



OPEN LETTER

REVISED Direct and indirect effects of COVID-19 on perinatal outcomes in low- and middle-income countries [version 2; peer review: 1 approved, 1 approved with reservations]

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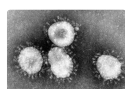
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Abstract

Similar to previous outbreaks, the coronavirus disease 2019 (COVID-19) pandemic will have both direct and indirect effects on perinatal outcomes, especially in low- and middle-income countries. Limited data on the direct impact of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection during pregnancy shows women who are Black, obese and with co-morbidities are at higher risk of hospitalisation due to COVID-19. Younger age groups in Africa and South Asia have shown increased COVID-19 mortality. Indigenous pregnant women in Pacific Island countries are likely to be high risk for severe outcomes from COVID-19 due to high rates of diabetes and obesity. It is important to involve pregnant women in research, especially with regards to vaccine development and therapeutics.

Keywords

COVID-19, perinatal outcomes, maternal outcomes, indigenous, Pacific Islands, comorbidities



This article is included in the [Coronavirus \(COVID-19\)](#) collection.

Open Peer Review

Approval Status ? ✓

	1	2
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version 1 16 Jul 2020	? view	✓ view

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Any reports and responses or comments on the article can be found at the end of the article.

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Author roles: Ratu FT: Writing – Review & Editing; Ryan K: Writing – Review & Editing; Gidi NW: Writing – Review & Editing; Vereti I: Writing – Review & Editing; Girma T: Writing – Review & Editing; Oats J: Writing – Review & Editing; Bucens I: Writing – Review & Editing; Robinson A: Writing – Review & Editing; von Mollendorf C: Writing – Original Draft Preparation, Writing – Review & Editing; Russell FM: Conceptualization, Writing – Original Draft Preparation, Writing – Review & Editing

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REVISED Amendments from Version 1

We have updated the manuscript based on the reviewer comments for additional specific details. We have added further information to the text regarding the (1) impact of the COVID-19 pandemic on maternal (reduction in antenatal and postnatal care and access to contraception) and vaccination healthcare services (reduction in immunization coverage); (2) roadmap for prioritisation of groups to receive COVID-19 vaccines and the inclusion of pregnant women in vaccination programmes; and (3) details regarding the collection of epidemiological data related to COVID-19 in LMICs. We thank the reviewer for their insightful comments and suggestions.

Any further responses from the reviewers can be found at the end of the article

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Open letter

Improvements in maternal and newborn health are essential to attain the 2030 UN SDG health targets¹. The coronavirus disease 2019 (COVID-19) pandemic will have a substantial impact on perinatal outcomes in low- and middle-income countries due to: the direct effect of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2); and its indirect effects on the disruption of essential maternity and newborn services². Whitehead *et al.* stressed the importance of including pregnant women in clinical trials as SARS-CoV-2 drugs and vaccines are developed³. However, it is also necessary to understand the perinatal epidemiology to determine whether inclusion into clinical trials is required.

The clinical manifestations of SARS-CoV-2 are rapidly evolving. So far, there are few data on the direct impact of SARS-CoV-2 infection during pregnancy. However, recent findings from a UK study are disturbing. This prospective cohort study from 194 hospitals found that approximately 100 pregnant women are hospitalised with COVID-19 each week. Of the 427 women included in the study, 9% needed intensive care unit (ICU) admission, four (1%) needed extra corporeal membrane oxygenation (ECMO), five (1%) mothers and five babies died⁴. There was a strong association between admission with COVID-19 and being Black or of minority ethnicity, having a comorbidity (e.g. diabetes) and being obese/overweight⁴. A recent US study found that compared to controls, 16 placentas from women with SARS-CoV-2 infection exhibited a higher frequency of placental injury reflecting irregularities in oxygenation associated with adverse perinatal outcomes⁵. This corroborates with other reports of COVID-19 cases having large and small blood vessel pathology⁶. Intrauterine vertical transmission of SARS-CoV-2 is possible, but direct evidence is lacking. There are only two reports of potential vertical transmission in three newborns⁷.

Of key importance to low- and middle-income countries is whether SARS-CoV-2 can be transmitted during breastfeeding. In these settings, early initiation and exclusive breastfeeding until six months of age is recommended by WHO, and exclusive breastfeeding has been shown to reduce infant morbidity and mortality. Current WHO and UNICEF guidelines recommend continuation of breastfeeding in SARS-CoV-2 positive mothers with appropriate prevention strategies, such as wearing of masks and hand hygiene. There is, however, sparse evidence with small case numbers to show that SARS-CoV-2 is present in human milk and no compelling evidence regarding its role in vertical transmission⁸.

Now that COVID-19 vaccines are available, the WHO SAGE committee has published a roadmap which outlines how to prioritise vaccination depending on vaccine availability and disease burden and risk. The roadmap acknowledges that pregnant women have been disadvantaged with regards to the development and use of vaccines in pandemics. Data needs to be generated for pregnant women and pregnant women should be included in roadmap stage 3 - when evidence should be available to determine whether the benefits of COVID-19 vaccination outweighs the risk of SARS-CoV2 infection and potential severe COVID-19⁹.

It is known that being Black or of South Asian ethnicity, having diabetes and obesity are key risk factors for COVID-19 mortality¹⁰. Elevated blood glucose levels have not only been shown to be an independent risk factor for death in COVID-19 patients, but also a predictor of subsequent clinical deterioration¹¹. Indigenous populations are also one of the most vulnerable COVID-19 populations. Pacific Island Countries have one of the highest rates of diabetes and obesity in the world^{12,13}. A recent perinatal review in Fiji, found that managing maternal diabetes was one of the key recommendations to improve perinatal outcomes and prevent stillbirths (J. Oats, personal communication). This situation is likely to be the same in other Pacific Island Countries. So far, Pacific Island Countries have averted community transmission of COVID-19, however, it is likely that importations will reoccur as the countries open up.

Recent data highlighted by Klugman *et al.*¹⁴ shows higher mortality in younger age groups in people of colour and in poorer communities in Africa. This also has implications for young pregnant women in Pacific Island Countries.

It is known that infection with influenza virus increases the risk of maternal hospitalisation¹⁵ and poor perinatal outcomes¹⁶. As such, influenza vaccination is recommended for pregnant women¹⁷. SARS-CoV-2 is likely to become a seasonal virus, similar to influenza. During the 2003 SARS outbreak, reports indicated that pregnant women infected with SARS had worse outcomes than non-pregnant women¹⁸. Perinatal epidemiology and immunology have been omitted in the previous coronavirus epidemics (MERS and SARS-1). Pregnant women have decreased T and B cell counts¹⁹ and increased expression of the angiotensin-converting enzyme 2 (ACE-2) receptor²⁰.

which may increase susceptibility to SARS-CoV-2. Pregnancy is a relative immunodeficient and pro-inflammatory state raising concerns regarding the effects of SARS-CoV-2 on pregnant patients²¹. A recent study described a pre-eclampsia-like syndrome in six COVID-19 infected pregnant women with severe pneumonia²². Viral hyperstimulation in pregnant women has been shown to have adverse effects on foetal brain development²¹. So far, nothing has been published on the immune response to SARS-CoV-2 in pregnancy.

Reports are surfacing about the impact of social distancing, cessation of transport, and pregnant women giving birth in home in low- and middle-income countries. These measures have made accessing essential health care much more difficult. In India, a 21% reduction in institutional deliveries have been reported²³. In addition, health staff are being diverted and some facilities are experiencing limits on equipment required for emergency obstetric care, such as blood supplies needed for post-partum haemorrhage. It is likely that all services ranging from contraceptive access to essential antenatal care will be affected without focused attention and effort. Reports in the media of unwanted pregnancies and lack of access to terminations, have come out of India, where community health workers responsible for distribution of contraception and reproductive health services have been diverted to do coronavirus screening and referrals. A mere 10% decline in contraception use in low- and middle-income countries could result in an additional 15 million unintended pregnancies over the course of a year²⁴. In the past, several African countries have suffered from the indirect effects of Ebola epidemics, resulting in the same number of maternal and newborn deaths as those caused by the direct effect of Ebola.

Early in the pandemic a study modelled the indirect effect of the pandemic on maternal and child health and resultant additional deaths in 118 LMICs using three possible scenarios². The scenarios varied in the extent of reduction in essential health intervention coverage (including a reduction in antenatal and postnatal care ranging from 18.5–51.9%) and increase in prevalence of wasting. It was estimated that under-5 child deaths could increase by 9.8–44.7% per month and maternal deaths by 8.3–38.6% per month depending on the associated disruptions². Data collected by the Population Council in five informal settlements in Nairobi in April 2020 found that women were twice as likely as men to miss essential health

services. Missed services including family planning and antenatal care²⁵. In addition, midwives in Kenya, Uganda and Tanzania, reported a reduction in the number of women attending maternal health clinics, and an increase in delayed labour presentations to hospital and insufficient antenatal care²⁶.

A systematic review which included LMICs evaluated the likely impact of the COVID-19 pandemic on immunisation coverage and the factors contributing to service disruption. The review found a reduction in vaccination coverage, reduction in doses administered and an increase in polio cases in polio endemic countries²⁷.

It is important to understand the direct and indirect effects of COVID-19 on routine essential health services and perinatal outcomes of SARS-CoV-2. It is vital to invest in research, especially in low- and middle-income countries to undertake special epidemiological studies in pregnant women, as large, existing datasets are usually not available to undertake rapid analyses of clinical data as in high-income countries, nor measure a future vaccine's impact. In 1875, one-third of the Fijian population died from a measles epidemic sweeping through a non-immune population²⁸. To avoid this, and end the current pandemic, 7 billion people need to be vaccinated, including pregnant women. Delays in including this vulnerable population in COVID-19 vaccine and other intervention studies, may erode the gains made in maternal and child health, globally, especially in resource-poor settings.

In terms of COVID-19 research in LMICs, it has been suggested that this is incorporated into public health and clinical activities to avoid these vital services being diverted, and also that this research should be driven by local investigators²⁹. The WHO has published a number of generic protocols for COVID-19 research and response, including surveillance, serology and case investigation³⁰. In 2020 the United Nations launched a global humanitarian response plan to fund the COVID-19 response in the poorest countries with both public and private sector support³¹.

Data availability

Underlying data

No data are associated with this article.

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Open Peer Review

Current Peer Review Status: ? ✓

Version 1

Reviewer Report 28 September 2020

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Salut Muhidin 

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The discussions on direct and indirect effects of COVID-19 are very time-appropriate and important during this current situation. However, the focus should not only be limited to low and middle income countries, it could also be expanded to disadvantaged communities.

The main effects are getting bigger and serious due to limited access that are often experienced by low income communities, regardless in which country they live.

Is the rationale for the Open Letter provided in sufficient detail?

Yes

Does the article adequately reference differing views and opinions?

Yes

Are all factual statements correct, and are statements and arguments made adequately supported by citations?

Partly

Is the Open Letter written in accessible language?

Yes

Where applicable, are recommendations and next steps explained clearly for others to follow?

Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Public health and demography

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Reviewer Report 02 September 2020

<https://doi.org/10.21956/gatesopenres.14351.r29108>

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Kenji Shibuya 

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This is a well written summary of key issues and future directions related to direct and indirect perinatal outcomes associated with COVID in low- and middle-income countries. The authors reviewed extensively the major maternal and perinatal risk factors of direct health outcomes from studies primarily done in high-income regions, but issues on indirect health outcomes, such as limited health service access (including other vaccines) and aggravating health inequality from lockdowns, and the impact of social determinants are somewhat limited.

The authors are advocating for the inclusion of pregnant women in the vaccine trials and the need for more basic research including immunology, but fail to address the lack of basic epidemiological data to track progress and monitor what works and what does not in low- and middle-income countries. This could be done in the context of ongoing efforts such as the Countdown and SDG monitoring processes.

The future directions clearly depend on a global concerted effort on collecting, synthesizing and analyzing basic epidemiological data in low- and middle-income countries and the authors should address how this could be implemented and by whom.

Is the rationale for the Open Letter provided in sufficient detail?

Yes

Does the article adequately reference differing views and opinions?

Yes

Are all factual statements correct, and are statements and arguments made adequately supported by citations?

Partly

Is the Open Letter written in accessible language?

Yes

Where applicable, are recommendations and next steps explained clearly for others to follow?

Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Health metrics and evaluation, health systems, global health policy.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 16 Mar 2021

Claire von Mollendorf, Murdoch Children's Research Institute, Melbourne, Australia

Response to reviewer 1 comments:

We thank the reviewer for their comments and have responded to each of their points separately below:

The authors reviewed extensively the major maternal and perinatal risk factors of direct health outcomes from studies primarily done in high-income regions, but issues on indirect health outcomes, such as limited health service access (including other vaccines) and aggravating health inequality from lockdowns, and the impact of social determinants are somewhat limited.

We have added some information into the review article which discusses the impact of pandemic on maternal and vaccination healthcare services:

"Early in the pandemic a study modelled the indirect effect of the pandemic on maternal and child health and resultant additional deaths in 118 LMICs using three possible scenarios (1). The scenarios varied in the extent of reduction in essential health intervention coverage (including a reduction in antenatal and postnatal care ranging from 18.5-51.9%) and increase in prevalence of wasting. It was estimated that under-5 child deaths could increase by 9.8-44.7% per month and maternal deaths by 8.3-38.6% per month depending on the associated disruptions (1). Data collected by the Population Council in five informal settlements in Nairobi in April 2020 found that women were twice as likely as men to miss essential health services. Missed services including family planning and antenatal care (2). In addition, midwives in Kenya, Uganda and Tanzania, reported a reduction in the number of women attending maternal health clinics, and an increase in delayed labour presentations to hospital and insufficient antenatal care (3).

A systematic review which included LMICs evaluated the likely impact of the COVID-19 pandemic on immunisation coverage and the factors contributing to service disruption. The review found a reduction in vaccination coverage, reduction in doses administered and an increase in polio cases in polio endemic countries (4)."

The authors are advocating for the inclusion of pregnant women in the vaccine trials and the need for more basic research including immunology, but fail to address the lack of basic epidemiological data to track progress and monitor what works and what does not in low- and middle-income countries. This could be done in the context of ongoing efforts such as

the Countdown and SDG monitoring processes.

We have added some information into the review article which discusses the roadmap for COVID-19 vaccines and the inclusion of pregnant women into vaccination programmes:

"Now that COVID-19 vaccines are available, the WHO SAGE committee has published a roadmap which outlines how to prioritise vaccination depending on vaccine availability and disease burden and risk. The roadmap acknowledges that pregnant women have been disadvantaged with regards to the development and use of vaccines in pandemics. Data needs to be generated for pregnant women and pregnant women should be included in roadmap stage 3 - when evidence should be available to determine whether the benefits of COVID-19 vaccination outweighs the risk of SARS-CoV2 infection and potential severe COVID-19 (5)."

The future directions clearly depend on a global concerted effort on collecting, synthesizing and analyzing basic epidemiological data in low- and middle-income countries and the authors should address how this could be implemented and by whom.

We have added some information into the review article which discusses collection of epidemiological data in LMICs:

"In terms of COVID-19 research in LMICs, it has been suggested that this is incorporated into public health and clinical activities to avoid these vital services being diverted, and also that this research should be driven by local investigators (6). The WHO has published a number of generic protocols for COVID-19 research and response, including surveillance, serology and case investigation (7). In 2020 the United Nations launched a global humanitarian response plan to fund the COVID-19 response in the poorest countries with both public and private sector support (8)."

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Competing Interests: No competing interests to disclose