STUDY PROTOCOL

Estimation of background incidence rates of coagulation disorders and the association with COVID-19 vaccines in pregnant population: a multi-database study from 3 European countries.

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	design * Refer to definition of coagulation disorders to section 10.3.1.
Country(-ies) of study	Spain Denmark Finland
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2 ABBREVIATIONS

AE	Adverse Event
ATC	Anatomical Therapeutic Chemical
CDC	Centers for Disease Control and Prevention
CDM	Common Data Model
CI	Confidence interval
COVID-19	Coronavirus disease 2019
CVST	Cerebral Venous Sinus Thrombosis
DIC	Disseminated Intravascular Coagulation
DEAP	Data Expert and Access Provider
DRE	Digital Research Environment
DVT	Deep vein thrombosis
EMA	European Medicines Agency
EMR	Electronic Medical Records
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance.
ETL	Extract, Transform, and Load
GDPR	General Data Protection Regulation
GPP	Good Pharmacoepidemiology Practice
GVP	Good Pharmacovigilance Practice
ICD	International Classification of Diseases
IDIAP JGol	Fundació Institut Universitari per a la Recerca a l'Atenció Primària de Salut Jordi Gol i Gurina
IR	Incidence Rate
IRB	Institutional Review Board
IRR	Incidence Rate Ratio
ICMJE	International Committee of Medical Journal Editors
J&J	Johnson & Johnson
LMP	Last Menstrual Period
NHS	National Health Service
PE	Pulmonary Embolism
QC	Quality Control
RI	Relative Incidence
SAP	Statistical Analysis Plan
SCCS	Self-Controlled case series
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
VAC4EU	Vaccine monitoring Collaboration for Europe
VTE	Venous thromboembolism
TIA	Transient Ischemic Attack
TTS	Thrombosis with thrombocytopenia syndrome
UMCU	University Medical Center Utrecht
WHO	World Health Organization

3 MARKETING AUTHORISATION HOLDER

Not applicable (N/A)

4 RESPONSIBLE PARTIES

Th key contributors of this study

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3. ABSTRACT

3.1 Rationale and background:

There is lack of evidence whether pregnant women had a higher incidence of coagulation disorders (including VTE) and whether COVID-19 vaccines could be implicated in the development of this adverse outcome. Therefore, the risk of coagulation disorders in pregnant women exposed to COVID-19 vaccine warrants prioritized investigation through robust causal inference studies.

3.2 Research question and objectives:

Main objectives:

1. To estimate the background incidence rates of coagulation disorders—including thromboembolic and hemorrhagic events— during pregnancies and prior to vaccination with the four-EMA approved COVID-19 vaccines (BioNTech/Pfizer, Moderna, AstraZeneca, J&J) (obj 1).
2. To evaluate the association between the exposure to each of the four EMA-approved COVID-19 vaccines (BioNTech/Pfizer, Moderna, AstraZeneca, J&J) and the coagulation disorders* in pregnant women through a self-controlled case series (SCCS) design – (Obj 2)

Secondary objectives of objective 2:

2.1 To evaluate the association between the exposure to the four EMA-approved COVID-19 vaccines by vaccine platform (vector-based and mRNA vaccines) and the coagulation disorders* during pregnancy, stratified by gestational trimester, using a self-controlled case series (SCCS) design

2.2 To estimate the association between exposure to vaccine platform (e.g.,vector-based and mRNA vaccines), including vaccine brands (e.g., Moderna) and the thromboembolic events during pregnancy, stratified by gestational trimester, using a SCCS design

2.3 To estimate the association between exposure to vaccine platform (e.g., vector-based and mRNA vaccines), including vaccine brand (e.g., Moderna) and the hemorrhagic events during pregnancy, stratified by gestational trimester, using a SCCS design

* Refer to definition of coagulation disorders to section 10.3.1.

3.3 Study design

This study will be conducted using routinely collected healthcare data including electronic health records and/or national register data from 4 data sources in 3 European countries (Spain, Denmark and Finland). A background incidence rate will be applied prior to vaccination with the four-EMA approved COVID-19 vaccines.

A self-controlled case series (SCCS) analysis will be conducted with all pregnant women with at least one COVID-19 vaccine dose (BioNTech/Pfizer, Moderna, AstraZeneca, J&J) during pregnancy and coagulation disorders diagnosis during pregnancy.

The study population comprises all pregnant individuals entered in the data sources from 01-Jan-2019, through the most recent data availability.

In the background rate (obj1), participants will be followed from the estimated start of pregnancy and will end at the earliest occurrence of any of the following events: diagnosis of a coagulation disorder, receipt of a COVID-19 vaccine, maternal death, loss to follow-up, or the end of pregnancy.

In SCCS design (obj 2), pregnant individuals are also considered eligible if they received at least one dose of COVID-19 vaccines and experienced the outcome of interest (coagulation disorders) up to the pregnancy end date.

3.4 Data analysis

The background Incidence rates of outcomes among pregnant women with coagulation disorders will be calculated using total cases and person-time at risk. The incidence rates will be adjusted for the covariates (age, gestational age, prior Venous thromboembolism and anti-thrombotic agents) via Poisson regression. A 95% confidence intervals will be computed using exact methods.

A modified SCCS analysis using conditional Poisson regression will be conducted to estimate the relative incidence, stratified by data source and gestational trimester. A 14-day risk window, pre-exposure transition window of 14 days and two-day post-exposure transition windows are proposed for this study. Sensitivity analyses using 7-day interval will be applied. Country specific estimates will be pooled via random-effects meta-analysis.

4. RATIONALE AND BACKGROUND

SARS-CoV-2 infection during pregnancy increases the risk of thrombotic and haemorrhagic events, which can be aggravated by pregnancy-related physiological changes. Severe COVID-19 infection occurring during pregnancy leads to maternal morbidity and mortality cases, including an increased risk of respiratory and thrombotic events[1,2]. Additionally, pregnancy is a hypercoagulable state that significantly increases the risk of venous thromboembolism (VTE), a common thrombotic event[3]. In fact, pregnant women are approximately 4–5 times more likely to develop VTE compared to non-pregnant women of the same age[3]. This indicates that the combination of pregnancy and COVID-19 infection further elevates the VTE risk. The World Health Organization (WHO) advises pregnant women to get vaccinated[4]. Despite the vaccine effectiveness in protecting pregnant women, it is vital to further contextualize the risks and uncertainty around COVID-19 vaccines.

Despite concerns regarding thrombotic events, several studies on the COVID-19 vaccine have not identified a risk of thrombotic disorders in pregnancy. However, this may be due to the study design. For instance, the disproportionality analysis has not found a health concern following COVID-19 vaccines in pregnant women[5–7]. The lack of identified risk may result from challenges in identifying rare adverse events in pregnancy-related case reports. Additionally, other research collected data from pregnant participants primarily through self-reported surveys[8–10]. However, this design is limited by their dependence on self-reported adverse events (AEs) without cross-referencing them with medical data. In contrast, other studies applied a more conservative design such as case-control and cohort[11,12]. Their study designs include a relatively small population size. This may explain why they have not found a health concern versus unvaccinated pregnant women. In summary, the evidence gap of thrombotic risks aligns with recent systematic reviews[13,14], which suggests that the study designs themselves may have influenced these results.

In contrast, our recent finding aligns with a large-scale study that suggested a potential causal association between embolism events and adenovirus COVID-19 vaccine in pregnant women[15,16]. Therefore, the risk of coagulation disorders in pregnant women exposed to COVID-19 vaccine warrants prioritized investigation through robust causal inference methods.

5. RESEARCH QUESTION AND OBJECTIVES

5.1 Study Objectives:

This study has main and secondary objectives.

Main objectives:

1. To estimate the background incidence rates of coagulation disorders—including thromboembolic and hemorrhagic events— during pregnancies and prior to vaccination with the four-EMA approved COVID-19 vaccines (BioNTech/Pfizer, Moderna, AstraZeneca, J&J) (obj 1).
2. To evaluate the association between the exposure to each of the four EMA-approved COVID-19 vaccines (BioNTech/Pfizer, Moderna, AstraZeneca, J&J) and the coagulation disorders* in pregnant women through a self-controlled case series (SCCS) design – (Obj 2)

Secondary objectives:

2.1 To evaluate the association between the exposure to the four EMA-approved COVID-19 vaccines by vaccine platform (vector-based and mRNA vaccines) and the coagulation disorders* during pregnancy, stratified by gestational trimester, using a self-controlled case series (SCCS) design

2.2 To estimate the association between exposure to vaccine platform (e.g.,vector-based and mRNA vaccines), including vaccine brands (e.g., Moderna) and the thromboembolic events during pregnancy, stratified by gestational trimester, using a SCCS design

2.3 To estimate the association between exposure to vaccine platform (e.g., vector-based and mRNA vaccines), including vaccine brands (e.g., Moderna) and the hemorrhagic events during pregnancy, stratified by gestational trimester, using a SCCS design

* Refer to definition of coagulation disorders to section 10.3.1.

5.2 Research Question

Does COVID-19 vaccination during pregnancy increase the risk of coagulation disorders during pregnancy?

Hypothesis: Within the same person during pregnancy, the incidence rate of coagulation disorders during exposed periods is not higher than that during unexposed periods.

6. RESEARCH METHODS

6.1 Study Setting

This study will be conducted across three European countries. Additional details are provided in Table 1. A background rate analysis and a self-controlled case series (SCCS) analysis will be applied[17].

6.2 Source and study population

The source population comprises all persons entered in the data sources from 01-Jan-2019, through the most recent data availability. The study population consists of pregnant individuals, identified using the IMI-ConcePTION pregnancy algorithm (see Table 1) which is used for background rate analysis. From this study population, we will define the study cohort. Eligible for inclusion in the self-controlled case series (SCCS) analysis are all pregnant women (which has one or more pregnancies) who received at least one dose of a COVID-19 vaccine and were diagnosed with a coagulation disorder during the follow-up period (refer to 10.2.1.2).

Table 1. Data expert and access providers (DEAP) and data characteristics

DEAP	Data source	Country	Population size	Data banks available for this study	Vocabularies
IDIAP J Gol	SIDIAP	Spain-Catalonia	5.8 million	Primary care record, outpatient specialist record, outpatient laboratory results, surveillance data, emergency room, hospital discharge diagnosis, long term facility diagnosis, date of death.	ICD10-CM for diagnosis. ATC for medicines. ATC and antigen for vaccines. ICD9-PCS and ICD10-PCS for procedures.
FISABIO	VID	Spain	5.0 million	Primary care record, outpatient specialist record, outpatient laboratory results, surveillance data, emergency room visits, hospital discharge diagnosis, in-hospital prescribing, pharmacy dispensing outpatient, in-hospital prescription/dispensing, long term facility diagnosis, date and reasons of death.	ICD10-CM and ICD9-CM for diagnosis and procedures. ATC for medicines. Disease + text information for vaccines.
Aarhus University	Danish registries	Denmark	5.9 million (approximately 60 000 births per year)	Outpatient clinic specialist diagnoses, emergency room visits, hospital discharge diagnoses, surgical procedures, outpatient pharmacy dispensing, , date of death, vaccinations, pregnancies	ICD-10 Danish modification for diagnosis. ATC and hospital internal codes for medicines. Internal code for vaccines. NOMESCO for surgical procedures.
University of Eastern Finland	Finnish national registers	Finland	2.9 million (50% random sample of total population)	Primary care, specialized care inpatient and outpatient diagnoses, procedures and laboratory results, vaccinations, outpatient pharmacy dispensing, long term facility diagnoses, date and causes of death.	ICD-10 for diagnosis. ATC for medicines. ATC and free text for vaccines. NOMESCO for procedures.

6.2.1 Selection criteria of study population and follow-up

Persons will be included in the study population for the background rates when they have:

- Pregnancies identified during the study period (1/1/2019- latest availability).
- At least one day of follow up in the study period (1/1/2019- latest availability).
- At least one year lookback history

Pregnancies will be identified using the IMI-ConcePTION pregnancy algorithm. Briefly, this algorithm allows the identification of pregnancies from 4 streams of information: perinatal or birth registries, administrative data banks using diagnosis codes, European registry of congenital abnormalities (EUROCAT) and a tailored-combined stream, which uses additional data from medical diagnoses. The algorithm first identifies pregnancies from any possible records and subsequently establishes the start and end date of pregnancy by processing all the available information on a hierarchical manner. Hierarchy is based on the quality of records[18]. If there is pregnancy with a record of at least one dose of any of the four COVID-19 vaccines during pregnancy, she may be eligible for the SCCS analysis (refer to section 6.2.1.2).

Follow-up will start on the latest of the following dates with a date at which they have one year of lookback time:

- Start date of pregnancy (7 days before the start pregnancy date from IMI-ConcePTION pregnancy algorithm (interpreted as the first day of LMP)))*

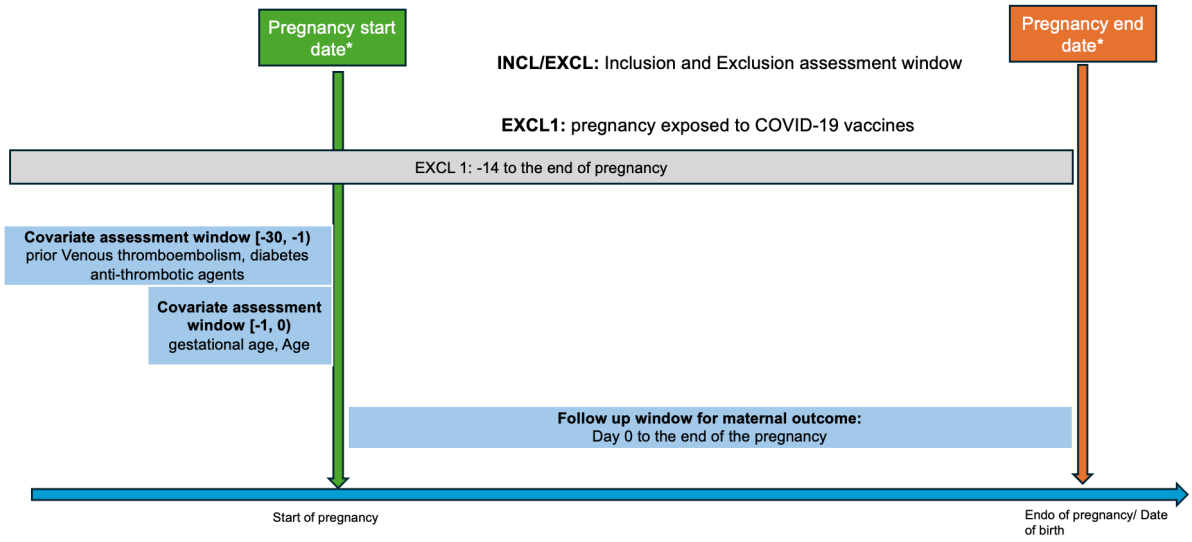
6.2.1.1 Background rates

Pregnant women who receive a COVID-19 vaccine within 14 days prior to the estimated date of the last menstrual period (LMP)/start pregnancy date from IMI ConcepPTION algorithm will be excluded from this part of the study (background rates). To minimize exposure misclassification, Individuals will be classified as unvaccinated only if no vaccination record (absence of validated COVID-19 codes) or missing immunization data is observed.

Participants will be followed from the estimated start date of pregnancy (see Figure 1). Follow-up will end, and individuals will be censored, at the earliest occurrence of any of the following events: diagnosis of a coagulation disorder, initiation of thrombotic agents, receipt of a COVID-19 vaccine, maternal death, loss to follow-up, or [20,21]at the end of pregnancy (see figure 1 for the definition of the end of pregnancy).

* The Pregnancy start date from IMI-ConcePTION pregnancy algorithm is either defined as the date of the first day of the last menstrual period (LMP or uses a hierarchical set of rules to determine the best estimate of LMP, prioritizing explicit LMP fields when available[18]. Because gestational age estimation based on the last menstrual period (LMP) depends on maternal recall and the assumption of ovulation occurring approximately two weeks after LMP and given that ultrasound-derived estimates are frequently used to confirm or adjust LMP-based dating within an accepted tolerance (often ±7 days), the start of pregnancy was defined as seven days prior to the reported LMP for this study. This approach provides a standardized temporal anchor that accommodates minor discrepancies between menstrual and ultrasound-based gestational age estimates while maintaining consistency across DEAPs

Figure 1: Background rate study scheme



* Pregnancy start date is defined as the Index date defined as 7 days either before LMP or the start pregnancy date from IMI-ConcePTION pregnancy algorithm. Index date defined as the earliest date of pregnancy (gestational age in weeks). Pregnancy end date is defined as the date of delivery. If the outcome is other than live birth occurs (e.g., preterm birth, stillbirth, pregnancy loss (miscarriage, spontaneous abortion, induced termination)) this is also defined as pregnancy end date.

6.2.1.2 Self-Controlled *Case Series (SCCS)* design

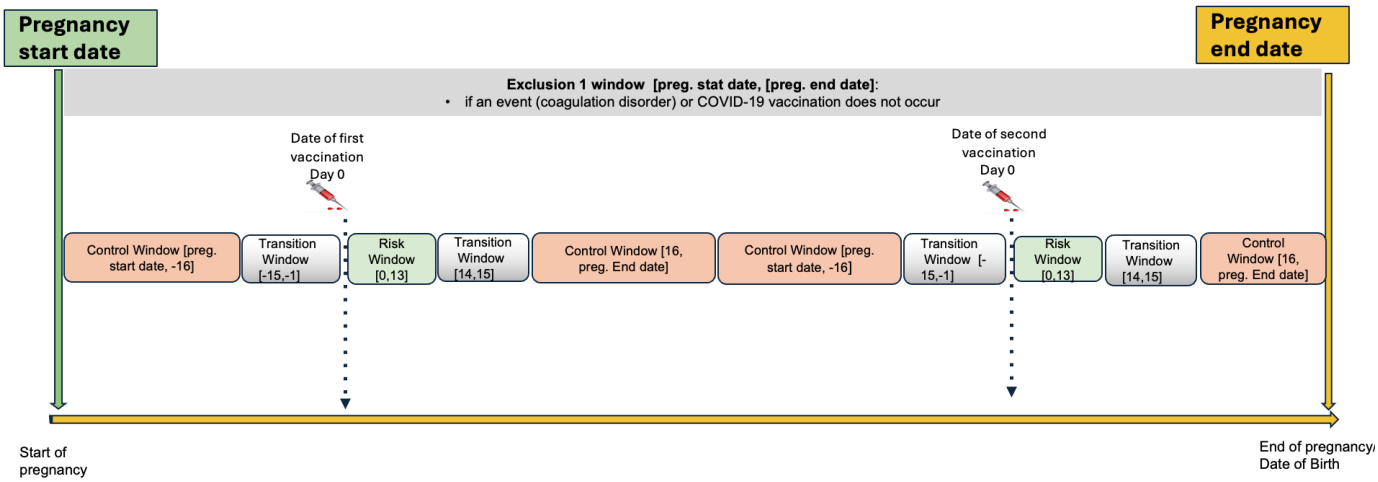
SCCS was chosen following guidance proposed by Bots et al.[17,19]:

Any pregnancy with a record of at least one dose of any of the four COVID-19 vaccines during pregnancy and experienced the outcome of interest (coagulation disorders) were eligible for inclusion. All vaccinated pregnancies with coagulation disorders (cases) occurring between 27 December 2020 (when COVID-19 vaccine was first available) and the date with most recent data were eligible for inclusion.

Eligibility begins on the index date (defined as the date of any COVID-19 vaccine administration dose). Pregnant individuals are also considered eligible if they received at least one dose of COVID-19 vaccines up to either the pregnancy end date or the next COVID-19 vaccine dose, as the risk control windows occur up to the end of pregnancy. Individuals were excluded from the study if they had not received at least one dose of a COVID-19 vaccine or received a COVID-19 vaccine 14 days prior the start of pregnancy, or did not experience a coagulation disorder, as outlined in Figure 2. The risk window last 14 days (based on the most common onset time of systematic review about thrombosis and COVID-19 vaccines[20–22]) and a pre-exposure transition window of 14 days and post-exposure transition windows are depicted in figure 2[17,19]. The occurrence of outcome of interest (e.g., thromboembolism) prior to vaccination (during control window) could either theoretically delay or prevent the vaccine (violation of SSCS assumption). To prevent the assumption violation, we employed a modified SCCS design developed by Farrington and colleagues[23–25]that accommodates event-dependent exposure. In this modified framework, the observation period ends at the time of the first event of coagulation disorder and post-event time will not be considered for the analysis.

Figure 2: Self-Controlled case series (SCCS) to assess the association between COVID-19

vaccines and coagulation disorders during pregnancy[17,19]



The occurrence of a diagnosis of interest for the selected events will be estimated per gestational trimester. Gestational trimesters are defined as follows (see figure 3):

I. First trimester (scenario 1) starts 7 days prior Last Menstrual Period (LMP)* until the last day of the 12th week from LMP[26]
II. Second trimester (scenario 2) starts on the first day of week 13 and ends until on the last day of the week 27 from LMP[26]
III. Third trimester (scenario 3) starts on the first day of the 28 week and ends either on the date of delivery [26] or 42 weeks from LMP whichever comes first

For the calculation of relative incidence rate (RIs) of outcomes in SCSS, the occurrence of the diagnosis of interest for the selected events will be estimated per gestational trimester:

The gestational trimester during which a person receives a COVID-19 vaccination may be an important risk factor, as the associated risk may differ across trimesters[27,28]. To control for the potential impact of vaccination timing across different gestational trimesters, we will treat gestational trimester as a time varying factor. For the analysis, the risk and control windows will be divided based on when an individual transitions into the next trimesters. The incidence rate between the risk and the control windows within the same trimesters will be adjusted for the length of time in each window. For example, consider two illustrative cases: Person 1 (P1) begins her risk window period in the first trimester but transitions into the second trimester during the same risk period; her period then falls partially in first and in the second trimester while her control window falls within the first trimester. Person 2 (P2) also begins her risk period in the second trimester and transitions, and her the control period also remains in the second trimester. In both cases, the time contributed to each window will be allocated by gestational trimester, ensuring that incidence rate comparisons are made within the same trimester strata. (see figure 4).

The analyses may be biased if many included individuals received a vaccination close to the end of their pregnancy, as there will be a higher chance for the control window to be censored due to the termination of pregnancy. We expect, however, that such cases would occur rarely. To evaluate the magnitude of potential bias, we will identify how many individuals are vaccinated 2-3 weeks before the end of pregnancy. If these individuals make up a small portion of the eligible study population (e.g., up to 3% of the eligible population), we will exclude them to avoid bias due to incomplete control periods.

* Because gestational age estimation based on the last menstrual period (LMP) depends on maternal recall and the assumption of ovulation occurring approximately two weeks after LMP and given that ultrasound-derived estimates are frequently used to confirm or adjust LMP-based dating within an accepted tolerance (often ±7 days), the start of pregnancy was defined as seven days prior to the reported LMP for this study. This approach provides a standardized temporal anchor that accommodates minor discrepancies between menstrual and ultrasound-based gestational age estimates while maintaining consistency across DEAPs

Figure 3: Gestational periods study

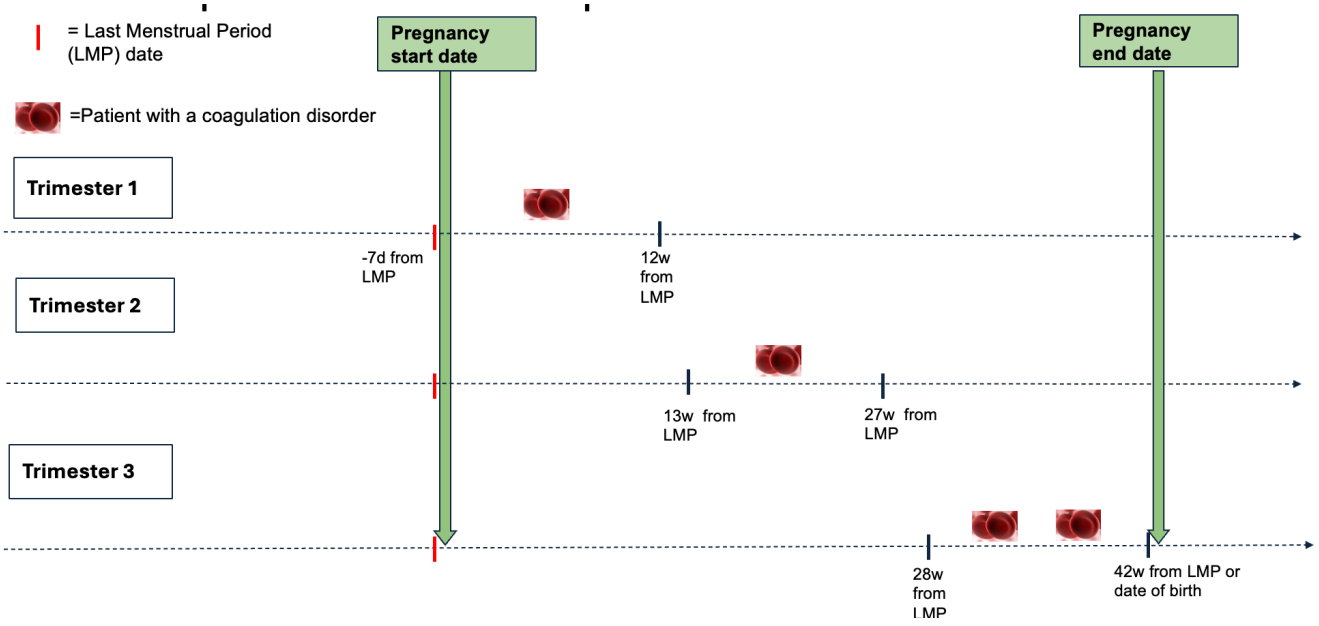
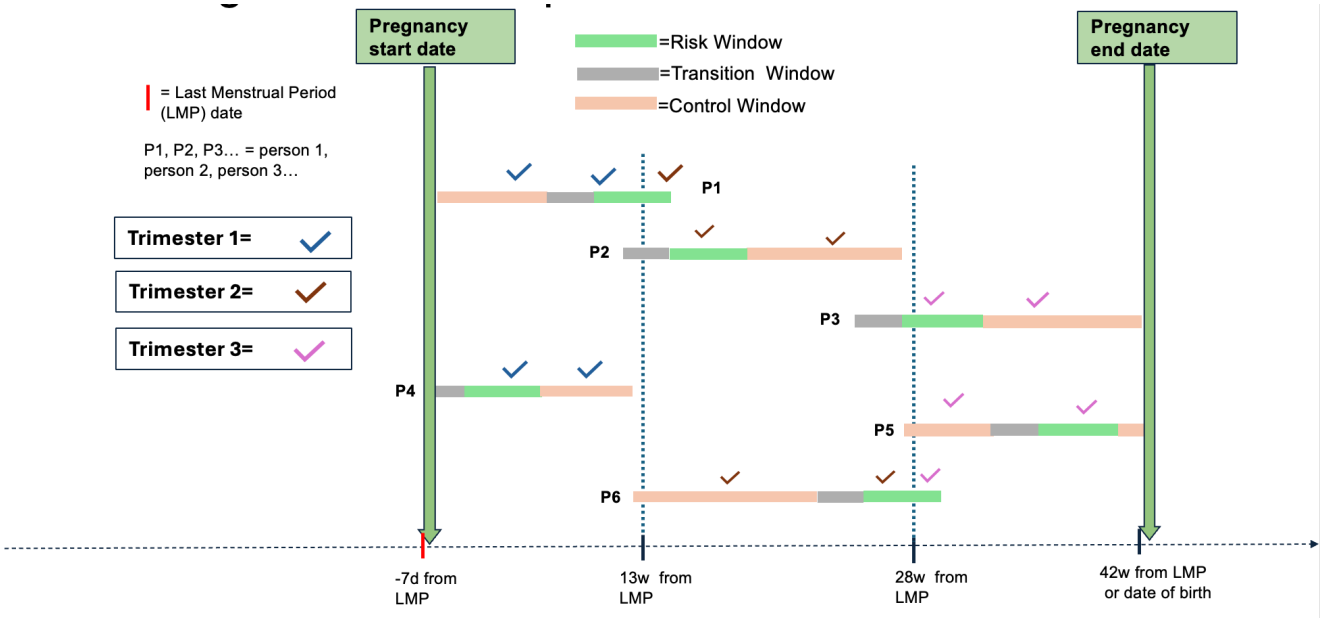


Figure 4: Self-Controlled case series (SCCS) - Relative Incidence per gestational trimester as time varying factor



6.3 Variables

6.3.1 Outcomes

Coagulation disorders are the main outcome of this study. We defined *coagulation disorders* as a composite outcome of any one of the following:

1. Venous thromboembolism (VTE)
2. Cerebral Venous Sinus Thrombosis (CVST)
3. Arterial Thrombosis
4. Thrombosis with thrombocytopenia syndrome (TTS)
5. Deep vein thrombosis (DVT)
6. Pulmonary Embolism (PE)
7. Hemorrhagic stroke
8. Ischemic stroke (IS)
9. Disseminated intravascular Coagulation (DIC)
10. Microangiopathy

These events will be captured from the EVENTS table using diagnosis code lists. A separate table of algorithms linked to diagnostic code list that will be submitted with the publication

Code lists to identify events have been created using the VAC4EU Code Mapper tool[29], which maps concepts across medical vocabularies based on the Unified Medical Language System. The output of the Code Mapper is a CSV list presented in Annex 1.

For the sub-analysis (objective 2.2), thromboembolic outcome will be composed by the following events: VTE, DVT, PE, CVST, IS, Arterial thrombosis, and TTS.

For the sub-analysis of haemorrhagic disorders (objective 2.3), we will combine the following events: DIC, Hemorrhagic stroke and Microangiopathy.

6.3.2 Covariates

Table 3 describes the list of selected covariates. For the events, code lists were created based on the same VAC4EU process as described previously. The occurrence of coagulation disorders or thrombosis events appears plausibly causally associated with covariates[30–38] which could be a relevant confounder for the study population.
Covariates will be presented in demographic tables within a lookback of 365 days for diagnoses codes, medicines and vaccines.

Table 3. List of study covariates

Covariate
Age
Diabetes type I and II
Obesity
Antiviral/antibiotics
Chronic Kidney disease
prior Venous Thromboembolism
anti-thrombotic agents

The evidence of any of the following vaccines during the lookback period of 365 days will be used to feed the covariate and for exclusion criteria as per figure.

four-EMA approved COVID-19 vaccine of interest (SCCS)):

1. 1.BioNTech/Pfizer
2. 2. Moderna
3. 3. AstraZeneca
4. 4. J&J

Lack of COVID-19 vaccine exposure is defined as the absence of receipt of any COVID-19 vaccine, and therefore the absence of vaccine-induced immune activation. Pregnant women without

COVID-19 vaccine exposure may be included in the estimation of background rates (see Section 10.2.1.1).

6.4 Data Sources

This study will use data from secondary electronic health record databases that are population-based. The following data sources were included: SIDIAP (access provided by the Fundació Institut Universitari per a la Recerca a l'Atenció Primària de Salut Jordi Gol i Gurina (IDIAP JGol)), VID (access provided by the Foundation for the Promotion of Health and Biomedical Research of Valencia Region; (FISABIO)); Danish National Registries (DHR) (access provided by Aarhus University) and Finnish registers (access provided by University of Eastern Finland).

Each data source will produce a study-specific data instance. A data instance is a subset of the data source that has been ETL'ed into the CDM at a certain point in time. This instance does not necessarily contain data from all databanks in the data source, but data required for one or more studies.

6.4.1 Danish National Registers (DHR)

All Danish registries used in this study have a nationwide coverage and an almost 100% capture of hospital contacts covering information on currently 5.9 million inhabitants plus historical information. Unambiguous person-level linkage across all data sources is possible via a unique identifier used in all Danish public records. Linked data from the following registries are available for the current project: the Danish Civil Registration System (identifier for linkage, age, sex, births, deaths, migrations); the Danish National Prescription Registry (outpatient dispensing in community pharmacies, no data on drugs administered in hospitals); the Danish National Health Service Register (GP contacts including vaccinations included in vaccination programmes other than COVID-19, there is no recording of diagnosis at GPs); the Danish National Patient Registry (diagnoses and procedures from all hospital encounters); the Danish Vaccination Register (COVID-19 vaccinations only); the Danish Medical Birth registry (deliveries form 22 weeks gestation). Data are linked using a unique pseudonymized identifier on the servers of the Danish Health Data Authority (SDS). Individual-level data will be analysed by uploading and running of analytic scripts on the SDS servers and aggregate data that does not allow backtracking to individuals in accordance with the data regulation will be used for reporting. The Danish national registries are listed as a resource in the Catalogue of RWD sources and studies by EMA. For further details of data characteristics, refer to table 1.

6.4.2 Finnish registers

Finnish national data registers account for a total population of 5.4 million inhabitants. Main linkable data banks are: 1. Hospital discharge register: use of in- and outpatient services. Diagnoses for each admission are made by the attending physician. The register contains the following information on each hospital visit: dates, reason for hospital stay, specialty of the caring unit, date of operation, up to five operational codes (NOMESCO classification), where the patient was discharged to and assessment of need for assistance in activities of daily life. Since 2009, the data bank contains outpatient visits to specialised healthcare and since 2011 to primary healthcare. Laboratory and physiological measurements are available since 2015. 2. Kanta electronic prescriptions: all prescribed medicines purchased by an individual. Medicines used in hospitals are not included, but the register covers prescriptions written by hospital physicians and dispensed in community settings. Data on dispensing date, number of packages, tablets and defined daily dose (DDD) are available. Medicines are classified according to Anatomical Therapeutic Chemical (ATC)–classification system. 3. Special reimbursement register: entitlement to special reimbursement due to severe chronic diseases such as Alzheimer's disease, diabetes, psychosis, epilepsy, asthma, chronic obstructive pulmonary disease and several cardiovascular diseases. The diagnoses are based on explicit predefined criteria. 4. Medical births register contains information on both mothers and children, with data on live births and stillbirths of

fetuses with a birth weight of at least 500 g or a gestational age of at least 22 weeks. 5. Statistics Finland is the statistical authority of Finland, producing the majority of official statistics and conducting the population census, which has solely been based on the register data since 1990. These censuses include indicators of socioeconomic position (e.g. education, occupational status and taxable income). The causes of death register are compiled from death certificate data containing underlying, direct, intervening, and contributing causes. Death certificates are issued by physicians and if an autopsy is required, by a medicolegal officer.

6.4.3 SIDIAP (ES)

The Information System for Research in Primary Care (Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària (SIDIAP) in Catalonia, Spain, is a primary care database set up by the Institute of Research in Primary Care (Fundació Institut Universitari per a la Recerca a l'Atenció Primària de Salut Jordi Gol i Gurina [IDIAP JGol]) and Catalan Institute of Health (Institut Català de la Salut). [ICS]). The database collects information from 278 primary health care centres and includes more than 5.8 million patients covered by the Catalan Institute of Health (approximately 78% of the Catalan population) and is highly representative of the Catalan population. SIDIAP data comprise the clinical and referral events registered by primary care health professionals (i.e., 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. SIDIAP 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 International Classification of Diseases, 10th Revision (ICD-10) codes, ATC codes for medicines, and structured forms designed for the collection of variables relevant to 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/urine test results. In relation to vaccines, information on all routine childhood and adult immunisations is included in addition to the antigen and the number of administered doses. SIDIAP was characterised in the IMI-ADVANCE project and considered fit for purpose for vaccine coverage, benefits, and risk assessment. An algorithm to identify pregnancies has been previously used within SIDIAP. The algorithm uses diagnosis codes recorded in primary healthcare records during pregnancy and information recorded in the sexual and reproductive healthcare registries, including LMP, gestational week, expected date of delivery, actual date of delivery or termination, and pregnancy outcomes. Approximately 50% to 60% of pregnant women in Catalonia are attended in the sexual and reproductive healthcare centres that contribute data to SIDIAP. Approximately 70% of infant records can be linked to maternal records and used for research. The protocol will be evaluated by the SIDIAP Scientific Committee and by the IDIAPJGol Ethics Committee, the approval can take up to 4 weeks. The timeframe for data availability after the approval by the two local Committees is one month.

6.4.4 FISABIO, VID database (ES)

The Valencia health system integrated database (VID) is a set of multiple, public, population-wide electronic databases for the Valencia Region, the fourth most populated Spanish region, with ≈5 million inhabitants and an annual birth cohort of 48,000 newborns, representing 10.7% of the Spanish population and around 1% of the European population. The VID provides exhaustive longitudinal information including sociodemographic and administrative data (sex, age, nationality, etc.), clinical (diagnoses, procedures, diagnostic tests, imaging, etc.), pharmaceutical (prescription, dispensation) and healthcare utilization data from hospital care, emergency departments, specialized care (including mental and obstetrics care), primary care and other public health services. It also includes a set of associated population databases and registries of significant care areas such as cancer, rare diseases, vaccines, congenital anomalies, microbiology and others, and public health databases from the population screening programmers. All electronic health systems in the VID use the ICD-9-CM and the

ICD-10-CM. All the information in the VID databases can be linked at the individual level through a single personal identification code. The databases were initiated at different moments in time, but all in all the VID provides comprehensive individual-level data fed by all the databases from 2008 to date. Information on PCR test results as well as serological/antibody tests results for the whole population of the Valencia region is available and linkable from the Microbiological Surveillance Network (RedMIVA). The Foundation for the Promotion of Health and Biomedical Research of Valencia RegionFISABIO) is Data Expert and Access Provider for Valencia Integrated Databases (VID).

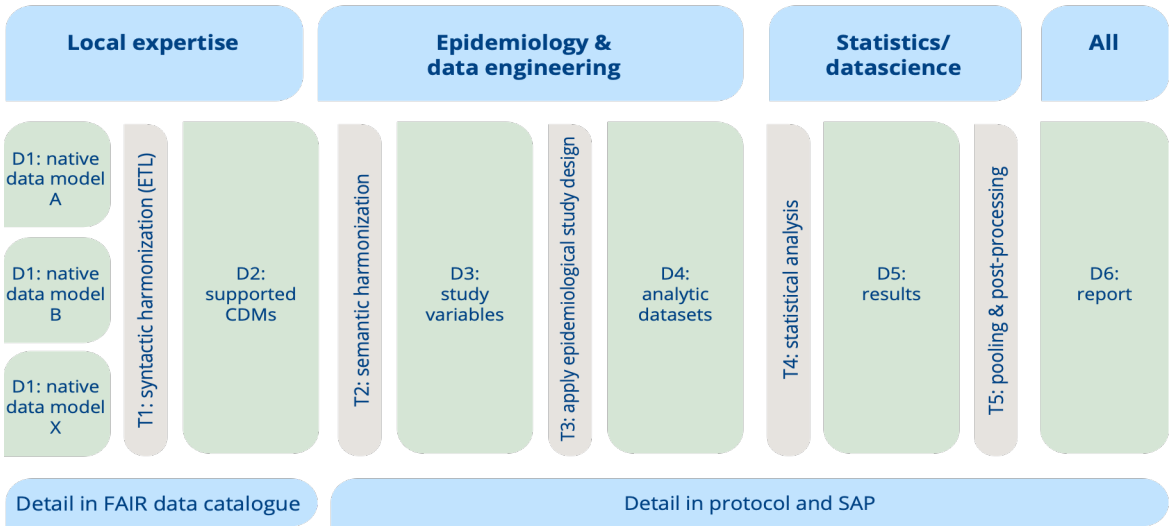
6.5 Study size

The study will include all subjects eligible in the data sources that could be utilized for the report.

6.6 Data Management

The study will be conducted in a distributed manner using the UMCU and VAC4EU tools, procedures, and pipeline. This pipeline can be viewed from a programming perspective (see figure 5). Figure 5 specifies the data sets (D) and transformation processes (T), programming follows this pipeline, with involvement of different types of experts.

Figure 5. Data Management from the data transformation perspective



D1: Original data can be in any native format

The RWD-RWE pipeline used by VAC4EU and EU PE&PV starts with data banks that are controlled by the DEAP, these can be in any format. This stays local. The ETL design is shared in a searchable FAIR VAC4EU catalogue. The VAC4EU FAIR Molgenis data catalogue is a meta-data management tool designed to contain searchable meta-data describing organisations that can provide access to specific data sources.

T1: Syntactic harmonisation (ETL)

T1: Syntactic harmonisation is conducted through an extraction, transformation, and loading (ETL) process of native data into the requested CDM. To harmonise the structure of the data sets stored and maintained by each data partner, a shared syntactic foundation is used. The ETL process has various structured steps as described by Thurin et al. [39]:

- DEAPs are asked to share the data dictionaries of their data banks (selected tables and variable names/structure)
- Metadata (descriptive data about the data sources and data banks) & data dictionaries, are uploaded in the VAC4EU metadata catalogue
- DEAPs make an ETL design
- The design is reviewed
- ETL is deployed

D2: Common data model

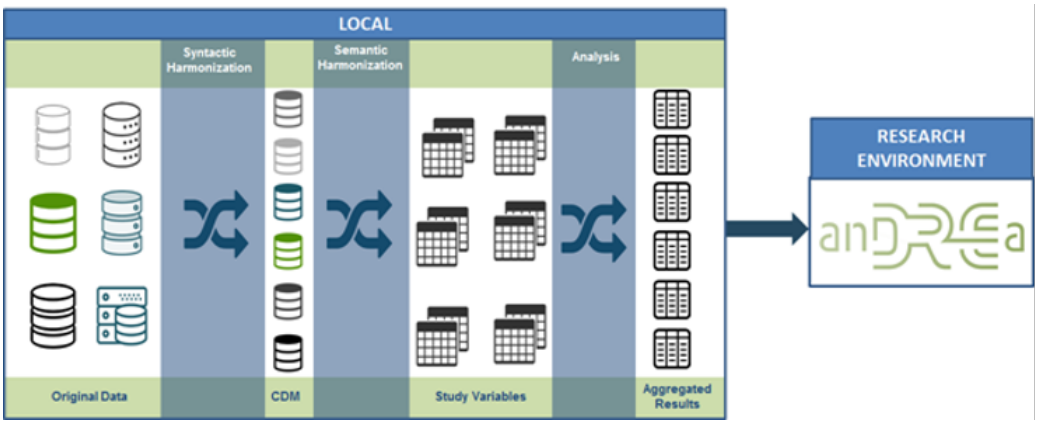
For this project we will use the ConcePTION CDM version v2.2. In the ConcePTION CDM the data is only syntactically harmonised, allowing for the data to remain in its original language (e.g., presence of different medical diagnostic systems such as ICD-9, ICD-10, SNOMED etc.).

T2: Semantic harmonisation

In this step we conduct time anchoring (observation periods, look back periods), clean the data such as the dose of vaccines, sort on record level, aggregate across multiple records, and combine concepts for implantation of algorithms, and rule-based creation of study variables. Based on the relevant diagnostic medical codes and keywords, as well as other relevant concepts (e.g., medications), one or more phenotype algorithms are constructed to operationalise the identification and measurement of each event or covariate.

In this phase of creation of study variables, the semantic mapping is conducted. This semantic mapping across different vocabularies is conducted as part of the R-study script using different functionalities. To reconcile differences between different terminologies and native data availability, machine readable code lists are used that comprise the terminologies that are used in the network (e.g. ICD-9, ICD10, SNOMED, ICPC and DEAP specific adaptations). This is combined with the BRIDGE metadata file that defines risk windows, look back periods, and algorithms for each study variable [40].

Figure 5. Data management from a systems' and location's perspective



D3: Study variables

D3 datasets are interim data sets with information on study variables for each study participant. The unit may be a person, a medicine or vaccine record, or episode of time. The design of these datasets is described in codebooks.

T3: application of epidemiological design

In the T3 step, epidemiological designs are applied such as sampling and selection based on inclusion and exclusion criteria using the study variables in the D3 datasets. The designs will be implemented for the various study objectives using R-scripts, and these may use the existing functions (R-cran) or functions that have been developed in the VAC4EU community.

D4: Analytical data set

D4 is an analytical dataset, and multiple D4 data sets may be produced based on the objectives of the study. The format is described initially in a code book for communication between programmers and statisticians.

6.7 Management and secure access of aggregate data

The result set of estimates, tables or aggregate data that is transferred from the DEAPs to the Digital Research Environment (DRE) (see figure 5). The DRE is made available through UMCU. The DRE is a cloud-based, globally available research environment where data are stored and organised securely and where researchers can collaborate. All researchers who need access to the DRE will be granted access to study-specific secure workspaces by UMCU. Access to the workspaces will be possible only after double authentication using an identification code and password together with the user's mobile phone for authentication. Downloading of files will be possible only after requesting and receiving permission from a workspace member with an "owner" role, who will be a UMCU team member.

6.8 Statistical analysis

6.8.1 Descriptive analysis

Baseline characteristics of covariables will be summarized for each DEAP using descriptive statistics. Categorical variables will be summarized using frequencies and percentages. Continuous variables will be summarized using the mean and standard deviation, as well as the median and interquartile range.

Baseline covariates will be defined using information recorded in the 365 days prior to the start of follow-up and will be reported as baseline frequencies.

6.8.2 Primary analysis in incidence rates/Background rates

To estimate the crude incidence rate (IR), we will first identify the total number of eligible pregnant women with coagulation disorders (including thrombotic disorders and hemorrhagic events). We will then calculate the number of cases of the outcome of interest that occurred during pregnancy. We will determine the total person-time of follow-up for all pregnancies accounting for varying lengths of observation. The IR will be expressed as the number of events per unit of person-time (e.g., events per 1,000 person-years or a larger denominator if practical). The incidence rate (IR) will be adjusted after controlling for the covariates: age, gestational age, prior Venous thromboembolism and anti-thrombotic agents) before the index date (t_0) using a multivariable regression model (Poisson regression). 95% Confidence intervals (CIs) for incidence rates will be computed using exact methods as described by Ulm et al[41].

6.8.3 Primary analysis in SCCS

Pregnant women who experienced both the outcome of interest and were vaccinated with a COVID-19 vaccines between 27 December 2020 and the end of data availability (which varied in the different databases) were eligible for inclusion. We will apply conditional Poisson regression models to calculate the relative incidences (RIs) for the association between exposure to the COVID-19 vaccines and Coagulation disorders using the {SCCS}package in R. For each pregnant woman, follow-up lasted from index date (date of COVID-19 vaccine) until the either the next vaccine dose or the end of pregnancy (see figure 2).

As part of the secondary objective, the RIs will be estimated for the association between exposure to the four EMA-approved COVID-19 vaccines—grouped by vaccine platform (vector-based and mRNA)—and coagulation disorders*, stratified by gestational trimester. RIs will be estimated for the association between vaccine platform and thromboembolic and haemorrhagic events, also stratified by gestational trimester. Finally, we will perform a random-effect meta-analysis to account for heterogeneity across the 4 data sources using the {meta} package in R.

Following the recommendation from Bots et al[17], we will perform sensitivity analyses by using the following 7-day risk window intervals (0-6days, 7-13 days,) to check for a potential time-response effect. The intervals are based on findings from two systematic reviews of thromboembolism cases after COVID-19 vaccinations[20–22]. Moreover, to support the choice of the modified SCCS model, we will conduct an additional analysis using the standard SCCS method. In addition, the observational period will also be censored at the commencement of anti-thrombotic agent initiation in sensitivity analyses to assess the potential impact of post-event treatment.

6.9 Quality control

This study makes use of pre-existing data-source instances whose quality has already been assessed using INSIGHT tool. Rigorous quality-control (QC) procedures were used. Data transformation into the ConcePTION CDM were conducted by each subcontracted research partner in its associated database, using the processes described in the following sections (see below), each of these steps is fully transparent and will be signed of/reviewed by local and central teams. Standard operating procedures or internal process guidance at each research centre were 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; QC procedures for programming; standards for writing analysis plans; and requirements for scientific review by senior staff.

Quality of data checks

This study makes use of pre-existing data-source instances whose quality has already been assessed using INSIGHT tool. The INSIGHT data-quality assessment R tool for ConcePTION CDM-standardized data facilitated a comprehensive characterisation of this instance, encompassing an overview of the anticipated availability and quality of exposure information for the chosen vaccines of interest. INSIGHT is a publicly available suite of R tools that detects potential data-quality issues in ConcePTION CDM–compliant datasets through the systematic execution and summarization of more than 588 configurable data-quality checks[42]. All INSIGHT scripts are publicly available on https://github.com/UMC-Utrecht-RWE.

Quality of study conduct

The work in this proposal 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). The quality management system is based on national and international external quality requirements where available and pertinent, including the guidelines for Good Pharmacoepidemiological Practices, RECORD-PE, ENCePP Guide on Methodological Standards in Pharmacoepidemiology, Good Clinical Practice, and Good Clinical Data management. Practice as well as national and international guidelines and legislation concerning data-handling and privacy issues.

6.10 Limitations of the research methods

6.10.1 Limitations in the methodology

Observational designs and pregnancy studies have several well-known drawbacks. Selection bias can result in non-representative samples and skewed effect estimates because pregnant people who seek care, enrol in research, or receive specific therapies tend to vary systematically from women who do not. Misclassification of gestational age, outcomes, or exposures, which may rely on the timing and quality of prenatal treatment, is a common example of information bias. As maternal age, comorbidities, socioeconomic factors, and health-seeking behaviours frequently affect exposure and pregnancy outcomes and are often unmeasured or incompletely measured, confounding remains an important concern. Pregnancy studies must also take into consideration time-dependent processes (such as trimester and foetal development), variations in healthcare utilisation, and possible exposure withholding due to contraindications. Even with sophisticated statistical techniques, these challenges can skew correlations[43–45].

4.1 Protection of human participant

This is a non-interventional study using secondary data and does not pose any health risks for individuals. Each data source research partner will apply for necessary research permits including ethical approvals where required. Data privacy related risks have been assessed in a data protection impact assessment, and risk minimisation procedures are implemented. All research data are pseudonymised and handled in secure remote use environments decreasing the likelihood of data privacy violations. Data protection and privacy regulations are adhered to while collecting, forwarding, processing, and storing data from study participants. Research parties will comply with all applicable laws, including the implementation of organisational and technical measures to ensure the protection of patient personal data. Such measures will include omitting directly identifiable data in any reports, publications, or other disclosures .

6.10.2 Patient information

This study involves data that exists in an anonymized or pseudonymized structured format and therefore direct information of the study participants is not possible. Each research site is responsible for informing potential study participants according to GDPR and local legislation.

Each DEAP/research site is responsible for informing potential study participants according to GDPR and local legislation. All parties will comply with all applicable laws, including laws regarding the implementation of organisational and technical measures to ensure the protection of patient personal data. Such measures will include omitting patient names or other directly identifiable data in any reports, publications, or other disclosures, except where required by applicable laws.

Patient personal data will be stored at DEAPs in encrypted electronic form and will be password protected to ensure that only authorised study staff have access.

DEAPs will implement appropriate technical and organisational measures to ensure that personal data can be recovered in the event of a disaster. In the event of a potential personal data breach, DEAPs shall be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

6.10.3 Patient consent

As this study does not involve data subject to privacy laws according to applicable legal requirements, obtaining informed consent from individuals is not required.

4.1.1 Ethical aspect

This study will adhere to the Guidelines for Good Pharmacoepidemiology Practices (GPP) and has been designed in line with the ENCePP Guide on Methodological Standards in Pharmacoepidemiology. The ENCePP Checklist for Study Protocols will be completed.

6.10.4 Institutional review board (IRB)/Independent ethics committee (IEC)

Each DEAP will be following the local country and data custodian requirements to apply for access to the data. All correspondence with the institutional review board or independent ethics committee and applicable documentation will be retained as part of the study materials.

7. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

As per EMA GVP Module VIII, the study and its protocol will be registered in the EMA-HMA catalogue prior to the start of data collection.

Study results will be published following established guidelines, including those for authorship, established by the ICMJE. When reporting the results of this study, the appropriate Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist and the RECORD-PE extension will be followed.

Upon study completion and finalisation of the study report, the results of this study will be or publication in a relevant peer-reviewed journal and posted to the EMA-HMA catalogue.

Analytical programs will be posted in a public GitHub and Zenodo repository. Final reports will also be publicly posted on Zenodo and cross-linked to the EMA-HMA catalogue.

8. MANAGEMENT AND REPORTING ADVERSE EVENTS/ADVERSE DRUG REACTIONS

For studies in which the research team uses only data from automated healthcare databases, the following applies according to the International Society for Pharmacoepidemiology Guidelines for GPP:

"Aggregate analysis of database studies can identify an unexpected increase in risk associated with a particular exposure. Such studies may be reportable as study reports, but typically do not require reporting of individual cases. Moreover, access to automated databases does not confer a special obligation to assess and/or report any individual events contained in the databases. Formal studies conducted using these databases should adhere to these guidelines."

For non-interventional study designs that are based on the secondary use of data, such as studies based on medical chart reviews or electronic health records, systematic reviews, or meta-analyses, reporting of adverse events/adverse drug reactions is not required. Reports of adverse events/adverse drug reactions should only be summarized in the study report, where applicable.

According to the EMA Guideline on GVP, Module VI – Management and Reporting of Adverse Reactions to Medicinal Products,

"All adverse events/reactions collected as part of [non-interventional post-authorization studies with a design based on secondary use of data], the submission of suspected adverse reactions in the form of [individual case safety reports] is not required. All adverse events/reactions collected for the study should be recorded and summarized in the interim safety analysis and in the final study report."

Module VIII – Post-Authorization Safety Studies echoes this approach. EU legislation further states that for certain study designs such as retrospective cohort studies, particularly those involving electronic health records, it may not be feasible to make a causality assessment at the individual case level.

Therefore, the management and reporting of adverse events/adverse reactions are not applicable for this study.

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