Protocol

Cohort monitoring of Adverse Events of Special Interest and COVID-19 diagnoses prior to and after COVID-19 vaccination

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Research question and objectives	This study will monitor exposure to COVID-19 vaccines and generate incidence rates of adverse events of special interest and COVID-19 diagnoses prior to and after COVID-19 vaccines using 4 healthcare databases in 4 European countries As secondary objective the incidence rates after vaccination with individual vaccine brands will be compared to non-vaccinated 2020 baseline data baseline
Country(-ies) of study	Netherlands, United Kingdom, Italy and Spain
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Contents

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
EMA	European Medicines Agency
EMR	Electronic Medical 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
IMI	Innovative Medicines Initiative
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

1.Title

Cohort monitoring of Adverse Events of Special Interest and COVID-19 diagnoses prior to and after COVID-19 vaccination

2. Marketing authorisation holder

Not applicable
This protocol has been developed as a deliverable of the framework contract No EMA/2018/28/PE with the European Medicines Agency.

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4. Abstract

Title:
Cohort monitoring of Adverse Events of Special Interest and COVID-19 diagnoses prior to and after COVID-19 vaccination

Main author:
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Rationale and background:
The global rapid spread of COVID-19 caused by the SARS-CoV2 triggered the need for developing vaccines to control for this pandemic. This study will generate incidence rates of adverse events of special interest (AESI) prior to and after COVID-19 vaccination, to facilitate monitoring of the benefit-risk profile of licensed COVID-19 vaccines. It is not the purpose to actually assess the benefit risk profile in a quantitative manner.

Research question and objectives:
Primary objectives

- To monitor and estimate the incidence rates of adverse events of special interest (AESI) in vaccinated and non-vaccinated persons by data source over the period January 1st 2020-October 31st 2021 by brand and dose of vaccine and age of the population
- To monitor and estimate the incidence rates of diagnosed COVID-19 in vaccinated and non-vaccinated persons by data source over the period January 1st 2020-October 31st 2021 by brand and dose of vaccine as well as age
- To monitor exposure and coverage to COVID-19 vaccines by brand and dose of vaccine as well as age

Secondary objectives

- To compare the incidence rates of AESIs in the risk window of 28 days after vaccination with dose 1 and/or dose 2 with the incidence rates of AESIs in 2020.
- To monitor and estimate vaccine exposure, incidence rates of adverse events of special interest (AESI) and of COVID-19 in vaccinated and non-vaccinated persons over the period January 1st 2020-October 31st 2021 in the at-risk population for developing severe COVID-19 by data source, brand and dose of vaccine as well as age

Study design:
A retrospective, multi-database, dynamic cohort study, conducted during the study period ranging from January 1st 2020-October 31st 2021.

Population:

All subjects in the source population in the participating data sources who were in follow-up since 1 January 2019 or were born into the cohort during the study period, and for whom vaccination data would be able to be obtained/linked in 2021.

Variables:

Variables of interest will be

- 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.
- Vaccines: vaccine brands and batch numbers (where possible)

AESI:

Event	Cohort	Naïve period
COVID disease*	✓	365 days
Multisystem inflammatory syndrome	✓	365 days
Acute respiratory distress syndrome	✓	365 days
Acute cardiovascular injury, including microangiopathy, heart failure, stress cardiomyopathy, coronary artery disease, arrhythmia, myocarditis	✓	365 days
Coagulation disorders, including deep vein thrombosis, pulmonary embolus, cerebrovascular stroke, haemorrhagic disease, cerebral vein sinus thrombosis, disseminated intravascular coagulation, thrombotic thrombocytopenia syndrome (TTS)	✓	365 days
Generalised convulsion	✓	365 days
Guillain Barré Syndrome	✓	365 days
Diabetes (type 1)	✓	365 days
Acute kidney injury	✓	365 days
Acute liver injury	✓	365 days
Anosmia, ageusia	✓	365 days
Chilblain-like lesions	✓	365 days
Single organ cutaneous vasculitis	✓	365 days
Erythema multiforme	✓	365 days
Anaphylaxis	✓	30 days
Death (any cause)	✓	365 days
Sudden death (by codes)	✓	365 days
Acute aseptic arthritis	✓	365 days
Meningoencephalitis	✓	365 days
Acute disseminated encephalomyelitis (ADEM)	✓	365 days
Narcolepsy	✓	365 days
Thrombocytopenia	✓	365 days

Event	Cohort	Naïve period
Transverse myelitis	✓	365 days
Bells' palsy	✓	365 days

*not an adverse event, but effectiveness outcome, included to be able to look at VAED

Data sources:
The study will include data from 4 data sources in 4 European countries (Italy, Netherlands, Spain, United Kingdom). Data sources contain record linkage from multiple origins (PHARMO in the Netherlands, ARS in Italy, BIFAP in Spain, CPRD in UK) in most cases including data from general practitioners (PHARMO, CPRD, BIFAP).

Study size:
The source population will comprise approximately 36 million individuals (7 million Netherlands, 8 million Spain, 3.5 million Italy and 16 million in UK).

Data analysis:
Incidence rates of listed AESI will be calculated in non-exposed time periods (prior to vaccination or in non-vaccinated) and during each one-week risk window since vaccination by each dose, stratified per brand of vaccine.
Data on vaccine exposures (doses), incidence rate of diagnosed COVID-19 and each AESI of interest by time since vaccination dose will be displayed on a dashboard. Incidence rates (and 95%CI) of COVID-19 and AESI among at-risk populations (in terms of comorbidity and by age) will also be computed.

Incidence rates of AESI in a risk window of 28 days after dose 1 and dose 2 will be compared to the non-vaccine exposed rates of AESI in the same data source in 2020. Adjustments will be made for measured confounders using Poisson regression analysis. Effect modification by age, gender, prior COVID-19 and presence of Co-morbidity, will be inspected by adding interaction terms into the Poisson model in a backward stepwise manner using Likelihood ratio tests.

Milestones:

Milestone	Planned date
Protocol submitted to the EMA	January 24, 2021
Data collection start	February 15, 2021
Planned analyses completed	31 October 2021
Final report of study results	November 30, 2021

5. Amendments and updates

Update of events: splitting coagulopathies in separate entities based on concerns around AstraZeneca	March 15, 2021

Inclusion of thrombotic thrombocytopenia syndrome in protocols	April 14, 2021
Inclusion of comparison of rates as secondary objective. Update of references and links to Zenodo instead of google Drive	October 13, 2021
Deletion of between vaccine comparisons from secondary objectives, considered out of scope by EMA	November 11, 2021

6. Deliverables

Deliverable	**Date**
D2. Protocol	January 24, 2021
D3. Interim statistical reports	30 April 2021, August 3, October 29th (CPRD) per DAP conditional on data availability/approvals
D4. Final study report	November 30, 2021

7. Rationale and Background

7.1 Background

COVID-19 vaccine development has been triggered on a global level following the release of the genetic sequence of SARS-CoV2 on 11 January 2020[1]. The landscape for COVID-19 vaccines is characterized by a wide range of technology platforms including nucleic acid (DNA and RNA), virus-like particle, peptide, viral vector (replicating and non-replicating), recombinant protein, live attenuated virus and inactivated virus approaches.

On December 21st, 2020, EMA has recommended granting a conditional marketing authorisation for the vaccine **Comirnaty**, developed by BioNTech and Pfizer, to prevent coronavirus disease 2019 (COVID-19) in people from 16 years of age[2]. On January 6, 2021, EMA has recommended granting a conditional marketing authorisation for **COVID-19 Vaccine Moderna** to prevent Coronavirus disease (COVID-19) in people from 18 years of age. This was the second COVID-19 vaccine that EMA has recommended for authorisation[3]. Other vaccines from AstraZeneca and Janssen followed (see table 1)

Table 1: Overview of COVID-19 products with market access in Europe (March 30, 2021)

product	**excipients**	**dosing**	**formulation**
Comirnaty 1 vial (0.45 mL) contains 5 doses of 30	((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate)	Comirnaty is administered intramuscularly	This is a multidose vial and must be diluted before use.

[1] Le, T. Thanh, et al. "The COVID-19 vaccine development landscape." *Nat Rev Drug Discov* 19.5 (2020): 305-6.
[2] https://www.ema.europa.eu/en/news/ema-recommends-first-covid-19-vaccine-authorisation-eu
[3] https://www.ema.europa.eu/en/news/ema-recommends-covid-19-vaccine-moderna-authorisation-eu

micrograms of BNT162b2 RNA (embedded in lipid nanoparticles). **Licensed** EMA: Dec 21, 2020 EUL: UK Dec 2, 2020 WHO: 31 December 2020	(ALC-0315) 2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide (ALC-0159) 1,2-Distearoyl-sn-glycero-3-phosphocholine (DSPC) Cholesterol Potassium chloride Potassium dihydrogen phosphate Sodium chloride Disodium phosphate dihydrate Sucrose Water for injections	after dilution as a course of 2 doses (0.3 mL each) at least 21 days apart	One vial (0.45 mL) contains 5 doses of 0.3 mL after dilution. 1 dose (0.3 mL) contains 30 micrograms of COVID-19 mRNA Vaccine (embedded in lipid nanoparticles).
Moderna Covid-19 vaccine (Spikevax) One dose (0.5 mL) contains 0.10 mg of mRNA (embedded in lipid nanoparticles) **Licensed** EMA: Jan 6, 2021 EUL: UK Jan 8, 2021 USA: Dec.18, 2020	Lipid SM-102 Cholesterol 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC) 1,2-Dimyristoyl-rac-glycero-3-methoxypolyethylene glycol-2000 (PEG2000 DMG) Tromethamol hydrochloride Acetic acid Sodium acetate trihydrate Sucrose Water for injections	COVID-19 Vaccine Moderna is administered as a course of 2 doses (0.5 mL each). It is recommended to administer the second dose 28 days after the first dose	This is a multidose vial which contains 10 doses of 0.5 mL. One dose (0.5 mL) contains 100 micrograms of messenger RNA (mRNA) (embedded in SM-102 lipid nanoparticles). The unopened vaccine may be stored refrigerated at 2°C to 8°C, protected from light, for maximum 30 days. Once thawed the vaccine should not be re-frozen. The unopened vaccine may be stored at 8°C to 25°C up to 12 hours after removal from refrigerated conditions. Vial should not be shaken
AstraZeneca (Vaxzevria) One dose (0.5 ml) contains: COVID 19 Vaccine (ChAdOx1-S* recombinant) 5 × 10^10 viral particles where ChAdOx1-S means the recombinant, replication-deficient chimpanzee adenovirus vector encoding the SARS-CoV-2 Spike (S) glycoprotein **Licensed** EMA: 29/01/2021 EUL UK: Dec 29, 2020 Argentina (30 Dec 2020) and India (03 Jan 2021) Mexico (04 Jan 2021)	L-histidine L-histidine hydrochloride monohydrate magnesium chloride hexahydrate polysorbate 80 ethanol sucrose sodium chloride disodium edetate dihydrate water for injections	COVID-19 Vaccine AstraZeneca is injected into a muscle (usually in the upper arm). Persons will receive 2 injections. The second injection can be given between 4 and 12 weeks after the first injection.	Pack sizes 10 dose vial (5 ml) in packs of 10 vials 8 dose vial (4 ml) in packs of 10 vials Store in a refrigerator (2°C to 8°C). Do not freeze. Keep vials in outer carton to protect from light. The vaccine does not contain any preservative and should be administered by a healthcare professional. After the first dose is withdrawn, the vaccine should be used as soon as practically possible and within 6 hours. During use it can be stored from 2°C to 25°C.
Janssen One dose (0.5 mL) contains: Adenovirus type 26 encoding the SARS-CoV-2 spike glycoprotein* (Ad26.COV2-S), not	2-hydroxypropyl-β-cyclodextrin (HBCD) Citric acid monohydrate Ethanol Hydrochloric acid Polysorbate-80 Sodium chloride Sodium hydroxide	COVID-19 Vaccine Janssen is for intramuscular injection only, preferably in the deltoid muscle of the upper arm.	The Janssen vaccine is packaged as a multi-dose vial which contains 5 doses of 0.5 mL.

less than 8.92 log10 infectious units (Inf.U). * Produced in the PER.C6 TetR Cell Line and by recombinant **Licensed** EMA: 11/03/2021 FDA: EUL: February 27, 2021	Trisodium citrate dihydrate Water for injections		

The European commission has secured contracts for other COVID-19 vaccines from Curevac, Janssen and Sanofi. Curevac and Janssen are in phase III studies. Curevac also uses an RNA platform and Janssen a human adenovirus platform.

7.2 Safety profile of COVID-19 vaccines that are on the market

7.2.1 Comirnaty (Pfizer/BioNTech)

Summary of safety profile[4]

The most common side effects with Comirnaty in the trial were usually mild or moderate and resolved within a few days after vaccination. These included pain and swelling at the injection site, tiredness, headache, muscle and joint pain, chills and fever. They affected more than 1 in 10 people.

Redness at the injection site and nausea occurred in less than 1 in 10 people. Itching at the injection site, pain in the limb, enlarged lymph nodes, difficulty sleeping and feeling unwell were uncommon side effects (affecting less than 1 in 100 people). Weakness in muscles on one side of face (acute peripheral facial paralysis or palsy) occurred rarely in less than 1 in 1,000 people.

Allergic reactions have occurred with Comirnaty, including a very small number of cases of severe allergic reactions (anaphylaxis) which have occurred when Comirnaty has been used in vaccination campaigns. People who have a severe allergic reaction when they are given the first dose of Comirnaty should not receive the second dose.

A recent CDC paper provided information on the experience with Comirnaty in the USA between December 14 and 23. As of December 23, 2020, a reported 1,893,360 first doses of Pfizer-BioNTech COVID-19 vaccine had been administered in the United States, and reports of 4,393 (0.2%) adverse events after receipt of Pfizer BioNTech COVID-19 vaccine had been submitted to the Vaccine Adverse Event Reporting System (VAERS). Twenty-one cases were determined to be anaphylaxis as per Brighton Collaboration case definition (a rate of 11.1 per million doses administered), including 17 in persons with a documented history of allergies or allergic reactions, seven of whom had a history of anaphylaxis. The median interval from vaccine receipt to symptom onset was 13 minutes (range = 2–150 minutes). There was female predominance.

CDC warns that if you have had an anaphylaxis following one mRNA vaccine you should not get a second dose nor one of another mRNA vaccine. The reaction is rare although more frequent than the estimated 1/million doses for other vaccines.

[4] https://www.ema.europa.eu/en/medicines/human/EPAR/comirnaty

7.2.2 Spikevax (Moderna Covid-19 vaccine)

Summary of the safety profile[5]

The safety of COVID-19 Vaccine Moderna was evaluated in an ongoing Phase 3 randomised, placebo-controlled, observer-blind clinical trial conducted in the United States involving 30,351 participants 18 years of age and older who received at least one dose of COVID-19 Vaccine Moderna (n=15,185) or placebo (n=15,166) (NCT04470427). At the time of vaccination, the mean age of the population was 52 years (range 18-95); 22,831 (75.2%) of participants were 18 to 64 years of age and 7,520 (24.8%) of participants were 65 years of age and older. The most frequently reported adverse reactions were pain at the injection site (92%), fatigue (70%), headache (64.7%), myalgia (61.5%), arthralgia (46.4%), chills (45.4%), nausea/vomiting (23%), axillary swelling/tenderness (19.8%), fever (15.5%), injection site swelling (14.7%) and redness (10%). Adverse reactions were usually mild or moderate in intensity and resolved within a few days after vaccination. A slightly lower frequency of reactogenicity events was associated with greater age. Overall, there was a higher incidence of some adverse reactions in younger age groups: the incidence of axillary swelling/tenderness, fatigue, headache, myalgia, arthralgia, chills, nausea/vomiting and fever was higher in adults aged 18 to < 65 years than in those aged 65 years and above. Local and systemic adverse reactions were more frequently reported after Dose 2 than after Dose 1. Throughout the safety follow-up period, acute peripheral facial paralysis (or palsy) was reported by three participants in the COVID-19 Vaccine Moderna group and one participant in the placebo group. Onset in the vaccine group participants was 22 days, 28 days, and 32 days after Dose 2. The reactogenicity and safety profile in 343 subjects receiving COVID-19 Vaccine Moderna, that were seropositive for SARS-CoV-2 at baseline, was comparable to that in subjects seronegative for SARS-CoV-2 at baseline.

7.2.3 Vaxzevria (AstraZeneca)

Summary of safety profile[6]

This medicinal product has been given authorisation for temporary supply by the UK Department of Health and Social Care and the Medicines and Healthcare products Regulatory Agency on December 29, 2020. It does not have a marketing authorisation, but this temporary authorisation grants permission for the medicine to be used for active immunisation of individuals aged 18 years and older for the prevention of coronavirus disease 2019 (COVID-19). It is not yet authorized by EMA, but expected for the end of January 2021.

COVID-19 Vaccine AstraZeneca has been given to approximately 24,000 individuals aged 18 years or older in four ongoing clinical trials in the UK, Brazil and South-Africa. The most common side effects with COVID-19 Vaccine AstraZeneca (which may affect more than 1 in 10 people) were tenderness, pain, warmth, redness, itching, swelling or bruising where the injection is given, generally feeling unwell, feeling tired (fatigue), chills or feeling feverish, headache, feeling sick (nausea), joint pain or muscle ache. In clinical studies, most side effects were mild to moderate in nature and resolved within a few days with some still present a week after vaccination.

In clinical trials there were very rare reports of events associated with inflammation of the nervous system, which may cause numbness, pins and needles sensations, and/or loss of feeling. However, it is not confirmed whether these events were due to the vaccine. On 7 March 2021, the Austrian National

[5] https://www.ema.europa.eu/en/documents/product-information/covid-19-vaccine-moderna-product-information_en.pdf (accessed January 9, 2021)

[6] https://www.gov.uk/government/publications/regulatory-approval-of-covid-19-vaccine-astrazeneca/information-for-uk-recipients-on-covid-19-vaccine-astrazeneca#possible-side-effects (accessed 9-1-2021)

Competent Authority suspended the use of one batch of the COVID-19 vaccine AstraZeneca (batch number ABV5300) as a precautionary measure following reports of events of thromboembolic events occurring with use of the vaccine, which led to the temporarily interruption in several EU countries, followed by changes in AstraZeneca vaccination strategies later in March (i.e restricted access). [7]

7.2.4 Janssen

Summary of safety profile (March 2021)
The safety of COVID-19 Vaccine Janssen was evaluated in an ongoing phase 3 study (COV3001) at the time of the first application. A total of 21 895 adults aged 18 years and older received COVID-19 Vaccine Janssen. The median age of individuals was 52 years (range 18-100 years). The safety analysis was performed once the median follow-up duration of 2 months after vaccination was reached. Longer safety follow-up of >2 months is available for 11 948 adults who received COVID-19 Vaccine Janssen.
In study COV3001, the most common local adverse reactions reported was injection site pain (48.6%). The most common systemic adverse reactions were headache (38.9%), fatigue (38.2%), myalgia (33.2%) and nausea (14.2%). Pyrexia (defined as body temperature ≥38.0°C) was observed in 9% of participants. Most adverse reactions occurred within 1–2 days following vaccination and were mild to moderate in severity and of short duration (1–2 days).
Reactogenicity was generally milder and reported less frequently in older adults (763 adults ≥65 years old). The safety profile was generally consistent across participants with or without prior evidence of SARS-CoV-2 infection at baseline; a total of 2 151 adults seropositive at baseline received COVID-19 Vaccine Janssen (9.8%).[8]

7.3 Monitoring COVID-19 vaccines in EU

In line with the EU's safety monitoring plan for COVID-19 vaccines[9], COVID-19 vaccines will be closely monitored and subject to several activities that apply specifically to COVID-19 vaccines. Although large numbers of people have received COVID-19 vaccines in clinical trials, certain side effects may only emerge when millions of people are vaccinated. This protocol is part of the European Medicines Agency activities to monitor the vaccines.

8. Research question and objectives

Primary objectives

- To monitor and estimate the incidence rates of adverse events of special interest (AESI) in vaccinated and non-vaccinated persons by data source over the period January 1st 2020-October 31st 2021 by brand and dose of vaccine and age of the population.

[7] https://www.ema.europa.eu/en/documents/prac-recommendation/signal-assessment-report-embolic-thrombotic-events-smq-covid-19-vaccine-chadox1-s-recombinant-covid_en.pdf
[8] https://www.ema.europa.eu/en/documents/product-information/covid-19-vaccine-janssen-epar-product-information_en.pdf
[9] https://www.ema.europa.eu/en/documents/other/pharmacovigilance-plan-eu-regulatory-network-covid-19-vaccines_en.pdf

- To monitor and estimate the incidence rates of diagnosed COVID-19 in vaccinated and non-vaccinated persons by data source over the period January 1st 2020-October 31st 2021 by brand and dose of vaccine as well as age.
- To monitor exposure and coverage to COVID-19 vaccines by brand and dose of vaccine as well as age

Secondary objectives

- To compare the incidence rates of AESIs in the risk window of 28 days after vaccination with dose 1 and/or dose 2 with the incidence rates of AESIs in 2020 from ECVM.
- To monitor and estimate vaccine exposure, incidence rates of adverse events of special interest (AESI) and of COVID-19 in vaccinated and non-vaccinated persons over the period January 1st 2020-October 31st 2021 in the at-risk population for developing severe COVID-19 by data source, brand and dose of vaccine as well as age

9. Research methods

9.1 Study design

The study will be a retrospective, multi-database, dynamic cohort study. The study will be conducted during January 1st 2020-October 31st 2021 or until the date of last data availability for each data source.

Person-time after cohort entry will be divided in non-exposed person-time, and person-time following vaccination by specific brands, labelled by dose and distance since last vaccination (-1, -2, -3 weeks etc).

The source population will include all individuals observed in one of the participating data sources for at least one day during the study period (01 January 2020 - last data availability) and who have at least 1 year of data availability before cohort entry, except for individuals with data available since birth.

Per event, for calculation of incidence, individuals will be followed from cohort entry and contribute to person-time in month (prior to vaccination) and in weeks after vaccination plus specific vaccine exposure (brand & dose) category. Follow-up will be censored upon the earliest of date of the event (except for recurrent events), death, exiting the data source, or last data draw-down.

Comparisons of incidence rates of AESIs will be conducted between the following sub-cohorts of vaccinated persons and non-exposed cohort from 2020 comprising person time prior to vaccination in 2020.

1a. Sub-cohort of vaccinated persons with Pfizer Dose 1, followed from time zero (vaccination) until 4 weeks after that or end of follow-up or dose 2 of the vaccine, whichever is earliest

1b. Sub-cohort of vaccinated persons with Pfizer Dose 2, followed from 2nd dose of vaccination until 4 weeks after that or end of follow-up, whichever is earliest

1c. Sub-cohort of vaccinated persons with Pfizer Dose 1& 2, followed from 1st dose of vaccination until 4 weeks after 2nd dose or end of follow-up, whichever is earliest

1d. Sub-cohort of vaccinated persons with J&J dose 1, followed from time zero (vaccination) until 4 weeks after that or end of follow-up, whichever is earliest

1e. Sub-cohort of vaccinated persons with AstraZeneca dose 1, followed from time zero (vaccination) until 4 weeks after that or end of follow-up or dose 2 of the vaccine, whichever is earliest

1f. Sub-cohort of vaccinated persons with AstraZeneca Dose 2, followed from 2nd dose of vaccination until 4 weeks after that or end of follow-up, whichever is earliest

1g. Sub-cohort of vaccinated persons with AstraZeneca Dose 1 & 2, followed from 1st dose of vaccination until 4 weeks after 2nd dose or end of follow-up, whichever is earliest

1h. Sub-cohort of vaccinated persons with AstraZeneca Dose 1 and mRNA vaccine dose 2 followed from 1st dose of vaccination until a maximum of 4 weeks after 2nd dose or end of follow-up, whichever is earliest.

1i. Sub-cohort of vaccinated persons with Moderna dose 1 followed from time zero (vaccination) until 4 weeks after that or end of follow-up or dose 3 of the vaccine, whichever is earliest

1j. Sub-cohort of vaccinated persons with Moderna dose 2, followed from 2nd dose of vaccination until 4 weeks after that or end of follow-up, whichever is earliest

1k. Sub-cohort of vaccinated persons with Moderna Dose 1& 2, followed from 1st dose of vaccination until 4 weeks after that 2nd dose or end of follow-up, whichever is earliest

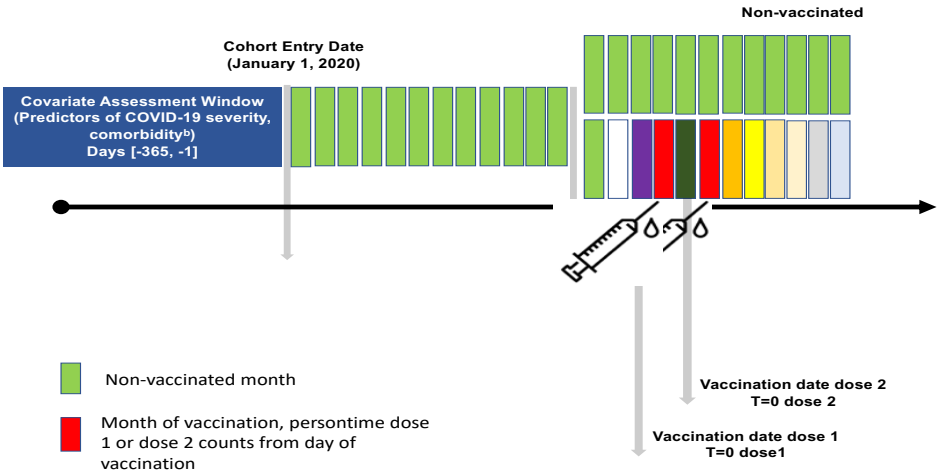


Figure 2 Key study design

Study period from January 1st 2020 until last data collected (last possible October 2021), the year 2019 is a run-in period
Censoring will occur at event date (except for anaphylaxis), last data collected, last data draw-down, or death, whichever occurs first

9.2 Setting

The study results will include data from 4 data sources in 4 European countries, comprising 36 million individuals (**Table 2**). Data sources are described in section 9.4.

Table 2. Overview of data sources to be used for the study

Country	Data Access Provider	Name Data source	Active population	Type of data source	Types of encounters for diagnoses	Access to vaccine brand name	Availability of mortality registry
Netherlands	PHARMO	PHARMO	6 million	Record linkage	GP	Yes	Yes
Spain	AEMPS	BIFAP	8 million	GP medical records	GP	Yes	No
Italy	ARS	ARS data	3.6 million	Record linkage	Hospital	Yes	Yes
United Kingdom	Utrecht University	CPRD/HES	13 million	GP & Hospital medical record	GP	No	No

GP: General practitioner

Data sources were chosen from those that have been able to prepare for monitoring COVID-19 vaccines in the ACCESS project, and have the ability to have short delays, access to COVID-19 vaccine data and 3 monthly updates.

9.3 Variables

Variables of interest will be those relevant for creation of:

- Person-time: birth and death dates as well as periods of observation, vaccination and occurrence of events
- Events: dates of medical and/or procedure and/or prescription/dispensing codes to identify AESI, at-risk medical conditions or COVID-19
- Vaccinations: brand and dose of vaccination

9.3.1 Person-time & Follow-up

For incidence rates of AESI & COVID-19, cohort entry start will be on 1st January 2020, for those who have at least one year of data (registered on January 1st, 2019) or are born in 2019. For those born after January 1st , 2020 date of birth will be start of cohort entry.
End of follow-up will be 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 will vary according to the event under evaluation. One person can contribute time to non-vaccinated category as well as to vaccinated category as displayed in figure 2. Within the vaccinated persons, person-time will be counted by brand and dose of vaccine (dose 1 or 2), and by distance (in weeks) to last vaccination in months. Exposure date (t=0 is the date of vaccination, and will be calculated as exposed)

9.3.2 AESI, At-risk medical conditions & Operationalization

9.3.2.1 Events

Events to be monitored comprise diagnosed COVID-19 and Adverse events of special interest (table 3). Definitions and code lists for each of these events have been made available through the ACCESS project and are available on the VAC4EU community in the open source Zenodo repository: https://zenodo.org/communities/vac4eu/?page=1&size=20

The date of an event will be the first occurrence (code) for such an event during follow-up. We will not consider recurrent events, except for anaphylaxis, where recurrence after 30 days will be permitted. Diagnoses may have different origins (provenance), we will distinguish between events originated from hospitalizations and from primary care in each data source.

Table 3. List of events

Event	Recurrence allowed#	In initial ACCESS AESI list	Naïve period
COVID disease*	NO	Yes	365 days
Multisystem inflammatory syndrome	NO	Yes	365 days
Acute respiratory distress syndrome	NO	Yes	365 days
Acute cardiovascular injury, including microangiopathy, heart failure, stress cardiomyopathy, coronary artery disease, arrhythmia, myocarditis	NO	Yes	365 days
Coagulation disorders, including deep vein thrombosis, pulmonary embolus, cerebrovascular stroke, limb ischaemia, haemorrhagic disease, thrombotic thrombocytopenia syndrome	NO	Yes (have been isolated now because of issues seen in AZ vaccine)	365 days
Generalised convulsion	Yes	Yes	30 days
Guillain Barré Syndrome	NO	Yes	365 days
Diabetes (type 1 and unspecified type)	NO	Yes	365 days
Acute kidney injury	NO	Yes	365 days
Acute liver injury	NO	Yes	365 days
Anosmia, ageusia	NO	Yes	365 days
Chilblain-like lesions	NO	Yes	365 days
Single organ cutaneous vasculitis	NO	Yes	365 days
Erythema multiforme	NO	Yes	365 days
Anaphylaxis	Yes	Yes	30 days
Death	NO	Yes	365 days
Sudden death	NO	Yes	365 days
Acute aseptic arthritis	NO	Yes	365 days

Event	Recurrence allowed#	In initial ACCESS AESI list	Naïve period
Meningoencephalitis	NO	Yes	365 days
Acute disseminated encephalomyelitis (ADEM)	NO	Yes	365 days
Narcolepsy	NO	Yes	365 days
Thrombocytopenia	No	Yes	365 days
Transverse myelitis	No	Yes but isolated now because of trial data	365 days
Bells' palsy	No	No, but included because of issues in trials	365 days

* vaccine-associated enhanced (respiratory) disease (VAED) is an AESI for COVID-19 vaccines
# Recurrence is allowed if an event is acute and may re-occur and can be distinguished from prior event

Using information contained in event definition forms together with data access provider experience, broad and narrow algorithms for definition of each AESI have been defined in the ACCESS project, these will be applied also in this study. Event definitions and codes have been updated throughout ACCESS to include DAP feedback. All forms & codes can be found online.

9.3.2.2 At-Risk Medical Conditions to develop severe COVID-19

At risk medical conditions for developing severe COVID-19 have been defined based on scientific evidence available on the US Centers for Disease Control and Prevention (CDC website, July 2020)[10] and National Health Services (NHS website, July 2020) websites[11]. Those websites are updated regularly and provide a classification of at-risk conditions for developing severe COVID-19 based on level of evidence.

The selected at-risk medical conditions are considered as at higher risk to develop severe COVID-19 (**Table 4**).

The following variables will be created:

- At-Risk groups: medical codes and associated dates for at-risk medical conditions characterizing at-risk groups for developing severe COVID-19 as well as prescription and/or dispensing records for drug exposures which may be used as proxies for their identification. At-risk groups will be created for each of the at-risk medical conditions listed in **Table 4**. Multimorbidity will be considered (subjects may belong to more than one at-risk group).

Table 4. Comorbid conditions with evidence of increased COVID-19 severity

At-risk medical conditions identified by diagnosis codes (see codesheets)	Medicinal product proxy(ies) (ATC code)

[10] https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html
[11] https://digital.nhs.uk/coronavirus/risk-assessment/population

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

9.3.2.3 Operationalization & validation

For each of the events of interest, living event definition forms (see annex 3) have been created comprising the following chapters:

- Event definition: using the Brighton Collaboration definitions if available and otherwise definitions from European learned societies
- Synonyms / lay terms used for the event: these show how an event may be described/called in free text
- Laboratory tests done specific for event (may be used as confirmation)
- Diagnostic tests done specific for event (may be used as confirmation in building algorithms)
- Drugs used to treat event (may be used as confirmation in building algorithms)
- Procedures used specific for event treatment (may be used as confirmation in building algorithms)
- Setting (outpatient specialist, in-hospital, GP, emergency room) where condition will be most frequently diagnosed
- Diagnosis codes or algorithms used in different papers to identify the events in Europe/USA
- Experience of participating data sources to identify or validate the events (to be completed by each data source)
- Proposed codes by Codemapper (Becker et al., 2017)
- Algorithm proposal for event identification

- Published background rates
- Extracted codes (upon characterization)
- Study design related information
- References

The event definition form is used throughout the project to transparently track how an event is defined and identified in each of the data sources, it is publicly available as well as the codes on the Zenodo repository.

Events will not be validated for this monitoring study due to lack of funding, benchmarking will occur against published rates, and between data sources (see quality checks)

9.3.3 Exposure to COVID-19 vaccinations

Exposure will be based on recorded receipt of any of the COVID-19 vaccines. Vaccine brand and date of vaccination should be obtained from all possible sources that capture COVID-19 vaccination, such as general practice records, immunisation registers, vaccination records, medical records, or other secondary data sources. Depending on the data source, vaccines may be identified via nationally used product codes—including batch numbers—where possible. As the Pfizer BioNTech, Moderna and Oxford/AstraZeneca COVID-19 vaccines are all licensed as a two-dose vaccine series, multiple vaccinations per person will be identified. Exposure to these vaccines will be classified by brand and dose and calendar month of administration and counted for exposure monitoring.

Exposure windows for event monitoring
Person time of follow up in the cohort will be categorized as at risk (vaccinated) and non-vaccinated periods. Person time will not be stopped at the occurrence of a vaccination. The vaccination day and monthly (28 days) risk-windows after vaccination will be classified as risk periods with increasing months of distance since last dose of vaccination. To keep track of dose, these periods will also be labelled by the number of previous COVID-19 containing vaccinations.

For comparisons of incidence rates we will limit post-vaccination rates to 28 days risk windows post-dose 1 and post-dose 2 to avoid misclassification.

9.3.4 Other variables

- Demographic characteristics: dates of birth and death, sex, country & data source.

In those data sources in which full date of birth is not available for privacy reasons, date of birth will be derived as follows:

- Date of birth will be defined as the 15th of the birth month and birth year. If the birth month is missing, the birth date will be defined as the 30th June of the birth year.

9.4 Data sources

9.4.1 Description of data sources participating in this protocol

The below mentioned data sources have indicated to be able to participate, have relatively short lag times on their outcomes and will be able to provide information on vaccination.

9.4.1.2 Netherlands: PHARMO Database Network

The PHARMO Database Network is a population-based network of electronic healthcare databases and combines anonymous data from different primary and secondary healthcare settings in the Netherlands. These different data sources, including data from general practices, in- and out-patient pharmacies, clinical laboratories, hospitals, the cancer registry, pathology registry and perinatal registry, are linked on a patient level through validated algorithms. To ensure the privacy of the data in the PHARMO Database Network, the collection, processing, linkage and anonymization of the data is performed by STIZON. STIZON is an independent, ISO/IEC 27001 certified foundation, which acts as a Trusted Third Party between the data sources and the PHARMO Institute. The longitudinal nature of the PHARMO Database Network system enables to follow-up more than 9 million persons of a well-defined population in the Netherlands for an average of twelve years. Currently, the PHARMO Database Network covers over 6 million active persons out of 17 million inhabitants of the Netherlands. Data collection period, catchment area and overlap between data sources differ. Therefore, the final cohort size for any study will depend on the data sources included. As data sources are linked on an annual basis, the average lag time of the data is one year. All electronic patient records in the PHARMO Database Network include information on age, sex, socioeconomic status and mortality. Other available information depends on the data source. A detailed description of the different data sources is given below. PHARMO is always seeking new opportunities to link with healthcare databases. Furthermore, it is possible to link additional data collections, such as data from chart reviews, patient-reported outcomes or data from general practice trials.

The General Practitioner database comprises data from electronic patient records registered by GPs. The records include information on diagnoses and symptoms, laboratory test results, referrals to specialists and healthcare 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 Classification System [www.whocc.no]. 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. GP data cover a catchment area representing 3.2 million residents (~20% of the Dutch population). Vaccinations will be linked to the GP records from the national immunization register.

The Out-patient Pharmacy Database comprises GP or specialist prescribed healthcare products dispensed by the out-patient pharmacy. The dispensing records include information on type of product, date, strength, dosage regimen, quantity, route of administration, prescriber specialty and costs. PHARMO is listed under the ENCePP resources database.

9.4.1.2 Spain: BIFAP

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). The project started in 2001 and current version of the database with information until December 2019 includes clinical information of 6,419 GPs and 1,147 paediatricians. Ten participant autonomous regions send their data to BIFAP every year. BIFAP database currently includes anonymized clinical and prescription/dispensing data from around 14 million (8 active population) patients representing 85% of all patients of those regions participating in the database, and 25% of the Spanish population. Mean duration of follow-up in the database is 8.6 years. Diagnoses are classified according to the International Classification of Primary Care (ICPC)-2,ICD-9 and ICD-10 code system. Information on hospital outpatient diagnosis is being progressively included. The BIFAP database was characterized in the ADVANCE project and considered fit for purpose for vaccine coverage, benefits and risk assessment[12]. BIFAP has been linked to a COVID registry for COVID monitoring.

9.4.1.3 Italy: ARS database

The Italian National Healthcare System is organized at regional level: the national government sets standards of assistance and a tax-based funding for each region, and regional governments are responsible to provide to all their inhabitants. Tuscany is an Italian region, with around 3.6 million inhabitants. The Agenzia Regionale di Sanita' della Toscana (ARS) is a research institute of the Tuscany Region. The ARS database comprises all information that are collected by the Tuscany Region to account for the healthcare delivered to its inhabitants. Moreover, ARS collects data from regional initiatives. All the data in the ARS data source can be linked with each other at the individual level, through a pseudo-anonymous identifier. The ARS database routinely collects primary care and secondary care prescriptions of drugs for outpatient use, and is able to link them at the individual level with hospital admissions, admissions to emergency care, records of exemptions from copayment, diagnostic tests and procedures, causes of death, mental health services registry, birth registry, spontaneous abortion registry, induced terminations registry. A pathology registry is available, mostly recorded in free text, but with morphology and topographic Snomed codes. Vaccine data is available since 2016 for children and since 2019 for adults. However, to date, 2019 vaccination data for adults may still be incomplete. The ARS database was characterized in the ADVANCE project and considered fit for purpose for vaccine coverage, benefits and risk assessment when using the new vaccine registry (from 2019)[11]

9.4.1.4 United Kingdom: CPRD & HES

The Clinical Practice Research Datalink (CPRD) from the UK collates the computerized medical records of general practitioners (GPs) in the UK who act as the gatekeepers of healthcare and maintain patients' life-long electronic health records. As such they are responsible for primary healthcare and specialist referrals, and they also store information stemming from specialist referrals, and hospitalizations. GPs 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 feedback information to GPs about their patients, including key diagnoses. The data recorded in the CPRD include demographic information, prescription details, clinical events,

[12] Sturkenboom M et al. ADVANCE database characterisation and fit for purpose assessment for multi-country studies on the coverage, benefits and risks of pertussis vaccinations. Vaccine (2020).

preventive care, specialist referrals, hospital admissions, and major outcomes, including death. The majority of the data are coded in Read Codes. Validation of data with original records (specialist letters) is also available.
The dataset is generalizable to the UK population based upon age, sex, socioeconomic class and national geographic coverage. There are currently approximately 50 million patients (acceptable for research purposes) – of which 16 million are active (still alive and registered with the GP practice) – in approximately 1,700 practices (https://cprd.com/Data). Data include demographics, all GP/healthcare professional consultations (phone, letter, email, in surgery, at home), diagnoses and symptoms, laboratory test results, treatments, including all prescriptions, all data referrals to other care, hospital discharge summary (date and Read codes), hospital clinic summary, preventive treatment and immunizations, death (date and cause). For a proportion of the CPRD panel practices (>80%), the GPs have agreed to permit CPRD to link at patient level to the Hospital Episode Statistics (HES) data. CPRD is listed under the ENCePP resources database, access will be provided by the Utrecht University. The CPRD was not yet characterized in the ADVANCE project, where the UK THIN and RCGP databases were used, but has been widely used in vaccine studies. COVID-19 vaccine administration will be linked in from the national registry.

9.5 Study size

The study population will include all individuals registered with at least one year of data prior to the start of the study period (January 1st 2020) or follow-up from birth. Overall, the estimated study population will comprise approximately 36 million individuals (see **Table 2**).

9.6 Data management

This study will be conducted in a distributed manner using a common protocol, common data model (CDM), and common analytics programs (**Figure 3**). The data pipeline has been developing from the EU-ADR project and was further improved in the IMI-ConcePTION project (https://www.imi-conception.eu/) and used to generate background rates in ACCESS project[13]. This process 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.

9.6.1 Data extraction

Each database access provider (DAP) will create ETL specifications using the standard ConcePTION ETL design template (accessible via this link: https://docs.google.com/document/d/1SWi31tnNJL7u5jJLbBHmoZa7AvfcVaqX7jiXgL9uAWg/edit.
Following completion of this template and review with study statisticians and principal investigators, each DAP will extract the relevant study data locally using their software (eg Stata, SAS, R, Oracle). This data will be loaded into the CDM structure in csv format. These data remain local (**Figure 3**).

[13] https://vac4eu.org/covid-19-tool/

9.6.2 Description of data transformation & analysis pipeline

This study will use data that is already collected for analysis and available in electronic health care data sources in 4 EU countries and follow the following principles.

First, to harmonize the structure of the data sets held by each partner, a shared syntactic foundation is utilized, we will use the generic common data model that was developed in the IMI-ConcePTION project (annex 1). In this common data model, data is represented in a common structure but the content of the data remain in their original format. The extraction, transform, and load (ETL) design will be made available on paper and later on the VAC4EU FAIR catalogue. The validity of the ETL will be assessed using Level 1 (completeness) and Level 2 (logical consistency) R scripts that have been developed as part of the IMI-ConcePTION project.

Second, to reconcile differences across terminologies a shared semantic foundation is built for the definition of events under study by collecting relevant concepts in a structured fashion using a standardized event definition template. The Codemapper tool (https://vac4eu.org/codemapper/) was used to create diagnosis code lists based upon completed event definition templates for each event and comorbid risk condition in the ACCES-BGR protocol. Based on the relevant diagnostic medical codes, as well as other relevant concepts (e.g. medications), one or more algorithms were constructed to operationalize the identification and measurement of each event. These algorithms may differ per data source, as the components that go into the study variable may differ. Wherever possible the event definition sheet specifies prior validation of algorithms and codes for benchmarking. Specifications for both ETL and semantic harmonization are made available in the event definition forms and statistical analysis plans. Scripts for semantic harmonization will be provided in R and distributed to data access providers for local deployment. This will result in a set of study variables which are both semantically and syntactically harmonized. The quality of the semantic harmonisation will be assessed using Level 3 checks that dive deeper into the component analysis and compare against published rates and between databases (benchmarking).

Third, following conversion to harmonized study variable sets, additional R scripts for calculation of analytical datasets will be distributed to data access providers for local deployment. The aggregated results produced by these R scripts will then be uploaded to the Digital Research Environment (DRE) for pooled analysis of incidence and visualization (see **Figure 3**). 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 will be performed on the DRE using R and SAS. Data access providers will have access to the project workspace for verification of the results.

Within the DRE, each project-specific area consists of a separate, secure folder, called a 'workspace'. Each workspace is completely secure, so researchers are in full control of their data. Each workspace has its own list of users, which is managed by its administrators. The architecture of the DRE allows researchers to use a solution within the boundaries of data management rules and regulations. Although General Data Protection Regulation (GDPR) and Good (Clinical) Research Practice still rely on researchers, the DRE offers tools to more easily control and monitor which activities take place within projects. All researchers who need access to DRE are granted access to study-specific secure workspaces through VAC4EU. Access to

this workspace is only possible with double authentication using an ID and password together with the user's mobile phone for authentication. Upload of files is possible for all researchers with access to the workspace within the DRE. Download of files is only possible after requesting and receiving permission from a workspace member with an 'owner' role.

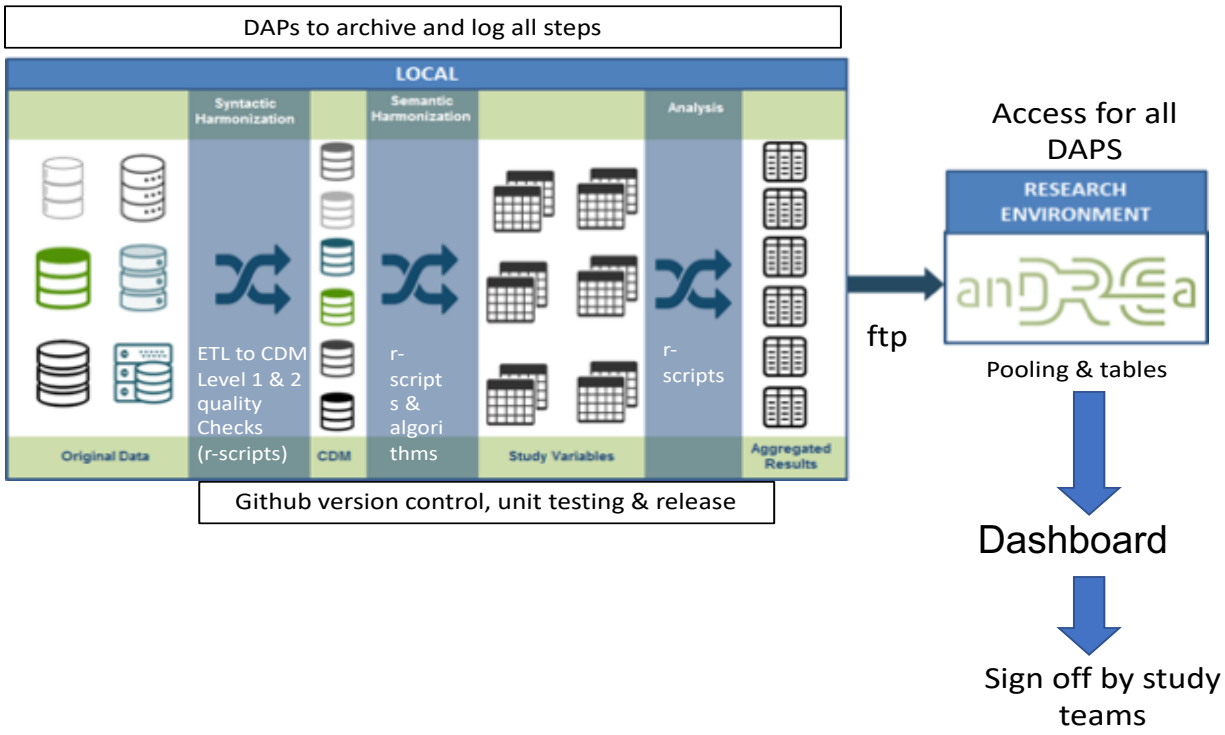


Figure 3 Data transformation and flow

9.6.3 Data processing

Due to the nature of the study, a repeated data processing procedure is envisioned, based on the pipeline described in the previous section. This will allow optimising the data processing timelines and archiving procedures (see next section).
In March 2021, a *baseline* data extraction will be requested to DAPs. This will create a *baseline instance* of the data source. This will be ETL'ed into the ConcePTION CDM, and form the b*aseline instance of the CDM*. The data pipeline will be run for the first time on the baseline instance of the CDM of each DAP, and produce a baseline set of analytic datasets that will be centrally analysed for the baseline assessment.
Periodically (every 3 months), DAPs will be requested to perform the extraction of the new data, which will be called the x^{th}*supplementary instance* of their data source. The supplementary instance of the data source will be ETL'ed to the ConcePTION CDM, to form a *supplementary instance of the CDM, which will be analysed,* this instance comprises all the prior data.

9.6.4 Data visualization

Once the results are postprocessed and pooled on the DRE they will be transferred to a POWERBI platform (https://powerbi.microsoft.com/en-us/for visualization). PowerBI runs on the UMCU Datawarehouse. Access to the visuals can be provided to selected group or openly through linkage to the VAC4EU website.

9.6.5 Archiving and 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 of 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. This needs to be retained for at least 5 years.

Aggregated results from DAPs, ETL design documents, and a repository of study scripts will be stored in the DRE for inspection by the study sponsor for at least five years. The final study aggregated results sets and statistical programs to pool and visualize will be archived and stored on the DRE for five years.

After this period all will be archived at the VAC4EU Sharepoint. The final study protocol and possible amendments, the final statistical report, statistical programs and output files will be archived on the VAC4EU Sharepoint for the specific project.

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 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.

9.7 Data analysis

All analyses will be fully detailed in a Statistical Analysis Plan that is developed ahead of data extraction.

9.7.1 Analysis of Demographics and Baseline Characteristics

Demographic characteristics (age at cohort entry and sex) and baseline characteristics such as at-risk medical conditions will be summarized for each data source using descriptive statistics.

Frequency tables including numbers and percentages will be generated for categorical variables (age at study entry in categories, sex, and presence of at-risk medical conditions at start of cohort entry and at the time of first vaccination by vaccine brand. We will compare baseline characteristics at first vaccination between the vaccination brands.

Mean, standard error, median and range will be provided for continuous variables.

9.7.2 Hypotheses

This study is not designed for causal inference, but is descriptive in nature, since rates are provided in non-vaccinated and post vaccination. Since the availability of incidence rates, draws one to comparisons, which may be confounded, as a secondary objective we will attempt to explore and adjust for measurable confounding, and explore presence of effect modification based on the data that has been collected through the monitoring protocol." As secondary objective we therefore provide some statistical analyses, based on the initial design, which may not fully deal with unmeasured confounding, but it is better than a crude comparison of rates. Because of the potential residual confounding we put a threshold at a RR of 2 for meaningful elevation, consistent with the threshold for signal detection in spontaneous reports.

a) H0: The rate of AESI after dose 1 and/or dose 2 is not meaningfully different from the background comparator rate of AESI

We will consider the relative risk to be meaningfully elevated if the RR is above 2 (to acknowledge that there may be residual confounding) and the lower limit of the 95% confidence interval of the relative risk is above 1.

9.7.3 Statistical Methods

Incidence rates of all events listed in table 3 will be calculated by year and week/month in the non-vaccinated time dividing the number of incident cases (not in run-in year) (numerator) by the total person-time at risk (denominator). Incidence rates of events in vaccinated subjects will be calculated by vaccine brand and dose and the week since last vaccination, aggregation/cumulation may be conducted if counts are low. A 95%CI will be computed using an exact method.

Incidence rates will also be provided among persons at higher risk for developing severe COVID-19 (as described in section 9.3.3).

To monitor vaccination exposure, the counts of administered doses with the following characteristics will be reported: Receipt of a first or second dose of any specific type of COVID-19 vaccine

9.7.4 Statistical Analysis

9.7.4.1 Vaccination exposure monitoring & coverage

For every data source, summary tables with number of administered doses per vaccine brand within the primary series (dose 1 and dose 2) by calendar time (in weeks) over the follow-up period and age at vaccination (in weeks) will be created. The following data transformation steps will be performed:

- Select vaccinations per dose
- Calculate age at vaccination (in months) through dividing age at vaccination (in days) by 30.4 and rounding to the nearest smaller integer

Calculate time by week and year

We will calculate the number of administered COVID-19 vaccine doses of specific brand by calendar time x age x dose. This table will be used as input to the vaccination exposure component of the dashboard. Bar charts will be created with weekly number of administered doses in the observed population.

For every data source, summary tables will be created, with the number of persons of a given birth year cohort who are present in the study cohort on January 1, 2021. The total number of persons as well as the persons vaccinated with dose 1, and dose 1 & dose 2 will be obtained by brand of vaccine. This table will be used as input to the COVID-19 vaccination coverage component of the dashboard. A separate and similar calculation will be done for persons with an at-risk medical condition.

For every birth cohort, we will evaluate the vaccination coverage by dose 1 and 1+2 over time. The coverage at week i for birth cohort j will be calculated by dividing the number of vaccinated subjects n_ij by the total number of subjects under follow-up at week i (N_ij), expressed as a percentage.

9.7.4.2 Benefits: plots with COVID-19 incidence rates

The weekly incidence (/100.000 person-years) of COVID-19 will be calculated as the number of COVID-19 events divided by the total person-time at risk multiplied with 100.000, in each calendar week, prior to vaccination and following dose 1 and 2 of a specific vaccine. Exact Poisson 95% confidence intervals will be calculated. COVID-19 events will be separated in outpatient diagnoses and hospitalizations (severe COVID-19).

9.7.4.3 Risks: plots with incidence of AESI

The incidence rate (per unit person- years) for the AESI will be estimated by week and months and stratified prior to vaccination and after vaccination by brand, dose and time since vaccination. Exact Poisson 95% confidence intervals will be calculated.

All data will be outputted in an excel table as well as displayed on a dashboard similar to the ADVANCE proof of concept dashboard[14]

9.7.4.4 Comparison of incidence rates of AESI

This study is not designed for causal inference, but is descriptive in nature, since rates are provided in non-vaccinated and post vaccination. Since the availability of incidence rates, draws one to comparisons, which may be confounded, as a secondary objective we will attempt to explore and adjust for measurable confounding, and explore presence of effect modification based on the data that has been collected through the monitoring protocol.
We will take the following stepwise approach to the analysis for each DAP

Inspection of trends and potential effect modification

1) Overall incidence rates in 2020 by calendar month (inspection of time trends in non-vaccinated)
    a. Overall AESI incidence rates in 2020 in age categories (<18, 18-59 and 60 years or older)
    b. Overall AESI incidence rates in 2020 by calendar month and by gender

[14] https://vac4eu.org/covid-19-tool/

    c. Overall incidence rates in 2020 by calendar month in with co-morbidity on 1 January 2020 that is associated with higher risk for severe Covid-19
2) Overall Incidence rates during 28 days (or until censoring) post-vaccination (week 1-4) by brand and dose (brand and dose specific rates)
    a. Stratification of the brand and dose specific incidence rates by age (<18, 18-59 and 60 years or older)
    b. Stratification of the brand and dose specific incidence rates by gender
    c. Stratification of the brand and dose specific rates by comorbidity that increases risk of severe COVID-19 at start of vaccination
    d. Stratification of the brand and dose specific rates by history of COVID-19 diagnosis at start of vaccination

Effect modification will be tested using the likelihood ratio test, we will first have a model without interaction, and subsequently a model with all potential interaction terms for age in categories, sex, and history of comorbidities and prior COVID-19 (for those vaccinated), a Likelihood Ratio (LR) test will be used. This LR test then serves as a global test whether there is evidence of any interaction (effect modification). If it is significant, backward elimination will be applied for the individual interaction terms. For the confounders we will also use backward elimination.
The log person-days in each risk or comparison interval will be included in the regression model as the offset. Incidence rate ratios – estimating the ratio of outcome incidence in the risk interval divided by outcome incidence in the comparison interval will be reported with 95% confidence intervals. P-values and 95% confidence intervals will be corrected for over-dispersion in a sensitivity analysis, using a negative binomial regression model instead of Poisson regression model.

Specific analyses will be conducted for each brand and dose of COVID-19 vaccine against the non-exposed. For each 2-dose vaccine, we will conduct analyses for each of three types of 28-day risk interval: the 28 days following Dose 1, the 28 days following Dose 2, and the days that are summed in the 28 days after either dose (total of up to 56 days).
For each of these risk intervals, the comparator will be background rates in non-vaccinated persons in 2020. The following exposure groups are defined, for dose 1 and 2 analyses, persons will be cloned.

Non-vaccinated: 2020 monthly incidence rates by age, sex, history of co-morbidity that increases COVID-19 severity
Exposure groups and time at risk for the Vaccinated with:

- Pfizer:

  1a. Sub-cohort of vaccinated persons with Pfizer Dose 1, followed from time zero (vaccination) until 4 weeks after that or end of follow-up or dose 2 of the vaccine, whichever is earliest
  1b. Sub-cohort of vaccinated persons with Pfizer Dose 2, followed from 2nd dose of vaccination until 4 weeks after that or end of follow-up, whichever is earliest
  1c. Sub-cohort of vaccinated persons with Pfizer Dose 1& 2, followed from 1st dose of vaccination until 4 weeks after 2nd dose or end of follow-up, whichever is earliest
- J&J

  1d. Sub-cohort of vaccinated persons with J&J dose 1, followed from time zero (vaccination) until 4 weeks after that or end of follow-up, whichever is earliest

- AZ:

1e. Sub-cohort of vaccinated persons with AstraZeneca dose 1, followed from time zero (vaccination) until 4 weeks after that or end of follow-up, whichever is earliest
1f. Sub-cohort of vaccinated persons with AstraZeneca Dose 2, followed from 2nd dose of vaccination until 4 weeks after that or end of follow-up, whichever is earliest
1g. Sub-cohort of vaccinated persons with AstraZeneca Dose 1 & 2, followed from 1st dose of vaccination until 4 weeks after 2nd dose or end of follow-up, whichever is earliest
1h. Sub-cohort of vaccinated persons with AstraZeneca Dose 1 and mRNA vaccine dose 2 followed from 1st dose of vaccination until a maximum of 4 weeks after 2nd dose or end of follow-up, whichever is earliest.

- Moderna:

1i. Sub-cohort of vaccinated persons with Moderna dose 1 followed from time zero (vaccination) until 4 weeks after that or end of follow-up, whichever is earliest
1j. Sub-cohort of vaccinated persons with Moderna dose 2, followed from 2nd dose of vaccination until 4 weeks after that or end of follow-up, whichever is earliest
1k. Sub-cohort of vaccinated persons with Moderna Dose 1& 2, followed from 1st dose of vaccination until 4 weeks after that 2nd dose or end of follow-up, whichever is earliest

9.7.5 Missing data

Since the underlying data represent attended medical care, we generally assume that absence of information of clinical events means absence of that condition. No imputation will be done for missing data.

10. Quality control

10.1 Quality management

The study will be conducted according to the guidelines for Good Pharmacoepidemiology Practice (GPP) (International Society for Pharmacoepidemiology 2008) and according to the ENCePP code of conduct (European Medicines Agency 2018). All data access providers have experience in conducting pharmacoepidemiological research and research is done by researchers trained in pharmacoepidemiology. All programs will be developed according to agreed coding standards and will be validated by double programming or source code review with second programmer involvement. Only validated software (Stata, R and/or SAS version 9.4, SAS Institute Inc., Cary, NC) will be used for statistical analyses.

10.2 Data Quality

Data quality will be characterized in a transparent manner according to the procedures developed in the IMI-ConcePTION project on the syntactically harmonized data. This process will proceed iteratively and in collaboration with each data access provider.

Level 1 data checks review the completeness and content of each variable in each table of the CDM to ensure that the required variables contain data and conform to the formats specified by the CDM specifications (e.g., data types, variable lengths, formats, acceptable values, etc.).

This is a check conducted in collaboration with DAPs to verify that the extract, transform, and load (ETL) procedure to convert from source data to the syntactically harmonized CDM has been completed as expected. Formats for all values will be assessed and compared to a list of acceptable formats. Frequency tables of variables with finite allowable values will be created to identify unacceptable values. Distributions of date variables to assess any rounding will be constructed.
The Level 1 checks proceed as follows for each table of interest in the CDM:

1. Within the METADATA table of the CDM, check for presence of the table of interest in the instance.
2. Verify that the table is present in the directory specified by the DAP. If the table is not present, print a notification of its absence to the report.
3. Verify that mandatory variables are present and contain data. If a mandatory variable is absent or contains only missing data, print a notification of this to the report.
4. Check that all conventions for the table of interest have been adhered to. If a convention is not adhered to, print a notification of this to the report.
5. Check consistency between listed allowable values in the METADATA table and data in the table of interest.
6. Tabulate missingness in all variables, overall and by calendar year.
7. Construct distributions of date variables.
8. Construct frequency tables of categorical variables, overall and by calendar year.

Each DAP will be responsible for running the script to complete the Level 1 checks. An R Markdown report describing results of the checks for each table of the CDM will be produced. After addressing any issues identified in Level 1 checks, DAPs may rerun the script and inspect the results. This may proceed iteratively until the DAP declares the ETL to be sufficiently complete and correct. An example R Markdown report produced using simulated data will be included as an annex to the study report.

Level 2 data checks assess the logical relationship and integrity of data values within a variable or between two or more variables within and between tables.

In the level 2 checks, we assess records occurring outside of recorded person time (i.e. before birth, after death, or outside of recorded observation periods). We will identify persons listed in the PERSONS table who do not have any associated records in the other tables of the CDM and verify that persons identified as the mother of an infant in the PERSON_RELATIONSHIPS table of the CDM have a birth date at least twelve years prior to the birth date of their identified child.

Each DAP will be responsible for running the script to complete the Level 2 checks. An R Markdown report describing results of the checks for each table of the CDM will be produced. After addressing any issues identified in Level 2 checks, DAPs may rerun the script and inspect the results. This may proceed iteratively until the DAP declares the ETL to be sufficiently complete and correct. An example R Markdown report produced using simulated data will be included as an annex to the study report.

Level 3 data checks produce incidence and prevalence rates or proportions and trends over time within a data source (by examining output by age and year) for benchmarking between data sources and against external sources.

For the current study, Level 3 checks will quantify person time in each data source for the study population as a whole as well as for subpopulations of interest. These will be calculated overall and by calendar year. Additionally, counts of codes extracted to identify each event and exposure of interest will be calculated overall and by calendar year. Finally, codes will be grouped into concept sets based upon Unified Medical Language System (UMLS) Concept Unique Identifiers (CUIs) as identified using the Codemapper tool (Becker et al., 2017). Counts and rates of each concept set will be calculated overall and by calendar year. Characterization summaries based upon level 3 checks will be included as an annex to the final study report.

External benchmark data will be incidence rates of disease that have been obtained from the literature and are listed in the event definition form. Incidence rates from literature will be presented together with incidence rates estimated for the current study in the final study report. Discrepancies will be identified and interpreted based upon descriptions of the data source(s), algorithms for identification of events, and design choices including in and exclusion criteria in published studies vs. those employed for this protocol.

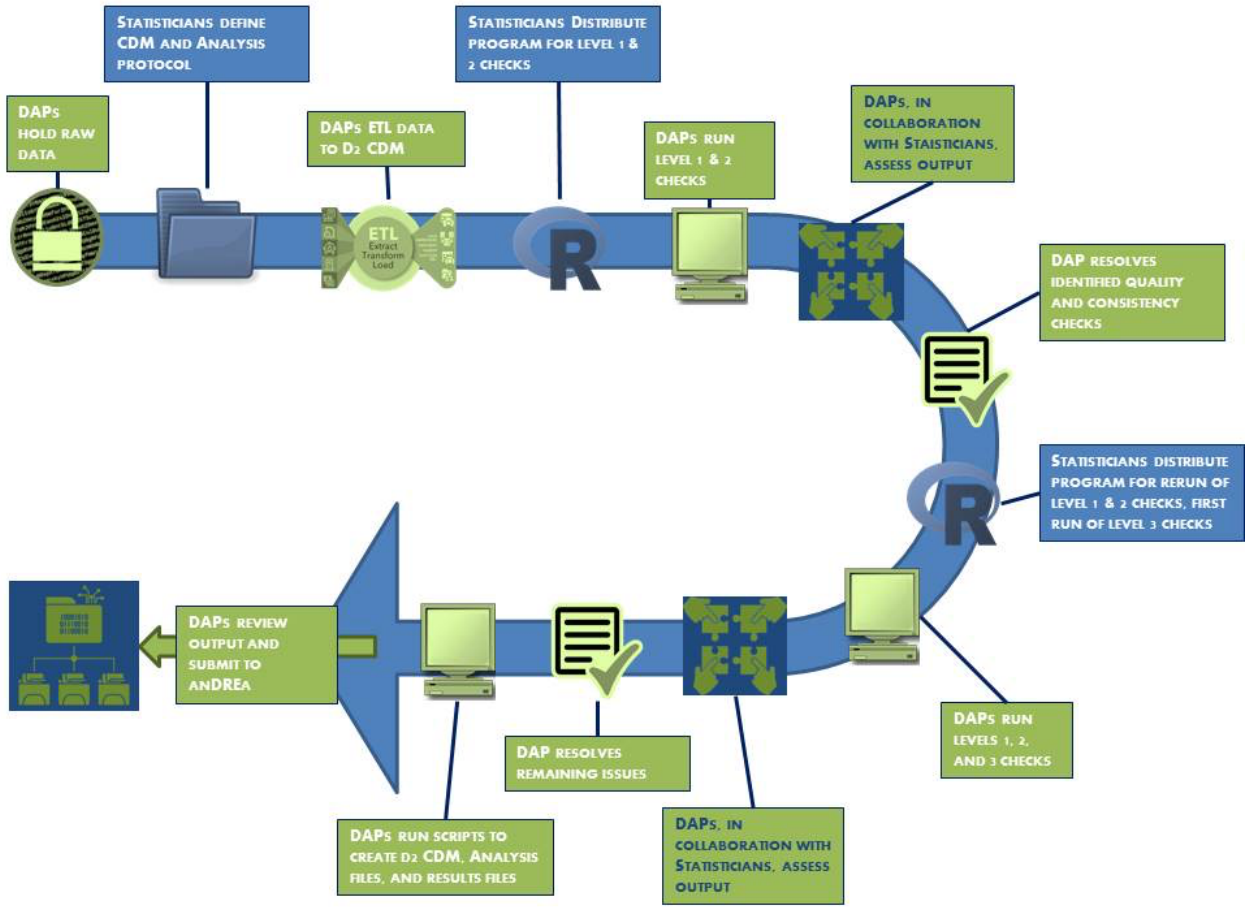


Figure 4 Data Quality Pipeline

11. Limitations of the research methods

11.1 Limitations related to the data sources

This study will include 4 different data sources in 4 countries. These data sources were chosen based on availability, ability to run multisite studies and experience in using common data models plus ability to join the consortium quickly in December 2020 during a very short tender period. These data sources contain various type of data which are either representative of the national population (eg. CPRD, PHARMO), or have a regional/multiregional scope (eg. BIFAP, ARS). Some data are collected at hospital level including or not emergency department or at GPs level only, others are collected at both hospital and GPs level. Given the heterogeneity in the type of encounters recorded, our analyses will be computed per data sources and no pooled estimates across data sources will be generated.

Most of the data sources were characterized in the ADVANCE project and considered fit for purpose for benefits and risk assessment. However, no reporting of medical events in a database does not imply an absence of the event.

A broad set of AESI that are known for being related to vaccination or associated with COVID-19 will be included in this study. For each of the events we will use narrow definitions which are specified in the event definition forms. More generally, case ascertainment will not be conducted to confirm disease diagnosis, therefore misclassification of outcomes cannot be excluded.

Recorded disease diagnosis will be used as date to classify a case as incident. For long latency diseases (e.g., autoimmune diseases), the disease onset may have started months prior to the recorded diagnosis, however this cannot be estimated without review of records, which is not resources in this study.

At this moment it is not clear how COVID-19 vaccination data are being recorded which may impact exposure misclassifications, especially in comparisons with non-vaccinated. Data access providers have provided confirmation that this will be possible but the quality and completeness of the information is not yet clear. This will be part of a quality assessment process using external benchmark data on vaccine exposures (e.g. ECDC vaccine tracker, OurWorldIndata)

11.2 Limitations in the methodology

It is expected that healthcare behaviours will be impacted during the SARS-CoV2 circulation period due to lockdown situations in most countries. To better take into account this period, the year 2020 will be divided analysed by month and when needed by week. This may impact the comparison of AESI rates of vaccinated with rates of the same events in the 2020 pre-vaccination period, where unmeasured confounding may be an issue. In a sensitivity analysis we will include 2019 as comparator, which was analysed in the ACCESS study. We will only use same provenance of data in the comparison.

It is acknowledged that Brighton Collaboration case definitions, which are utilized in many case definitions for the current study, are developed primarily for prospective studies, limiting their utility in observational data. However, they are a well-recognized standard and reference to develop code lists. For events without definition definitions from learned societies as well as experience of DAPs in identifying events are recorded in event definition forms and considered in algorithm development.

12. Protection of human subjects

12.1 Regulatory and Ethical Compliance

The study will be conducted in accordance with all applicable regulatory requirements, including all applicable subject privacy requirements and the guiding principles of the Declaration of Helsinki.

The study is part of the Early-Covid-Vaccine-Monitor project which follows the framework contract stipulations of the EMA and EU PV&PE network. It also follows principles of the Vaccine monitoring Collaboration for Europe (VAC4EU) acting under a well-defined governance with articles of association and bylaws (https://vac4eu.org/governance/).

Governance approvals will be obtained and collected from DAPs prior to data extraction.

12.2 Informed Consent

Data sources with an internal review board approval indicating that informed consent is waived or obtained will be included in the analyses.

12.3 Responsibilities of the Investigator and IRB/IEC/REB

The protocol and waiver of informed consent must be reviewed and approved by a properly constituted institutional review board/independent ethics committee/research ethics board (IRB/IEC/REB) before study start. A signed and dated statement that the protocol has been approved by the IRB/IEC/REB and waiver of informed consent must be given to the principal investigator before study initiation.

12.4 Protocol Adherence

Investigators will apply due diligence to avoid protocol deviations. If the investigator feels a change to the protocol would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by all partners involved and approved by the IRB/IEC/REB it cannot be implemented. All significant protocol deviations will be recorded and reported in the Study Report. Specifically, observational reportable Protocol Deviations are those Protocol Deviations which directly or indirectly have a significant impact on any 1 or more of the following:

- Subject's rights, safety, or well-being
- Data integrity, i.e. completeness, accuracy, and reliability of safety, efficacy, and
- Regulatory compliance.

13. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ ADVERSE REACTIONS

This study is observational and based on secondary use of data. Therefore, the reporting of suspected adverse reactions in the form of individual case safety reports (ICSRs) is not required. Reports of adverse events/reactions will be summarised in the final study report unless the protocol provides differently.

The study protocol and study report will be posted on the EU PAS register.

14. PLANS FOR DISSEMINATING AND COMMUNICATING RESULTS

14.1 Registration in Public Database(s)

The principal investigator assures that the key design elements of this protocol will be posted in the EU PAS register.

The principal investigator also assures that key results of this study will be posted in the EU PAS database within the required time-frame from completion of the data collection where applicable and in compliance with current regulations.

14.2 Publications

Upon study completion and finalization of the final study report, the results of this non-interventional study will be submitted for publication. Publications will comply with the International Committee of Medical Journal Editors (ICMJE) guidelines.

14.3 Dashboard

The results of the periodic monitoring will be made available in two formats

1) Excel sheets that will be sent to EMA periodically
2) Dashboard to monitor occurrence of exposure, coverage, AESI and COVID-19.

The dashboard will be tested and optimized in the first months, once EMA and DAPs are comfortable it can be made available to dedicated EMA committees and the public.

15. References

1. Becker, Benedikt FH, et al. "CodeMapper: semiautomatic coding of case definitions. A contribution from the ADVANCE project." *Pharmacoepidemiology and drug safety* 26.8 (2017): 998-1005.

16. Annexes

Annex 1. Syntactically Harmonized Common Data Model

METADATA TABLES

The metadata tables contain data in a machine readable format which allows for processing of the data in the CDM.

PRODUCTS
Listing of national product codes for medicinal products. Contains a product ID foreign key to the DRUGS and VACCINES table. The PRODUCT_CODE table contains detailed data on products at the package level.

METADATA
The metadata table contains indicators which can act as machine readable guides for code written against the CDM. For instance, whether data in the drug table represents prescription or dispensing.

INSTANCE
The instance table contains data on the specific instance of the ConcePTION CDM, such as tables and columns from source data which have been included.

CDM_SOURCE
Contains high-level meta data describing the source data for the current instance such as the name of the source, data access provider, and date of last update.

CURATED TABLES

Curated tables differ from the other tables of the CDM in that data access providers are asked to create these tables using rule-based algorithms. These tables therefore represent a *syntactic* and *semantic* harmonization.

PERSON
One row of data per subject present in the data and meeting inclusion criteria for the CDM instance at any point during the study period. Data on each subject includes sex at the date of the instance creation, one date of birth, and one date of death (these may be derived using DAP-specific rules)

OBSERVATION_PERIODS
One row per period during which a subject is present in the data source. This may be based upon registration in a geographical area, registration in a GP practice, presence in a registry, etc.

PERSON_RELATIONSHIPS
Contains one row of data for each child present in the data and meeting inclusion for the CDM instance at any point during the study period, together with an identifier for the mother of the child and the father of the child if available.

ROUTINE HEALTH DATA TABLES

Routine health care data tables capture data observed in the course of routine health care in hospitals, GP offices, pharmacies, outpatient clinics, etc.

VISIT_OCCURRENCE
Contains an identifier of a visit to allow for linkage of diagnoses, procedures, dispensings, etc in the same visit if this information is available in a data source.

EVENTS
Contains data on events indicated by a diagnosis code or free text. It contains one row per diagnosed event.

MEDICINES
One record per prescription or dispensing. Contains data required to estimate duration of exposure. Linkage to PRODUCT_CODE table to access data on drugs at the package level.

PROCEDURES
Contains data on procedures ordered or completed. For those procedures with an associated result, results and units are recorded. It contains one row per procedure.

MEDICAL_OBSERVATIONS
Contains observations recorded during routine healthcar. Can be a result from a laboratory test, or physical measurement, but also level of education, or sex, or a pathology report.

SURVEILLANCE TABLES
Surveillance tables contain data collected for purposes beyond routine health care either for surveillance of specific events or for recording of detailed information related to a unit of observation such as a pregnancy or chronic illness.

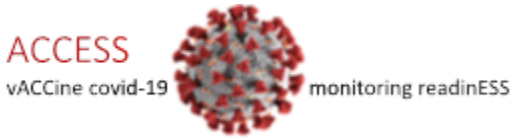
SURVEY_ID
Contains metadata on observations contained in the SURVEY_OBSERVATION table and allows for linkage between mothers and infants captured in a medical birth registry.

SURVEY_OBSERVATION
Contains one row per observation in any survey or registry data table – such as a medical birth registry, well child program database, cancer registry, etc.

Full CDM specifications can be accessed here:
https://drive.google.com/file/d/1hc-TBOfEzRBthGP78ZWIa13C0RdhU7bK/view?usp=sharing

Associated CDM vocabularies can be accessed here:
https://docs.google.com/spreadsheets/d/1idAEKC440rkIYIxCSRmEVgEPj_UouUI-I3kxNCpJt3U/edit?usp=sharing

Annex 2. Event definition form template



EVENT DEFINITION FORM

Event:
Outcome/covariate:
Version:
Status:

Contributing authors

authors	Role

Contents

Annex 3. Event Definition Forms

Event definition forms have been drafted for each of the AESI. These are available on the public Zenodo repository in the VAC4EU community

Auto-immune diseases

1. Guillain-Barré Syndrome
2. Acute disseminated encephalomyelitis
3. Narcolepsy
4. Acute aseptic arthritis
5. Diabetes
6. Idiopathic Thrombocytopenia

Cardiovascular system

Acute cardiovascular injury including:

7. Microangiopathy,
8. Heart failure,
9. Stress cardiomyopathy,
10. Coronary artery disease,
11. Arrhythmia,
12. Myocarditis

Circulatory system

13. Coagulation disorders: Thromboembolism, Haemorrhage disease
14. Single Organ Cutaneous Vasculitis

Hepato-gastrointestinal and renal system

15. Acute liver injury
16. Acute kidney injury

Nerves and central nervous system

17. Generalized convulsion
18. Meningoencephalitis

Respiratory system

19. Acute respiratory distress syndrome

Skin and mucous membrane, bone and joints system

20. Erythema multiforme
21. Chilblain – like lesions

Other

22. Anosmia, ageusia
23. Anaphylaxis
24. Multisystem inflammatory syndrome in children
25. Death (any causes)
26. COVID-19 Enhancement of disease
27. Sudden death

Newly added Sept 21 :

38. transverse myelitis

Newly added January 21

39. Bell's palsy

Newly added April 14

40. Thrombotic thrombocytopenia syndrome as part of the coagulation disorders