# **Protocol for analyses of COVID-19 vaccine safety (and parallel analyses on impact of COVID-19 infection) in pregnant women**

## Draft analytical plan, version 1.0

## 18/11/2021

# Version Control

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| --- | --- | --- |
| Version number | Date | Change from previous version |
| 0.1 | 31/05/2021 | Provisional version |
| 0.2 | 10/06/2021 | Updated following review by MOL |
| 0.3 | 08/07/2021 | Updated following comments from MOL and RW, and meeting with CR and JP |
| 0.4 | 23/07/2021 | Updated following further comments from MOL, RW, JP |
| 0.5 | 06/08/2021 | Updated following further comments from MOL, RW, JP |
| 0.6 | 13/08/2021 | Substantial revision following comments from MOL & RW |
| 0.7 | 01/09/2021 | Further additions following meetings with stats and maternity colleagues |
| 0.8 | 13/09/2021 | Further round of changes following meetings with stats and maternity colleagues |
| 0.9 | 15/11/2021 | Further revisions following discussion between JP, RW & CC |
| 1.0 | 18/11/2021 | Further revisions following discussion between SS, RW & CC |

## 1.0: Introduction

The COVID-19 immunisation programme was initiated in Scotland on 8th December 2020. Following advice from the Joint Committee on Vaccination and Immunisation (JCVI), vaccinations have been offered to individuals in sequential priority groups based on an individual’s risk of infection or severe outcomes of infection. During the first phase of the immunisation programme, the vaccination of risk groups including older adults, health and social care workers and staff in care homes for older adults, and those that were clinically extremely vulnerable, was prioritised. During this initial phase, pregnant women were not called specifically for vaccination because they were pregnant but, as clarified by the JCVI on the 30th December 2020, women in the highest risk groups that were being called for vaccination at that time, and who happened to be pregnant, could be offered vaccination during pregnancy. In practice this affected pregnant women who were care home workers, frontline health or social care workers, and women who were clinically extremely vulnerable/on the shielding list.

From the 22nd February 2021, a national pathway for vaccination for pregnant women was clarified, with information leaflets provided for women, and on the 9th March pregnant women with current gestational diabetes were added to the list of individuals clinically vulnerable to severe COVID-19 disease, making this group of women eligible for vaccination. On the 16th April 2021, the JCVI issued further guidance, confirming that women called for vaccination due to being in any priority group (including all adults aged 18-49 years) could be offered vaccination during pregnancy. The JCVI recommendation issued on [16 April 2021](https://www.gov.uk/government/news/jcvi-issues-new-advice-on-covid-19-vaccination-for-pregnant-women) remains unchanged and therefore women who are pregnant should be offered vaccination at the same time as non-pregnant women, based on their age and clinical risk group. At the time of the last JCVI recommendation, most of the safety data on vaccination in pregnancy related to the use of the Pfizer–BioNTech (Comirnaty) and Moderna (Spikevax) vaccines; consequently, the JCVI recommended that pregnant women in the UK should be offered the Pfizer/BioNTech or Moderna vaccine if stocks of those vaccines were available. However, as there is no evidence to suggest that other vaccines are unsafe for pregnant women, all the approved vaccines can be given in pregnancy. For example, if a woman had a first dose of vaccine prior to pregnancy, she should complete her course with the same vaccine if possible, regardless of vaccine type.

As COVID-19 vaccines are now being offered routinely to pregnant women in Scotland, it is necessary to monitor the safety of these vaccines in this population. This protocol details the technical specification for the assessment of the safety of COVID-19 vaccines in pregnant women in Scotland. This will be done through monitoring a series of pre-specified pregnancy, maternal and neonatal outcomes. Specifically, we will monitor whether the risk of these outcomes is different among vaccinated pregnant women compared to unvaccinated pregnant women.

# 2.0: Objectives

The main aim of this work is to assess the safety of receiving COVID-19 vaccines during pregnancy. This will be achieved through the following objectives:

1. To estimate the risk of adverse pregnancy, maternal and neonatal outcomes in vaccinated and unvaccinated pregnant women.
2. To investigate whether the risk of adverse pregnancy, maternal and neonatal outcomes is different in vaccinated pregnant women, compared with unvaccinated pregnant women.

# 3.0: Study Design

## 3.1: Overview

This matched cohort study will compare adverse outcomes in women vaccinated in pregnancy to unvaccinated pregnant women. The primary analysis will draw the unvaccinated pregnant women from the pre-pandemic period, with supplementary analyses conducted with controls from the pandemic vaccination period. The matching process is detailed in section 3.6.

## 3.2: Study population

Pregnant women will be identified for inclusion in the matched cohort study through the COPS study database[[1]](#footnote-1). The COPS study database includes all women aged 11 to 55 at the time of conception who were known to be pregnant in Scotland from 01 January 2015 to the present date. In the COPS database, pregnancies are followed-up from conception to the end of the puerperium (six weeks after end of pregnancy) for women and the end of the neonatal period (28 days following birth) for live born babies.

## 3.3: Study period

The matched cohort study will cover the time period 01 January 2015 to the date of data extraction for the analyses. There are three study periods referred to in this protocol, as follows:

* Pre-pandemic period (01 January 2015 to 29 February 2020)
* Pandemic pre-vaccination period (from 01 March 2020 to 07 December 2020; not included in the analyses described in this protocol)
* Pandemic vaccination period (from 08 December 2020 to date of data extraction)

Vaccinated individuals will have received any COVID-19 vaccine in the six weeks preceding conception or at any point between conception and the end of pregnancy between 08 December 2020 to the date of data extraction, and unvaccinated individuals will be identified from the pre-pandemic period (primary analysis) and the pandemic vaccination period (supplementary analyses 1 & 2).

## 3.4: Data Sources

This study will involve linkage and analysis of routinely collected electronic health records on maternal, pregnancy and neonatal outcomes, vaccination data and other covariates of interest. Pregnant women will be identified through the COPS[[2]](#footnote-2) study database if they appear on one or more of the data sources listed for the identification of pregnant women in Table 1.

Table 1: Overview of data sources used for analysis

|  |  |
| --- | --- |
| **Data** | **Data source** |
| **Datasets required to identify pregnant women in the general population and associated pregnancy start and end dates:** | * New national data return developed as part of the response to the COVID-19 pandemic providing information on women booking for antenatal care with NHS maternity services: for identification of women with ongoing pregnancies in near real-time (all other records that identify end of pregnancy events) * GP consultation data: for identification of women with early miscarriage or ectopic pregnancy not managed in hospitals * Scottish Morbidity Record (SMR) 01: for identification of women with early miscarriage or ectopic pregnancy managed in hospitals * Termination of pregnancy statutory notifications (AAS records) * SMR 02: for identification of later miscarriage, stillbirth, and live births managed in hospital (and some home births) * National Records of Scotland (NRS) statutory stillbirth registrations * National Records of Scotland (NRS) statutory live birth registrations * New national data return developed as part of the response to the COVID-19 pandemic providing information on live births notified by maternity services to NHS Board child health administrative departments: for near real-time access to data that allows intergenerational linkage of records relating to mothers and their babies whilst statutory live birth registration is suspended.   Note that this is already established as part of the COPS study and methodology is set out in the [*Protocol for estimating the number of COVID-19 vaccinations delivered to pregnant women in Scotland and for describing the uptake and coverage of vaccination in the pregnant population.*](https://github.com/Public-Health-Scotland/COPS-public/tree/main/Study%20Protocol) |
| **Datasets required to identify characteristics of pregnant population** | * Covariates of interest include: Maternal age, deprivation score, urban/ rurality score, ethnicity, clinical vulnerability (shielding flag), and linked PCR test data to capture confirmed cases of COVID-19 infection.   Note that all are available through the COPS study database. |
| **Datasets required to identify vaccinated individuals** | * Data from the National Clinical Data Store (NCDS). Information recorded on the National Vaccine Management Tool (VMT) and GPIT system (Primary care practice medical record database) flows to the NCDS, from where it is cleaned and then linked to the COPS data. Relevant data of interest: vaccination date, type, dose. Through data linkage with the National Clinical Data Store (NCDS), vaccine status can be ascertained. |
| **Datasets required to identify outcomes of interest** | * Data from a number of sources that hold pregnancy, maternal and neonatal outcome data will be brought into the COPS study dataset. Sources include: SMR01, SMR02, NRS, Congenital Anomalies and Rare Diseases Registration and Information Service for Scotland (CARDRISS), critical care admission. |

## 3.5: Study Variables

### 3.5.1: Study Outcomes

Maternal, pregnancy and neonatal outcomes of interest are listed in Table 2. In our main analyses, we will assess the risk of each outcome in vaccinated women and their unvaccinated controls (i.e. classifying each woman as having the outcome or not), and will not attempt to capture any differences between the groups in the time to these events. As noted in Table 2, there are different periods of risk for each outcome (referred to as “outcome-specific follow-up period” throughout this protocol). For example, women will be considered at risk of any miscarriage from conception up to 23+6 weeks gestation, and at risk for stillbirth from 24+0 weeks gestation to the end of pregnancy. Women without an observed outcome who had not completed follow-up to the end of the follow-up period for a specific outcome in either the pre-pandemic (i.e. outcome-specific follow-up period not completed before 01 March 2020) or in the pandemic time period (i.e. outcome-specific follow-up period not completed before date of data extraction) will not be eligible for inclusion in the analysis for that outcome.

Outcomes have been aligned as far as possible with the relevant Brighton/GAIA outcome definitions, and also agreed with those in the MHRA / four nations working group on COVID-19 vaccination in pregnancy and comply with those recommended by the WHO[[3]](#footnote-3). See Appendix 2 for full rational and sources of information behind included outcomes, definitions, timings etc. as presented in Table 2.

Both primary and secondary outcomes are of interest, with the former being a composite measure including the associated secondary outcomes, and the latter being a narrower measure or subset of the associated primary outcome, e.g. primary outcome = small for gestational age, secondary outcome = very small for gestational age.

Venous thromboembolism in pregnancy is a standard maternal outcome that may be influenced by vaccination and is not the same as thrombosis with thrombocytopenia, the condition associated with the AstraZeneca vaccine[[4]](#footnote-4). ICD-10 codes for identifying both venous thromboembolism in pregnancy and hypertensive disorders of pregnancy are shown in Appendix 1.

‘Clean windows’ will be applied to outcomes, where appropriate, so that only new or incident cases will be counted. Specifically, a clean window of the current pregnancy will be applied for hypertensive disorders of pregnancy and venous thromboembolism (i.e. women will only be included if there is no prior record of these outcomes in the current pregnancy). See Table 2.

Longer term child outcomes, including immune function and infection and neurodevelopment, will be addressed in future work as required.

Other adverse outcomes that are not specific to pregnant women, will be investigated separately for the whole population as part of wider adverse events monitoring in Scotland. If these analyses suggest any signals in the pregnant population, those outcomes would be investigated in the pregnant population using the COPS data infrastructure, as required.

Table 2: Maternal, pregnancy and neonatal outcome measures for monitoring of safety of COVID-19 vaccination in pregnancy (version dated 14/07/2021)

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Outcome measure** | **Definition** | **Primary or secondary outcome?** | **Clean window requirement to identify incident cases** | **Timing of vaccination to be included** | **Post vaccination risk period to be examined** | **Estimated background risk of outcome (%)** |
| **Maternal outcomes** | | | | | |  |
| Hypertensive disorders of pregnancy | See ICD10 code list. Note that hypertensive disorders can only be diagnosed at >20 weeks. | Primary | No prior record in this pregnancy | Any | Up to E plus PP | 10.0 |
| Venous thromboembolism | See ICD10 code list | Primary | No prior record in this pregnancy | Any | Up to E plus PP | 0.15 |
| ICU admission or death (any cause) | ICU admission as identified on SICSAG record Death from any cause | Primary | None (but exploration to be undertaken of reasons for any pre-vaccination ICU admission where these are documented) | Any | Up to E plus PP | Unknown |
| **Pregnancy outcomes** | | | | | |  |
| Miscarriage | Miscarriage at <24 completed weeks gestation | Primary | None | Up to 23w+6d gestation | Up to 23+6 gestation | 10.0 – 20.0 |
| * First trimester miscarriage | Miscarriage at <14 completed weeks gestation | Secondary | None | Up to 13+6 gestation | Up to 13+6 gestation | Unknown |
| * Second trimester miscarriage | Miscarriage at 14-<24 completed weeks gestation | Secondary | None | Up to 23+6 gestation | 14+0 to 23+6 gestation | Unknown |
| Ectopic pregnancy | Ectopic pregnancy ending at any gestation | Primary | None | Up to 2+6 gestation | Up to E | 1.0 |
| Stillbirth | Spontaneous fetal loss at ≥24 completed weeks gestation Any cause of fetal death Losses related to termination of pregnancy excluded | Primary | None | Any | 24+0 to E | 0.4 |
| **Baby outcomes (live births only unless otherwise stated)** | | | | | |  |
| Any congenital anomaly (relevant pregnancy outcome only) | Any major congenital anomaly as defined by EUROCAT (including live born babies diagnosed at <28 days of age and affected pregnancies resulting in spontaneous loss at ≥20 weeks or termination of pregnancy at any gestation) | Primary | None | Up to 9+6 gestation | At E plus NN | 2.7 |
| * Any non-genetic congenital anomaly (relevant pregnancy outcome only) | Any major congenital anomaly as defined by EUROCAT, excluding anomalies with known underlying genetic basis as per standard EUROCAT rules (including live born babies diagnosed at <28 days of age and affected pregnancies resulting in spontaneous loss at ≥20 weeks or termination of pregnancy at any gestation) | Secondary | None | Up to 9+6 gestation | At E plus NN | 2.3 |
| Microcephaly | Congenital microcephaly (i.e. present at birth) OFC on delivery record <2SD below mean for sex and gestation at delivery by WHO-UK90 growth reference Babies with anencephaly excluded | Primary | None | Any | At E | 2.0 |
| * Severe microcephaly | Congenital microcephaly (i.e. present at birth) OFC on delivery record <3SD below mean for sex and gestation at delivery by WHO-UK90 growth reference Babies with anencephaly excluded | Secondary | None | Any | At E | 0.4 |
| Preterm birth | Delivery at <37 completed weeks gestation | Primary | None | Up to 36+6 gestation | Up to 36+6 gestation | 7.0 |
| * Very preterm birth | Delivery at <32 completed weeks gestation | Secondary | None | Up to 31+6 gestation | Up to 31+6 gestation | 1.0 |
| Spontaneous preterm birth | Delivery at <37 completed weeks gestation following P-PROM or spontaneous onset of labour | Primary | None | Up to 36+6 gestation | Up to 36+6 gestation | 4.0 |
| * Spontaneous very preterm birth | Delivery at <32 completed weeks gestation following P-PROM or spontaneous onset of labour | Secondary | None | Up to 31+6 gestation | Up to 31+6 gestation | 0.6 |
| Small for gestational age | Birthweight <10th centile by WHO-UK90 growth reference | Primary | None | Any | At E | 10.0 |
| * Very small for gestational age | Birthweight <3rd centile by WHO-UK90 growth reference | Secondary | None | Any | At E | 3.0 |
| Low Apgar score | 5 min Apgar <7 | Primary | None | Any | At E | 1.5 |
| * Very low APGAR score | 5 min Apgar <4 | Secondary | None | Any | At E | 0.5 |
| Neonatal death | Death from any cause | Primary | None | Any | E plus NN | 0.2 |
| Extended perinatal mortality (total births) | Stillbirth or neonatal death from any cause | Primary | None | Any | Up to E plus NN | 0.6 |

Notes: If timing of vaccination during pregnancy is specified as 'any', this means that women vaccinated at any point from six weeks preconception to date of end of pregnancy (E) will potentially be included in the analysis dependent on the woman being followed-up to the end of the outcome-specific follow-up period. For longer term risk periods: E is date of end of pregnancy; PP is mother's postpartum period, i.e. 6 weeks following delivery (E+1 to E+41); NN is baby's neonatal period, i.e. 4 weeks following live birth (E+1 to E+27). The pregnancy specific maternal outcomes listed above require follow-up to the end of the postpartum period (E+41) for mothers and the end of the postnatal period (E+27) for babies.

### 3.5.2: Exposure

The primary exposure to be investigated in the analyses is ***any*** receipt of COVID-19 vaccine from six weeks before conception to the end of an outcome-specific exposure period within pregnancy (Yes/No). The exposure periods for vaccination varies for each outcome (referred to as “outcome-specific exposure period” throughout this protocol), as outlined in Table 2. For ectopic pregnancy, for example, the exposed group will include women who were vaccinated between six weeks before conception up to 2+6 weeks gestation, while for stillbirth the vaccine exposure period is extended up to the end of the pregnancy.

Subgroup analyses will be conducted where sample size permits, further stratifying women who received their COVID-19 vaccine within the outcome-specific exposure period by: (1) the number of doses received; (2) by the class of vaccine(s) received and; (3) by the type of vaccine(s) received. For the latter two subgroup analyses, we will exclude women who received multiple different classes or types of vaccine within the outcome-specific exposure period. Table 3 outlines the key information on vaccination exposure, integrated into the COPS study databased from the National Services Scotland (NSS) National Clinical Data Store (NCDS).

Table 3: Exposure variables

|  |  |  |
| --- | --- | --- |
| **Variable** | **Definition** | **Notes** |
| Dose 1 received | No  Yes | Exposure variable for inclusion in model  Additional exposure variables for inclusion in database, descriptive analyses and any further investigation, where appropriate. |
| Vaccination date dose 1 | dd/mm/yyyy |
| Vaccine batch number 1 | Unique alphanumerical code assigned to each vaccine batch |
| Vaccine type 1 | Pfizer/ BNT162b2  AstraZeneca/ ChAdox1nCov-19  Moderna  Janssen |
| Vaccination class 1 | mRNA (Pfizer and Moderna)  Viral Vector (AstraZeneca and Janssen) |
| Dose 2 received | No  Yes |
| Vaccination date dose 2 | dd/mm/yyyy |
| Vaccine batch number 2 | Unique alphanumerical code assigned to each vaccine batch |
| Vaccine type 2 | Pfizer/ BNT162b2  AstraZeneca/ ChAdox1nCov-19  Moderna  Janssen |
| Vaccination class 2 | mRNA (Pfizer and Moderna)  Viral Vector (AstraZeneca and Janssen) |
| Dose 3 received\* | No  Yes |
| Vaccination date dose 3\* | dd/mm/yyyy |
| Vaccine batch number 3\* | Unique alphanumerical code assigned to each vaccine batch |
| Vaccine type 3\* | Pfizer/ BNT162b2  AstraZeneca/ ChAdox1nCov-19  Moderna  Janssen |
| Vaccination class 3\* | mRNA (Pfizer and Moderna)  Viral Vector (AstraZeneca and Janssen) |

\*Currently disaggregation by whether this was a third dose or a booster dose is not available in the COPS study database but as these data become available we will further stratify by third dose and boosters dose.

### 3.5.3: Covariates

Covariates of importance are shown in Table 4. Note that covariate groupings will be collapsed into fewer groups where clinically appropriate to do so. Prior to statistical modelling, each covariate will be examined for collinearity.

Table 4: Covariates of interest

|  |  |  |
| --- | --- | --- |
| **Covariate** | **Category** | **Notes** |
| Deprivation Score | SIMD 1 - most deprived |  |
| SIMD 2 |
| SIMD 3 |
| SIMD 4 |
| SIMD 5 - least deprived |
| Unknown |
| Maternal urban-rural status | Large Urban Areas | Regrouping as binary variable to be explored. |
| Other Urban Areas |
| Accessible Small Towns |
| Remote Small Towns |
| Very Remote Small Towns |
| Accessible Rural Areas |
| Remote Rural Areas |
| Very Remote Rural Areas |
| Unknown |
| Maternal ethnicity | White Scottish | Regrouping into fewer categories to be explored. |
| White Other British |
| White Other |
| South Asian |
| Chinese |
| Black/Caribbean/African |
| Mixed or other ethnic group |
| Unknown |
| Maternal clinical vulnerability | Clinically extremely vulnerable  (on shielding list) |  |
| Clinically vulnerable (Q-COVID comorbidity or hypertension) |
| Not clinically vulnerable |
| BMI at antenatal booking | Underweight (<18.5)  Healthy weight (18.5-<25)  Overweight (25-<30)  Obese (30-<40) or severely obese (≥40)  Unknown | Obese and severely obese will be combined. |
| Smoking at antenatal booking | Yes - current |  |
| Yes - former |
| No - never |
| Don’t know |

Note: categories will be collapsed as required.

## 3.6: Cohort study matching

For the matched cohort study, the primary comparison for each outcome will be between women vaccinated in the six weeks preceding conception or up to the end of the outcome-specific exposure period within pregnancy and unvaccinated pregnant women from the pre-pandemic period. Only women who had been followed-up to the end of the outcome-specific follow-up period on the 29 February 2020 are eligible to be controls for that outcome analysis. Women who have COVID-19 infection from six weeks preconception up to the end of the outcome-specific follow-up period will not be eligible for inclusion in the vaccinated group for this primary analysis. Each individual in the pregnant vaccinated cohort will be matched to three individual unvaccinated pregnant controls, if possible[[5]](#footnote-5). Different pregnancies from a single woman can be matched to different cases, and if a case had a pregnancy in the pre-pandemic period, that pregnancy is a valid control, as long as the women is not matched to herself. Here the assumption is that pregnancies are independent. A sensitivity analysis will be conducted, removing women who are vaccinated in the six weeks preconception – and her controls – from the analysis.

With the pre-pandemic period being used as the baseline, there is an assumption that the pandemic has not substantially affected the outcomes of interest through, for example, changes in engagement and provision of maternity services. To investigate this, a supplementary analysis will be conducted with pregnant unvaccinated controls from the pandemic vaccination period (from 08 December 2020 to date of data extraction). In this supplementary analysis, we will exclude women (from both the vaccinated and unvaccinated group) who had any record of COVID-19 infection from six weeks preconception to the end of the outcome-specific follow-up period. However, given that there is potential for vaccination to impact on maternal, pregnancy and neonatal outcomes by changing the risks of acquiring COVID-19 and experiencing severe illness, we will also conduct a second supplementary analysis with pregnant unvaccinated controls from the pandemic. In this, we will retain both vaccinated and unvaccinated women with a confirmed record of COVID-19 infection during pregnancy and preceding the end of the outcome-specific follow-up period. For both these supplementary analyses, women who were vaccinated >6 weeks pre-conception will be included in the control group (as not vaccinated in pregnancy), however sensitivity analyses (if sample size permits) will be conducted to investigate any differences between pairs where the control is completely unvaccinated versus pairs where the control received vaccination >6 weeks pre-conception (e.g. vaccinated pre-‘pregnancy’). Additional supplementary analyses removing women who are vaccinated in the six weeks preconception will be considered for the analyses using women from the pandemic period as controls, if we observe an impact of removing these women in the primary analysis using pre-pandemic controls.

Maternal and gestational age are known to be important risk factors for adverse events in pregnancy (e.g. miscarriage strongly influenced by maternal age). Consequently, the cohorts will be matched by maternal age (±1 years but relaxed (i.e. possibly ± >1year) at the tails of maternal age distribution as fewer individuals available for matching), and gestational age (exact match, i.e. same week however allow for relaxation of this at the tails of the gestation distribution).

In addition, vaccinated pregnant women will also be matched by season of conception (quarter) to historical controls from the pandemic and pre-pandemic periods due to the seasonality of some outcomes. It is not necessary to do this for contemporary controls (from the pandemic vaccination period) as those pairs will be matched by calendar date (i.e. matching a vaccinated woman by maternal and gestational age, on the day of vaccination to a control of the same maternal and gestation age, on the same date).

For comparisons between vaccinated and unvaccinated matched individuals, the index date (reference point for matching maternal and gestational age, and season of gestation for analyses involving controls from historical periods only) will be the date of vaccination.

The matching strategy for each of the three analyses is shown in Table 5.

Table 5: Matching strategy for each analyses of the matched cohort study

|  |  |  |  |
| --- | --- | --- | --- |
| **Analysis** | **Time period for control group\*** | **Matched three controls to each case by:** | **Notes** |
| Primary analysis | Pre-pandemic period (01 January 2015 to 29 February 2020) | * Maternal age * Gestational age * Season of conception (quarter) | * Aim to match to three unvaccinated controls * Maternal age matched by ±1 year but relaxed at tails of maternal age distribution * Gestational age matched by same week but relaxed at tails of the gestation distribution |
| Supplementary analysis 1 | Pandemic vaccination period (from 08 December 2020 to date of data extraction), excluding any women with a confirmed COVID-19 diagnosis between six weeks preconception to end of outcome-specific follow-up period | * Maternal age * Gestational age |
| Supplementary analysis 2 | Pandemic vaccination period (from 08 December 2020 to date of data extraction), including women with a confirmed COVID-19 diagnosis between six weeks preconception to end of outcome-specific follow-up period | * Maternal age * Gestational age |

\*Note that only women who have been followed-up to the end of the outcome-specific follow-up period at the end of each study period (i.e. 29 February 2020 for pre-pandemic controls and data of data extraction for pandemic controls) are eligible to be controls for a given outcome analysis.

## 3.7: Power calculation for matched cohort

It is estimated that by the end of 2021, full outcome and follow-up data will be available for approximately 5,000 vaccinated pregnant women, and by end of 2022, data available for 10,000 vaccinated pregnant women[[6]](#footnote-6).

Outcomes can be grouped as frequent (risk approximately 10%), moderate (approximately 3%), and rare (approximately 0.5%). Risk estimates for each adverse outcome are provided in Table 2. Based on these estimates and assumptions, with the relative risk of an event occurring post-vaccination set at 0.5, 1.2 and 2.0, and with statistical significance set at 0.05 and 0.01; power calculations for the various scenarios were calculated and are shown in Table 6. The power to detect a relative risk of 0.5, based on 5000 vaccinated pregnant woman against 15000 controls (ratio 1:3), when estimated adverse event occurrence is 0.5%, is 94%. This means that the study has a 94% chance of having a p-value of less than 5% (a statistically significant result and strong evidence against the null hypothesis) if there is really a difference in risk between vaccinated and unvaccinated women.

If the statistical power is low, the study sample size may be too small to detect any differences (i.e. under-powered) and therefore null results will need to be interpreted with caution. By convention, 80% is an acceptable level of power. It is acknowledged that the study may be under-powered to identify rarer outcomes.

Table 6: Power calculations scenarios

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Cases** | **Controls** | **Estimated risk** | **Relative risk** | **Power %** |
| 5000 | 15000 | 0.50% | 0.5 | 94 |
| 1.2 | 10 |
| 2.0 | 66 |
| 3.00% | 0.5 | 100 |
| 1.2 | 45 |
| 2.0 | 100 |
| 10.00% | 0.5 | 100 |
| 1.2 | 94 |
| 2.0 | 100 |
| 10000 | 30000 | 0.50% | 0.5 | 100 |
| 1.2 | 17 |
| 2.0 | 94 |
| 3.00% | 0.5 | 100 |
| 1.2 | 75 |
| 2.0 | 100 |
| 10.00% | 0.5 | 100 |
| 1.2 | 100 |
| 2.0 | 100 |

## 4.0: Data Analyses

## 4.3: Descriptive analyses

Characteristics (e.g. covariates) of the vaccinated and unvaccinated cohorts (from the pre-pandemic and pandemic vaccination time periods), and of the number and risk of all outcome events in the vaccinated and unvaccinated groups will be described to assess the comparability of the groups and to provide better understanding of the data. Summary statistics on the dose, type and class of vaccination in the vaccinated population will be described. Median, range and inter-quartile range of the gestational week of vaccination will be calculated.

Summary statistics and plots of time from vaccination (or matching) to date of outcome will be conducted to provide additional contextual information and to explore plausibility of gaps or clustering of the outcomes in time. As this will not be a time-to event analysis, it will be important to explore descriptively whether there are differences in the temporal trends of the outcomes by vaccination status.

Summary tables of the number and risk of each outcome in the vaccinated and unvaccinated pregnant cohorts, overall, by covariates, and by vaccine type, class, dose number, will be produced.

## 4.4: Statistical analyses

Maternal, pregnancy and neonatal outcomes in the vaccinated and unvaccinated pregnant cohorts will be compared using conditional logistic regression, where possible. This model type is used to account for matching. Odds ratios (ORs) with 95% confidence intervals will be produced for each comparison and a correction for multiple testing applied (e.g. Benjamini and Hochberg).

The exception will be for pregnancy outcomes where there is a competing risk (i.e. each woman can only have one of these outcomes), such as miscarriage, ectopic pregnancy, termination of pregnancy, stillbirth and live healthy baby. These will be examined using conditional multinomial logistic regression. The reference for each comparison when examining pregnancy outcomes will be healthy, full-term live births. Age, gestational week and season/quarter (when included in the matching strategy) will also be included in the model to account for matching. Termination of pregnancy is not an outcome of interest but it will need to be included a model as a competing risk.

First, a model with no covariates will be fitted to calculate the unadjusted OR for the association between vaccination status and each outcomes of interest. Subsequently, we will calculate an adjusted OR for the association between vaccination status and each outcomes of interest, by adding all covariates to the model (Table 4). P-values and confidence intervals will be reported for all models. For some rarer outcomes, we will adjust our modelling approach as required (e.g. re-classification of groupings or removing insignificant covariates). Covariate pairs will be assessed for collinearity before adding to the model. For any covariate pairs that are highly correlated, only the covariate which has the biggest impact on the association between the exposure and outcome will be included in the model.

As previously described (section 3.5.2), analyses will be conducted first looking at the association between having any vaccination and outcomes, and then in sub-group analyses stratified by vaccine classes and individual vaccine types;

* Vaccine type: Pfizer, AstraZeneca, Moderna, Janssen
* Vaccine group: Pfizer and Moderna (mRNA); AstraZeneca and Janssen ((adeno)virus vector)
* Number of vaccine doses

## 4.5: Additional analyses

There are two potential analyses that will be subsequently be conducted to assess the association between vaccination and adverse outcomes, as follows:

1. We will consider using all data from the pre-pandemic period to predict the expected number of outcomes among the vaccinated pregnant women, and compare this predicted number to the observed number within the vaccinated group of women.
2. For rarer outcomes (e.g. for congenital anomalies, microcephaly), we will consider a nested case control study if signals are identified in this present matched cohort analysis but wide confidence intervals due to the small number of events negate any meaningful conclusions. This design maximises power to assess any association between vaccination and these rare outcomes.

Additionally, we will extend our analysis to look at the impact of COVID-19 infection (rather than vaccination) in pregnancy on pregnancy, maternal and neonatal outcomes. Amendments required to the data preparation and analysis to change our exposure from vaccination status to infection status are provided in Appendix 3.

# 5.0 Potential limitations

There are a number of limitations that need to be considered when conducting the analysis and interpreting the results. Some of the key limitations are as follows:

1. Lag in data becoming available for women recently captured within the COPS study database:

Due to the way the COPS cohort is derived, there is a lag of up to three months before conceptions are identified and hence the corresponding pregnancies included in the study dataset. This is because either antenatal booking, or an early spontaneous pregnancy loss or termination of pregnancy prior to booking, must occur, and the relevant record be returned to PHS, prior to the pregnancy being identified and the conception retrospectively imputed. These events will usually occur within three months of conception. The COPS cohort is refreshed monthly: more frequent refreshes are not feasible as key source datasets (in particular SMR02) are only updated monthly. This means that, using any month’s COPS cohort plus up-to-date vaccination data, will likely fail to identify some recent vaccination events as occurring during early pregnancy. These will be picked up in subsequent months as the COPS cohort is refreshed. This means that initial data outputs must be understood as provisional.

1. Capture of early pregnancy loss:

Women who have early pregnancy loss and do not seek medical advice will not be captured in the COPS dataset.

1. Insufficient sample size for rare outcomes:

For rarer outcomes, there may be insufficient power to assess the association between vaccination status and the outcome using a match cohort study design. We will still provide descriptive data for these outcomes and, as mentioned in Section 4.5, we will consider different analytical approaches for rare outcomes.

1. Missing data:

For some covariates, there will be missing data, but this is expected to be minimal based on ongoing assessments of data quality.

1. Recording errors:

There may be errors in recording the pregnancy, maternity or neonatal outcomes and the way in which outcomes are recorded may have changed over time.

1. Unmeasured confounding:

There is the potential for unmeasured confounding given the inherent differences between vaccinated and unvaccinated women which might not be accounted for. Specific examples include type of profession and specific comorbidities.

# 6.0 Publication of results

Core information on vaccine uptake and coverage of pregnant women against COVID-19 is published in the PHS COVID-19 weekly report on a monthly basis.

All interim and final results will be shared with the PHS Vaccine Safety Advisory Group and potentially other key stakeholders including:

* The Clinical Governance Group for the Flu Vaccine COVID Vaccine (FVCV) programme. The group is responsible for providing clinical oversight for the delivery of the vaccination programme. This group meets weekly to discuss clinical issues of importance (e.g. any arising safety issues and any actions required) and involves senior PHS, National Services Scotland (NSS) and Scottish Government colleagues.
* Medicines and Healthcare products Regulatory Agency (MHRA). If a signal is detected in these analyses, it may be useful to share with MHRA colleagues to see if they have further intelligence on this.
* Four-nations working group on vaccine safety in pregnancy. The other UK nations are also planning similar analyses and so a discussion on results would be useful.
* EAVE steering group. EAVE-II is a collaborative study involving PHS and Scottish universities to answer important questions on COVID-19 using linked national data.
* Global Vaccine Data Network. This is a network of sites that contribute to globally coordinated active surveillance epidemiologic studies of the safety of vaccines, including COVID-19 vaccines. Sharing of information for potential inclusion in meta-analyses to generate global estimates of the risk of AESI following COVID-19 vaccination.

# Appendix 1: ICD 10 codes for maternal venous thromboembolism and hypertensive disorders of pregnancy

Appendix Table 1: Separate ICD-10 codes for identifying maternal venous thromboembolism1

|  |  |
| --- | --- |
| **ICD-10** | **Condition** |
| I26.0 | Pulmonary embolism with mention of acute cor pulmonale |
| I26.9 | Pulmonary embolism without mention of acute cor pulmonale |
| I80.1 | Phlebitis and thrombophlebitis of femoral vein |
| I80.2 | Phlebitis and thrombophlebitis of other deep vessels of lower extremities |
| I80.3 | Phlebitis and thrombophlebitis of lower extremities, unspecified |
| O08.2 | Embolism following abortion and ectopic and molar pregnancy |
| O22.3 | Deep thrombophlebitis in pregnancy |
| O87.1 | Deep phlebothrombosis in the puerperium |
| O88.2 | Obstetric blood-clot embolism |
| I80.8 | Phlebitis and thrombophlebitis of other sites |
| I80.9 | Phlebitis and thrombophlebitis of unspecified site |
| I81 | Portal vein thrombosis |
| I82.0 | Budd Chiari syndrome |
| I82.1 | Thrombophlebitis migrans |
| I82.2 | Embolism and thrombosis of vena cava |
| I82.3 | Embolism and thrombosis of renal vein |
| I82.8 | Embolism and thrombosis of other specified veins |
| I82.9 | Embolism and thrombosis of unspecified vein |
| O22.9 | Venous complication in pregnancy, unspecified |
| O87.9 | Venous complication in the puerperium, unspecified |
| G08 | Intracranial and intraspinal phlebitis and thrombophlebitis |
| I63.6 | Cerebral infarction due to cerebral venous thrombosis, nonpyogenic |
| I67.6 | Nonpyogenic thrombosis of intracranial venous system |
| O22.5 | Cerebral venous thrombosis in pregnancy |
| O87.3 | Cerebral venous thrombosis in the puerperium |
| *Considered but not included* | |
| *G95.1* | *Vascular myelopathies* |
| *H34.8* | *Other retinal vascular occlusions* |
| *I51.3* | *Intracardiac thrombosis, not elsewhere classified* |
| *I80.0* | *Phlebitis and thrombophlebitis of superficial vessels of lower extremities* |
| *K55.0* | *Acute vascular disorders of intestine* |
| *K64.5* | *Perianal venous thrombosis* |
| *K75.1* | *Phlebitis of portal vein* |
| *O22.2* | *Superficial thrombophlebitis in pregnancy* |
| *O22.8* | *Other venous complications in pregnancy* |
| *O69.5* | *Labour and delivery complicated by vascular lesion of cord* |
| *O87.0* | *Superficial thrombophlebitis in the puerperium* |
| *O87.8* | *Other venous complications in the puerperium* |
| *T80.1* | *Vascular complications following infusion, transfusion and therapeutic injection* |

1Relevant ICD10 codes for deep venous thrombosis and/or pulmonary embolus in pregnancy, recorded against main condition or any other condition on an SMR01 or SMR02 record with a relevant date of admission. All SMR02 record types are included (i.e. antenatal, delivery, and postpartum admissions).

Appendix Table 2: Separate ICD-10 codes for identifying hypertensive disorders of pregnancy1

|  |  |
| --- | --- |
| **ICD-10** | **Condition** |
| O11 | Pre-eclampsia superimposed on chronic hypertension |
| O13 | Gestational [pregnancy-induced] hypertension |
| O14.0 | Mild to moderate pre-eclampsia |
| O14.1 | Severe pre-eclampsia |
| O14.2 | HELLP syndrome |
| O14.9 | Pre-eclampsia, unspecified |
| O15.0 | Eclampsia in pregnancy |
| O15.1 | Eclampsia in labour |
| O15.2 | Eclampsia in the puerperium |
| O15.9 | Eclampsia, unspecified as to time period |
|  |  |
| *Considered but not included for this category* | |
| *O10* | *Pre-existing hypertension complicating pregnancy, childbirth and the puerperium* |
| *O12* | *Gestational [pregnancy-induced] oedema and proteinuria without hypertension* |
| *O16* | *Unspecified maternal hypertension* |

1*Relevant ICD10 codes for hypertensive disorders in pregnancy, recorded against main condition or any other condition on an SMR01 or SMR02 record with a relevant date of admission. All SMR02 record types are included (i.e. antenatal, delivery, and postpartum admissions).*

## Appendix 2: Rationale for selection of pregnancy-related outcome measures to be used in COPS study to assess impact of COVID-19 infection and safety of COVID-19 vaccination

A list of outcomes to be examined post-infection was drawn up in May 2020 for the initial COPS protocol document, based on what was known about COVID-19 at that point. A provisional list of outcomes to be examined post-vaccination (as part of vaccine safety monitoring) was drawn up in April 2021, based on a review of the following sources conducted up to 12 Feb 2021.

* MHRA public assessment record for the Pfizer vaccine (released at the time the MHRA first gave approval for use on 2 Dec 2020) - <https://www.gov.uk/government/publications/regulatory-approval-of-pfizer-biontech-vaccine-for-covid-19>
* MHRA public assessment record for the Oxford vaccine (released at the time the MHRA first gave approval for use on 30 Dec 2020) - <https://www.gov.uk/government/publications/regulatory-approval-of-covid-19-vaccine-astrazeneca>. No public assessment records for other vaccine types available at the time of review
* Data from the MHRA on possible adverse events reported through the Yellow Card scheme up to 31 Jan 2021. <https://www.gov.uk/government/publications/coronavirus-covid-19-vaccine-adverse-reactions>
* MHRA’s strategy for post marketing surveillance of the safety of COVID vaccines - <https://www.gov.uk/government/publications/report-of-the-commission-on-human-medicines-expert-working-group-on-covid-19-vaccine-safety-surveillance>
* PHE’s strategy for post implementation surveillance of COVID vaccine uptake, safety, and effectiveness - <https://www.gov.uk/government/publications/covid-19-vaccine-surveillance-strategy>
* PHE’s plans for monitoring of outcomes following inadvertent COVID-19 vaccination in pregnancy through the VIP programme - <https://www.gov.uk/guidance/vaccination-in-pregnancy-vip>
* The Biologics Effectiveness and Safety (BEST) Initiative's (part of the FDA's Center for Biologics Evaluation and Research) strategy for post implementation surveillance of COVID vaccine safety

<https://www.bestinitiative.org/vaccines-and-allergenics>

* Information from the Safety Platform for Emergency vACcines (SPEAC) collaboration (collaboration between the Coalition for Epidemic Preparedness Innovations (CEPI) and the Brighton Collaboration) on AESIs following COVID-19 vaccination. Information on pregnancy specific AESIs not available at the time of review - <https://brightoncollaboration.us/covid-19/>
* COVAX. No published information from the Maternal Immunization Working Group available at the time of review. <https://www.who.int/initiatives/act-accelerator/covax>
* ICBDSR. No published information on COVID-19 vaccination and anomaly risk available at the time of review. <http://www.icbdsr.org/>
* EUROCAT. No published information on COVID-19 vaccination and anomaly risk available at the time of review. <https://eu-rd-platform.jrc.ec.europa.eu/eurocat_en>
* The UKtis/BUMPS information sheet on COVID vaccination in pregnancy. [https://www.medicinesinpregnancy.org/Medicine--pregnancy/COVID-19-Vaccine/#](https://www.medicinesinpregnancy.org/Medicine--pregnancy/COVID-19-Vaccine/)
* Rapid literature scan for papers on COVID-19 and associated therapies and anomalies
  + https://science-sciencemag-org.ezproxy.is.ed.ac.uk/content/369/6504/607
  + http://jogh.org/documents/issue202002/jogh-10-020378.pdf
  + https://onlinelibrary-wiley-com.ezproxy.is.ed.ac.uk/doi/full/10.1002/bdr2.1710
* In July 2021, the two provisional lists were harmonised to provide one set of outcomes to be examined post infection and vaccination, taking into account the following additional information.
* Feedback from the MHRA 4 nation group on monitoring of safety of COVID-19 vaccination in pregnancy.
* Emerging evidence on the risk of thrombocytopenia and associated thromboembolism and haemorrhage risk following COVID-19 vaccination - COVID-19 | British Society for Haematology (b-s-h.org.uk)
* A report from the ConcePTION project on best practice in in utero pharmacovigilance studies <https://www.imi-conception.eu/wp-content/uploads/2021/03/ConcePTION-D1.2.pdf>
* A draft module on Safety surveillance of COVID-19 vaccines in pregnant and breastfeeding women from the WHO's COVID-19 vaccines: safety surveillance manual - <https://www.who.int/publications/m/item/safety-surveillance-of-covid-19-vaccines-in-pregnant-and-breastfeeding-women>; <https://apps.who.int/iris/handle/10665/338400>
* The EU’s ACCESS (vACcine Covid-19 monitoring ReadinESS) project which drew up a list of suggested outcomes for vaccine safety monitoring, based on ‘events that are or are potentially related to marketed vaccines, events related to vaccine platforms or adjuvants, and events that may be associated with COVID-19'. <https://vac4eu.org/covid-19-vaccine-monitoring/>; <http://www.encepp.eu/encepp/openAttachment/fullProtocol/37296;jsessionid=gcYfr6HBMTY-QycjtWODhMHJ6uQ-2THoP7zw5hnKDHaTwKWarjE6!456884888>
* Outcome definitions from the Brighton Collaboration and the Global Alignment of Immunization Safety Assessment in Pregnancy (GAIA) programme - <https://brightoncollaboration.us/>; <https://brightoncollaboration.us/gaia/>
* Outcome definitions included in relevant RCOG or NICE guidance - <https://www.rcog.org.uk/en/guidelines-research-services/guidelines/>; <https://www.nice.org.uk/guidance/conditions-and-diseases/fertility--pregnancy-and-childbirth>
* Early observational evidence from CDC on vaccine safety - <https://www.nejm.org/doi/10.1056/NEJMoa2104983>
* The C-VIPER planned international cohort study of vaccine safety - <https://corona.pregistry.com/cviper>; <http://www.encepp.eu/encepp/viewResource.htm?id=41101>
* Recent papers on the impact of COVID-19 infection on pregnancy-related outcomes, in particular UKOSS study on the characteristics and outcomes of pregnant women admitted to hospital in the UK with confirmed SARS-CoV-2 infection - <https://www.bmj.com/content/369/bmj.m2107>
* Study on the outcomes of women in England with and without confirmed COVID-19 at the time of delivery - <https://www.ajog.org/article/S0002-9378(21)00565-2/fulltext>
* The INTERCOVID international cohort study of pregnant women with confirmed COVID and non-infected controls - <https://jamanetwork.com/journals/jamapediatrics/fullarticle/2779182>
* The living systematic reviews on COVID in pregnancy maintained by the University of Birmingham - <https://www.birmingham.ac.uk/research/who-collaborating-centre/pregcov/index.aspx>

## Appendix 3: Measuring the impact of infection on adverse pregnancy, maternal and neonatal outcomes

Noted below are amendments required to the study design to instead look at the impact of COVID-19 infection on adverse pregnancy, maternal and neonatal outcomes.

|  |  |
| --- | --- |
| **Study population** | Same study population as for vaccination exposure (described in Section 3.2). |
| **Exposure** | The primary exposure to be investigated in the analyses is ***any*** confirmed PCR test for COVID-19 from six weeks preconception to the end of an outcome-specific exposure period within pregnancy (Yes/No). |
| **Outcomes** | As outlined in Table 2; timing of COVID-19 infection for each outcome the same as is included for vaccination (i.e. for the outcome of miscarriage, we will include women in the COVID-19 infection group if they have a confirmed COVID-19 diagnosis between six weeks preconception and 23+6 weeks of gestation). |
| **Covariates** | Same covariates as for vaccination exposure (described in Section 4). |
| **Matching** | There will be three main analyses for all outcomes, each with a different set of inclusion criteria for the matching process, as follows:  **Match 1 (primary):**  *Exposed:* women who had COVID-19 infection from six weeks preconception or in pregnancy but before the end of the outcome-specific exposure period, excluding any women who received vaccination for COVID-19 within the outcome-specific follow-up period.  *Unexposed group:* women from the pre-COVID-19 time period who had been followed-up to the end of the outcome-specific follow-up period by the 29th February 2020, matched to exposed women on maternal age, gestational age and season of conception.  **Match 2:**  *Exposed:* women who had COVID-19 infection from six weeks preconception and before the end of the outcome-specific exposure period, excluding any women who received vaccination for COVID-19 within the outcome-specific follow-up period.  *Unexposed group:* women from the COVID-19 time period (i.e. from 1st March 2020) who did not have confirmed COVID-19 infection from six weeks preconception and before the end of outcome-specific exposure period and did not receive vaccination for COVID-19 within the outcome-specific follow-up period, matched to exposed women by maternal age and gestational age.  **Match 3:**  *Exposed:* all women who had COVID-19 infection from six weeks preconception and before the end of the outcome-specific exposure period (i.e. including any women who received vaccination for COVID-19)  *Unexposed group:* women from the COVID-19 time period (i.e. from 1st March 2020) who did not have confirmed COVID-19 infection but could have had vaccination for COVID-19 from six weeks preconception and before the end of the outcome-specific exposure period, matched to exposed women on maternal age, gestational week and season of conception. |
| **Analytical approach** | Same analytical approach as for vaccination exposure (described in Section 4). |

1. Stock SJ, McAllister D, Vasileiou E*, et al.* COVID-19 in Pregnancy in Scotland (COPS): protocol for an observational study using linked Scottish national data. *BMJ Open*2020;**10:**e042813. doi: 10.1136/bmjopen-2020-042813. Available from:

   [COVID-19 in Pregnancy in Scotland (COPS): protocol for an observational study using linked Scottish national data | BMJ Open](https://bmjopen.bmj.com/content/10/11/e042813) [↑](#footnote-ref-1)
2. Stock SJ, McAllister D, Vasileiou E*, et al.* COVID-19 in Pregnancy in Scotland (COPS): protocol for an observational study using linked Scottish national data. *BMJ Open*2020;**10:**e042813. doi: 10.1136/bmjopen-2020-042813. Available from:

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3. <https://www.who.int/publications/m/item/safety-surveillance-of-covid-19-vaccines-in-pregnant-and-breastfeeding-women> [↑](#footnote-ref-3)
4. Pavord, S et al (2021). Clinical Features of Vaccine-Induced Immune Thrombocytopenia and Thrombosis. NEJM. DOI: 10.1056/NEJMoa2109908 [↑](#footnote-ref-4)
5. Donegan K, King B, Bryan P. Safety of pertussis vaccination in pregnant women in UK: observational study BMJ 2014; 349:g4219 doi:10.1136/bmj.g4219. Available from: <https://www.bmj.comcontent/349/bmj.g4219> [↑](#footnote-ref-5)
6. Personal communication with R. Wood, July 2021. [↑](#footnote-ref-6)