# **Comparison of short-term outcomes of infections with SARS-CoV-2 variant in pregnancy: protocol**

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# Version Control

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| Version number | Date | Change from previous version |
| 0.1 | 05/04/2022 | Provisional version |
| 0.2 | 19/04/2022 | Comments From EM added. References added |
| 1.0 | 20/04/2022 | Provisional version for github |
| 1.1 | 25/05/2022 | Add sensitivity analyses |

## 1.0: Introduction

* The SARS-CoV-2 Omicron (B.1.1.529) variant rapidly become dominant in Scotland in December 2021.(1)
* Understanding the impact of Omicron in pregnancy is important for policy around maternity care provision, for example, for guidance on partners attending hospital and provision of infertility treatments.(2,3)
* Little is known about the effect of Omicron on pregnancy and neonatal outcomes, although, there have been reports of less maternal severe disease with Omicron when compared to Delta (B.1.617.2) variant in the selected population of pregnant women who attended maternity units.(4)

## 2.0: Objectives

The main aim of this work is to assess the short-term outcomes following infection in pregnancy with Delta and Omicron SARS-CoV-2 variants. This will be achieved through the following objectives:

* To estimate the risk of short-term adverse pregnancy, maternal and neonatal outcomes in pregnant women with delta and omicron infection in pregnancy.
* To investigate whether the risk of short-term adverse pregnancy, maternal and neonatal outcomes is different in women with omicron and delta variant infections.

## 3.0: Study Design

Population cohort study

## 3.2: Study population

Pregnant women will be identified for inclusion in the cohort study through the COPS study database.(5,6) 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

For these analyses we will include women who were pregnant during the period 17th May 2021 to 31st January 2021.

There are two study periods referred to in this protocol, defined by the time that delta and omicron variants were dominant (>50%; based on >50% S gene positivity in PCR tests for which this data was available):

* Delta period (17th May 2021 to 14th December 2021)
* Omicron period (from 15th December 2021 to 31st January 2022)

These periods were used as

* viral sequencing is only performed on a small proportion of all population tests.
* S+ (delta)/S-(omicron) status, which serves as a proxy for delta vs omicron BA1, is unavailable for many tests post January 6th when legislation changed allowing diagnosis by LFD without need for follow-up PCR
* Omicron BA2, which is S+, began increasing in Scotland in mid January 2022 further compromising the ability to use S gene status as a proxy for variant

To allow for adequate follow-up and outcome ascertainment from healthcare records, we will limit cases to those occurring up to the 31st January 2022. Source data latency is described in (6).

## 3.4: Data Sources

This study will involve linkage and analysis of routinely collected electronic health records on maternal, pregnancy and neonatal outcomes, SARS-Cov-2 infections, vaccination data and other covariates of interest.

Pregnant women will be identified through the COPS study database (5,6) 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.*](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, 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 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

1. Maternal outcomes:
   * Admission to critical care or death within 21 days of COVID-19 infection (defined as ICU admission as identified on SICSAG record or maternal death)
   * Admission to critical care for COVID-19 (defined as ICU admission as identified on SICSAG record with COVID-19 included in a diagnostic field indicating clinically significant infection; or death with COVID-19 recorded on death certificate)
   * Maternal death
2. Pregnancy outcomes:
   * Stillbirth within 28 days of infection. For this analysis we will use a broader definition of stillbirth encompassing late fetal losses and stillbirths from 20 weeks gestation onwards.
   * Preterm birth (<37 weeks gestation) within 28 days of infection.
3. Neonatal outcomes:
   * Early neonatal death (within 7 days of birth), in births within 28 days of maternal infection
   * Neonatal infection within 7 days of birth, in births within 28 days of maternal infection
   * Neonatal death (within 28 days of birth), in births within 28 days of infection
   * Low Apgar score (<7), in births within 28 days of infection

Completeness of the outcome data will be assessed before carrying out analyses. Some data sources have latency before they are complete. There may also be delays in record linkage, which similarly would be biased to the omicron period. Incomplete data in the omicron period will decrease robustness of our estimates, and for some outcomes may bias the results. Data completeness and its potential impact will be assessed for each outcome. High levels of incompleteness may necessitate some outcomes being dropped. We anticipate this is most likely to affect the outcomes of Neonatal death within 28 days of birth and Low Apgar score.

### 3.5.2: Exposure

In the absence of SARS-CoV2 sequencing data for all pregnant women, we will use the time period of infection to designate SARS-CoV-2 variant.

* Delta period (infections 15th June 2021 to 14th December 2021)
* Omicron period (infections from 15th December 2021 to 31st January 2022)

Infection in pregnancy is defined as infection diagnosed at any point from the date of conception (2+0 weeks gestation) to the date the pregnancy ends inclusive (censoring infections and vaccinations occurring at 44+0 weeks gestation or over as it is very likely that these women have completed their pregnancy, but the end of pregnancy record has not yet been received by Public Health Scotland). The date of first positive sample collection will be taken as the date of onset of the first episode of COVID-19. Subsequent episodes were recorded if a positive sample was taken ≥90 days after a first positive sample. Infections are determined by positive Reverse Transcription (RT) Polymerase chain reaction (PCR) test, and from 6th January 2022 onwards are determined by positive PCR or positive LFD (provided the LFD is not followed by a negative PCR within 48hours).

The exposure periods for infection varies for each outcome (referred to as “outcome-specific exposure period” throughout this protocol) as shown in table 3.

Table 3: Maternal, pregnancy and neonatal outcome measures

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Outcome measure** | **Definition** | **Primary or secondary outcome?** | **Timing of infection to be included** | **Post infection risk period to be examined** |
| ICU admission or death (any cause) | Admission to critical care within 21 days of COVID-19 infection (defined as ICU admission as identified on SICSAG record) | Primary | Any | 28 days post infection |
| ICU admission or death (COVID-19) | Admission to critical care for COVID-19 (defined as ICU admission as identified on SICSAG record with COVID-19 included in a diagnostic field indicating clinically significant infection; or death with COVID-19 recorded on the death certificate) | Secondary | Any | 28 days post infection |
| Stillbirth | Spontaneous fetal loss at ≥20 completed weeks gestation Any cause of fetal  losses related to termination of pregnancy excluded | Primary | Any | In births within 28 days of infection from 20+0 weeks gestation onwards |
| Preterm birth | Delivery at <37 completed weeks gestation | Primary | Up to 36+6 gestation | In births within 28 days of infection from 20+0 up to 36+6 gestation |
| Low Apgar score | 5 min Apgar <7 | Secondary | Any | At end of pregnancy in births within 28 days of infection ≥37 weeks gestation |
| Early neonatal death | Death from any cause | Primary | Any | In births within 28 days of infection from end of pregnancy to 7 days post birth |
| Neonatal death | Death from any cause | Primary | Any | In births within 28 days of infection from end of pregnancy to 28 days post birth |
| Neonatal infection | Positive RT-PCR | Primary | Any | In births within 28 days of infection from end of pregnancy to 7 days post birth |

### 3.5.3: Covariates

Covariates of importance are shown in Table 3. 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 3: Covariates of interest

|  |  |  |
| --- | --- | --- |
| **Covariate** | **Category** | **Notes** |
| Deprivation Score | SIMD 1 - most deprived |  |
| SIMD 2 |
| SIMD 3 |
| SIMD 4 |
| SIMD 5 - least deprived |
| Unknown |
| Accessible Rural Areas |
| Remote Rural Areas |
| Very Remote Rural Areas |
| Unknown |
| Maternal ethnicity | White Scottish | We will include if we have sufficient numbers to allow meaningful analysis. Regrouping into fewer categories to be explored. |
| White Other British |
| White Other |
| South Asian |
| Chinese |
| Black/Caribbean/African |
| Mixed or other ethnic group |
| Unknown |
| Gestation at time of infection | Week of gestation |  |
| Vaccination status at time of infection | Unvaccinated (no prior COVID-19 vaccination prior to the date of onset of COVID-19, or with one dose of vaccination ≤21 days prior to the date of onset) |  |
| Partially vaccinated (one dose of vaccination >21 days prior to the date of onset of COVID-19, or two doses of vaccination with the second dose ≤14 days prior to the date of onset) |
|  | Two doses (two doses with the second >14 days before infection |  |
|  | Three or more doses (three or more doses, with the third dose >14 days before infection) |  |

### 4.0: Data Analyses

Analyses will be carried out in R 3.6.1. The package “survey” (v 4.1-1) will be used for clustered logistic regression.

## 4.1: Descriptive analyses

Monthly infection rates will be calculated as the number of pregnant women vaccinated during the month divided by the number of women with ongoing pregnancies at the start of the month of interest. Infection rates will be stratified by trimester (first trimester 2 + 0 to 13 + 6 weeks gestation; second trimester 14 + 0 to 27 + 6 weeks gestation; and third trimester is 28 + 0 weeks gestation or over) at the time of infection.

Characteristics (i.e. covariates) of the women with delta and omicron, and the number and risk of all outcome events in the delta and omicron groups will be described to assess the comparability of the groups and to provide better understanding of the data. Median, range and inter-quartile range of the gestational week of infection will be calculated.

Summary tables of the number and risk of each outcome in the delta and omicron pregnant cohorts, overall, by covariates, and by variant will be produced.

## 4.2: Statistical analyses

Maternal, pregnancy and neonatal outcomes in the delta and omicron pregnant cohorts will be compared using logistic regression. Clustering will be used to account for pregnancies with multiple babies (as babies from the same pregnancy are more likely to have the same outcome as each other). Odds ratios (ORs) with 95% confidence intervals will be produced for each comparison.

## 4.3 Sensitivity analyses

A sensitivity analysis will be performed on any significant results, using a 90% cutoff to ascertain the impact of using a 50% cutoff – with the associated uncertainty around actual variant causing each infection – on our results.

Previous infections are not controlled for in the main analysis. A sensitivity analysis excluding second and subsequent infections will be run.

# 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:
2. Insufficient sample size for rare outcomes
3. 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

1. Unmeasured confounding:

There is the potential for unmeasured confounding given the inherent differences between women in the omicron and delta periods, especially relating vaccination status, which might not be accounted for.

# 6.0 Data access

Aggregate data files of infections among pregnant women are available here: https://www.opendata.nhs.scot/organization/health\_protection. Patient-level data underlying this article cannot be shared publicly due to data protection and confidentiality requirements. Public Health Scotland and the Chief Medical Officer for Scotland are the data holders for the data used in this study. Data can be made available to approved researchers for analysis after securing relevant permissions from the data holders via the Public Benefit and Privacy Panel. Enquiries regarding data availability should be directed to phs.edris@phs.scot.

# References

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