Safety of mRNA COVID-19 vaccines during pregnancy

First published: 18/08/2025

Last updated: 18/08/2025

Study Ongoing

Administrative details

EU PAS number

EUPAS1000000712

Study ID

1000000712

DARWIN EU® study

No

Study countries

- [ ] Norway
- [ ] Spain
- [ ] Sweden
- [ ] United Kingdom

Study description

In this study we aim to improve the understanding of complications during pregnancy, and to find out if COVID-19
vaccination during pregnancy increases the risk of these complications. To do so, we will use data from four
European countries: the United Kingdom, Spain, Norway, and Sweden.
First, we will analyse the data to find out how often complications like blood clots, strokes, or miscarriage, happen
during pregnancy. Then, we will investigate if there are differences between pregnant women who experienced
complications and those who did not.
Second, we will compare pregnant women receiving the 1st, 2nd, or booster (3rd or subsequent doses) COVID-19
vaccine doses with those eligible for the same dose, but who have not received it yet. We will compare how often
complication happened between groups to see if vaccination increased risk of complications. The study will be
restricted to COVID-19 vaccines recommended for used on pregnant women.

Study status

Ongoing

Research institutions and networks

Institutions

Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences (NDORMS), University

of Oxford

United Kingdom

First published: 01/02/2024

Last updated: 01/02/2024

Institution | Educational Institution | Hospital/Clinic/Other health care facility

University of Oxford

Fundació Institut Universitari per a la Recerca a l'Atenció Primària de Salut Jordi Gol i Gurina, IDIAPJGol

Spain

First published: 05/10/2012

Last updated: 23/05/2025

Institution | Educational Institution | Laboratory/Research/Testing facility | Not-for-profit | ENCePP partner

University of Oslo

First published: 01/02/2024

Last updated: 01/02/2024

Institution

University of Gothenburg

Contact details

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Primary lead investigator

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Primary lead investigator

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Study timelines

Date when funding contract was signed

Planned: 05/06/2024

Actual: 05/06/2024

Study start date

Planned: 01/12/2024

Actual: 01/12/2024

Date of final study report
Planned: 31/03/2026

Sources of funding

- No external funding

More details on funding

NMB is funded trhough the Claredon Scholarship at the University of Oxford.
Prof. Prieto-Alhambra reported receiving grant support from Les Laboratoires Servier; that his research group has received grants and advisory or speaker fees from Amgen, Astellas, AstraZeneca,
Chesi-Taylor, Johnson and Johnson and UCD; and that Janssen, on behalf of Innovative Medicines Initiative-funded European Health Data Evidence Network and European Medical Information Framework
consortium and Synapse Management Partners, have supported training programs, open to external participants, organized by his department.
SVW reports ad hoc consulting for Exponent Inc, Cytel Inc, and MITRE a federally funded research and development center for the Centers for Medicare and Medicaid Services.
The Department of Pharmacy at the University of Oslo takes part in multinational studies conducted under VAC4EU, an initiative receiving funding from pharmaceutical companies that manufacture COVID-19
vaccines (Pfizer, Moderna).
FN has funding from SciLifeLab / the Knut and Alice Wallenberg Foundation (KAW 2021-0010/ VC2021.0018 and KAW 2020.0299/VC 2022.0008) and the

Swedish Research Council (2021-05045 and
2021-05450). The overarching SCIFI-PEARL study (contributing Swedish data to the current analysis) through P.I. FN also has core funding from the Swedish state under the agreement between the Swedish
government and the county councils, the ALF-agreement (Avtal om Läkarutbildning och Forskning/Medical Training and Research Agreement), grants ALFGBG-938453, ALFGBG-971130, ALFGBG-978954, A
LFGBG-1006729, a grant from FORTE (Research Council for Health, Working Life, and Welfare), grant 2024-01711, and previously from a joint grant from FORTE and FORMAS (Research Council for Environment, Agricultural Sciences and Spatial Planning), grant 2020-02828.
FN owns some AstraZeneca shares.

Study protocol

Protocol_FINAL_15082025.pdf (1.6 MB)

Regulatory

Was the study required by a regulatory body?

No

Is the study required by a Risk Management Plan (RMP)?

Not applicable

Methodological aspects

Study type

Study type list

Study topic:

Other

Study topic, other:

Vaccines

Study type:

Non-interventional study

Scope of the study:

Disease epidemiology

Effectiveness study (incl. comparative)

Data collection methods:

Secondary use of data

Study design:

Objective 1) estimate background rates of adverse descriptive epidemiology.
Objective 2) safety of mRNA COVID-19 vaccines following the Targe Trial Emulation framework.

Main study objective:

Research Question 1: What are the background incidence rates of selected adverse events during pregnancy? Which are the differences in baseline characteristics between women who experience an adverse event during pregnancy vs. those who do not?
Research Question 2: What is the risk of adverse events associated with receiving a 1st, 2nd, or booster (3rd or subsequent doses) of an mRNA COVID-19 vaccine during pregnancy, compared to pregnant women eligible for the same dose but who have not yet received it?
Each research question corresponds to a study objective. To answer the first

question (Objective 1), we aim to provide epidemiological context to adverse events occurring during pregnancy and post-partum.
For the second research question (Objective 2), where the objective is to assess the safety of mRNA COVID-19 vaccination during pregnancy, we have three specific objectives (SOs):
• SO 2.1: To estimate the risk of pregnant AESI and MAE when receiving a 1st COVID-19 vaccine dose (mRNA type) during pregnancy compared to unvaccinated pregnant individuals.
• SO 2.2: To estimate the risk of AESI and MAE when receiving a 2nd COVID-19 vaccine dose (mRNA type) during pregnancy compared to individuals who are eligible for a 2nd dose during pregnancy but have not yet receive it.
• SO 2.3: To estimate the risk of AESI and MAE when receiving a booster (3rd or subsequent doses) COVID-19 vaccine dose (mRNA type) during pregnancy compared to individuals who are eligible for a booster dose during pregnancy but have not receive it.

Study Design

Non-interventional study design

Cohort

Study drug and medical condition

Medicinal product name, other

mRNA-BNT162b2, mRNA-1273

Medical condition to be studied

Deep vein thrombosis

Pulmonary embolism

Myocardial infarction

Ischaemic stroke

Bell's palsy

Encephalitis

Guillain-Barre syndrome

Myelitis transverse

Haemorrhagic stroke

Myocarditis

Pericarditis

Immune thrombocytopenia

Anaphylactic reaction

Narcolepsy

Disseminated intravascular coagulation

Abortion spontaneous

Stillbirth

Premature labour

Eclampsia

HELLP syndrome

Haemorrhage in pregnancy

Abnormal labour

Postpartum haemorrhage

Endometritis

Maternal death

Thrombosis with thrombocytopenia syndrome

Population studied

Short description of the study population

In Objective 1, all pregnancies starting between 1st January 2018, and up to 9 months before end of data will be eligible to enter the study. Pregnant women aged 12 to 55 years old at pregnancy start day and with 365 days or more of previous follow-up will be included. Pregnant women with an occurrence of the outcome of interest in the wash-out period relative to pregnancy start date will be excluded.
In Objective 2, the source population will include everyone who is pregnant during the enrolment period* and who satisfy the following inclusion criteria: 1) aged 12 to 55 (both included) at pregnancy start date, 2) sex recorded as female, 3) ≥365 days of previous continuous observation at pregnancy start date, and 4) eligible to receive the exposure based on previous exposures: unvaccinated of COVID-19 (for first dose vs. unvaccinated), 16 days or more from first dose (for second dose vs. first dose), and 90 days or more since previous dose, with at least 2 previous doses (for booster vs. unboosted)
*The enrolment period for SO 2.1 (1st vs. 0) goes from 01/04/2021 to 28/02/2022, aligning with the period when COVID-19 vaccination was recommended during pregnancy and when the majority started receiving their first dose. For SO 2.2 (2nd vs. 1st) enrolment period goes from 01/05/2021 to 31/03/2022, a 1-month extension from the enrolment in the first SO, as typically 2nd dose is ≥21 days after the 1st. Finally, enrolment period for SO 2.3 (Booster vs. 2nd) goes from when boosters were available, 01/10/2021, up until 12 months before data-cut. We will stop enrolling at that time for SO 2.3 to ensure there is enough follow-up time to see all the pregnant outcomes of interest. These periods are in-line with pregnant vaccination uptake seen in a previous study on COVID-19 vaccine effectiveness during pregnancy.

Age groups

- **Adult and elderly population (≥18 years)**

Special population of interest

Pregnant women

Study design details

Setting

For the first objective, all pregnancies meeting inclusion criteria from 01-01-2018 to the end of data availability will be included.

For the second objective, all pregnancies meeting inclusion criteria during the dose-specific enrolment period (see “Study population”) will be eligible to enter the study.

Risk Set Sampling will be used to create exposed and comparator cohorts. Each day during the enrolment period, when a pregnant woman from the source population becomes exposed (receives the vaccine dose of interest), we will select a group of unexposed pregnant women to enter the comparator cohort on the same day (index date). For each exposed woman, we will sample unexposed women matched by maternal age (within a 2-year range) and gestational age (within a 2-week range), ensuring they meet the inclusion and exclusion criteria at that date. Comparator sampling will be performed with replacement, and the sampling ratio will be determined based on prior exploratory analysis of the proportion of exposed to unexposed pregnant women in the database. An exposed woman will only be included in the cohorts if at least one suitable comparator can be identified from the source population. If a comparator later becomes exposed during the enrolment period, they will be allowed to re-enter the study as an exposed individual, provided that appropriate comparators are available.

Comparators

Not applicable for the first objective.
In the second objective, we will compare pregnant women who receive a first, second, or booster mRNA COVID-19 dose, with pregnant women eligible to receive the same dose but unvaccinated with it yet.

Outcomes

The study's outcomes include Adverse Events of Special Interest (AESI) and pregnancy-specific adverse events, Maternal Adverse Events (MAE). The outcome list is based on the prioritized COVID-19 vaccine AESI list by the Brighton Collaboration, and the Global Alignment on Immunization Safety Assessment in Pregnancy consortium. Outcomes include:
- 15 AESI: Deep vein thrombosis, Pulmonary embolism, Myocardial infarction, Ischaemic stroke, Bell’s palsy, Encephalitis, Guillain Barré Syndrome, Transverse Myelitis, Haemorrhagic stroke, Myocarditis or pericarditis, Thrombosis with Thrombocytopenia, Immune Thrombocytopenia, Anaphylaxis, Narcolepsy, Disseminated Intravascular Coagulation
- 13 MAE: Miscarriage, Stillbirth, Preterm labour, Eclampsia, HELLP syndrome, Antepartum Haemorrhage, Dysfunctional labour, Postpartum haemorrhage, Postpartum endometritis, Maternal death, Gestational diabetes, Ectopic pregnancy, Pre-eclampsia

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Data analysis plan

In the first objective incidence rates per 100,000 person-years will be calculated as the number of incident cases divided by the total person-time at risk. Incidence rates will be estimated for calendar year and month using the R package `Incidence Prevalence, and stratified by age group (12-17, 18-34, and 35-55 years) and gestational trimester (0 to 90, 91 to 180, and 181 and more days). Incidence rates will not be estimated if there are less than 5 events in a given stratum.

In the second objective, Propensity Score with Overlap weighting will be used to account for observed confounding. Standardised mean difference on diagnosis and prescriptions before index date will be estimated between cohorts to assess covariate balance. Residual confounding will be assessed with a set of negative control outcomes.
Incidence rate ratios (IRR) will be used to measure the relative incidence rate between exposed and comparator cohorts for each analysis and outcome of interest. 95% confidence intervals will be computed using the bootstrap method to account for non-independence of samples. IRR estimates will be calculated locally for each participating database and then combined using random-effects meta-analysis. Where heterogeneity (I2) is greater than 50%, estimates will not be meta-analysed and action will be taken to investigate which are the causes on this discrepancy. IRR will not be estimated if there are less than 5 events between exposed and comparator cohorts.

Summary results

At study completion, we will report incidence rates of adverse events occurring during pregnancy and the postpartum period. In addition, we will estimate the relative incidence of these adverse events among pregnant women who received a COVID-19 vaccine compared to those who did not.

Data management

ENCePP Seal

The use of the ENCePP Seal has been discontinued since February 2025.
The ENCePP Seal fields are retained in the display mode for transparency

but are no longer maintained.

Data sources

Data source(s)

Clinical Practice Research Datalink (CPRD) GOLD

The Information System for Research in Primary Care (SIDIAP)

Health Impact - Swedish Population Evidence Enabling Data-linkage

Norwegian Linked Health registry at University of Oslo

Data source(s), other

CPRD AURUM

Data sources (types)

Electronic healthcare records (EHR)

Population registry

Use of a Common Data Model (CDM)

CDM mapping

Yes

CDM Mappings

CDM name

OMOP

CDM website

https://www.ohdsi.org/Data-standardization/

CDM version

5.4

Data quality specifications

Check conformance

Yes

Check completeness

Yes

Check stability

Yes

Check logical consistency

Unknown

Data characterisation

Data characterisation conducted

No