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|  | **INTERCOVID STUDY** | **C:\Users\awinsey\AppData\Local\Temp\Temp1_Intercovid.zip\Intercovid\Intercovid_green.png** |

The International Fetal and Newborn Growth Consortium for the 21st Century (INTERGROWTH-21st)

**INTERCOVID**

**A prospective cohort study of the effects of COVID-19**

**in pregnancy and the**

**neonatal period**

**Study Protocol**

Version 5.0

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**Summary**

INTERCOVID is a large, multi-national, prospective cohort study with the aim of assessing the effect of COVID-19 in pregnancy on maternal, fetal and neonatal outcomes worldwide. The first phase of data collection for the study ran from March 2020 to March 2021.

A second phase of data collection will run from December 2021 to June 2022. Pregnant women who have had COVID-19, confirmed by a test (Polymerase Chain Reaction (PCR), Loop-mediated isothermal amplification (LAMP) or Antigen (Lateral Flow)), during their current pregnancy will be recruited as ‘exposed cases’. Each ‘exposed case’ is compared with two ‘non-exposed’ pregnant women, considered as representative of the pregnant population at each study site. Both ‘exposed’ and ‘non-exposed’ pregnant women will be recruited at any stage of pregnancy; women and their babies will be followed up until hospital discharge post-delivery. Pregnancy, delivery and neonatal information will be obtained from the medical records, alongside vaccination history. “Predominant viral variant” data from the catchment area of the participating institutions will be documented. We will also conduct a nested case/non-case analysis to identify either risk factors or effect modifiers of the outcomes. Primary outcomes will be: Maternal morbidity and mortality index; severe neonatal morbidity and severe perinatal morbidity and mortality indices. The effect modification of vaccination status and gestational age at diagnosis will also be explored.

A total of 1500 covid-19 diagnosed pregnant women and their corresponding reference group (3000 non exposed women) will provide 80% power to the study to evaluate all substantive outcomes. We are using the same data collection forms and data management system as in all INTERGROWTH-21st Project studies (MedSciNet, London, UK). All data will be entered locally into the online system with its built-in extensive quality control facility. Ethical approval has already been obtained from the Oxford Tropical Research Ethics Committee (OxTREC), ref no 526-20.

Phase 2 of the study commenced preparations in December 2021. All 43 of the institutions from Phase 1 have agreed to participate and some new institutions have asked to join. We achieved the aim of the phase 1 study: to collect invaluable baseline outcome data, as recommended by the Pregnancy Research Ethics for Vaccines, Epidemics and New Technologies (PREVENT) Report,1 to inform risk-benefit analyses for future vaccine trials in pregnant women by providing “potential risk relationships between vaccination and adverse events”. After our initial reports, the wild-type SARS‑CoV‑2 has undergone genetic mutations that have changed the clinical and epidemiological profile of the pandemic. There is little data on the effects of the new variants in pregnant women, vaccinated or unvaccinated so the new phase will explore this.

**Introduction**

As a result of the COVID-19 pandemic, the world is confronting arguably one of the greatest socio-economic challenges we have faced in the last 100 years. Millions of COVID-19 related deaths have already been reported and whole countries have had significant periods of lockdown with catastrophic financial consequences for society at large.

Perhaps the most dramatic feature of the pandemic is the speed with which COVID-19 has spread through the developed economies of the western hemisphere. The health sector, in its various forms, has reacted by providing emergency care on an unprecedented scale, while the scientific community has focused on evaluating the limited curative options available and the production of a vaccine to prevent future waves of the pandemic.

The most vulnerable people in the population have been identified based on the best evidence currently available and public health preventive measures have been implemented with varying degrees of compliance. This study focusses on pregnant women, newborns and infants. At the start of the pandemic these sub groups were regarded as low risk, which was surprising because pregnancy is usually a principal target of infectious diseases, as was proven to be the case in the recent Zika virus epidemic.

In the first phase of the study, conducted between March 2020 and March 2021, our aim was to ensure we fully understood the effects of COVID-19 in pregnancy. The results clearly demonstrated that COVID in pregnancy was associated significantly increased risks, including a much higher maternal mortality rate, than in pregnant women not exposed to the virus. These results have been published,2-5 and we launched an online ‘COVID in pregnancy’ training course6 to reach out to clinicians and healthcare providers across the world. Now, in early 2022, we will collect the same base data again, with the addition of the mothers’ vaccine status and the predominant virus variant in the local area, to determine how virus mutations and vaccination have changed the risk profile.

The history of medicine contains many examples, during such acute episodes, of debates around the need to produce hard scientific evidence versus the need to implement current knowledge. This pandemic is no exception. We should remember, however, that even in the most extraordinary circumstances, solid research was required and conducted before actions or treatments were promoted at large scale. This is best illustrated by the case of the large, multicentre cluster randomised field trial, conducted in the USA to test the effectiveness of the first poliomyelitis vaccine, involving 650,000 children who received

the vaccine or a placebo, and another 1.18 million who served as controls.

**Background**

Background: We have previously shown there is a consistent association between COVID-19 in pregnancy and higher rates of adverse maternal and neonatal outcomes when compared with pregnant women without a COVID-19 diagnosis. 2-6

After our initial report, the wild-type SARS‑CoV‑2 has experienced several genetic mutations (Alpha, Beta, Gamma, Delta, Omicron) that have changed the clinical and epidemiological profile of the pandemic. These variants have progressively become dominant across regions with periods of epidemiological overlap. The latest of these variants, Omicron, may produce milder disease in non-pregnant individuals although, as large parts of the population are vaccinated, this could act as an effect modifier on disease severity.

Our January 10th 2022 update of the available information demonstrates no large-scale data on the effects of the Omicron variant in pregnant women. Specifically, we did not identify any clinical papers on Omicron in pregnancy.

There is one paper in the vaccine database [*https://ripe-tomato.org/2021/01/14/covid-19-vaccines-pregnancy-fertility/*](https://ripe-tomato.org/2021/01/14/covid-19-vaccines-pregnancy-fertility/)*); (medRxiv 2022.01.01.22268615 doi:*[*https://doi.org/10.1101/2022.01.01.22268615*](https://doi.org/10.1101/2022.01.01.22268615)*)* 7 that measured theoretical immunity against Omicron after vaccination among non-infected women.

The only relevant clinical data found are in the news reports database *(*[*https://ripe-tomato.org/2020/05/17/covid-19-pregnancy-news-reports-101-onwards/*](https://ripe-tomato.org/2020/05/17/covid-19-pregnancy-news-reports-101-onwards/)*)* 8 based on 13 asymptomatic women, presumably infected with Omicron in a single South African hospital during one day in December 2021.

**Study aim**

We aim, in this new phase of the INTERCOVID study, to: a) examine the effects of COVID-19 on maternal, pregnancy and perinatal outcomes; b) assess the effect modification of maternal vaccination status on these outcomes, and c) relate these results to the ecologically reported predominant SARS‑CoV‑2 variants in the participating geographical areas. This will provide women, families, health care providers and policymakers with up-to-date high- quality evidence regarding the effects of COVID-19 on maternal, fetal and neonatal outcomes. Monthly data monitoring and interim analyses will provide evidence of the emerging trends. The information is needed quickly and at scale to optimise maternal and newborn care, reduce maternal anxiety, inform decision-making about vaccination, and guide the process toward social adaptation.

**Study design**

This is a large, multi-centre, multi-country, case-reference study involving >40 institutions in >18 countries. From December 2021 to June 2022, we will enrol women diagnosed at any time during pregnancy and delivery (a single positive test qualifies as a case) with COVID-19 (based on a positive PCR, LAMP or lateral flow test) who are delivering in the participating medical institutions. For each “case”, two unmatched, consecutive, not-infected women will be concomitantly enrolled immediately after each diagnosed woman identified at delivery or at the same level of care (if identified during antenatal care), so as to minimize bias. Pregnancy, delivery and neonatal information will be obtained from the medical records, alongside vaccination history. Mothers and their newborns will be followed until hospital discharge. Ecological level information from officially reported monthly “predominant viral variant” data from the catchment area of the participating institutions will be documented.

This strategy will miss asymptomatic women who were not tested, which is a clear limitation. However, in sites without systematic testing of all pregnant women, it is not possible to detect these women. They will be potentially eligible as ‘non-exposed’ because they remain in the general population.

‘Exposed’ cases will be compared with two ‘non-exposed’ pregnant women per case considered as representative of the pregnant population at each study site. The selection of the ‘non-exposed’ women is a central point of the study to reduce selection bias. Ideally, we should select all pregnant women in the study sites, but that is clearly impractical. Instead, we decided that the two ‘non-exposed women’ should be selected immediately after the ‘exposure’ was identified at the same level of care (e.g. antenatal clinic, hospital in-patient, or labour and delivery) following the routine practice of the unit and within the possibilities of the care demands. The key issue here is the need to avoid systematic bias, i.e. through selecting women because they are too healthy or have other characteristics

Both ‘exposed’ and ‘non-exposed’ women will be recruited at any stage of pregnancy. They and their newborns will be followed up until hospital discharge to quantify the risks associated with SARS-CoV-2 exposure.

We have considered the definition of non-exposed cases in depth. The first option is to only include those women with regular, negative tests. However, this has two important limitations: firstly, due to lack of availability and cost, testing of asymptomatic women is not available in many settings; the requirement for negative testing would therefore introduce bias in these settings, whereby negatively tested women would be selected based on symptoms. Secondly, a negative test at one point in pregnancy does not preclude previous or subsequent asymptomatic disease. The second option is to include as non-exposed those women who have a negative test *or* have had no symptoms of COVID-19 even without testing. This would allow unbiased recruitment in those settings where there is a lack of tests. There is a risk that asymptomatic Covid-expose women will be included in this non-exposed group. However, we believe this is a minor limitation, as it would reduce the observed differences between those “exposed” and “non-exposed” leading to more conservative estimates.

To complement the evaluation of ‘exposed’ and ‘non-exposed groups’ we will also conduct a nested case/non-case analysis (like a retrospective case-control study) to identify socio-economic and clinical features that are either risk factors or effect modifiers of the effect of COVID-19 on outcomes (see Barros et al.9 for this analytical strategy). This analysis will be mostly based on the data collected in the Pregnancy and Delivery Form.

**Study outcomes**

We will use, as primary outcomes maternal morbidity and mortality index; severe neonatal morbidity and severe perinatal morbidity and mortality indices. Secondary outcomes will be the individual components of these indices. Adjustment by country, month entering study, maternal age, and history of morbidity will be undertaken. The effect modification of vaccination status (completed/partial/completed plus 3rd dose) and gestational age at positive diagnosis test will be explored at the individual level adjusted by study-site. Ecological level data on the predominant variant will be considered for stratification in a meta-analysis using study site effect as the unit of analysis.

**Sample size considerations**

Sample size estimates were calculated using two unexposed women for each pregnant woman with COVID-19 for 80% power with a Type 1 error of 0.05 (95% confidence intervals). We will use Poisson regression models to calculate the relative risk of adverse maternal and neonatal outcomes. The required sample size is related to the proportion of unexposed women that experience the outcome and estimated relative risk. To estimate relative risks, we used 50% of the relative risk observed in our previous publication or the relative risk among asymptomatic pregnant women with COVID-19. The number of COVID-19 exposed pregnant women that would need to be enrolled for the primary maternal morbidity outcome was 536, 919 for preterm birth and 1041 for neonatal morbidity. For pre-eclampsia the sample size using unexposed women was1859 higher than considering asymptomatic women (n=883). This is because the difference in the RR. An average sample size estimation gives 1400 Covid-19 diagnosed women.

Hence, an arbitrary, pragmatic total of 1500 covid-19 diagnosed pregnant women and their corresponding reference group will provide power to the study to evaluate all substantive outcomes. In practical terms, if we reach the same number of participant institutions (40 hospitals) as in the first study, to achieve this sample size will require that each institutions will recruit a total of 50 diagnoses and 100 un-diagnosed pregnant women (including lost to follow up) during a period of 3 months.

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| Outcome | Estimated Relative Risk | Proportion in COVID-19 unexposed | Sample Size for COVID-19 exposed |
| Maternal morbidity | 1.3 | 0.208 | 536 |
| Neonatal morbidity | 1.8 | 0.023 | 1041 |
| Perinatal morbidity | 1.6 | 0.079 | 468 |
| ICU admission | 2.5 | 0.016 | 522 |
| Pre-eclampsia | 1.4 | 0.044 | 1859 |
| Preterm birth (all) | 1.3 | 0.136 | 919 |
| Preterm birth medically indicated | 1.5 | 0.089 | 566 |
| Maternal morbidity asymptomatic | 1.2 | 0.208 | 835 |
| Pre-eclampsia asymptomatic | 1.6 | 0.044 | 883 |

**INTERGROWTH-21st Network**

This large study benefits from the University of Oxford having hosted the well-established network of standardised researchers across the world, who have participated in the various studies of the INTERGROWTH-21st Project ([intergrowth21.tghn.org](https://intergrowth21.tghn.org/)) over the last 12 years. The network has produced >130 scientific papers with over 3,000 citations since 2015, which have influenced national and international guidelines in the field of maternal, newborn and infant health, demonstrating its translational value. As a result, we have in place trained research staff and standardised data collection forms focused on maternal and neonatal outcomes, as well as environmental exposures at cluster level. All the documentation links to an online data collection system and quality control measures that provide information almost in real-time. For the INTERCOVID study, we have simply added two forms relating to COVID- 19, which explains why we can start the study immediately.

**Participating medical institutions**

In Phase 1 of the study 43 hospitals from 18 countries took part. We anticipate that all of these will join the second phase, and that some new institutions and new countries will take part.

**Ethical considerations**

Ethical approval has already been obtained from the Oxford Tropical Research Ethics Committee (OxTREC), ref no 526-20, and an updated letter confirming data collection can continue for the second phase has been issued. Informed consent will be obtained according to local practices. The approved consent form includes the statement that anonymised clinical information, test results and images can be ‘shared with academic collaborators around the world including the Bill & Melinda Gates Foundation and commercial companies’. Those medical institutions that require local approval as well are doing so, but they do not envisage much delay in starting the study. It is important to stress that the study will not interfere with the clinical management of affected women that will be carried out based on current guidelines.10

**Publication policy**

We will adopt the publication policy that has served the INTERGROWTH-21st Project successfully for the last 12 years: namely that a Principal Investigator from every participating site will be a co-author on all publications resulting from the INTERCOVID Study.

**Data management**

We will use the same data management system that was specifically developed for the INTERGROWTH-21st Project studies (MedSciNet, London, UK). It is coordinated centrally by the same team that has accumulated extensive experience with our previous studies. All data will be entered locally into the on-line system with its built-in extensive quality control facility. Queries can be dispatched immediately to the study sites, which provides continuously clean data sets for intermediate analysis.

**Data sharing**

The intention is to pursue an open data policy in keeping with the principles set out in the Wellcome Trust statement on sharing data during the COVID-19 pandemic (31 January 2020),11 to which all major journals are signatories. Our commitment is to ensure that all stakeholders have rapid access to emerging findings that could aid the global response.

**Study Committees**

**Scientific Advisory Board**

We have established a Scientific Advisory Board, with global representation, consisting of experts in maternal, newborn health, epidemiology, virology and public health.

**Data Monitoring Group**

An independent Data Monitoring Group, (School of Public Health at Berkeley), will evaluate the study’s progress every 2 weeks to guide the recruitment process and conduct interim analyses, without statistical testing, informing an external evaluation committee.

**Acknowledgements**

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**Appendix**



