

Enhanced surveillance of COVID-19 in pregnancy, and associated pregnancy outcomes

Project protocol

Contributors:

Sarah Stock, University of Edinburgh

Rachael Wood, Public Health Scotland and University of Edinburgh

David McAllister, Public Health Scotland and University of Glasgow

Chris Robertson, Public Health Scotland and University of Strathclyde

Version control:

|  |  |  |
| --- | --- | --- |
| Version number | Date | Change from previous version |
| 1.0 | 26/05/2020 | First version |
|  |  |  |
|  |  |  |
|  |  |  |

# Introduction

The effects of novel coronavirus (SARS-CoV-2) in pregnancy are unknown, but, to inform public health policy, it is crucial to determine both

i) the effects of pregnancy on the susceptibility to, and progression, of COVID-19 infection

*and*

ii) the effects of COVID-19 infection on maternal, pregnancy, and neonatal outcomes.

The first of these evidence gaps will be addressed within the related research study, EAVE II (Establishing a real-time national Scottish surveillance platform to identify vulnerable adults and enable contact tracing for COVID-19). EAVE II aims to build a national, real-time, data platform to identify the population groups most at risk from SARS-CoV-2 infection and COVID-19 disease and mortality. Pregnancy will be assessed as one of these at-risk groups. This project protocol clarifies the national datasets that will need to be incorporated within the EAVE II platform to enable pregnant women (and associated pregnancy start and end dates) to be reliably identified as part of this work.

In addition, in this study protocol we outline additional analyses that will be required to address the second uncertainty, i.e. to determine the effects of COVID-19 on pregnancy outcomes, and maternal and newborn health. COVID-19 transmission from mother to baby (antenatally or intrapartum) appears to be possible[[1]](#footnote-1) but the proportion of pregnancies affected and the clinical significance is uncertain. Potential effects of the virus on miscarriage, congenital anomalies, fetal growth, timing of delivery, and stillbirth are unknown. We know from other viral infections in pregnancy that infections with mild maternal symptomatology can have substantial impacts on the developing fetus (e.g. Cytomegalovirus, Zika virus). There are also plausible links to preterm birth, mediated either through maternal infection itself; or indirectly through increased stress due to the pandemic and containment measures, or through altered physician threshold for iatrogenic preterm delivery in women with infection. Newborns may be affected through true vertical transmission, or, more commonly through exposure to infected family members or nosocomially.

There are a number of surveillance studies gathering data on pregnant women with COVID-19 currently underway in the UK. A [UKOSS](https://www.npeu.ox.ac.uk/ukoss/current-surveillance/covid-19-in-pregnancy) study is gathering data on women admitted to hospital in the UK with confirmed COVID-19 at any stage of pregnancy. Reporting is by front line clinicians. Patient consent is not required for data return. Coverage of women admitted to obstetric departments in Scotland is likely to be high. [PAN-COVID](https://pan-covid.org/) is a global study based in the UK gathering data on women admitted to hospital for pregnancy loss or delivery who have had COVID-19 at any stage during pregnancy. Patient consent is required for data return. Coverage of data return in Scotland is not currently known but likely to be low. The ISARIC Clinical Characterisation Protocol Tier 0 study (also known as [CO-CIN](https://isaric.tghn.org/covid-19-clinical-research-resources/)) is gathering data on any patient admitted to hospital in the UK with confirmed COVID-19. Reporting is by research nurses. Patient consent is not required for data return. Data collection from obstetric hospitals/units in Scotland, and hence coverage of pregnant women admitted to hospital, is currently low in Scotland although this may increase. In addition, a [BPSU](https://www.rcpch.ac.uk/work-we-do/bpsu/study-neonatal-complications-coronavirus-disease-covid-19) study is gathering data on neonates with confirmed COVID-19, and on all babies born to mothers with COVID-19 who are admitted to neonatal care (whether the baby has COVID-19 or not). Reporting is by front line clinicians. Patient consent is not required for data return. Coverage of babies admitted to neonatal units in Scotland is likely to be high.

Collectively these studies can provide detailed characterisation of selected groups of pregnant women affected by COVID-19. The study outlined in this protocol will complement these existing studies by providing population based information (for the whole of Scotland) on the risk of, and outcomes following, confirmed or suspected COVID-19 at any stage of pregnancy for women in the community and/or admitted to hospital.

Understanding the effects of COVD-19 at different stages in pregnancy and perinatally will help inform policy on shielding strategies, and advice to pregnant women and those considering pregnancy. It is also essential for immunisation strategies when vaccines are available, as different approaches may be preferable. For example, immunisation in early pregnancy may help protect against maternal infection during pregnancy and reduce complications; but immunisation in later pregnancy may be preferential to provide passive immunisation to babies if neonatal infection is the predominant concern.

# Aims and objectives

## Aims

To extend the EAVE II national, real-time, linked data platform to enable the epidemiology of SARS-CoV-2 infection in pregnancy to be determined, and to examine the effects of COVID-19 on pregnancy and babies.

## Objectives

### Primary objectives

1. Describe the incidence of COVID-19 in the pregnant population, specifically

* Incidence of virologically or clinically confirmed COVID-19 (positive viral PCR or serology, diagnosis coded on hospital admission record, stillbirth, or death record), and
* Incidence of clinically suspected infection (NHS24 call coded as possible COVID-19, triaged to NHS24 COVID-19 phone assessment hub or clinical assessment centre, A&E attendance coded as possible COVID-19, negative viral PCR test)

2. Determine associations between confirmed and suspected COVID-19 and adverse pregnancy, neonatal and maternal outcomes

### Secondary objectives

3. Assess the safety of any new or existing prophylactic or therapeutic interventions (e.g. new or repurposed therapies, vaccines, antimicrobials) in pregnant women and their babies

4. Set up a platform to enable other and longer-term sequelae of SARS-CoV-2 or therapeutic interventions to mitigate SARS-CoV-2 infections in pregnancy, on childhood outcomes

# Study Design

## Study design

Prospective cohort study using routinely collected data, in accordance with relevant guidance including RECORD[[2]](#footnote-2) and STROBE[[3]](#footnote-3).

## Setting

Scotland, UK.

## Population

All women in Scotland who were pregnant on, or became pregnant after 1st March 2020 (the date of the first confirmed case of COVID 19 in Scotland).

## Data sources

The following national datasets will be linked. Datasets already included in the EAVE II linked data platform are marked in *italics*.

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 (cf all other records that identify end of pregnancy events)
* *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

Datasets required to identify women with confirmed or suspected COVID-19:

* *Electronic Communication of Surveillance in Scotland (ECOSS) and other viral PCR and serology results held separately by Public Health Scotland (PHS): for identification of women and neonates with positive vital PCR and serology, and women with negative viral PCR*
* *National Records of Scotland (NRS) statutory death registrations: for identification of any women with COVID-19 recorded as cause of death*
* *SMR01, SMR02,* and NRS stillbirths will also identify additional women with COVID-19 recorded as cause of admission/stillbirth
* *NHS24 call, COVID-19 phone assessment hub, or COVID-19 clinical assessment centre record: for identification of women with clinically suspected COVID-19*
* *A&E attendance record: for identification of women with clinically suspected COVID-19*

Datasets required to identify relevant outcomes of pregnant women and their neonates:

* Records listed above plus
* *Scottish Intensive Care Society Audit Group (SICSAG) records: to identify women admitted to intensive care*
* Scottish Birth Record (SBR): to identify neonates admitted to neonatal care

The following additional datasets, all included in the EAVE II platform, may also be used to identify:

* *Early miscarriage not managed in hospital (GP consultation records extracted by Albasoft Ltd)*
* *Potential confounders such as comorbidity (GP consultation, SMR01, and community prescribing [PIS] look back records)*
* *Vaccination provided to prevent COVID-19 (GP consultation records and SIRS/CHSP-S records)*
* *Treatment provided for COVID-19 (PIS and hospital prescribing [HEPMA])*

Finally, we will also explore the possibility of linking in flag variables indicating patients that have been reported to existing COVID-19 surveillance studies (specifically the UKOSS, BPSU neonatal, and CO-CIN studies). This will allow us to identify any women with COVID-19 not identified through the other linkages (should be minimal), and to inform the leads of the external studies of their achieved case ascertainment and any resulting selection bias.

## Inclusion/exclusion criteria

All pregnant women identified in one or more of the data sources listed above with estimated date of conception from 20 May 2019 onwards and no end of pregnancy before 1 March 2020 will be included.

Women with date of conception 20 May 2019 would have reached their due date on 10 Feb 2020 and the reasonable upper limit of their pregnancy duration (43+0 weeks) on 1 March 2020 hence this cohort will capture all women at risk of confirmed or suspected COVID-19 during pregnancy. Whilst some (unrecognised) imported cases of infection, and low levels of community transmission, may have occurred in Scotland prior to March 2020, the first virologically confirmed case occurred on 1 March 2020.

Women in the cohort with the earliest dates of conception will only have been at risk of COVID-19 at the very end of their pregnancy. Women with more recent dates of conception will have been at risk for longer, up to women with date of conception from 1 March 2020 onwards who will be at risk from conception onwards (unless viral transmission is completed suppressed).

We aim to use the entire pregnant population; therefore, selection bias is not anticipated and the dataset will be fully generalisable to Scotland (with extensive generalisability to the other high income nations).

## Sample size calculation

There are approximately 5,000 miscarriages managed in hospital, 13,000 terminations of pregnancy, 200 stillbirths, and 50,000 live births in Scotland per year. The estimated number of women in the population who are pregnant at any one time is around 42,000.

The number of pregnant women with confirmed COVID-19 will be influenced by testing and diagnostic strategies which are evolving over the course of the pandemic. Initially, the threshold for viral PCR testing to detect active infection was high, with testing reserved for patients unwell enough to require hospital admission and for key workers (in particular health and social care staff) to inform decisions about ability to work. Since late May 2020, PCR testing has been more widely available, with all individuals in the general population aged 5 years or older with relevant symptoms also able to access a test.

Serological testing to identify antibodies to SARS-CoV-2 and hence prior exposure or infection is also developing as the pandemic progresses. Residual serum samples (from blood tests taken from patients in primary care or in hospital for any indication) processed by the QEUH biochemistry lab in Glasgow have been tested from mid-March 2020 onwards. Further residual serum samples from NHS labs across Scotland, and the national blood transfusion service, have been tested from late April/early May 2020 onwards. It is possible that additional surveillance testing may be added in the future, e.g. of stored serum samples from blood tests taken at antenatal booking. In addition, diagnostic serology testing (to inform the care of individual patients with suspected previous COVID-19) is being introduced from late May 2020 onwards.

Reflecting the testing strategies outlined above, the numbers of pregnant women with confirmed COVID-19 is likely to be small in the initial phase of the pandemic, and these women are likely to be the ‘tip of the iceberg’ with relatively severe disease. As time progresses, numbers of women with confirmed COVID-19 will tend to increase due to increased testing, but this should be offset by decreasing levels of community transmission of infection. Confirmed cases are likely to become more representative of the spectrum of illness caused by SARS-CoV-2 over time.

To account for the variable ascertainment of true incidence over time, as well as examining confirmed cases, we will also examine the number of women with clinically suspected COVID-19, using information from NHS community triage and assessment processes and A&E attendances as noted above.

We cannot influence the number of women with confirmed and suspected COVID-19 available for analysis. However, to guide decisions on formal modelling of the impact of COVID-19 on the outcomes of interest (see below), we will conduct indicative ‘sample size’ calculations to indicate the power we will have to ascertain a clinically feasible impact on specific outcomes given different numbers of cases, as outlined below.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Outcome of interest | Baseline risk | Feasible impact of COVID-19  (% relative change in risk) | Power to detect feasible impact given stated number of women with COVID-19 available for analysis | | |
| 10 | 50 | 100 |
| e.g. Preterm delivery  (<37 weeks) | 7% | 20% increase to 8.4% | X% | X% | X% |
| etc |  |  |  |  |  |
|  |  |  |  |  |  |

# Data and data validation

## Data variables available

The list of variables to be requested from each of the data sources listed in section 3.4 is provided in Appendix 1.

## Constructed variables

To be confirmed.

## Consistency and error checking

To be confirmed.

# Statistical analyses

Each research objective is addressed separately.

## Objective 1: Describe the incidence of COVID-19 in the pregnant population

### Population

All women in Scotland who were pregnant on, or became pregnant after 1st March 2020.

### Outcomes of interest

Virologically or clinically confirmed COVID-19 defined as:

* Positive viral PCR for SARS-CoV-2 on test taken from 14 days prior to estimated date of conception up to date of end of pregnancy
* Positive serology for SARS-CoV-2 with sample date indicating infection very likely to have occurred during pregnancy (e.g. positive serology test on sample taken in May 2020 from women pregnant from Sep 2019 to June 2020.
* COVID-19 (virologically or clinically confirmed) recorded on a hospital admission, stillbirth, or death record (using ICD10 code U07.1 or U07.2)

Clinically suspected COVID-19 defined as:

* NHS24 call coded as possible COVID-19
* Patient triaged to NHS24 COVID-19 phone assessment hub or clinical assessment centre
* A&E attendance coded as possible COVID-19
* Negative viral PCR test

The pathway for management of patients in the community with symptoms suggestive of COVID-19 has evolved as the pandemic has progressed. In early March 2020, patients with symptoms were advised to phone their GP in hours or NHS 24 out of hours for advice. Patients requiring face to face assessment were then seen in GP surgeries or GP out of hours centres. On 17 March 2020, the Scottish Government published details of a new national patient pathway, whereby all patients with symptoms (in or out of hours) were encouraged call NHS 24 as the initial point of contact. Patients thought likely to have COVID-19 were then passed to a new, dedicated NHS24 COVID-19 phone assessment hub. Those requiring face to face assessment in general were then seen in (or visited at home by staff from) an NHS24 COVID-19 clinical assessment centre, although pregnant women could alternatively be directed to their maternity service triage base[[4]](#footnote-4).

### Analytical techniques

We will use summary statistics to describe the cohort by presence and absence of confirmed or suspected COVID-19.

We will perform descriptive analysis of the number of cases over the total number of pregnancies i.e. how many pregnant women have had confirmed or suspected COVID-19/ total number of pregnant women. Where timing of infection is known, we will describe incidence of SARS-CoV-2 infection by trimester of exposure - first trimester; second trimester; third trimester (with denominators consisting of ongoing pregnancies in each trimester).

Due to the lag inherent in the various national datasets (see Appendix 2), we anticipate being able to identify women who were pregnant in March 2020 (i.e. women becoming pregnant, with a continuing pregnancy, or ending their pregnancy during March), and the subset who had confirmed or suspected COVID-19 in March 2020, in July 2020. Our first analyses will therefore provide results for this initial month of interest. Analyses will subsequently be updated monthly, providing results for sequential months, and also information on the cumulative risk of COVID-19 as women progress through their pregnancies.

### Potential confounders and effect modifiers

NA

### Sub-group analysis

If/when numbers of cases allow, we will examine incidence of confirmed and suspected COVID-19 by:

* Maternal age
* Maternal deprivation level
* Maternal NHS Board area of residence
* Maternal comorbidity status

We will also explore the possibility of examining incidence by maternal ethnicity, although missing data on ethnicity status may preclude this.

### Corrections for multiple testing

NA

### Sensitivity analysis

NA

### Other analysis

If a flag variable indicating patient inclusion in other COVID-19 surveillance studies (specifically UKOSS, BPSU neonatal, and CO-CIN) is available, we will produce summary statistics on the number and proportion of pregnant women with confirmed and suspected COVID-19 included in the external surveillance studies, and any factors associated with inclusion e.g. hospital admission status and NHS Board area of residence.

## Objective 2: Determine associations between confirmed and suspected COVID-19 and adverse pregnancy, neonatal and maternal outcomes

### Population

All women in Scotland who were pregnant on, or became pregnant after 1st March 2020.

### Exposures of interest

Confirmed or suspected COVID-19 as defined above.

### Outcomes of interest

Maternal outcomes:

* Severe COVID-19 disease defined as ICU admission or death

Pregnancy outcome:

* Pregnancy outcome categorised as miscarriage (any spontaneous loss at <24 weeks, including ectopic pregnancy); termination of pregnancy (at any gestation); stillbirth (any spontaneous loss at ≥24 weeks; or live birth (at any gestation)

Fetal and neonatal outcomes:

* Congenital anomaly (major structural anomaly as defined by EUROCAT diagnosed in pregnancy terminated at any gestation due to anomaly; miscarriage or stillbirth at ≥20 weeks; or live born baby diagnosed at <28 days of age)
* Preterm delivery (<37 weeks)
* Small for gestational age (birthweight <10th centile by WHO-UK90 growth reference)
* Admission to neonatal care
* Neonatal SARS-CoV-2 infection (currently defined as positive viral PCR test on sample taken from baby at <28 days of age, definition may be expanded to include results of serology tests as evidence and testing options accumulate[[5]](#footnote-5))
* Neonatal mortality (death of a live born baby at <28 days of age)

The composite outcome of extended perinatal mortality (stillbirth or neonatal mortality) will also be examined.

### Analytical techniques

Initially we will focus on describing the above outcomes in women with confirmed and suspected COVID-19, and comparing occurrence to that seen in control women at the same stage of pregnancy from the general pregnant population.

So, as above, all women pregnant in March 2020, and the subset with confirmed or suspected COVID-19 during that month, will be known in July 2020. At that time, we will ascertain the outcomes listed above (occurring at up to end March 2020) for the women with COVID-19. For each woman with COVID-19, we will select at random 10 control women from the general pregnant population, matched on:

* Maternal age (same age in years)
* Maternal deprivation level (same SIMD quintile based on postcode of residence)
* Gestation at the time of COVID-19 diagnosis (same gestation in completed weeks)

We will also ascertain the outcomes listed above (occurring at up to end March 2020) for the control women. We will update analyses on a monthly basis, providing results for sequential months, and also additional cumulative information on all outcomes that have accrued to the time of analysis (given that many will be unknown close to the time of the SARS-CoV-2 infection if infection occurs early in a continuing pregnancy).

We will then present summary results for each outcome of interest using a template similar to that shown below. We will take into account that some outcomes are only applicable to women with certain (known) pregnancy outcomes status, for example preterm delivery is only relevant to women who have had a live birth.

Number of women with a live birth

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Trimester\* | March 2020 | | | April 2020 | | | etc | | | Total since March 2020 | | |
| Confirmed COVID-19 | Suspected COVID-19 | Controls | Confirmed COVID-19 | Suspected COVID-19 | Controls | Confirmed COVID-19 | Suspected COVID-19 | Controls | Confirmed COVID-19 | Suspected COVID-19 | Controls |
| 1st  (0-13w) |  |  |  |  |  |  |  |  |  |  |  |  |
| 2nd  (14-27w) |  |  |  |  |  |  |  |  |  |  |  |  |
| 3rd  (≥28w) |  |  |  |  |  |  |  |  |  |  |  |  |
| Total |  |  |  |  |  |  |  |  |  |  |  |  |

\* Trimester at COVID-19 diagnosis or matching

Preterm delivery (number of women with a live birth with outcome of interest)

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Trimester\* | March 2020 | | | April 2020 | | | etc | | | Total since March 2020 | | |
| Confirmed COVID-19 | Suspected COVID-19 | Controls | Confirmed COVID-19 | Suspected COVID-19 | Controls | Confirmed COVID-19 | Suspected COVID-19 | Controls | Confirmed COVID-19 | Suspected COVID-19 | Controls |
| 1st  (0-13w) |  |  |  |  |  |  |  |  |  |  |  |  |
| 2nd  (14-27w) |  |  |  |  |  |  |  |  |  |  |  |  |
| 3rd  (≥28w) |  |  |  |  |  |  |  |  |  |  |  |  |
| Total |  |  |  |  |  |  |  |  |  |  |  |  |

Preterm delivery (number of women per 1,000 with a live birth with outcome of interest)

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Trimester\* | March 2020 | | | April 2020 | | | etc | | | Total since March 2020 | | |
| Confirmed COVID-19 | Suspected COVID-19 | Controls | Confirmed COVID-19 | Suspected COVID-19 | Controls | Confirmed COVID-19 | Suspected COVID-19 | Controls | Confirmed COVID-19 | Suspected COVID-19 | Controls |
| 1st  (0-13w) |  |  |  |  |  |  |  |  |  |  |  |  |
| 2nd  (14-27w) |  |  |  |  |  |  |  |  |  |  |  |  |
| 3rd  (≥28w) |  |  |  |  |  |  |  |  |  |  |  |  |
| Total |  |  |  |  |  |  |  |  |  |  |  |  |

Note that by end March 2020, it is not feasible that any women with COVID-19 in their first trimester during that month will have progressed to a live birth by the end of the month. In time, however, final pregnancy outcome for all women with COVID-19 in March 2020 will be known.

Occurrence of the outcomes of interest in women with COVID-19 and controls will be compared using simple descriptive statistics (e.g. confidence interval for difference in proportion) and visualised appropriately.

If sufficient cases of COVID-19 among pregnant women accrue, and the univariate comparisons described above suggest that outcomes different between women with and without COVID-19, formal modelling will be undertaken to quantify the impact of COVID-19 on outcomes, taking relevant confounders into account. An appropriate method that can accommodate the competing risk and time to event nature of some of the outcomes (for example multistate modelling) will be used where necessary.

### Potential confounders and effect modifiers

To be confirmed.

### Sub-group analysis

We will consider whether a subgroup analysis restricted to singleton pregnancies only is required.

### Corrections for multiple testing

We do not propose to make any formal statistical adjustment for the multiple comparisons. However, a caveat will be clearly expressed regarding the dangers of over interpreting these data, given the multiple outcomes used.

### Sensitivity analysis

NA

### Other analysis

Other sensitivity and subgroup analyses may be indicated by initial findings. We will clearly state which analyses were prespecified and which were post-hoc.

## Objective 3: Assess the safety of any new or existing prophylactic or therapeutic interventions (e.g. new or repurposed therapies, vaccines, antimicrobials) in pregnant women and their babies

To be confirmed.

## Objective 4: Set up a platform to enable other and longer-term sequelae of SARS-CoV-2 or therapeutic interventions to mitigate SARS-CoV-2 infections in pregnancy, on childhood outcomes

To be confirmed.

## Dealing with missing data

The approach to imputing estimated date of conception when gestation is missing on records indicating pregnancy status is detailed in Appendix 2.

Missing data is otherwise not anticipated to be a substantial problem but this will be confirmed once initial data extracts are available.

## Statistical software

R Version 3.4.2 and RStudio (Version 1.0.143).

# Reporting results

The results of monthly analyses summarising the incidence of COVID-19 in pregnant women, and outcomes seen in women with COVID-19 and pregnant controls, will be reported through the Public Health Scotland COVID-19 enhanced surveillance cell to the Scottish Government COVID-19 Advisory Group. Any results of formal modelling of outcomes that is undertaken will be reported through the same route. Results reported through this route may be provided as management information (i.e. without application of statistical disclosure control restrictions) as appropriate.

Results will also be submitted for peer reviewed academic publication. All results put into the public domain will be subject to statistical disclosure control according to usual Public Health Scotland processes.

It is currently anticipated that all linkage and analysis will be undertaken within Public Health Scotland. It is possible that the EAVE II linked data platform will be moved to the NHS national safe haven managed by the PHS eDRIS team at some point. If so, it is possible that later analyses may take place within this environment.

The following governance approvals will be secured prior to any linkage or analysis taking place:

* Approval from the University of Edinburgh Usher Institute ethics committee
* Approval from the Public Benefit and Privacy Panel to amend the application already approved for EAVE II to cover the additional datasets required to ascertain COVID-19 occurring in pregnancy and associated outcomes

In addition, as Public Health Scotland and the Chief Medical Officer for Scotland are both (independent) data controllers for the national AAS database of termination of pregnancy notifications, we will write to the Chief Medical Officer to inform him of the intended use of AAS records for this study.

Results submitted for peer reviewed academic publication will be reported according to STROBE and RECORD (via the COVID-19 extension) guidelines. Confidence intervals will be reported where feasible to indicate the level of uncertainty of findings. Where p-values are given, these will be quoted to two decimal places, unless they are less than 0.001 (whereby the p-value will be given as <0.001) or between <0.005 and >0.001, in which case they will be stated to three decimal places.

Appendix 1: Variables to be requested from all data sources

To be completed

Appendix 2: Additional information on identifying pregnant women, and associated start and end of pregnancy dates, from national data sources

National data sources identifying end of pregnancy events

There are three possible outcomes for any pregnancy

|  |  |
| --- | --- |
| Pregnancy outcome | Comments |
| Spontaneous loss | ‘Miscarriage’ at <24w  Sometime ‘late fetal loss’ at 20-23w as a subset of miscarriages  ‘Stillbirth’ at ≥24w) |
| Termination of pregnancy | Legal at <24w under Grounds C and D of the Abortion Act 1967  Legal at any gestation under Grounds A, B, E, F, G |
| Live birth | No lower gestational limit although in practice around 22w would be considered the lower limit at which live born babies may survive |

Various national records may be returned following these end of pregnancy events, as summarised below

|  |  |  |  |
| --- | --- | --- | --- |
| National record | Description | Pregnancy outcomes identified | Coding to identify relevant records |
| Identifying spontaneous pregnancy losses | | | |
| SMR01 | Record of day case or inpatient admission to any general unit (excluding neonatal, maternity, and mental health care), including admissions under gynaecology specialty | Will identify early (first trimester) spontaneous losses managed in hospital in most Board areas | ICD10:  O00 (ectopic pregnancy)  O01 (hydatidiform mole)  O02 (missed miscarriage)  O03, O05, O06 (spontaneous miscarriage), all .5-.9 |
| OR  SMR02 | Record of day case or inpatient admission to a maternity unit, including admissions under obstetrics or midwifery specialties | Will identify early (first trimester) spontaneous losses managed in hospital in some Board areas  Will identify later (second and third trimester) spontaneous losses managed in hospital in all areas | Miscarriages  Condition on discharge=2 (aborted)  Type of abortion=1, 2, 3, 6, 8, 9 (spontaneous)  Stillbirths  Condition on discharge=3 (delivered)  Outcome of pregnancy=2 (stillbirth) |
| AND/OR  NRS stillbirths | Record of statutory registration of a stillbirth (baby born at ≥24w showing no signs of life) | Will identify spontaneous stillbirths | ICD10:  P96.4 not recorded |
| Identifying terminations of pregnancy | | | |
| AAS | Record of statutory notification of a termination of pregnancy | Should identify all terminations of pregnancy but known under-notification of later ToPs done for fetal anomaly from some maternity units |  |
| AND/OR  SMR02 | As above | Will identify later ToPs done for fetal anomaly in maternity units | Condition on discharge=2 (aborted)  Type of abortion=4 (ToP) |
| AND/OR  NRS stillbirths | As above | Will identify the small number of stillbirths following a termination of pregnancy | ICD10:  P96.4 recorded in any position |
| Identifying live births | | | |
| SMR02 | As above | Will identify live births occurring in hospital  SMR02 returns were enabled to cover home (as well as in hospital) births from Apr 2019, and coverage of home births should have been mandatory from Oct 2019, however technical difficulties mean that home births are still not all recorded on SMR02 | Condition on discharge=3 (delivered)  Outcome of pregnancy=1, 3, 4, 5 (live birth) |
| AND/OR  NRS live births | Record of statutory registration of a live birth (live born baby at any gestation) | Usually identifies all live births however statutory registration of live births has been suspended from 23.3.2020 when registrar offices closed  The only babies being registered during the lockdown period are those that subsequently die: this is being done remotely along with the death registration to avoid parents having to register the birth in person later |  |
| AND/OR  NHS live birth notifications | Notification of live births from NHS Board maternity units to child health administration departments  This notification allows a record to be created for the child on the national child health information system: this in turn ensures the child is called for immunisations and child health reviews | As NRS live birth registration is suspended, PHS has recently developed a new data extraction from the national child health information system of birth notification data  This will identify all live births known to NHS maternity services from Sep 2019 onwards  A small number of babies who die very soon after birth (before that day’s notification data has been sent) will not be included as these babies do not need to be notified for ongoing care, however they will be covered by NRS registration as noted above |  |

It is possible that the same woman/pregnancy may have multiple records giving conflicting information on the outcome of the pregnancy. In general, if any record indicates a termination of pregnancy, this should be taken as the outcome.

The relevant gestation and date of event information in the various records, and how to deal with missing gestation information, is summarised below

|  |  |  |  |
| --- | --- | --- | --- |
| National record | Gestation information available | Date of event information available | Dealing with missing gestation information (due to not recorded on that record, missing, or recorded but unfeasible) |
| SMR01 | None | Date of admission  Date of discharge | Assume 12 weeks gestation at date of admission |
| SMR02 | Gestation in completed weeks available on records where Condition on discharge=2 or 3 (aborted, delivered) | Date of admission  Date of discharge  Date of delivery on records where Condition on discharge=3 (delivered) | Miscarriage records with missing gestation, assume 12 weeks gestation at date of admission  ToP records with missing gestation (and not available from AAS), assume 16 weeks gestation at date of admission  Stillbirth delivery records with missing gestation (and not available from NRS), assume 32 weeks gestation at date of delivery  Live birth delivery records with missing gestation, assume 40 weeks gestation at date of delivery |
| NRS stillbirths | Gestation in completed weeks at date of stillbirth available | Date of stillbirth | Assume 32 weeks gestation at date of delivery (if not available from SMR02) |
| AAS | Gestation in completed weeks at date of termination available | Date of termination (date of administration of antiprogesterone for medical ToPs) | Assume 10 weeks gestation at date of termination (if not available from SMR02) |
| NRS live births | None | Date of birth | Assume 40 weeks gestation at date of birth (if not available from SMR02) |
| NHS live birth notifications | None | Date of birth | Assume 40 weeks gestation at date of birth (if not available from SMR02) |

The time lag inherent in the different data returns is summarised below

|  |  |
| --- | --- |
| National record | Time lag inherent in data source |
| SMR01 | Records should be returned to PHS within 6 weeks of patient’s discharge (in practice sometimes longer)  Monthly batches (all records received to that point) are then uploaded to the analysis platform around the middle of each month  Records are CHI seeded as they are uploaded to the analysis platform (and CHI seeding is refreshed monthly thereafter to pick up any previously unseeded records)  CHI seeding usually complete on first attempt  So: records relating to discharges in Jan XX should be available for linkage and analysis within PHS in mid Apr XX (2.5 month lag) |
| SMR02 | Records should be returned to PHS within 6 weeks of patient’s discharge (in practice sometimes longer)  Monthly batches (all records received to that point) are then uploaded to the analysis platform around the middle of each month  Records are CHI seeded as they are uploaded to the analysis platform (and CHI seeding is refreshed monthly thereafter to pick up any previously unseeded records)  Maternal CHI seeding usually complete on first attempt  Baby CHI seeding usually complete on second attempt  So: as linkage of SMR02 records is generally through maternal CHI, records relating to discharges in Jan XX should be available for linkage and analysis within PHS in mid Apr XX (2.5 month lag) |
| NRS stillbirths | Registration required within 21 days of birth  Data transferred by NRS to PHS weekly  Monthly batches (stillbirths registered up to the end of the previous month) are then uploaded to the analysis platform around the middle of each month  In parallel, records are sent to NHSCR monthly for seeding of maternal CHI  As seeded records are returned from NHSCR, the CHIs are added to the records on the analysis platform  So: records relating to stillbirths occurring in Jan XX should be available for linkage and analysis within PHS in mid May XX (3.5 month lag)  (Note: almost all stillbirths will have an SMR02 record so can be identified and linked with 2.5 month lag) |
| AAS | Notification to CMO required within 7 days of termination  Records forwarded to PHS and entered into AAS system (includes automated CHI seeding) within 6 weeks of date of termination  So: records relating to terminations occurring in Jan XX should be available for linkage and analysis within PHS in mid Mar XX (1.5 month lag) |
| NRS live births | Registration required within 21 days of birth  Data transferred by NRS to PHS weekly  Monthly batches (live births registered up to the end of the previous month) are then uploaded to the analysis platform around the middle of each month  Records are seeded with baby CHI as they are uploaded to the analysis platform (and CHI seeding is refreshed monthly thereafter to pick up any previously unseeded records)  Baby CHI seeding usually complete on second attempt  In parallel, monthly batches are seeded with the mother’s CHI by bespoke linkage to SMR02 after a 6 month lag  Records with no maternal CHI found are then matched against the full CHI database  Residual records with still no maternal CHI are then sent to NHSCR in monthly batches  So: as linkage of NRS live birth records generally requires both maternal and baby CHI (to allow intergenerational linkage), records relating to births in Jan XX should be available for linkage and analysis within PHS in mid Oct XX (8.5 month lag)  (Note: all live births from Sep 2019 onwards (check) will have a birth notification record available so can be identified and linked with a 1 month lag) |
| NHS live birth notifications | Live births are notified to the NHS Board child health admin department within 1 working day of date of birth and are keyed into the national child health info system promptly (same or subsequent day)  PHS extracts notification data (including baby’s CHI) from the national child health info system weekly  Maternal CHI is then seeded onto the data extracts weekly  So: records relating to births in Jan XX should be available for linkage and analysis within PHS in Feb XX (1 month lag) (check) |

National data sources identifying continuing pregnancies as early as possible

As part of the response to Covid 19, PHS has established a new national data return providing information on women booking for antenatal care. This will allow us to identify pregnant women before the end of their pregnancy, and hence monitor SARS-CoV-2 infections occurring in pregnant women in closer to real time. Further information on this data source is provided below.

Data items being requested in the new data feed

* Maternal CHI
* Mother’s Forename, Surname, Date of Birth, and Postcode in case CHI is missing and needs to be appended
* Date of Booking
* Gestation at booking
* Date of Last Menstrual Period (in case gestation is missing)
* Smoking status
* NHS Board booked with

PHS has asked NHS Boards to provide an initial submission of historic data on all women booking from 1 April 2019, then subsequent weekly updates. The weekly updates will give information on women who have booked in the most recent week, and also update any records relating to the previous 2 weeks if those have changed since the previous submission. The current assumption is that this data will be submitted with maternal CHI complete, hence additional lag for CHI seeding will not be required.

This dataset will identify all women booking for NHS antenatal care. The method of providing booking services has changed in many areas due to Covid, with many Boards now providing the initial booking appointment remotely, with the woman subsequently attending in person for her initial ultrasound scan and blood tests. To ensure that the dataset allows us to identify pregnant women as early as possible in their maternity care journey, the ‘booking’ event that is captured in the above dataset has therefore been defined as ‘*the date on which maternity services had the first planned/structured contact with a pregnant woman to assess her history and needs so that local maternity services can provide further care such as an early pregnancy scan and antenatal screening tests*’. Available national data shows that at least 90% of pregnant woman attend booking by 12+6 weeks gestation.

Defining start and end date of pregnancies

*For pregnancies that have ended*

Pregnancy end dates will be taken from end of pregnancy records as noted above

Pregnancy start date (date of conception) will be imputed from the pregnancy end date and the gestation at pregnancy end – 2 weeks

*For continuing pregnancies*

Pregnancy start date (date of conception) will be imputed from the date of antenatal booking and the gestation at booking – 2 weeks

If gestation at booking is missing, pregnancy start date (date of conception) will be imputed from the date of last menstrual period + 2 weeks

1. Gajbhiye RK et al. Pregnancy outcomes, newborn complications and maternal-fetal transmission of SARS-CoV-2 in women with COVID-19: A systematic review of 441 cases. MedRxiv preprint doi: <https://doi.org/10.1101/2020.04.11.20062356> [↑](#footnote-ref-1)
2. <http://www.record-statement.org/> [↑](#footnote-ref-2)
3. <https://www.strobe-statement.org/> [↑](#footnote-ref-3)
4. <https://www.sehd.scot.nhs.uk/publications/DC20200317Covid-19.pdf> [↑](#footnote-ref-4)
5. <https://www.rcpch.ac.uk/resources/covid-19-guidance-neonatal-settings> [↑](#footnote-ref-5)