



# ISARIC (International Severe Acute Respiratory and Emerging Infections Consortium)

*A global federation of clinical research networks, providing a proficient, coordinated, and agile research response to outbreak-prone infectious disease*

## Analysis Plan for ISARIC International COVID-19 Patients

Please complete the following sections:

Title of proposed research
Impact of COVID-19 in Pregnancy
Version: (Date: Day/Month/Year)
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<sup>1</sup> Either chair and/or co-chair are based in an institution in an LMIC. If you would like to be connected with an eligible co-chair please let us know at [ncov@isaric.org](mailto:ncov@isaric.org).

Final draft SAPs will be circulated to all ISARIC partners for their input with an invitation to participate. ISARIC can help to set up collaborator meetings; form a working group; support communications; and accessing data. Please note that the details of all approved applications will be made publicly available on the ISARIC website. Please complete all sections of this form fully and return to [ncov@isaric.org](mailto:ncov@isaric.org)

## Introduction

The novel coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), continues to spread. As of March 2022, there have been 464,809,377 confirmed cases of COVID-19, including 6,062,536 deaths(1). Pregnant women are considered a high-risk group as Coronaviruses have the potential to cause adverse birth outcomes including miscarriage, preterm birth, preeclampsia, preterm prelabour rupture of membranes and fetal growth restriction (2,3).

Studies have shown that pregnant or recently pregnant women with COVID-19 are less symptomatic compared with non-pregnant women of reproductive age (4). Conversely, pregnant women are more likely to be admitted to the ICU or required invasive ventilation compared to non-pregnant women. Moreover, pregnant women were shown to develop severe or critical COVID-19 disease compared to their non-pregnant counterparts (5). These studies however are limited by their sample sizes (n=50-201), geographical spread and ethnic background hence limiting their generalisability.

COVID-19 poses continuing health systems and clinical outcomes challenges on maternal health, which are made worse by current knowledge gaps. This proposal aims to address this gap by utilising the ISARIC and IDDO large registries to evaluate the impact of COVID-19 in pregnant women. This will provide insights on risk profiles and may improve clinical care and pregnancy outcomes in women infected and hospitalized with COVID-19. The evidence generated will help to quantify the impact of COVID-19 in pregnancy which is key to planning clinical maternal care and management during a pandemic.

## Participatory Approach

All contributors to the ISARIC database are invited to participate in this analysis through review and input on the statistical analysis plan and resulting publication. The outputs of this work will be disseminated as widely as possible to inform patient care and public health policy, this will include submission for publication in an international, peer-reviewed journal. ISARIC aims to include the names of all those who contribute data in the cited authorship of this publication, subject to the submission of contact details and confirmation of acceptance of the final manuscript within the required timelines, per ICMJE policies and the ISARIC publication policy.

## Research Plan

Summary of Research Objectives
To investigate factors associated with COVID-19 and pregnancy, including risk factors for severe disease or death, as well as treatments and outcomes of pregnant women compared with non-pregnant women, and assess associations by ethnic background, gestational age, vaccination status (if sufficient sample size) and geographic region.
Proposed Target Population
Hospitalised pregnant and non-pregnant women aged 15-45
Clinical Questions/Descriptive Analyses
<ul style="list-style-type: none"> <li>Describe the demographic and clinical characteristics of pregnant women stratified by gestational age and overall, and non-pregnant women admitted to hospital with COVID-19.</li> <li>Investigate factors associated with mortality in pregnant women with COVID-19.</li> <li>Determine risk factors associated with severe or critical COVID-19 among pregnant and non-pregnant women. Severity definitions are as described by WHO recommendations <a href="https://www.who.int/publications/i/item/WHO-2019-nCoV-clinical-2021-1">https://www.who.int/publications/i/item/WHO-2019-nCoV-clinical-2021-1</a></li> <li>Compare predictors of critical illness and death from COVID-19 in pregnant women compared with non-pregnant women</li> <li>Investigate outcomes for pregnant women with COVID-19 who received vaccination compared to those who were not vaccinated.</li> <li>Compare treatments and outcomes of pregnant and non-pregnant women with COVID-19 in different geographic regions.</li> <li>Investigate the effects of COVID-19 on pregnancy outcome as recorded during hospitalisation.</li> </ul> <p><i>Outcome definitions:</i>  Primary outcome measures:</p> <ul style="list-style-type: none"> <li>Death</li> <li>Admission to ICU.</li> </ul> <p>Secondary outcome measures:</p> <ul style="list-style-type: none"> <li>Blood biochemistry and haematological parameters in different severities of COVID-19 infection</li> <li>Profiling of clinical severity, determined by clinical symptoms and observations in pregnant COVID-19 positive women</li> </ul>
Planned Statistical Analyses, Methodology and Representation

- Overall frequencies of key demographic variables for pregnant women overall and stratified by gestational age, and non-pregnant women.
- Frequencies of vaccinations received among pregnant women and non-pregnant women.
- Frequency of severe and critical COVID-19 will be ascertained and compared amongst pregnant women of different gestational age versus non-pregnant women.
- we will describe biochemical and hematological parameters of cases including Ferritin, D-Dimer, CRP, IL-6, LDH, ALT, AST, APTT, hemoglobin levels, WBC count, lymphocytes, platelets, comparing the profile of pregnant and non-pregnant women with COVID-19.
- We will describe symptoms on admission, pre-existing comorbidities and treatments administered in pregnant and non-pregnant women accounting for patient characteristics and comparing geographic regions.
- We will use Cox regression models and other survival models to estimate the relative risk of death and admission to ICU associated with pregnancy and identify risk factors for death for pregnant and non-pregnant women.

#### Handling of Missing Data

Preliminary analysis will be performed to ascertain a detailed overview of the extent of missingness in the data. This should enable the identification of variables which lack sufficient data to allow for any useful analysis to be performed on them. Type of missingness shall be considered including whether data are not missing at random and follow-up with sites will be conducted if appropriate. Variables with greater than 30% missingness will be excluded from analysis. Where appropriate, imputation will be performed using Multiple Imputation by Chained Equations (MICE).

## Other Information

We will publish findings in pre-prints to avail them to the public as soon as possible as we pursue peer-reviewed open access journal publications. We anticipate to share findings in 2 international research meetings either in-person or virtually depending on international travel situation and regulations.

## References

- 1) WHO Coronavirus (COVID-19) Dashboard, 2021 <https://covid19.who.int/>
- 2) Di Mascio, D., Khalil, A., Saccone, G., Rizzo, G., Buca, D., Liberati, M., Vecchiet, J., Nappi, L., Scambia, G., Berghella, V. and D'Antonio, F., 2020. Outcome of coronavirus spectrum infections (SARS, MERS, COVID-19) during pregnancy: a systematic review and meta-analysis. *American journal of obstetrics & gynecology MFM*, 2(2), p.100107.
- 3) Diriba, K., Awulachew, E. and Getu, E., 2020. The effect of coronavirus infection (SARS-CoV-2, MERS-CoV, and SARS-CoV) during pregnancy and the possibility of vertical maternal-fetal transmission: a systematic review and meta-analysis. *European journal of medical research*, 25(1), pp.1-14.

- 4) Allotey, J., Stallings, E., Bonet, M., Yap, M., Chatterjee, S., Kew, T., Debenham, L., Llavall, A.C., Dixit, A., Zhou, D. and Balaji, R., 2020. Clinical manifestations, risk factors, and maternal and perinatal outcomes of coronavirus disease 2019 in pregnancy: living systematic review and meta-analysis. *Bmj*, 370.
- 5) Badr, D.A., Mattern, J., Carlin, A., Cordier, A.G., Maillart, E., El Hachem, L., El Kenz, H., Andronikof, M., De Bels, D., Damoiseil, C. and Preseau, T., 2020. Are clinical outcomes worse for pregnant women at  $\geq 20$  weeks' gestation infected with coronavirus disease 2019? A multicenter case-control study with propensity score matching. *American Journal of Obstetrics & Gynecology*, 223(5), pp.764-768.