided publicly on Zenodo. (Carlos Duran, Judit Riera, Sima Mohammadi, Joan Fortuny, Vera Ehrenstein, Cristina Rebordosa, & Miriam Sturkenboom. (2023). Covid-19 Vaccine Monitoring project (CVM)-Electronic Health Record data sources Codelist (1.0) [Data set]. Zenodo. https://doi.org/10.5281/zenodo.8199481)
Outcome misclassification was assessed as part of the methodological assessment.

Table 2. List of AESI and the negative control events, design and primary risk period duration

Event	ACCESS	SCRI	cohort	Naïve period to estimate new onset	Primary Risk period*
Multisystem inflammatory syndrome	✓	✓	✓	365 days	28 days
Acute respiratory distress syndrome	✓	✓	✓	365 days	28 days
Acute cardiovascular injury	✓	✓	✓	365 days	
Microangiopathy	✓	✓	✓	365 days	28 days
Acute CAD	✓	✓	✓	365 days	28 days
Arrhythmia	✓	✓	✓	365 days	28 days
Myocarditis	✓	✓	✓	365 days	28 days
Pericarditis	✓	✓	✓	365 days	28 days
Coagulation disorders, including deep vein thrombosis, pulmonary embolus, cerebrovascular stroke, limb ischaemia, haemorrhagic disease	✓				
VTE (DVT & PE & Splanchnic)	✓	✓	✓	365 days	28 days
CVST	✓	✓	✓	365 days	28 days
Arterial thrombosis (AMI /Ischemic stroke)	✓	✓	✓	365 days	28 days
TTS (VTE, arterial thrombosis, or CVST with thrombocytopenia in 10 days)	✓	✓	✓	365 days	28 days
Hemorrhagic stroke	✓	✓	✓	365 days	28 days
DIC	✓	✓	✓	365 days	28 days
Generalised convulsion	✓	✓	✓	365 days	14 days
Guillain Barré Syndrome	✓	✓	✓	365 days	42 days

[10] https://brightoncollaboration.us/category/pubs-tools/case-definitions/

Event	ACCESS	SCRI	cohort	Naïve period to estimate new onset	Primary Risk period*
Diabetes (type 1)	✓		✓	365 days	180 days
Acute kidney injury	✓		✓	365 days	180 days
Acute liver injury	✓		✓	365 days	180 days
Anosmia, ageusia	✓	✓	✓	365 days	28 days
Chilblain-like lesions	✓	✓	✓	365 days	28 days
Single organ cutaneous vasculitis	✓	✓	✓	365 days	28 days
Erythema multiforme	✓	✓	✓	365 days	7 days
Anaphylaxis	✓	✓	✓	30 days	2 days
Death (any cause)** (postvaccination control window)	✓	✓	✓	365 days	7 days
Sudden death (by codes)** (postvaccination control window)	✓	✓	✓	365 days	7 days
Meningoencephalitis	✓	✓	✓	365 days	28 days
Acute disseminated encephalomyelitis (ADEM)	✓	✓	✓	365 days	28 days
Narcolepsy	✓		✓	365 days	180 days
Thrombocytopenia	✓	✓	✓	365 days	28 days
Transverse myelitis	✓	✓	✓	365 days	28 days
Bells' palsy		✓	✓	365 days	28 days
Haemophagocytic lymphohistiocytosis		✓	✓	365 days	180 days
Kawasaki's disease		✓	✓	365 days	28 days
Pancreatitis		✓	✓	365 days	28 days
Rhabdomyolysis		✓	✓	365 days	28 days
SCARs		✓	✓	365 days	28 days
Sensorineural hearing loss			✓	365 days	180 days
Thyroiditis			✓	365 days	180 days
Negative control events					
Gout		✓	✓	365 days	28 days
Otitis externa		✓	✓	365 days	28 days
Trigeminal neuralgia		✓	✓	365 days	28 days
Acute kidney injury	✓	✓	✓	365 days	28 days
Anaphylaxis (not drug-induced)	✓	✓	✓	365 days	28 days
C. difficile infection		✓	✓	365 days	28 days
Conjunctivitis		✓	✓	365 days	28 days
COVID-19 within 12 days after vaccination	✓	✓	✓	365 days	28 days
Diverticulitis	✓	✓	✓	365 days	28 days
Fractures		✓	✓	365 days	28 days
Gall stones		✓	✓	365 days	28 days
Influenza		✓		365 days	28 days
Liver cirrhosis		✓	✓	365 days	28 days
Organic (secondary) psychosis		✓	✓	365 days	28 days
Osteoarthritis		✓	✓	365 days	28 days
Osteomyelitis		✓	✓	365 days	28 days
Reactive arthritis		✓	✓	365 days	28 days
Renovascular disease		✓	✓	365 days	28 days
Sjögren's syndrome		✓	✓	365 days	28 days
Urinary tract infections		✓	✓	365 days	28 days
Valvular heart disease (non-congenital, not rheumatic)		✓	✓	365 days	28 days

*For death we may conduct different SCRI analyses

Negative control outcomes had to have two important features, which are (a) no association with the exposure of interest and (b) similar sources of bias as the true outcome. This second feature ensures that the negative control outcome tests the same mechanisms of potential confounding that could be present for the true outcome (1). Negative control outcomes that lack feature (b) are of little value in detecting unmeasured confounding, as illustrated by https://pubmed.ncbi.nlm.nih.gov/23632712/ Groenwold et al. Table 2 lists the selected negative control outcomes.

8.3.3 Covariate Definition

Readiness study

In the readiness study covariates (as listed below for the rapid assessment study) were extracted and assessed.

Rapid hypothesis testing (rapid assessment) study

Time-varying variables for the SCRI design were measured at time of occurrence for time-varying factors (e.g. COVID-19). For the cohort design and SCRI, covariate status for stable factors will be measured at time zero. All covariates were assessed in specific periods, default was during the one-year prior time zero.

Population characteristics were identified based on diagnoses, medicines, laboratory data, survey observation or medical observations, and observation period information.

Demographic characteristics (all measured at time zero)

- Age (0-1, 1-4, 5-11, 12-17, 18-29, 30-59, 60-79, 80+)
- Sex

Pregnancy

- Pregnancy status at time zero (if available), using the pregnancy algorithm developed in the ConcePTION project.[11]

Comorbidities with conclusive and higher suggestive evidence for more severe COVID-19 disease, all measured at time zero and considered when recorded in year prior to time zero.

- Cancer diagnosis or cancer medicines (L01A*, L01B*, L01C*, L01D*, L01X*, L02A*, L02B*, L03*, L04*)
- Chronic kidney disease diagnosis (exclusion criterium for assessment for acute kidney injury)
- Chronic liver disease diagnosis (cirrhosis, non-alcoholic fatty liver disease, alcoholic liver disease, autoimmune hepatitis)
- Chronic respiratory disease diagnosis (chronic obstructive pulmonary disease, bronchiectasis, asthma, interstitial lung disease, cystic fibrosis) or drug proxies (R03*, R07A*)
- Cardio/Cerebrovascular disease (CVD) diagnosis (stroke, transient ischemic attack (TIA), aneurysm, and vascular malformation, coronary artery disease, heart failure or cardiomyopathies) or drug proxies for such disease (C01*, C03*, C07*, C08*, C09*, B01AC*)
- Obesity diagnoses or anti-obesity medicines as proxy (A08AB*, A08AA*)
- Down syndrome diagnoses
- Mental health disease (depression, dementia, and schizophrenia spectrum disorders) or drug proxies (N05A*, N06A*, N06D*)
- Sickle cell disease diagnosis or drug proxies (L01XX05, B06AX01)
- Diabetes (type 1 or 2) or diabetes medicines as proxy (A10B*, A10A*)
- Human immunodeficiency virus diagnoses or drug proxies (J05AE*, J05AR*, J05AF*, J05AG*)
- Immunosuppressants: Use of corticosteroids or other immunosuppressive medications (H02*, L04*)

COVID-19 History

[11] Thurin NH, Pajouheshnia R, Roberto G, et al. From inception to ConcePTION: genesis of a network to support better monitoring and communication of medication safety during pregnancy and breastfeeding. Clin Pharmacol Ther 2022;111(1):321–31.

- COVID-19 infection: Covid-19 Dx diagnosis code or positive test further classified by severity:
- Level 1: any recorded COVID-19 diagnosis or positive test.
- Level 2: hospitalization for COVID-19 (COVID-19 diagnosis in primary/secondary discharge diagnosis)
- Level 3: ICU admission in those with COVID-19 related admission
- Level 4: death during hospitalization for COVID-19 (any cause)

Table 3. Retrieval of COVID-19 PCR/Antigen test

Data source	Medical observations (labs)	Survey Observations
Italy, ARS Tuscany		*survey_meaning=`covid_registry´*
Italy, Pedianet	*"mo_origin = TAMPONI_COVID19 AND mo_source_value = positive"*	
Spain, Valencia VID	*mo_meaning='covid19_pcr_test' AND mo_source_value=`positive´ or (mo_meaning='*covid19_antigen_test*' AND mo_source_value=*`positive´*)*	
Spain SIDIAP	mo_meaning='covid19_pcr_test' AND mo_source_value=`positive´ OR mo_meaning='covid19_antigen_test' AND mo_source_value=`positive´	
Spain, BIFAP	NA	
Norway, Norwegian Registers	mo_meaning = COVID-19 positive test AND mo_code = 713	
Netherlands, PHARMO	NA	
UK, CPRD	mo_meaning= "covid_lab_test " AND mo_unit= `positive´	

Prior history of events

- prior VTE (deep venous thromboembolism, Pulmonary embolism, splanchnic) or drug proxies (B01AB*)
- History of anaphylaxis diagnosis or use of injectable epinephrine (C01CA24)
- History of allergic reactions

Comedication that may be associated with any of the AESI, assessed at start of follow-up and at time zero (prescription/dispensing 90 days prior)

- Antithrombotic agents (B01A*)
- Sex hormones (G03*) year prior
- Antibiotics (J01*)
- Antiviral medications (J05*)
- Lipid lowering drugs (C10*)
- Vaccines (J07 not J07BX03)

The AESI could have different sets of **risk factors**, and outcome-specific analyses could contain different covariate sets.
For subgroup analyses, we used the following groups

- immunocompromised persons (yes/no) (defined as a combination of immunodeficiencies-related diagnoses, including HIV, and evidence of use of drug proxies such as HIV medication and immunosuppressants).

- persons with the presence of co-morbidities elevating the risk of serious COVID-19 (yes/no)
- persons with a history of diagnosed COVID-19 disease (yes/no)
- pregnant women at time zero (yes/no)
- age groups
- gender

8.4 Data Sources and measurement

The study used data from secondary electronic health record databases that are population-based. All data sources can provide data on COVID-19 vaccines, outcomes (diagnoses, procedures, and treatments), and important covariates.

8.4.1 PHARMO (NL)

The PHARMO Database Network, which is maintained by the PHARMO Institute for Drug Outcomes Research, is a population-based network of electronic health record databases that combines anonymous data from different primary and secondary health care settings in the Netherlands. These different data banks—including data from general practices, in- and outpatient pharmacies, clinical laboratories, hospitals, the cancer register, the pathology register, and the perinatal register—are linked on a patient level through validated algorithms. To ensure data privacy in the PHARMO Database Network, the collection, processing, linkage, and anonymization of the data are performed by STIZON, which is an independent, ISO/IEC 27001 certified foundation that acts as a trusted third party between the data sources and the PHARMO Institute. The General Practitioner databank comprises data from electronic patient records registered by GPs. The records include information on diagnoses and symptoms, laboratory test results, referrals to specialists, and health care product/drug prescriptions. The prescription records include information on type of product, prescription date, strength, dosage regimen, quantity, and route of administration. Drug prescriptions are coded according to the WHO ATC coding system. Diagnoses and symptoms are coded according to the International Classification of Primary Care (ICPC) [www.nhg.org], which can be mapped to the International Classification of Diseases (ICD) codes but can also be entered as free text. General practitioner data cover a catchment area representing 3.2 million residents (~20% of the Dutch population). PHARMO GP databank captures vaccinations supplied by the GP (influenza, zoster, COVID-19).

8.4.2 Clinical Practice Research Datalink and Hospital Episode Statistics (UK)

The CPRD from the UK collates the computerized medical records of GPs in the UK who act as the gatekeepers of health care and maintain patients' life-long electronic health records. Accordingly, GPs are responsible for primary health care and specialist referrals, and they also store information about specialist referrals and hospitalizations. General practitioners act as the first point of contact for any non-emergency health-related issues, which may then be managed within primary care and/or referred to secondary care, as necessary. Secondary care teams also provide information to GPs about their patients, including key diagnoses. The data recorded in the CPRD include demographic information, prescription details, clinical events, preventive care, specialist referrals, hospital admissions, and major outcomes, including death. Most of the data is coded using Read or SNOMED codes. Data validation with original records (specialist letters) is also available. The population in the data bank is generalizable to the UK population based on age, sex, socioeconomic class, and national geographic coverage CPRD Aurum versions is used. There are currently approximately 59 million

individuals (acceptable for research purposes) -16 millions of whom are active (ie, still alive and registered with the GP practice)- in over 2,000 primary care practices (https://cprd.com/Data). Data include demographics, all GP/health care professional consultations (eg, phone calls, letters, e- mails, in surgery, at home), diagnoses and symptoms, laboratory test results, treatments (including all prescriptions), all data referrals to other care providers, hospital discharge summary (date and Read/SNOMED codes), hospital clinic summary, preventive treatment and immunizations, and death (date and cause). For a proportion of the CPRD panel practices (> 80%), the GPs have agreed to permit the CPRD to link at the patient level to HES data. The CPRD is listed under the ENCePP resources database, and access will be provided by University Utrecht). Other CPRD-linked COVID-19 data sets, which may provide further follow-up information on AESI, include the Public Health England (PHE) Second Generation Surveillance System (SGSS) COVID-19 positive virology test pillar 1 tests, PHE COVID-19 Hospitalization in England Surveillance System, and the Intensive Care National Audit and Research Centre data on COVID-19 intensive care admissions.

8.4.3 Norwegian Health Registers (NO)

The Norwegian data sources in this project are several national health registers, ie, the Medical Birth Registry of Norway (MBRN), the National Patient Register (NPR), Norway Control and Payment of Health Reimbursement (KUHR), the Norwegian Immunization Registry (SYSVAK), the National Prescription Registry, and Statistics Norway. The source population will be identified using the Norwegian Institute of Health's (NIPH) copy of the Norwegian population data file from the National Registry. The NPR and KUHR (and the MBRN for the pregnant population) provide data on inpatient and outpatient diagnostic codes. Information on population background data is derived from Statistics Norway (eg, education, occupation status, sex, age). Data on vaccination status are derived from SYSVAK and the Norwegian Prescription Database. The latter register includes data on filled prescriptions for possible co-medications and other prescription drug use.

Norwegian Immunization Registry

The SYSVAK is the national electronic immunization register that records an individual's vaccination status and vaccination coverage in Norway. It became nationwide in 1995, and includes information such as personal identity number, the vaccine code, disease vaccinated against, and vaccination date.

The Norwegian Patient Registry

The NPR is an administrative database of records reported by all government-owned hospitals and outpatient clinics and by all private health clinics that receive governmental reimbursement. The NPR contains information on admission to hospitals and specialist health care on an individual level from 2008. The data include date of admission and discharge as well as primary and secondary diagnosis. The NPR has included Norwegian national identification numbers since 2008. Consequently, person-specific data from 2008 onwards are available. Diagnostic codes in the NPR follow ICD-10.

Norway Control and Payment of Health Reimbursement

The KUHR is an administrative database based on electronically submitted reimbursement claims from physicians to the Norwegian Health Economics Administration. It contains information from primary health care, GP, and emergency services on morbidity, utilization of health care services, and health care use. Person-specific data are available since 2006. Diagnostic codes in the KUHR follow ICD-10, but the ICPC is more frequently used by GPs.

The Norwegian Prescription Database
Since January 2004, all pharmacies in Norway have been obliged to send data electronically to the Norwegian Institute of Public Health regarding all prescribed drugs (irrespective of reimbursement) dispensed to individuals in ambulatory care. Relevant variables for this project include detailed information on drugs dispensed and date of dispensing.

The Medical Birth Registry of Norway
The MBRN is a population-based register containing information on all births in Norway since 1967 (more than 2.3 million births). The MBRN is based on mandatory notification of all births or late abortions occurring at 12 weeks of gestation onwards. The MBRN includes identification of the mother and father, including national identification numbers, parental demographic information, the mother's health before and during pregnancy, complications during pregnancy and delivery, and length of pregnancy, as well as information on the infant, including congenital malformations and other perinatal outcomes.

Statistics Norway
Statistics Norway provides microdata for research projects and includes information on population characteristics, housing conditions, education, income, and welfare benefits. These data are potentially important confounders.

The National Registry
The National Registry (Folkeregisteret) holds information about all inhabitants in Norway. The NIPH holds a copy of the Norwegian population data file from the National Registry that will be used to identify the source population in Norway.

Norwegian Surveillance System for Communicable Diseases
Notification of infectious diseases to the Norwegian Surveillance System for Communicable Diseases (MSIS) is an important part in the surveillance of infectious diseases in Norway. Microbiological laboratories analyzing specimens from humans, and all doctors in Norway, are required by law to notify cases of certain diseases (71 in total including SARS-CoV-2) to the MSIS central unit at the Norwegian Institute of Public Health. The following variables are available since 1977: notifiable disease, month and year of diagnosis, age groups, county of residence, and place of infection. Data on positive COVID-19 tests are updated continuously.

8.4.4 SIDIAP (ES)

The Information System for the Improvement of Research in Primary Care (Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària' [SIDIAP]; www.sidiap.org) was created in 2010 by the Catalan Health Institute and the IDIAP Jordi Gol Institute. It includes information collected since 01 January 2006 during routine visits at 328 primary care centres pertaining to the Catalan Health Institute in Catalonia (North-East Spain) with 3,414 participating GPs. SIDIAP has pseudo-anonymised records for 5.8 million people (75% of the Catalan population) and is highly representative of the Catalan population. The SIDIAP data comprise the clinical and referral events registered by primary care health professionals (eg, GPs, paediatricians, and nurses) and administrative staff in electronic medical records, comprehensive demographic information, community pharmacy invoicing data, specialist referrals, and primary care laboratory test results. The SIDIAP data can also be linked to other data sources, such as the hospital discharge database, on a project-by-project basis. Health professionals gather this information using ICD-10 codes, ATC

codes, and structured forms designed for the collection of variables relevant for primary care clinical management, such as country of origin, sex, age, height, weight, body mass index, tobacco and alcohol use, blood pressure measurements, and blood and urine test results. Regarding vaccinations, SIDIAP includes all routine childhood and adult immunisations, including the antigen and the number of administered doses. Encoding personal and clinic identifiers ensures the confidentiality of the information in the SIDIAP database. Currently, with the COVID-19 pandemic, there is the possibility to have shorter term updates in order to monitor the evolution of the pandemic. Recent reports have shown the SIDIAP data to be useful for epidemiological research. SIDIAP is listed under the ENCePP resources database[12].

8.4.5 BIFAP database (ES)

BIFAP (Base de Datos para la Investigación Farmacoepidemiológica en Atención Primaria) is a longitudinal population-based database of EHRs from patients attended in primary care facilities of the SNS (Sistema Nacional de Salud), the Spanish National Health System, and located in one of the participating regions throughout Spain. Since 2001, this database has been progressively and increasingly collecting health data, with annual updates, and the current complete version of the database with information until December 2021 includes clinical data of 14,810 Primary Care Practitioners (PCPs) and pediatricians. Nine participant Autonomous Region send their data to BIFAP every year. BIFAP database currently includes anonymized clinical and prescription/dispensing data from more than 21 million (17.4 active population) patients representing 91.6% of all patients of those regions participating in the database, and 35.9% of the Spanish population. The mean duration of follow-up in the database is 9.04 years. Information collected by PCPs includes administrative data, socio-demographic data, lifestyle, and other general data, clinical diagnosis and health problems, results of diagnostic procedures, interventions, and prescriptions/dispensations. Diagnoses are classified according to the International Classification of Primary Care (ICPC)-2 and ICD-9 code and SNOMED-CT system, and a variable proportion of clinical information is registered in "medical notes" in free text fields in the EHR. Additionally, information on hospital discharge diagnoses coded in ICD-10 terminology is linked to patients included in BIFAP for a subset of periods and regions participating in the database. All information on prescriptions of medicines by the PCP is incorporated and linked by the PCP to a health problem (episode of care), and information on the dispensation of medicines at pharmacies is extracted from the e-prescription system that is widely implemented in Spain.
The BIFAP database was characterized in the ADVANCE project and considered fit for purpose for vaccine coverage, benefits and risk assessment.[13] The BIFAP program also participated in several European projects financed by the EMA, the main objective of some of them is to contribute to the surveillance of vaccine safety against COVID-19: ACCESS ("VACcine Covid-19 tracking readinESS") and "Early-Covid-Vaccine-Monitoring".

8.4.6 FISABIO, VID database (ES)

The VID is a set of population-wide electronic databases covering residents of the Valencia region in Spain, representing approximately 5 million individuals. The information in the VID databases can be linked at the individual level through a single personal identification. The data sets in the VID are as follows:

[12] Martina Recalde, et al., Data Resource Profile: The Information System for Research in Primary Care (SIDIAP), International Journal of Epidemiology, Volume 51, Issue 6, December 2022, Pages e324–e336, https://doi.org/10.1093/ije/dyac068
[13] Miriam Sturkenboom, et al. ADVANCE database characterisation and fit for purpose assessment for multi-country studies on the coverage, benefits and risks of pertussis vaccinations, Vaccine, Volume 38, Supplement 2, 2020, https://doi.org/10.1016/j.vaccine.2020.01.100

The Population Information System (SIP) is a database that provides basic information on health system coverage (eg, dates and causes of Valencia health system entitlement or disentitlement, insurance modality, pharmaceutical co-payment status, assigned Healthcare Department) as well as some sociodemographic data (eg, sex, date of birth, nationality, employment status, geographic location). Importantly, the SIP database includes the date of death captured from the Mortality Registry. The SIP database is paramount to the VID, as it is the source of the individual, exclusive, and permanent identifier number associated with each individual (the SIP number), which is then used throughout the rest of the databases, thereby allowing data linkage across the multiple databases in the network.
The Ambulatory Medical Record (ABUCASIS) is the electronic medical record for primary and specialized outpatient activity, with 96% population coverage since 2009. ABUCASIS is integrated by two main modules: the Ambulatory Information System (SIA) and the Pharmaceutical Module (GAIA), including pediatric and adult primary care, mental health care, prenatal care, and specialist outpatient services, as well as providing information about dates, visits, procedures, laboratory test results, diagnoses, and clinical and lifestyle information. It also includes information on several health programs (e.g., healthy children, vaccines, pregnancy, notifiable diseases), the primary care nurse clinical record, and the health-related social assistance record. The SIA module uses the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) for coding diagnoses (and, partially, ICD-10-ES from 2019). The SIA also uses the Clinical Risk Groups system to stratify the morbidity of the entire population.
The GAIA Pharmaceutical module stores data on all outpatient pharmaceutical prescriptions and dispensing, including both primary care and outpatient hospital departments, using the Anatomical Therapeutic Chemical (ATC) classification system and the National Pharmaceutical Catalogue, which allow the identification of the exact content of each dispensing. GAIA does not include in-hospital medication or medication administered in the Accident and Emergency Department (AED). GAIA provides detailed information on prescriptions issued by physicians, such as the duration of treatment and dosage.
The Hospital Medical Record (ORION) provides comprehensive information covering all areas of specialized care, from admission, outpatient consultations, hospitalization, emergencies, diagnostic services (e.g., laboratory tests, imaging, microbiology, pathology), pharmacy, surgical block including day surgery, critical care, prevention and safety, social work, at-home hospitalization, and day hospitalization. ORION is currently in the process of being integrated for the whole region, with several databases already fully integrated and available for all hospitals, including the Minimum Basic Data Set at Hospital Discharge (MBDS) and the AED clinical record.
The MBDS is a synopsis of clinical and administrative information on all hospital admissions and major ambulatory surgery in the Valencia health system hospitals, including public-private partnership hospitals (approximately 450,000 admissions per year in the region). The MBDS includes admission and discharge dates, age, sex, geographic area and zone of residence, main diagnosis at discharge, up to 30 secondary diagnoses (comorbidities or complications), clinical procedures performed during the hospital episode, and the diagnosis-related group(s) assigned at discharge. The MBDS used the ICD-9-CM system for coding through December 2015 and ICD-10-ES afterwards. The MBDS was extended in 2015 to include the “present on admission” diagnosis marker and information on tumor morphology.
The AED clinical record was launched in 2008 and collects triage data, diagnoses, tests, and procedures performed in public emergency departments. As with the MBDS, the coding system used the ICD-9-CM until December 2015 and the ICD-10-ES thereafter. Diagnosis codification has increased from approximately 45% of all emergency department visits

between 2008 and 2014 up to approximately 75% in 2017, largely due to the progressive incorporation of hospital coding.
Data on vaccine exposure is obtained from the Vaccine Information System (VIS), which includes information on vaccine type, manufacturer, batch number, number of doses, location and administration date, adverse reactions related to vaccines, and if applicable, risk groups. Information in the VIS is updated daily. All databases included in the VID are updated frequently (every 1 to 3 months), except the MBDS database, which is updated every 6 months.

8.4.7 ARS Toscana Database (IT)

The Italian National Healthcare System is organized at the regional level: the national government sets standards of assistance and tax-based funding for each region, which regional governments are responsible for providing to all their inhabitants. Tuscany is an Italian region, with approximately 3.6 million inhabitants. The Agenzia Regionale di Sanità della Toscana (ARS Toscana) is a research institute of the Tuscany region. The ARS Toscana database comprises all information collected by the Tuscany region to account for the health care delivered to its inhabitants. Moreover, ARS Toscana collects data from regional initiatives. All data banks in the ARS Toscana data source can be linked at the individual level through a pseudo-anonymous identifier. Two data banks collect dispensing of reimbursed medicines from, respectively, community pharmacies and hospital pharmacies. In the latter data bank, dispensing for outpatient and ambulatory use are complete, and dispensing for inpatient use are partial. Other data banks include hospital discharges, emergency care admissions, records of exemptions from copayment, diagnostic tests and procedures, causes of death, the mental health services register, the birth register, the spontaneous abortion register, and the induced terminations register. A pathology register is available, mostly recorded in free text, but with morphology and topographic SNOMED codes. A COVID-19 registry including all positive cases with clinical follow up is also available. Mother-child linkage is possible through the birth register. Vaccination data are available for children since 2016 and for adults since 2019. All the data banks can be linked at the individual level through a pseudonymous identifier. Data banks are updated approximately every 2 months. Some of them are updated at the date of transmission (e.g., vaccines, COVID-19 registry, access to emergency room), others (e.g., medicines dispensing and hospital discharge records) have a delay of approximately 4 months.

8.4.8 Caserta LHU database (IT)

The Caserta database is a claims database containing patient-level data from the city of Caserta, in the Campania region. The coverage of this database is very high: from 2005-2020 the catchment area population in Caserta consists of more than 1 million persons (15% of the Campania regional population). The Caserta linkage databases consists of several databases which are linked through a unique patient identifier: a demographic registry, pharmacy claims database with information on concerning all dispensed drugs reimbursed by the Italian NHS, a as well as hospital discharge diagnose databases, emergency department admissions database, claims for diagnostic and laboratory tests ordered, and a registry of patients exempt from reasons for healthcare service co-payment exemptions (e.g. diabetes mellitus, dementia, and other chronic diseases), emergency department visit diagnoses and diagnostic tests. Patient level data from these claims databases, including other drugs reimbursed by the NHS and dispensed by community pharmacies, can be linked together, using a unique patient identifier. The healthcare information in the databases is coded using international coding systems, such as International Classification of Diseases, 9th Edition (ICD 9 CM) for

diagnoses and Anatomic Therapeutic and Chemical (ATC) classification for drugs. A COVID-19 registry including all positive cases with clinical follow up is also available.

8.4.9 PEDIANET (IT)

PEDIANET, a pediatric general practice research database, contains reason for accessing healthcare, health status (according to the Guidelines of Health Supervision of the American Academy of Pediatrics), demographic data, diagnosis and clinical details (free text or coded using the ICD-9 CM), prescriptions (pharmaceutical prescriptions identified by the ATC code), specialist appointments, diagnostic procedures, hospital admissions, growth parameters and outcome data of the children habitually seen by about 140 family pediatricians (FPs) distributed throughout Italy.
PEDIANET can link to other databases using unique patient identifiers. In the first database, information on routine childhood vaccination is captured including vaccine brand and dose. In the second database, information on patient hospitalization date, reason for hospitalization, days of hospitalizations and discharge diagnosis (up to six diagnosis) are captured. The FPs participation in the database is voluntary and patients and their parents provide consent for use of their data for research purposes. In Italy each child is assigned to a FP, who is the referral for any health visit or any drug prescription, thus the database contains a very detailed personal medical history. The data, generated during routine practice care using common software (JuniorBit®), are anonymized and sent monthly to a centralized database in Padua for validation. The PEDIANET database can be linked to regional vaccination data which was successfully tested in the ADVANCE project where it was characterized and deemed fit for purpose for pediatric routine vaccines.[14]

8.5 Data transformation

This study was conducted in a distributed manner using a common protocol, the ConcePTION common data model (CDM), and a common analytics program (Figure 2). The data pipeline has been developing from the EU-ADR project and was further improved in the IMI-ConcePTION project[15] and used in multiple EMA-tendered and VAC4EU studies. The ConcepPTION CDM has been described by Thurin et al, 2022.[16] The pipeline maximizes the involvement of the data providers in the study by utilizing their knowledge on the characteristics and the process underlying the data collection which makes analysis more efficient.

8.5.1 Data Extraction & ETL

Each database access provider (DAP) creates extraction, transform, and load (ETL) specifications using the standard ConcePTION ETL design template.[17] Version 2.2 of the ConcePTION CDM is used for this analysis. Following completion of this template and review with study statisticians and principal investigators, each DAP extracts the relevant study data locally using their software (eg, Stata, SAS, R, Oracle). This data is loaded into the CDM structure in csv format. These data remain local.

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[14] Miriam Sturkenboom, et al. ADVANCE database characterisation and fit for purpose assessment for multi-country studies on the coverage, benefits and risks of pertussis vaccinations, Vaccine, Volume 38, Supplement 2, 2020, https://doi.org/10.1016/j.vaccine.2020.01.100

[15] https://www.imiconception.eu/

[16] Thurin NH, Pajouheshnia R, Roberto G, et al. From inception to ConcePTION: genesis of a network to support better monitoring and communication of medication safety during pregnancy and breastfeeding. Clin Pharmacol Ther 2022;111(1):321–31. https://doi.org/10.1002/cpt.2476

[17] https://docs.google.com/document/d/1SWi31tnNJL7u5jJLbBHmoZa7AvfcVaqX7jiXgL9uAWg/edit

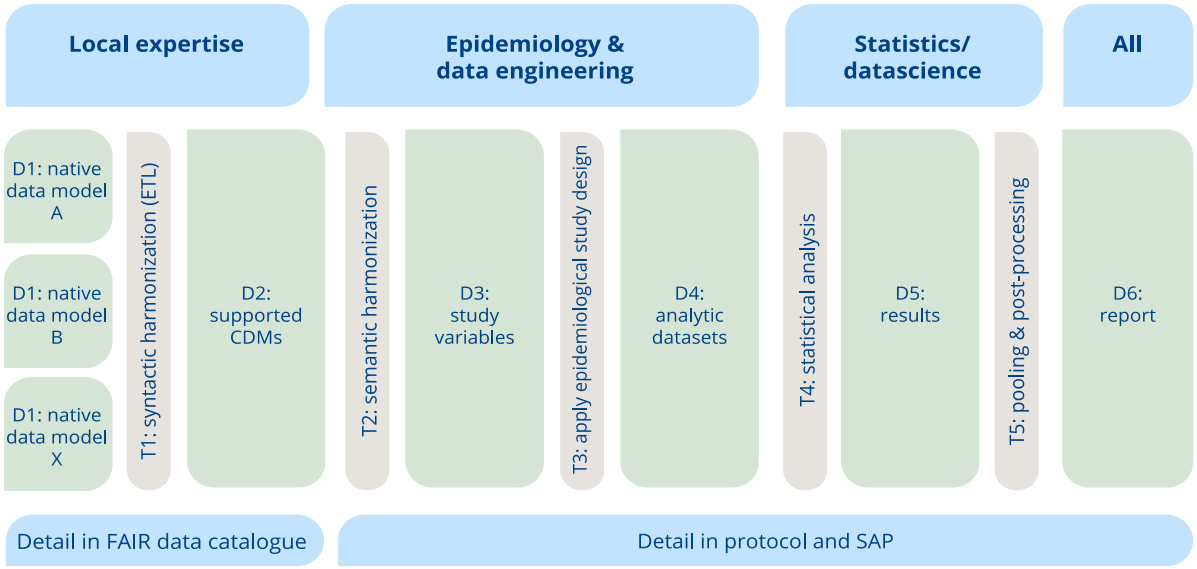


Figure 2: Analytics pipeline. D = Data set(s), T = Data transformation step(s)

8.5.2 Data transformation

Generic data analytics pipeline

The data analytics tools comprised a suite of open-source R-based scripts and functions that are hosted on the VAC4EU GitHub and are designed in the sequence provided in Figure 2. Briefly:

T1 = syntactic (structural) transformation of native data into the ConcePTION CDM tables and variables, this is done by the data access providers locally. The quality of T1 was verified using level 1 (completeness) and 2 (consistency) data quality checks during onboarding of data partners, and upon every refresh of their data (below in readiness phase). Scripts and instructions for level checks are available on Github.[18][19]

T2 = Transformation of data to study variables for the requested units of analysis by creation of the study population, time anchoring, completion/cleaning missing features in data (e.g., treatment duration, vaccine doses), ordering records in time for one subject, applying algorithms to define events, recoding. The key input for this step is definitions and rules for 'phenotypes', algorithms and code sets (e.g., ICD9/10, ICPC, Read, SNOMED) (See Annex 1). These rules are defined in a machine-readable metadata table, called the BRIDGE, which is defined by the epidemiologist and allows for communication with the programmers. For this study, the T2 step was programmed by ARS Toscana.
Data quality of study variables (D3) was benchmarked within (temporal trends) and between data-sources using level 3 checks for each study using level 3 checks.[20] Quality of data was assessed by UMC Utrecht with the DAPs.

T3= Application of the epidemiological study design (cohort, case control, self-controlled), such as sampling from the study population, matching, censoring. We will re-use and tailor existing packages if possible. The T3 step was programmed by University Utrecht and London School of Hygiene and inserted in the VAC4EU Github after T2.

[18] https://github.com/UMC-Utrecht-RWE/ConcePTION-Level1
[19] https://github.com/UMC-Utrecht-RWE/ConcePTION-Level2
[20] https://github.com/UMC-Utrecht-RWE/ConcePTION-Level3

T4= Statistical estimations: counting, rates, regression analyses, generalized models etc. This step was scripted by University Utrecht and included in the VAC4EU Github.

T5= Two-stage pooling of the results and the postprocessing to create overall tables and figures. T5 was conducted on the digital research environment. This was conducted by ARS Toscana (readiness), University Utrecht and UMC Utrecht (SCRI/SCSS/Cohort).

Ensuring quality of R-scripts

Quality control process was used in development of R-functions and study scripts, versioning was done through Git. [21] Before launching a new script, the script was tested on a simulated test dataset and on a real-world dataset.

8.5.3 Data Access

Within the DRE (see figure 3), each project-specific area consists of a separate secure folder called a "workspace." Each workspace is completely secure, and researchers were in full control of their data. Each workspace has its own list of users, which can be managed by its administrators. The DRE architecture allowed researchers to use a solution within the boundaries of data management rules and regulations. Although General Data Protection Regulation and Good (Clinical) Research Practice still apply to researchers, the DRE offers tools to more easily control and monitor which activities take place within projects. All researchers who need access to the DRE are granted access to study specific secure workspaces. Access to this workspace is only possible with double authentication using an identification code and password together with the user's mobile phone for authentication. Uploading files is possible for all researchers with access to the workspace within the DRE. The Download of files is only possible after requesting and receiving permission from a workspace member with an "owner" role.

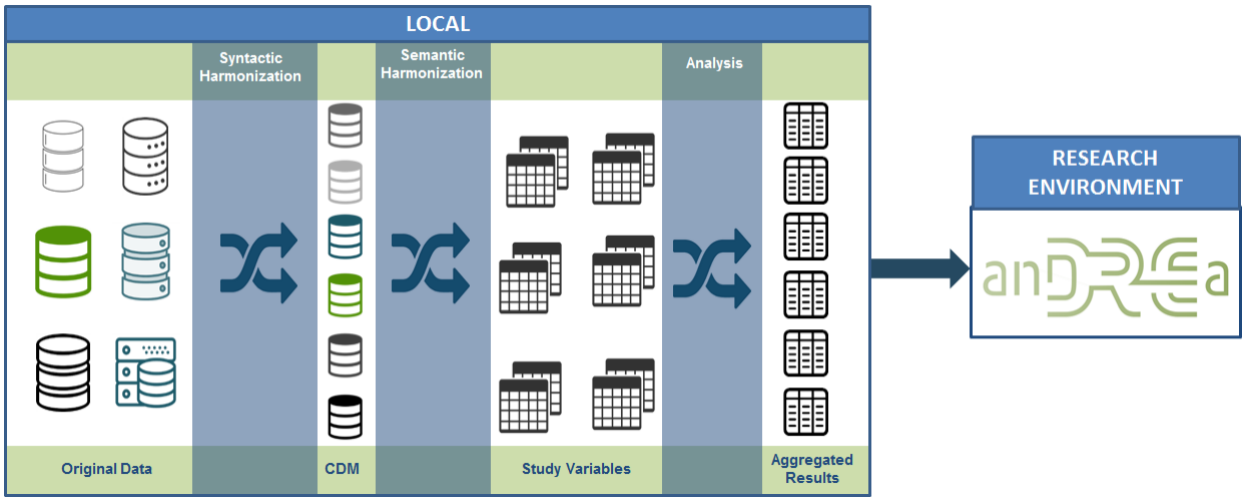


Figure 3: Data transformation and flow

Data Processing

Due to the nature of the study, a repeated data processing procedure was envisioned for readiness and for each novel study request, based on the pipeline described in the previous section. This allowed optimizing the data processing timelines and archiving procedures. The script for data processing was documented and edited on VAC4EU GitHub.

[21] https://github.com/VAC4EU/CVM

The output datasets produced by these scripts were uploaded to the Digital Research Environment (DRE) for pooled analysis of incidence and visualization. The DRE is made available through UMCU/VAC4EU (https://www.andrea-consortium.org/).
The DRE is a cloud-based, globally available research environment where data is stored and organized securely and where researchers can collaborate (https://www.andrea-consortium.org/azure-dre/).
All final statistical computations were performed on the DRE using R/SAS or Stata. Data access providers had access to the project workspace for verification of the results.

Record Retention

DAPs are responsible locally to archive each data source instance that is used for the study. The meta-data table in the CDM allows for storing details on the data source instance. The DAP has the obligation to archive the data source instances, the ETL scripts, the R-scripts that were used, and the results that were uploaded to the DRE, locally.
Aggregated results from DAPs will be stored in the DRE for inspection by the study sponsor for at least five years.
Documents that individually and collectively permit evaluation of the conduct of a study and the quality of the data produced will be retained for a period of 5 years in accordance with Good Pharmacoepidemiology Practices (GPP) guidelines. Study records or documents may also include the analyses files, syntaxes (usually stored at the site of the database), ETL specifications, and output of data quality checks.
All materials from the DRE will be retained for at least 15 years on a UMCU secure drive. The final study protocol and possible amendments, the final statistical report, statistical programs and output files will be archived on the UMCU secure drive according to Julius Clinical standard operating procedures.

8.6 Statistical methods

Detailed methodology for summary and statistical analyses of collected data are documented in the SAP; both, the SAP and the common analysis script used in this study are publicly available in Zenodo[22,23]. All analyses are conducted using R version R-4.0.3 or higher (Foundation for Statistical Computing, Vienna, Austria[24]) or SAS version 9.3 software or higher (Cary, North Carolina, USA; SAS Institute, Inc.).

8.7 Quality control

Data transformation into the CDM was conducted by each data access provider in its associated database, with processes as described in this report and the protocol (EUPAS42467). Standard operating procedures or internal process guidance at each research center are used to guide the conduct of the study. These procedures include rules for secure and confidential data storage, backup, and recovery, methods to maintain and archive project documents, quality check procedures for programming, standards for writing analysis plans, and requirements for scientific review by senior staff.

[22] Sturkenboom M, Perez-Gutthan S, Durán CE, Schultze A, Bots S, Belitser S, Garcia-Albeniz X, Martin I, Klungel O. (2023). Covid-19 Vaccine Monitoring project (CVM) - Statistical analysis plan for EHR data sources (1.2). Zenodo. https://doi.org/10.5281/zenodo.8244051
[23] Messina D, Paoletti O, Belitser S, Gini R, Limoncella G, Schultze A. (2023). VAC4EU/CVM: Readiness v3.3.1 (v3.3.1). Zenodo. https://doi.org/10.5281/zenodo.8272058
[24] https://www.R-project.org

9 Results

9.1 Readiness (Objective 1)

During the readiness phase, all Data Access Providers (DAP) requested approvals to participate in the studies specified in the CVM readiness and rapid assessment protocol (including all potential AESI). The *Extraction, Transformation, and Load* (ETL) design document was updated based on required data. Required data was ETL'ed into the ConcePTION CDM. To assess the quality of the data, level 1-3 quality checks were conducted. These quality checks were reported in the interim report and comprise assessment of completeness, correctness, plausibility of the data, and accuracy. They were conducted for each data instance, and some data sources conducted these multiple times when data was refreshed (e.g. for updated rapid assessments for myocarditis).
Nine data sources from Italy (ARS, Pedianet, Caserta), Spain (BIFAP, VID, SIDIAP), Netherlands (PHARMO), UK (CPRD) and Norway (National Registers) completed this phase. The regional database from Lazio (Italy) could not participate because of administrative issues and data access rules.

9.1.1 Descriptive and demographic information of the populations

The study population of subjects registered in the data sources after 1/1/2019 with complete data on date of birth and gender and at least one year of valid data which was required for the readiness phase comprised 52,306,672 subjects (BIFAP HOSP was not counted to avoid double counting). During the project DAPs created multiple data instances and converted them into the ConcePTION CDM. Table 4 provides the recommended end date for the last data instance that was used for the readiness phase. This was the end of 2021, for most data sources during this project, but others had data in 2022. This date may be before the extraction date if the DAP suspects knows that not all databanks would be complete (lag times may differ).

Table 4. Attrition for readiness phase per DAP.

	ARS-IT	PEDIANET-IT	Caserta-IT	PHARMO-NL	CPRD-UK	UOSL-NO	BIFAP_PC-ES	BIFAP_PC/HOSP-ES	FISABIO-ES	SIDIAP-ES
Recommended end date of last data instance	31/12/2021	31/12/2021	11/02/2022	30/06/2022	21/03/2022	31/12/2021	30/04/2022	30/04/22	31/12/2021	30/06/2022
Persons in the instance	4,090,784	51,078	951,463	2,660,157	17,666,696	5,664,825	16,244,090	16,244,090	5,371,422	7,203,481
Sex or birth date missing or absurd, or no dates of entry or exit	94			464	855		62	5,007,210	24,979	
Exit from data source before 1/1/2019	257,699		1,010	<5		66,538	2,706,016	842,032	175,745	756,977
Less than 365 days history at any point in time after 01/01/2019	105,604	201	<5	41,017	1,874,789		520,254	392,229	99,896	168,657
Less than 365 days before first COVID-19 vaccine	23,098	<5		12,870	558,946	<5	104,845	71,861	19,758	57,675
Final study population	3,704,289	50,876	950,452	2,605,325	15,214,165	5,598,285	12,912,064	9,930,652	5,051,044	6,220,172

9.1.2 Covariates at baseline

Table 5. Demographic characteristics at start of follow-up.

Characteristics	IT-ARS	IT-CASERTA	IT-PEDIANET	ES-BIFAP-PC	ES-BIFAP-PC-HOSP	ES-FISABIO	ES-SIDIAP	UK-CPRD	NL-PHARMO	NK-UOSL
Study population	3,704,289 (100%)	950,452 (100%)	50,876 (100%)	12,912,064 (100%)	9,930,652 (100%)	5,051,044 (100%)	6,220,172 (100%)	15,214,165 (100%)	2,605,325 (100%)	5,598,285 (100%)
follow-up (years)	13,917,091	3,650,330	161,019	49,511,556	37,081,164	19,474,172 (PY)	26,275,256	53,640,800	10,569,082	21,711,608
Age in years						.	.	.	.	
Minimum	0	0	0.0	0	0	0	0	0	0	0
25%	27	23	0	24	24	23	23	19	21	19
Median	48	41	4.0	42	43	43	41	36	41	38
Mean	46	41	4.3	42	42	42	41	37	41	38
75%	65	57	8	59	59	59	58	55	59	57
Maximum	118	119	12.0	113	113	113	118	114	121	112
Age in categories	.	.	.	.	.	.	.	.	.	
0-4	201,927 (5.5%)	39,998 (4.2%)	27,450 (54%)	770,696 (6.0%)	562,571 (5.7%)	320,805 (6.4%)	405,800 (6.5%)	1,292,137 (8.5%)	181,536 (7.0%)	456,480 (8.2%)
5-11	226,058 (6.1%)	66,478 (7.0%)	22,554 (44%)	921,387 (7.1%)	694,104 (7.0%)	368,161 (7.3%)	445,824 (7.2%)	1,280,448 (8.4%)	189,886 (7.3%)	458,366 (8.2%)
12-17	193,003 (5.2%)	63,443 (6.7%)	872 (1.7%)	757,538 (5.9%)	572,563 (5.8%)	312,329 (6.2%)	373,364 (6.0%)	958,875 (6.3%)	175,098 (6.7%)	384,740 (6.9%)
18-24	222,185 (6.0%)	80,599 (8.5%)	0 (0%)	862,924 (6.7%)	655,273 (6.6%)	330,498 (6.5%)	435,260 (7.0%)	1,475,981 (9.7%)	219,550 (8.4%)	494,918 (8.8%)
25-29	170,463 (4.6%)	62,796 (6.6%)	0 (0%)	720,414 (5.6%)	555,579 (5.6%)	255,748 (5.1%)	365,983 (5.9%)	1,187,315 (7.8%)	168,763 (6.5%)	394,103 (7.0%)
30-39	394,263 (11%)	135,776 (14%)	0 (0%)	1,814,335 (14%)	1,404,532 (14%)	657,604 (13%)	880,824 (14%)	2,279,386 (15%)	319,128 (12%)	745,458 (13%)
40-49	555,566 (15%)	154,652 (16%)	0 (0%)	2,160,003 (17%)	1,674,567 (17%)	833,148 (16%)	1,037,392 (17%)	1,917,555 (13%)	333,411 (13%)	741,734 (13%)
50-59	569,259 (15%)	144,017 (15%)	0 (0%)	1,810,575 (14%)	1,406,808 (14%)	727,660 (14%)	826,288 (13%)	1,852,071 (12%)	368,575 (14%)	696,871 (12%)
60-69	455,189 (12%)	101,884 (11%)	0 (0%)	1,319,636 (10%)	1,027,964 (10%)	557,076 (11%)	625,682 (10%)	1,340,106 (8.8%)	311,588 (12%)	578,519 (10%)
70-79	405,475 (11%)	67,884 (7.1%)	0 (0%)	975,096 (7.6%)	757,269 (7.6%)	412,742 (8.2%)	464,930 (7.5%)	1,013,958 (6.7%)	226,211 (8.7%)	420,775 (7.5%)
80+	310,901 (8.4%)	32,925 (3.5%)	0 (0%)	799,460 (6.2%)	619,422 (6.2%)	275,273 (5.4%)	358,825 (5.8%)	616,333 (4.1%)	111,579 (4.3%)	226,321 (4.0%)
Persons	.	.	.	.	.	.	.	.	.	.
Female	1,920,775 (52%)	485,910 (51%)	24,625 (48%)	6,660,688 (52%)	5,155,006 (52%)	2,569,650 (51%)	3,142,609 (51%)	7,604,939 (50%)	1,316,668 (51%)	2,772,771 (50%)
Immunodeficiency	13671 (0.4%)	896 (<0.1%)	41 (<0.1%)	13976 (0.1%)	18938 (0.2%)	27,436 (0.5%)	699 (<0.1%)	7888 (<0.1%)	11372 (0.4%)	70130 (1.3%)
Pregnant	17,506 (0.9%)	3,807 (0.8%)	NA	NA	NA	28,905 (1.1%)	40,760 (1.3%)	NA	NA	48,172 (1.7%)
History of Covid	223 (<0.1%)	.	.	42,506 (0.3%)	42,516 (0.4%)	1,294 (<0.1%)	9,313 (0.1%)	29,056 (0.2%)	4,088 (0.2%)	59 (<0.1%)
Cancer	50,526 (1.4%)	7,842 (0.8%)	8 (<0.1%)	70,405 (0.5%)	95,513 (1.0%)	58,889 (1.2%)	50,811 (0.8%)	68,503 (0.5%)	32,961 (1.3%)	161,179 (2.9%)
CVD	1,045,971 (28%)	238,857 (25%)	117 (0.2%)	2,619,086 (20%)	1,965,333 (20%)	1,241,627 (25%)	1,286,065 (21%)	2,446,443 (16%)	565,024 (22%)	1,154,643 (21%)
Diabetes 1 or 2	207,824 (5.6%)	51,586 (5.4%)	20 (<0.1%)	665,139 (5.2%)	505,827 (5.1%)	369,199 (7.3%)	365,060 (5.9%)	691,432 (4.5%)	111,335 (4.3%)	233,856 (4.2%)
CKD	1,962 (<0.1%)	174 (<0.1%)	0 (0%)	6,854 (<0.1%)	39,944 (0.4%)	12,283 (0.2%)	2,644 (<0.1%)	2,250 (<0.1%)	0 (0%)	28,367 (0.5%)
Liver chronic disease	1,338 (<0.1%)	578 (<0.1%)	0 (0%)	1,289 (<0.1%)	21,080 (0.2%)	13,616 (0.3%)	32,840 (0.5%)	27,769 (0.2%)	203 (<0.1%)	10,257 (0.2%)
Allergy	10,497 (0.3%)	396 (<0.1%)	34 (<0.1%)	19,956 (0.2%)	20,393 (0.2%)	34,138 (0.7%)	17,026 (0.3%)	38,204 (0.3%)	7,718 (0.3%)	31,653 (0.6%)
Anaphylaxis	8,548 (0.2%)	58 (<0.1%)	32 (<0.1%)	15,183 (0.1%)	12,480 (0.1%)	10,450 (0.2%)	11,520 (0.2%)	2,115 (<0.1%)	7,718 (0.3%)	29,212 (0.5%)
Down syndrome	218 (<0.1%)	86 (<0.1%)	.	0 (0%)	512 (<0.1%)	1,679 (<0.1%)	437 (<0.1%)	0 (0%)	0 (0%)	2,044 (<0.1%)
HIV	9,068 (0.2%)	89 (<0.1%)	0 (0%)	282 (<0.1%)	2,021 (<0.1%)	12,016 (0.2%)	0 (0%)	4,214 (<0.1%)	2,542 (<0.1%)	6,558 (0.1%)
Hypersensitivity	1,955 (<0.1%)	338 (<0.1%)	.	4,783 (<0.1%)	7,932 (<0.1%)	23,756 (0.5%)	5,520 (<0.1%)	36,100 (0.2%)	0 (0%)	2,463 (<0.1%)
Mental health	388,005 (10%)	50,796 (5.3%)	28 (<0.1%)	1,045,015 (8.1%)	793,506 (8.0%)	549,880 (11%)	602,763 (9.7%)	467,098 (3.1%)	180,014 (6.9%)	516,670 (9.2%)
Obesity	223 (<0.1%)	39 (<0.1%)	0 (0%)	61 (<0.1%)	32,854 (0.3%)	215 (<0.1%)	208 (<0.1%)	30 (<0.1%)	5,701 (0.2%)	66,742 (1.2%)
Previous VTE	192,930 (5.2%)	29,814 (3.1%)	.	135,765 (1.1%)	111,672 (1.1%)	139,685 (2.8%)	83,311 (1.3%)	29,217 (0.2%)	23,759 (0.9%)	75,023 (1.3%)
Chronic resiratory disease	362,522 (9.8%)	135,678 (14%)	6,610 (13%)	836,959 (6.5%)	640,623 (6.5%)	732,165 (14%)	600,202 (9.6%)	1,192,004 (7.8%)	219,771 (8.4%)	484,823 (8.7%)
Sicke cell disease	3,603 (<0.1%)	631 (<0.1%)	11 (<0.1%)	8,476 (<0.1%)	8,663 (<0.1%)	9,249 (0.2%)	6,181 (<0.1%)	9,820 (<0.1%)	721 (<0.1%)	2,356 (<0.1%)
Antibiotics	521,018 (14%)	171,616 (18%)	4,467 (8.8%)	487,668 (3.8%)	344,343 (3.5%)	575,429 (11%)	450,027 (7.2%)	0 (0%)	157,708 (6.1%)	344,986 (6.2%)
Antithrombotics	411,460 (11%)	72,230 (7.6%)	8 (<0.1%)	723,995 (5.6%)	529,141 (5.3%)	368,298 (7.3%)	407,396 (6.5%)	560,055 (3.7%)	207,307 (8.0%)	427,837 (7.6%)
Antivirals	19,076 (0.5%)	2,258 (0.2%)	45 (<0.1%)	13,199 (0.1%)	10,786 (0.1%)	23,228 (0.5%)	10,671 (0.2%)	1,013 (<0.1%)	6,139 (0.2%)	24,288 (0.4%)
Lipid lowering drugs	329,013 (8.9%)	83,539 (8.8%)	0 (0%)	1,258,759 (9.7%)	909,147 (9.2%)	644,984 (13%)	563,724 (9.1%)	0 (0%)	255,114 (9.8%)	465,489 (8.3%)
Sexual hormones	22,041 (0.6%)	4,751 (0.5%)	10 (<0.1%)	147,529 (1.1%)	101,258 (1.0%)	75,426 (1.5%)	78,065 (1.3%)	0 (0%)	122,528 (4.7%)	375,204 (6.7%)
Immunosuppressants	208,598 (5.6%)	42,275 (4.4%)	965 (1.9%)	171,405 (1.3%)	122,837 (1.2%)	142,942 (2.8%)	137,592 (2.2%)	73,361 (0.5%)	59,225 (2.3%)	132,527 (2.4%)

Other Vaccines	10,563 (0.3%)	0 (0%)	154 (0.3%)	0 (0%)	0 (0%)	0 (0%)	730,187 (12%)	0 (0%)	0 (0%)	662,891 (12%)

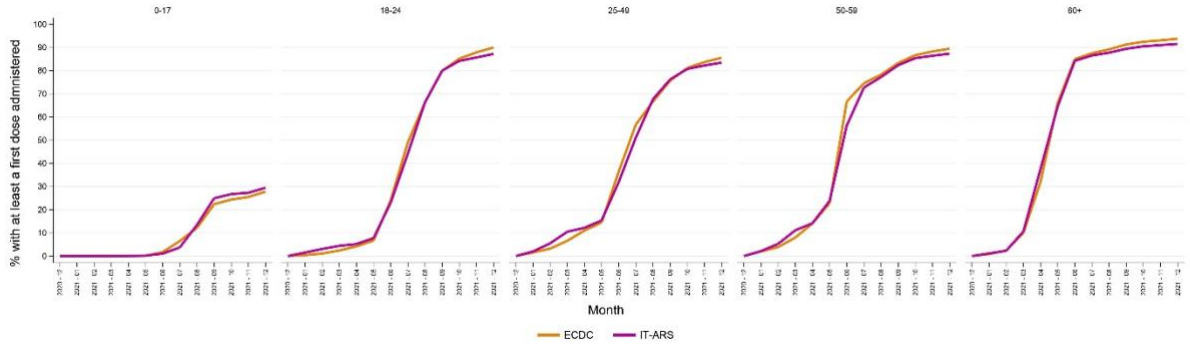
Table 5 shows that the ARS population is oldest with a relatively high percentage of persons above 80 (8.4%). The youngest population is Pedianet, which only comprises children till age 14, since this is a family pediatricians data source. Median age of other data sources was very similar. The majority of participants is female, except in Pedianet (48%). Median age of other data sources was very similar.
Table 5 shows the co-variates at baseline for co-morbidities that increase the risk of severe Covid-19 and for history of medicines that are measured in 90 days prior. The most frequent co-morbidity is cardio-cerebrovascular disease with highest prevalence in ARS (28%) followed by Caserta and FISABIO. The prevalence of some of the medicines (e.g. sex hormones) varied which may be due to reimbursement by the health system. Prevalence rates of some conditions were zero or very low, which means that DAPs did not extract these data, these cells have been indicated with NA.

9.1.3 Vaccine coverage

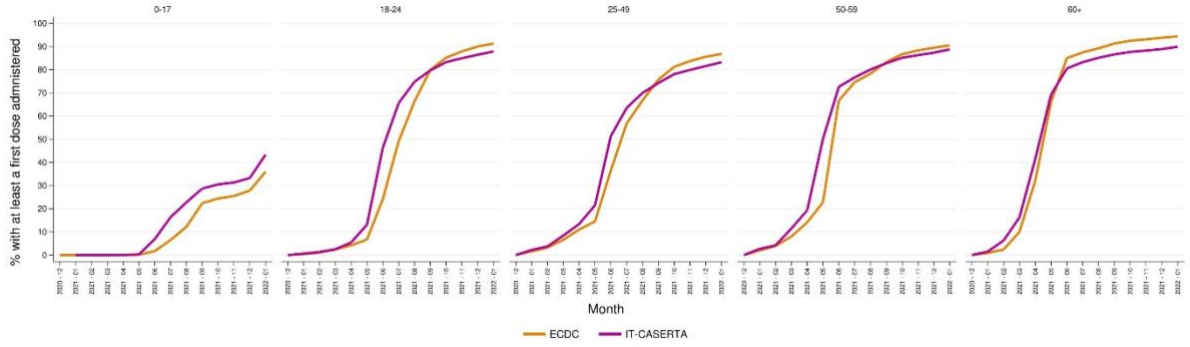
Vaccination data for COVID-19 vaccines was obtained from various types of data. Exposure to COVID-19 vaccines was based on available recorded prescription, dispensing, or administration of the COVID-19 vaccines. The main exposure of interest for the rapid assessment studies was the receipt of COVID-19 vaccine(s).

- ARS Toscana (IT): ARS identified vaccines from the regional immunization register using the national product code, including batch number.
- Pedianet (IT): Information on COVID-19 vaccine was obtained from the regional immunization register and included the date of immunization, type of vaccine, vaccine batches, dose.
- Caserta LHU database (IT): Caserta LHU record linkage database contains information from all claims databases (e.g. hospitalizations, drug dispensing, etc.) of Caserta province catchment area (around 1 million population). Those claims data could be linked to the local immunization registry which includes name and batch of the vaccine; manufacturing company; dose; administration route; administration location (eg, general practice); date of administration.
- PHARMO (NL): Data on vaccination were obtained from PHARMO's GP database. Information on vaccines include ATC code, brand, and date of administration/recording. Several COVID-19 vaccines have been administered through other routes and information was provided to GP with different lag times.
- CPRD (UK): The CPRD contains information recorded by National Health Service (NHS) primary care general practitioners (GPs); and information on the administration of COVID-19 vaccines to individuals is available. This includes, alongside an encrypted unique patient identifier; the name of the vaccine; manufacturing company; dose; and date
- Norwegian health registers (NO): The national, electronic immunization register (SYSVAK) was used. In SYSVAK, the following data are registered: individual personal identifier, vaccine name and Anatomical Therapeutic Chemical (ATC) code, vaccine batch number, date of vaccination, reason for vaccination as health care professional versus risk-group patient, and the center where the vaccine was administered.
- SIDIAP (ES): SIDIAP has available information on the administration of COVID-19 vaccines to individuals linked to a unique and anonymous identifier. The information originated from electronic medical records. For each patient, SIDIAP had date and center of administration, dose, brand, reasons for vaccination (eg, risk group), and other information related to vaccination.
- BIFAP (ES): BIFAP (Base de Datos para la Investigación Farmacoepidemiológica en Atencion Primaria), a computerized database of medical records of primary care (www.bifap.aemps.es) is a non-profit research project funded by the Spanish Agency for Medicines and Medical Devices (AEMPS). Data on vaccination with COVID-19 vaccines were obtained from the COVID-19 vaccination registries in the participating regions and linked to the primary care medical records in BIFAP. Date of vaccination, brand, batch, and dose are registered.
- FISABIO (ES): Data on vaccine exposure were obtained from the Vaccine Information System (VIS), which includes information on vaccine type, manufacturer, batch number, number of doses, location and administration date.

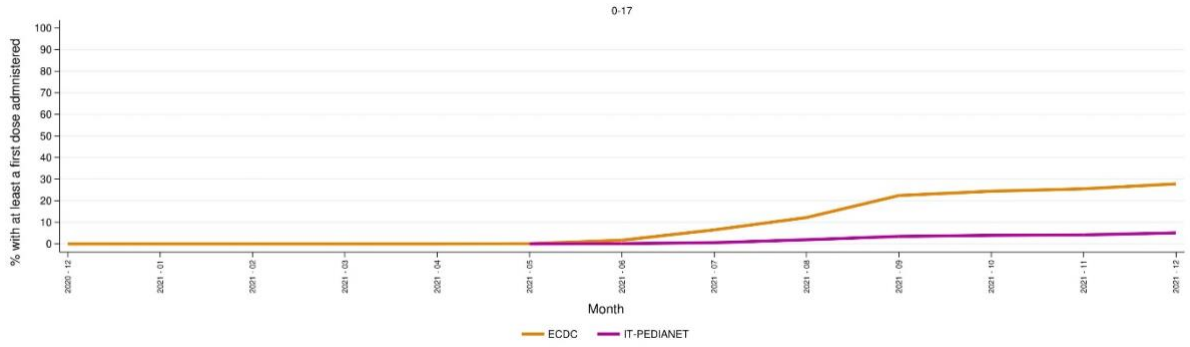
Coverage for first dose of COVID-19 vaccine in the population was compared with the coverage rates at the ECDC COVID-19 vaccine tracker.



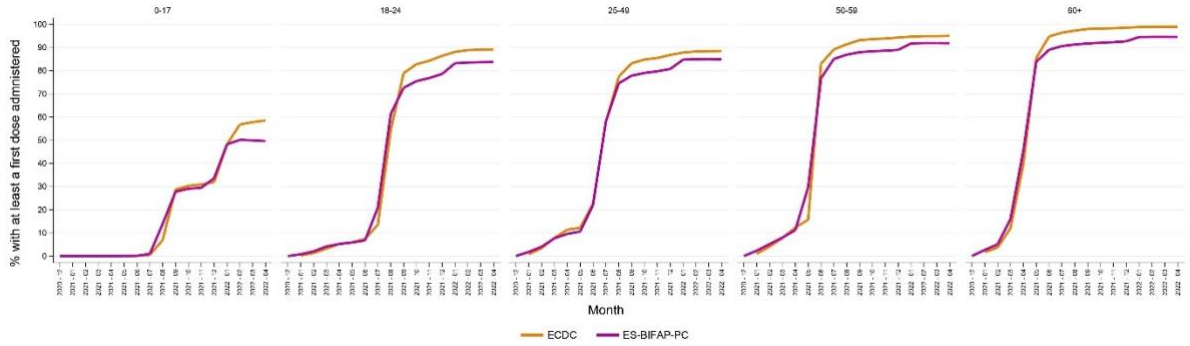
CVM vaccine coverage in **IT-ARS** versus ECDC data, stratified by age.



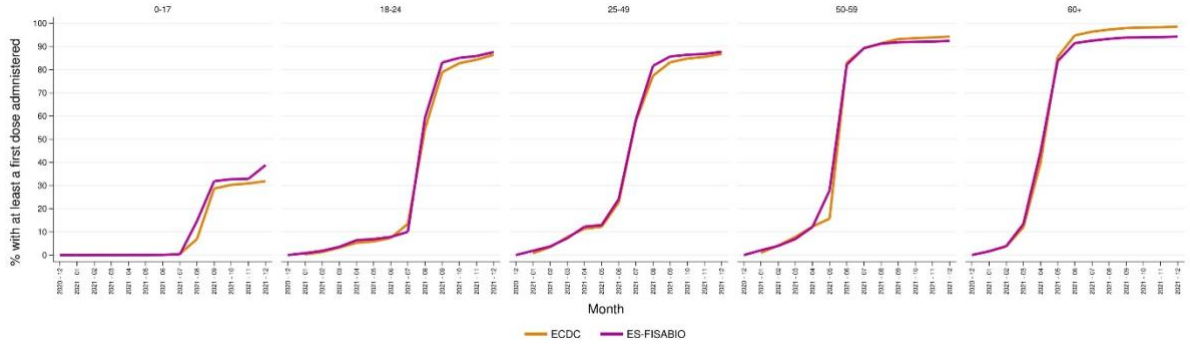
CVM vaccine coverage in **IT-Caserta** *versus* ECDC data, stratified by age



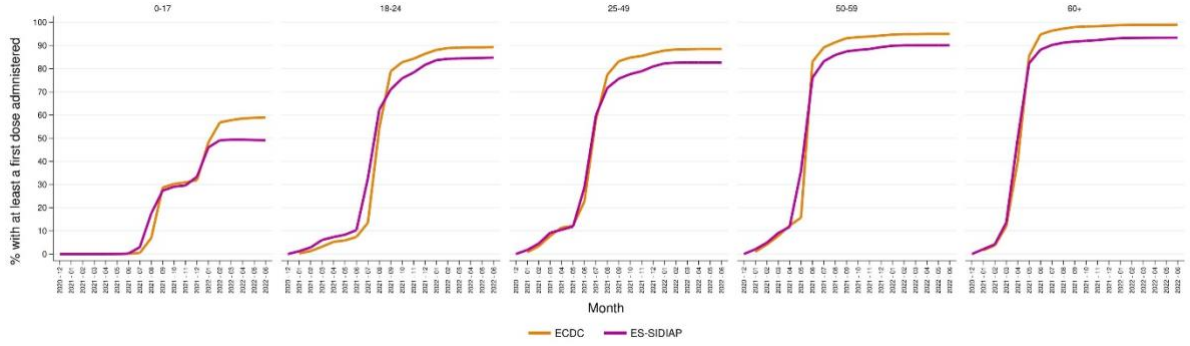
CVM vaccine coverage in **IT-PEDIANET** versus ECDC data, stratified by age.



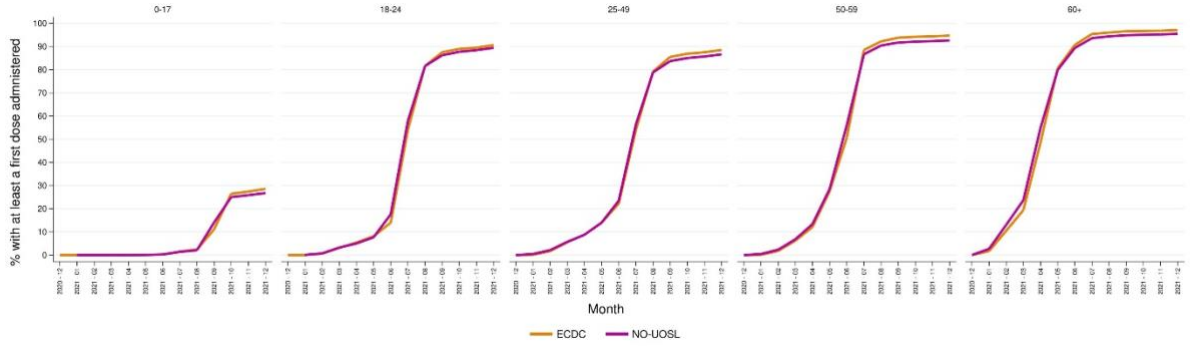
CVM vaccine coverage in **ES-BIFAP-PC** *versus* ECDC data, stratified by age.



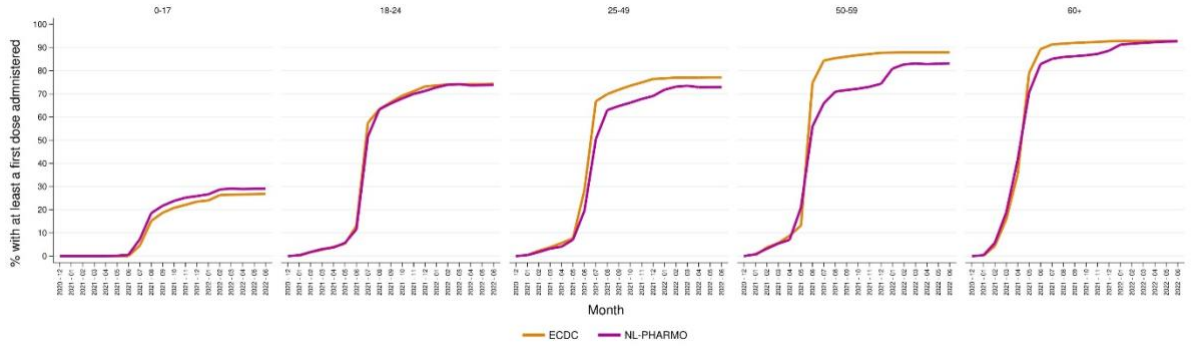
CVM vaccine coverage in **ES-FISABIO** *versus* ECDC data, stratified by age.



CVM vaccine coverage in **ES-SIDIAP** *versus* ECDC data, stratified by age.



CVM vaccine coverage in **NO-UOSL** *versus* ECDC data, stratified by age.



CVM vaccine coverage in **NL-PHARMO** *versus* ECDC data, stratified by age.

Figure 4: Benchmarking of CVM COVID-19 vaccine coverage rates versus ECDC data for age groups 0-17, 18-2425-49, 50-59, 60+

Figure 4 is showing the coverage of first COVID-19 vaccination in each data source compared to the data from the COVID-19 vaccine tracker based on all country data, by month and age group. For ARS we see perfect overlap both in time and height of the curve, for each of the age groups. For CASERTA we show that uptake/administration was earlier than at national level in Italy, and in the eldest group, remains slightly lower than the national level of uptake, this could be a regional difference compared to national difference. In Pedianet recorded vaccinations were lower than the national data for the youngest age group. This is due to ECDC grouping 0-17 all together in the Italian data, while the population in Pedianet only covers until 14 years of age, and vaccine was not administered to younger age bands during the study period.
The BIFAP-PC data source comprises data from multiple regions in Spain, but not all. As compared to the national data, submitted to ECDC, we observe that the identified Covid-19 vaccine dates are well aligned with the national data, but that the overall coverage is slightly lower in all age groups, in the regions that can also link to the hospital data, this pattern is not observed and the timing and level is very comparable to national coverage data as recorded in ECDC tracker. In FISABIO (region Valencia) that timing and level of COVID-19 vaccine uptake is almost identical to the national data except for the oldest age group. In SIDIAP the pattern of timing overlaps with national data and the level is slightly lower than national data. In Norway data are national and identical (probably both the SYSVAK source). In PHARMO uptake in children and young adults was recorded as in national data submitted to ECDC, and there is no delay in the first months, whereas there is a delay in recording this in the data sources in later month, as the same uptake is reached but later. Important to note is that the data submitted to ECDC do not reflect the complete picture of vaccination, since not all subjects gave approval to have their data recorded in the vaccination register.

9.1.4 Descriptions of vaccination cohorts per DAP

Recommended end date of last data instance is (see Table 4):

- 31 December 2021 for ARS-IT, PEDIANET-IT, UOSL-NO, and FISABIO-ES
- 11 February 2022 for CASERTA-IT
- 21 March 2022 for CPRD-UK
- 30 April 2022 for BIFAP-ES
- 30 June 2022 for PHARMO-NL and SIDIAP-ES

Table 6. Characteristics of the vaccinated cohorts at first dose (ARS)

Characteristic	IT-ARS	at first pfizer	at first astrazeneca	at first moderna	at first janssen	nova vax	unknown
Study population	3,704,289 (100%)	1,923,403 (70%)	335,936 (12%)	432,600 (16%)	74,964 (2.7%)	0 (0%)	0 (0%)
follow-up (years)	13,917,091 (PY)	1,075,902 (PY)	246,547 (PY)	205,128 (PY)	42,204 (PY)		
Age in years							
Minimum	0	1	10	3	12		
25%	27	35	56	28	60		
Median	48	52	69	43	63		
Mean	46	52	63	42	65		
75%	65	69	74	57	69		
Maximum	118	108	91	103	102		
Age in categories							
0-4	201,927 (5.5%)	7 (<0.1%)	0 (0%)	.	0 (0%)		
5-11	226,058 (6.1%)	16,615 (0.9%)	.	21 (<0.1%)	0 (0%)		
12-17	193,003 (5.2%)	118,173 (6.1%)	.	35,893 (8.3%)	9 (<0.1%)		
18-24	222,185 (6.0%)	133,829 (7.0%)	2,040 (0.6%)	52,990 (12%)	92 (0.1%)		
25-29	170,463 (4.6%)	93,178 (4.8%)	5,882 (1.8%)	27,688 (6.4%)	117 (0.2%)		
30-39	394,263 (11%)	199,662 (10%)	16,398 (4.9%)	69,834 (16%)	291 (0.4%)		
40-49	555,566 (15%)	287,711 (15%)	35,435 (11%)	97,743 (23%)	609 (0.8%)		
50-59	569,259 (15%)	374,161 (19%)	36,642 (11%)	78,132 (18%)	7,706 (10%)		
60-69	455,189 (12%)	238,829 (12%)	80,450 (24%)	41,187 (9.5%)	47,886 (64%)		
70-79	405,475 (11%)	164,700 (8.6%)	158,970 (47%)	26,910 (6.2%)	17,984 (24%)		
80+	310,901 (8.4%)	296,538 (15%)	117 (<0.1%)	2,199 (0.5%)	270 (0.4%)		
Persons							
Female	1,920,775 (52%)	1,013,097 (53%)	186,166 (55%)	208,353 (48%)	38,321 (51%)		
Male	1,783,514 (48%)	910,306 (47%)	149,770 (45%)	224,247 (52%)	36,643 (49%)		
Immune deficiency	13671 (0.4%)	6988 (0.4%)	596 (0.2%)	2708 (0.6%)	169 (0.2%)		
Pregnant	17,506 (0.9%)	119 (<0.1%)	42 (<0.1%)	20 (<0.1%)	0 (0%)		
Previous episodes of Covid-19	0 (0%)	127,564 (6.6%)	7,040 (2.1%)	34,070 (7.9%)	6,085 (8.1%)		
Cancer	59,165 (1.6%)	35,563 (1.8%)	4,273 (1.3%)	13,358 (3.1%)	813 (1.1%)		
Cardio-cerebrovascular disease	1,045,971 (28%)	680,055 (35%)	166,760 (50%)	92,897 (21%)	37,720 (50%)		
Diabetes 1 or 2	207,824 (5.6%)	146,935 (7.6%)	18,946 (5.6%)	23,436 (5.4%)	4,741 (6.3%)		
Kidney chronic disease	5,821 (0.2%)	3,057 (0.2%)	213 (<0.1%)	1,290 (0.3%)	60 (<0.1%)		
Liver chronic disease	1,338 (<0.1%)	708 (<0.1%)	25 (<0.1%)	208 (<0.1%)	20 (<0.1%)		
Allergy	10,497 (0.3%)	6,695 (0.3%)	838 (0.2%)	1,474 (0.3%)	230 (0.3%)		
Anaphylaxis	8,548 (0.2%)	5,589 (0.3%)	763 (0.2%)	1,182 (0.3%)	209 (0.3%)		
Down syndrome	218 (<0.1%)	61 (<0.1%)	.	12 (<0.1%)	0 (0%)		
HIV	9,068 (0.2%)	5,239 (0.3%)	373 (0.1%)	2,178 (0.5%)	112 (0.1%)		
Hypersensitivity	1,955 (<0.1%)	1,108 (<0.1%)	75 (<0.1%)	293 (<0.1%)	21 (<0.1%)		
Mental health	388,005 (10%)	257,859 (13%)	46,834 (14%)	38,479 (8.9%)	10,281 (14%)		
Obesity	223 (<0.1%)	72 (<0.1%)	8 (<0.1%)	13 (<0.1%)	.		
Previous VTE	192,930 (5.2%)	123,363 (6.4%)	18,086 (5.4%)	23,168 (5.4%)	5,431 (7.2%)		
Chronic resiratory disease	362,522 (9.8%)	139,886 (7.3%)	23,725 (7.1%)	25,664 (5.9%)	4,973 (6.6%)		
Sicke cell disease	3,603 (<0.1%)	2,605 (0.1%)	186 (<0.1%)	627 (0.1%)	30 (<0.1%)		
Antibiotics	521,018 (14%)	184,127 (9.6%)	30,564 (9.1%)	37,327 (8.6%)	7,341 (9.8%)		
Antithrombotics	411,460 (11%)	303,289 (16%)	53,223 (16%)	35,165 (8.1%)	10,106 (13%)		
Antivirals	19,076 (0.5%)	10,640 (0.6%)	1,347 (0.4%)	3,706 (0.9%)	354 (0.5%)		
Lipid lowering drugs	329,013 (8.9%)	238,562 (12%)	62,229 (19%)	33,505 (7.7%)	12,672 (17%)		
Sexual hormones	22,041 (0.6%)	14,035 (0.7%)	2,159 (0.6%)	3,701 (0.9%)	392 (0.5%)		
Immunosuppressants	208,598 (5.6%)	101,695 (5.3%)	15,784 (4.7%)	25,613 (5.9%)	3,711 (5.0%)		
Vaccines	10,563 (0.3%)	68,000 (3.5%)	8,523 (2.5%)	10,138 (2.3%)	518 (0.7%)		

In ARS (Data until 31-12-2021, Table 6), 70% of the vaccinated persons received Pfizer vaccine, among them 15% was above 80 years of age and 7% children/adolescents.

AstraZeneca vaccine was 12% of the vaccinated population and they were mostly between 30 and 79 years of age with 47% of them for 70-79 years of age. First dose Moderna, were the youngest (median age 43 years), as by the time this was on the market the older persons had been vaccinated. In ARS Janssen vaccine was used very little and almost only in persons between 60 and 79 years of age. Due to age channeling prevalence of co-morbidities differ, especially for CVD. Out of 18,194 pregnant women observed in ARS, 993 were vaccinated, mostly with Pfizer vaccine.

Table 7. Characteristics of the vaccinated cohorts at first dose (CASERTA)

Characteristic	IT-CASERTA	at first pfizer	at first astrazeneca	at first moderna	at first janssen	nova vax	unknown
Study population	950,452 (100%)	499,993 (70%)	112,711 (16%)	92,185 (13%)	4,720 (0.7%)	0 (0%)	16 (<0.1%)
follow-up (years)	3,650,330 (PY)	312,097 (PY)	91,397 (PY)	49,480 (PY)	2,904 (PY)		9 (PY)
Age in years							
Minimum	0	5	18	12	18		30
25%	23	26	41	34	18		34
Median	41	45	59	48	19		44
Mean	41	44	53	49	27		47
75%	57	58	66	64	36		65
Maximum	119	105	98	106	86		68
Age in categories							
0-4	39,998 (4.2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)		0 (0%)
5-11	66,478 (7.0%)	17,502 (3.5%)	0 (0%)	0 (0%)	0 (0%)		0 (0%)
12-17	63,443 (6.7%)	51,144 (10%)	0 (0%)	1,700 (1.8%)	0 (0%)		0 (0%)
18-24	80,599 (8.5%)	46,019 (9.2%)	8,209 (7.3%)	8,272 (9.0%)	2,970 (63%)		0 (0%)
25-29	62,796 (6.6%)	30,035 (6.0%)	6,374 (5.7%)	7,100 (7.7%)	238 (5.0%)		0 (0%)
30-39	135,776 (14%)	64,633 (13%)	11,920 (11%)	14,969 (16%)	582 (12%)		6 (38%)
40-49	154,652 (16%)	81,879 (16%)	14,544 (13%)	17,474 (19%)	515 (11%)		.
50-59	144,017 (15%)	92,233 (18%)	17,383 (15%)	14,659 (16%)	258 (5.5%)		.
60-69	101,884 (11%)	46,382 (9.3%)	37,309 (33%)	11,276 (12%)	109 (2.3%)		5 (31%)
70-79	67,884 (7.1%)	42,485 (8.5%)	16,947 (15%)	8,360 (9.1%)	43 (0.9%)		0 (0%)
80+	32,925 (3.5%)	27,681 (5.5%)	25 (<0.1%)	8,375 (9.1%)	5 (0.1%)		0 (0%)
Persons							.
Female	485,910 (51%)	256,149 (51%)	59,947 (53%)	49,135 (53%)	1,879 (40%)		9 (56%)
Male	464,542 (49%)	243,844 (49%)	52,764 (47%)	43,050 (47%)	2,841 (60%)		7 (44%)
Immune deficiency	896 (<0.1%)	1061 (0.2%)	121 (0.1%)	114 (0.1%)	<5		0 (0%)
Pregnant	3,807 (0.8%)	395 (0.2%)	29 (<0.1%)	63 (0.1%)	0 (0%)		0 (0%)
Previous episodes of Covid-19	0 (0%)	40,330 (8.1%)	4,574 (4.1%)	8,540 (9.3%)	203 (4.3%)		0 (0%)
Cancer	7,531 (0.8%)	6,032 (1.2%)	583 (0.5%)	807 (0.9%)	.		0 (0%)
Cardio-cerebrovascular disease	238,857 (25%)	161,175 (32%)	46,227 (41%)	33,393 (36%)	239 (5.1%)		0 (0%)
Diabetes 1 or 2	51,586 (5.4%)	42,759 (8.6%)	4,201 (3.7%)	7,323 (7.9%)	32 (0.7%)		0 (0%)
Kidney chronic disease	174 (<0.1%)	42 (<0.1%)	.	10 (<0.1%)	0 (0%)		0 (0%)
Liver chronic disease	578 (<0.1%)	1,343 (0.3%)	134 (0.1%)	179 (0.2%)	9 (0.2%)		0 (0%)
Allergy	396 (<0.1%)	239 (<0.1%)	34 (<0.1%)	34 (<0.1%)	0 (0%)		0 (0%)
Anaphylaxis	58 (<0.1%)	135 (<0.1%)	14 (<0.1%)	16 (<0.1%)	0 (0%)		0 (0%)
Down syndrome	86 (<0.1%)	7 (<0.1%)	0 (0%)	0 (0%)	0 (0%)		0 (0%)
HIV	89 (<0.1%)	942 (0.2%)	103 (<0.1%)	100 (0.1%)	.		0 (0%)
Hypersensitivity	338 (<0.1%)	104 (<0.1%)	20 (<0.1%)	18 (<0.1%)	0 (0%)		0 (0%)
Mental health	50,796 (5.3%)	35,109 (7.0%)	7,449 (6.6%)	9,368 (10%)	96 (2.0%)		0 (0%)
Obesity	39 (<0.1%)	16 (<0.1%)	.	6 (<0.1%)	0 (0%)		0 (0%)
Previous VTE	29,814 (3.1%)	26,664 (5.3%)	3,869 (3.4%)	6,969 (7.6%)	65 (1.4%)		0 (0%)
Chronic resiratory disease	135,678 (14%)	52,655 (11%)	10,316 (9.2%)	10,290 (11%)	194 (4.1%)		0 (0%)
Sicke cell disease	631 (<0.1%)	444 (<0.1%)	22 (<0.1%)	69 (<0.1%)	0 (0%)		0 (0%)
Antibiotics	171,616 (18%)	71,371 (14%)	15,599 (14%)	15,603 (17%)	307 (6.5%)		0 (0%)
Antithrombotics	72,230 (7.6%)	57,926 (12%)	9,574 (8.5%)	12,885 (14%)	32 (0.7%)		0 (0%)
Antivirals	2,258 (0.2%)	1,971 (0.4%)	335 (0.3%)	277 (0.3%)	5 (0.1%)		0 (0%)
Lipid lowering drugs	83,539 (8.8%)	66,803 (13%)	17,704 (16%)	12,237 (13%)	47 (1.0%)		0 (0%)
Sexual hormones	4,751 (0.5%)	2,368 (0.5%)	441 (0.4%)	498 (0.5%)	8 (0.2%)		0 (0%)
Immunosuppressants	42,275 (4.4%)	24,098 (4.8%)	3,888 (3.4%)	4,885 (5.3%)	89 (1.9%)		0 (0%)
Vaccines	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)		0 (0%)

In CASERTA (data until February 2022,Table 7), 70% of the vaccinated persons received Pfizer vaccine, among them 5.5% was above 80 years of age and 13.5% children/adolescents. AstraZeneca vaccine was 16% of the vaccinated population and they were mostly between 30 and 79 years of age with 48% of them for 60-79 years of age. Moderna users had 18% in the 70 years and older, and only few adolescents received Moderna. First dose Janssen was very low (0.7%) and were the youngest (median age 19 years), as by the time this was on the market the older persons had been vaccinated. Due to age channeling, prevalence of co-morbidities differ between the vaccine cohorts, especially for CVD. Very few vaccinated persons were pregnant at the time of vaccination.

Table 8.Characteristics of the vaccinated cohorts at first dose (PEDIANET)

Characteristic	IT-PEDIANET	at first pfizer	at first astrazeneca	at first moderna	at first janssen	at first novavax	at first unk
Study population	50,876 (100%)	2,743 (84%)	.	530 (16%)	0 (0%)	0	0
follow-up (years)	161,019 (PY)	539 (PY)	.	139 (PY)			
Age in years							
Minimum	0.0	3.00	10.00	8.00			
25%	0	9	10	12			
Median	4.0	12.00	10.00	12.00			
Mean	4.3	10.76	10.00	12.27			
75%	8	12	10	13			
Maximum	12.0	13.00	10.00	13.00			
Age in categories							
0-4	27,450 (54%)		0 (0%)	0 (0%)			
5-11	22,554 (44%)	1,176 (43%)		31 (5.8%)			
12-17	872 (1.7%)	1,563 (57%)	0 (0%)	499 (94%)			
18-24							
25-29							
30-39							
40-49							
50-59							
60-69							
70-79							
80+							
Persons	.	.	.	.			
Female	24,625 (48%)	1,329 (48%)	.	248 (47%)			
Male	26,251 (52%)	1,414 (52%)	0 (0%)	282 (53%)			
Immune deficiency	41 (<0.1%)	<5	0 (0%)	0 (0%)			
Pregnant	0 (0%)	0 (0%)	0 (0%)	0 (0%)			
History of Covid diagnosis	0 (0%)	131 (4.8%)	0 (0%)	39 (7.4%)			
Cancer	8 (<0.1%)	0 (0%)	0 (0%)	0 (0%)			
Cardio-cerebrovascular disease	117 (0.2%)	9 (0.3%)	0 (0%)	0 (0%)			
Diabetes 1 or 2	20 (<0.1%)	9 (0.3%)	0 (0%)	0 (0%)			
Kidney chronic disease	0 (0%)	0 (0%)	0 (0%)	0 (0%)			
Liver chronic disease	0 (0%)	0 (0%)	0 (0%)	0 (0%)			
Allergy	34 (<0.1%)	0 (0%)	0 (0%)	0 (0%)			
Anaphylaxis	32 (<0.1%)	0 (0%)	0 (0%)	0 (0%)			
Down syndrome	.	0 (0%)	0 (0%)	0 (0%)			
HIV	0 (0%)	0 (0%)	0 (0%)	0 (0%)			
Hypersensitivity	0 (0%)	0 (0%)	0 (0%)	0 (0%)			
Mental health	28 (<0.1%)	12 (0.4%)	0 (0%)	0 (0%)			
Obesity	0 (0%)	0 (0%)	0 (0%)	0 (0%)			
Previous VTE	0 (0%)	0 (0%)	0 (0%)	0 (0%)			
Chronic resiratory disease	6,610 (13%)	265 (9.7%)	0 (0%)	44 (8.3%)			
Sicke cell disease	11 (<0.1%)	0 (0%)	0 (0%)	0 (0%)			
Antibiotics	4,467 (8.8%)	91 (3.3%)	0 (0%)	15 (2.8%)			
Antithrombotics	8 (<0.1%)	0 (0%)	0 (0%)	0 (0%)			
Antivirals	45 (<0.1%)	0 (0%)	0 (0%)	0 (0%)			
Lipid lowering drugs	0 (0%)	0 (0%)	0 (0%)	0 (0%)			
Sexual hormones	10 (<0.1%)	0 (0%)	0 (0%)	0 (0%)			
Immunosuppressants	965 (1.9%)	33 (1.2%)	0 (0%)	0 (0%)			
Vaccines	154 (0.3%)	507 (18%)	0 (0%)	107 (20%)			

In PEDIANET (Data until 31-12-2021, Table 8) (children only), 84% of the vaccinated persons received Pfizer vaccine and the rest Moderna, there were no children 0-4 years of age who were vaccinated. In the 5-11 years old mostly Pfizer was used. Comorbidity rates were low, which is expected because of the pediatric age.

Table 9. Characteristics of the vaccinated cohorts at first dose (ES-BIFAP_PC)

Characteristic	ES-BIFAP-PC	at first pfizer	at first astrazeneca	at first moderna	at first janssen	at first novavax	at first unk
Study population	12,912,064 (100%)	6,753,325 (71%)	1,105,938 (12%)	1,268,050 (13%)	425,080 (4.4%)		755 (<0.1%)
follow-up (years)	49,511,556 (PY)	4,530,837 (PY)	923,433 (PY)	769,613 (PY)	285,091 (PY)		461 (PY)
Age in years	.	.	.	.	.		.
Minimum	0	1	2	1	9		3
25%	24	33	59	23	42		26
Median	42	47	61	34	49		43
Mean	42	48	57	39	49		46
75%	59	68	64	54	56		63
Maximum	113	112	101	103	107		102
Age in categories							
0-4	770,696 (6.0%)	89 (<0.1%)	0 (0%)	9 (<0.1%)	0 (0%)		13 (1.7%)
5-11	921,387 (7.1%)	281,658 (4.2%)	0 (0%)	1,699 (0.1%)	0 (0%)		23 (3.0%)
12-17	757,538 (5.9%)	524,968 (7.8%)	155 (<0.1%)	101,651 (8.0%)	1,096 (0.3%)		32 (4.2%)
18-24	862,924 (6.7%)	333,053 (4.9%)	20,168 (1.8%)	281,351 (22%)	18,560 (4.4%)		108 (14%)
25-29	720,414 (5.6%)	304,540 (4.5%)	28,079 (2.5%)	136,818 (11%)	8,850 (2.1%)		57 (7.5%)
30-39	1,814,335 (14%)	910,976 (13%)	68,278 (6.2%)	212,403 (17%)	22,825 (5.4%)		106 (14%)
40-49	2,160,003 (17%)	1,363,814 (20%)	91,848 (8.3%)	126,905 (10%)	174,672 (41%)		101 (13%)
50-59	1,810,575 (14%)	1,117,039 (17%)	132,507 (12%)	259,889 (20%)	130,934 (31%)		89 (12%)
60-69	1,319,636 (10%)	358,832 (5.3%)	764,383 (69%)	64,420 (5.1%)	52,353 (12%)		81 (11%)
70-79	975,096 (7.6%)	869,293 (13%)	458 (<0.1%)	51,380 (4.1%)	13,180 (3.1%)		38 (5.0%)
80+	799,460 (6.2%)	689,063 (10%)	58 (<0.1%)	31,525 (2.5%)	2,607 (0.6%)		107 (14%)
Persons							
Female	6,660,688 (52%)	3,553,260 (53%)	613,834 (56%)	647,587 (51%)	196,319 (46%)		458 (61%)
Male	6,251,376 (48%)	3,200,065 (47%)	492,104 (44%)	620,463 (49%)	228,761 (54%)		297 (39%)
Immuno deficiency	13976 (0.1%)	5162 (<0.1%)	863 (<0.1%)	916 (<0.1%)	331 (<0.1%)		<5
Pregnant							
History of Covid diagnosis	42,506 (0.3%)	850,379 (13%)	129,455 (12%)	178,668 (14%)	45,491 (11%)		12 (1.6%)
Cancer	124,885 (1.0%)	78,684 (1.2%)	12,983 (1.2%)	18,226 (1.4%)	3,027 (0.7%)		5 (0.7%)
Cardio-cerebrovascular disease	2,619,086 (20%)	2,015,869 (30%)	476,551 (43%)	222,842 (18%)	100,379 (24%)		192 (25%)
Diabetes 1 or 2	665,139 (5.2%)	519,097 (7.7%)	115,918 (10%)	55,578 (4.4%)	24,270 (5.7%)		51 (6.8%)
Kidney chronic disease	30,246 (0.2%)	18,064 (0.3%)	1,797 (0.2%)	1,637 (0.1%)	491 (0.1%)		.
Liver chronic disease	2,185 (<0.1%)	949 (<0.1%)	247 (<0.1%)	138 (<0.1%)	91 (<0.1%)		0 (0%)
Allergy	19,956 (0.2%)	15,128 (0.2%)	2,109 (0.2%)	2,714 (0.2%)	739 (0.2%)		.
Anaphylaxis	15,183 (0.1%)	13,264 (0.2%)	1,667 (0.2%)	2,396 (0.2%)	605 (0.1%)		.
Down syndrome	293 (<0.1%)	102 (<0.1%)	5 (<0.1%)	16 (<0.1%)	.		0 (0%)
HIV	640 (<0.1%)	111 (<0.1%)	10 (<0.1%)	48 (<0.1%)	8 (<0.1%)		0 (0%)
Hypersensitivity	4,783 (<0.1%)	1,867 (<0.1%)	442 (<0.1%)	318 (<0.1%)	134 (<0.1%)		.
Mental health	1,044,703 (8.1%)	878,176 (13%)	160,017 (14%)	113,658 (9.0%)	47,702 (11%)		85 (11%)
Obesity	87,728 (0.7%)	25,673 (0.4%)	4,183 (0.4%)	3,910 (0.3%)	1,856 (0.4%)		.
Previous VTE	135,764 (1.1%)	160,833 (2.4%)	22,829 (2.1%)	24,648 (1.9%)	7,475 (1.8%)		16 (2.1%)
Chronic resiratory disease	836,959 (6.5%)	525,468 (7.8%)	88,063 (8.0%)	73,725 (5.8%)	25,634 (6.0%)		66 (8.7%)
Sicke cell disease	8,470 (<0.1%)	5,218 (<0.1%)	650 (<0.1%)	1,217 (<0.1%)	140 (<0.1%)		.
Antibiotics	487,668 (3.8%)	342,108 (5.1%)	50,453 (4.6%)	59,031 (4.7%)	18,182 (4.3%)		40 (5.3%)
Antithrombotics	723,995 (5.6%)	625,216 (9.3%)	90,573 (8.2%)	58,801 (4.6%)	18,557 (4.4%)		64 (8.5%)
Antivirals	13,199 (0.1%)	12,959 (0.2%)	2,315 (0.2%)	3,375 (0.3%)	685 (0.2%)		.
Lipid lowering drugs	1,258,759 (9.7%)	964,376 (14%)	256,982 (23%)	105,028 (8.3%)	45,548 (11%)		87 (12%)
Sexual hormones	147,529 (1.1%)	125,157 (1.9%)	15,807 (1.4%)	39,849 (3.1%)	6,984 (1.6%)		23 (3.0%)
Immunosuppressants	171,405 (1.3%)	134,942 (2.0%)	23,338 (2.1%)	25,898 (2.0%)	6,737 (1.6%)		17 (2.3%)
Vaccines	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)		0 (0%)

In BIFAP (Data until April 2022, Table 9), 71% of the vaccinated persons received Pfizer vaccine, among them 10% was above 80 years of age and 12% children/adolescents. AstraZeneca vaccine was 12% of the vaccinated population and they were mostly (81%) between 50 and 69 years of age. First dose Moderna, were the youngest (median age 34 years), as by the time this was on the market the older persons had been vaccinated. Janssen vaccine was used very little (4.4%) and almost only in persons between 40 and 69 years of

age. Due to strong age channeling, prevalence of co-morbidities differs, especially for CVD. Pregnancy has not yet been assessed.

Table 10. Characteristics of the vaccinated cohorts at first dose (ES-SIDIAP)

Characteristic	ES-SIDIAP	at first pfizer	at first astrazeneca	at first moderna	at first janssen	at first nova vax	at first unk
Study population	6,220,172 (100%)	3,217,959 (68%)	612,895 (13%)	634,149 (13%)	260,420 (5.5%)	0 (0%)	0 (0%)
follow-up (years)	26,275,256 (PY)	3,291,040 (PY)	750,118 (PY)	582,797 (PY)	261,622 (PY)		
Age in years							
Minimum	0	1	1	2	8		
25%	23	28	59	25	40		
Median	41	45	62	36	45		
Mean	41	46	58	39	48		
75%	58	61	65	52	58		
Maximum	118	120	92	105	103		
Age in categories							
0-4	405,800 (6.5%)	24 (<0.1%)	0 (0%)	8 (<0.1%)	0 (0%)		
5-11	445,824 (7.2%)	188,144 (5.8%)	0 (0%)	48 (<0.1%)	0 (0%)		
12-17	373,364 (6.0%)	297,635 (9.2%)	26 (<0.1%)	44,829 (7.1%)	284 (0.1%)		
18-24	435,260 (7.0%)	211,893 (6.6%)	13,545 (2.2%)	107,395 (17%)	16,109 (6.2%)		
25-29	365,983 (5.9%)	143,618 (4.5%)	15,628 (2.5%)	77,196 (12%)	11,484 (4.4%)		
30-39	880,824 (14%)	412,798 (13%)	37,603 (6.1%)	121,836 (19%)	30,796 (12%)		
40-49	1,037,392 (17%)	621,718 (19%)	54,087 (8.8%)	83,370 (13%)	105,202 (40%)		
50-59	826,288 (13%)	525,508 (16%)	58,638 (9.6%)	141,336 (22%)	35,542 (14%)		
60-69	625,682 (10%)	87,675 (2.7%)	432,763 (71%)	28,330 (4.5%)	36,525 (14%)		
70-79	464,930 (7.5%)	407,845 (13%)	527 (<0.1%)	24,677 (3.9%)	23,885 (9.2%)		
80+	358,825 (5.8%)	321,101 (10.0%)	76 (<0.1%)	5,124 (0.8%)	591 (0.2%)		
Persons							
Female	3,142,609 (51%)	1,671,754 (52%)	333,978 (54%)	306,324 (48%)	115,032 (44%)		
Male	3,077,563 (49%)	1,546,205 (48%)	278,917 (46%)	327,825 (52%)	145,388 (56%)		
Immune deficiency	699 (<0.1%)	141 (<0.1%)	22 (<0.1%)	41 (<0.1%)	8 (<0.1%)		
Pregnant	40,760 (1.3%)	14,599 (0.9%)	379 (0.1%)	4,155 (1.4%)	526 (0.5%)		
History of Covid diagnosis	9,313 (0.1%)	293,637 (9.1%)	18,652 (3.0%)	79,333 (13%)	24,362 (9.4%)		
Cancer	34,893 (0.6%)	22,769 (0.7%)	4,885 (0.8%)	5,346 (0.8%)	995 (0.4%)		
Cardio-cerebrovascular disease	1,286,065 (21%)	835,628 (26%)	239,664 (39%)	91,386 (14%)	53,166 (20%)		
Diabetes 1 or 2	365,060 (5.9%)	239,669 (7.4%)	67,553 (11%)	26,605 (4.2%)	17,223 (6.6%)		
Kidney chronic disease	2,644 (<0.1%)	1,147 (<0.1%)	167 (<0.1%)	403 (<0.1%)	70 (<0.1%)		
Liver chronic disease	32,840 (0.5%)	17,202 (0.5%)	5,120 (0.8%)	4,494 (0.7%)	1,993 (0.8%)		
Allergy	17,026 (0.3%)	9,671 (0.3%)	1,669 (0.3%)	2,680 (0.4%)	506 (0.2%)		
Anaphylaxis	11,520 (0.2%)	6,745 (0.2%)	1,004 (0.2%)	1,389 (0.2%)	332 (0.1%)		
Down syndrome	437 (<0.1%)	264 (<0.1%)	.	17 (<0.1%)	6 (<0.1%)		
HIV	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)		
Hypersensitivity	5,520 (<0.1%)	2,932 (<0.1%)	667 (0.1%)	1,297 (0.2%)	177 (<0.1%)		
Mental health	602,763 (9.7%)	404,825 (13%)	88,965 (15%)	56,849 (9.0%)	30,420 (12%)		
Obesity	208 (<0.1%)	71 (<0.1%)	10 (<0.1%)	14 (<0.1%)	5 (<0.1%)		
Previous VTE	83,311 (1.3%)	57,266 (1.8%)	10,432 (1.7%)	12,166 (1.9%)	3,760 (1.4%)		
Chronic resiratory disease	600,202 (9.6%)	257,757 (8.0%)	51,191 (8.4%)	37,916 (6.0%)	17,515 (6.7%)		
Sicke cell disease	6,181 (<0.1%)	3,282 (0.1%)	419 (<0.1%)	854 (0.1%)	186 (<0.1%)		
Antibiotics	450,027 (7.2%)	172,125 (5.3%)	28,972 (4.7%)	32,324 (5.1%)	13,128 (5.0%)		
Antithrombotics	407,396 (6.5%)	297,416 (9.2%)	55,790 (9.1%)	24,714 (3.9%)	13,346 (5.1%)		
Antivirals	10,671 (0.2%)	6,662 (0.2%)	1,561 (0.3%)	2,043 (0.3%)	487 (0.2%)		
Lipid lowering drugs	563,724 (9.1%)	377,527 (12%)	119,344 (19%)	37,363 (5.9%)	23,197 (8.9%)		
Sexual hormones	78,065 (1.3%)	47,657 (1.5%)	6,062 (1.0%)	14,832 (2.3%)	4,346 (1.7%)		
Immunosuppressants	137,592 (2.2%)	61,003 (1.9%)	11,093 (1.8%)	20,700 (3.3%)	3,436 (1.3%)		
Vaccines	730,187 (12%)	67,212 (2.1%)	4,468 (0.7%)	4,858 (0.8%)	41 (<0.1%)		

In SIDIAP (Data until June 30, 2022 Table 10), 68% of the vaccinated persons received Pfizer vaccine, among them 5.8% was above 80 years of age and 20% children/adolescents, notably 6.5% between 0-4 years of age. AstraZeneca vaccine was 13% of the vaccinated population and they were mostly (90%) between 40 and 69 years of age. First dose Moderna, were the youngest (median age 36 years), as by the time this was on the market the older persons had been vaccinated. Janssen vaccine was used very little (5.5%) and almost only in persons between 40 and 69 years of age. Due to strong age channeling prevalence of co-

morbidities differ, especially for CVD. Most of the pregnant women (prevalence very low in each cohort), received Pfizer or Moderna vaccine during pregnancy.

Table 11. Characteristics of the vaccinated cohorts at first dose (ES-VID; FISABIO)

Characteristic	ES-FISABIO	at first pfizer	at first astrazeneca	at first moderna	at first janssen	at first novavax	at first unk
Study population	5,051,044 (100%)	2,891,970 (70%)	498,950 (12%)	513,458 (12%)	204,156 (5.0%)	8 (<0.1%)	3,217 (<0.1%)
follow-up (years)	19,474,172 (PY)	1,558,501 (PY)	362,928 (PY)	260,438 (PY)	111,790 (PY)	6 (PY)	1,889 (PY)
Age in years	.	.	.	.	.	.	.
Minimum	0	1	9	11	12	41	5
25%	23	28	46	31	45	45	36
Median	43	46	60	40	50	59	47
Mean	42	47	54	44	51	58	47
75%	59	67	62	57	56	69	58
Maximum	113	110	94	103	101	77	95
Age in categories	.	.	.	.	.	.	.
0-4	320,805 (6.4%)	14 (<0.1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
5-11	368,161 (7.3%)	107,057 (3.7%)	.	78 (<0.1%)	0 (0%)	0 (0%)	13 (0.4%)
12-17	312,329 (6.2%)	267,278 (9.2%)	264 (<0.1%)	36,684 (7.1%)	41 (<0.1%)	0 (0%)	33 (1.0%)
18-24	330,498 (6.5%)	244,468 (8.5%)	14,193 (2.8%)	41,540 (8.1%)	1,928 (0.9%)	0 (0%)	240 (7.5%)
25-29	255,748 (5.1%)	154,147 (5.3%)	18,608 (3.7%)	33,570 (6.5%)	1,427 (0.7%)	0 (0%)	188 (5.8%)
30-39	657,604 (13%)	317,650 (11%)	45,780 (9.2%)	142,608 (28%)	5,434 (2.7%)	0 (0%)	554 (17%)
40-49	833,148 (16%)	533,601 (18%)	66,169 (13%)	65,098 (13%)	84,726 (42%)	.	816 (25%)
50-59	727,660 (14%)	438,536 (15%)	81,145 (16%)	96,698 (19%)	80,716 (40%)	.	635 (20%)
60-69	557,076 (11%)	207,514 (7.2%)	272,270 (55%)	54,292 (11%)	12,626 (6.2%)	.	427 (13%)
70-79	412,742 (8.2%)	385,145 (13%)	443 (<0.1%)	10,190 (2.0%)	16,863 (8.3%)	.	234 (7.3%)
80+	275,273 (5.4%)	236,560 (8.2%)	76 (<0.1%)	32,700 (6.4%)	395 (0.2%)	0 (0%)	77 (2.4%)
Persons							
Female	2,569,650 (51%)	1,484,270 (51%)	279,330 (56%)	256,750 (50%)	94,292 (46%)	.	1,500 (47%)
Male	2,481,394 (49%)	1,407,700 (49%)	219,620 (44%)	256,708 (50%)	109,864 (54%)	.	1,717 (53%)
Pregnant	28,905 (1.1%)	13,952 (0.9%)	429 (0.2%)	3,265 (1.3%)	146 (0.2%)	0 (0%)	6 (0.4%)
Previous episodes of Covid-19	0 (0%)	223,318 (7.7%)	24,848 (5.0%)	56,074 (11%)	14,483 (7.1%)	0 (0%)	99 (3.1%)
Cancer	58,889 (1.2%)	39,436 (1.4%)	5,409 (1.1%)	10,061 (2.0%)	1,716 (0.8%)	0 (0%)	11 (0.3%)
Cardio-cerebrovascular disease	1,241,627 (25%)	878,727 (30%)	180,864 (36%)	122,137 (24%)	55,995 (27%)	.	420 (13%)
Diabetes 1 or 2	369,199 (7.3%)	274,508 (9.5%)	49,686 (10.0%)	36,447 (7.1%)	14,931 (7.3%)	.	155 (4.8%)
Immuno deficiency	27,436 (0.5%)	9,090 (0.3%)	1,867 (0.4%)	3,043 (0.6%)	1,288 (0.6%)	0 (0%)	8 (0.2%)
Kidney chronic disease	12,283 (0.2%)	16,675 (0.6%)	1,365 (0.3%)	2,381 (0.5%)	579 (0.3%)	0 (0%)	.
Liver chronic disease	13,616 (0.3%)	21,272 (0.7%)	5,435 (1.1%)	4,049 (0.8%)	2,076 (1.0%)	0 (0%)	12 (0.4%)
Allergy	34,138 (0.7%)	21,137 (0.7%)	3,722 (0.7%)	2,999 (0.6%)	1,121 (0.5%)	0 (0%)	9 (0.3%)
Anaphylaxis	10,450 (0.2%)	6,216 (0.2%)	765 (0.2%)	964 (0.2%)	281 (0.1%)	0 (0%)	.
Down syndrome	1,679 (<0.1%)	688 (<0.1%)	532 (0.1%)	119 (<0.1%)	5 (<0.1%)	0 (0%)	0 (0%)
HIV	12,016 (0.2%)	8,363 (0.3%)	1,760 (0.4%)	2,950 (0.6%)	1,238 (0.6%)	0 (0%)	8 (0.2%)
Hypersensitivity	23,756 (0.5%)	14,968 (0.5%)	2,967 (0.6%)	2,041 (0.4%)	844 (0.4%)	0 (0%)	6 (0.2%)
Mental health	549,880 (11%)	400,491 (14%)	71,836 (14%)	59,534 (12%)	27,555 (13%)	0 (0%)	114 (3.5%)
Obesity	215 (<0.1%)	154 (<0.1%)	31 (<0.1%)	26 (<0.1%)	10 (<0.1%)	0 (0%)	0 (0%)
Previous VTE	139,685 (2.8%)	96,511 (3.3%)	12,726 (2.6%)	17,256 (3.4%)	5,325 (2.6%)	0 (0%)	26 (0.8%)
Chronic respiratory disease	732,165 (14%)	282,956 (9.8%)	42,790 (8.6%)	43,030 (8.4%)	16,018 (7.8%)	0 (0%)	107 (3.3%)
Sicke cell disease	9,249 (0.2%)	5,491 (0.2%)	763 (0.2%)	1,074 (0.2%)	269 (0.1%)	0 (0%)	.
Antibiotics	575,429 (11%)	242,236 (8.4%)	33,018 (6.6%)	39,943 (7.8%)	13,518 (6.6%)	0 (0%)	71 (2.2%)
Antithrombotics	368,298 (7.3%)	285,325 (9.9%)	33,878 (6.8%)	35,712 (7.0%)	10,984 (5.4%)	0 (0%)	65 (2.0%)
Antivirals	23,228 (0.5%)	16,362 (0.6%)	3,131 (0.6%)	4,692 (0.9%)	1,628 (0.8%)	0 (0%)	8 (0.2%)
Lipid lowering drugs	644,984 (13%)	483,952 (17%)	104,856 (21%)	67,070 (13%)	29,929 (15%)	.	152 (4.7%)
Sexual hormones	75,426 (1.5%)	59,781 (2.1%)	8,449 (1.7%)	11,560 (2.3%)	2,513 (1.2%)	0 (0%)	30 (0.9%)
Immunosuppressants	142,942 (2.8%)	80,394 (2.8%)	13,157 (2.6%)	17,167 (3.3%)	4,949 (2.4%)	0 (0%)	21 (0.7%)
Non-covid vaccines	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

In FISABIO (Data until December 31, 2021 Table 11), 70% of the vaccinated persons received Pfizer vaccine, among them 8.2% was above 80 years of age and 12.9% children/adolescents. AstraZeneca vaccine was 12% of the vaccinated population and they were mostly between 40 and 69 years of age. First dose Moderna were the youngest (median age 40 years), as by the time this was on the market the older persons had been vaccinated. Janssen vaccine was used very little (5.0%) and almost only in persons between 40 and 69 years of age (82%). Due to strong age channeling prevalence of co-morbidities differ,

especially for CVD. Most of the pregnant women (prevalence very low in each cohort), received Pfizer or Moderna vaccine during pregnancy.

Table 12. Characteristics of the vaccinated cohorts at first dose (NL-PHARMO)

Study population	2,605,325 (100%)	1,117,016 (68%)	134,321 (8.1%)	153,258 (9.3%)	45,654 (2.8%)	0 (0%)	198,148 (12%)
follow-up (years)	10,569,082 (PY)	1,073,587 (PY)	155,037 (PY)	124,109 (PY)	39,721 (PY)		183,235 (PY)
Age in years	.	.	.	.	.		.
Minimum	0	4	1	4	13		1
25%	21	30	60	39	21		40
Median	41	49	61	49	26		56
Mean	41	49	58	47	32		53
75%	59	68	63	55	42		66
Maximum	121	119	120	108	95		119
Age in categories	.	.	.	.	.		.
0-4	181,536 (7.0%)	78 (<0.1%)	.	.	0 (0%)		112 (<0.1%)
5-11	189,886 (7.3%)	9,415 (0.8%)	11 (<0.1%)	.	0 (0%)		1,698 (0.9%)
12-17	175,098 (6.7%)	104,123 (9.3%)	139 (0.1%)	209 (0.1%)	516 (1.1%)		7,236 (3.7%)
18-24	219,550 (8.4%)	92,483 (8.3%)	3,488 (2.6%)	14,499 (9.5%)	19,181 (42%)		12,649 (6.4%)
25-29	168,763 (6.5%)	64,572 (5.8%)	2,290 (1.7%)	7,605 (5.0%)	6,708 (15%)		8,892 (4.5%)
30-39	319,128 (12%)	143,615 (13%)	5,096 (3.8%)	18,225 (12%)	6,701 (15%)		18,706 (9.4%)
40-49	333,411 (13%)	153,194 (14%)	7,548 (5.6%)	40,048 (26%)	3,683 (8.1%)		24,733 (12%)
50-59	368,575 (14%)	183,009 (16%)	13,181 (9.8%)	52,133 (34%)	7,824 (17%)		35,837 (18%)
60-69	311,588 (12%)	110,093 (9.9%)	99,448 (74%)	9,879 (6.4%)	691 (1.5%)		51,410 (26%)
70-79	226,211 (8.7%)	178,178 (16%)	1,402 (1.0%)	8,392 (5.5%)	263 (0.6%)		24,076 (12%)
80+	111,579 (4.3%)	78,256 (7.0%)	1,716 (1.3%)	2,265 (1.5%)	87 (0.2%)		12,799 (6.5%)
Persons	.	.	.	.	.		.
Female	1,316,668 (51%)	566,233 (51%)	73,022 (54%)	72,151 (47%)	16,649 (36%)		100,753 (51%)
Male	1,288,566 (49%)	550,741 (49%)	61,297 (46%)	81,105 (53%)	29,004 (64%)		97,393 (49%)
Other	91 (<0.1%)	42 (<0.1%)	<5	<5	<5		<5
Immune deficiency diagnosis	11372 (0.4%)	3376 (0.3%)	511 (0.4%)	580 (0.4%)	89 (0.2%)		779 (0.4%)
Pregnant	NA	NA	NA	NA	NA		NA
Previous episodes of Covid-19	0 (0%)	184,894 (17%)	23,933 (18%)	30,714 (20%)	5,600 (12%)		29,639 (15%)
Cancer	32,961 (1.3%)	20,833 (1.9%)	2,482 (1.8%)	2,097 (1.4%)	150 (0.3%)		4,218 (2.1%)
Cardio-cerebrovascular disease	565,024 (22%)	328,621 (29%)	53,395 (40%)	32,313 (21%)	2,574 (5.6%)		64,311 (32%)
Diabetes 1 or 2	111,335 (4.3%)	64,573 (5.8%)	10,911 (8.1%)	6,280 (4.1%)	245 (0.5%)		13,394 (6.8%)
Kidney chronic disease	NA	NA	NA	NA	NA		NA
Liver chronic disease	203 (<0.1%)	29 (<0.1%)	0 (0%)	0 (0%)	0 (0%)		7 (<0.1%)
Allergy	7,718 (0.3%)	3,444 (0.3%)	446 (0.3%)	453 (0.3%)	105 (0.2%)		605 (0.3%)
Anaphylaxis	7,718 (0.3%)	3,444 (0.3%)	446 (0.3%)	453 (0.3%)	105 (0.2%)		605 (0.3%)
Down syndrome	NA	NA	NA	NA	NA		0 (0%)
HIV	2,542 (<0.1%)	1,163 (0.1%)	180 (0.1%)	233 (0.2%)	30 (<0.1%)		312 (0.2%)
Hypersensitivity	NA	NA	NA	NA	NA		NA
Mental health	180,014 (6.9%)	89,603 (8.0%)	14,897 (11%)	13,223 (8.6%)	2,355 (5.2%)		19,042 (9.6%)
Obesity	5,701 (0.2%)	2,595 (0.2%)	384 (0.3%)	379 (0.2%)	66 (0.1%)		520 (0.3%)
Previous VTE	23,759 (0.9%)	10,394 (0.9%)	1,591 (1.2%)	1,239 (0.8%)	210 (0.5%)		1,852 (0.9%)
Chronic resiratory disease	219,771 (8.4%)	96,406 (8.6%)	15,384 (11%)	11,736 (7.7%)	1,087 (2.4%)		18,898 (9.5%)
Sicke cell disease	721 (<0.1%)	452 (<0.1%)	28 (<0.1%)	70 (<0.1%)	.		102 (<0.1%)
Antibiotics	157,708 (6.1%)	57,115 (5.1%)	7,689 (5.7%)	7,200 (4.7%)	1,525 (3.3%)		11,375 (5.7%)
Antithrombotics	207,307 (8.0%)	134,336 (12%)	17,674 (13%)	9,808 (6.4%)	440 (1.0%)		22,860 (12%)
Antivirals	6,139 (0.2%)	2,952 (0.3%)	410 (0.3%)	477 (0.3%)	77 (0.2%)		677 (0.3%)
Lipid lowering drugs	255,114 (9.8%)	158,342 (14%)	26,491 (20%)	13,661 (8.9%)	641 (1.4%)		26,436 (13%)
Sexual hormones	122,528 (4.7%)	56,829 (5.1%)	4,088 (3.0%)	7,901 (5.2%)	3,425 (7.5%)		6,490 (3.3%)
Immunosuppressants	59,225 (2.3%)	32,064 (2.9%)	5,143 (3.8%)	3,867 (2.5%)	278 (0.6%)		6,042 (3.0%)
Other Vaccines	NA	NA	NA	NA	NA		NA

NA: not assessed

In PHARMO (Data until June 2022, Table 12), 68% of the vaccinated persons received Pfizer vaccine, among them 7% was above 80 years of age and 10% children/adolescents. AstraZeneca vaccine was 8% of the vaccinated population and they were mostly (85%) between 50 and 69 years of age. Janssen vaccine users was used very little (2.8%) and mostly in young persons (72% in 18-39 years). Moderna vaccine was used mostly in persons 40-49, and hardly in children. In PHARMO 12% of vaccines had an unknown brand, the profile looks like Pfizer vaccine. Due to strong age channelling prevalence of co-morbidities differ, especially for CVD. Pregnancy has not yet been assessed.

Table 13. Population characteristics at first COVID-19 vaccination per DAP/ UK-CPRD

Characteristic	UK-CPRD	at first pfizer	at first astrazeneca	at first moderna	at first janssen	at first novavax	at first unk
Study population	15,214,165 (100%)	4,119,937 (49%)	4,057,331 (48%)	258,841 (3.1%)	0	688 (<0.1%)	7,079 (<0.1%)
follow-up (years)	53,640,800 (PY)	3,356,362 (PY)	4,004,746 (PY)	174,878 (PY)	.	458 (PY)	1,582 (PY)
Age in years							
Minimum	0	1	4	7		18	4
25%	19	23	45	25		38	8
Median	36	36	54	32		52	10
Mean	37	42	54	33		50	15
75%	55	61	65	39		62	11
Maximum	114	111	110	99		83	79
Age in categories	.	.	.	.		.	.
0-4	1,292,137 (8.5%)	9 (<0.1%)	.	0 (0%)		0 (0%)	.
5-11	1,280,448 (8.4%)	1,838 (<0.1%)	16 (<0.1%)	5 (<0.1%)		0 (0%)	5,701 (81%)
12-17	958,875 (6.3%)	554,278 (13%)	4,178 (0.1%)	1,713 (0.7%)		0 (0%)	42 (0.6%)
18-24	1,475,981 (9.7%)	565,506 (14%)	107,186 (2.6%)	60,999 (24%)		19 (2.8%)	172 (2.4%)
25-29	1,187,315 (7.8%)	394,908 (9.6%)	103,354 (2.5%)	44,634 (17%)		57 (8.3%)	133 (1.9%)
30-39	2,279,386 (15%)	828,223 (20%)	342,566 (8.4%)	93,397 (36%)		121 (18%)	278 (3.9%)
40-49	1,917,555 (13%)	352,457 (8.6%)	922,472 (23%)	50,678 (20%)		122 (18%)	311 (4.4%)
50-59	1,852,071 (12%)	342,422 (8.3%)	1,121,272 (28%)	4,887 (1.9%)		155 (23%)	232 (3.3%)
60-69	1,340,106 (8.8%)	340,804 (8.3%)	785,765 (19%)	1,669 (0.6%)		146 (21%)	163 (2.3%)
70-79	1,013,958 (6.7%)	375,938 (9.1%)	520,081 (13%)	601 (0.2%)		63 (9.2%)	44 (0.6%)
80+	616,333 (4.1%)	363,554 (8.8%)	150,440 (3.7%)	258 (<0.1%)		5 (0.7%)	0 (0%)
Persons							
Female	7,604,939 (50%)	2,169,873 (53%)	2,071,955 (51%)	114,407 (44%)		318 (46%)	3,090 (44%)
Male	7,609,226 (50%)	1,950,064 (47%)	1,985,376 (49%)	144,434 (56%)		370 (54%)	3,989 (56%)
Immune deficiency	7888 (<0.1%)	1510 (<0.1%)	1965 (<0.1%)	31 (<0.1%)		0 (0%)	8 (0.1%)
Pregnant	NA	NA	NA	NA		NA	NA
Previous episodes of Covid-19	0 (0%)	213,050 (5.2%)	210,323 (5.2%)	15,492 (6.0%)		25 (3.6%)	417 (5.9%)
Cancer	179,628 (1.2%)	65,132 (1.6%)	72,905 (1.8%)	360 (0.1%)		9 (1.3%)	36 (0.5%)
Cardio-cerebrovascular disease	2,446,443 (16%)	899,540 (22%)	1,132,993 (28%)	10,380 (4.0%)		113 (16%)	303 (4.3%)
Diabetes 1 or 2	691,432 (4.5%)	256,954 (6.2%)	317,322 (7.8%)	1,742 (0.7%)		33 (4.8%)	316 (4.5%)
Kidney chronic disease	27,802 (0.2%)	8,725 (0.2%)	8,317 (0.2%)	39 (<0.1%)		.	21 (0.3%)
Liver chronic disease	27,769 (0.2%)	7,629 (0.2%)	11,304 (0.3%)	214 (<0.1%)		.	5 (<0.1%)
Allergy	38,204 (0.3%)	11,619 (0.3%)	15,290 (0.4%)	105 (<0.1%)		0 (0%)	8 (0.1%)
Anaphylaxis	2,115 (<0.1%)	504 (<0.1%)	799 (<0.1%)	36 (<0.1%)		0 (0%)	.
Down syndrome	NA	NA	NA	NA		NA	NA
HIV	4,214 (<0.1%)	927 (<0.1%)	1,328 (<0.1%)	18 (<0.1%)		0 (0%)	.
Hypersensitivity	36,100 (0.2%)	11,116 (0.3%)	14,511 (0.4%)	69 (<0.1%)		0 (0%)	6 (<0.1%)
Mental health	467,098 (3.1%)	138,184 (3.4%)	139,580 (3.4%)	10,401 (4.0%)		23 (3.3%)	35 (0.5%)
Obesity	30 (<0.1%)	8 (<0.1%)	11 (<0.1%)	0 (0%)		0 (0%)	0 (0%)
Previous VTE	29,217 (0.2%)	10,014 (0.2%)	13,941 (0.3%)	157 (<0.1%)		.	.
Chronic resiratory disease	1,192,004 (7.8%)	379,599 (9.2%)	463,888 (11%)	9,902 (3.8%)		59 (8.6%)	1,170 (17%)
Sicke cell disease	9,820 (<0.1%)	2,734 (<0.1%)	2,474 (<0.1%)	62 (<0.1%)		0 (0%)	10 (0.1%)
Antibiotics	0 (0%)	0 (0%)	0 (0%)	0 (0%)		0 (0%)	0 (0%)
Antithrombotics	560,055 (3.7%)	248,563 (6.0%)	253,570 (6.2%)	744 (0.3%)		.	32 (0.5%)
Antivirals	1,013 (<0.1%)	242 (<0.1%)	336 (<0.1%)	5 (<0.1%)		0 (0%)	.
Lipid lowering drugs	NA	NA	NA	NA		NA	NA
Sexual hormones	NA	NA	NA	NA		NA	NA
Immunosuppressants	73,361 (0.5%)	22,287 (0.5%)	29,928 (0.7%)	203 (<0.1%)		.	81 (1.1%)
Other Vaccines	NA	NA	NA	NA		NA	NA

NA: not assessed

In CPRD (Data until March 2022, Table 13), 49% of the vaccinated persons received Pfizer vaccine, among them 8.8% was above 80 years of age and 13% children/adolescents. AstraZeneca vaccine was 48% of the vaccinated population and they covered many age categories. Janssen vaccine users was not used. Moderna vaccine was used infrequently, and the median age was youngest, but it was hardly used in children. In CPRD very few

vaccines were for Novavax, or unknown. Due to age channeling prevalence of co-morbidities differ, especially for CVD.

Table 14. Population characteristics at first COVID-19 vaccination per DAP (NO-UOSL)

Characteristic	NK-UOSL	at first pfizer	at first astrazeneca	at first moderna	at first janssen	no va va x	at first unk
Study population	5,598,285 (100%)	3,561,396 (84%)	137,181 (3.2%)	542,204 (13%)	5,065 (0.1%)	0	81 (<0.1%)
follow-up (years)	21,711,608 (PY)	1,992,517 (PY)	112,936 (PY)	292,756 (PY)	2,033 (PY)		16 (PY)
Age in years							
Minimum	0	1	1	1	15		14
25%	19	29	32	30	30		29
Median	38	47	45	41	36		34
Mean	38	47	44	44	37		38
75%	57	64	55	56	43		41
Maximum	112	110	98	106	87		85
Age in categories							
0-4	456,480 (8.2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)		0 (0%)
5-11	458,366 (8.2%)	306 (<0.1%)	0 (0%)	0 (0%)	0 (0%)		0 (0%)
12-17	384,740 (6.9%)	316,366 (8.9%)	155 (0.1%)	4,808 (0.9%)	12 (0.2%)		0 (0%)
18-24	494,918 (8.8%)	341,494 (9.6%)	13,554 (9.9%)	61,974 (11%)	436 (8.6%)		10 (12%)
25-29	394,103 (7.0%)	235,228 (6.6%)	13,136 (9.6%)	66,860 (12%)	760 (15%)		10 (12%)
30-39	745,458 (13%)	489,491 (14%)	26,766 (20%)	120,184 (22%)	2,050 (40%)		35 (43%)
40-49	741,734 (13%)	517,143 (15%)	30,564 (22%)	96,040 (18%)	1,258 (25%)		11 (14%)
50-59	696,871 (12%)	551,224 (15%)	34,216 (25%)	85,520 (16%)	422 (8.3%)		6 (7.4%)
60-69	578,519 (10%)	485,207 (14%)	18,120 (13%)	63,006 (12%)	103 (2.0%)		5 (6.2%)
70-79	420,775 (7.5%)	411,394 (12%)	494 (0.4%)	31,183 (5.8%)	22 (0.4%)		0 (0%)
80+	226,321 (4.0%)	213,540 (6.0%)	175 (0.1%)	12,626 (2.3%)	0 (0%)		0 (0%)
Persons							
Female	2,772,771 (50%)	1,768,556 (50%)	105,465 (77%)	266,260 (49%)	1,648 (33%)		33 (41%)
Male	2,825,514 (50%)	1,792,840 (50%)	31,716 (23%)	275,944 (51%)	3,417 (67%)		48 (59%)
Immune deficiency	70130 (1.3%)	58897 (1.7%)	2328 (1.7%)	8355 (1.5%)	79 (1.6%)		<5
Pregnant	48,172 (1.7%)	7,066 (0.4%)	419 (0.4%)	3,773 (1.4%)	5 (0.3%)		0 (0%)
Previous episodes of Covid-19	0 (0%)	65,749 (1.8%)	1,952 (1.4%)	23,006 (4.2%)	176 (3.5%)		0 (0%)
Cancer	161,177 (2.9%)	149,648 (4.2%)	3,031 (2.2%)	15,080 (2.8%)	40 (0.8%)		.
Cardio-cerebrovascular disease	1,154,643 (21%)	1,022,119 (29%)	27,716 (20%)	111,248 (21%)	319 (6.3%)		9 (11%)
Diabetes 1 or 2	233,856 (4.2%)	220,696 (6.2%)	6,920 (5.0%)	24,984 (4.6%)	47 (0.9%)		6 (7.4%)
Kidney chronic disease	28,367 (0.5%)	25,095 (0.7%)	174 (0.1%)	1,788 (0.3%)	.		0 (0%)
Liver chronic disease	10,257 (0.2%)	5,169 (0.1%)	167 (0.1%)	1,351 (0.2%)	6 (0.1%)		0 (0%)
Allergy	31,653 (0.6%)	20,154 (0.6%)	887 (0.6%)	2,801 (0.5%)	8 (0.2%)		0 (0%)
Anaphylaxis	29,212 (0.5%)	18,159 (0.5%)	792 (0.6%)	2,595 (0.5%)	8 (0.2%)		0 (0%)
Down syndrome	2,044 (<0.1%)	1,082 (<0.1%)	0 (0%)	45 (<0.1%)	0 (0%)		0 (0%)
HIV	6,558 (0.1%)	5,286 (0.1%)	304 (0.2%)	1,455 (0.3%)	24 (0.5%)		0 (0%)
Hypersensitivity	2,463 (<0.1%)	2,019 (<0.1%)	96 (<0.1%)	206 (<0.1%)	0 (0%)		0 (0%)
Mental health	516,670 (9.2%)	427,909 (12%)	16,931 (12%)	64,720 (12%)	322 (6.4%)		0 (0%)
Obesity	66,742 (1.2%)	72,213 (2.0%)	3,582 (2.6%)	10,017 (1.8%)	33 (0.7%)		0 (0%)
Previous VTE	75,023 (1.3%)	59,022 (1.7%)	1,597 (1.2%)	6,998 (1.3%)	21 (0.4%)		0 (0%)
Chronic resiratory disease	484,823 (8.7%)	353,518 (9.9%)	13,970 (10%)	43,374 (8.0%)	110 (2.2%)		0 (0%)
Sicke cell disease	2,356 (<0.1%)	2,171 (<0.1%)	23 (<0.1%)	210 (<0.1%)	0 (0%)		0 (0%)
Antibiotics	344,986 (6.2%)	203,771 (5.7%)	7,901 (5.8%)	27,387 (5.1%)	157 (3.1%)		0 (0%)
Antithrombotics	427,837 (7.6%)	360,773 (10%)	5,445 (4.0%)	30,936 (5.7%)	22 (0.4%)		0 (0%)
Antivirals	24,288 (0.4%)	19,884 (0.6%)	1,042 (0.8%)	4,314 (0.8%)	36 (0.7%)		0 (0%)
Lipid lowering drugs	465,489 (8.3%)	406,869 (11%)	9,028 (6.6%)	41,787 (7.7%)	38 (0.8%)		0 (0%)
Sexual hormones	375,204 (6.7%)	298,089 (8.4%)	20,946 (15%)	47,963 (8.8%)	194 (3.8%)		0 (0%)
Immunosuppressants	132,527 (2.4%)	125,402 (3.5%)	3,453 (2.5%)	12,984 (2.4%)	45 (0.9%)		0 (0%)
Vaccines	662,891 (12%)	132,657 (3.7%)	26,805 (20%)	17,312 (3.2%)	89 (1.8%)		5 (6.2%)

In Norway (Data available until Dec 2021, **Table** 14), 84% of the vaccinated persons received Pfizer vaccine, among them 6% was above 80 years of age and 9% children/adolescents. AstraZeneca vaccine was only 3.2% of the vaccinated population and they covered mostly age 30-59. Janssen vaccine users was not used (0.1%). Moderna vaccine was used by 13% vaccinated persons were younger than those with Pfizer and only very few children received Moderna vaccine. Due to age channeling prevalence of co-morbidities differ, especially for CVD.

9.1.5 Descriptions of doses per DAP

Recommended end date of last data instance is (see Table 4):

- 31 December 2021 for ARS-IT, PEDIANET-IT, UOSL-NO, and FISABIO-ES
- 11 February 2022 for CASERTA-IT
- 21 March 2022 for CPRD-UK
- 30 April 2022 for BIFAP-ES
- 30 June 2022 for PHARMO-NL and SIDIAP-ES

Table 15. Description of doses per DAP (those with Pfizer dose 1)

Measure	IT-ARS	IT-CASERTA	IT-PEDIANET	ES-BIFAP-PC	ES-BIFAP-PC-HOSP	ES-FISABIO	ES-SIDIAP	UK-CPRD	NL-PHARMO	NK-UOSL
Study population	3,704,289 (100%)	950,452 (100%)	50,876 (100%)	12,912,064 (100%)	9,930,652 (100%)	5,051,044 (100%)	6,220,172 (100%)	15,214,165 (100%)	2,605,325 (100%)	5,598,285 (100%)
pfizer dose 1	1,923,403 (51.92%)	499,993 (52.61%)	2,743 (5.39%)	6,753,325 (52.30%)	5,188,454 (52.25%)	2,891,970 (57.25%)	3,217,959 (51.73%)	4,119,937 (27.08%)	1,117,016 (42.87%)	3,561,396 (63.62%)
pfizer dose 2	1,794,716 (93.31%)	454,871 (90.98%)	1,346 (49.07%)	5,893,031 (87.26%)	4,529,090 (87.29%)	2,574,312 (89.02%)	2,916,198 (90.62%)	3,579,902 (86.89%)	860,882 (77.07%)	2,636,067 (74.02%)
other dose 2	14,045 (0.73%)	8,715 (1.74%)	0 (0.00%)	83,892 (1.24%)	59,769 (1.15%)	11,728 (0.41%)	83,365 (2.59%)	27,446 (0.67%)	122,620 (10.98%)	580,327 (16.29%)
novavax dose 2	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	558 (0.01%)	0 (0.00%)	0 (0.00%)
moderna dose 2	13,852 (0.72%)	8,715 (1.74%)	0 (0.00%)	83,114 (1.23%)	59,686 (1.15%)	11,297 (0.39%)	83,245 (2.59%)	16,602 (0.40%)	91,441 (8.19%)	578,582 (16.25%)
astrazeneca dose 2	172 (0.01%)	0 (0.00%)	0 (0.00%)	580 (0.01%)	51 (0.00%)	360 (0.01%)	101 (0.00%)	10,203 (0.25%)	458 (0.04%)	1,669 (0.05%)
janssen dose 2	21 (0.00%)	0 (0.00%)	0 (0.00%)	62 (0.00%)	26 (0.00%)	14 (0.00%)	19 (0.00%)	0 (0.00%)	32 (0.00%)	62 (0.00%)
unk dose 2	0 (0.00%)	0 (0.00%)	0 (0.00%)	136 (0.00%)	6 (0.00%)	57 (0.00%)	0 (0.00%)	82 (0.00%)	30,689 (2.75%)	14 (0.00%)
Amongst persons with pfizer dose 2 distance										
Minimum	19	19	20	19	19	19	19	19	19	19
25%	21	21	21	21	21	21	21	60	35	41
50%	42	21	25	21	21	21	21	74	35	42
75%	42	35	35	22	22	21	23	79	36	51
Maximum	357	380	85	399	390	352	524	451	474	357
Amongst persons with other dose 2 distance										
Minimum	19	122	35	19	19	19	19	19	19	19
25%	171	149	65	159	156	24	165	77	178	36
50%	188	170	94	181	175	127	196	127	207	48
75%	206	195	124	204	197	189	215	215	236	58
Maximum	355	347	153	398	398	350	429	431	520	355
pfizer dose 3	459,813 (23.91%)	203,394 (40.68%)	0 (0.00%)	1,556,101 (23.04%)	1,362,472 (26.26%)	624,913 (21.61%)	443,863 (13.79%)	1,939,137 (47.07%)	206,109 (18.45%)	1,101,620 (30.93%)
other dose 3	293,376 (15.25%)	121,613 (24.32%)	0 (0.00%)	719,832 (10.66%)	318,773 (6.14%)	218,942 (7.57%)	1,269,494 (39.45%)	370,879 (9.00%)	344,880 (30.88%)	167,014 (4.69%)
novavax dose 3	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	.	0 (0.00%)	28 (0.00%)	0 (0.00%)	0 (0.00%)

Measure	IT-ARS	IT-CASERTA	IT-PEDIANET	ES-BIFAP-PC	ES-BIFAP-PC-HOSP	ES-FISABIO	ES-SIDIAP	UK-CPRD	NL-PHARMO	NK-UOSL
moderna dose 3	293,350 (15.25%)	121,613 (24.32%)	0 (0.00%)	719,665 (10.66%)	318,752 (6.14%)	218,831 (7.57%)	1,269,372 (39.45%)	369,790 (8.98%)	262,073 (23.46%)	166,934 (4.69%)
astrazeneca dose 3	14 (0.00%)	0 (0.00%)	0 (0.00%)	39 (0.00%)	15 (0.00%)	30 (0.00%)	97 (0.00%)	1,018 (0.02%)	479 (0.04%)	72 (0.00%)
janssen dose 3	12 (0.00%)	0 (0.00%)	0 (0.00%)	8 (0.00%)	6 (0.00%)	.	25 (0.00%)	.	13 (0.00%)	8 (0.00%)
unk dose 3	0 (0.00%)	0 (0.00%)	0 (0.00%)	120 (0.00%)	0 (0.00%)	76 (0.00%)	0 (0.00%)	42 (0.00%)	82,315 (7.37%)	0 (0.00%)
Amongst persons with pfizer dose 3 distance										
Minimum	49	52	.	48	48	48	47	49	48	49
25%	210	205	.	211	211	209	211	230	195	218
50%	224	208	.	226	226	218	226	266	213	231
75%	245	228	.	250	250	238	259	280	252	250
Maximum	363	380	.	422	422	368	544	461	535	359
Amongst persons with other dose 3 distance										
Minimum	51	88	.	47	48	47	49	47	47	47
25%	201	198	.	210	210	220	213	197	227	196
50%	209	213	.	224	225	232	226	217	246	224
75%	223	225	.	253	297	314	245	276	282	237
Maximum	368	385	.	414	414	368	534	452	530	357

Table 15 shows that Pfizer COVID-19 vaccine was used as first dose by more than 50% as first dose, except in UK and NL, the majority of those (>80%), had a homologous two dose regimen, except in NL and in Pedianet where 2nd dose was low. In most countries the median distance to second Pfizer dose was 21 days, except in ARS, PHARMO, CPRD and Norway where the distance was longer. For the low percentages of persons with a heterologous 2nd dose, the distance to second dose was much longer.

Table 16. Description of doses per DAP (those with Novavax dose 1)

Data sources	IT-ARS	IT-CASERTA	IT-PEDIANET	ES-BIFAP-PC	ES-BIFAP-PC-HOSP	ES-FISABIO	ES-SIDIAP	NL-PHARMO	UK-CPRD	NO-UOSL
novavax dose 1	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	11 (0.00%)	0 (0.00%)	0 (0.00%)	688 (0.00%)	0 (0.00%)

Table 16 shows that Novavax, which was introduced late, was captured only by the data sources which had data instances with data in 2022 (CPRD, FISABIO)

Table 17. Description of doses per DAP (those with Moderna dose 1)

Measure	IT-ARS	IT-CASERTA	IT-PEDIANET	ES-BIFAP-PC	ES-BIFAP-PC-HOSP	ES-FISABIO	ES-SIDIAP	UK-CPRD	NL-PHARMO	NK-UOSL
moderna dose 1	432,600 (11.68%)	92,185 (9.70%)	530 (1.04%)	1,268,050 (9.82%)	982,686 (9.90%)	513,458 (10.17%)	634,149 (10.20%)	258,841 (1.70%)	153,258 (5.88%)	542,204 (9.69%)
moderna dose 2	378,749 (87.55%)	79,373 (86.10%)	392 (73.96%)	1,073,967 (84.69%)	828,392 (84.30%)	440,137 (85.72%)	539,383 (85.06%)	217,067 (83.86%)	81,451 (53.15%)	430,399 (79.38%)
other dose 2	2,065 (0.48%)	89 (0.10%)	5 (0.94%)	6,001 (0.47%)	3,522 (0.36%)	1,934 (0.38%)	6,169 (0.97%)	6,862 (2.65%)	26,690 (17.42%)	70,238 (12.95%)
pfizer dose 2	2,008 (0.46%)	89 (0.10%)	.	5,876 (0.46%)	3,490 (0.36%)	1,830 (0.36%)	6,124 (0.97%)	6,556 (2.53%)	22,456 (14.65%)	70,158 (12.94%)
novavax dose 2	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	6 (0.00%)	0 (0.00%)	0 (0.00%)
astrazeneca dose 2	52 (0.01%)	0 (0.00%)	0 (0.00%)	105 (0.01%)	28 (0.00%)	76 (0.01%)	38 (0.01%)	296 (0.11%)	35 (0.02%)	52 (0.01%)
janssen dose 2	5 (0.00%)	0 (0.00%)	0 (0.00%)	12 (0.00%)	.	14 (0.00%)	7 (0.00%)	0 (0.00%)	13 (0.01%)	20 (0.00%)
unk dose 2	0 (0.00%)	0 (0.00%)	.	8 (0.00%)	.	14 (0.00%)	0 (0.00%)	.	4,186 (2.73%)	8 (0.00%)
Amongst persons with moderna dose 2 distance										
Minimum	19	22	26	19	19	19	19	19	19	19
25%	28	28	28	28	28	28	28	56	35	42
50%	42	29	29	28	28	28	28	63	35	44
75%	42	35	34	29	29	28	31	77	42	60
Maximum	316	368	51	357	333	331	413	325	423	330
Amongst persons with other dose 2 distance										
Minimum	20	21	28	19	19	19	19	19	19	19
25%	42	191	28	49	129	29	148	61	167	39
50%	68	202	33	154	159	60	192	114	177	52
75%	189	219	33	197	199	116	246	175	200	69
Maximum	294	299	50	330	325	312	498	327	453	331
moderna dose 3	73,656 (17.03%)	47,595 (51.63%)	0 (0.00%)	233,517 (18.42%)	155,887 (15.86%)	100,299 (19.53%)	228,961 (36.11%)	59,012 (22.80%)	19,912 (12.99%)	70,238 (12.95%)
other dose 3	35,425 (8.19%)	2,112 (2.29%)	0 (0.00%)	57,522 (4.54%)	47,030 (4.79%)	9,908 (1.93%)	27,153 (4.28%)	66,214 (25.58%)	26,958 (17.59%)	67,243 (12.40%)
pfizer dose 3	35,424 (8.19%)	2,112 (2.29%)	0 (0.00%)	57,493 (4.53%)	47,029 (4.79%)	9,892 (1.93%)	27,141 (4.28%)	66,189 (25.57%)	22,461 (14.66%)	67,238 (12.40%)
novavax dose 3	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	.	0 (0.00%)	0 (0.00%)
astrazeneca dose 3	.	0 (0.00%)	0 (0.00%)	16 (0.00%)	.	13 (0.00%)	11 (0.00%)	19 (0.01%)	41 (0.03%)	.
janssen dose 3	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	.	.	0 (0.00%)	.	.
unk dose 3	0 (0.00%)	0 (0.00%)	0 (0.00%)	13 (0.00%)	0 (0.00%)	.	0 (0.00%)	.	4,455 (2.91%)	0 (0.00%)
Amongst persons with moderna dose 3 distance										
Minimum	60	68	.	50	50	56	47	50	50	47
25%	202	191	.	209	210	211	209	193	210	210
50%	214	203	.	222	221	222	225	209	218	232
75%	230	221	.	238	235	232	238	230	226	245
Maximum	346	361	.	400	400	351	499	391	474	342
Amongst persons with other dose 3 distance										
Minimum	56	133	.	50	59	57	56	71	51	48
25%	212	213	.	208	208	213	211	191	192	226
50%	221	217	.	219	219	220	271	209	209	242
75%	239	230	.	231	231	232	327	231	225	258
Maximum	346	358	.	403	403	348	527	365	501	343

Table 17 shows that Moderna 1st dose was around 10% in most countries, except in CPRD and Pedianet, where it was very low. In most data sources, people with 1st Moderna vaccine received a homologous second dose, the rate was lower in PHARMO. Median distance to second dose was 28 days, except in ARS, PHARMO, CPRD and Norway, where the distance to 2nd dose of Moderna was longer. Upon heterologous schedule the second dose distance was longer.

Table 18. Description of doses per DAP (those with AstraZeneca dose 1)

Measure	IT-ARS	IT-CASERTA	IT-PEDIANET	ES-BIFAP-PC	ES-BIFAP-PC-HOSP	ES-FISABIO	ES-SIDIAP	UK-CPRD	NL-PHARMO	NK-UOSL
astrazeneca dose 1	335,936 (9.07%)	112,711 (11.86%)	.	1,105,938 (8.57%)	864,268 (8.70%)	498,950 (9.88%)	612,895 (9.85%)	4,057,331 (26.67%)	134,321 (5.16%)	137,181 (2.45%)
astrazeneca dose 2	308,709 (91.90%)	86,144 (76.43%)	.	1,000,445 (90.46%)	780,367 (90.29%)	436,553 (87.49%)	572,157 (93.35%)	3,760,592 (92.69%)	114,401 (85.17%)	182 (0.13%)
other dose 2	24,207 (7.21%)	25,781 (22.87%)	.	75,010 (6.78%)	58,670 (6.79%)	51,850 (10.39%)	33,706 (5.50%)	161,537 (3.98%)	15,148 (11.28%)	133,554 (97.36%)
pfizer dose 2	17,622 (5.25%)	23,945 (21.24%)	.	43,875 (3.97%)	34,643 (4.01%)	36,644 (7.34%)	19,568 (3.19%)	130,291 (3.21%)	5,640 (4.20%)	129,953 (94.73%)
novavax dose 2	0 (0.00%)	0 (0.00%)	.	0 (0.00%)	0 (0.00%)	5 (0.00%)	0 (0.00%)	.	0 (0.00%)	0 (0.00%)
moderna dose 2	6,573 (1.96%)	1,836 (1.63%)	.	31,052 (2.81%)	23,989 (2.78%)	15,143 (3.03%)	14,097 (2.30%)	31,226 (0.77%)	3,797 (2.83%)	3,596 (2.62%)
janssen dose 2	12 (0.00%)	0 (0.00%)	.	56 (0.01%)	38 (0.00%)	10 (0.00%)	41 (0.01%)	0 (0.00%)	41 (0.03%)	.
unk dose 2	0 (0.00%)	0 (0.00%)	.	27 (0.00%)	0 (0.00%)	48 (0.01%)	0 (0.00%)	18 (0.00%)	5,670 (4.22%)	.
Amongst persons with astrazeneca dose 2 distance										
Minimum	25	29	.	19	19	19	19	19	19	19
25%	84	72	.	71	70	77	70	68	56	31
50%	84	80	.	78	76	84	80	77	76	58
75%	84	80	.	84	84	93	88	79	77	96
Maximum	200	231	.	307	248	343	315	407	314	273
Amongst persons with other dose 2 distance										
Minimum	20	24	.	19	20	19	20	19	19	19
25%	84	72	.	136	159	88	98	189	63	79
50%	84	80	.	225	231	107	168	260	148	84
75%	197	104	.	250	253	209	246	276	233	86
Maximum	320	336	.	356	321	326	503	420	494	315
astrazeneca dose 3	6 (0.00%)	0 (0.00%)	.	175 (0.02%)	102 (0.01%)	27 (0.01%)	127 (0.02%)	10,581 (0.26%)	15,541 (11.57%)	14 (0.01%)
other dose 3	204,998 (61.02%)	97,972 (86.92%)	.	714,354 (64.59%)	544,179 (62.96%)	297,923 (59.71%)	526,171 (85.85%)	3,146,056 (77.54%)	86,614 (64.48%)	102,238 (74.53%)
pfizer dose 3	58,578 (17.44%)	41,875 (37.15%)	.	318,372 (28.79%)	269,679 (31.20%)	51,840 (10.39%)	21,968 (3.58%)	2,347,220 (57.85%)	24,122 (17.96%)	92,099 (67.14%)
novavax dose 3	0 (0.00%)	0 (0.00%)	.	0 (0.00%)	0 (0.00%)	.	0 (0.00%)	10 (0.00%)	0 (0.00%)	0 (0.00%)
moderna dose 3	146,419 (43.59%)	56,097 (49.77%)	.	395,969 (35.80%)	274,500 (31.76%)	246,058 (49.32%)	504,196 (82.26%)	798,783 (19.69%)	39,090 (29.10%)	10,137 (7.39%)
janssen dose 3	.	0 (0.00%)	.	0 (0.00%)	0 (0.00%)	.	7 (0.00%)	0 (0.00%)	.	.
unk dose 3	0 (0.00%)	0 (0.00%)	.	13 (0.00%)	0 (0.00%)	23 (0.00%)	0 (0.00%)	43 (0.00%)	23,398 (17.42%)	0 (0.00%)
Amongst persons with astrazeneca dose 3 distance										
Minimum	84	.	.	70	72	125	63	48	47	66
25%	84	.	.	126	171	204	198	245	72	118
50%	84	.	.	171	187	233	236	273	82	119
75%	104	.	.	201	203	258	266	303	98	119
Maximum	125	.	.	321	258	285	424	407	429	193
Amongst persons with other dose 3 distance										
Minimum	58	.	.	52	52	88	74	51	48	57
25%	246	.	.	227	227	238	236	258	240	273
50%	259	.	.	242	242	252	253	267	266	280
75%	276	.	.	257	257	268	273	279	299	288
Maximum	323	.	.	371	367	359	505	438	498	320

Table 18 shows that AstraZeneca COVID-19 vaccine 1st dose was less than 10% in most countries, except in CPRD, where it was higher. In most data sources, people with 1st AstraZeneca vaccine received a homologous second dose, except in Norway. Median distance to second dose was between 75-80 days, except in Norway. Upon heterologous schedule the second dose distance was longer.

Table 19. Description of doses per DAP (those with Janssen dose 1)

Measure	IT-ARS	IT-CASERTA	IT-PEDIANET	ES-BIFAP-PC	ES-BIFAP-PC-HOSP	ES-FISABIO	ES-SIDIAP	UK-CPRD	NL-PHARMO	NK-UOSL
janssen dose 1	74,964 (2.02%)	4,720 (0.50%)	0 (0.00%)	425,080 (3.29%)	320,661 (3.23%)	204,156 (4.04%)	260,420 (4.19%)	.	45,654 (1.75%)	5,065 (0.09%)
janssen dose 2	12 (0.02%)	0 (0.00%)		680 (0.16%)	673 (0.21%)	13 (0.01%)	71 (0.03%)	.	223 (0.49%)	23 (0.45%)
other dose 2	51,761 (69.05%)	3,482 (73.77%)		303,130 (71.31%)	231,177 (72.09%)	152,680 (74.79%)	176,990 (67.96%)		20,803 (45.57%)	907 (17.91%)
pfizer dose 2	21,661 (28.90%)	1,406 (29.79%)		158,884 (37.38%)	141,270 (44.06%)	82,791 (40.55%)	23,316 (8.95%)		15,747 (34.49%)	682 (13.46%)
novavax dose 2	0 (0.00%)	0 (0.00%)		0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)		0 (0.00%)	0 (0.00%)
moderna dose 2	30,100 (40.15%)	2,076 (43.98%)		144,226 (33.93%)	89,903 (28.04%)	69,882 (34.23%)	153,660 (59.00%)		3,872 (8.48%)	225 (4.44%)
astrazeneca dose 2	0 (0.00%)	0 (0.00%)		10 (0.00%)	.	.	14 (0.01%)		13 (0.03%)	0 (0.00%)
unk dose 2	0 (0.00%)	0 (0.00%)		10 (0.00%)	0 (0.00%)	.	0 (0.00%)		1,171 (2.56%)	0 (0.00%)
Amongst persons with janssen dose 2 distance	.	.		.	.	.	.		.	.
Minimum	41	.		21	21	23	19		19	37
25%	153	.		49	49	81	57		38	109
50%	163	.		55	55	154	150		117	158
75%	183	.		74	74	185	190		199	176
Maximum	187	.		231	231	213	362		362	188
Amongst persons with other dose 2 distance	.	.		.	.	.	.	.	.	.
Minimum	24	.		19	19	19	19	.	19	19
25%	184	.		160	159	161	162	.	190	118
50%	189	.		177	179	176	181	.	199	152
75%	199	.		191	191	192	204	.	212	172
Maximum	250	.		348	348	327	518	.	406	277
janssen dose 3	0 (0.00%)	.		.	.	0 (0.00%)	.	.	.	0 (0.00%)
other dose 3	12 (0.02%)	.		405 (0.10%)	313 (0.10%)	114 (0.06%)	571 (0.22%)	.	924 (2.02%)	21 (0.41%)
pfizer dose 3	11 (0.01%)	.		107 (0.03%)	72 (0.02%)	63 (0.03%)	399 (0.15%)	.	492 (1.08%)	15 (0.30%)
novavax dose 3	0 (0.00%)	.		0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	.	0 (0.00%)	0 (0.00%)
moderna dose 3	.	.		297 (0.07%)	240 (0.07%)	50 (0.02%)	170 (0.07%)	.	374 (0.82%)	6 (0.12%)
astrazeneca dose 3	0 (0.00%)	.		.	.	0 (0.00%)	.	.	.	0 (0.00%)
unk dose 3	0 (0.00%)	.		0 (0.00%)	0 (0.00%)	.	0 (0.00%)	.	56 (0.12%)	0 (0.00%)
Amongst persons with other dose 3 distance	.	.		.	.	.	.	.	.	.
Minimum	73	.		50	121	88	57	.	.	55
25%	140	.		235	286	173	256	.	.	95
50%	160	.		292	300	196	321	.	.	142
75%	221	.		311	317	214	353	.	.	176
Maximum	246	.		365	365	244	423	.	.	247
unk dose 1	0 (0.00%)	16 (0.00%)		755 (0.01%)	75 (0.00%)	3,217 (0.06%)	0 (0.00%)	7,079 (0.05%)	198,148 (7.61%)	81 (0.00%)

Table 19 shows that Janssen COVID-19 vaccine 1st dose was used very little, especially in Norway and UK. In most data sources, people with 1st Janssen vaccine did not receive a second dose with Janssen. The majority had a booster dose with either Moderna or Pfizer vaccine, with highly variable distances across regions.

9.1.6 Background rates for AESI & Negative control outcomes

Table 20. Standardized background incidence rates (CI 95%) for AESIs and NCO per DAP: incidence rate 2019 and 2020 before COVID-19 infection, and 2020 after COVID-19 infection, before vaccination. This table is not readable in word. Annex 3 has a readable output.

9.1.7 AESIs

9.1.7.1 Acute Coronary Artery Disease (CAD)

Coronary Artery Disease is characterized by the presence of atherosclerotic plaques in the coronary arteries potentially leading to an inadequate blood supply to the myocardium. Acute symptoms almost always include unstable angina and myocardial infarction, with a high mortality burden[25]. Except for PEDIANET-IT (children only), CAD cases were frequently identified in all databases during the study period. In general, the 2020 rates before COVID-19 diagnosis were lower than the rates in 2019 (Annex 3), this pattern has been already described by Willame C., et al.[26]and it is most likely due to underutilization of healthcare services during the COVID-19 pandemic waves in 2020. In 2019, the lowest incidence rates were observed in PHARMO-NL (47.43/100,000 PY), followed by UK-CPRD and ES-BIFAP-PC, which may at least partly be explained by the provenance of the events in these data sources which are GP-based. In data sources with GP and Hospital linkage, background rates in 2019 were from 140.5/100,000 (ES-BIFAP-PC_HOSP), 214.9 (ES-SIDIAP) to 315.94/100,000 P Y (ES-FISABIO) (Annex 3). FISABIO included also outpatient specialist visits. Code counts and meanings are available in annex 4. The incidence rates in Norway (NO-UOSL) in 2019 is twice the rate of ES-FISABIO (685.65/100,000 PY), and the meaning of the events was from GP, outpatient specialists, hospitalization (primary & secondary) and causes of death (annex 4). Incidence rates of CAD *after COVID-19 diagnosis* are around three fold higher than in 2020 or 2019 in all data sources. A clear pattern of increasing incidence rates of CAD with age was observed but was less pronounced in PHARMO (Figure 5). Rates in IT-Caserta were too low, based on selection in ETL process that needs correction for next data instance.

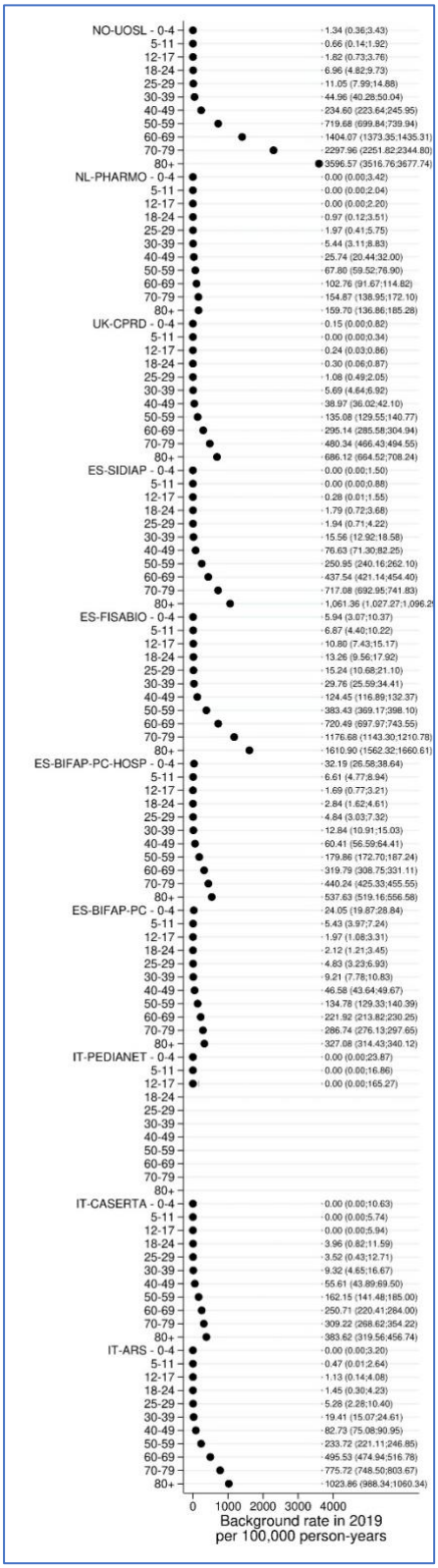


Figure 5: Incidence rates 2019 stratified by DAP and age for CAD

[25] Ralapanawa U, Sivakanesan R. Epidemiology and the Magnitude of Coronary Artery Disease and Acute Coronary Syndrome: A Narrative Review. Journal of Epidemiology and Global Health 2021;11(2):169-177.

[26] Willame C, Dodd C, Durán CE, Elbers R, Gini R, Bartolini C, Paoletti O, Wang L, Ehrenstein V, Kahlert J, Haug U, Schink T, Diez-Domingo J, Mira-Iglesias A, Carreras JJ, Vergara-Hernández C, Giaquinto C, Barbieri E, Stona L, Huerta C, Martín-Pérez M, García-Poza P, de Burgos A, Martínez-González M, Bryant V, Villalobos F, Pallejà-Millán M, Aragón M, Carreras JJ, Souverein P, Thurin NH, Weibel D, Klungel OH, Sturkenboom M. Background rates of 41 adverse events of special interest for COVID-19 vaccines in 10 European healthcare databases - an ACCESS cohort study. Vaccine. 2023 Jan 4;41(1):251-262. doi: 10.1016/j.vaccine.2022.11.031.

9.1.7.2 Acute Disseminated Encephalomyelitis (ADEM)

Acute Disseminated Encephalomyelitis (ADEM) is an autoimmune acute multifocal disease of the central nervous system (CNS) typically following an infectious disease or immunization. Clinically, it mostly appears in the pediatric population, however it may also occur in adults (Figure 6)[27]. No cases of ADEM were identified in IT-CASERTA, IT-PEDIANET (small pediatric cohort) and NL-PHARMO (no ICPC codes), or Norway (no ICPC codes and ICD10 codes were not available at enough decimals). Rates in IT-Caserta were too low, based on selection in ETL process that needs correction for next data instance. Incidence rates of ADEM in 2019 and 2020 before COVID-19 remained were very low in GP-only data sources such as UK-CPRD or ES BIFAP-PC, highest rates were observed in data sources that had hospital discharge data (ARS (0.15/100,000PY), FISABIO (0.58), SIDIAP (0.11), BIFAP_PC_HOSP (0.20)) (Annex 3). Similar figures have been described in the ACCESS project.[28] Only Spanish databases BIFAP-PC_HOSP and SIDIAP reported cases in 2020 and a slightly increased incidence rate of ADEM after COVID-19 infection. No age-specific pattern could be observed. Rates in IT-Caserta were too low, based on selection in ETL process that needs correction for next data instance.

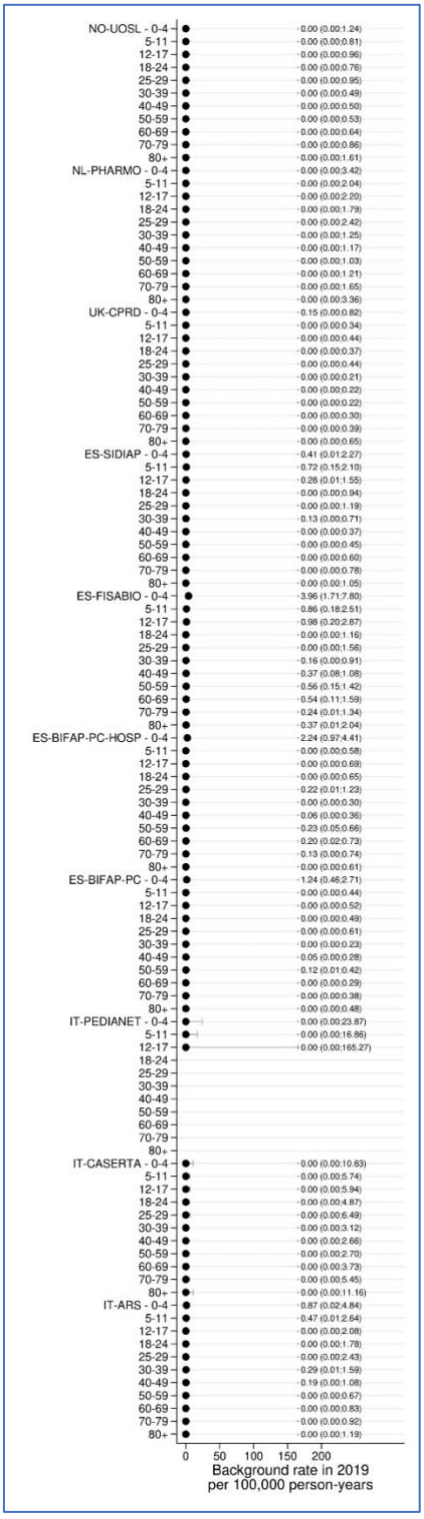


Figure 6: Incidence rates 2019 stratified by DAP and age for ADEM

[27] Javed A, Khan O. Acute disseminated encephalomyelitis. In: Tselis A.C, Booss J, Eds. Handbook of Clinical Neurology. Elsevier Ed. 2014.
[28] Willame C, Dodd C, Durán CE, Elbers R, Gini R, Bartolini C, et al. Background rates of 41 adverse events of special interest for COVID-19 vaccines in 10 European healthcare databases - an ACCESS cohort study. Vaccine. 2023 Jan 4;41(1):251-262. doi: 10.1016/j.vaccine.2022.11.031.

9.1.7.3 Acute Respiratory Distress Syndrome

Acute Respiratory Distress Syndrome (ARDS) is a life-threatening condition. It occurs when a diversity of triggers causes acute, bilateral pulmonary inflammation and increased capillary permeability leading to acute hypoxemic respiratory failure[29]. According to the latest 2012 "Berlin definition"[30], the diagnosis of ARDS requires, in summary: An acute process developing within one week of a new clinical insult or new or worsening respiratory symptoms. Radiography images showing bilateral opacities not fully explained by effusions, lobal or lung collapse, or nodules, and; Impairment of oxygenation as measured by a $Pa_{O2}/Fi_{O2} \leq 300$ mm Hg in the presence of a positive end-expiratory pressure of at least 5 cm H2O. There are no ICPC codes, therefore rates are absent in PHARMO. Code counts show (annex4) that most cases are observed in hospital and coded as secondary diagnoses. Data sources including hospital settings and primary and secondary diagnoses (ES-FISABIO, ES-SIDIAP, IT-ARS, IT-CASERTA, NO-UOSL) showed low rates in 2019: 0.76/100,000 PY (ARS), 0.15 (IT-CASERTA), 23.2 (ES-FISABIO), 6.29 (ES-SIDIAP) and 3.8 (NO-UOSL). ES-BIFAP-PC-HOSP (0.80/100,000) only used primary discharge diagnoses and had a lower rate. Rates in NO-UOSL were lower because of lack of decimals in ICD10 codes for hospitalization. Rates in IT-Caserta were too low, based on selection in ETL process that needs correction for next data instance.
The rates increased 10-800 fold after COVID-19 infection (Annex 3). In data sources that could identify ARDS well (ES-SIDIAP, ES-FISABIO) we observed a U-shaped age related pattern (Figure 7).

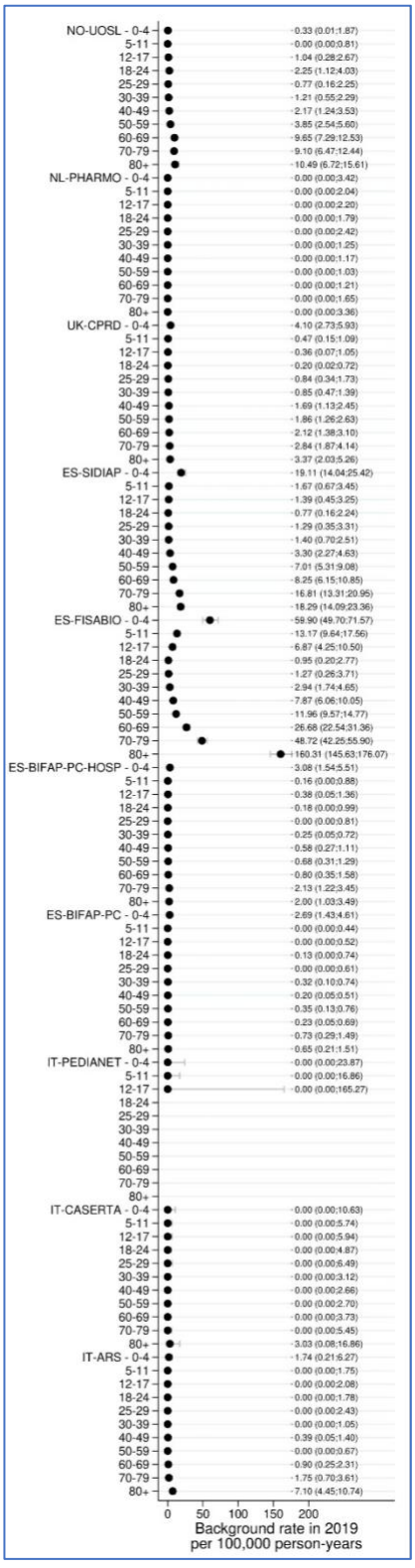


Figure 7: Incidence rates 2019 stratified by DAP and age for ARDS

[29] Hendrickson K, Peltan Ithan, Brown S. The Epidemiology of Acute Respiratory Distress Syndrome Before and After Coronavirus Disease 2019. Crit Care Clin 2012;37:703-716.
[30] The ARDS Definition Task Force. Acute Respiratory Distress Syndrome: The Berlin Definition. JAMA.2012;307(23):2526–2533. doi:10.1001/jama.2012.5669

9.1.7.4 Acute Kidney Injury

Acute kidney injury (AKI) is defined as an abrupt (within hours) decrease in kidney function, which encompasses both injury (structural damage) and impairment (loss of function) generally asymptomatic. It is a syndrome that rarely has a sole and distinct pathophysiology[31]. AKI usually begins with sudden decrease in glomerular filtration rate (GFR) followed by an increase in serum creatinine concentration or oliguria. It occurs in the frame of both an acute and chronic illness. Patients present in two ways: I) a patient might present with an acute illness such as sepsis, or II) the patient is exposed to condition known to be associated with AKI such as a major surgery[32]. Definition and rates in ACCESS.[33]

AKI rates were increasing with age (Figure 8), which is as expected. Rates in PHARMO, Oslo, Caserta and Pedianet were very low and not reliable due to lack of codes (ICPC) or detail in available hospitalization ICD10 codes (Norway). Rates in IT-Caserta were too low, based on selection in ETL process that needs correction for next data instance. Code counts (annex 4) show that AKI is mostly identified as secondary diagnosis in hospital. In BIFAP-PC-HOSP only primary discharge diagnoses were used.

In 2019 rates were highest in ES-SIDIAP (533.6/100,000PY) followed by ES-FISABIO (360.3/100,000PY and IT-ARS (163.2). Rates were 64.2 (BIFAP-PC), 167.1 (UK-CPRD) in GP only data sources.AKI rates decreased during the lock down in 2020, prior to COVID-19 disease and increased after COVID-19 infection between 5- 10 fold in IT-ARS, ES-FISABIO and ES-SIDIAP. Increases in GP data sources were lower (Annex 3). AKI rates were consistent with the background rates from ACCESS (Willame et al.).[34] Rates increased with increasing age.

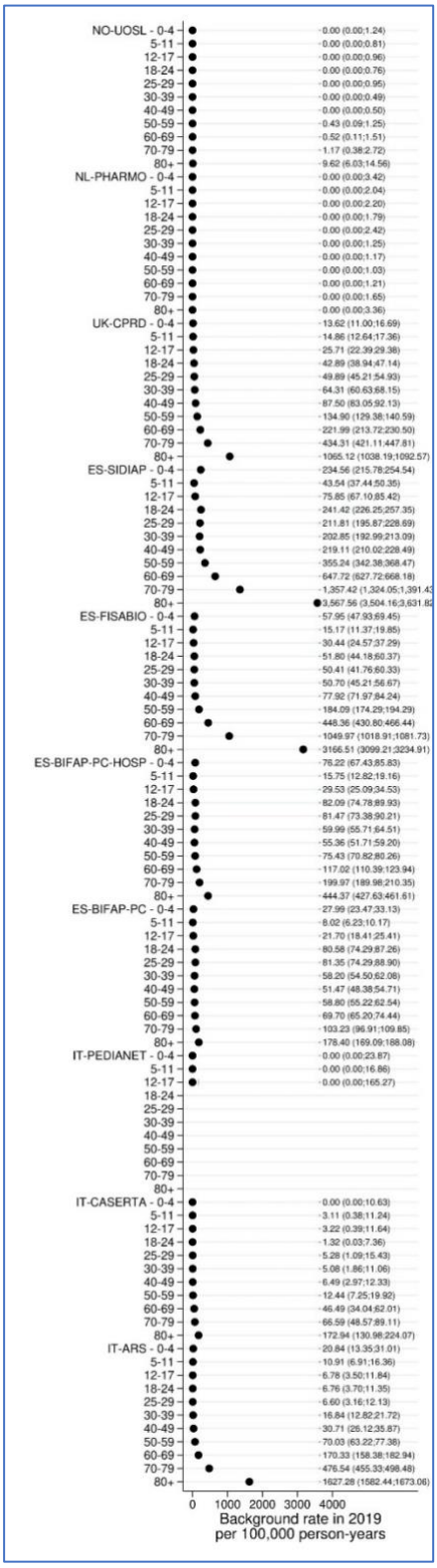


Figure 8: Incidence rates 2019 stratified by DAP and age for AKI

[31] Makris K, Spanou L. Acute Kidney Injury: Definition, Pathophysiology and Clinical Phenotypes. Clin Biochem Rev. 2016;37(2):85-98.

[32] Ronco C, Bellomo R, Kellum JA. Acute kidney injury. The Lancet [Internet]. 23 november 2019 [geciteerd 16 juli 2020];394(10212):1949/64. Beschikbaar op: http://www.sciencedirect.com/science/article/pii/S0140673619325632

[33] https://zenodo.org/record/5235557#.ZFP_N3ZBxPY

[34] Willame C, Dodd C, Durán CE, Elbers R, Gini R, Bartolini C, et al. Background rates of 41 adverse events of special interest for COVID-19 vaccines in 10 European healthcare databases - an ACCESS cohort study. Vaccine. 2023 Jan 4;41(1):251-262. doi: 10.1016/j.vaccine.2022.11.031.

9.1.7.5 Acute Liver Injury (ALI)

Acute liver failure is characterized by an acute abnormality of liver blood tests (equal or more than two-to three times elevation of transaminases) in an individual without underlying chronic liver disease. The disease process is associated with development of a coagulopathy of liver etiology, jaundice and clinically apparent altered level of consciousness due to hepatic encephalopathy. The condition of patients who develop coagulopathy, but do not have any alteration to their level of consciousness is defined as acute liver injury (ALI). The clinical course of ALF is initiated with a severe ALI.[35]

Background rates of ALI are consistent with rates reported in ACCESS.[36]

There were no cases detected in NL-PHARMO (no ICPC codes) and IT-PEDIANET (only children). Rates in IT-Caserta were too low, based on selection in ETL process that needs correction for next data instance.

Event counts showed that this diagnosis is often made in primary care, emergency room and hospital setting.

Incidence rates in 2019 were 7.2/100,000 PY in ES-BIFAP-PC, 6.75 in UK-CPRD GP data sources. In GP+hospital settings rates were 10.4 (ES-SIDIAP), 27.4 (ES-FISABIO) and 10.3 in ES-BIFAP-PC-HOSP (no secondary discharge diagnoses). The incidence was 9.3 100,000 PY in NO-UOSL, but not all ICD10 subcodes could be identified since only 3 digits were available for hospitalizations. Incidence rates decreased slightly in 2020 but doubled after COVID-19 infection.

Incidence rates showed an increase in the rate of ALI with increasing age in most data sources.

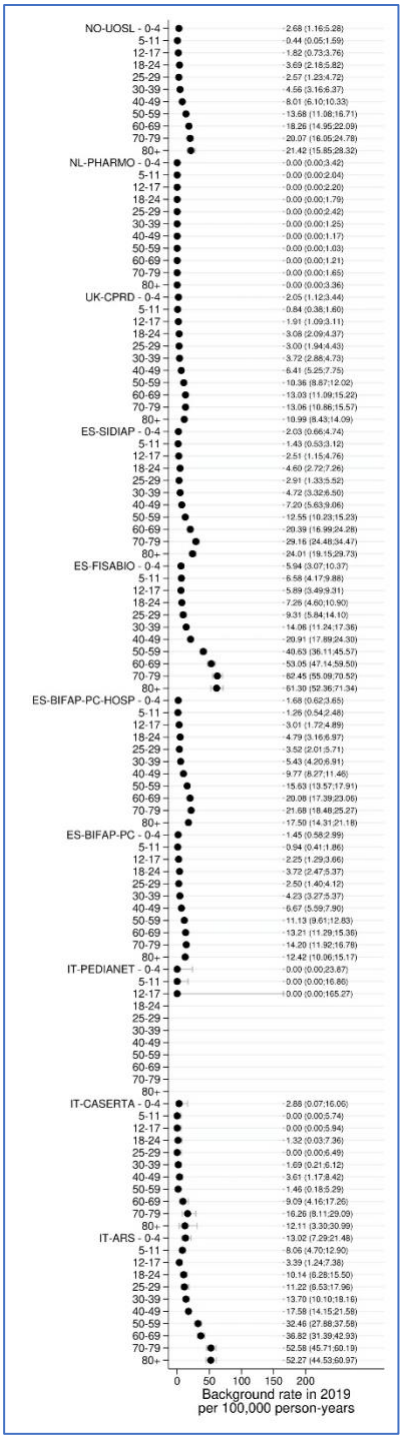


Figure 9: Incidence rates 2019 stratified by DAP and age for AL

I

[35] Wendon J, Cordoba J, Dhawan A, Larsen FS, Manns M, Nevens F, et al. EASL Clinical Practical Guidelines on the management of acute (fulminant) liver failure. Journal of Hepatology 2017;66(5):1047–81.

[36] Willame C, et al. Background rates of 41 adverse events of special interest for COVID-19 vaccines in 10 European healthcare databases - an ACCESS cohort study. Vaccine. 2023 Jan 4;41(1):251-262. doi: 10.1016/j.vaccine.2022.11.031

9.1.7.6 Anaphylaxis

Anaphylaxis is a serious systemic hypersensitivity reaction that is usually rapid in onset (from minutes to hours) and may cause death. Severe anaphylaxis is characterized by potentially life-threatening compromise in breathing and/or the circulation and may occur without typical skin features or circulatory shock being present. It may also affect a huge variety of organs (respiratory, skin, cardiovascular, or gastrointestinal system)[37]. In ACCESS, background rates varied between 1.5 and 25 /100,000 PY, which is comparable with the background rates in this study for 2019 and to previous studies as well (Annex 3).[38] Code counts (annex 4) by meanings (origin of the code) show that most cases are diagnosed in primary care or in emergency rooms. No specific ICPC codes were available, leading to zero cases in NL-PHARMO and NO-UOSL. Rates in 2019 were 5.7 /100,000 PY in IT-ARS (no GP data), 1.8 in IT-PEDIANET (only children), 21.9 in ES-BIFAP-PC, 23.9 in ES-BIFAP-PC-HOSP, 14.95 in ES-SIDIAP and 42.5 in ES-FISABIO. Rates decreased in 2020 in most data sources. As compared to 2019 rates, incidence did not change a lot after COVID-19 (Annex 3). As expected, rates were highest in youngest age groups (figure 10).

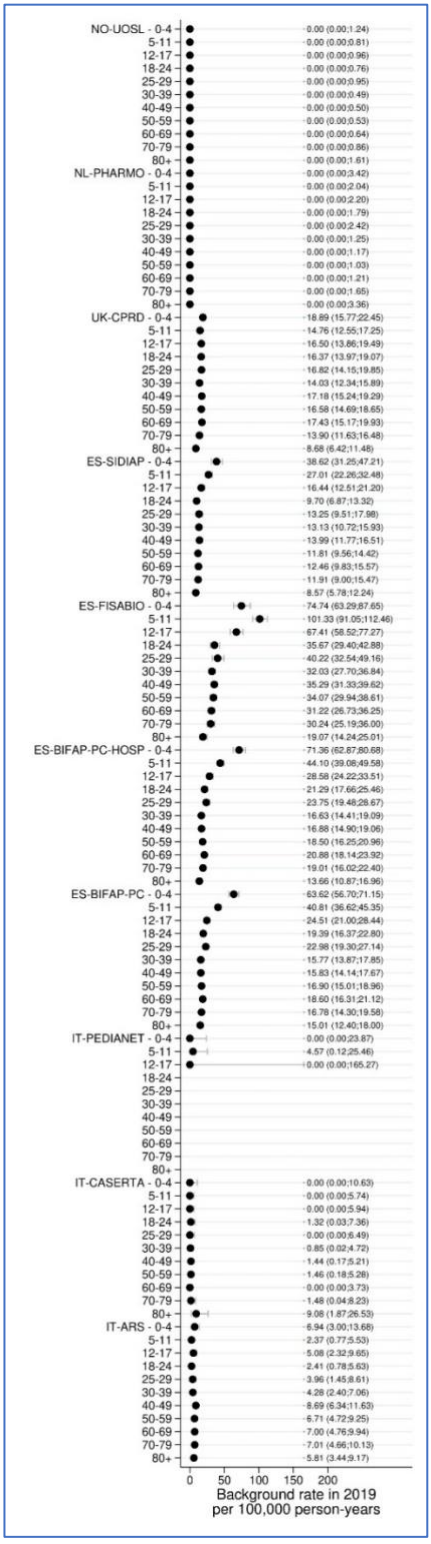


Figure 10: Incidence rates 2019 stratified by DAP and age for Anaphylaxis

[37] Turner PJ, Worm M, Ansotegui IJ, El-Gamal Y, Rivas MF, Fineman S, Geller M, Gonzalez-Estrada A, Greenberger PA, Tanno LK, Borges MS, Senna G, Sheikh A, Thong BY, Ebisawa M, Cardona V; WAO Anaphylaxis Committee. Time to revisit the definition and clinical criteria for anaphylaxis? World Allergy Organ J. 2019 Oct 31;12(10):100066. doi: 10.1016/j.waojou.2019.100066. PMID: 31719946; PMCID: PMC6838992.

[38] Law B, Sturkenboom M. AESI Background Rates Literature Review & Visualitzation for Anaphylaxis [Data set]. Zenodo. 2022. https://doi.org/10.5281/zenodo.6676584

9.1.7.7 Anosmia, ageusia

Anosmia is the loss of smell function, which can affect one or more specific smells. Two typical mechanisms are: i) conductive/traumatic (e.g., chronic rhinosinusitis), or ii) sensorineural (e.g, Alzheimer or drug-related).[39,40] Ageusia is the loss of taste function. A scale that ranges from 0, which refers to no taste, to 4, which refers to total loss of taste, may be useful in evaluation.[41]

Variation of background rates of anosmia and ageusia among data bases is explained by their data provenance (mostly diagnosed in primary care). The rates presented in this report are consistent with the ones reported in the ACCESS project.[42] In 2019, rates in data sources with GP information were 23.5 100,000 PY in ES-BIFAP-PC, 33.8 in ES-FISABIO, 25.1 in ES-SIDIAP, 7.5 in UK-CPRD, 5.1 in NL-PHARMO and 37.7 in NO-UOSL. Rates increased in 2020 before COVID-19 recorded diagnoses and increased 20-100 fold after COVID-19 diagnosis. Consistently with the clinical characterization of symptomatic COVID-19 disease, post-COVID-19 rates of anosmia and ageusia increased several times over the background incidence in all databases; just as example, in ES-SIDIAP the rate increased from 25.13 in 2019 to 1,324.61/100,000 PY in 2020 (Annex 3). Stratification by age shows the highest incidence of anosmia and ageusia between 50 and 80 years of age (Figure 11).

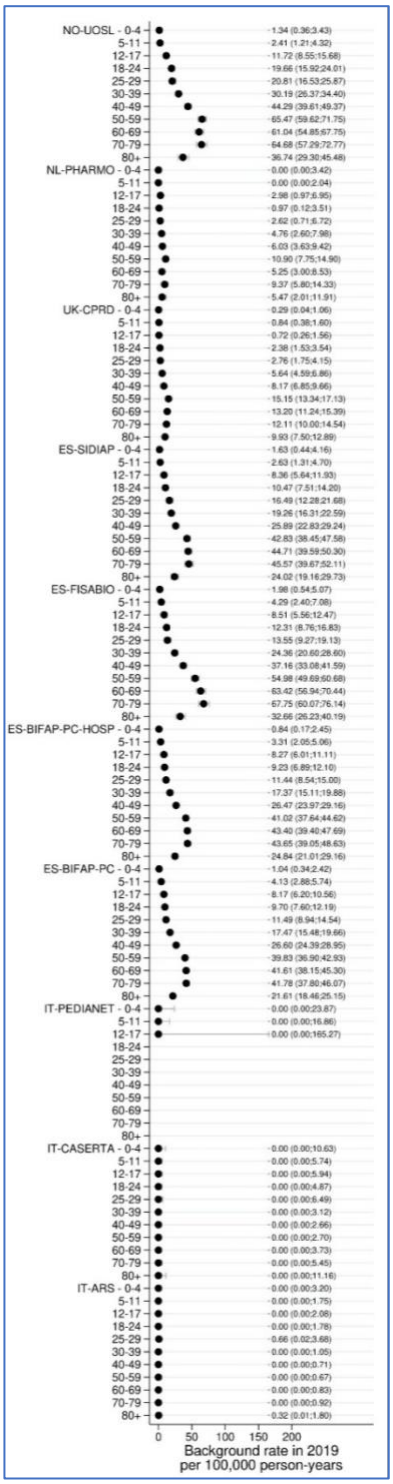


Figure 11: Incidence rates 2019 stratified by DAP and age for anosmia/ageusia

[39] Egbers, T, Willame, C, Belbachir, L, Souverein, P, Martín-Pérez, M, García-Poza, P, & Sturkenboom, MCJM. (2021). ACCESS-Background rate of adverse events-definition –Anosmia & Ageusia (1.0). Zenodo. https://doi.org/10.5281/zenodo.5236687

[40] Boesveldt S, Postma EM, Boak D, Welge-Luessen A, Schöpf V, Mainland JD, Martens J, Ngai J, Duffy VB. Anosmia-A Clinical Review. Chem Senses. 2017 Sep 1;42(7):513-523. doi: 10.1093/chemse/bjx025.

[41] Vaira LA, Salzano G, Deiana G, De Riu G. Anosmia and Ageusia: Common Findings in COVID19 Patients. Laryngoscope. 2020 Jul;130(7):1787. doi: 10.1002/lary.28692.

[42] Willame C, Dodd C, Durán CE, Elbers R, Gini R, Bartolini C, et al. Background rates of 41 adverse events of special interest for COVID-19 vaccines in 10 European healthcare databases - an ACCESS cohort study. Vaccine. 2023 Jan 4;41(1):251-262. doi: 10.1016/j.vaccine.2022.11.031.

9.1.7.8 Arrhythmia

According to the U.S. National Library of Medicine, cardiac arrhythmias are defined as any disturbances of the normal rhythmic beating of the heart or myocardial contraction. Cardiac arrhythmias can be classified by the abnormalities in heart rate, disorders of electrical impulse generation, or impulse conduction.[43]

Background rates of arrhythmia in 2019 and 2020 are comparable among databases according to their data provenance, and against ACCESS rates.[44]

The code counts showed that GP diagnosis was very frequently the meaning of the diagnosis code, followed by secondary discharge diagnosis (annex 4). In 2019, rates of arrhythmia were highest in datasources covering primary and secondary care: 661/100,000 PY in BIFAP-PC-HOSP (included GP and primary discharge diagnoses only), 1587 in ES-FISABIO, 1600 in SIDIAP and 2272 in NO-UOSL. IN GP only data sources incidence was 605/100,000 PY in ES-BIFAP-PC, 840 in UK-CPRD, 0 in PHARMO (no specific ICPC codes). In IT-ARS rates were 654/100,000PY. Rates were lower in CASERTA, due to ETL error for the instance that needs correction. Rates in 2020 decreased slightly (Annex 3). The incidence of arrhythmia increases after the age of 50 years, *see Figure 12*. Rates after COVID-19 increased 2-5-fold in all databases (Annex 3).

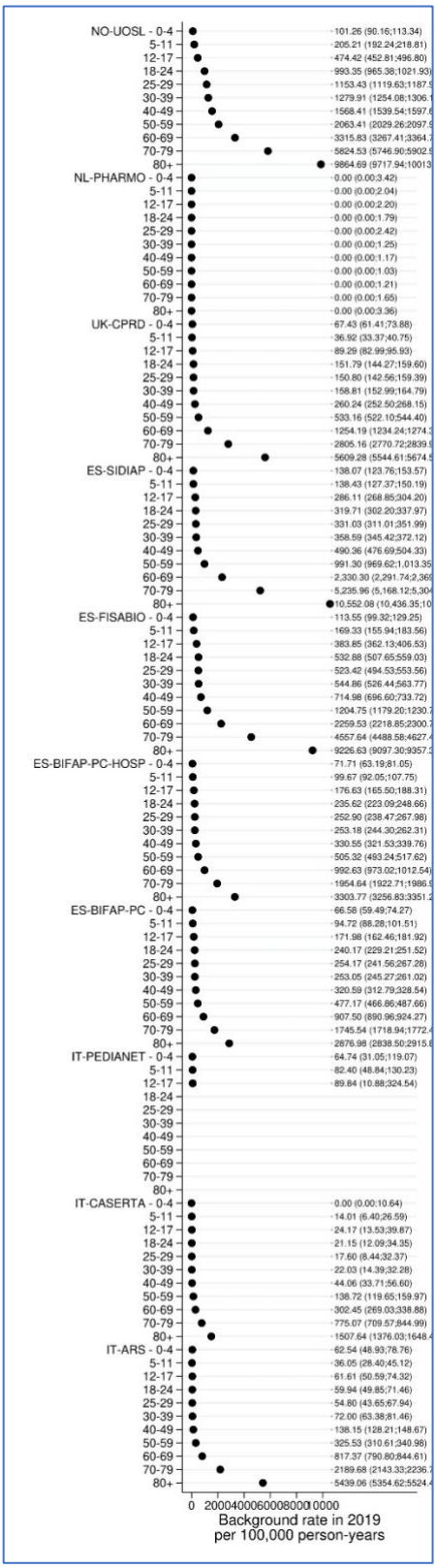


Figure 12: Incidence rates 2019 stratified by DAP and age for anosmia/ageusia.

[43] Arrhythmias, Cardiac. National Library of Medicine. Accessed: May 8, 2023. Available at: https://www.ncbi.nlm.nih.gov/mesh/68001145

[44] Willame C, Dodd C, Durán CE, Elbers R, Gini R, Bartolini C, et al. Background rates of 41 adverse events of special interest for COVID-19 vaccines in 10 European healthcare databases - an ACCESS cohort study. Vaccine. 2023 Jan 4;41(1):251-262. doi: 10.1016/j.vaccine.2022.11.031.

9.1.7.9 Arterial thrombosis

Arterial thrombosis is the pathological counterpart of the normal hemostatic process. Platelets adhere to collagen fibers surrounding the transected blood vessels, aggregate and a plug is formed. The main difference in the origin of arterial thrombosis is that the initial trauma is usually much less, in most cases consisting of damage to, or contraction of endothelial cells exposing subendothelial tissue to the blood stream. Arterial thrombosis frequently leads to rupture of the plaque in the artery wall and the ensuing thrombotic events are the triggers for acute ischemic injury in these diseases[45]. In this definition we include ischemic stroke and myocardial infarction as arterial thrombosis.
This aggregated condition was not separately investigated in ACCESS, its components were. Code counts (annex 4) show that these codes often have meaning emergency room visit (ARS) or primary discharge diagnosis, in data sources that include primary care, this is more often the meaning of codes than hospitalizations. Standardized rates in 2019 for GP only data sources were 122.3/100,000 PY for ES-BIFAP-PC, 95.9 for UK-CPRD, and 23.9 for NL-PHARMO. In data sources with primary and secondary care rates in 2019 were 208/100,000 PY (BIFAP-PC-HOSP), 521 in ES-FISABIO, 351 in ES-SIDIAP and 532 in NO-UOSL. Rates lowered in 2020 prior to COVID-19 infections as compared to 2019 and increased after COVID-19 infection (Annex 3). Data from Pottegard et al. shows the rate of arterial thrombosis to be 452/100,000PY in Denmark and 471 in Norway in 2019 which are like our rates[46]. We observe that arterial thrombosis is age dependent in most data sources, except in PHARMO (Figure 13).

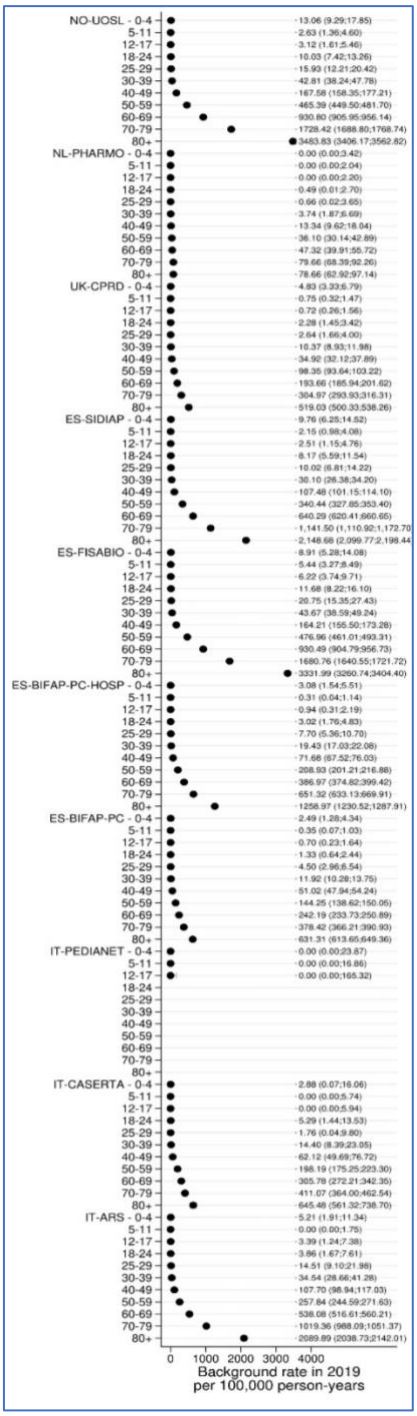


Figure 13: Incidence rates 2019 stratified by DAP and age for arterial thrombosis.

[45] Choi J, Kermode JC. New therapeutic approaches to combat arterial thrombosis: better drugs for old targets, novel targets, and future prospects. Mol Interv. 2011 Apr;11(2):111-23. doi: 10.1124/mi.11.2.9. PMID: 21540471.
[46] Pottegård A, Lund LC, Karlstad Ø, Dahl J, Andersen M, Hallas J, Lidegaard Ø, Tapia G, Gulseth HL, Ruiz PL, Watle SV, Mikkelsen AP, Pedersen L, Sørensen HT, Thomsen RW, Hviid A. Arterial events, venous thromboembolism, thrombocytopenia, and bleeding after vaccination with Oxford-AstraZeneca ChAdOx1-S in Denmark and Norway: population based cohort study. BMJ. 2021 May 5;373:n1114. doi: 10.1136/bmj.n1114. PMID: 33952445; PMCID: PMC8097496.

9.1.7.10 Bell's Palsy

Facial nerve palsy is a peripheral neuropathy (impairment of the ability to wrinkle the forehead or to raise the eyebrow on the affected side); most cases are unilateral and occurs unexpectedly, with rapid progression (worsening over a short period of time). The resolution can be partial or complete with or without medical treatment in less than 10 days[47].
Code counts Annex 4) showed that diagnoses most often are made in primary care and emergency room visits. Standardized incidence rates of Bell´s Palsy in 2019 for GP-only data sources were 1.68 in IT-PEDIANET (children only), 43.6 in ES-BIFAP-PC, 43.6 in UK-CPRD and 7.7 in NL-PHARMO. In data sources with GP and secondary care data standardized rates were 43/100,00 PY (ES-BIFAP-PC-HOSP), 78.6 in ES-FISABIO, 79 in ES-SIDIAP and 44.6 in NO-UOSL (lacking detail in hospital codes). In datasources with hospitalization and emergency room visit rates were 27.3 for IT-ARS. These figures are similar the ones reported by Nasrren et al., in Canadian population.[48]
The incidence post-COVID-19 disease (2020) increased in all databases, except in IT-ARS, probably due to the data provenance of this data source (Annex 3). Increased rates of Bell's Palsy after COVID-19 have been also reported by Tamaki et al., in 348,088 COVID-19 patients (82/100,000 persons)[49]. Bell's palsy has been proposed as the only major neurological manifestation in COVID-19 patients[50]. There were no cases reported after COVID-19 in IT-CASERTA and IT-PEDIANET. Data in the instance used by NL-PHARMO (GP data not covering the ICPC code) and IT-CASERTA (restricted population to survivors) seem not fit for purpose for this event. (Figure 14) As depicted in figure 14, there is a clear age-dependent trend in the incidence of this event, with no cases in IT-PEDIANET (pediatric cohort).

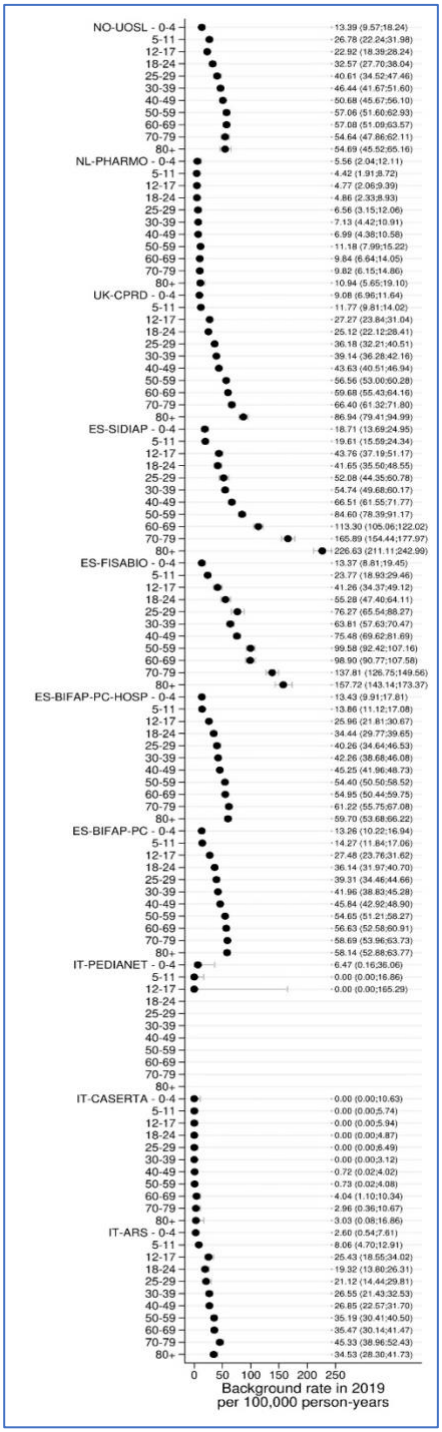


Figure 14: Incidence rates 2019 stratified by DAP and age for Bell's Palsy

[47] Law B. Facial Nerve Palsy. AESI Case Definition Companion. Guide for 1st Tier AESI. SPEAC V1.0. 11-Feb-2021.
[48] Nasreen S, Calzavara A, Buchan SA, Thampi N, Johnson C, Wilson SE, Kwong JC; Canadian Immunization Research Network (CIRN) Provincial Collaborative Network (PCN) Ontario investigators. Background incidence rates of adverse events of special interest related to COVID-19 vaccines in Ontario, Canada, 2015 to 2020, to inform COVID-19 vaccine safety surveillance. Vaccine. 2022 May 26;40(24):3305-3312. doi: 10.1016/j.vaccine.2022.04.065.
[49] Tamaki A, Cabrera CI, Li S, Rabbani C, Thuener JE, Rezaee RP, Fowler N. Incidence of Bell Palsy in Patients With COVID-19. JAMA Otolaryngol Head Neck Surg. 2021 Aug 1;147(8):767-768. doi: 10.1001/jamaoto.2021.1266.
[50] Gupta S, Jawanda MK, Taneja N, Taneja T. A systematic review of Bell's Palsy as the only major neurological manifestation in COVID-19 patients. J Clin Neurosci. 2021 Aug;90:284-292. doi: 10.1016/j.jocn.2021.06.016.

9.1.7.11 Chilblain-like lesions

Chilblains, also referred to as perniosis or pernio, is a condition of the skin which manifests as erythematous to violaceous macules, papules, plaques, or nodules in sites of cold exposure and damp environments (idiopathic chilblains). The most common sites for involvement are the fingers and toes and it is frequently accompanied by a sensation of itching, burning, or pain. It is postulated that pernio results from an abnormal vascular response to cold exposure. Cold-induced vasoconstriction of vasospasm resulting in hypoxemia that stimulates an inflammatory response is a potential mechanism for the formation of skin lesions.
During the recent COVID-19 pandemic some patients were diagnosed with chilblain-like lesions located on the toes and fingers, without an underlying autoimmune disease or cold-exposure. The chilblain-like lesions manifest as multiple red-violaceous edematous lesions with papules and macules located on acral regions such as toes, the feet (heel, sole) and/or the fingers, asymptomatic or associated with pruritis of mild pain. Because of the similar presentation with chilblains, it is referred to as pseudo-chilblain of chilblain-like lesions[51]. Code counts (annex 4) show that this diagnosis is most commonly captured in GP records. Standardized rates (2019) in data sources with GP data kind of data sources were 5.68/100,000 PY in NL-PHARMO to 21.4 ES-BIFAP-PC, 49.3 in ES-FISABIO, 13.6 in ES-SIDIAP, 16.4 in UK-CPRD and 0 in NO-UOSL (Annex 3). These rates are like the ones reported in the ACCESS project. There is a slight increment of rates after COVID-19 diagnosis in the Spanish databases BIFAP_PC, BIFAP_PC-HOSP, FISABIO, and SIDIAP, and in Dutch PHARMO and the British CPRD (Annex 3).
There were no cases identified after COVID-19 in NO-UOSL, and in the Italian ARS, PEDIANET and Caserta. NL-PHARMO data were also low (Figure 15). Rates are highest in adolescents and increase again at old age.

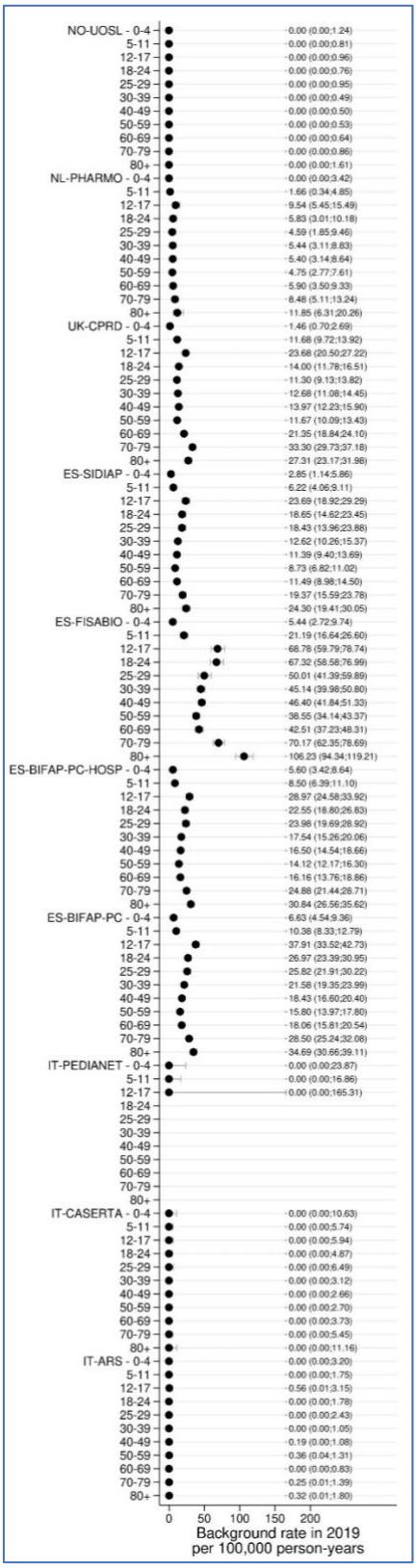


Figure 15: Incidence rates 2019 stratified by DAP and age for chilblain like lesions.

[51] Landa N, Mendieta-Eckert M, Fonda-Pascual P, Aguirre T. Chilblain-like lesions on feet and hands during the COVID-19 Pandemic. Int J Dermatol. 2020;59(6):739-743. doi:10.1111/ijd.14937

9.1.7.12 Coagulation disorders

A coagulation disorder is a problem with blood clotting. This can either be too much clotting leading to thrombosis, emboli or stroke, or little clotting leading to bleeding and stroke again. It includes entities such as deep vein thrombosis (DVT), pulmonary thromboembolism (PE), deep vein thrombosis (DVT), cerebrovascular stroke, limb ischemia, arterial thrombosis, or bleeding disorders, among others. In this study, the event *coagulation disorders* were defined as the combination of following events:

- Ischemic stroke
- Hemorrhagic stroke
- Cerebral venous sinus thrombosis
- Disseminated intravascular coagulation
- Acute myocardial infarction
- Thrombocytopenia
- Splanchnic venous thrombosis
- Deep venous thrombosis
- Pulmonary embolism, and
- Other venous thromboembolism diagnoses

Code counts show diagnosis is made most often through primary care, hospitalization or emergency room visit. Incidence rates of coagulation disorders among databases sharing the same data provenance appear similar both, in 2019 and 2020 before COVID-19. In GP only standardized rates were 425/100,000 PY in ES-BIFAP-PC, 347 in UK-CPRD and 88 in NL-PHARMO. In data sources with GP & hospital care rates were: 523/100,000 PY in ES-BIFAP-PC-HOSP, 655 in ES-FISABIO, 347 in ES-SIDIAP and 1057 in NO-UOSL. Rates in IT-ARS (hospital and emergency room) were 484/100,000 PY These figures are comparable to rates published elsewhere[52]. Rates lowered in 2020 prior to COVID. After COVID-19 disease increased importantly in all databases, in ES-FISABIO where the standardized incidence rate upraised from 425.23/100,000 PY in 2019 to 1196.57 /100,000 PY in 2020 after COVID-19 (Annex 3). This finding correlates with the clinical observation that SARS-CoV-2 infection may lead thromboembolic complications[53].

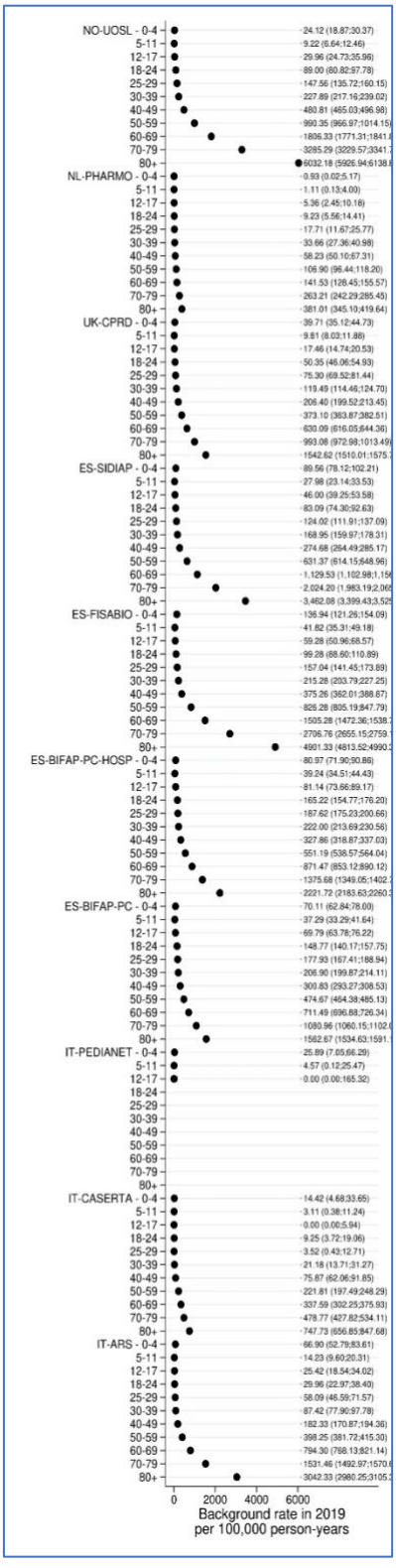


Figure 16: Incidence rates 2019 stratified by DAP and age for coagulation disorders

[52] Pottegård A, Lund LC, Karlstad Ø, Dahl J, Andersen M, Hallas J, Lidegaard Ø, Tapia G, Gulseth HL, Ruiz PL, Watle SV, Mikkelsen AP, Pedersen L, Sørensen HT, Thomsen RW, Hviid A. Arterial events, venous thromboembolism, thrombocytopenia, and bleeding after vaccination with Oxford-AstraZeneca ChAdOx1-S in Denmark and Norway: population based cohort study. BMJ. 2021 May 5;373:n1114. doi: 10.1136/bmj.n1114.

[53] Pottegård A, Lund LC, Karlstad Ø, Dahl J, Andersen M, Hallas J, Lidegaard Ø, Tapia G, Gulseth HL, Ruiz PL, Watle SV, Mikkelsen AP, Pedersen L, Sørensen HT, Thomsen RW, Hviid A. Arterial events, venous thromboembolism, thrombocytopenia, and bleeding after vaccination with Oxford-AstraZeneca ChAdOx1-S in Denmark and Norway: population based cohort study. BMJ. 2021 May 5;373:n1114. doi: 10.1136/bmj.n1114.

9.1.7.13 Cerebral Venous Sinus Thrombosis (CVST)

Cerebral venous sinus thrombosis (CVST) is a stroke subtype. It occurs when a blood clot forms in the brain's venous sinuses. This prevents blood from draining out of the brain. As a result, blood cells may break and leak blood into the brain tissues, forming a hemorrhage[54].

Code counts (annex 4) show that diagnosis is often made in hospital and recorded as secondary diagnosis. CVST is rare, standardized incidence rates in 2019 are lowest in GP only data sources: 0.31 cases per 100,000 PY in ES-BIFAP_PC, 0.60 in UK-CPRD, 0 in PHARMO (no ICPC code), whereas rates are higher in data sources with hospitalization data: 1.44 in IT-ARS, 0.92 in ES-BIFAP-PC-HOSP (no secondary discharge), 1.72 in ES-FISABIO, 1.24 in ES-SIDIAP and 0.84 in NO-UOSL (however lack of detailed discharge diagnosis codes leading to underestimation) (Annex 3). These rates are comparable to the ones reported in ACCESS and other studies on thromboembolic events[55]. Rates did not change in 2020, prior to COVID-19 diagnosis. Incidence rates (2020) of CVST after COVID-19 increased in ES-BIFAP_PC from 0.31 to 2.11 cases/100,000 PY, from 0.99 to 4.44/100,000 PY in ES-BIFAP_PC/HOSP, from 1.35 to 4.88/100,000 PY in ES-SIDIAP, and from 0.52 to 1.93/100,000 in UK-CPRD. There were no identified cases after COVID-19 disease in IT-ARS, ES-FISABIO, IT-Caserta, IT-PEDIANET, NL-PHARMO, and NO-UOSL (Figure 17).

Pottegard et al. reported rates of CVST of 1-2/100,000 in Denmark and Norway, consistent with our rates.

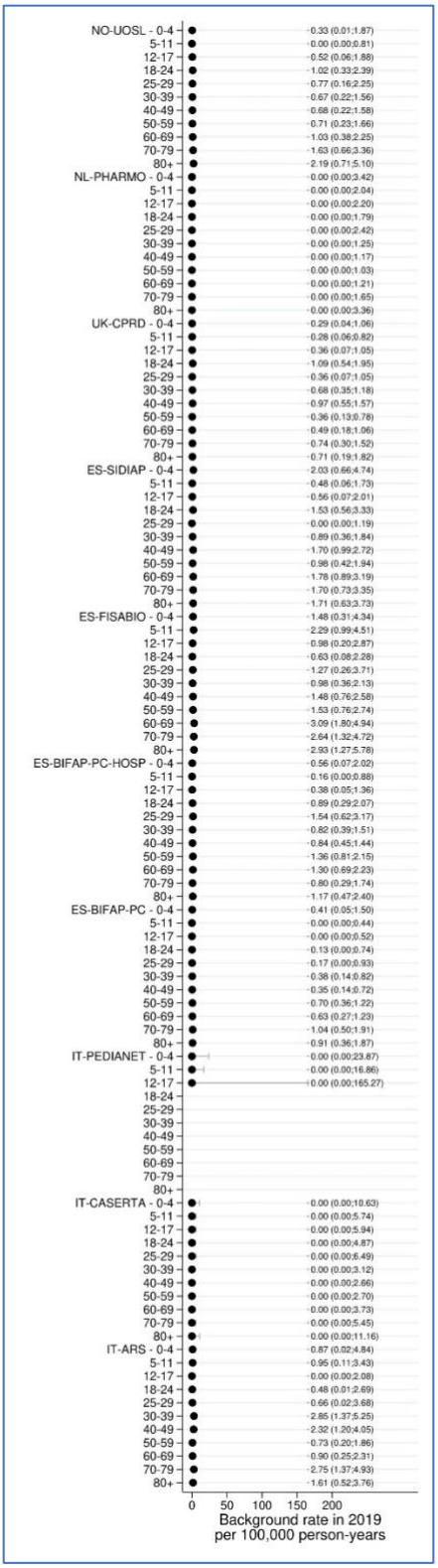


Figure 17: Incidence rates 2019 stratified by DAP and age for CVST

[54] Meng R, Dornbos D 3rd, Meng L, Wu Y, Liu Y, Li G, Li G, Li S, Sun F, Wang X, Ding Y, Ji X. Clinical differences between acute CVST and non-thrombotic CVSS. Clin Neurol Neurosurg. 2012 Nov;114(9):1257-62. doi: 10.1016/j.clineuro.2012.03.036. Epub 2012 Jun 5. PMID: 22676956.

[55] Pottegård A, Lund LC, Karlstad Ø, Dahl J, Andersen M, Hallas J,et al. Arterial events, venous thromboembolism, thrombocytopenia, and bleeding after vaccination with Oxford-AstraZeneca ChAdOx1-S in Denmark and Norway: population based cohort study. BMJ 2021;373:n1114. doi: 10.1136/bmj.n1114.

9.1.7.14 Diabetes type 1

Diabetes mellitus (diabetes) is a group of metabolic diseases characterized by metabolic and hormonal changes in the form of hyperglycemia and defects in insulin secretion. The clinical classification of diabetes includes type 1 diabetes, type 2 diabetes, gestational diabetes and diabetes due to other causes (e.g., genetic defects in b-cell function, genetic defects in insulin action, diseases of the exocrine pancreas, drug or chemical-induced, etc). Type 1 diabetes results from b-cell destruction, usually leading to absolute insulin deficiency. Thus, the patient becomes absolutely dependent of insulin from early ages. Long term effects of chronic diabetic hyperglycemia are associated with long-term damage, dysfunction, and failure of different organs, especially the eyes, kidneys, nerves, heart, and blood vessels[56].

Reported background rates of Diabetes type 1 in this study report are based on an algorithm based on medicines for diabetes type 1 (first insulin and no non-insulin glucose blood lowering agents prior)(Figure 18). It shows a bimodal peak with increase in younger age till age 40, and an increase in very old age. In very old age, there is misclassification of type 2 diabetes that is directly treated with insulin. ES-BIFAP requested these rates not be shown. For proper diabetes type 1, age should be restricted to age 25, to avoid misclassification of type 1 by gestational diabetes (peak in 25-39) and diabetes type 2 (peak after age 59).

Rates after COVID-19 go up 2-10 fold in most data sources compared to 2019 rates (annex 3).

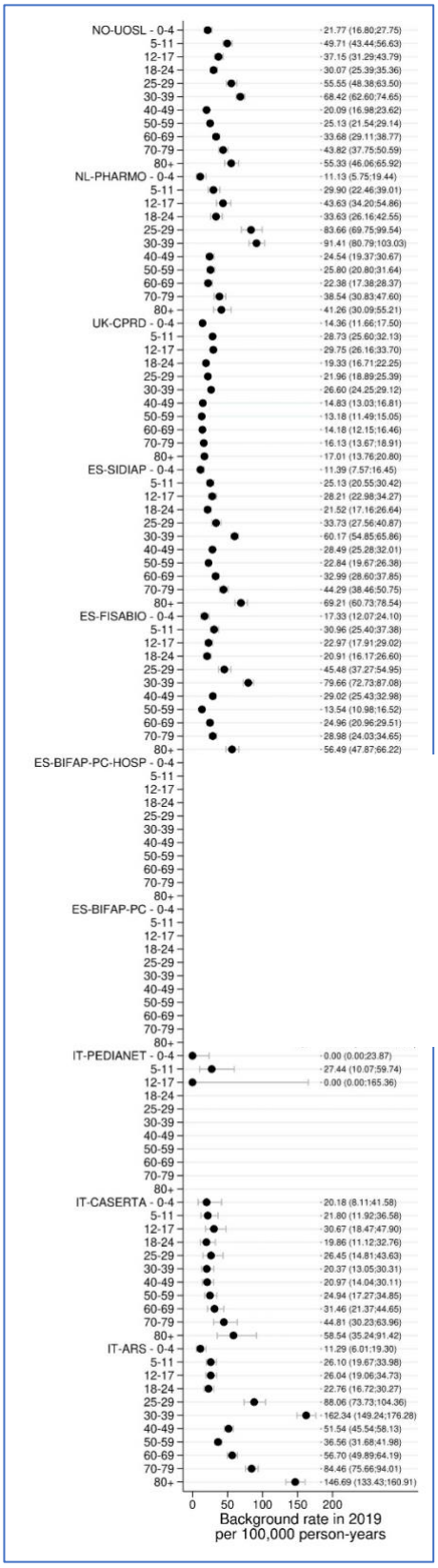


Figure 18: Incidence rates 2019 stratified by DAP and age for Diabetes type 1

[56] American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care. 2009 Jan;32 Suppl 1(Suppl 1):S62-7. doi: 10.2337/dc09-S062. PMID: 19118289; PMCID: PMC2613584.

9.1.7.15 Disseminated Intravascular Coagulation (DIC)

Disseminated intravascular coagulation (DIC) is a systemic pathophysiologic process and not a single disease entity. It results from an overwhelming activation of the coagulation cascade that consumes platelets and coagulation factors causing microvascular fibrin thrombi, which can result in multiorgan dysfunction syndrome from tissue ischemia. Some conditions associated with acute DIC include septic shock, exsanguinating trauma, burns, or acute promyelocytic leukemia[57].

Code counts (Annex 4) show that the diagnosis typically is recorded as a secondary discharge diagnosis or ICU admission.

In data sources with hospitalization data the standardized rate in 2019 was 1.13/100,000 PY (IT-ARS), 0.06 in ES-BIFAP-PC-HOSP (only primary discharge), 6.7 in ES-FISABIO, 3.11 in ES-SIDIAP and 2.4 in NO-UOSL (missing decimals in discharge codes and therefore potentially underestimated). Incidence rates were lower in GP only data sources: 0.11 ES-BIFAP-PC, 0.16 in UK-CPRD, 0 in NL-PHARMO (no ICPC codes). Rates in IT-CASERTA were too low due to ETL error that needs to be corrected.

In 2020 prior to COVI-19 infection, rates were slightly lower. The incidence rate of DIC after the diagnosis of COVID-19 disease increased 5-20 fold in IT-ARS, ES-BIFAP-PC_HOSP, ES-SIDIAP, ES-FISABIO (Annex 3). In data sources where the provenance of the data did not include hospital and/or emergency room information, there were 0 cases identified in 2020 after COVID-19. In general, background rates for same meaning are similar to the ones reported by Willame et al.[58] Data from BIFAP were lower than from other Spanish data sources, which is likely due to the use of primary discharge code only (Figure 19).

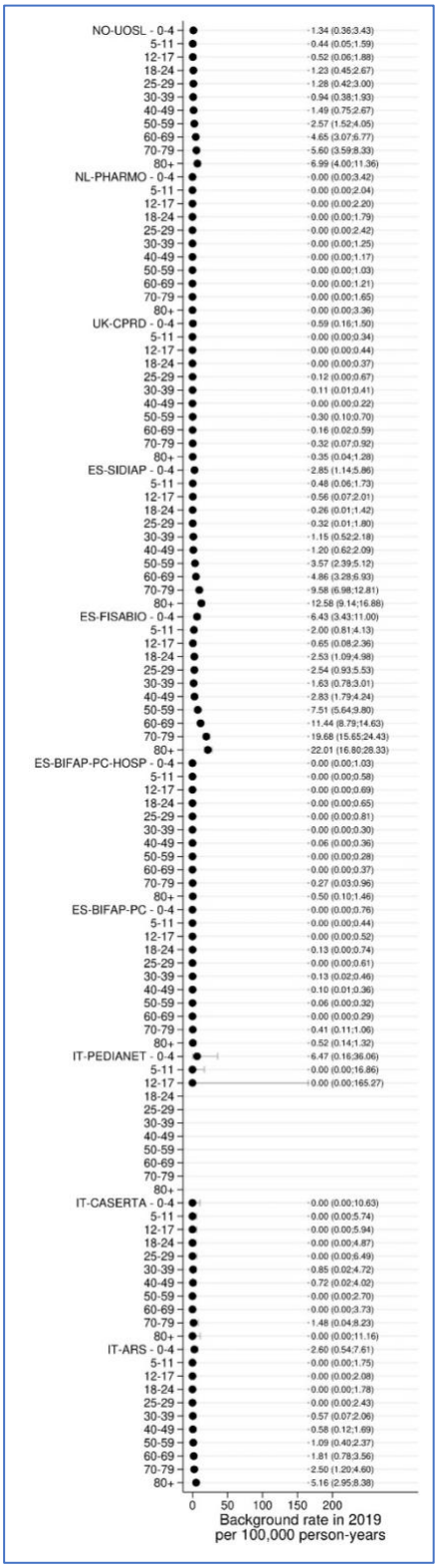


Figure 19: Incidence rates 2019 stratified by DAP and age for DIC

[57] Boral BM, Williams DJ, Boral LI. Disseminated Intravascular Coagulation. Am J Clin Pathol. 2016 Dec;146(6):670-680. doi: 10.1093/ajcp/aqw195. Epub 2016 Dec 24. PMID: 28013226.

[58] Willame C, Dodd C, Durán CE, Elbers R, Gini R, Bartolini C, Paoletti O, et al. Background rates of 41 adverse events of special interest for COVID-19 vaccines in 10 European healthcare databases - an ACCESS cohort study. Vaccine. 2023 Jan 4;41(1):251-262. doi: 10.1016/j.vaccine.2022.11.031.

9.1.7.16 Death (any cause)

Death takes place when the bodily processes that maintain homeostasis finally cease. Among all causes, this can happen as cardiopulmonary death, whole brain death, brainstem death, and higher brain death but each of those may have counter-intuitive results. Death is identified primarily from the persons or cause of death table, with the date of death, rather than diagnosis.

Standardized incidence rates in 2019 show zero cases in IT-PEDIANET (children only), and a very low rate in IT-CASERTA, because of the selection on survivors in the ETL, which is being corrected.

In other data sources IR in 2019 were 777/100,000 for IT-ARS, 712 in ES-BIFAP-PC, 796 in ES-FISABIO, 744 in ES-SIDIAP, 820 in UK-CPRD, 857 in NO-UOSL. The rate was lower in NL-PHARMO 446/100,000 PY, and the age-related increase was less.

In 2020 prior to COVID-19, standardized death rates were higher than in 2019. Death rates increased considerably (more than 10-fold) after a COVID-19 diagnosis in 2020. The age-related pattern is very consistent.

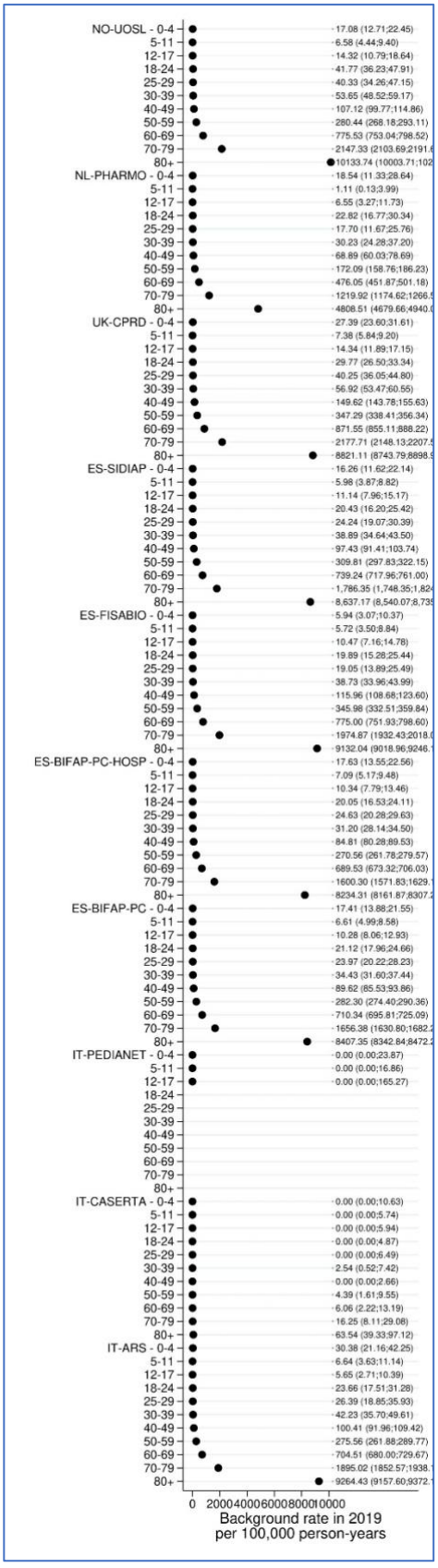


Figure 20: Incidence rates 2019 stratified by DAP and age for death

9.1.7.17 Death – sudden

The diagnosis and definition of sudden death are variable, but the generally recognized definition is based on the length of time between the onset of symptoms and death. It is considered as "sudden" when a non-violent and not otherwise explained death occurs in less than 24 hours from the onset of symptoms. It can occur in all age groups. The use of the term "sudden infant death syndrome" or "SIDS" should be restricted to deaths in the first year of life which remain unexplained after autopsy, i.e., meeting the criteria of level 1 or level 2 of diagnostic certainty and in the first year of life[59].
Sudden death is not easy to identify without a register with causes of death, which was available in NO-UOSL. In health care systems where the GP assesses causes of death, these may also be recorded.
Rates were 1.33/100,000 PY in IT-ARS, 0 in IT-CASERTA (due to ETL issue that is being corrected), 0.97 in ES-BIFAP-PC, 8.26 in ES-FISABIO, 3.9 in UK-CPRD and 11.8/100,000 PY in NO-UOSL.
Figure 21 shows the age specific rates, with very low incidence. In PHARMO, SIDIAP, and CASERTA no cases were discovered. In data sources that could identify cases of sudden death the rates increased considerably (2-12 fold) after COVID-19.

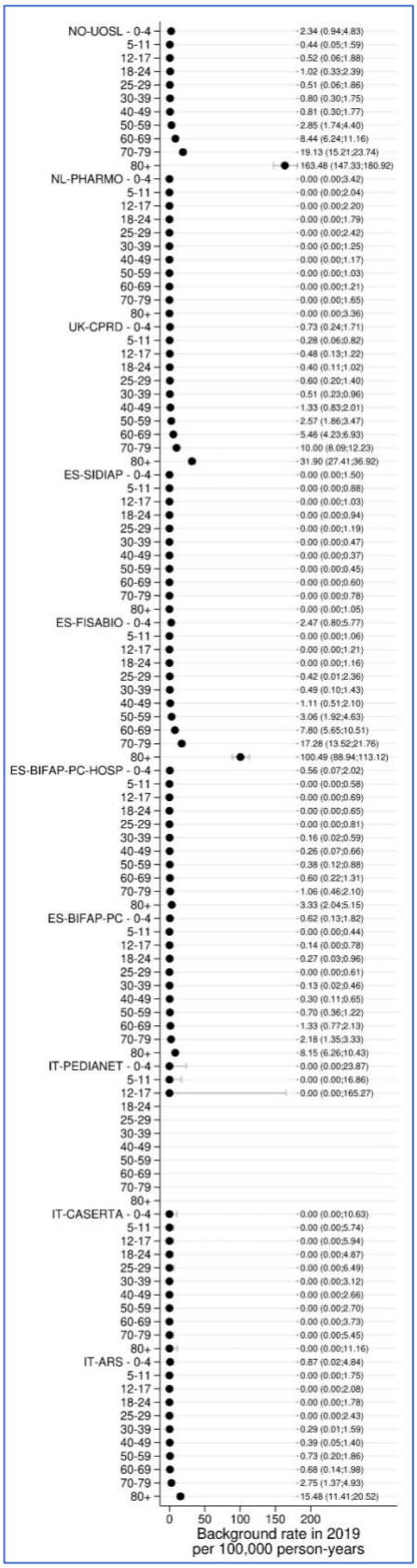


Figure 21: Incidence rates 2019 stratified by DAP and age for sudden death

[59] Jorch G, Tapiainen T, Bonhoeffer J, et al. Unexplained sudden death, including sudden infant death syndrome (SIDS), in the first and second years of life: case definition and guidelines for collection, analysis, and presentation of immunization safety data. Vaccine. 2007;25(31):5707- 5716. doi:10.1016/j.vaccine.2007.02.068

9.1.7.18 Erythema multiforme

Erythema multiforme (EM) is an acute hypersensitivity disorder characterized by symmetric red, patchy lesions, primarily on the arms and legs, and affecting mostly children and young adults. The cause is unknown, but EM frequently occurs as an immunologic process initiated by the virus or medications, including anticonvulsants, sulfonamides, nonsteroidal anti-inflammatory drugs, and other antibiotics. EM is the mildest of three skin disorders that are often discussed in relation to each other: more severe is Stevens-Johnson syndrome and the most severe of the three is toxic epidermal necrolysis (TEN). EM is defined by the morphology of the individual lesions and the pattern of distribution. Clinically, EM can be classified into with/without mucosal involvement.

Incidence rates of EM in 2019 and 2020 (Annex 3) are similar to the rates reported by the ACCESS project.[60] There were no cases identified in NL-PHARMO and NO-UOSL (lack of specific codes).

Code counts (annex 4) showed that this diagnosis is most often recorded in primary care or emergency rooms. In data sources with primary care data standardized incidence rates in 2019 were: 1.68/100,000 PY in IT-PEDIANET (children only), 4.3 in ES-BIFAP-PC, 14.0 in ES-FISABIO, 8.2 in ES-SIDIAP, 7.5 in UK-CPRD. In IT-ARS the rate was 9.4/100,000 PY mostly based on emergency room visits.

Regarding to the rates after COVID-19, Age standardized rates increased after COVID-19 in data sources with hospital diagnoses (Annex 3).

Standardized rates lowered during 2020 prior to COVID-19, and after COVID-19 in most data sources, except in ES-SIDIAP and ES-BIFAP-PC-HOSP.

Incidence rates of EM are higher during the childhood, as it is observed in figure 22 in data sources that could capture the diagnoses in primary care or in emergency rooms.

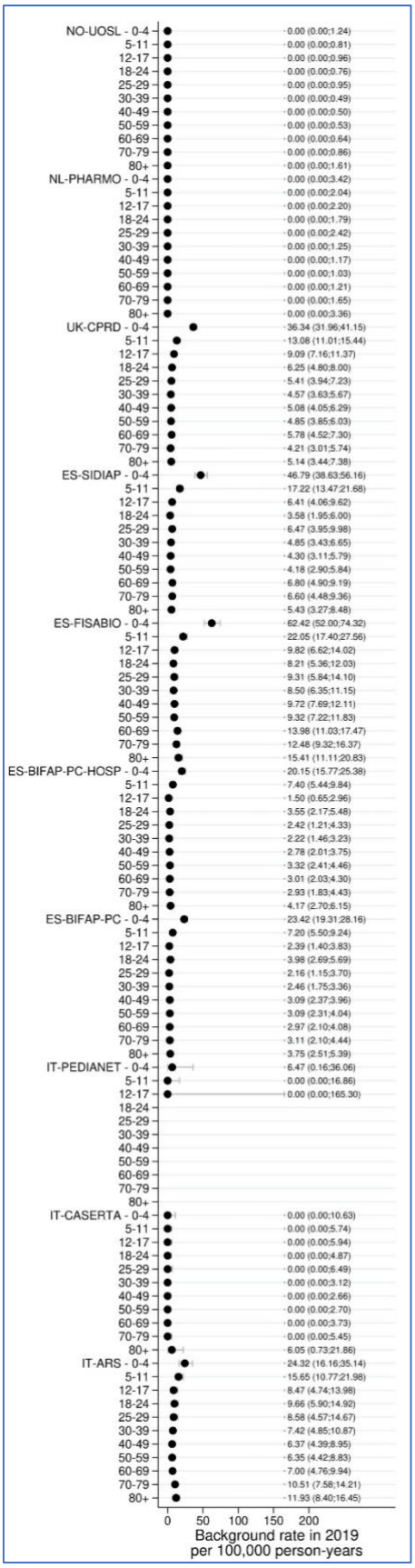


Figure 22: Incidence rates 2019 stratified by DAP and age for erythema multiforme

[60] Willame C, Dodd C, Durán CE, Elbers R, Gini R, Bartolini C, et al. Background rates of 41 adverse events of special interest for COVID-19 vaccines in 10 European healthcare databases - an ACCESS cohort study. Vaccine. 2023;41(1):251-262. doi: 10.1016/j.vaccine.2022.11.031.

9.1.7.19 Generalized convulsion (non-epileptic, non-febrile)

Seizures are paroxysmal alterations of neurologic functions caused by the excessive, hypersynchronous discharge of neurons in the brain, most commonly resulting in sudden, involuntary muscular contractions, sensory disturbances, autonomic dysfunction and behavioral abnormalities, and impairment or loss of consciousness. Epilepsy is one of the most common and disabling neurologic conditions, characterized by a recurrent and enduring predisposition to generate unprovoked brain seizures.
Code lists for generalized convulsions were restricted to non-epileptic and non-febrile generalized convulsions by the code list task force, and used for this run. This phenotype will be changed in subsequent analyses. The current restrictions makes the rates incompatible with ACCESS[61] rates or other publications[62].
Code counts show that this condition was mostly diagnosed in primary care or emergency rooms.
Rates in NO-UOSL are very low, due to the fact that they had only 3rd level ICD10 codes and missed the specific codes in their instance, fort he same reason rates in NL-PHARMO were zero.
In data sources with primary care or emergency room visits standardized rates were 30.5/100,000 PY in IT-ARS, 3.7 in ES-BIFAP-PC, 4.3 in ES-BIFAP-PC-HOSP, 38.3 in ES-FISABIO, 0 in ES-SIDIAP and 18.4 in UK-CPRD.
Post-COVID-19 rates of generalized convulsion did not really increase.
There were no post-COVID-19 cases in NO-UOSL, NL-PHARMO, IT-PEDIANET, ES-FISABIO and IT Caserta.

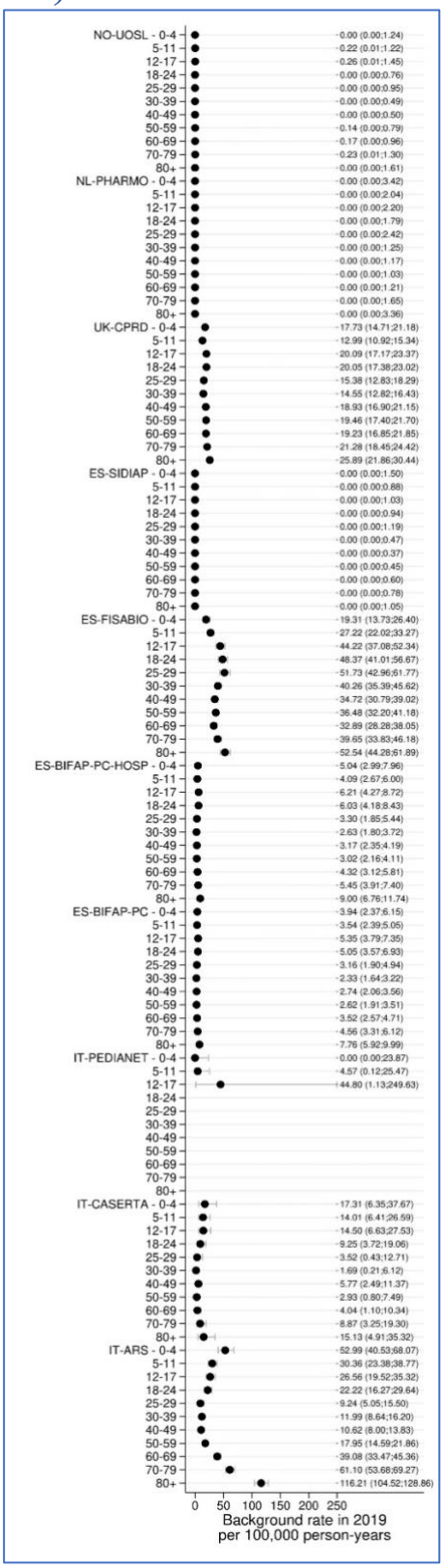


Figure 23: Incidence rates 2019 stratified by DAP and age for erythema multiforme

[61] Willame C, Dodd C, Durán CE, Elbers R, Gini R, Bartolini C, et al. Background rates of 41 adverse events of special interest for COVID-19 vaccines in 10 European healthcare databases - an ACCESS cohort study. Vaccine. 2023;41(1):251-262. doi: 10.1016/j.vaccine.2022.11.031.

[62] Law, Barbara, & Sturkenboom, Miriam. Generalized convulsion: Background rates literature review and visualization (1.0) [Data set]. Zenodo. 2021. https://doi.org/10.5281/zenodo.7638909

9.1.7.20 Guillain Barré Syndrome (GBS)

Guillain–Barré syndrome (GBS) is considered an immune-mediated disorder that constitutes an important proportion of acute flaccid paralyses cases worldwide. Its etiology and pathophysiology are not fully understood. Autoimmune antibodies and/or inflammatory cells are known to cross-react targeting peripheral nerves and roots. This leads to their demyelination and/or axonal damage, resulting in sensory abnormalities, weakness in limbs or cranial nerve-innervated muscles, hypo- or areflexia, autonomic dysfunctions, and a cytoalbuminologic dissociation in the cerebrospinal fluid (CSF). The weakness can reach its clinical nadir within 2–4 weeks. In approximately a quarter of cases, this disorder may lead to neuromuscular respiratory failure[63].

The global annual incidence of GBS is estimated to be between 0.6 and 4 cases per 100,000 persons,[64] the ACCESS project in 10 European databases reported rates between 1.34 and 4.42/100,000 PY.[65] The code counts showed that GBS is most often recorded in primary care and as primary discharge diagnosis of hospitalization.

In 2019 standardized incidence rates were 3.6/100,000 PY in IT-ARS, 1.16 in ES-BIFAP-PC, 1.94 in ES-BIFAP-PC-HOSP, 5.0 in ES-FISABIO, 4.8 in ES-SIDIAP, 2.4 in UK-CPRD (annex 3). In NL-PHARMO, IT-CASERTA and NO-UOSL rates were not reliable due to issues in specific codes and or ETL for these data instances.

Rates in 2020 were lower, which may be due to less influenza due to lock down measures, but strong increases after COVID-19 infections. The most important increases are seen in ES-FISABIO and ES-SIDIAP (from 4.77 to 26.88/100,000).

As presented in figure 24, GBS incidence increases after the age of 50 and reduces again in 80+, which is consistent with known age patterns.

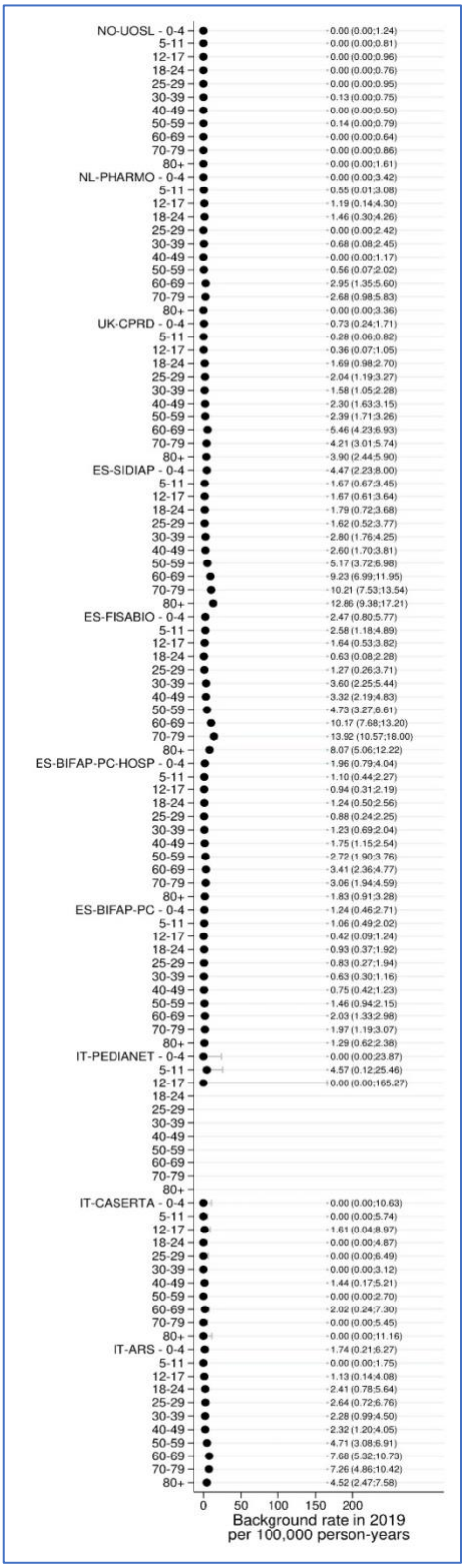


Figure 24: Incidence rates 2019 stratified by DAP and age for erythema multiforme

63 Sejvar JJ, Kohl KS, Gidudu J, et al.; Brighton Collaboration GBS Working GroupGuillain-Barre syndrome and Fisher syndrome: case definitions and guidelines for collection, analysis, and presentation of immunization safety data. Vaccine. 2011;29(3):599-612. https://doi.org/10.1016/j.vaccine.2010.06.003.

64 Hughes RA, Cornblath DR. Guillain–Barre syndrome. Lancet 2005;366(9497):1653–66.

65 Willame C, Dodd C, Gini R, Durán CE, Thomsen RM, Wang L, et al. Background rates of Adverse Events of Special Interest for monitoring COVID-19 vaccines (2.0). Zenodo. 2011. https://doi.org/10.5281/zenodo.5255870

9.1.7.21 Haemophagocytic lymphohistiocytosis (HLH)

Haemophagocytic lymphohistiocytosis (HLH) is an uncommon hematologic systemic inflammatory disorder characterized by an uncontrolled proliferation of activated lymphocytes, histiocytes, and macrophages in organs (skin, spleen, and liver) which secrete high amounts of inflammatory cytokines and destroy other blood cells. The onset of HLH occurs before the age of one year in approximately 70 percent of cases and can be potentially life-threatening. This disorder can be inherited or acquired, caused by certain conditions or diseases such as infections, immunodeficiency, and cancer. Signs and symptoms include fever, lymphadenopathy, hepatomegaly, splenomegaly, and pancytopenia.[66]
The code counts (annex 4) show that this condition is often diagnosed in hospital, but also primary care. Standardized incidence rates in 2019 are 0.22/100,000 PY in IT-ARS, 0.05 in ES-BIFAP-PC, 0.18 in ES-BIFAP-PC-HOSP, 0.91 in ES-FISABIO, 0.44 in ES-SIDIAP, 0.18 in UK-CPRD (Annex 3). There were no cases detected in IT-Caserta, IT-PEDIANET, and NL-PHARMO and NO-UOSL (Figure 25). Rates in 2020 prior to COVID-19 were similar. Standardized rates increased (2-10 fold) post COVID-19 in ES-BIFAP-PC, ES-BIFAP-PC/HOSP, ES-FISABIO, ES-BIFAP, and UK-CPRD (Annex 3).

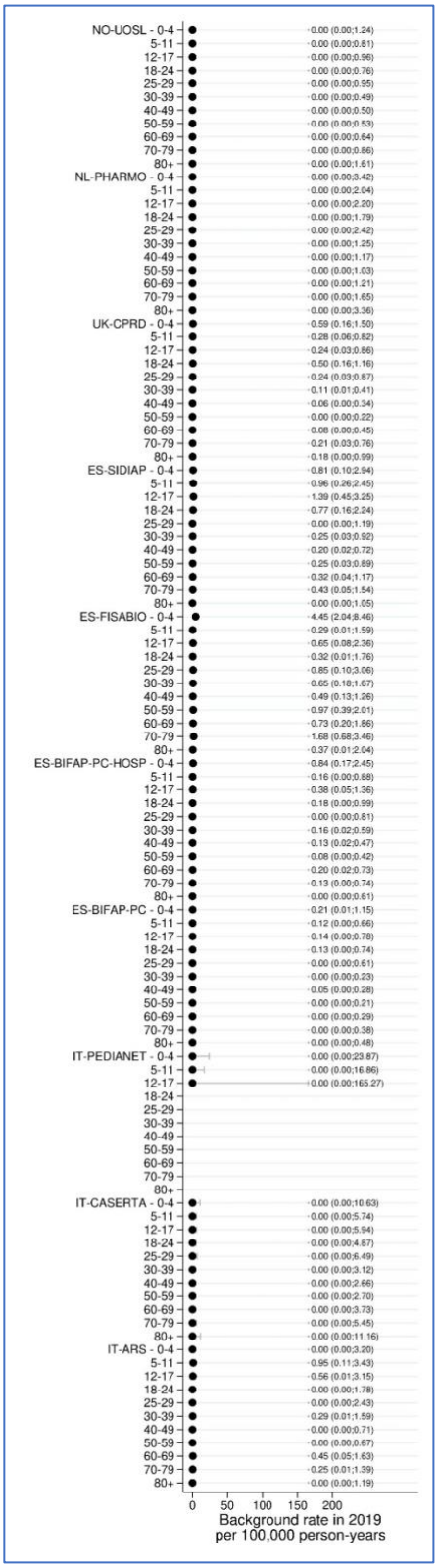


Figure 25: Incidence rates 2019 stratified by DAP and age for HLH

[66] Jordan MB, Allen CE, Greenberg J, Henry M, Hermiston ML, Kumar A, Hines M, Eckstein O, Ladisch S, Nichols KE, Rodriguez-Galindo C, Wistinghausen B, McClain KL. Challenges in the diagnosis of hemophagocytic lymphohistiocytosis: Recommendations from the North American Consortium for Histiocytosis (NACHO). Pediatr Blood Cancer. 2019 Nov;66(11):e27929. doi: 10.1002/pbc.27929.

9.1.7.22 Kawasaki´s disease (KD)

Kawasaki disease (KD), also known as Kawasaki syndrome, is an acute febrile illness characterized by inflammation of blood vessels throughout the body that primarily affects children younger than 5 years of age (80% of cases). Older children and teenagers can also get KD, but this is uncommon. The syndrome is more common in boys than girls. KD's etiology is unknown, although a virus is suspected to be the cause. Clinical diagnosis is based on symptoms and physical findings, which include 5 days of a fever higher than 39ºC, trunk and/or genital area rash, swelling of the hands and feet, irritation and redness of the whites of the eyes (conjunctivitis), swollen lymph glands in the neck and tongue, irritation and inflammation of the mouth, lips, and throat, joint pain, diarrhea, vomiting, and abdominal pain. KD can be a leading cause of acquired heart disease, coronary artery dilatations, and aneurysms.[67]

Code counts (annex 4) showed that the diagnosis is made but in hospital and in primary care. No ICPC codes were available (zero cases for PHARMO) and ICD10 required at least one decimal (not available for NO-UOSL in this instance). IT-Caserta rates were low to the ETL error that needs to be corrected.

Standardized incidence rates in 2019 showed rates of 1.22 /100,000 PY in IT-ARS, 3.50 IT-PEDIANET, 0.73 in ES-BIFAP-PC, 1.24 in ES-BIFPA-PC-HOSP, 2.66 in ES-FISABIO, 1.03 in ES-SIDIAP, 0.89 in UK-CPRD.

Rates were similar in 2020 prior to COVID-19 diagnoses and in increased 2-10 fold after COVID-19 diagnosis

Rates of KD are higher in children less than 4 years-old, with rates going from 6.47/100,000 PY in IT-PEDIANET to 20.94/100,000 PY in IT-ARS (Figure 26). These results are similar to the rates reported by the ACCESS project[68], by Gubernot et al., in US children[69], and by Nasreen et al., in Canadian children[70]. High post-COVID-19 rates of KD must be understood with caution due to clinical similarities of KD and multi-inflammatory syndrome; this situation could lead a potential misclassification bias, *see more* in 10.1.3.23 Multi-inflammatory Syndrome.

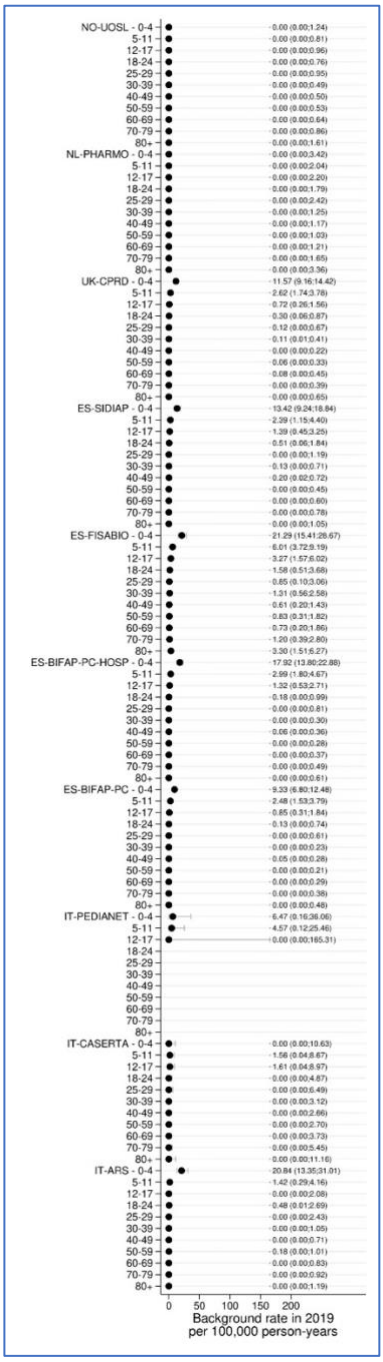


Figure 26: Incidence rates 2019 stratified by DAP and age for Kawasaki's disease.

[67] Phuong LK, Bonetto C, Buttery J, Pernus YB, Chandler R, Goldenthal KL, Kucuku M, Monaco G, Pahud B, Shulman ST, Top KA, Ulloa-Gutierrez R, Varricchio F, de Ferranti S, Newburger JW, Dahdah N, Singh S, Bonhoeffer J, Burgner D; Brighton Collaboration Kawasaki Disease (KD) Working Group. Kawasaki disease and immunisation: Standardised case definition & guidelines for data collection, analysis. Vaccine. 2016 Dec 12;34(51):6582-6596. doi: 10.1016/j.vaccine.2016.09.025. Epub 2016 Nov 15. PMID: 27863715.

[68] Willame C, Dodd C, Gini R, Durán CE, Thomsen RM, Wang L., et al. Background rates of Adverse Events of Special Interest for monitoring COVID-19 vaccines (2.0). Zenodo. 2021. https://doi.org/10.5281/zenodo.5255870

[69] Gubernot D, Jazwa A, Niu M, Baumblatt J, Gee J, Moro P, et al. U.S. Population-Based background incidence rates of medical conditions for use in safety assessment of COVID-19 vaccines. Vaccine. 2021 Jun 23;39(28):3666-3677. doi: 10.1016/j.vaccine.2021.05.016.

[70] Nasreen S, Calzavara A, Buchan SA, Thampi N, Johnson C, Wilson SE, Kwong JC; Canadian Immunization Research Network (CIRN) Provincial Collaborative Network (PCN) Ontario investigators. Background incidence rates of adverse events of special interest related to COVID-19 vaccines in Ontario, Canada, 2015 to 2020, to inform COVID-19 vaccine safety surveillance. Vaccine. 2022 May 26;40(24):3305-3312. doi: 10.1016/j.vaccine.2022.04.065.

9.1.7.23 (Meningo) encephalitis

Encephalitis is defined as inflammation of the parenchyma of the brain. It is a pathologic diagnosis, in which the presence of inflammation, oedema, and neuronophagia (neuronal cell death) is demonstrated by histopathology.[71] Meningoencephalitis is diagnosed with the focal accumulations of a mixed inflammatory cell infiltrate in the meninges and brain and is characterized by necrosis of brain parenchyma (with all cellular elements affected, especially in the periventricular region, and often associated with calcification), reactive microglial and astroglial proliferation, and the occurrence of enlarged cells (neuronal and glial elements) with intranuclear inclusions.[72]
Code counts (annex 4) show that the diagnoses is most often recorded in primary care and hospital diagnoses.
In 2019 the standardized incidence rates in settings with hospital or primary care were 6.1/100,000 PY in IT-ARS, 3.4 ES-BIFAP-PC, 6.5 in ES-BIFAP-PC-HOSP, 12.6 in ES-FISABIO, 7.7 in ES-SIDIAP, 3.6 in UK-CPRD, 6.6 in NL-PHARMO and 22.9 in NO-UOSL.
Incidence rates of (meningo)encephalitis are higher in children 0 to 4 year-of-age, and in 70 years and older, which was consistently observed (*see figure 27)*. In general, 2019 overall rates of meningo(encephalitis) in this study are comparable to the ones reported in the ACCESS project;[73] (Annex 3). Gubernot et al., reported a rate of 6.9 to 7.3/ 100,000 in general US population.[74] With exception of NL-PHARMO, IT-Caserta, and IT-PEDIANET, all data sources reported a decrease in the rates in 2020 before COVID-19 and an increment in the 2020 rates of (meningo) in the period after COVID-19 diagnosis (Annex 3).

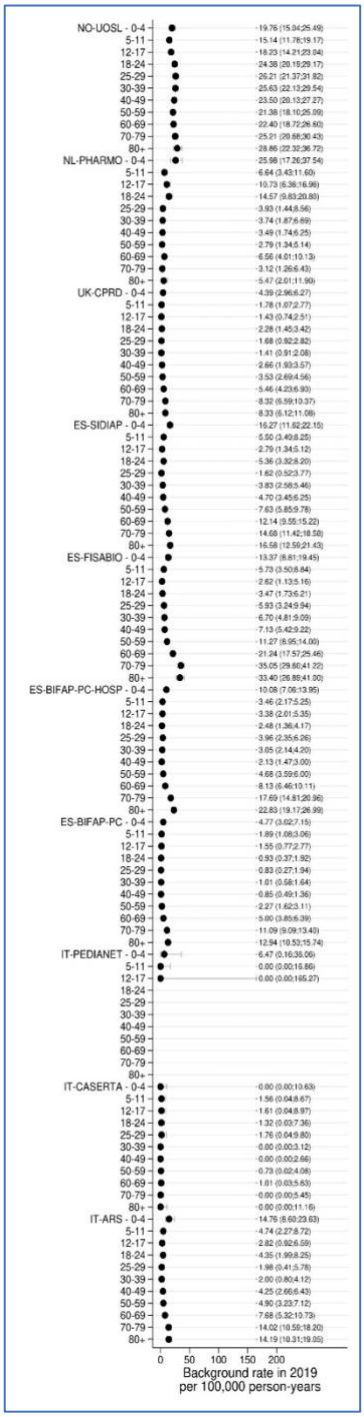


Figure 27: Incidence rates 2019 stratified by DAP and age for (meningo)encephalitis

[71] van Wijngaarden, P, Belbachir, L, Durán, C, Souverein, P, Martín-Pérez, M, García-Poza, P, & Sturkenboom, MCJM. ACCESS-Background rate of adverse events-definition –(Meningo)encephalitis (Version 1). Zenodo. 2021. https://doi.org/10.5281/zenodo.5236137

[72] Sejvar JJ, Kohl KS, Bilynsky R, Blumberg D, Cvetkovich T, Galama J, Gidudu J, Katikaneni L, Khuri-Bulos N, Oleske J, Tapiainen T, Wiznitzer M; Brighton Collaboration Encephalitis Working Group. Encephalitis, myelitis, and acute disseminated encephalomyelitis (ADEM): case definitions and guidelines for collection, analysis, and presentation of immunization safety data. Vaccine. 2007 Aug 1;25(31):5771-92. doi: 10.1016/j.vaccine.2007.04.060.

[73] Willame C, Dodd C, Gini R, Durán CE, Thomsen RM, Wang L. Background rates of Adverse Events of Special Interest for monitoring COVID-19 vaccines (2.0). Zenodo 2021. https://doi.org/10.5281/zenodo.5255870

[74] Gubernot D, Jazwa A, Niu M, Baumblatt J, Gee J, Moro P, Duffy J, Harrington T, McNeil MM, Broder K, Su J, Kamidani S, Olson CK, Panagiotakopoulos L, Shimabukuro T, Forshee R, Anderson S, Bennett S. U.S. Population-Based background incidence rates of medical conditions for use in safety assessment of COVID-19 vaccines. Vaccine. 2021 Jun 23;39(28):3666-3677. doi: 10.1016/j.vaccine.2021.05.016

9.1.7.24 Microangiopathy

Microangiopathy is a disease of the small blood vessels in the microcirculation. It leads to microvascular dysfunction which can manifest in different clinical scenarios. Cardiac microangiopathy can manifest through events of ischemic heart disease in the absence of angiographically significant coronary atherosclerosis, causing inflammation and/or abnormal vasomotor regulation, or through inadequate post-percutaneous coronary intervention (PCI) and/or -thrombolysis coronary reperfusion, including micro-embolic mechanism, or in the context of epicardial vessel disease.[75]

Code counts (annex 4) shows that microangiopathy is mostly often diagnosed as secondary diagnosis in hospital. Standardized incidence rates in 2019 were 2.15/100,000 PY in IT-ARS, 0.76 in ES-BIFAP-PC-HOSP (only primary discharge diagnoses), 10.8 in ES-FISABIO, 6.7 in ES-SIDIAP, and 2,44 in NO-UOSL (missing potential detailed ICD10 codes). These rates are comparable to the ones reported by Willame et al.,[76] from the ACCESS project. All pre-COVID-19 rates went down in 2020, probably due to restrictions in the healthcare utilization during COVID-19 waves (Annex 3).

Post-COVID-19 rates were much increased in IT-ARS, ES-BIFAP-PC, ES-BIFAP-PC/HOSP, ES-FISABIO, and ES-SIDIAP. Post-COVID-19 rates raised up to 2-18 fold from 6.69 to 55.11/100,000 PY in ES-SIDIAP. There were 0 cases identified in NL-PHARMO before and after COVID-19, because of the lack of an ICPC code for this. Data from IT-CASERTA were not reliable because of an issue in the ETL for this instance.

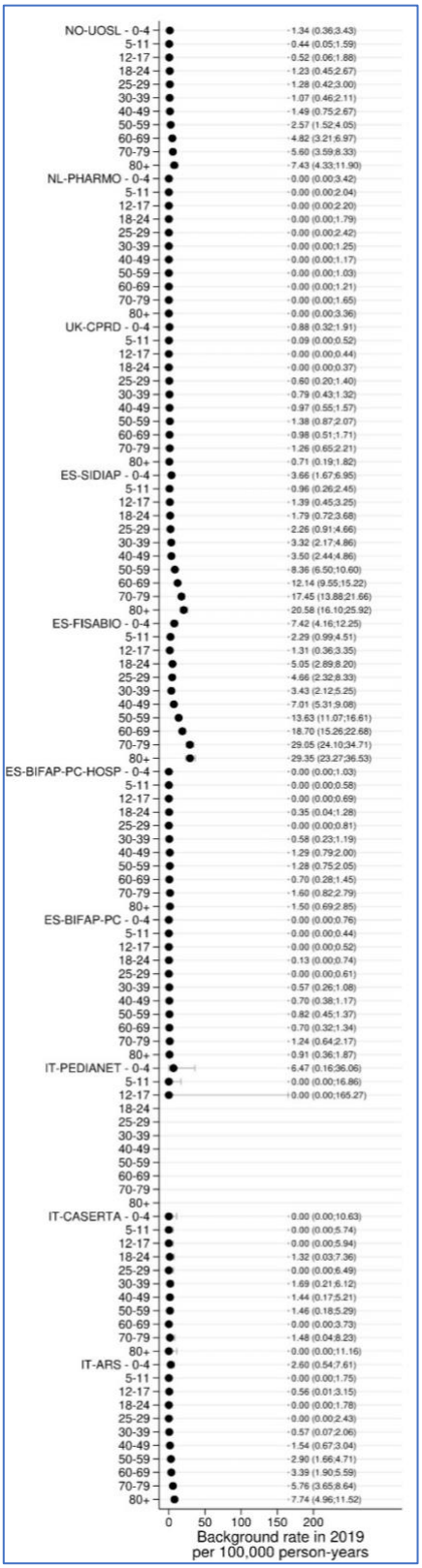


Figure 28: Incidence rates stratified by DAP and age for microangiopathy

[75] Kelters L, Sturkenboom MCJM, Willame C, Belchabir, L & Durán CE. ACCESS-Background rate of adverse events-definition – Microangiopathy. Zenodo. 2021 https://doi.org/10.5281/zenodo.5169451

[76] Willame C, Dodd C, Durán CE, Elbers R, Gini R, Bartolini C, et al. Background rates of 41 adverse events of special interest for COVID-19 vaccines in 10 European healthcare databases - an ACCESS cohort study. Vaccine. 2023 Jan 4;41(1):251-262. doi: 10.1016/j.vaccine.2022.11.031.

9.1.7.25 Multi-Inflammatory Syndrome (MIS)

Multisystem inflammatory syndrome (MIS) is a systemic hyperinflammatory and febrile state of unknown pathophysiology characterized by elevated levels of inflammatory markers. The fever should be accompanied by laboratory evidence of inflammation (altered levels of C-reactive protein, erythrocyte sedimentation rate, ferritin, or procalcitonin), two or more symptoms (shock-hypotension, mucocutaneous, gastrointestinal, neurologic alterations), or disease-related alterations of cardiovascular activity (elevation of (N-terminal pro b-type-)brain natriuretic peptide or troponin, heart failure, electrocardiogram changes consistent with myocarditis or myo-pericarditis, neutrophilia, lymphopenia, or thrombocytopenia). MIS-C affects young individuals up to 20 years old; MIS-A affects 21 years old or older adults. MIS shares some features with Kawasaki disease (KD), toxic shock syndrome, or Stevens Johnson's syndrome (SJS). It can be distinguished among the others for its association with cardiac dysfunctions and with a characteristic superantigen-like activation of Vβ21.3-expressing T cells.

MIS was initially described as KD-like disease, and only during the pandemic codes were created in ICD10 and in SNOMED. The code counts show codes in NO-UOSL and in ES-SIDIAP (Annex 4).

Rates in this report are lower than the rates reported by the ACCESS project, which included also KD.[77] Moreover, we also used a narrow MIS definition following the recommendation of SPEAC.[78] In NO-UOSL no cases were identified in 2019, and some in 2020 prior to COVID-19. The rates after COVID-19 diagnosis increased from 0.07 in 2020 to 258.72/100,000 PY). All MIS cases in NO-UOSL are identified by the ICD-10 code *U10.9 - Multisystem inflammatory syndrome associated with COVID-19*, mainly from hospital setting (secondary diagnosis) and outpatient (primary and secondary diagnoses). Databases using ICD9 codes such IT-ARS and IT-CASERTA were unable to retrieve cases due to the lack of a specific code associated to MIS; in these databases, all codes we tagged as possible (no specific codes) and therefore no rates were produced. Given similarities in the clinical presentation of MIS and KD, low rates of this event could be masked by higher post-COVID-19 rates of KD in 2020. To study this event properly, `KD and MIS should be combined.

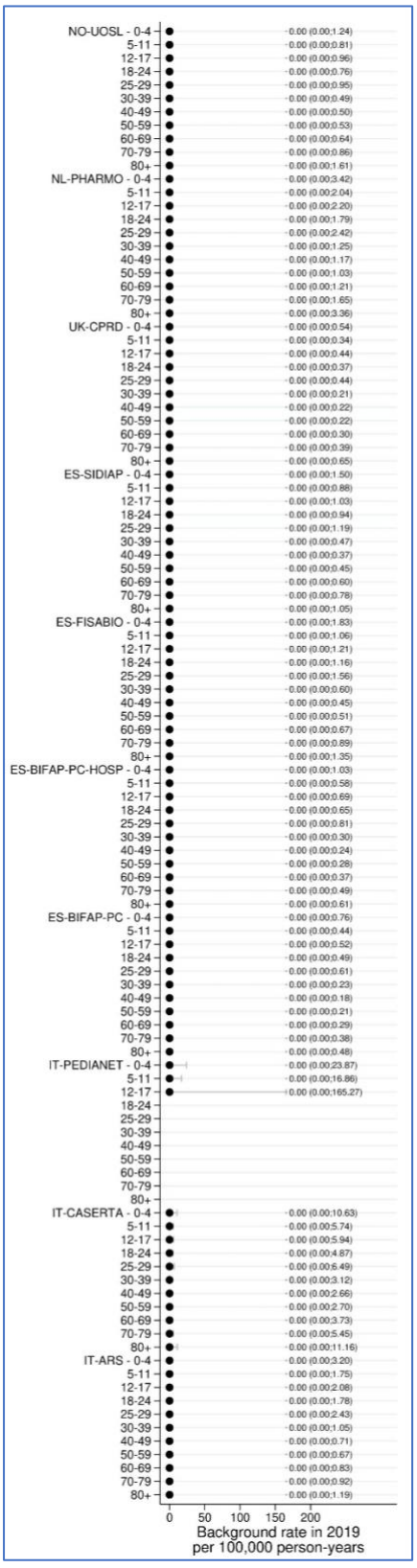


Figure 29: Incidence rates 2019 stratified by DAP and age for MIS

[77] Willame C, Dodd C, Durán CE, Elbers R, Gini R., et al. Background rates of 41 adverse events of special interest for COVID-19 vaccines in 10 European healthcare databases - an ACCESS cohort study. Vaccine. 2023 Jan 4;41(1):251-262. doi: 10.1016/j.vaccine.2022.11.031.

[78] Law, Barbara. (2022). AESI Case Definition Companion Guide: Multisystem Inflammatory Syndrome in Children and Adults (MIS-C/A) (V1.0). Zenodo. https://doi.org/10.5281/zenodo.7248905

9.1.7.26 Myocarditis

Myocarditis is an inflammatory disease of the muscular portion (myocardium) of the heart. It encompasses several different diseases with diverse etiologies and variable clinical presentations. It frequently results from viral and nonviral infections or post-viral immune-mediated responses or noninfectious triggers (autoimmune diseases, hypersensitivity reactions to drugs, toxic reactions to drugs, toxins, etc.). Diagnosis is established by histological, immunological, and immunohistochemical criteria, which may differ with respect to the appearance under the microscope and to clinical etiology.[79]
Code counts (Annex 4) show that myocarditis is diagnosed in all type of settings: primary care, emergency room, outpatient specialist and hospitalizations.
In 2019 standardized rates were below 10/100,000 PY in all datasources: 8.0/100,000PY in IT-ARS, 2.5 in ES-BIFAP-PC, 3.8 in ES-BIFAP-PC-HOSP, 8.3 in ES-FISABIO, 6.0 in ES-SIDIAP, 4.0 in UK-CPRD and 7.0 in NO-UOSL. GP-only data sources had half the rates of data sources where GP and hospital diagnoses were both available. Rates were consistent with ACCESS data and with published data from Gubernot. PHARMO could not identify myocarditis specifically. Rates are slightly higher in adolescents and young adults (18-24 years of age). Rates were lower during 2020 and increased more than 10-20 fold after COVID-19 disease (Annex 3) although confidence intervals were wide.[80]

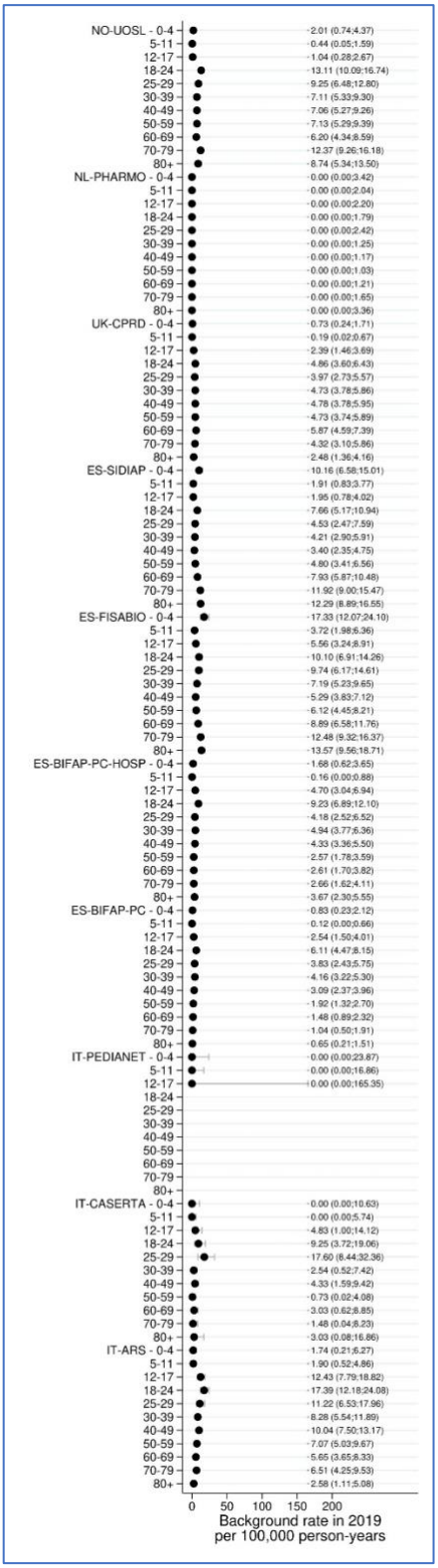


Figure 30: Incidence rates 2019 stratified by DAP and age for myocarditis

[79] https://zenodo.org/record/5172798#.ZFJ203ZByUk
[80] https://www.sciencedirect.com/science/article/pii/S0735109711052004 and https://zenodo.org/record/6668895#.ZFJ0znZByUk

9.1.7.27 Narcolepsy

Narcolepsy is a chronic neurological disorder that affects the brain's ability to control sleep- wake cycles, primarily characterized by excessive daytime sleepiness and cataplexy episodes of muscle weakness brought on by emotions. Individuals with narcolepsy may also experience uneven/interrupted sleep that can involve waking up frequently during the night and frequently entering REM sleep rapidly, within 15 minutes of falling asleep. Other symptoms may include hypnagogic hallucinations, sleep paralysis, fragmented nocturnal sleep, as well as impaired ability for sustained attention, and non-sleep symptoms such as obesity, anxiety, cognitive and emotional disturbances, behavioral problems, and early puberty in children[81].

Code counts (annex 4) showed that narcolepsy is often recorded in primary care.

Standardized incidence rates in 2019 are aligned with reported rates in the literature (1-2/100,000): 1.66/100,000 PY in ES-BIFAP-PC, 1.1 in ES-BIFAP-PC-HOSP, 2.96 in ES-FISABIO, 1.8 in ES-SIDIAP, 1.9 in UK-CPRD. In Norway, Caserta and PHARMO rates could not be obtained.

Narcolepsy rates in 2019 were similar to the rates obtained in the ACCESS project.[82]

Post-COVID-19 rates increased in ES-FISABIO and ES-SIDIAP, and decreased in BIFAP-PC and PC/HOSP. There were no narcolepsy cases post-COVID-19 in IT-ARS, IT-Caserta, IT-PEDIANET, NL-PHARMO, UK-CPRD, and NO-UOSL.

PHARMO data were not fit for purpose due to lack of ICPC code for this condition, the Norwegian data instance was also not fit for purpose due to lack of enough detail in available ICD10 codes.

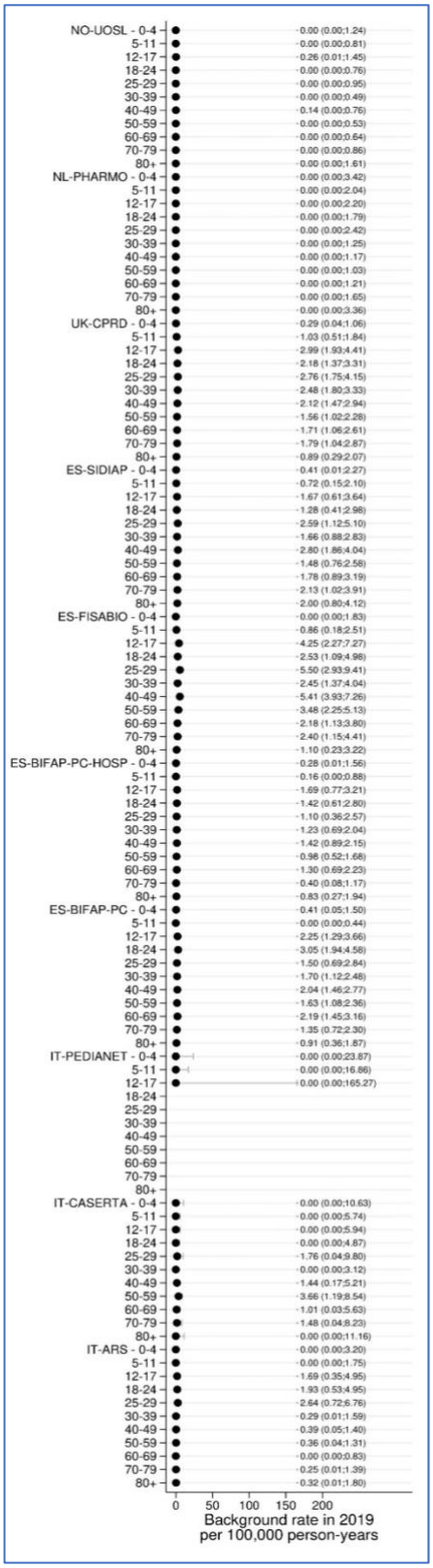


Figure 31: Incidence rates 2019 stratified by DAP and age for narcolepsy

[81] High post-COVID-19 rates of KD must be understood with caution due to clinical similarities of KD and multi-inflammatory syndrome; this situation could lead a potential misclassification bias, *see more* in 10.1.3.23 Multi-inflammatory Syndrome.

[82] Willame C, Dodd C, Durán CE, Elbers R, Gini R., et al. Background rates of 41 adverse events of special interest for COVID-19 vaccines in 10 European healthcare databases - an ACCESS cohort study. Vaccine. 2023 Jan 4;41(1):251-262. doi: 10.1016/j.vaccine.2022.11.031.

9.1.7.28 Pancreatitis

Pancreatitis is an inflammatory condition of the pancreas due to digestive enzymes damaging the organ. This inflammatory condition can be acute or chronic. Common causes of acute pancreatitis are gallstones, heavy alcohol abuse, direct trauma, certain medications, infections, or tumors. The acute form may evolve into chronic due to heavy alcohol consumption, high levels of blood fats, high blood calcium, or certain genetic disorders, such as cystic fibrosis. Symptoms of pancreatitis include pain in the upper abdomen, nausea, and vomiting. The diagnosis of acute pancreatitis requires abdominal pain, three times greater serum lipase activity (or amylase activity), and characteristic medical imaging findings through contrast-enhanced computed tomography (CECT), magnetic resonance imaging (MRI), or transabdominal ultrasonography. Code counts (annex 4) show that the diagnosis is often recorded in primary care and in emergency room visits.

Rates of pancreatitis in 2019 in settings with primary care and emergency room/hospital care were: 47.1/100,000 PY for IT-ARS, 13.7 in ES-BIFAP-PC, 17.0 in ES-BIFAP-PC-HOSP, 48 in ES-FISABIO and 22 in UK-CPRD. These are comparable to what we know from incidences reported in UK[83]. Rates were very low in ES-SIDIAP, PHARMO and NO-UOSL. Norway could only extract the causes of death and there were no ICPC codes, it is not clear why rates in ES-SIDIAP were missing, since ICD10 codes were available, this will be explored further for any future study. Rates in 2020 remained stable but increased post-COVID-19 rates in IT-ARS, IT-Caserta, ES-BIFAP-PC, ES-BIFAP-PC/HOSP and UK-CPRD. There were no post-COVID-19 cases detected in ES-SIDIAP, ES-FISABIO and IT-PEDIANET.

Rates stratified by age shows a clear age-related pattern with higher incidences in the adulthood (Figure 32).

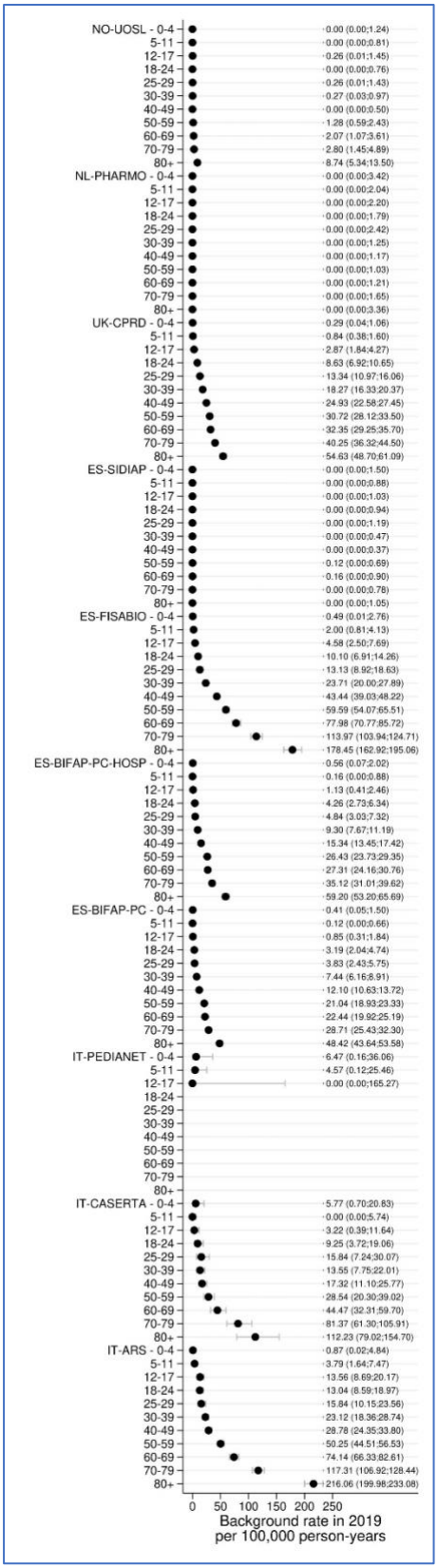


Figure 32: Incidence rates 2019 stratified by DAP and age for pancreatitis.

[83] Pancreatitis. NICE Guideline. Published: 5 September 2018. Available at: https://www.nice.org.uk/guidance/ng104/chapter/Context#acute-pancreatitis-2

9.1.7.29 Pericarditis

Pericarditis is a syndrome caused by the inflammation of the pericardium resulting in an increase in the normal volume of fluid surrounding the heart and usually leading to pericardial effusion or constrictive pericarditis. The etiology and pathophysiology of this pericardial disease can be infectious (most commonly), or non-infectious, such as neoplasm, autoimmune process, injuries, or drug induced. Pericardium inflammation disease can be acute or chronic. Clinically, it is suggested by a characteristic chest pain description and the presence of a pericardial friction rub on auscultation. Electrocardiogram (ECG) and echocardiography are needed to confirm the diagnosis[82].
Code counts (annex 4) show that the diagnoses is captured both in primary care, emergency rooms and hospitalizations.
Pericarditis cases were identified in all data bases, except in NL-PHARMO (no specific ICPC codes) and IT-PEDIANET (only children).
Pre-COVID-19 rates in 2019 and 2020 were low in IT-Caserta (probably because of ETL error).
Standardized rates in 2019 in data sources capturing different settings are: 26.9/100,000 PY in IT-ARS, 12.8 in ES-BIFAP-PC, 16.0 in ES-BIFAP-PC-HOSP, 21.6 in ES-FISABIO, 22.9 in ES-SIDIAP, 10.9 in UK-CPRD, and 21 in NO-UOSL (Annex 3). These rates are comparable to previous studies conducted in Europe.[84]
Stratification by age shows an age-related pattern with higher rates in adults and older population (Figure 33).
Post-COVID-19 rates increased 1.5-5 fold in all databases. A detailed analysis of this event in the manuscript by Bots et al.[85]

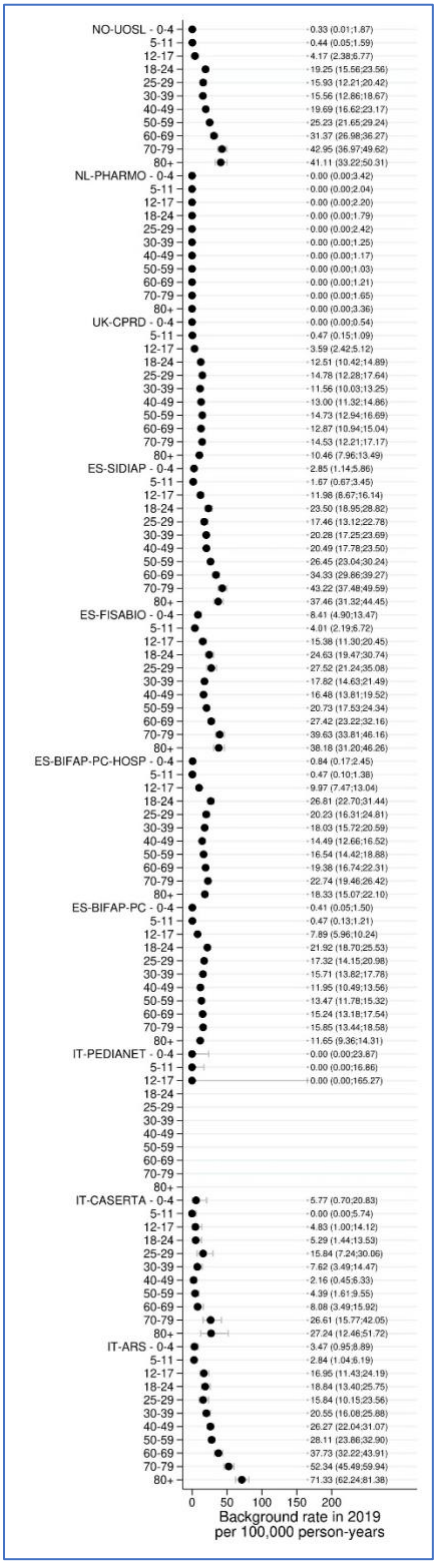


Figure 33: Incidence rates 2019 stratified by DAP and age for pericarditis

[84] Law, Barbara. Myocarditis and Pericarditis Case Definition Companion Guide (SO2-D2.5.2.2). Zenodo. 2022 https://doi.org/10.5281/zenodo.6668895

[85] Bots SH, Riera-Arnau J, Belitser SV, Messina D, Aragón M, et al. Myocarditis and pericarditis associated with SARS-CoV-2 vaccines: A population-based descriptive cohort and a nested self-controlled risk interval study using electronic health care data from four European countries. Front Pharmacol. 2022 Nov 24;13:1038043. doi: 10.3389/fphar.2022.1038043.

9.1.7.30 Rhabdomyolysis

Rhabdomyolysis is a condition produced by the damage of the muscle cell injury followed by the release of cell components into circulation, mainly proteins and electrolytes. It consists of a set of symptoms and signs including acute muscle weakness, myalgia, and muscle swelling combined with a creatine kinase cut-off value of > 1000 IU/L or > 5 × upper normal limit.
Additionally, the substances released may cause acute kidney injury or heart damage, indicating a severe type of rhabdomyolysis.[86]
Code counts (Annex 4) show that diagnoses are mostly recorded in hospital (often secondary) and emergency rooms, and less in primary care.
Incidence rates of rhabdomyolysis in 2019 in data sources with hospital data were: 11.9 /100,000 PY in IT-ARS, 4.0 in ES-BIFAP-PC-HOSP (only primary diagnosis), 25.7 in ES-FISABIO, 18.7 in ES-SIDIAP. Rates remained similar in 2020, prior to COVID-19. Post-Covid rates increased up to 10 fold in data sources that had hospital data. There were no cases identified in NO-UOSL, NL-PHARMO, IT-PEDIANET, and IT-Caserta (after COVID-19) and these data instances are not fit for purpose of this event (Figure 34). Rates in GP data sources are lower.

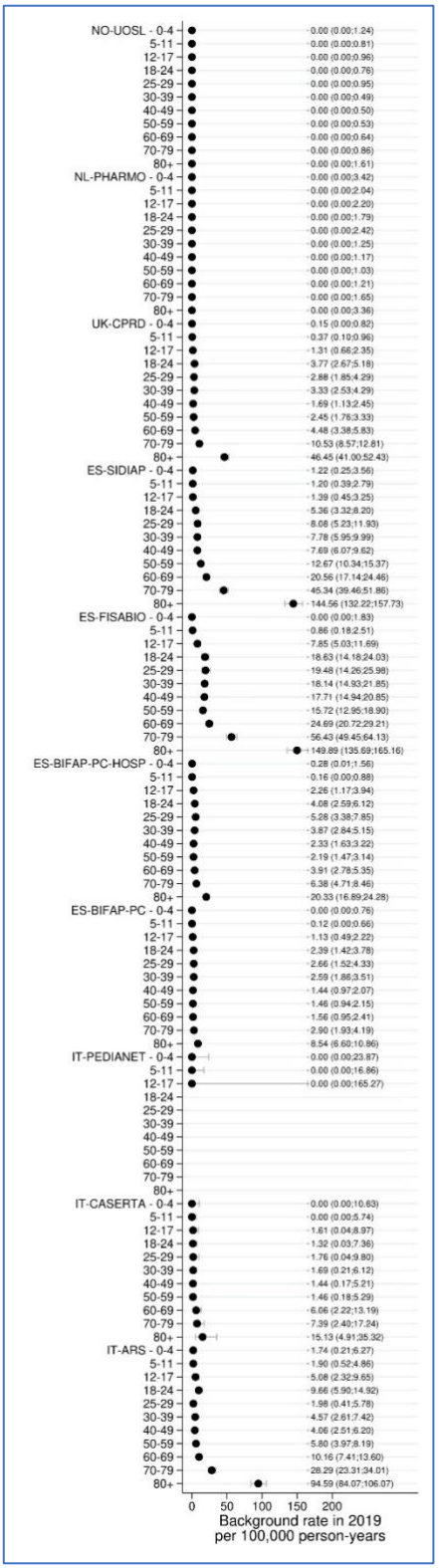


Figure 34: Incidence rates 2019 stratified by DAP and age for rhabdomyolysis

[86] Stahl K, Rastelli E, Schoser B. A systematic review on the definition of rhabdomyolysis. J Neurol. 2020 Apr;267(4):877-882. doi: 10.1007/s00415-019-09185-4

9.1.7.31 Severe Cutaneous Adverse Reactions (SCARs) to drugs

Severe cutaneous adverse reactions to drugs (SCARs) include a broad spectrum of entities, mainly consisting of:[87]

1. *Stevens-Johnson syndrome (SJS) and Toxic epidermal necrolysis (TEN):* Both are variants of epidermal necrolysis. They occur 4–28 days after drug exposure. Disease is characterized by general physical deterioration, fever, and skin pain. SJS and TEN might be accompanied by lympho- and neutropenia, and renal impairment.
2. *Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome:* It usually begins 2–6 weeks after drug exposure. Clinical dermatological symptoms consist of facial oedema, erythroderma, distal oedema, purpura, pustules, and sometimes mucosal involvement. DRESS is accompanied by significant eosinophilia.
3. *Acute generalised exanthematous pustulosis (AGEP):* Its onset is 2–11 days after drug exposure. Cutaneous symptoms develop simultaneously with high fever and numerous small, primarily non-follicular sterile pustules, arising on large areas of oedematous erythema in the major intertriginous zones.

Code counts showed the condition is recorded both in hospital and primary care.

There were no cases of SCARs in Italian and Dutch databases during the study period due to lack of ICPC and 2 decimal ICD9 codes that are specific for the conditions. Norwegian data was not suitable, due to lack of decimals in the ICD10 code of the hospitalization /specialist event codes (beyond cause of death) in their instance.

Incidence rates in 2019 are 0.31/100,000 PY in ES-BIFAP-PC, 0.47 in ES-BIFAP-PC-HOSP, 0.81 in ES-FISABIO, 0.56 in ES-SIDIAP, 0.88 in UK-CPRD. Rates in 2020 are quite comparable (Annex 3). Post COVID-19 rates can increase more than 10-fold, hospital data is important.

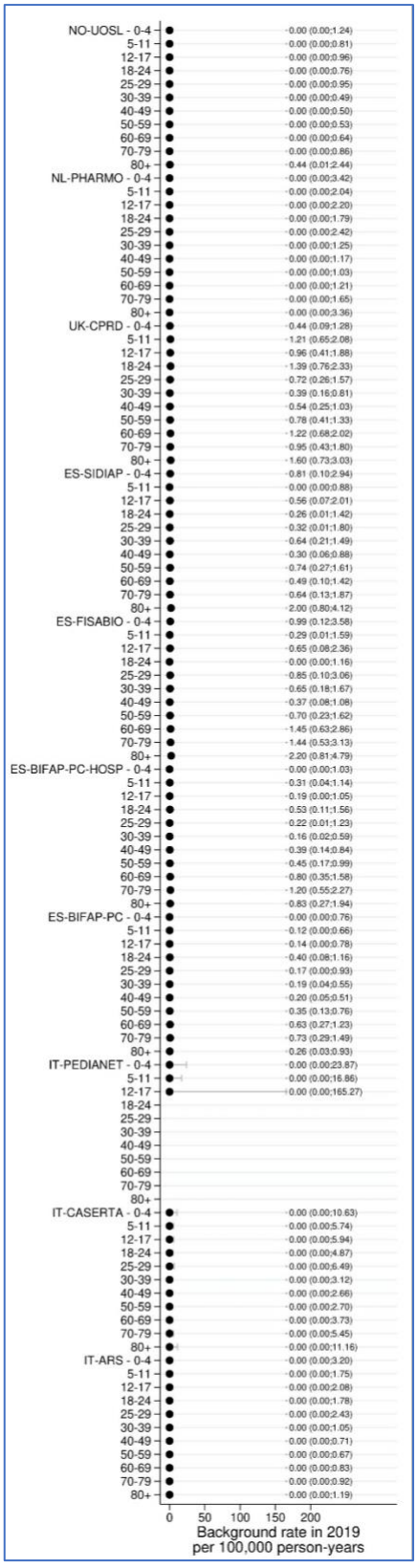


Figure 35: Incidence rates 2019 stratified by DAP and age for SCARs

[87] Duong TA, Valeyrie-Allanore L, Wolkenstein P, Chosidow O. Severe cutaneous adverse reactions to drugs. Lancet. 2017;390(10106):1996-2011. doi: 10.1016/S0140-6736(16)30378-6.

9.1.7.32 Sensorineural hearing loss

Hearing loss is the most prevalent sensory deficit and by the 5th leading cause of disability in adulthood. WHO estimates that 6.1% of the world population has disabling hearing loss. There are a few types of hearing loss, including conductive hearing loss (due to middle ear disease) and sensorineural hearing loss (SNHL). It is essential to objectively assess hearing with audiometry to properly identify the type of hearing loss. An audiometry showing hearing loss of ≥30 dB in three consecutive frequencies is mandatory to diagnose SNHL. Some risk factors are congenital or acquired infections, or ototoxic drugs, among others.[88]

Code counts (annex 4) show that the diagnosis is most often recorded in primary care.

Incidence of SNHL in 2019 in data sources with primary care data show: 59/100,000 PY in ES-BIFAP-PC, 74 in ES-BIFAP-PC-HOSP, 361 in ES-FISABIO, 99.6 in ES-SIDIAP, 78 in UK-CPRD, 97 in NL-PHARMO, and 186 in NO-UOSL. Rates decreased in 2020 prior to COVID-19. In general, background rates of SNHL presented in this report are slightly higher that rates from other epidemiologic studies.[89], which may be due to inclusion of other types of hearing loss. Rates after COVID-19 increased in all data sources, except in IT-Caserta and IT-PEDIANET, where there were no detected cases in 2020.

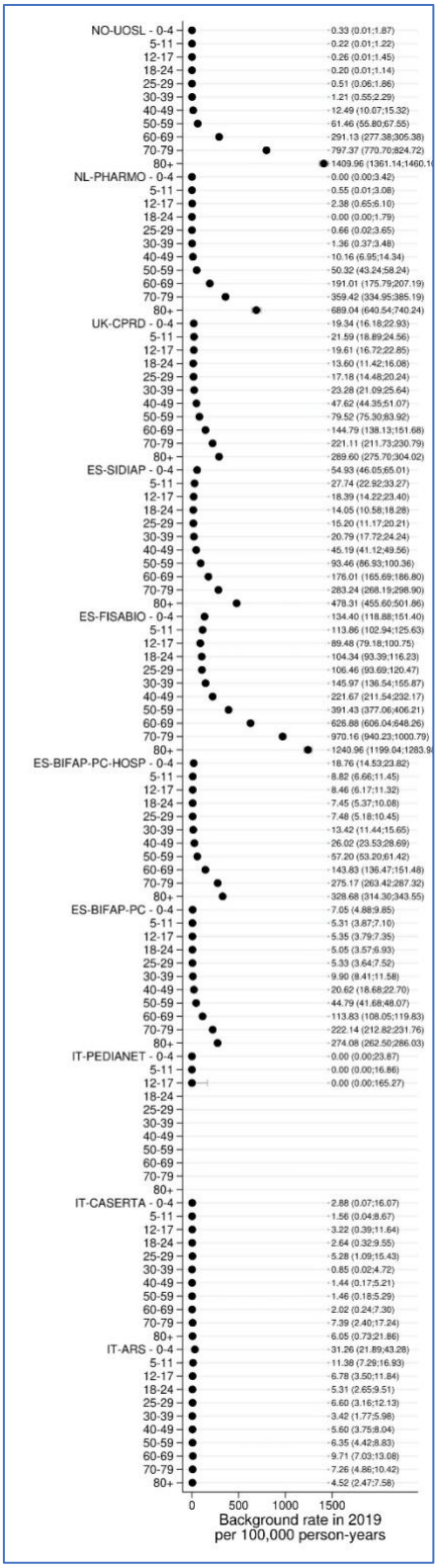


Figure 36: Incidence rates 2019 stratified by DAP and age for SNHL

[88] Schreiber BE, Agrup C, Haskard DO, Luxon LM. Sudden sensorineural hearing loss. Lancet 2010; 375:1203-11

[89] Law, Barbara, & Rojo Villaescusa, Marta. (2023). Sensorineural Hearing Loss: AESI Case Definition Companion Guide (V1.0). Zenodo. https://doi.org/10.5281/zenodo.7705371

9.1.7.33 Single organ cutaneous vasculitis (SOCV)

Single Organ Cutaneous Vasculitis (SOCV) is a syndrome characterized by clinical and histological features of small vessel vasculitis of the skin without the involvement of other organ systems. It can be the first clinical sign of systemic vasculitis. Skin biopsy is the gold standard diagnostic procedure. Histology typically shows perivascular inflammatory cells infiltrate with leukocytoclasia, erythrocyte extravasation, or hemorrhage into the dermis and fibrinoid necrosis or degeneration of the dermal postcapillary venules. In 90% of patients, SOCV will be resolved in weeks to months of onset and only simple measures are recommended like bed rest with elevation of the lower limbs and treatment with nonsteroidal anti-inflammatory drugs or antihistamines.[90] Code counts show that the diagnosis is mostly recorded in GP records.

There were no cases detected of SOCV in Italian databases (ARS, Caserta and PEDIANET) and in the Dutch database PHARMO (Figure 37), ICD9 codes were available, no ICPC codes are available. The incidence rate in 2019 varied and was 0.64/100,000 PY in IT-ARS, 5.2 in 100,000 PY, 1.6 in ES-BIFAP-PC, 2.6 in ES-BIFAP-PC-HOSP, 21.1 in ES-FISABIO, 4.4 in ES-SIDIAP and 1.0 in UK-CPRD. Rates in this project are lower to the rates reported in ACCESS[91]. Rates of SOCV in 2020 prior to COVID-19 lowered and post COVID-19 diagnosis increased 3-5 fold in all data sources (Annex 3) as compared to 2019 rates.

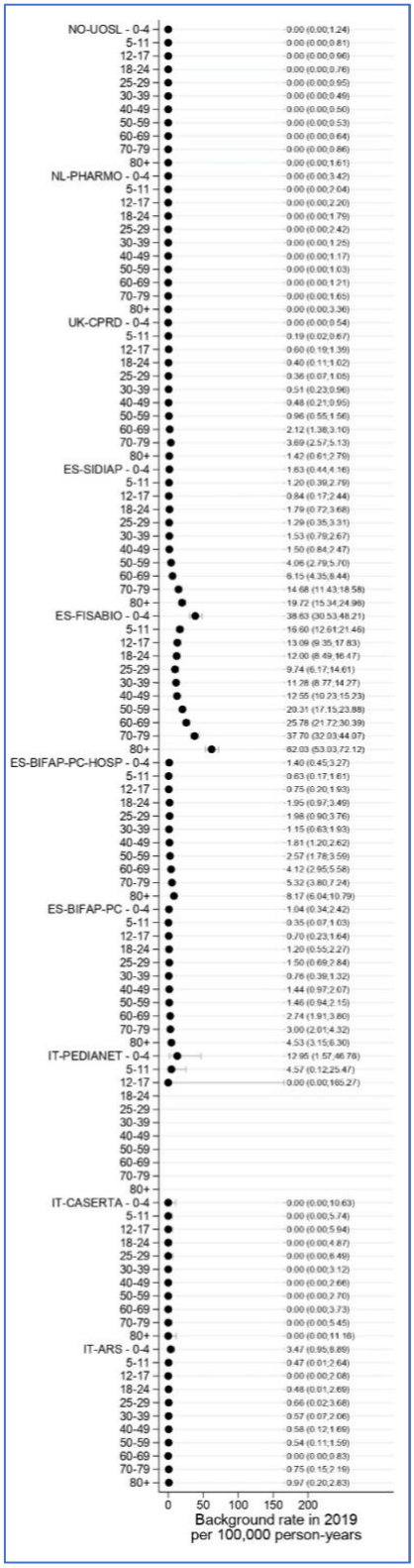


Figure 37: Incidence rates 2019, stratified by DAP and age for SOCV

[90] Zanoni G, Girolomoni G, Bonetto C, Trotta F, Häusermann P, Opri R, Bonhoeffer J; Brighton Collaboration Single Organ Cutaneous Vasculitis Working Group. Single organ cutaneous vasculitis: Case definition & guidelines for data collection, analysis, and presentation of immunization safety data. Vaccine. 2016 Dec 12;34(51):6561-6571. doi: 10.1016/j.vaccine.2016.09.032. Epub 2016 Oct 28. PMID: 28029543.

[91] Willame C, Dodd C, Gini R, Durán CE, Thomsen RM, Wang L, et al. Background rates of Adverse Events of Special Interest for monitoring COVID-19 vaccines (2.0). Zenodo. 2021. https://doi.org/10.5281/zenodo.5255870

9.1.7.34 Stroke haemorrhagic

A stroke is the result of an underlying cerebrovascular disease which leads to focal neurological findings in a vascular territory. This can happen in two ways. One is an ischemic stroke (which accounts for 85% of all acute strokes) and haemorragic stroke (15%). Haemorrhagic strokes are caused by bursting of a blood vessel i.e. acute haemorrhage. There are numerous causes behind a stroke, such as prolonged hypertension, arteriosclerosis, and emboli that have formed in the heart because of atrial fibrillation or rheumatic heart disease.[92]
Code counts (annex 4) show that this diagnosis is recorded in GP records and hospitalizations.
Rates reported by Pottegard were 20 and 14/100,000 PY in Denmark and Norway respectively. Rates from ACCESS were comparable to current rates observed [93]. Arachnoid, subarachnoid and traumatic-related intracerebral hemorrhage are not part of the narrow algorithm. Incidence rates in 2019 and 2020 are like the rates reported by Pottegard et al., for Norway and Denmark.[94] Standardized incidence rates in 2019 were 48.8/100,000 PY in IT-ARS, 9.2 in ES-BIFAP-PC, 19.4 in ES-BIFAP-HOSP-PC, 49.8 in ES-FISABIO, 35.5 in ES-SIDIAP and 17.0 in UK-CPRD. Rates for PHARMO, Caserta and Oslo should not be considered. Rates remained similar in 2020 prior to COVID-19 but increased 3-4 fold after COVID-19 diagnoses. Rates of heamorrhagic stroke increased with age, as it is observed in the Figure 38.

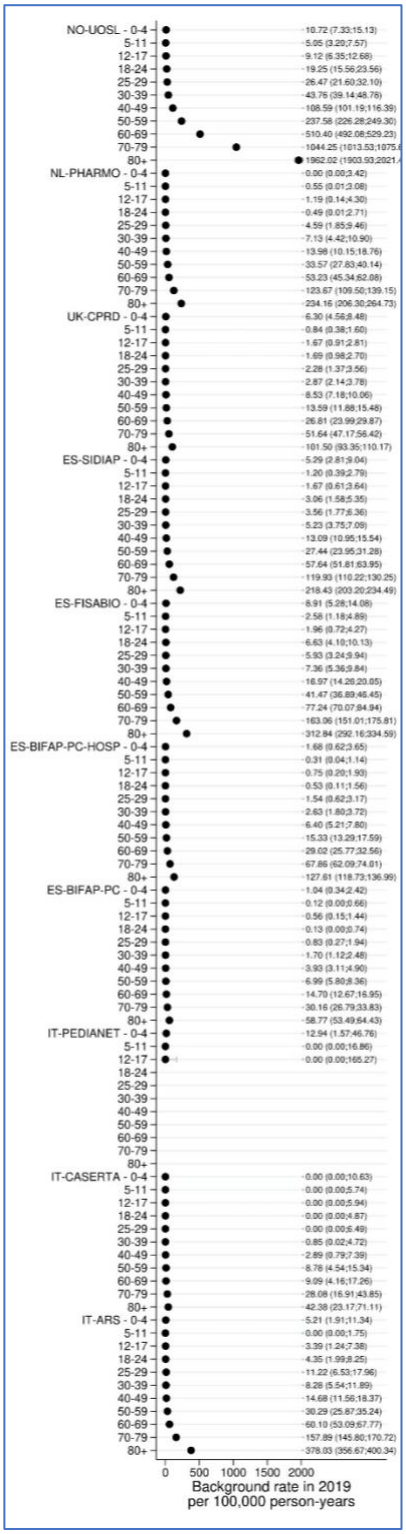


Figure 38: Incidence rates 2019 stratified by DAP and age for Hemorrhagic stroke

[92] Global stroke statistics - Amanda G Thrift, Tharshanah Thayabaranathan, George Howard, Virginia J Howard, Peter M Rothwell, Valery L Feigin, Bo Norrving, Geoffrey A Donnan, Dominique A Cadilhac, 2017 [Internet]. [cited 2020 Aug 14]. Available from: https://journals.sagepub.com/doi/10.1177/1747493016676285

[93] Willame C, Dodd C, Gini R, Durán CE, Thomsen RM, Wang L, et al. Background rates of Adverse Events of Special Interest for monitoring COVID-19 vaccines (2.0). Zenodo. 2021. https://doi.org/10.5281/zenodo.5255870

[94] Pottegård A, Lund LC, Karlstad Ø, Dahl J, Andersen M, Hallas J, et al. Arterial events, venous thromboembolism, thrombocytopenia, and bleeding after vaccination with Oxford-AstraZeneca ChAdOx1-S in Denmark and Norway: population based cohort study. BMJ 2021;373:n1114. doi: 10.1136/bmj.n1114.

9.1.7.35 TTS

The algorithm utilized in this study to define TTS was presence of thrombocytopenia plus any of following events: deep venous thrombosis, pulmonary embolism, ischemic stroke, splanchnic venous thrombosis, acute myocardial infarction, central venous sinus thrombosis, and VTE in other locations, occurring within 10 days, before or after, from each other.
Code counts show that components of the diagnosis are often obtained from hospitalization diagnoses.
Standardized incidence rates in 2019 in data sources capturing hospitalizations show rates of 1.19/100,000 PY in IT-ARS, 0.11 in ES-BIFAP-PC-HOSP, 8.82 in ES-FISABIO and 7.0 in ES-SIDIAP. Rates were similar in 2020 prior to COVID-19 but increased in UK-CPRD, ES-SIDIAP, ES-FISABIO and less so in ES-BIFAP-PC-HOSP after COVID-19 infection.
In ES-FISABIO and ES-SIDIAP an increase was seen with increasing age (figure 39), probably due to increase in thromboembolic events. Rates were much lower in GP-based data sources.
TTS rates in the background rate study by Burn et al. did not provide an overall rate of TTS but separated the same components with high variability in the rates across different data sources[95].

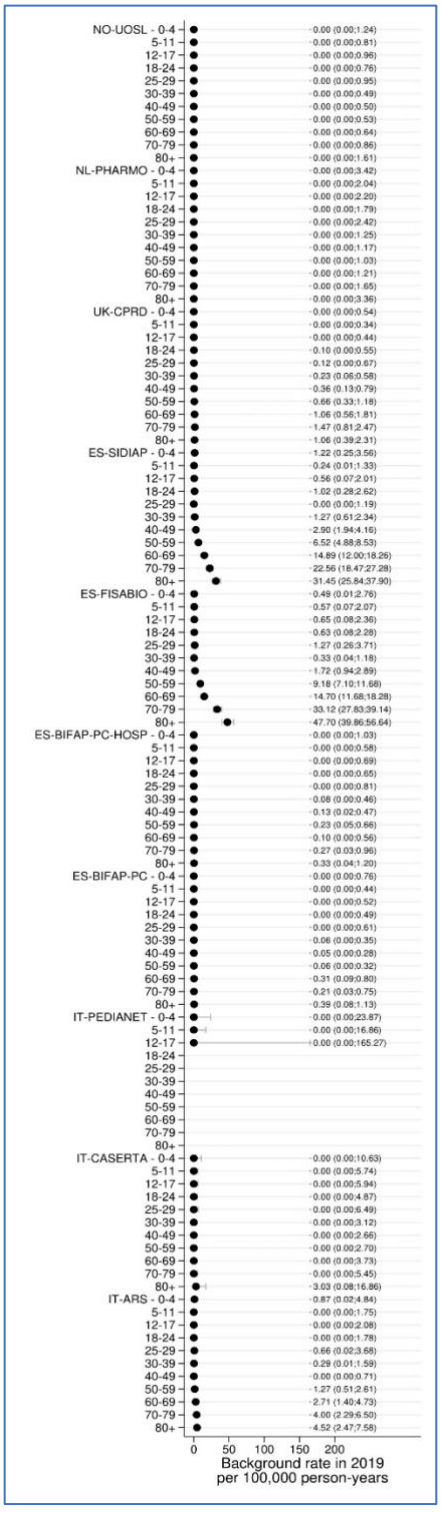


Figure 39: Incidence rates 2019 stratified by DAP and age for TTS

[95] Burn E, Li X, Kostka K, Stewart HM, Reich C, Seager S, Duarte-Salles T, Fernandez-Bertolin S, Aragón M, Reyes C, Martinez-Hernandez E, Marti E, Delmestri A, Verhamme K, Rijnbeek P, Horban S, Morales DR, Prieto-Alhambra D. Background rates of five thrombosis with thrombocytopenia syndromes of special interest for COVID-19 vaccine safety surveillance: Incidence between 2017 and 2019 and patient profiles from 38.6 million people in six European countries. Pharmacoepidemiol Drug Saf. 2022 May;31(5):495-510. doi: 10.1002/pds.5419. Epub 2022 Feb 27. PMID: 35191114; PMCID: PMC9088543.

9.1.7.36 (Immune) Thrombocytopenia

Thrombocytopenia (TP) is an abnormally low platelet count (usually less than 150x10^9/L). Pathogenic mechanisms include insufficient production, abnormal distribution, or excessive destruction of platelets. Excessive destruction can be caused by microangiopathy, hereditary platelet abnormalities, or immunologic mechanisms. Immunologic TP can be caused by autoimmune mechanisms, neonatal isoimmunization, or a nonspecific immune response. Idiopathic TP (ITP) refers to TP without an identified aetiology, although an autoimmune aetiology is frequently suspected but not always verified through exhaustive exclusion of differential diagnoses. It is usually related to the presence of clinical signs and symptoms of spontaneous bleeding.[96]

In this report, diagnosis codes were used to identify thrombocytopenia and laboratory measurements (even if available) were not used. Code counts (annex 4) show that thrombocytopenia diagnosis is most often captured in primary care data sources.

Due to the required of decimals in diagnostic codes, which were not available for the instance, rates could not be reliably estimated in Norway and PHARMO. Caserta instance was not corrected ETl'ed and needs update to be fit for purpose.

In data sources capturing primary care settings standardized rates in 2019 were: 192/100,000 PY in ES-BIFAP-PC, 185 in ES-BIFAP-PC-HOSP, 165 in ES-FISABIO, 155 in ES-SIDIAP, 42 in UK-CPRD. Rates decreased in 2020, prior to COVID-19 diagnosis, but increased up to 2-10 fold after COVID-19 diagnosis. Rates of ITP in the background rate paper by Li et al. varied based on data source between 1-100/100,000 PY and are not comparable[97]. The recent paper by Burn et al looking at TTS, did not provide rates of thrombocytopenia in the publication.[93]

Thrombocytopenia rates presented are comparable to the rates reported in previous studies in European and North American population.[98] They are higher than in the ACCESS study.

Special care needs to be paid to inclusion of secondary thrombocytopenia, which increases a lot with age.

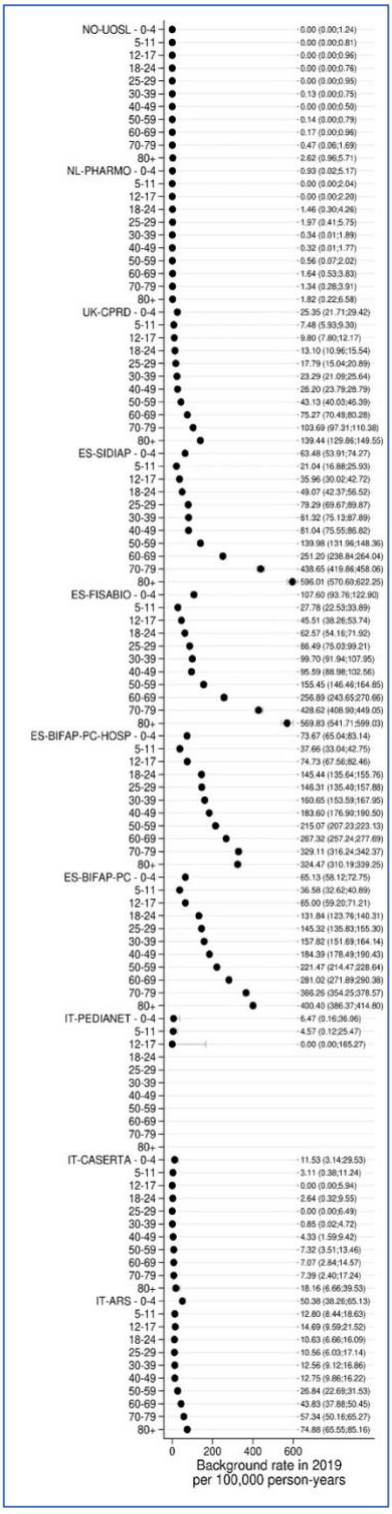


Figure 40: Incidence rates 2019 stratified by DAP and age for (I)TP

[96] Wise RP, Bonhoeffer J, Beeler J, Donato H, Downie P, Matthews D, et al., Brighton Collaboration Thrombocytopenia Working Group. Thrombocytopenia: case definition and guidelines for collection, analysis, and presentation of immunization safety data. Vaccine. 2007 Aug 1;25(31):5717-24. doi: 10.1016/j.vaccine.2007.02.067.

[97] Li X, Ostropolets A, Makadia R, Shoaibi A, Rao G, Sena AG, Martinez-Hernandez E, Delmestri A, Verhamme K, Rijnbeek PR, Duarte-Salles T, Suchard MA, Ryan PB, Hripcsak G, Prieto-Alhambra D. Characterising the background incidence rates of adverse events of special interest for covid-19 vaccines in eight countries: multinational network cohort study. BMJ. 2021 Jun 14;373:n1435. doi: 10.1136/bmj.n1435. PMID: 35727911; PMCID: PMC8193077.

[98] Law, Barbara, & Sturkenboom, Miriam. (2022). Immune Thrombocytopenia: Background rates literature review and visualization (1.0) [Data set]. Zenodo. https://doi.org/10.5281/zenodo.7643493

9.1.7.37 Thyroiditis (autoimmune)

Autoimmune thyroiditis is defined as an inflammatory disease of the thyroid gland due to autoimmune responses leading to lymphocytic infiltration of the gland. It is characterized by the presence of circulating thyroid antigen-specific T-cells and thyroid autoantibodies. The clinical signs can range from hypothyroidism to thyrotoxicosis depending on the type of autoimmune thyroiditis.[99]

Code counts (annex 4) show that the diagnosis is most captured in primary care, and as secondary discharge diagnosis.

Standardized autoimmune thyroiditis rates in 2019 were 8.9 /100,000 PY in IT-ARS, 18.5 in ES-BIFAP-PC, 20.5 in ES-BIFAP-PC-HOSP, 50.0 in ES-FISABIO, 36 in ES-SIDIAP, 8.8 in UK-CPRD. There were no cases identified in NL-PHARMO and NO-UOSL because of the lack of specific ICPC codes. Rates decreased in 2020 prior to COVID-19. Post COVID-19 rates increased up to 4-fold. The IT-Caserta, ARS data and Norwegian and PHARMO data were not fit for purpose.

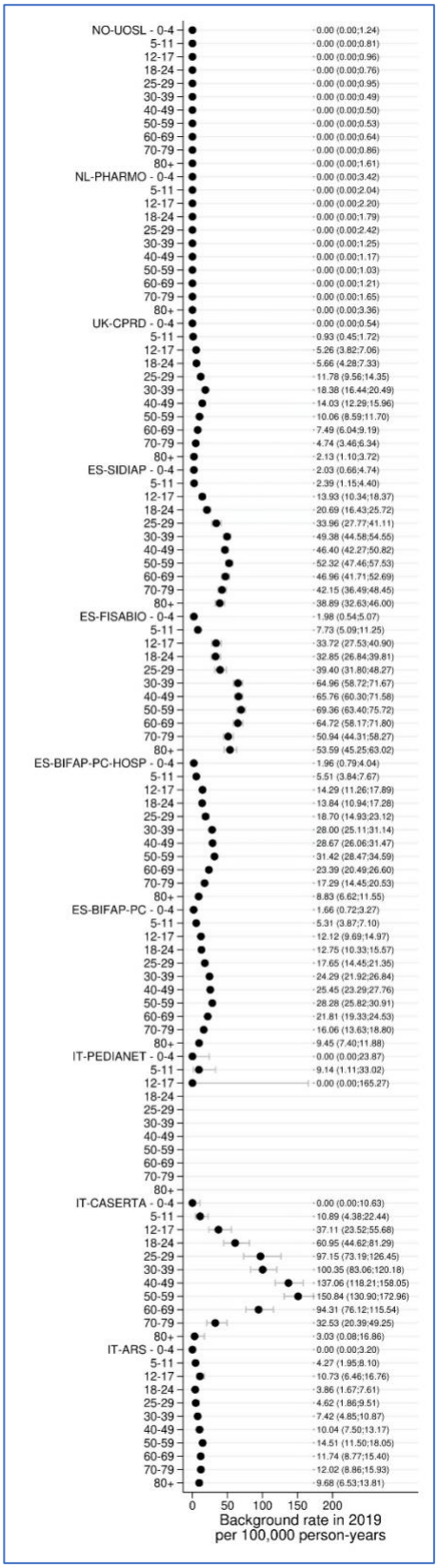


Figure 41: Incidence rates 2019 stratified by DAP and age for thyroiditis

[99] Thyroiditis, Autoimmune. National Library of Medicine. Accessed 08.05.2023. https://www.ncbi.nlm.nih.gov/mesh/68013967

9.1.7.38 Transverse myelitis

Transverse myelitis is an inflammation of the spinal cord. The term *myelitis* refers to inflammation of the spinal cord; *transverse* refers to the pattern of changes in sensation— there is often a band-like sensation across the trunk of the body, with sensory changes below. Although some people recover from transverse myelitis with minor or no residual problems, the healing process may take months to years. There is no cure for transverse myelitis, but there are treatments to prevent or minimize permanent neurological deficits.[100]

Code counts (annex 4) show that diagnoses are recorded in hospital and primary care.

Standardized rates in 2019 for data sources with secondary care are: 0.85/100,000 PY in IT-ARS, 0.36 in ES-BIFAP-PC-HOSP, 1.1 in ES-FISABIO, 0.55 in ES-SIDIAP.

Our results (background rates) are consistent with the results obtained in ACCESS project[101] and elsewhere.[102]

Due to the nature of the disease, which is diagnosed in hospital settings, rates are consistently lower in databases containing GP-only databases see Figure 42. There were no cases identified in IT-PEDIANET, IT-CASERTA, NL-PHARMO and Norwegian data. Post-COVID-19 incidence of transverse myelitis in 2020 increased 5-10 fold in all databases (Annex 3).

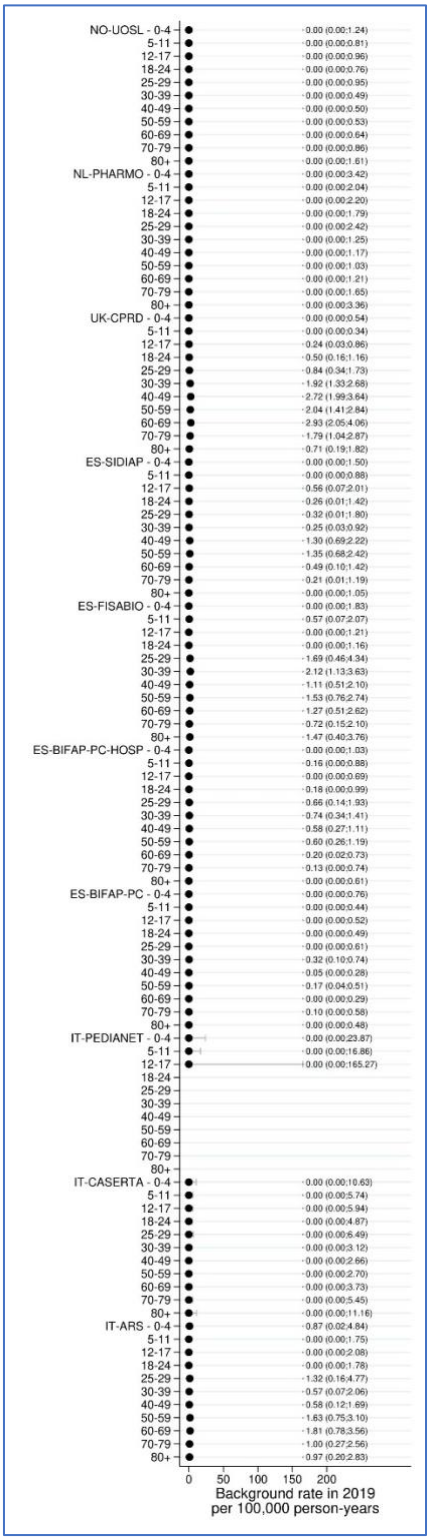


Figure 42: Incidence rates 2019 stratified by DAP and age for transverse myelitis

[100] Sturkenboom MCJM, Belbachir L, Souverein P, Martín-Pérez M, García-Poza P, Durán C. ACCESS-Background rate of adverse events-definition –transverse myelitis (1.0). Zenodo.2021. https://doi.org/10.5281/zenodo.5237332

[101] Willame C, Dodd C, Durán CE, Elbers R, Gini R, Bartolini C, et al. Background rates of 41 adverse events of special interest for COVID-19 vaccines in 10 European healthcare databases - an ACCESS cohort study. Vaccine. 2023 Jan 4;41(1):251-262. doi: 10.1016/j.vaccine.2022.11.031.

[102] Nasreen S, Calzavara A, Buchan SA, Thampi N, Johnson C, Wilson SE, Kwong JC; Canadian Immunization Research Network (CIRN) Provincial Collaborative Network (PCN) Ontario investigators. Background incidence rates of adverse events of special interest related to

9.1.7.39 VTE

Venous thromboembolism includes the following: deep vein thrombosis (DVT) which embolizes (VTE), and pulmonary thromboembolism (PE). DVT refers to the formation of a blood clot in one of the body's large veins. Most of the time this formation happens in the lower limbs. The blood clot is called a thrombus. The result of this process is that the leg will swell due to a higher pressure in the vein. It means a high risk of developing PE.[103] When a thrombus breaks loose from the vessel wall it travels freely through the blood vessel until it hits a narrow point in the circulation where it gets blocked. In PE the thrombus gets trapped in the long artery and closes the blood supply to the part of the lung after the occlusion. This causes a drop in lung perfusion, declining blood oxygen saturation, and sharp chest pain. PE happens in one third of DVT patients and has a high mortality rate.[104]
Code counts (annex 4) shows that diagnoses are recorded in primary care and hospital/emergency rooms.
Incidence rates in 2019 and 2020 before COVID-19 are comparable to the background rates reported by the ACCESS project in several European databases[105], by Gubernot et al. in the US,[106] and by Pottegard et al., in Norway and Denmark.[107]
Standardized rates in 2019 in data sources with primary care/emergency rooms and hospital are: 108/100,000 PY in IT-ARS, 120 in ES-BIFPA-PC-HOSP, 215 in ES-FISABIO, 166 in ES-SIDIAP and 364 in NO-UOSL.
Databases containing GP-only diagnoses have lower rates.
VTE rates in 2020 prior to COVID-19 decreased slightly, but increased 2-10 fold after COVID-19 diagnosis increased.
Incidence rates increased nicely with increasing age see Figure 43.

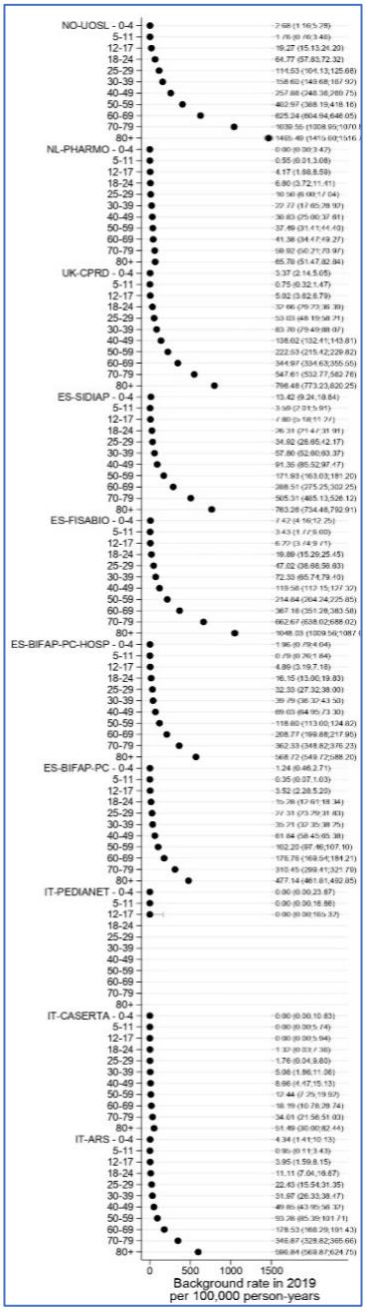


Figure 43: Incidence rates 2019, stratified by DAP and age for VTE

COVID-19 vaccines in Ontario, Canada, 2015 to 2020, to inform COVID-19 vaccine safety surveillance. Vaccine. 2022 May 26;40(24):3305-3312. doi: 10.1016/j.vaccine.2022.04.065.

[103] Overview of the treatment of lower extremity deep vein thrombosis (DVT) - UpToDate [Internet]. [cited 2020 Aug 13]. https://www-uptodatecom.proxy.library.uu.nl/contents/overview-of-the-treatment-of-lower-extremity-deepvein-thrombosisdvt?search=deep%20vein%20trombosis&source=search_result&selectedTitle=1~150&us age_type=default&display_rank=1

[104] Treatment, prognosis, and follow-up of acute pulmonary embolism in adults - UpToDate [Internet]. [cited 2020 Aug 13]. Available from: https://www-uptodatecom.proxy.library.uu.nl/contents/treatment-prognosis-and-follow-up-of-acutepulmonary-embolism-inadults?search=deep%20vein%20trombosis&topicRef=1362&source=see_link

[105] Willame Cet al. Background rates of 41 adverse events of special interest for COVID-19 vaccines in 10 European healthcare databases - an ACCESS cohort study. Vaccine. 2023 Jan 4;41(1):251-262. doi: 10.1016/j.vaccine.2022.11.031.

[106] Gubernot D, et al. Population-Based background incidence rates of medical conditions for use in safety assessment of COVID-19 vaccines. Vaccine. 2021 Jun 23;39(28):3666-3677. doi: 10.1016/j.vaccine.2021.05.016.

[107] Pottegård A, Lund LC, Karlstad Ø, Dahl J, Andersen M, Hallas J, Lidegaard Ø, Tapia G, Gulseth HL, Ruiz PL, Watle SV, Mikkelsen AP, Pedersen L, Sørensen HT, Thomsen RW, Hviid A. Arterial events, venous thromboembolism, thrombocytopenia, and bleeding after

9.2 Electronic healthcare records-based rapid assessment studies (Objective 2)

9.2.1 Multi-inflammatory syndrome (MIS)

- EMA study request: 10 September 2021
- CVM study results: 2 November 2021 (PRAC meeting presentation)
- CVM update of the study results: 8 May 2023 (Final Report; sections 9.1.7.22 and 9.1.7.25)

Background

In April 2020, following severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, emerging cases of a hyperinflammatory shock syndrome have been identified in children who experienced >24 hours of fever, inflammation involvement of >2 organ systems, and detection of >1 inflammatory markers from laboratory results[108] [109] [110] In October 2020, adult patients experiencing a clinically similar MIS after a laboratory-confirmed recent SARS-CoV-2 infection were also reported, but with a less clear prevalence than children[111] . MIS is identified to occur 4 to 6 weeks after coronavirus disease (COVID-19) diagnosis, generally with low or one existent viral loads, and may overlap with the acute respiratory symptoms' presentation[112].

MIS pathophysiology remains unknown. It follows a COVID-19-related acute cytokine release causing multiorgan damages due to vascular hyperpermeability, edema, and hypercoagulation. MIS shares some features with Kawasaki disease (KD), toxic shock syndrome, or Stevens Johnson's syndrome (SJS).

In August 2021, a 17-year-old male in Denmark, not infected with SARS-CoV-2, was reported as a case of severe MIS after the receipt of the Comirnaty (developed by BioNTech/Pfizer) COVID-19 vaccine[113]. Other MIS cases were also reported in the Europe and other countries, within 12 weeks of vaccination with mRNA-based and other authorized COVID-19 vaccines[114]. Before the COVID-19 pandemic, the estimated incidence rate (IR) of MIS in European countries was reported to be rare and around 2 to 6 cases per 100,000 per year in pediatric populations (MIS-C) and <2 cases per 100,000 in adults (MIS-A). EMA's safety committee (PRAC) and the Food and Drug Administration (FDA) prioritized the

vaccination with Oxford-AstraZeneca ChAdOx1-S in Denmark and Norway: population based cohort study. BMJ. 2021 May 5;373:n1114. doi: 10.1136/bmj.n1114.

[108] Riphagen S, Gomez X, Gonzalez-Martinez C, et al. Hyperinflammatory shock in children during COVID-19 pandemic. Lancet 2020;395:1607–8. doi:10.1016/S0140-6736(20)31094-1pmid:http://www.ncbi.nlm.nih.gov/pubmed/32386565

[109] Verdoni L, Mazza A, Gervasoni A, et al. An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study. Lancet 2020;395:1771–8.doi:10.1016/S0140-6736(20)31103-X

[110] Center for Disease Control and Prevention. Health Department-Reported cases of multisystem inflammatory syndrome in children (MIS-C) in the United States, 2021. Available: https://www.cdc.gov/mis/cases/index.html

[111] Morris SB, Schwartz NG, Patel P, Abbo L, Beauchamps L, Balan S, Lee EH, Paneth-Pollak R, Geevarughese A, Lash MK, Dorsinville MS, Ballen V, Eiras DP, Newton-Cheh C, Smith E, Robinson S, Stogsdill P, Lim S, Fox SE, Richardson G, Hand J, Oliver NT, Kofman A, Bryant B, Ende Z, Datta D, Belay E, Godfred-Cato S. Case Series of Multisystem Inflammatory Syndrome in Adults Associated with SARS-CoV-2 Infection - United Kingdom and United States, March-August 2020. MMWR Morb Mortal Wkly Rep. 2020 Oct 9;69(40):1450-1456. doi: 10.15585/mmwr.mm6940e1. PMID: 33031361; PMCID: PMC7561225.

[112] Davogustto GE, Clark DE, Hardison E, et al. Characteristics associated with multisystem inflammatory syndrome among adults with SARS-CoV-2 infection. *JAMA Netw Open.* 2021;4(5):e2110323.

[113] https://laegemiddelstyrelsen.dk/en/news/2021/danish-medicines-agency-investigates-a-case-of-inflammatory-condition-reported-after-covid-19-vaccination/

[114] https://www.ema.europa.eu/en/news/meeting-highlights-pharmacovigilance-risk-assessment-committee-prac-30-august-2-september-2021

monitoring of whether MIS development in reaction to the authorized COVID-19 vaccines is causality or if this hyperinflammatory state is a possible rare side effect to the vaccine.

In September 2021, EMA was requested by PRAC to conduct an O/E analysis based on appropriate incidence rates to reflect the expected number of MIS cases in relevant populations.

Objective

Upon request by EMA, in September 2021, the CVM consortium performed a retrospective, multi-database, dynamic cohort study to:

(1) estimate the incidence rate of MIS in children and adults across different study periods and study populations, before vaccination and following vaccination by age group, and by the data source.

(2) assess the incidence rate of MIS in (a) persons with the presence of co-morbidities elevating the risk of serious COVID-19 effects, (b) persons with a history of diagnosed COVID-19 disease, (c) age groups of 0-4, 5-11, 12-17, 18-24, 25-29, and in 10-year categories above.

Methods (27 September 2021)

The study request was sent to the CVM DAPs who were ready to participate, which at that point in time were those that had also participated in the ECVM. These partners had already quality-verified COVID-19 vaccination data (PHARMO-ES, BIFAP-ES, CPRD-UK_UU, and ARS-IT) and had studied MISC as AESI. The study period ranged from the 1st of January 2020 to the 31st of October 2021, or until the date of last data availability for each data source. The source population included all individuals observed in one of the participating data sources for at least one day during the study period and who had at least 1 year of data availability before cohort entry, except for individuals with data available since birth.

Variables

The considered variables of interest were those relevant for the creation of:

- Person-time and follow-up period: birth and death dates, observation periods within different databanks, vaccination, and occurrence of events.
- Events: dates of medical and/or procedure and/or prescription/dispensing codes to identify MIS, at-risk medical conditions, or COVID-19 diagnosis.
- Vaccinations: date, brand, and dose of vaccination.

The end of follow-up was defined per event as the earliest of date of event (except for anaphylaxis & generalized convulsions), death, last data draw-down, or exiting the data source. Individual person-time varies according to the event under evaluation. One person could contribute time to non-vaccinated category as well as to vaccinated category. Within the vaccinated persons, person-time is counted by brand and dose of vaccine (1st or 2nd dose), and by distance (in weeks and then aggregated in months) to last vaccination in months. Exposure date (t=0) is the date of vaccination. Whenever a person switched from non-vaccinated to vaccinated or between doses, contribution of person time is halted in the prior category. Events to be monitored comprised diagnosed COVID-19 and MIS. The date of an event was the first occurrence of a record of a diagnostic code for such an event during follow-up. Due to the high similarities between MIS and KD symptomatology, the association with COVID-19 infection is the main feature to distinguish MIS from KD.

Specific coding for MIS condition did not exist prior to COVID-19. Therefore, we operationalize the definition using the following concepts and codes:

- MIS_narrow: No ICD9 or READ codes (yet); ICD10="R65.1","R65.10","R65.11", "U10.9","M35.81"; SNOMED="895448002", "1119306006", "638810001221104", "65791000122106".
- Kawasaki_narrow: ICD9=446.1; ICD10=M30.3; READ="G7510","G751z"; ICPC2P ="B99022"; SNOMED="155444003","195348009","195349001","75053002".
- MIS_narrow & Kawasaki_narrow.

Exposure

Receipt of any of the COVID-19 vaccines. Vaccine brand and date of vaccination were obtained from general practice records in all data sources except ARS-IT, where the immunization register was used. Exposure to these vaccines was classified by brand, dose, administration month, and counted for exposure monitoring. Vaccination records were cleaned by deleting: (a) duplicates of the same vaccine on the same day for a person, (b) subsequent doses if 2nd dose was within 14 days distance of the 1st dose, (c) the 3rd dose if recorded within 90 days from the 1st dose.

Four cohorts were defined for the study:

- the 2017-2019 KD-like rates from the ACCESS reports (MIS codes from ACCESS did not exist);
- from the 1st of January 2020 until the COVID-19 vaccine or disease occurs.
- from COVID-19 diagnosis until COVID-19 vaccination or the end of follow-up.
- from COVID-19 vaccination until COVID-19 diagnosis or end of follow-up.

DAPs were requested to perform the extraction of the updated data in October 2021, and to ETL to the ConcePTION CDM which constituted the current instance of their data source. Data in the ConcepTION CDM and was processed and analyzed using the same R-script, which was adapted to include these cohorts and new concept sets for the requested events. The R script is available with documentation in the VAC4EU GitHub repository.

To calculate the incidence rate (per 100,000 PY) for the AESI of interest (MIS), individuals were followed from cohort entry. Incidence rates were estimated by year and week/month in the non-vaccinated/non-COVID/post-COVID time dividing the number of incident cases (numerator) by the total person-time at risk (denominator). Incidence rates of events in vaccinated subjects were calculated by vaccine brand and dose and the week since last vaccination and were cumulated to a maximum of 28 days (4 weeks after each dose). Exact 95% confidence intervals (CIs) are calculated. Censoring of the follow-up occurred at the earliest event date, last data collected, last data draw-down, or death, whichever happened first.

Results (27 September 2021)

Results were provided to EMA in September 2021. The key table with incidence rates is provided in Table 21.

Table 21. Incidence rates of MIS and Kawasaki disease

Data source	**BIFAP-ES***				**ARS-IT**			
Cohort	**0-11 yrs**	**12-17 yrs**	**0-11 yrs**	**12-17 yrs**	**0-11 yrs**	**12-17 yrs**	**0-11 yrs**	**12-17yrs**
	Males	Males	Females	Females	Males	Males	Females	Females
No Covid- No vaccine 2020								
MIS	0 (0-5.03)	0 (0-7.36)	0 (0-5.35)	0 (0-7.75)	-	-	-	-
KD like	6.82 (2.21-15.92)	0 (0-7.36)	5.8 (1.58-14.9)	0 (0-7.75)	5.61 (1.16-16.4)	0(0-4.73	1.98 (0.05-11.1)	0(0-5.08)
KD+MIS	6.82 (2.21-15.92)	0 (0-7.36)	5.8 (1.58-14.9)	0 (0-7.75)	-	-	-	-
After COVID-19 2020								
MIS	0 (0-4026)	0 (0-4291)	0(0-4672)	0(0-4515)	-	-	-	-
KD like	1095 (28-6099)	0 (0-4291)	0(0-4681)	0(0-4515)	0 (0-2093)	0(0-876.56)	0(0-2300)	0(0-974.5)
KD+MIS	1095 (28-6099)	0 (0-4291)	0(0-4681)	0(0-4515)	-	-	-	-
After COVID-19 2021								
MIS	0 (0-670)	0 (0-857)	189 (4.8-1054)	0 (0-906)	-	-	-	-
KD like	0 (0-670)	0 (0-857)	0 (0-698)	0 (0-906)	0(0-517)	0(0-245)	0(0-569)	0(0-270.9)
KD+MIS	0 (0-670)	0 (0-857)	189 (4.8-1054)	0 (0-906)	-	-	-	-
After COVID-19 Vaccination no cases for any of the vaccines in children 0-11 or 12-17 yet								

Discussion

With to objective to provide a rapid response to this urgent study request, we could make use of two European data sources, BIFAP-ES from Spain, and ARS-IT from Italy, that had already verified the quality of COVID-19 vaccination data as part of the ECVM study and were promptly ready to run the required analyses. The analysed study population included more than 6 million persons, with 650,731 children aged between 0 and 17 years old. Since MIS is a condition related to COVID-19 disease, MIS codes were created only at the end of 2020. It has been observed that specific MIS codes were not being frequently used, but only in 2021 in SNOMED. ARS-IT could not identify MIS codes as this data source makes use of ICD9 codes, which are not updated anymore. In the absence of MIS codes, KD-like disease codes were used by the Italian colleagues due to the reported association between MIS and KD in children. Based on this assumption, rates of KD have been found highest in 0-11 years old individuals, both in males and females, with only one case of MIS effectively occurring after the COVID-19 pandemic, in 2021. An increment of the KD-like disease cases in 0-11 years old children was also observed in 2020, during the COVID-19 pandemic. KD and MIS rates were both very low. No cases of KD & MIS in children post-vaccination were observed, also because very few vaccinated children were present on the April and May 2021 data extractions of BIFAP and ARS, respectively.

Comparing our results with another cohort study in the USA in children after COVID-19 reports, MIS rates of 5.1/1,000,000 person-months (61.2 /100,000 PY) were described, which fall in the range of our estimates in the cohort after COVID-19 disease.[115]

The ACCESS study has also provided incidence rates for KD_narrow (and broad) across a number of data sources. These rates can also be used for the required observed/expected analyses, keeping in mind that children were not age stratified.

Limitations

It was difficult to estimate the MIS incidence rates with the specific codes, since these codes were included in SNOMED and ICD10 only at the end of 2020, therefore it may be better to use KD-like rates. Post-vaccination rates were zero because very few children had been vaccinated at the moment that the data instances were created.

[115] Godfred-Cato, S., Bryant, B., Leung, J., et. al., COVID-19–Associated Multisystem Inflammatory Syndrome in Children — United States, March–July 2020. MMWR Morb Mortal Wkly Rep, 2020. 69(32): p. 1074-1080.

Conclusions
In October 2021, in agreement with EMA, the MIS study request was placed on hold since PRAC concluded that there was insufficient evidence on a possible link between COVID-19 vaccines and the very rare cases of MIS and that no update of the product information was warranted at this time.

Updated Results (8 May 2023)

Withing the production of the readiness results (section 10.1), MIS incidence rates (IRs) before and after the beginning of the COVID-19 pandemic, and before vaccination, were re-estimated using additional data sources from Spain and Norway. Italy and PHARMO could not contribute since these sources use ICD-9 and ICPC codes. Given the similarities in the clinical presentation of MIS and Kawasaki disease (KD), KD IRs were also estimated. It was possible to identify KD cases in the Italian data sources. The used MIS and KD concepts and codes can be found in the code list (Annex 2).

We found MIS cases only in ES-BIFAP-PC_HOSP, ES-FISABIO, ES-SIDIAP, and NO-UOSL. KD cases were found in the Italian data sources IT-PEDIANET and IT-ARS. Baseline characteristics statistics for age categories are summarized for each data source.

Results are shown and discussed in sections 9.1.7.22 and 9.1.7.25.

Overall, it is still difficult to estimate the MIS incidence rates with the specific codes and the combination of Kawasaki and MIS should be used.

9.2.2 COVID-19 severity in children

- EMA study request: 8 March 2022
- CVM study results: 21 July 2022 (PDCO presentation)
- EMA study update request (inclusion of at-risk pediatric populations): 13 September 2022
- CVM update of the study results: 8 May 2023 (Final Report and Manuscript - Annex 6)

Background
Detailed and high-quality epidemiological description of COVID-19 disease in the pediatric population is essential to implement evidence-based clinical and policy responses to protect children's and adolescents' health. Therefore, this study aimed to estimate the incidence rate of COVID-19 disease stratified by severity of clinical presentation in healthy and at-risk pediatric population from Italy, Spain and Norway. The overview of the study results is reported below. Detailed results are reported in a ready-to-submit (at the time of writing of this report) manuscript entitled "*Incidence of COVID-19 disease severity in a cohort of 6.7 million Italian, Spanish, and Norwegian children from 7 healthcare databases*". (Annex 4).

Objective
To estimate the incidence rate (IR) of SARS-CoV-2 infections stratified by severity of disease and vaccine intake in the general and high-risk pediatric populations.

Methods
Descriptive, retrospective, multi-center/multi-database, cohort study. Descriptive demographic and baseline characteristics statistics (age, sex, at-risk medical condition) are summarized for each data source.
We used data from 7 electronic healthcare records databases in Spain, Italy and Norway. The study is conducted from the 1st of January 2020 to the latest data availability for each data source (mostly end of 2021). Three age categories were chosen (0-4, 5-11, 12-17 years old). The follow-up time was split into vaccinated and non-vaccinated person-time periods. Four COVID-19 severity levels were considered (diagnosis, hospitalization, intensive care unit admission, and death after COVID-19). Monthly COVID-19 vaccination rollout is shown. IRs per 100,000 person years (PY) for COVID-19 disease outcomes (non-severe and severe COVID-19 infection) were estimated in both non-vaccinated and post-vaccinated time. Exact 95% confidence intervals were calculated.

Results
The total study population comprised 6,719,867 under 18 years old individuals (51% women) across the 7 data sources. Median age ranged from 6-10 years old. At-risk population comprised 445,174 (6.5%) children and adolescents with comorbidities. Vaccine uptake in children (mostly Comirnaty) was mainly from July 2021 and September 2021 in Italy and Spain, respectively, whereas in Norway was in September 2021.

In children and adolescents without risk factors, the highest incidence rates across data sources varied between 27 to 143 cases/100 PY in December 2021 and January 2022. Rates were lower (0 to 1/100 PY) for severe COVID-19 infection. Incidence rates of complicated COVID-19 were higher among children and adolescents with at-risk conditions for a severe disease. Overall, mortality cases were almost zero across all databases and cohorts.

Conclusions
We demonstrated that we could monitor severity of COVID-19 infections 0–17-year-olds in Italy, Spain and Norway using electronic health record data and show that COVID-19 vaccination uptake was late, whereas the peak of infections was high in the winter of 2021. Severe COVID-19 infections were very rare in children, but more frequent in children with at-risk conditions as compared to general population.

9.2.3 Myocarditis and pericarditis associated with SARS-CoV-2 vaccines.

- EMA study request: 22 September 2021
- CVM study results: 21 October 2021
- CVM update of the study results: 22 April 2022 (published in Front. Pharmacol[116]., 24 November 2022, Annex 5)
- CVM update of the study results: 5 January 2023 (PRAC presentation)
- CVM update of the study results: 8 May 2023

Background
In July 2021, the EMA's Pharmacovigilance Risk Assessment Committee (PRAC) published a statement on the potentially elevated risk of myocarditis and pericarditis (myo-/pericarditis) following vaccination with mRNA based COVID-19 vaccines. Pericarditis and myocarditis

[116] Front. Pharmacol., 24 November 2022 Sec. Pharmacoepidemiology Volume 13 - 2022 | https://doi.org/10.3389/fphar.2022.1038043

are inflammatory heart diseases whose etiopathology can be both infectious and non-infectious. Viral causes are presumed to explain more than 80% of cases, despite they have also been described as rare adverse drug reactions (ADR) for previous vaccines, such as influenza or smallpox, among others. Usual symptoms include breathlessness, strong irregular heartbeat feeling and chest pain, that usually solves with rest, NSAID, corticosteroids or colchicine[117] [118].
Evidence for myo-/pericarditis as rare adverse effects of the mRNA-based platform COVID-19 vaccines is growing based on case series as well as electronic healthcare database studies and have been included as potential ADR in their Summary of Product Characteristics (SmPC)[119] Based on spontaneous reports, the typical onset was at 14 days after vaccination, and mainly affecting elderly people with comorbidities and mortality was very low (0.1%)[120]
There have been spontaneous reports of myocarditis in children and adolescents following the extension of the indication for both vaccines in individuals 12 years of age and older.
The PRAC has asked EMA to update its O/E analysis for these events.
To address an adequate monitoring of the risks of myo-/pericarditis, for all vaccine types, age bands, and doses, the CVM study reported three updates of the absolute and relative incidence rates of myocarditis and pericarditis before and after COVID-19 disease and after vaccination with the EMA-approved COVID-19 vaccine brands.
Results obtained until April 2022 have been published in Front. Pharmacol. (November 2022) and summarized below. Further updated results and in-depth analyses are included in this report (section **Error! Reference source not found.**)

Objective
To report the absolute and relative incidence rates of myocarditis and pericarditis before and after COVID-19 disease and after vaccination with EMA-approved COVID-19 vaccine brands.

9.2.3.1 Analysis 22 April 2022[121]

Methods
Population-based cohort study with nested self-controlled risk interval (SCRI) using healthcare data from five European databases: the Dutch PHARMO-NL, the Spanish BIFAP- and SIDIAP-ES, the Italian ARS-IT, and the British CPRD-UK (Aurum) data sources.
Individuals were followed from 01/01/2020 until end of data availability (31/12/2021 latest).
The outcome was the first myo-/pericarditis diagnosis. Exposures were 1st and 2nd dose of Pfizer, AstraZeneca, Moderna, and Janssen COVID-19 vaccines. Baseline incidence rates (IRs), and vaccine- and dose-specific IRs and rate differences were calculated from the cohort
The SCRI calculated calendar time-adjusted IR ratios (IRR), using a 60-day pre-vaccination control period and dose-specific 28-day risk windows. IRRs were pooled using random effects meta-analysis.

[117] European Medicines Agency. Comirnaty and Spikevax: possible link to very rare cases of myocarditis and pericarditis. 2021. https://www.ema.europa.eu/en/news/comirnaty-spikevax-possible-link-very-rare-cases-myocarditis-pericarditis
[118] Imazio M, Gaita F, LeWinter M. Evaluation and Treatment of Pericarditis: A Systematic Review. JAMA 2015;314(14):1498–506. https://doi.org/10.1001/jama.2015.12763
[119] European Medicines Agency. Spikevax (previously COVID-19 Vaccine Moderna). 2021. https://www.ema.europa.eu/en/medicines/human/EPAR/spikevax
European Medicines Agency. Comirnaty. 2021. https://www.ema.europa.eu/en/medicines/human/EPAR/comirnaty#authorisation-details-section
[120] European Medicines Agency. Comirnaty and Spikevax: possible link to very rare cases of myocarditis and pericarditis. 2021. https://www.ema.europa.eu/en/news/comirnaty-spikevax-possible-link-very-rare-cases-myocarditis-pericarditis
[121] Front. Pharmacol., 24 November 2022 Sec. Pharmacoepidemiology Volume 13 - 2022 | https://doi.org/10.3389/fphar.2022.1038043

Results

Over 35 million individuals (49.2% women, median age 39–49 years) were included, of which 57.4% received at least one COVID-19 vaccine dose. Baseline incidence of myocarditis was low. Myocarditis IRRs were elevated after vaccination in those aged < 30 years, after both Pfizer vaccine doses (IRR = 3.3, 95%CI 1.2-9.4; 7.8, 95%CI 2.6-23.5, respectively) and Moderna vaccine dose 2 (IRR = 6.1, 95%CI 1.1-33.5). An effect of AstraZeneca vaccine dose 2 could not be excluded (IRR = 2.42, 95%CI 0.96-6.07). Pericarditis was not associated with vaccination.

mRNA-based COVID-19 vaccines and potentially AstraZeneca are associated with increased myocarditis risk in younger individuals, although absolute incidence remains low. More data on children (≤ 11 years) are needed.

9.2.3.2 Analysis January 5, 2023

Methods

As pericarditis was not associated with vaccination in the published paper, the January 2023 update focused on myocarditis only. The Dutch PHARMO-NL data source was excluded from this update as they could not identify myocarditis separately form pericarditis.

The study design was a self-controlled risk interval (SCRI). We included healthcare data from five European databases: the Spanish FISABIO-ES, which was not included in the previous study, BIFAP-ES and SIDIAP-ES, the Italian ARS-IT, and the British CPRD-UK (Aurum) data sources.

Individuals were followed from 01/01/2020 until end of data availability (ARS-IT: August 2021; SIDIAP- and FISABIO-ES: December 2021; CPRD-UK: March 2022; BIFAP-ES: April 2022).

The outcome was a new myocarditis diagnosis. Exposures were 1st, 2nd and 3rd dose of Pfizer, Moderna, AstraZeneca, and Janssen (only 1st dose) COVID-19 vaccines. The SCRI calculated calendar time-adjusted IR ratios (IRR), using a 60-day pre-vaccination control period and dose-specific 28-day risk windows. IRRs were pooled using random effects meta-analysis.

Results

Total vaccinated population accounted for 29,714,841 persons. Across data sources, ages, and gender, myocarditis IRRs were higher after the 2nd dose for the mRNA platform vaccines, but not after the 3rd dose, whereas, for AstraZeneca vaccine, an increment in point estimate after 1st and 2nd dose was not significant (Table 22). Sensitivity analyses have been performed by investigating the dose-specific risk windows for 7 days (1-7; 8-14; 14-21; 21-28 days) for each vaccine brand and dose, across genders and all ages (

Figure 44, Figure 45), red points indicate IRRs values statistically significant). Days 1-7 and 8-14 were associated with higher risk after dose 1 and 2 for mRNA vaccines. Day 8-14 are significantly associated with risk of myocarditis for AstraZeneca vaccine doses 1 and 2 (Consistent with Patone M et al)[122].

[122] Patone M, Mei XW, Handunnetthi L, Dixon S, Zaccardi F, Shankar-Hari M, Watkinson P, Khunti K, Harnden A, Coupland CAC, Channon KM, Mills NL, Sheikh A, Hippisley-Cox J. Risks of myocarditis, pericarditis, and cardiac arrhythmias associated with COVID-19 vaccination or SARS-CoV-2 infection. Nat Med. 2022 Feb;28(2):410-422. doi: 10.1038/s41591-021-01630-0.

Table 22. Meta-analysed myocarditis IRRs across data sources, ages, stratified by vaccine brands and doses (January 2023 analysis).

Vaccine Brand and dose	IRR	LCI	UCI	Control Window N of events	Risk Window N of events
Pfizer dose 1	1.54	0.88	2.70	116	57
Pfizer dose 2	1.85	1.32	2.60	110	98
Pfizer dose 3	0.87	0.46	1.65	47	21
Moderna dose 1	1.23	0.60	2.55	34	15
Moderna dose 2	2.39	1.40	4.10	34	43
Moderna dose 3	0.77	0.34	1.74	30	10
AstraZeneca dose 1	1.63	0.88	3.01	44	21
AstraZeneca dose 2	1.74	0.88	3.44	38	22
Janssen dose 1	1.84	0.48	6.99	7	<5

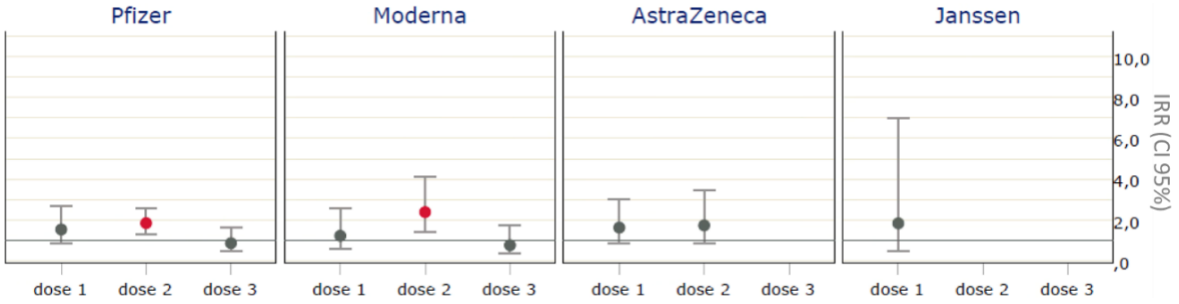


Figure 44: Meta-analysed myocarditis IRRs across data sources, ages, stratified by vaccine brands and doses (January 2023 analyses).

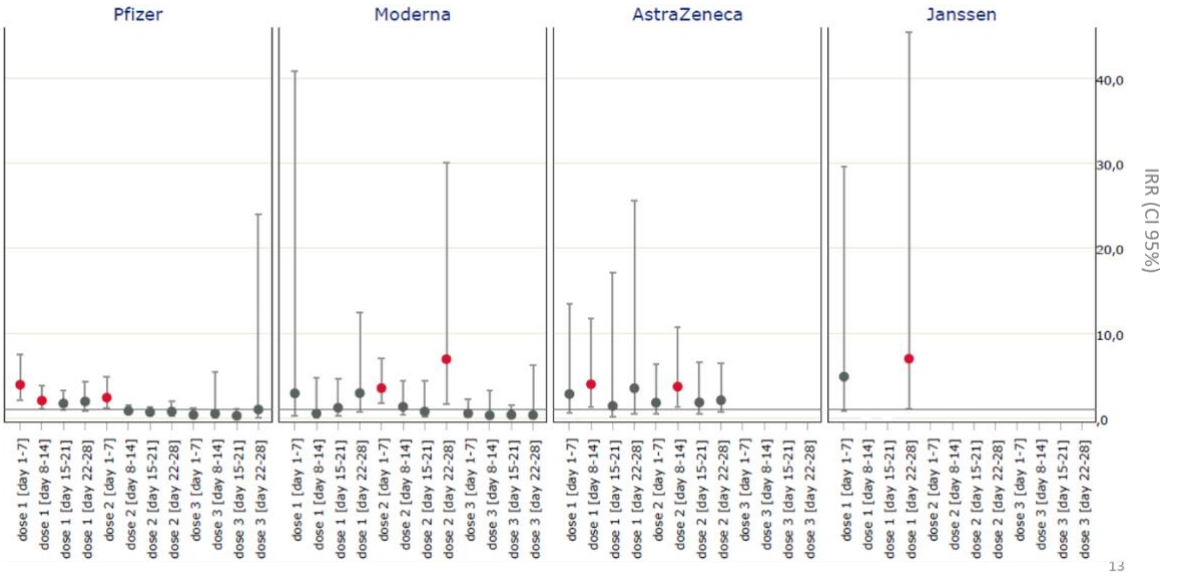


Figure 45: Meta-analysed myocarditis IRRs across data sources, ages, stratified by vaccine brands and doses divided in 7 days interval risk windows (January 23 analysis).

Stratifying between vaccinees aged < 30 and those >30 years old (Table 23), myocarditis IRRs were higher in those aged < 30 years, after Pfizer vaccine doses 1 and 2 (IRR = 1.40, 95%CI 0.3-7.0; 2.38, 95%CI 1.2-4.8, respectively) and Moderna vaccine doses 1 and 2 (IRR = 1.49, 95%CI 0.4-5.2; 3.21, 95%CI 1.3-8.1, respectively). In persons > 30 years of an increased IRR (not significant) was found for AstraZeneca vaccine doses 1 and 2 (IRR = 1.35, 95%CI 0.7-2.7; 1.56, 95%CI 0.7-3.3, respectively) and Janssen dose 1 (IRR = 1.95, 95%CI, 0.5-8.4), which were not seen in November 2021.
Dose 3 of Pfizer vaccine was not associated with an increased risk of myocarditis in either below or above 30 years old categories, whereas for Moderna vaccine dose 3 the risk was

elevated (not significantly) after dose 3 in <30 (3.71, 95%CI 0.3-48.6), but not in the >30 years old (Figure 46, Figure 47)

Table 23. Meta-analyzed myocarditis IRRs across data sources, stratified by vaccine brands and doses, and age bands (<30 and >30 years old) (January 2023 analyses)..

Age band (years old)	Vaccine Brand and dose	IRR	LCI	UCI	Control Window N of events	Risk Window N of events
>30	Pfizer dose 1	1.20	0.76	1.90	83	36
	Pfizer dose 2	1.21	0.78	1.88	84	53
	Pfizer dose 3	0.87	0.42	1.79	39	18
<30	Pfizer dose 1	1.40	0.28	6.97	33	21
	Pfizer dose 2	2.38	1.18	4.78	26	45
	Pfizer dose 3	0.99	0.19	5.11	8	<5
>30	Moderna dose 1	0.57	0.20	1.60	22	7
	Moderna dose 2	0.71	0.29	1.78	24	10
	Moderna dose 3	0.43	0.15	1.27	28	5
<30	Moderna dose 1	1.49	0.43	5.17	12	8
	Moderna dose 2	3.21	1.27	8.13	10	33
	Moderna dose 3	3.71	0.28	48.64	<5	5
>30	Janssen dose 1	1.95	0.45	8.39	6	<5
<30	Janssen dose 1	-	-	-	<5	<5
>30	AstraZeneca dose 1	1.35	0.69	2.65	35	18
	AstraZeneca dose 2	1.56	0.73	3.32	30	20
	AstraZeneca dose 3	-	-	-	<5	<5
<30	AstraZeneca dose 1	0.48	0.06	3.75	9	<5
	AstraZeneca dose 2	0.47	0.07	3.28	8	<5

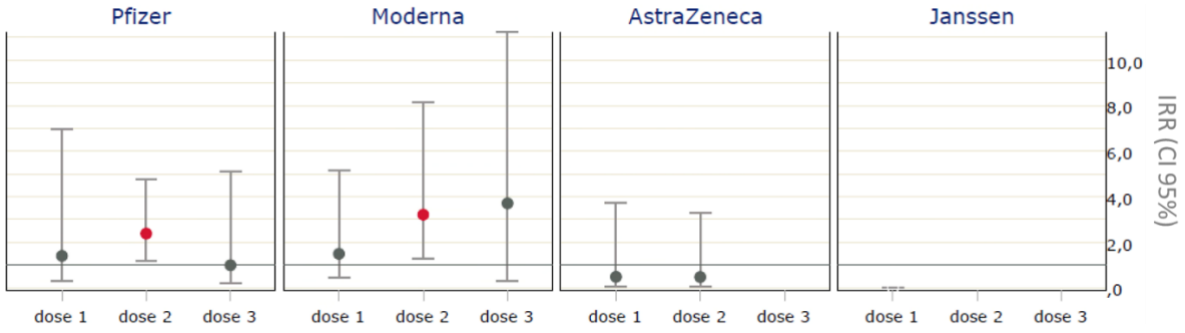


Figure 46: Meta-analysed myocarditis IRRs across data sources, in <30 years old vaccinees, stratified by vaccine brands and doses (January 2023 analyses).

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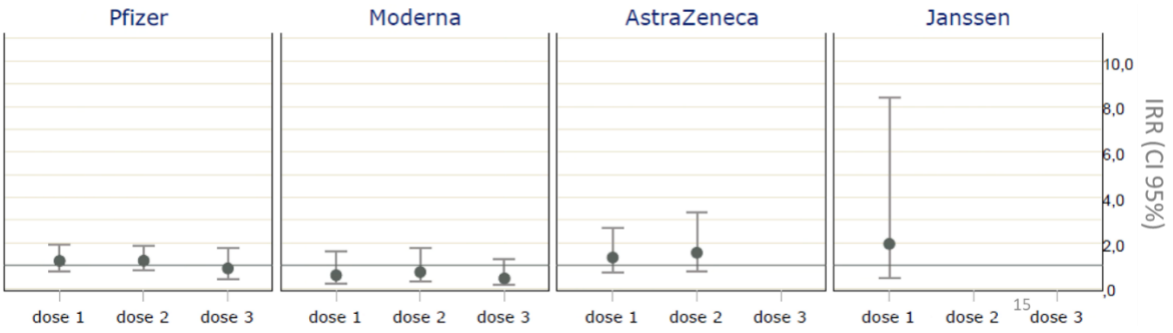

Figure 47: Meta-analyzed myocarditis IRRs across data sources, in >30 years old vaccinees, stratified by vaccine brands and doses (January 2023 analyses).

Stratifying by both age bands (< 30 and >30 years old) and gender (Table 24 and Figure 48), no significant gender specific risk related to vaccination can be demonstrated. The absolute

number of women with myocarditis is much lower than men, because of the much lower background rate in women.

Table 24. Meta-analyzed myocarditis IRRs across data sources, stratified by vaccine brands and doses, age bands (<30 and >30 years old) and gender.

Gender	Age Band (years old)	Vaccine brand	dose	IRR	LCI	UCI	Control Window N of events	Risk Window N of events
Women	<30	Pfizer	1	3.13	0.49	19.79	10	6
		Pfizer	2	0.70	0.08	6.43	7	<5
		Pfizer	3	4.44	0.15	135.41	<5	<5
	>30	Pfizer	1	0.88	0.41	1.92	34	12
		Pfizer	2	1.19	0.49	2.93	36	20
		Pfizer	3	0.47	0.15	1.49	27	7
Men	<30	Pfizer	1	2.02	0.57	7.19	23	15
		Pfizer	2	3.37	1.50	7.56	19	41
		Pfizer	3	0.79	0.12	5.42	7	<5
	>30	Pfizer	1	1.35	0.75	2.46	49	24
		Pfizer	2	1.21	0.69	2.12	48	33
		Pfizer	3	1.47	0.49	4.37	12	11
Women	<30	Moderna	1	-	-	-	<5	<5
		Moderna	2	-	-	-	<5	<5
		Moderna	3	-	-	-	<5	<5
	>30	Moderna	1	0.61	0.05	7.39	8	<5
		Moderna	2	0.51	0.04	6.40	9	<5
		Moderna	3	0.42	0.09	1.96	16	<5
Men	<30	Moderna	1	2.47	0.66	9.26	11	8
		Moderna	2	3.87	1.40	10.70	9	30
		Moderna	3	1.01	0.19	5.26	<5	<5
	>30	Moderna	1	0.85	0.25	2.81	14	<5
		Moderna	2	1.05	0.36	3.07	15	9
		Moderna	3	1.00	0.16	6.44	12	<5
Women	<30	AstraZeneca	1	-	-	-	<5	<5
		AstraZeneca	2	0.76	0.02	34.88	<5	<5
	>30	AstraZeneca	1	0.64	0.15	2.67	17	<5
		AstraZeneca	2	1.47	0.41	5.22	14	7
Men	<30	AstraZeneca	1	0.44	0.03	6.04	8	<5
		AstraZeneca	2	0.39	0.03	4.97	7	<5
	>30	AstraZeneca	1	1.55	0.68	3.53	18	14
		AstraZeneca	2	1.86	0.65	5.35	16	13

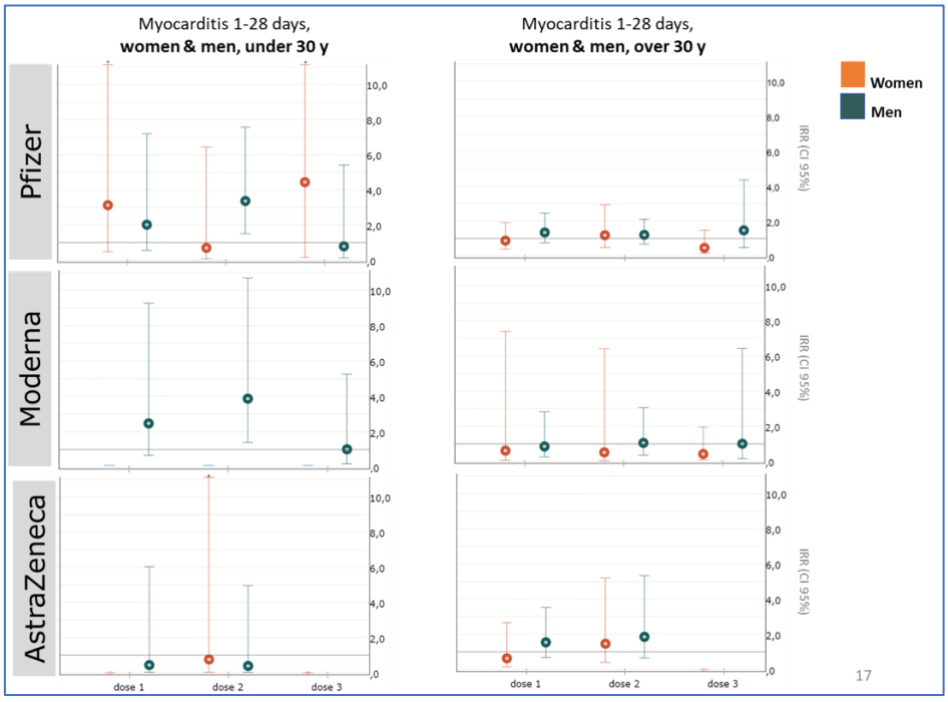

Figure 48: Meta-analyzed myocarditis IRRs across data sources, stratified by vaccine brands and doses, age bands (<30 and >30 years old) and gender (January 2023 analyses).

9.2.3.3 Analysis May 8, 2023

Methods

The study design was a self-controlled risk interval (SCRI). We included healthcare data from five European databases who were fit for purpose: the Spanish FISABIO-ES, BIFAP-ES and SIDIAP-ES, the Italian ARS-IT, and the British CPRD-UK (Aurum) data sources. Individuals were followed from 01/01/2020 until end of data availability (ARS-IT: December 2021; ES-SIDIAP and FISABIO-ES: December 2021; CPRD-UK: March 2022; BIFAP-ES: April 2022).

The outcome was a new myocarditis diagnosis. Exposures were 1st, 2nd and 3rd dose of Pfizer, Moderna, AstraZeneca, and Janssen (only 1st dose) COVID-19 vaccines. The SCRI calculated calendar time-adjusted IR ratios (IRR), using a 60-day pre-vaccination control period and dose-specific 28-day risk windows. IRRs were pooled using random effects meta-analysis. In this analysis we also used a negative control outcome, otitis externa, and many sensitivity analyses that are addressed in the methodological assessment (see section 10.3).

To restrict confounding due to the time-varying risk of COVID-19 infections, cases with a COVID-19 infection during follow-up were excluded. Moreover, to avoid biased results, vaccinated persons 1 month before the recommended end date were excluded from the analysis because possible events in the control window could be found while in the risk window those are not. A further refinement of the code list was also applied but had no major impact on the background rates as observed in section 10.1.

Results

In this re-analysis of May 2023, data partners run the same data instances analyzed in January 2023.

Total vaccinated population accounted for 29,570,176 persons. It decreased by 144,665 persons due to small modifications in the methodology.

Main results are confirmed. IRR of the second dose of mRNA-platform vaccines is significantly higher than other doses and AstraZeneca vaccine. When excluding patients diagnosed with COVID-19 disease, first and second dose of Pfizer, second dose of Moderna, and second dose of AstraZeneca resulted significant as well, see Table 25.

Table 25. Risk estimates for the association between COVID-19 vaccines and selected safety (myocarditis) and negative control (otitis externa) outcomes, stratified by vaccine brand and dosing instance Analysis May 2023 (all ages)

	Myocarditis		Otitis externa	
	N (risk/control)	**IRR (95% CI)**	**N (risk/control)**	**IRR (95% CI)**
Main analysis				
Dose 1				
Pfizer	63/127	1.36 (0.99-1.87)	5234/11,710	1.01 (0.92-1.10)
Moderna	16/30	1.38 (0.59-3.24)	914/1433	1.09 (1.01-1.09)
AstraZeneca	23/54	1.86 (0.68-5.07)	2421/5605	1.08 (0.90-1.28)
Janssen	<5/6	1.66 (0.45-6.16)	292/401	1.21 (0.97-1.50)
Dose 2				
Pfizer	110/119	2.15 (1.63-2.85)	5788/10,460	1.00 (0.96-1.03)
Moderna	44/37	2.50 (1.55-4.02)	920/1467	1.05 (0.97-1.15)
AstraZeneca	22/44	1.50 (0.84-2.67)	2430/5167	0.97 (0.88-1.06)
Dose 3				
Pfizer	22/54	0.92 (0.50-1.68)	3226/6613	0.96 (0.91-1.02)
Moderna	17/34	0.88 (0.47-1.66)	1283/2786	0.92 (0.91-1.05)
AstraZeneca	<4/6	*insufficient data*	<5/11	0.73 (0.23-2.31)
Analysis excluding patients diagnosed with COVID-19 disease during the study period				
Dose 1				
Pfizer	48/84	1.53 (1.06-2.23)	4287/9774	1.02 (0.91-1.14)
Moderna	14/24	1.48 (0.43-5.18)	741/1136	1.12 (1.02-.123)
AstraZeneca	19/35	1.88 (0.56-6.34)	2154/5023	1.10 (0.89-1.37)
Janssen	<5/<5	2.16 (0.53-8.90)	239/324	1.18 (1.00-1.40)
Dose 2				
Pfizer	91/83	2.58 (1.87-3.56)	5030/9107	1.01 (0.97-1.07)
Moderna	36/30	2.72 (1.07-6.89)	788/1206	1.08 (0.99-1.19)
AstraZeneca	18/29	1.93 (1.00-3.73)	2183/4673	0.97 (0.91-1.03)
Dose 3				
Pfizer	17/34	1.17 (0.46-2.98)	2916/5982	0.95 (0.82-1.09)
Moderna	15/23	1.23 (0.60-2.53)	1139/2463	0.86 (0.79-0.93)
AstraZeneca		*insufficient data*	<5/10	0.80 (0.25-2.54)

Table 26. Meta-analyzed myocarditis IRRs across data sources, stratified by vaccine brands and doses, and age bands (<30 and >30 years old) (May 2023 analyses).

Age band (years old)	Vaccine Brand and dose	IRR	LCI	UCI	Control Window N of events	Risk Window N of events
>30	Pfizer dose 1	1,14	0,78	1,67	93	42
	Pfizer dose 2	1,45	1,03	2,06	92	59
	Pfizer dose 3	1,04	0,42	2,61	45	18
<30	Pfizer dose 1	1,19	0,38	3,73	34	21
	Pfizer dose 2	3,77	2,28	6,24	27	51
	Pfizer dose 3	1,26	0,28	5,78	7	<5
>30	Moderna dose 1	0,7	0,26	1,94	19	5
	Moderna dose 2	0,8	0,31	2,11	25	8
	Moderna dose 3	0,66	0,32	1,37	32	12
<30	Moderna dose 1	1,33	0,49	3,56	11	9
	Moderna dose 2	5,11	2,52	10,38	12	34
	Moderna dose 3	5,27	0,92	30,07	<5	<5
>30	Janssen dose 1	1,71	0,41	7,11	5	<5
<30	Janssen dose 1					
>30	AstraZeneca dose 1	1,42	0,6	3,38	44	20
	AstraZeneca dose 2	1,38	0,77	2,49	35	20
	AstraZeneca dose 3					
<30	AstraZeneca dose 1	0,25	0,04	1,44	10	< 5
	AstraZeneca dose 2	0,62	0,12	3,07	9	< 5

Table 27 presents the results from the stratification by gender and age. As observed in previous analysis from January 2023 (Table 24), the risk to develop myocarditis is higher in men under 30 for mRNA-based vaccines. Results in Table 27 also confirms a higher IRR in men above 30 for Pfizer, which is a new finding of this re-analysis.

Table 27. Meta-analyzed myocarditis IRRs across data sources, stratified by vaccine brands and doses, age bands (<30 and >30 years old) and gender.

Gender	Age Band (years old)	Vaccine brand	dose	IRR	LCI	UCI	Control Window N of events	Risk Window N of events
Women	<30	Pfizer	1	3,19	0,81	12,57	<5	5
		Pfizer	2	2,15	0,64	7,17	7	7
		Pfizer	3	2,18	0,14	34,83	< 5	< 5
	>30	Pfizer	1	0,83	0,43	1,6	40	14
		Pfizer	2	1,14	0,65	2	42	21
		Pfizer	3	1,03	0,24	4,39	25	7
Men	<30	Pfizer	1	1,3	0,44	3,83	24	15
		Pfizer	2	4,07	2,3	7,21	20	43
		Pfizer	3	0,8	0,14	4,6	6	< 5
	>30	Pfizer	1	1,4	0,87	2,27	53	28
		Pfizer	2	1,78	1,13	2,79	50	38
		Pfizer	3	1,16	0,45	3,04	16	9
Women	<30	Moderna	1	-	-	-	-	-
		Moderna	2	-	-	-	-	-
		Moderna	3	-	-	-	-	-
	>30	Moderna	1	0,75	0,15	3,83	6	<5
		Moderna	2	0,78	0,08	7,82	<5	<5
		Moderna	3	1,25	0,49	3,21	14	7
Men	<30	Moderna	1	1,44	0,52	4,01	10	9
		Moderna	2	5,48	2,62	11,43	11	31
		Moderna	3	-	-	-	-	-
	>30	Moderna	1	0,59	0,16	2,17	13	<5
		Moderna	2	1,14	0,43	3,04	16	7
		Moderna	3	0,55	0,18	1,7	14	5
Women	<30	AstraZeneca	1	-	-	-	-	-
		AstraZeneca	2	2,59	0,14	46,41	< 5	< 5
	>30	AstraZeneca	1	0,36	0,1	1,27	21	< 5
		AstraZeneca	2	0,88	0,33	2,31	18	6
Men	<30	AstraZeneca	1	0,16	0,02	1,32	9	< 5
		AstraZeneca	2	0,3	0,04	2,57	8	< 5
	>30	AstraZeneca	1	1,37	0,69	2,72	23	16
		AstraZeneca	2	1,95	0,88	4,35	15	13
Men	>30	Janssen	1	1,79	0,14	23,13	< 5	< 5

Discussion and Conclusions

The main conclusions from results from November 2021 and January 2023 results have been confirmed. We found an increased risk of myocarditis following 2nd dose of mRNA-based vaccines using the 28-day risk window. The association between COVID-19 vaccines and myocarditis in those <30 years of age the risk was highest for mRNA platform vaccines. A new finding of this re-analysis is the elevated risk of myocarditis in persons above 30 years of age for the second dose of Pfizer vaccine.

Dose 3 of Pfizer vaccine is not associated with increased risk of myocarditis in either below or above 30 years old individuals, whereas for the Moderna vaccine the myocarditis risk is elevated (but not significantly) after dose 3 in under 30, but not in above 30 years old.

Exclusion of persons with COVID-19 disease (May 2023 results) resulted in a significant IRR for AstraZeneca vaccine dose 2, Moderna vaccine dose 2, and Pfizer vaccine doses 1 and 2. For discussion about the negative control outcomes (otitis externa), please see WP4 report on methods.

Differently from COVID-19 association with myocarditis, mainly related to a monocyte-predominant infiltrate recruited via CCL2 and other cytokines released with direct viral infection of cardiomyocytes, the mechanistic insights about the pathophysiology of the myocarditis associated with COVID-19 vaccine remain scarce and unknown. Its association with mRNA vaccines and <30 years of age subjects finds theoretical mechanisms in: a)

molecular mimicry between the vaccine product and self-antigens; b) mRNA vaccines lipid nanoparticle and RNA components of COVID-19 vaccines excessive innate immune activation, and c) the myocarditis higher risk in association with high sex hormone levels and tissue-dependent TLR4/IL-18 pathways, which could explain the myocarditis preference for young male.[123]

10 Discussion

10.1 Key findings

10.1.1 Readiness

During the Readiness phase, all DAPs requested approvals to participate in the studies specified in the protocol (including all potential AESI), created an ETL design document towards the ConcePTIOn CDM and conducted level 1-3 quality checks, 9 data sources from Italy (ARS, Pedianet, Caserta), Spain (BIFAP, VID, SIDIAP), Netherlands (PHARMO), UK (CPRD) and Norway (national registers). The region Lazio could not participate because of administrative issues and data access rules.
The total study population that was included in the readiness assessment comprised 52,862,735 persons, CPRD and BIFAP contributed the largest populations. Most data sources had an instance with data completeness until end for 2021 or Q2 2022, they could update repeatedly with 2 ETl's per year except for Norway, which can only update once per year.

Population characteristics

ARS has a relatively old population (8.4% is above 80 years of age) whereas the PEDIANET population is very young since it only captures children 0-14 years of age. The rest of the data sources all had median ages are 40 years of age, with a slightly higher prevalence of women in all data sources. This reflects the national populations well. The most prevalent co-morbidity at baseline (1/1/2020), was a history of cardio/cerebrovascular disease (28% in ARS and lower in others). Some of the comorbidities were not extracted in the data instances and would need to be updated for participation in a that requires them as covariates. The populations were representative, and date of birth and gender were available and follow-up could be calculated adequately which is a requirement for cohort studies and vaccine uptake studies. Some DAPs censored data instances to earlier dates than the extraction dates, to ensure that all databanks would have had the time to be updated.

COVID-19 vaccinations data

COVID-19 vaccination data was available in each of the data sources, and timing of recording as well as uptake percentage was comparable with data from the COVID-19 vaccine tracker at ECDC, the PHARMO data source saw some delays since it was based on GP data, and GPs received the data from the national health agency. All data sources were considered fit for purpose to study COVID-19 vaccination uptake or in studies evaluating COVID-19 vaccines.

[123] John R. et al. (2022) Myocarditis following COVID-19 vaccination: incidence, mechanisms, and clinical considerations, Expert Review of Cardiovascular Therapy, 20:4, 241-251, DOI: 10.1080/14779072.2022.2066522; Vojdani A, et al. Potential antigenic cross-reactivity between SARS-CoV-2 and human tissue with a possible link to an increase in autoimmune diseases. Clin Immunol. 2020;217:108480; https://doi.org/10.1016/j.clim.2020.108480;

In general, more than 70% of persons received Pfizer vaccine in each data source except in UK, followed by Moderna, AstraZeneca and Janssen. In the UK the pattern was different, AstraZeneca had a much higher percentage of first dose (48%), Pfizer was first dose for 49% of population, and Janssen vaccine was not used. In Norway, mostly Pfizer and Moderna were used and no Janssen.

For those starting with Pfizer vaccine dose 1, more than 80% had a homologous second Pfizer dose, in Pedianet second dose was lower, in Norway second dose was frequently Moderna (16.25%). Median distance to second dose differed between regions from 21-63 days (UK) and was much longer when there was a heterologous second dose. In most countries, those vaccinated first with Moderna vaccine had a homologous second dose, in NL-PHARMO and Norway second dose was also frequently Pfizer (14.7% and 12.95% respectively), median distance to second dose was usually 28 days, but there was variation across regions. In persons with AstraZeneca dose 1 a large proportion had a homologous second dose, except in Norway, where 97% used either Pfizer or Moderna as a second dose. Median distance to second dose was between 75-80 days. Boosters after Janssen vaccine were infrequently a Janssen vaccine, the majority had a booster with an mRNA platform vaccine (Pfizer or Moderna).

Strong channeling of different vaccines to certain age groups was observed, which within country could even change per region. Due to the age channeling: Pfizer to very old, and children, AstraZeneca mostly between 50-69 and Moderna distributed, prevalence of co-morbidity was highest in AstraZeneca 1st dose users on a population level.

AESI

Age and gender standardized and age-specific incidence rates of AESI were created for 2019, and 2020 prior to COVID-19 disease, as well as post-COVID-19 disease until vaccination, rates were benchmarked with published data from the ACCESS project (Willame et al.) and other publications. Based on the type of event data that the DAP can access and the setting in which these events are assessed (e.g. in primary care, emergency rooms, outpatient specialist and or discharge/emergency) as well as the vocabularies of diagnostic codes, the rates differed, as was described already by Willame et al. The methodological assessment on misclassification shows the impact of the differences of event provenance in studies and this should be considered in the choice of data sources when conducting evaluation studies (Table 39).

Table 39 AESI list and comparison with ACCESS literature, impact of COVID-19 pandemic and lock down, and heterogeneity by provenance.

AESI	Comparison ACCESS and literature	Effect of lock down	Effect of COVID-19 infection	Heterogeneity by provenance and impact on fitness for purpose
CAD	Consistent	Consistent absolute decrease of 20-40/100,000 PY	1.5-3 fold increase after infection	Underestimation in GP only or hosp. only highest when hosp & outpatient & GP. Norwegian data overestimate due to lack of precise codes, Caserta data instance not fit for purpose.
ADEM	Consistently very low (<0.6/100,000)	Not visible, but very rare event	Increased rate after COVID-19	Small data sources do not observe, and neither those with ICPC coding. Hospital data required to identify the event. Caserta data instance not fit for purpose.
ARDS	Lower rates than in ACCESS due to retagging of codes	Lowering of rates	5-800 fold increase	Extreme effect of having hospital data, only data sources with hospital are fit for purpose. Caserta data instance should not be used.
AKI	consistent	Decrease of rates	2-10 fold increase	Underestimation in GP only or hosp. only highest when hosp & outpatient & GP.

AESI	Comparison ACCESS and literature	Effect of lock down	Effect of COVID-19 infection	Heterogeneity by provenance and impact on fitness for purpose
				Norwegian, Caserta and PHARMO instances not fit for purpose.
ALI	consistent	Decrease of rates	2-10 fold increase	No adequate data in Pedianet, Caserta and PHARMO instances. Rest of source fit for purpose. Best to have GP & hospital data
Anaphylaxis	consistent	Decrease of rates	1.5-2 fold increase	No adequate data in the data instance from Norway, more specific ICD10 codes are required. GP data is required. Caserta data instance not fit for purpose.
Anosmia, ageusia	consistent	Increase of rates (maybe undetected COVID-19	10-100 fold increase	Hospital data alone are not fit for purpose. GP data are required. Caserta data instance should not be used.
Arrhythmia	consistent	Decrease of rates	2-5 fold increase	All provenances add sensitivity. Caserta data instance not fit for purpose.
Arterial thrombosis	Not done in ACCESS	Decrease of rates	2-5 fold increase	GP data alone underestimate, inclusion of hospital data doubles the rate
Bell's Palsy	Not done in ACCESS, but consistent with literature	Small decrease	1.5 fold increase	Caserta and PHARMO data instance not fit for purpose
Chilblain-like lesions	consistent	Small increase	2-5 fold increase	Data from hospital alone not adequate, GP data are required. Instances from Caserta, Norway are not fit for purpose
Coagulation disorders	Not done as aggregate in ACCESS	decrease	2-10 fold increase	PHARMO, Caserta instance not fit for purpose, hospital & GP data required
Cerebral Venous Sinus Thrombosis (CVST)	consistent	Not much impact	2-5 fold increase	PHARMO, Caserta instance not fit for purpose, hospital & GP data required
Diabetes type 1	higher	Not much impact	2-10 fold increase	Homogeneous across data sources based on medicines algorithm
Disseminated Intravascular Coagulation (DIC)	consistent	Small decrease	5-20 fold increase	GP data alone not fit for purpose for this event. CASERTA data instance not fit for purpose
Death (any cause)	consistent	Small increase	>10 fold increase	Homogeneous patterns, CASERTA data instance not fit for purpose
Erythema multiforme	consistent	decrease	No real impact	GP data alone not fit for purpose for this event. CASERTA data instance not fit for purpose
Generalized convulsion	Lower (due to exclusion of febrile)	No impact	No big change	PHARMO , Caserta, and Norwegian instance not fit for purpose
Guillain Barré Syndrome (GBS)	consistent	decrease	substantial increase	PHARMO, Norwegian and Caserta instances not fit for purpose
Haemophagocytic lymphohistiocytosis	Not measured in ACCESS	decrease	2-5-fold increase	Hospital data are required, Caserta, Norwegian, PHARMO instance not fit for purpose
Kawasaki´s disease	consistent	No impact	>10 fold (may be MIS)	Caserta, Norwegian and PHARMO instance not fit for purpose
(Meningo) encephalitis	Slightly higher	Decrease in rates	2-5-fold higher	Norwegian data very high. Caserta instance not fit for purpose
Microangiopathy	consistent	Decrease	2-10 fold higher	Data instance from Caserta, CPRD and BIFAP not fit for purpose for this event
Multisystem inflammatory syndrome (MIS)	Lower, since kawasaki was not included anymore	Did not exist as code	Strong increase	ICD9 and ICPC codes do not exist for this condition. Only ICD10 and SNOMED codes. To study MIS & KD should be combined
Myocarditis	consistent	decrease	10-200 fold increase	GP only data underestimate by 50%. PHARMO data not fit for purpose due to lack of specific ICPC
Narcolepsy	consistent	decrease	No increase	Hospital only data underestimate. Data instance of PHARMO, Caserta and Norway not fit for purpose for this event
Pancreatitis	Not measured in ACCESS	Slight decrease	increase	PHARMO, Caserta and Norway not fit for purpose for this event. SIDIAP requires inspection

AESI	Comparison ACCESS and literature	Effect of lock down	Effect of COVID-19 infection	Heterogeneity by provenance and impact on fitness for purpose
Pericarditis	consistent	No major impact	1.5-5 fold increase	PHARMO, Caserta data not fit for purpose for this event
Rhabdomyolysis	Not measured in ACCESS	decrease	10-fold increase	PHARMO, Norwegian, Pedianet, Caserta data instances not fit for purpose. Hospital data required
Severe cutaneous adverse reactions to drugs (SCARs)	Not measured in ACCESS	decrease	Up to tenfold increase	ARS, Caserta, PHARMO and Norwegian data sources not fit for purpose for this event. Hospital data required.
Sensorineural hearing loss	Not measured in ACCESS	decrease	2-fold increase	Caserta and ARS data instances not fit for purpose, GP data is required
Single organ cutaneous vasculitis (SOCV)	Decrease due to reclassification of narrow codes	decrease	3-5 fold increase	PHARMO, Caserta, ARS, Pedianet and Norwegian data instances not fit for purpose
Stroke haemorrhagic	Lower	decrease	3-4 fold increase	Hospital data are required. Caserta, Pedianet, Norwegian data not fit for purpose. GP only underestimates
Sudden death	Not measured in ACCESS	No observable impact	Strong increase	Cause of death not able to be detected in many data sources. Only ARS, BIFAP and Norway
Thrombocytopenia	Higher than in ACCESS	decrease	2-10 fold increase	Caserta, Norwegian, PHARMO data instances not fit for purpose
TTS	Consistent	No major impact	10-fold increase	Caserta not fit for purpose, hospital data required
Thyroiditis (autoimmune)	Not measured in ACCESS	decrease	4-fold Increase	Norwegian, ARS, PHARMO, Caserta data not fit for purpose, GP & Hospital data are required
Transverse myelitis	consistent	decrease	5-10 fold increase	Norwegian, PHARMO, Caserta and Pedianet instances not fit for purpose.
VTE	consistent	decrease	2-10 fold increase	Both GP & Hospital data are required, otherwise underestimation, Norwegian data overestimate. Caserta data not fit for purpose

10.1.2 Conduct of electronic healthcare records-based rapid assessment studies

During the 2-year phase of the project, EMA requested 3 rapid evaluation studies.

Multi-inflammatory syndrome (MIS)

The request from EMA was to generate incidence rates (IRs) for MIS stratified by COVID-19 and pre-post-vaccination. The analysed study population included more than 6 million persons, with 650,731 children aged between 0 and 17 years old. Since MIS is a condition related to COVID-19 disease, MIS codes (SNOMED and ICD10) were created only at the end of 2020 and low rates of this event could be masked by higher post-COVID-19 rates of KD in 2020. ARS-IT could not identify MIS codes as this data source makes use of ICD9 codes, which are not updated anymore. In the absence of MIS codes, KD-like disease codes were used by the Italian colleagues due to the reported association between MIS and KD in children. Rates of KD were highest in 0-11 years old individuals, both in males and females, with only one case of MIS effectively occurring after the COVID-19 pandemic, in 2021. An increment of the KD-like disease cases in 0-11 years old children was also observed in 2020, during the COVID-19 pandemic. KD and MIS rates were both very low. It is still difficult to estimate the MIS incidence rates with the specific codes and the combination of KD and MIS should be used. No cases of KD & MIS in children post-vaccination were observed, also because very few vaccinated children were present on the April and May 2021 data extractions of BIFAP and ARS, respectively.

For this final report updated Kawasaki and MIS specific incidence rates were calculated. Kawasaki disease rates increased more than 10-fold after COVID-19 diagnosis, and MIS also increased very much, but could only be observed in Norwegian data after COVID-19, which have issues with specificity of the codes.

COVID-19 severity in children

The pediatric committee requested an estimation of the incidence rates of serious COVID-19 in children, prior and after vaccination. Data were delivered and presented to the PDCO. Results have been updated for this final report including Norway as well since it has good COVID-19 data.
Four COVID-19 severity levels were considered (diagnosis, hospitalization, intensive care unit admission, and death after COVID-19*).* Non hospitalized COVID-19 disease was considered non-severe, and severe disease was hospitalization, ICU or death).
The total study population comprised 6,719,867 under 18 years old individuals (51% women) across the 7 data sources. Median age ranged from 6-10 years old. The at-risk of severe COVID-19 disease population comprised 445,174 (6.6%) children and adolescents with comorbidities. Vaccine uptake in children (mostly Comirnaty) was mainly from July 2021 and September 2021 in Italy and Spain, respectively, whereas in Norway in September 2021 for adolescents. In children and adolescents without risk factors, the highest incidence rates of non-severe COVID-19 across data sources varied between 27 to 143 cases/100 PY in December 2021 and January 2022. Rates were much lower (0 to 1/100 PY) for severe COVID-19 infection. Incidence rates of severe COVID-19 was higher among children and adolescents with at-risk conditions for a severe disease. Overall, mortality cases were almost zero across all databases and cohorts.

Myocarditis and pericarditis

EMA requested to evaluate the signal of COVID-19 vaccines and Myocarditis/pericarditis at the end of September 2021. Study results were first reported to EMA and PRAC in November 2021, updates with additional data sources and more follow-up were conducted and results have been published in a peer-reviewed journal.[124] In order to include longer follow-up and data sources, an update of the SCRI myocarditis was again presented to PRAC in January 2023, in this report we include an additional analysis with more follow-up and this update was also used for methodological studies.
Key primary results from the April 2023 analysis with fit for purpose data sources confirmed what had been found before: Pfizer dose 2 and Moderna dose 2 were associated with an increased risk of myocarditis (independent of brand of first dose) in persons below 30 years of age, and not for a booster Pfizer dose the effect was not observed, but it persisted when the third dose was Moderna (not significantly). Analyses by week rather than 28 days, showed that elevations of risk occurred.
Exclusion of subjects with COVID-19 during follow-up resulted in an increase of the IRR (not stratified by age) for second dose of Pfizer, Moderna and AstraZeneca, which were all significantly elevated. After exclusion of persons with COVID-19 disease, third doses were not associated with significant elevation anymore. The negative control sensitivity analysis showed estimates around 1 and an effect towards the 1 when persons with COVID-19 were excluded.

[124] Front. Pharmacol., 24 November 2022. Sec. Pharmacoepidemiology Volume 13 - 2022 | https://doi.org/10.3389/fphar.2022.1038043

10.2 Limitations

The part of the CVM study on EHR data had various objectives, first to assess readiness and assess whether data sources were fit for purpose. All data sources were fit as regards population and COVID-19 vaccinations, but depending on the AESI would not be fit to participate in evaluation studies due to misclassification of the AESI (e.g.; PHARMO could not identify myocarditis specifically; no SCARs cases in Italian and Dutch databases during the study period due to lack of ICPC and ICD9 codes that are specific for the conditions). Post COVID-19 rates can increase more than 10-fold, and we should underlie that hospital data have important impact on the rates. Misclassification depended on type of databanks available (primary care, outpatient specialist and hospitalization), meanings (primary discharge vs. secondary discharge diagnoses) as well as the use of narrow (specific) codes and/or broad codes (sensitive). A review of the literature on the PPV of these codes showed a range of false positive rates and an impact on the RR which would lead to bias towards the null in case of non-differential misclassification and different directions when there would be differential misclassification in comparative studies.
Confounding may have impacted the results of the evaluation study on COVID-19 vaccines and myocarditis which the EMA requested. We showed a large channeling of age between different COVID-19 vaccines, which could confound comparative studies. The self-controlled designs would take care of the stable confounding factors but not the time varying. COVID-19 disease was a strong time varying confounder, and lack of control resulted in effect estimates that were biased towards the null. Post vaccination follow-up data are not rapidly available during a vaccination campaign. Design choices such as pre-vaccination control or post-vaccination control period needed to be made. It was shown that a pre-vaccination control period did not overestimate the effect, on the contrary yielded a more conservative estimate. The SCRI design was less susceptible to time varying confounding than the SCCS design.

10.3 Interpretation

The readiness assessment, and the various studies requested by EMA, could be conducted in time, and using data sources that were fit for purpose. The design chosen in the protocol was suitable, and through a series of sensitivity analyses we showed that the pre-vaccination control period would yield conservative estimates, and did control well for confounding, better than a SCCS. Not every data source is fit for purpose to assess each AESI, misclassification due to lack of certain databanks and false positive rates of codes, may impact considerably.

10.4 Generalisability

This study used data from 9 data sources in 6 European countries. Data sources were representative for the regions they represented.

11 Conclusion

The CVM EHR and methodology studies showed that several data sources are ready to evaluate COVID-19 vaccine-AESI associations. Misclassification of the outcome may have large impact on the absolute and relative estimates and the ‘fit’ data sources should be used.

Confounding was likely because of the large channeling of the different vaccines, but the designs chosen (SCRI) dealt best with time stable and time varying confounding. By using this design, we were able to estimate the associations between COVID-19 vaccines and myocarditis repeatedly. For myocarditis, we showed significant associations between the second dose of mRNA platform vaccines and myocarditis, when COVID-19 affected patients were excluded the relative risks increased and also showed a significant association for AstraZeneca vaccine and myocarditis. Other associations can be studied using this design with fit-for-purpose data sources for the AESI.

12 List of Annexes

1. SAP for EHR studies (published on: Miriam Sturkenboom, Susana Perez-Gutthan, Carlos Durán, Anna Schultze, Sophie Bots, Svetlana Belitser, Xabier Garcia-Albeniz, Ivonne Martin, & Olaf Klungel. (2023). Covid-19 Vaccine Monitoring project (CVM) - Statistical analysis plan for EHR data sources (1.2). Zenodo. https://doi.org/10.5281/zenodo.8244051)
2. Codelists for AESI and covariates. Published on: Carlos Durán, Judit Riera, Sima Mohammadi, Joan Fortuny, Vera Ehrenstein, Cristina Rebordosa, & Miriam Sturkenboom. (2023). Covid-19 Vaccine Monitoring project (CVM)-Electronic Health Record data sources Codelist (1.0) [Data set]. Zenodo. https://doi.org/10.5281/zenodo.8199481
3. Table with standardized rates for AESI (excel sheet)
4. Code counts for AESI