**DaCVaP2: Severe perinatal outcomes following SARS-CoV-2 infection.**

**Analysis Plan**

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**Aims:**

1. To describe, at population level, the incidence of SARS-CoV-2 infection in pregnancy in Scotland, Wales and Northern Ireland (+/- England)
2. To describe rates of preterm birth and perinatal mortality post SARS-CoV-2 infection in pregnancy
3. To explore the effect of vaccination status on these post infection outcomes in women with SARS-CoV-2 infection in pregnancy

**Methods:**

**Data sources and linkage:**

SCOTLAND: The Covid-19 in Pregnancy in Scotland (COPS) database.

WALES: Anonymised electronic health record and administrative data sources available within the Secure Anonymised Information Linkage (SAIL) Databank.

N IRELAND: Data from The Northern Ireland Maternity System (NIMATS) will be used to identify all women in who were pregnant on or became pregnant during the study period.

**Definitions:**

***Inclusion:***

Any pregnancy resulting in a birth ≥24 weeks gestation between 08 December 2020 to 31 January 2022.

***Outcomes:***

*Extended perinatal mortality:* a baby born dead or live birth that subsequently died within 28 days of birth.

*Preterm birth rate*: a birth before 37 weeks gestation (i.e., births up to 36+6 weeks gestation).

***Exposure:***

Infection in pregnancy will be defined as SARS-CoV-2 infection diagnosed at any point from the date of conception (2 + 0 weeks gestation) to the end of an outcome-specific exposure period, which is the end of pregnancy for the perinatal mortality outcome and up to 36+6 weeks gestation for the preterm birth outcome.

The date of first positive viral RT−PCR sample collection will be taken as the date of onset of the first episode of COVID-19. Subsequent episodes will be recorded if a positive viral RT−PCR sample was taken ≥90 d after a first positive sample. *Lateral flow test results will not be considered. For the duration of our study period, anyone in UK having a positive lateral flow test was advised to have a follow up RT-PCR test to confirm COVID-19****.***

For pregnancies with SARS-CoV-2 infection, we will further categorise these by their COVID-19 vaccination status at time of infection and the gestation at infection. Vaccination status will be defined as unvaccinated (no previous COVID-19 vaccination before the date of onset of COVID-19 or with one dose of vaccination ≤21 d before the date of onset), partially vaccinated (one dose of vaccination >21 d before the date of onset of COVID-19 or two doses of vaccination with the second dose ≤14 d before the date of onset) or fully vaccinated (two doses of vaccination with the second dose >14 d before the date of onset of COVID-19). For gestation at infection, we will group pregnancies by the trimester at which the infection occurred (<14 weeks gestation for first trimester, 14-27 weeks for second trimester and ≥28 weeks for third trimester). If there are multiple infections in pregnancy, we will take the infection closest to birth.

***Covariates:***

Where possible the following covariates will be create according to the following groupings:

Maternal age at conception: continuous

Ethnicity: grouped according to the ONS five-groups (White, Mixed, Asian, Black/Caribbean, Other)

Deprivation: grouped by quintiles, from 1 which is the most deprived to 5 which is the least deprived

Body mass index: grouped as <20, 20-24, 25-29, 30-34, 35+

Smoking status: grouped as Neve, Ex-smoker, Current

Diabetes: grouped as None, Pre-existing, Gestational/onset unknown

Parity: grouped as 0 or 1+

Plurality: grouped as Singleton or Multiple

Clinical vulnerability: grouped as Extremely vulnerable, Vulnerable and Not vulnerable

There might be slight variations between the datasets from each nation depending on data availability and quality that will be fully documented.

**Statistical Analysis Plan:**

We will initially conduct descriptive analyses, first looking at the perinatal outcomes overall, and then by key socio-demographics. We will also describe rates of perinatal outcomes by trimester of SARS-CoV-2 infection and by vaccination status at SARS-CoV-2 infection among only pregnancies where there was SARS-CoV-2 infection documented. These will be done separately for each Nation, and combined if necessary in the final presentation of the data if there are small numbers for any individual national (i.e. <10 in a group).

We will then use logistic regression in each dataset separately:

1. To compare our outcomes between births by SARS-CoV-2 infection in pregnancy (exposure coded as no infection/infection in first trimester/infection in second trimester/ infection in third trimester)
2. To compare our outcomes between births whether the woman was unvaccinated, partially vaccinated and fully vaccinated at time of SARS-CoV-2 infection in pregnancy

For all regression analysis, we will produce crude estimates, as well as adjusted estimates firstly for a minimum set of indicators (age, ethnicity and deprivation) and, if sample size permits, also for all covariates listed above. The analyses will be conducted separately in each Nation, with results reported for combined analysis using an Excel sheet (Data\_Variables\_Perinatal\_Mortality\_v5).

Fixed effects meta-analysis will then be used to combine adjusted ORs for each outcome from the four nations.

**Ethics and data governance:**

SCOTLAND: COPS is a sub-study of EAVE II, using unconsented data that is covered by National Research Ethics Service Committee, South East Scotland 02 approval reference REC 12/SS/0201: SA 2. COPS has been approved by the Public Benefit and Privacy Panel approval reference 2021-0116. Public Health Scotland and the Chief Medical Officer for Scotland are both (independent) data controllers for the national Abortion Act Scotland (AAS) database of termination of pregnancy notifications, thus the Chief Medical Officer has been informed of the use of AAS records. All data were housed within a secure trusted research environment within Public Health Scotland and accessed only by approved researchers.

WALES: Individual-level, linked, anonymised electronic health record and administrative data sources available within the Secure Anonymised Information Linkage (SAIL) Databank. (REF: Lyons, R.A., Jones, K.H., John, G. et al. The SAIL databank: linking multiple health and social care datasets. BMC Med Inform Decis Mak 9, 3 (2009). <https://doi.org/10.1186/1472-6947-9-3>).

N IRELAND: TBC Anonymised data were obtained via the Honest Broker Service and made accessible to the approved researchers via the Secure Anonymised Information Linkage (SAIL) Databank. Ethical approval was granted from the Honest Broker Service Governance Board (Project 064).