Protocol for COVID-19 vaccine safety analyses in pregnant women

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Version Control

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
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1.1	15/12/2021	Further revisions following discussions with LSHTM/PHE/MHRA colleagues

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 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]. 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.

[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

Pregnant women will be identified through the COPS[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. 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.*
Datasets required to identify characteristics of pregnant population	• Covariates of interest include: Maternal age, deprivation score, urban/ rurality score, ethnicity, pre-pregnancy clinical vulnerability exc diabetes, diabetes, BMI, smoking status, 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

[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: COVID-19 in Pregnancy in Scotland (COPS): protocol for an observational study using linked Scottish national data | BMJ Open

	NCDS, from where it is cleaned and then linked to the COPS data. Relevant data of interest: vaccination date, type, dose.
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, national linked anomaly database, SICSAG critical care admissions, NRS deaths.

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]. 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 infection or vaccination and is not the same as vaccine associated thrombosis with thrombocytopenia (VATT), the condition associated with the AstraZeneca vaccine[4]. Similarly, the pregnancy related bleeding outcome includes disseminated intravascular coagulation (DIC) which can occur in association with massive obstetric haemorrhage: again, this is distinct from VATT. Full lists of ICD10 codes used to identify the maternal outcomes venous thromboembolism, pregnancy-related bleeding, and hypertensive disorders of pregnancy are shown in Appendix 1.

[3] https://www.who.int/publications/m/item/safety-surveillance-of-covid-19-vaccines-in-pregnant-and-breastfeeding-women

[4] Pavord, S et al (2021). Clinical Features of Vaccine-Induced Immune Thrombocytopenia and Thrombosis. NEJM. DOI: 10.1056/NEJMoa2109908

'Clean windows' will be applied to outcomes, where appropriate, so that only new or incident cases occurring post vaccination will be counted. Specifically, a clean window of the current pregnancy will be applied for the venous thromboembolism, pregnancy-related bleeding, and hypertensive disorders of pregnancy outcomes (i.e. women will only be included if there is no prior record of these outcomes in the current pregnancy). See Table 2. For both congenital anomalies and pregnancy-related bleeding, further descriptive analyses will be conducted looking at more specific diagnoses within these broader outcome groups if we find evidence for an association between vaccination and these outcomes. For example, for pregnancy-related bleeding, we can further disaggregate into early pregnancy bleeding, obstetric haemorrhage, and DIC.

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

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
Pregnancy-related bleeding	See ICD10 code list	Primary	No prior record in this pregnancy	Any	Up to E plus PP	30.0 (for postpartum haemorrhage)
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	Primary	None	Any	At E	2.0

	mean for sex and gestation at delivery by WHO-UK90 growth reference Babies with anencephaly excluded					
• 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 to E+41); NN is baby's neonatal period, i.e. 4 weeks following live birth (E 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. These results will need to be interpreted with caution given that some types of vaccination will be linked to specific sub-groups of women. For example, early in the vaccination programme women who were frontline health or care workers were more likely to receive the Pfizer/BioNTech vaccine, whereas women who were clinically (extremely) vulnerable were more likely to receive the AstraZeneca vaccine. There is therefore potential for residual confounding in comparative analyses examining outcomes following receipt of specific vaccine types.

Table 3 outlines the key information on vaccination exposure, integrated into the COPS study database 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 booster 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 pre-pregnancy clinical vulnerability (excluding diabetes)	Clinically extremely vulnerable (on shielding list)	
	Clinically vulnerable (Q-COVID comorbidity excluded diabetes or hypertension)	
	Not clinically vulnerable	
Diabetes	Yes – pre-existing diabetes	If we only have a small number of women that are identified as having diabetes but it is unknown as to whether this is gestational or pre-existing, then we will combine gestational diabetes & unknown diabetes groups.
	Yes – gestational diabetes	
	Yes – diabetes onset unknown	
	No diabetes	
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.

We have considered, but are currently not planning to include, several other covariates. These include parity and pregnancy-related complications other than gestational diabetes. Information on parity is only available on delivery records, negating its inclusion for any of the early pregnancy outcomes, and there are concerns about the quality of these data. Theoretically, pregnancy-related complications (e.g. pregnancy-induced hypertension and pregnancy-related bleeding) could be on the causal pathway between vaccination status and other adverse outcomes so will not be included as potential confounders. However, additional analyses will be conducted as appropriate if we see signals of associations between vaccination and outcomes that might be due to differential vaccination uptake in women with pregnancy-related complications. Gestational diabetes was considered as an exception to this and included as a covariate. This is because pregnant women with gestational diabetes were added to the list of individuals clinically vulnerable and therefore eligible for vaccination in priority risk group 6 early in the vaccination programme (March 2021), possibly leading to high uptake in this group, and the known association between diabetes and many of the outcomes under study.

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]. 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.

[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

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

Table 5: Matching strategy for each analysis 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 cases and controls with confirmed COVID-19 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 cases and controls with confirmed COVID-19 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].

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

[6] Personal communication with R. Wood, July 2021.

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 birth. These will be examined using conditional multinomial logistic regression. The reference for each comparison when examining pregnancy outcomes will be live births (or ongoing pregnancies at a relevant gestation when studying early pregnancy outcomes only). 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 in models 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

Our main analyses will include all pregnancies/births, regardless of whether there is evidence that it was singleton or multiple, with sensitivity analyses conducted restricting to only pregnancies/births where there was no evidence it was a multiple. We often do not know whether pregnancies which end early (e.g. due to miscarriage) were singleton or multiple, hence the decision to only include pregnancies with *no evidence* of being a multiple in these sensitivity analyses.

4.5: Additional analyses

There are two further analyses that may subsequently be conducted to assess the association between vaccination and adverse outcomes, specifically:

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.

2. 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.

3. 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 matched 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.

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

5. 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.

6. 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 occupation, specific comorbidities, and wider healthcare seeking behaviours including engagement with antenatal care.

6.0 Publication of results

Core information on vaccine uptake and coverage among pregnant women 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.
- DaCVaP steering group. DaCVaP is a collaborative study within the suite of COVID-19 national core studies that is conducting UK wide studies on vaccine safety and effectiveness.
- 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 to identify admissions due to pregnancy-related bleeding, maternal venous thromboembolism, and hypertensive disorders of pregnancy

Appendix Table 1: ICD-10 codes for identifying pregnancy-related bleeding

ICD-10	Condition
	Obstetric haemorrhage
O44.1	Placenta praevia with haemorrhage
O45.0	Premature separation of placenta with coagulation defect
O45.8	Other premature separation of placenta
O45.9	Premature separation of placenta, unspecified
O46.0	Antepartum haemorrhage with coagulation defect
O46.8	Other antepartum haemorrhage
O46.9	Antepartum haemorrhage, unspecified
O67.0	Intrapartum haemorrhage with coagulation defect
O67.8	Other intrapartum haemorrhage
O67.9	Intrapartum haemorrhage, unspecified
O69.4	Labour and delivery complicated by haemorrhage from vasa praevia
O72.0	Third stage haemorrhage
O72.1	Other immediate postpartum haemorrhage
O72.2	Delayed and secondary postpartum haemorrhage
O72.3	Postpartum coagulation defects
O44.1	Placenta praevia with haemorrhage
	Early pregnancy bleeding
O03.1	Incomplete spontaneous abortion (miscarriage), complicated by haemorrhage
O03.6	Complete spontaneous abortion (miscarriage), complicated by haemorrhage
O04.1	Incomplete medical abortion (TOP), complicated by haemorrhage
O04.6	Complete medical abortion (TOP), complicated by haemorrhage
O05.1	Incomplete other abortion, complicated by haemorrhage
O05.6	Complete other abortion, complicated by haemorrhage
O06.1	Incomplete unspecified abortion, complicated by haemorrhage
O06.6	Complete unspecified abortion, complicated by haemorrhage
O07.1	Failed medical abortion, complicated by haemorrhage
O07.6	Other and unspecified failed medical abortion, complicated by haemorrhage
O08.1	Delayed or excessive haemorrhage following abortion and ectopic and molar pregnancy
O20.0	Threatened abortion
O20.8	Other haemorrhage in early pregnancy
O20.9	Haemorrhage in early pregnancy, unspecified
	Disseminated intravascular coagulation
D65	Disseminated intravascular coagulation
Considered but not included	
O43.2	*Morbidly adherent placenta*
O69.5	*Labour and delivery complicated by vascular lesion of cord*

Appendix Table 2: ICD-10 codes for identifying maternal venous thromboembolism

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*

Appendix Table 3: ICD-10 codes for identifying hypertensive disorders of pregnancy

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*

SMR01 and SMR02 records with a relevant date of admission and any relevant ICD10 code recorded against main condition or any other condition will be used to identify admissions for the above 3 conditions. All SMR02 record types will be 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/#

- 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 examine the impact of COVID-19 infection (rather than vaccination) on adverse pregnancy, maternal and neonatal outcomes.

Study population	Same study population as for vaccination exposure (described in Section 3.2).
Study period	This matched cohort study will cover the time period 01 January 2015 to the date of data extraction for the analyses, with the exclusion of the time period when testing for COVID-19 infection was not widespread: • Pre-pandemic period (01 January 2015 to 29 February 2020) • Pandemic pre-widespread testing period (from 01 March 2020 to 17 May 2020; not included in the analyses on impact of infection on outcomes) • Pandemic widespread testing period (from 18 May 2020 to date of data extraction)
Exposure	The primary exposure to be investigated in the analyses is ***any*** confirmed COVID-19 (indicated by positive PCR test for SARS-CoV-2 virus) from six weeks preconception to the end of an outcome-specific exposure period within pregnancy (Yes/No). The date of onset of COVID-19 is defined as the date the woman's first positive PCR sample was taken. Subsequent positive PCRs within 90 days of an index positive result are discounted. Any positive test taken >90days following the first positive sample is taken as indicating a second infection, and so on.
Outcomes	The timing of COVID-19 infection for each outcome (ie the outcome specific exposure period) is the same as is included for vaccination (see Table 2). So, for example, 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 during the pandemic widespread testing period 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 from six weeks preconception to the end of 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 during the pandemic widespread testing period from six weeks preconception up to the end of the outcome-specific exposure period, excluding any women who received vaccination for COVID-19 from six weeks preconception up to the end of the outcome-specific follow-up period. *Unexposed group:* women from the pandemic widespread testing period who did not have confirmed COVID-19 infection from six weeks preconception up to the end of outcome-specific exposure period and did not receive vaccination for COVID-19 from six weeks preconception to the end of the outcome-specific follow-up period, matched to exposed women by maternal age, gestational age, and date of infection. **Match 3:** *Exposed:* all women who had COVID-19 infection during the pandemic widespread testing period from six weeks preconception up to the end of the outcome-specific exposure period (i.e. <u>including</u> any women who received vaccination for COVID-19 at any time). *Unexposed group:* women from the pandemic widespread testing period who did not have confirmed COVID-19 infection from six weeks preconception up to the end of the outcome-specific exposure period (i.e. including any women who received vaccination for COVID-19 at any time), matched to exposed women on maternal age, gestational age, and date of infection.
Analytical approach	Same analytical approach as for vaccination exposure (described in Section 4).