BMJ Global Health

Adverse maternal, fetal, and newborn outcomes among pregnant women with SARS-CoV-2 infection: an individual participant data meta-analysis

Emily R Smith ,[1] Erin Oakley,[1] Gargi Wable Grandner,[1] Kacey Ferguson,[1] Fouzia Farooq,[1] Yalda Afshar,[2] Mia Ahlberg,[3] Homa Ahmadzia,[4] Victor Akelo,[5] Grace Aldrovandi,[6] Beth A Tippett Barr,[5] Elisa Bevilacqua,[7] Justin S Brandt,[8] Nathalie Broutet,[9] Irene Fernández Buhigas ,[10] Jorge Carrillo,[11] Rebecca Clifton,[12] Jeanne Conry,[13] Erich Cosmi,[14] Fatima Crispi,[15] Francesca Crovetto,[15] Camille Delgado-López ,[16] Hema Divakar,[17] Amanda J Driscoll,[18] Guillaume Favre,[19] Valerie J Flaherman,[20] Chris Gale ,[21] Maria M Gil,[10] Sami L Gottlieb,[9] Eduard Gratacós,[15] Olivia Hernandez,[22] Stephanie Jones,[23] Erkan Kalafat,[24] Sammy Khagayi ,[25] Marian Knight,[26] Karen Kotloff,[27] Antonio Lanzone,[7] Kirsty Le Doare,[28,29] Christoph Lees,[30] Ethan Litman,[4] Erica M Lokken,[31] Valentina Laurita Longo,[32] Shabir A Madhi,[23] Laura A Magee,[33] Raigam Jafet Martinez-Portilla ,[34] Elizabeth M McClure,[35] Tori D Metz,[36] Emily S Miller,[37] Deborah Money,[38] Sakita Moungmaithong,[39] Edward Mullins,[30] Jean B Nachega,[40] Marta C Nunes,[23] Dickens Onyango,[41] Alice Panchaud,[42] Liona C Poon,[39] Daniel Raiten,[43] Lesley Regan,[13] Gordon Rukundo,[28] Daljit Sahota,[39] Allie Sakowicz,[37] Jose Sanin-Blair,[44] Jonas Söderling,[3] Olof Stephansson,[3] Marleen Temmerman,[45] Anna Thorson,[9] Jorge E Tolosa,[46] Julia Townson,[47] Miguel Valencia-Prado,[48] Silvia Visentin,[14] Peter von Dadelszen ,[49] Kristina Adams Waldorf,[31] Clare Whitehead,[50] Murat Yassa,[51] Jim M Tielsch,[1] Perinatal COVID PMA Study Collaborators

To cite: Smith ER, Oakley E, Grandner GW, *et al*. Adverse maternal, fetal, and newborn outcomes among pregnant women with SARS-CoV-2 infection: an individual participant data meta-analysis. *BMJ Global Health* 2023;**8**:e009495. doi:10.1136/bmjgh-2022-009495

Handling editor Seye Abimbola

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/bmjgh-2022-009495).

Received 2 May 2022
Accepted 24 August 2022

For numbered affiliations see end of article.

Correspondence to
Dr Emily R Smith;
emilysmith@gwu.edu

ABSTRACT

Introduction Despite a growing body of research on the risks of SARS-CoV-2 infection during pregnancy, there is continued controversy given heterogeneity in the quality and design of published studies.

Methods We screened ongoing studies in our sequential, prospective meta-analysis. We pooled individual participant data to estimate the absolute and relative risk (RR) of adverse outcomes among pregnant women with SARS-CoV-2 infection, compared with confirmed negative pregnancies. We evaluated the risk of bias using a modified Newcastle-Ottawa Scale.

Results We screened 137 studies and included 12 studies in 12 countries involving 13 136 pregnant women. Pregnant women with SARS-CoV-2 infection—as compared with uninfected pregnant women—were at significantly increased risk of maternal mortality (10 studies; n=1490; RR 7.68, 95% CI 1.70 to 34.61); admission to intensive care unit (8 studies; n=6660; RR 3.81, 95% CI 2.03 to 7.17); receiving mechanical ventilation (7 studies; n=4887; RR 15.23, 95% CI 4.32 to 53.71); receiving any critical care (7 studies; n=4735; RR 5.48, 95% CI 2.57 to 11.72); and being diagnosed with pneumonia (6 studies; n=4573; RR 23.46, 95% CI 3.03 to 181.39) and thromboembolic disease (8 studies; n=5146; RR 5.50, 95% CI 1.12 to 27.12).
Neonates born to women with SARS-CoV-2 infection were more likely to be admitted to a neonatal care unit after birth (7 studies; n=7637; RR 1.86, 95% CI 1.12 to 3.08); be born preterm (7 studies; n=6233; RR 1.71, 95% CI 1.28 to 2.29) or moderately preterm (7 studies; n=6071; RR 2.92, 95% CI 1.88 to 4.54); and to be born low birth weight (12 studies; n=11 930; RR 1.19, 95% CI 1.02 to 1.40). Infection was not linked to stillbirth. Studies were generally at low or moderate risk of bias.

Conclusions This analysis indicates that SARS-CoV-2 infection at any time during pregnancy increases the risk of maternal death, severe maternal morbidities and neonatal morbidity, but not stillbirth or intrauterine growth restriction. As more data become available, we will update these findings per the published protocol.

INTRODUCTION

Since early in the pandemic, a key question has been how SARS-CoV-2 infection affects pregnant women and pregnant people, given

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Despite the ballooning literature regarding SARS-CoV-2 infection during pregnancy, it is difficult to synthesise the information and evaluate the overall quality of evidence given the heterogeneity in study design, selection of comparison groups, methods for assessing infection, population-specific baseline risks and definitions of key outcomes.

⇒ Prior reviews based on published data have included limited data from low-income countries.

WHAT THIS STUDY ADDS

⇒ We established plans for a sequential, prospective meta-analysis in April 2020 with a goal of better understanding the excess risks—or lack thereof—of COVID-19 during pregnancy.

⇒ This individual patient data meta-analysis of unpublished and published data from a dozen studies includes more than 13 000 pregnant women and shows that COVID-19 during pregnancy increases the risk of maternal mortality, intensive care unit admission, receiving mechanical ventilation, receiving any critical care or being diagnosed with pneumonia or thromboembolic disease.

⇒ Infants born to infected pregnant women were more likely to be admitted to the neonatal intensive care unit and to be born premature.

⇒ In contrast to other reviews, we did not find any link between SARS-CoV-2 infection during pregnancy and an increased risk of stillbirth at or beyond 28 weeks' gestation, nor any link with intrauterine growth restriction.

⇒ Further, we include the first large set of pregnancy cohort data from sub-Saharan Africa.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Global guidance has been equivocal on the potential risks of infection and benefits and safety of vaccination, and more than 80 countries do not currently recommend that all pregnant and lactating women should be vaccinated.

⇒ Given the clear and consistent findings regarding the risk of COVID-19 infection during pregnancy, global effort to improve access to safe preventives and therapeutics is an urgent priority.

the physiological, immunomodulatory and mechanical changes that occur during pregnancy. A living systematic review published in February 2021 identified 47 studies comparing pregnant women with COVID-19 versus a contemporaneous or historical group of pregnant women without the disease.[1] The meta-analysis suggested COVID-19 during pregnancy is linked to increased risk of mortality, intensive care unit (ICU) admission, preterm birth, stillbirth and neonatal care unit admission.[1] However, for most maternal, fetal and newborn outcomes examined, there were fewer than 10 studies available to synthesise.

More recent electronic healthcare record studies from the USA and a multicountry cohort study found that pregnant women with SARS-CoV-2 infection had higher risks than uninfected pregnant women for pre-eclampsia, eclampsia, caesarean section, ICU admission, stillbirth, preterm birth and neonatal intensive care unit (NICU) admission.[2–4] A recent population cohort study in England has also linked infection at the time of birth to prolonged hospital stay, often requiring critical care for both mothers and neonates.[5] Evidence regarding other outcomes such as neonatal mortality, as well as linkages between maternal and child health outcomes, and any potential differences between symptomatic and asymptomatic infections, is limited.[6 7]

Despite the ballooning literature regarding SARS-CoV-2 infection during pregnancy, it is difficult to synthesise the information and evaluate the overall quality of evidence given the heterogeneity in study design, selection of comparison groups, methods for assessing infection, population-specific baseline risks and definitions of key maternal and child health outcomes.[8] Studies using a universal screening approach to identify SARS-CoV-2 infections are likely to have a higher proportion of asymptomatic or mild cases, and a Swedish study demonstrated that estimates based on non-universal screening data are indeed inflated as compared with universal screening estimates.[6] Using a 'not positive' comparison group results in exposure misclassification and related bias. Globally, key health outcomes such as stillbirth have various definitions, and the published literature does not report on a comprehensive set of maternal and newborn outcomes.

A unified, collaborative analytical plan is required to overcome many of these issues. Accordingly, we established plans for a sequential, prospective meta-analysis (sPMA) in April 2020 with a goal of better understanding the excess risks—or lack thereof—of COVID-19 during pregnancy.[8] These basic epidemiological data are necessary for conducting appropriate risk-benefit analyses when new preventives and therapeutics are developed and ultimately for guiding global prevention and treatment plans. Our consortium obtained high-quality data from studies being conducted in a variety of countries and analysed them based on a harmonised data collection and analytical strategy. Here, we report the first set of results in this individual participant data (IPD) meta-analysis. We assessed the risk of maternal, fetal and neonatal morbidity and mortality among pregnant women with confirmed or probable SARS-CoV-2 infection during pregnancy as compared with pregnant women who were confirmed SARS-CoV-2 negative.

METHODS

This analysis is part of a larger sPMA study that aims to answer epidemiological questions about COVID-19 and its association with maternal and newborn health by pooling data from independent studies using harmonised data definitions and an IPD meta-analytical framework to minimise data variability. The protocol for the sPMA was registered with PROSPERO (ID: CRD42020188955) on 28 May 2020; the full protocol has been published elsewhere.[8]

Eligibility criteria

Eligible study designs included registries, single or multisite cohorts, or case–control studies enrolling

pregnant women with suspected or confirmed COVID-19. To be eligible, studies must have had a defined catchment area, included at least 25 pregnant women with confirmed or suspected SARS-COV-2 infection and had a contemporaneously recruited comparison group of pregnant women who had not been diagnosed with COVID-19.

Given the heterogeneity of study designs, we also applied participant-level inclusion and exclusion criteria. The SARS-CoV-2 infected group included pregnant women with a diagnosis during pregnancy or within 7 days of pregnancy outcome based on: (a) PCR testing or antigen testing; (b) WHO suspected case definition[9]; or (c) serology testing where exposure was known to occur during pregnancy based on the dates of the pregnancy and the COVID-19 pandemic. We restricted the analyses to a comparison group of pregnant women who were confirmed SARS-CoV-2 negative based on one or more laboratory tests for SARS-CoV-2 infection during pregnancy (including PCR, antigen or serology testing).

Identifying studies

For this comparative analysis, we identified studies using two approaches. Studies were recruited into the sPMA via professional research networks and support from key stakeholder networks a priori,[8] and those who had agreed to participate by 1 August 2020 were screened for eligibility to participate in this analysis. We also identified studies by reviewing the most recently published (February 2021) PregCOV-19 Living Systematic Review[1] to identify studies that might be eligible for postpublication inclusion into the analysis; we contacted all corresponding authors of apparently eligible studies. Studies were first screened for eligibility based on published protocols or manuscripts; we also confirmed eligibility through discussions with study investigators.

Data collection

Data contributors shared deidentified IPD with the sPMA coordinating team based on a core variable list.[8] The coordinating team ran a standardised set of data quality codes and resolved any queries through discussion with the study investigators. Subsequently, we created new, harmonised outcome variables and analysed the data to ensure consistent methods were used to generate site-specific estimates. Study investigators reviewed these estimates. Where data contributors were unable to share IPD, the coordinating team worked with the contributing statistical team to use the same set of standardised outcome definitions and/or codes for data quality assessment, outcome construction and generating site-specific estimates; these teams shared analysis log files and outputs to confirm the same analysis process was followed. We checked each data set for potentially overlapping participants based on the geographic area or facility and enrolment dates; we worked with study investigators to deduplicate any potential overlapping observations. For each previously published study, online supplemental table S1 documents reasons for any differences between the data included in this study as compared with prior publications. This secondary use of deidentified data was considered non-human subjects research and thus exempt from institutional review board approval at The George Washington University.

Data items

The core variables for the larger sPMA study were established a priori along with the protocol.[8] For this analysis, the coordinating team developed an analysis plan, which was reviewed and approved by the steering committee. Participating study sites contributed data based on this shortlist of high-priority variables. Based on IPD from each study, we derived each study outcome described below.

IPD integrity (data quality assessment)

Data quality was assessed for each study by examining the distribution and frequency of each variable. We identified outliers and inconsistent values for key data points such as gestational age at birth, maternal age and neonatal birth weight and checked that the timing of outcomes was consistent with our definitions (eg, neonatal death within 28 days). For all published data, we also compared the distribution and frequency of outcomes to published manuscripts and resolved discrepancies through discussion with study investigators.

Risk of bias

We assessed the quality of individual studies, by outcome, based on criteria for participant selection and outcome ascertainment using an adapted Newcastle-Ottawa Scale.[10] A description of study design elements classified as lower or higher risk of bias is outlined in online supplemental table S2.

Outcomes and effect measures

We considered four categories of outcomes including hospital and critical care indicators, maternal mortality and morbidity, fetal and neonatal mortality and morbidities and adverse birth outcomes. Maternal, fetal and neonatal death and adverse birth outcomes were defined using WHO case definitions. Hospital and critical care indicators and maternal morbidities were defined by each contributing study. *Critical care indicators* included outcomes related to COVID-19 severity: admission to the ICU, receipt of critical care (defined as admitted to ICU or received ventilation or any site-defined indicator), any ventilation use and clinician-diagnosed pneumonia. *Maternal mortality and morbidity outcomes* included maternal death (due to any cause during pregnancy or 42 days post partum),[11] haemorrhage around the time of labour, placental abruption, hypertensive disorders of pregnancy (diagnosed at or after testing positive for COVID-19), hypertensive disorders of pregnancy (diagnosed at any time), pre-eclampsia, eclampsia, pre-eclampsia or eclampsia (a combined indicator), thromboembolic disease, preterm labour, any caesarean delivery

and intrapartum or non-scheduled caesarean delivery. *Fetal and neonatal mortality and morbidity outcomes* included stillbirth (fetal death >28 weeks),[12] perinatal death (stillbirth >28 weeks or neonatal death in the first 7 days of life),[13] early neonatal death (death in the first 7 days of life),[14] neonatal death (death in the first 28 days of life) and admission to the NICU; in one study (Crovetto, 2020), we collected a combined outcome of NICU admission and/or admission to a high-dependency care unit. *Adverse birth outcomes* included combined extremely, very and moderate preterm birth (<34 weeks' gestational age at birth), preterm birth (<37 weeks' gestational age at birth), very low birth weight (<1500 g), low birth weight (<2500 g) and small for gestational age (<3rd or <10th percentile of sex-specific size for gestational age based on the INTERGROWTH-21st reference values[15]; for studies without data on infant sex, we used the midpoint of sex-specific percentiles).

Statistical analysis (synthesis methods)

We applied a two-stage IPD meta-analytical framework (accounting for site-specific clustering) to generate pooled absolute risks and relative risks (RR), along with 95% CIs, for each outcome. First, we estimated site-specific prevalence estimates for the infected and uninfected groups, as well as unadjusted and adjusted RR with 95% CIs. We originally produced unadjusted and adjusted RRs for each site contributing data. We adjusted for maternal age and, where available, pre-pregnancy obesity (pre-pregnancy body mass index (BMI) >30 kg/m^2). Because we found very little difference in adjusted and unadjusted RRs within each site, we proceeded with the meta-analysis using unadjusted RRs to allow inclusion of studies with zero outcome event in either the exposed or unexposed group. We pooled the absolute risks of each outcome using the Freeman-Tukey double arcsine transformation with DerSimonian and Laird random-effects model; we calculated exact 95% CIs.[16 17] RRs were pooled using DerSimonian and Laird random-effects meta-analysis.[18] Heterogeneity was assessed using the I^2 statistic.

In cases of zero event for an outcome in the exposed or unexposed group, we applied a continuity correction of 0.5. Outcomes with zero event in both arms were omitted when estimating pooled absolute risk and pooled RRs because the infected and uninfected groups varied in size. All participants in a study were excluded from an analysis if more than 25% of participants were missing outcome information.

Not all studies collected information about the date of COVID-19 onset (symptoms or test dates) and the date of each outcome; however, we performed a sensitivity analysis restricting the analysis to those studies with known date of onset as well as dates for three outcomes: preterm labour, preterm birth and moderate preterm birth. For preterm labour and preterm birth outcomes, we restricted the sensitivity analyses to women with gestational age of COVID-19 onset at less than 37 weeks and for moderate preterm birth by restricting the analyses to women with gestational age of onset at less than 34 weeks. For the outcome hypertensive disorders of pregnancy, we conducted a sensitivity analysis looking at diagnoses that occurred at or after COVID-19 diagnosis.

To address concerns about the varying degree to which studies employed universal screening strategies and thus identified asymptomatic pregnant women, we conducted a secondary analysis restricting exclusively to symptomatic cases of COVID-19. Further, we conducted a sensitivity analysis comparing our results to those studies included in the PregCOV-19 Living Systematic Review that were eligible for the PMA but not successfully recruited to examine any major differences in results across seven common outcomes. Finally, we conducted a sensitivity analysis using different definitions of stillbirth to examine differences based on gestational age cut-offs. All analyses were performed using Stata (V.16), SAS (V.9.4) and R (V.4.2.0).

Patient and public involvement

Patients or the public were not involved in the design, conduct, reporting or dissemination plans of our meta-analysis. However, many contributing studies did involve patients and community stakeholders in the design and dissemination of their study results.

RESULTS

Study selection

Among the 26 studies that had prospectively joined the PMA study team, 16 had a study design that allowed for the comparison of SARS-CoV-2 infected and uninfected pregnancies. Six of these studies had completed data collection or were willing to contribute ongoing cohort data to the current analysis (Akelo and Tippett Barr 2021, Bevilacqua and Laurita Longo 2020, Le Doare 2021, Nachega 2021, Nunes 2021, Poon 2021). We additionally contacted the corresponding authors of apparently eligible studies included in the Allotey *et al*'s living systematic review and identified five additional studies that were willing to participate in this round of the sPMA[19–23] (figure 1). One of these studies included two different testing strategies for two cohorts of pregnant women (Crovetto, 2020); accordingly, we consider this publication and related data collection as two separate studies.

We identified and deduplicated three participants who were included in both the current AFREhealth (Nachega) and PREPARE Uganda (Le Doare) data sets. No other overlapping participants were identified.

Study characteristics

In total, we analysed IPD from *12 studies conducted in 12 countries* (Ghana, China-Hong Kong, Italy, Kenya, Nigeria, South Africa, Spain, Sweden, the Democratic Republic of Congo, Turkey, Uganda and the USA) (table 1). Across studies, the recruitment period spanned from February 2020 to July 2021 (online supplemental figure S1).[24 25]

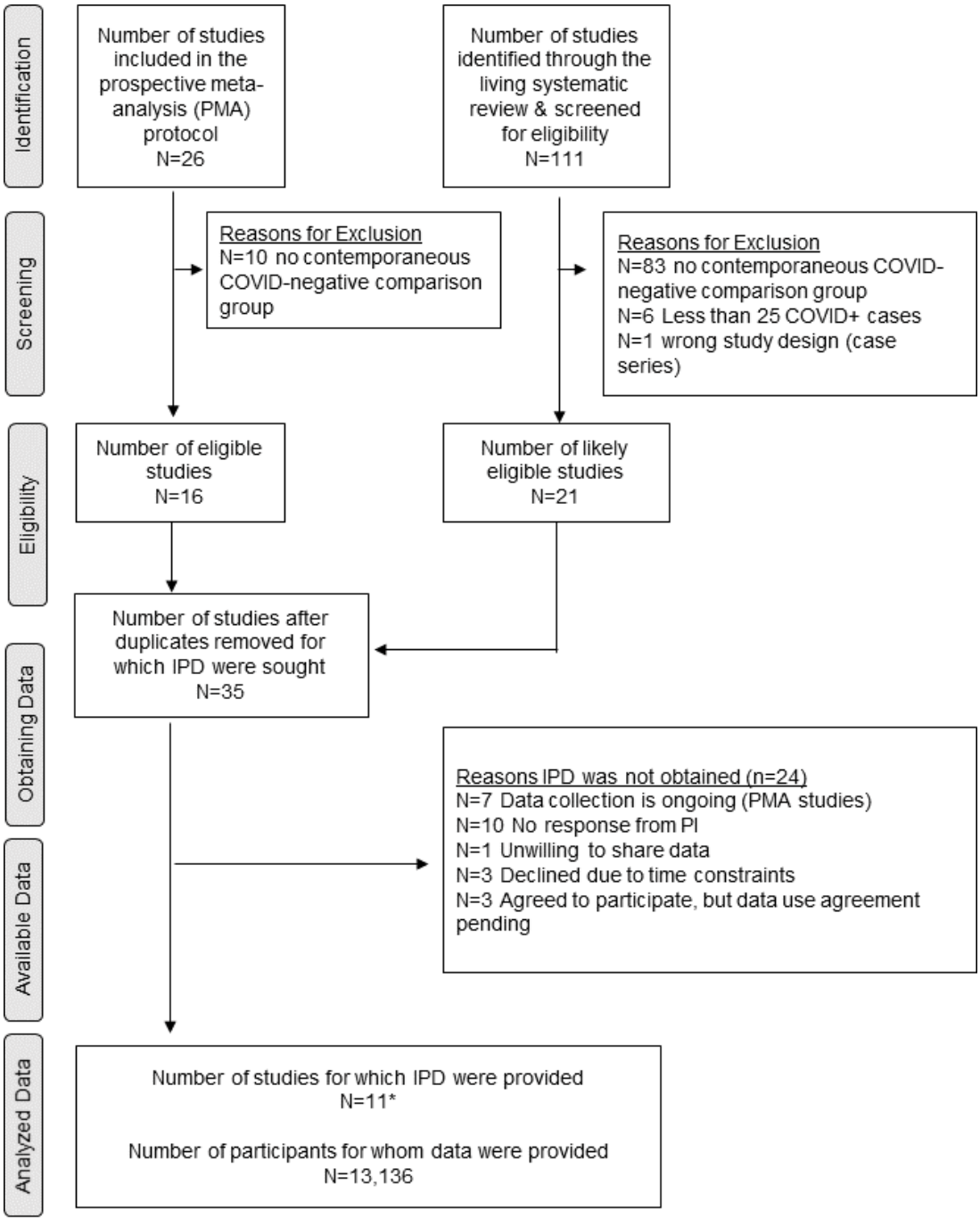


Figure 1 PRISMA-IPD flow diagram documenting study identification, screening and analysis. IPD, individual participant data; PI, principal investigator; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Across all studies, SARS-CoV-2 *infection was confirmed by PCR test*, except in the following studies: Crovetto 2020 Cohort I study administered antibody tests at recruitment in early pregnancy and PCR tests at delivery; Crovetto 2020 Cohort II study used antibody tests at delivery for all participants (and 85% also received a PCR test); Le Doare (2021) used the WHO case definition for probable cases of COVID-19 when testing was unavailable in addition to PCR and antibody testing at recruitment; and Ahlberg *et al* [19] where three cases were identified on admission for delivery based on positive antibody test results during antenatal care (ANC). *Selection of the SARS-CoV-2-negative group* varied slightly between studies; seven studies defined SARS-CoV-2-negative pregnancy based on a single negative PCR test result (Nachega, Nunes, Sakowicz, Ahlberg, Bevilacqua and Laurita Longo, Kalafat, Brandt), one study based the selection on repeated negative PCR tests throughout pregnancy (Akelo and Tippett Barr), two studies used a negative antibody test result (Crovetto, Poon) and one population-based pregnancy surveillance

Table 1 Study characteristics

Data source	Study	Location	Dates of data collection	Recruitment strategy*	COVID-19 case definition	COVID-negative comparison group
Prospective pregnancy cohort studies	Akelo and Tippett Barr (2021)	Kenya	July 2020 to May 2021, with follow-up through delivery	a b c d e	Positive PCR test	Negative PCR test
	Le Doare (2021)	Uganda	September 2020 to July 2021, with follow-up through delivery	a b c	Positive PCR or diagnosed probable COVID-19	Negative PCR or antibody test (recruitment)
	Crovetto (2020), Cohort I	Spain	March to May 2020, with follow-up through delivery	a b	Positive PCR or antibody test†	Negative antibody test (ANC) and negative PCR test (delivery)
Other cohort studies	Poon (2021)	China-Hong Kong	March 2020 to January 2021	a b c d e	Positive PCR test or antibody test	Negative antibody test (ANC and delivery)
	Crovetto (2020), Cohort II	Spain	March to May 2020	b	Positive PCR or antibody test‡	Negative antibody test and PCR test (delivery)
	Bevilacqua and Laurita Longo (2020)	Italy	February 2020 to March 2021	b c d e	Positive PCR test	Negative PCR test
	Nachega (2021)	Africa§ (6 countries)	March to October 2020	c e	Positive PCR test	Negative PCR (hospital controls)
	Nunes (2021)	South Africa	April to September 2020	a¶ c d e	Positive PCR test	Negative PCR test
	Sakowicz (2021)	Chicago, USA	March 2020 to February 2021	b d e	Positive PCR test	Negative PCR test (at delivery)
	Ahlberg *et al*[19]	Sweden	March to July 2020	b d	Positive PCR test or antibody test	Negative PCR test (at delivery)
	Kalafat *et al*[22]	Turkey	May to June 2020	b d	Positive PCR test	Negative PCR test
	Brandt (2020)	New Brunswick, USA	March to June 2020	b d	Positive PCR test	Negative PCR test

*Recruitment strategies categorised as: (a) universal screening at antenatal care, (b) universal screening at delivery, (c) hospitalised for COVID-19, (d) other COVID-19 testing for clinical concern, (e) tested based on admission for other medical reasons.
†Antibody tests were administered to women recruited at first trimester or early second trimester ANC. Participants were also administered follow-up PCR tests at labour and delivery.
‡Antibody tests were administered to all participating women at labour and delivery; most participants (85%) also received a PCR test at labour and delivery.
§Democratic Republic of Congo, Ghana, Kenya, Nigeria, South Africa, Uganda.
¶10 asymptomatic patients were tested a day during the recruitment period.
ANC, antenatal care.

study ascertained SARS-CoV-2 infection using PCR and/or antibody testing at recruitment, followed by testing or assessment for probable diagnosis based on clinical concern (Le Doare). The timing of testing varied by study, but most studies included infections in all three trimesters (table 2).

Participant characteristics

The pooled data included 1942 pregnant women with confirmed or probable SARS-CoV-2 infection during pregnancy or within 7 days of pregnancy outcome and 11 194 pregnant women who were either PCR negative at delivery (seven studies, 7274 pregnancies); antibody negative at delivery (one study, 1128 pregnancies), both antibody negative and PCR negative at delivery (one study, 127 pregnancies); antibody negative at an early ANC visit with PCR testing at delivery (one study, 748 pregnancies); negative throughout pregnancy based on repeated PCR or antibody testing offered at ANC visits and delivery (one study, 1454 pregnancies); or who were antibody and/or PCR negative at recruitment in early pregnancy with no subsequent positive test (completed for clinical concern) or clinical diagnosis of probable COVID-19 (one study, 463 pregnancies) (table 2). The total number of pregnancies included in each study ranged from 152 in China-Hong Kong (Poon, 2021) to 2682 in Sweden. [19] The mean age across all studies was 31 years, with the youngest study population in Kenya (Akelo and Tippett Barr, 2021) and the oldest study population in Italy (Bevilacqua and Laurita Longo, 2020). The prevalence of obesity ranged from 10% in Spain (Crovetto, 2020, Cohort I) to 15.6% in Sweden [19] although pre-pregnancy BMI was generally not available across studies. There were relatively few instances of SARS-CoV-2 infection identified during the first trimester; the majority of cases were identified during the third trimester (table 2). The mean age was similar between SARS-CoV-2-infected women and those in the negative comparison group (online supplemental table S3). Only four studies collected data on pre-pregnancy BMI; SARS-CoV-2-infected women were more likely to be obese (online supplemental table S3).

Critical care indicators

Compared with pregnant women without infection, women with SARS-CoV-2 infection at any time during pregnancy had an increased risk of all outcomes related to critical care (table 3). The pooled absolute risk of ICU admission among pregnant women with SARS-COV-2 infection was 3% (95% CI 0% to 9%). Pregnant women with SARS-COV-2 infection were at a significantly increased risk of *ICU admission* (8 studies; 6660 pregnant women; RR 3.81, 95% CI 2.03 to 7.17) and *ventilation* (7 studies; 4887 pregnant women; RR 15.23, 95% CI 4.32 to 53.71). Across seven studies, about 4% of pregnant women with COVID-19 received any critical care (95% CI 0% to 13%) and they were more than five times more likely to receive critical care than their COVID-19-negative peers (7 studies; 4735 pregnant women; RR 5.48, 95% CI 2.57 to 11.72).

Maternal mortality and morbidity

While 10 studies collected data regarding maternal deaths, only three studies (Nachega 2021, Nunes 2021 and Le Doare 2021) recorded deaths during the study period and thus contributed information to the pooled estimate. All the remaining studies recorded zero death in both groups. Based on these three studies, women with SARS-CoV-2 infection had an increased risk of *maternal death* (10 studies; 1490 pregnant women; RR 7.68, 95% CI 1.70 to 34.61) as compared with uninfected pregnant women.

Regarding maternal morbidity, we found a greater risk for *pre-eclampsia* (9 studies; 8777 pregnant women; RR 1.42, 95% CI 1.13 to 1.78), *pre-eclampsia or eclampsia* (10 studies; 11 472 women; RR 1.46, 95% CI 1.17 to 1.81) and *thromboembolic disease* (8 studies; 5146 pregnant women; RR 5.50, 95% CI 1.12 to 27.12) among pregnant women with SARS-COV-2 infection compared with those without. We also found an increased risk for *hypertensive disorders of pregnancy* (10 studies; 11 472 pregnant women; RR 1.25, 95% CI 1.04 to 1.50) among pregnant women with SARS-CoV-2. Although most studies did not collect data on the timing of diagnosis of hypertensive disorders of pregnancy, we conducted this analysis again restricting to only those cases of hypertensive disorders of pregnancy diagnosed at or after a positive SARS-CoV-2 test; we found a similar increased risk but a wider CI (three studies representing 3651 women; RR 1.33, 95% CI 0.89 to 1.98). The risk for caesarean delivery was slightly higher among pregnant women with SARS-CoV-2 (10 studies; 10 571 pregnant women; RR 1.10, 95% CI 1.01 to 1.20). While there was no significant difference in the risk of preterm labour across both groups overall, we find an increased risk of preterm labour (<37 weeks' gestational age) for pregnant women with SARS-CoV-2 onset before 37 weeks' gestational age as compared with pregnant women without SARS-CoV-2 for those studies where data on gestational age at onset and preterm labour as a maternal morbidity are available (4 studies; 3769 pregnant women; RR 2.47, 95% CI 1.28 to 4.79). There was no difference between the two groups on the risk of other maternal morbidity outcomes (haemorrhage, placental abruption, eclampsia or intrapartum caesarean delivery).

Fetal and neonatal mortality and morbidity

Among the five fetal and neonatal outcomes examined, we found an elevated risk only for NICU admission after birth among infants born to women with SARS-CoV-2 infection (7 studies; 7637 neonates; RR 1.86, 95% CI 1.12 to 3.08).

Adverse birth outcomes

Infants born to women with confirmed or probable SARS-CoV-2 infection during pregnancy were more likely to be born *preterm* (12 studies; 11 884 live births; RR 1.27,

Table 2 Description of participants contributing to the individual patient data meta-analysis

Study author (year), country	Number of COVID-19 cases/ total pregnancies	Live births	Among all pregnancies		Among COVID-19 cases				
			Mean age (SD)	% obese (BMI ≥30)	Asymptomatic (%)	Onset in trimester 1 (%)	Onset in trimester 2 (%)	Onset in trimester 3 (%)	Unknown GA at onset (%)
Akelo and Tippett Barr (2021), Kenya	106/1560	805	25.62 (5.35)*	–	37.7*	1	14	51	34
Le Doare (2021), Uganda	69/532	516	25.93 (5.72)	–	4.0	1	42	54	3
Crovetto (2020), Spain, Cohort I	173/921	761	33.17 (5.3)	10.0	80.3	–	–	–	100†
Poon (2021), China-Hong Kong	25/152	155	33.00 (4.53)	–	24.0	4	28	64	4
Crovetto (2020), Spain, Cohort II	176/1304	1332	31.90 (5.78)	12.00	59.1	0†	0†	14†	86†
Bevilacqua and Laurita Longo (2020), Italy	109/2465	2413	33.74 (5.4)	15.0‡	51.4	7	7	85	0
Nachega (2021), Multi-country Africa	349/442	183	30.54 (5.72)	–	0.0	6§	18§	64§	12§
Nunes (2021), South Africa	139/781	756	30.90 (6.74)	–	12.9¶	2	22	71	5
Sakowicz (2021), USA	503/1773	1788	32.22 (5.10)	–	31.6**	5	21	73	1
Ahlberg *et al* (2020),[19] Sweden	156/2682	2714	32.2 (5.07)	15.6††	68.6	0	3	97	0
Kalafat *et al* (2020),[22] Turkey	77/362	346	27.15 (5.63)	–	24.7	–	–	–	100
Brandt (2020), USA	60/162	161	30.90 (6.34)	–	55.0	0	5	95	0

*This study includes 12 participants with unknown age (all COVID-negative comparisons). Two COVID-19 cases had unknown symptom status.
†Antibody testing at ANC (Cohort I) and at labour and delivery (Cohort II) was the primary method of diagnosis, thus gestational age at COVID-19 onset is unknown for almost all observations.
‡167 participants had missing BMI data (7%).
§Gestational age at COVID-19 onset was not recorded. We use trimester of hospital admission as a proxy. n=41 participants were missing trimester of hospital admission (12%).
¶Approximately 1.4% of the COVID-19 case sample in this study (Nunes, 2021, South Africa) have unknown symptom status (n=2).
**Approximately 2% of the COVID-19 case sample in this study (Sakowicz, 2021, USA) have unknown symptom status (n=8).
††100 participants had missing BMI data (4%).
ANC, antenatal care; BMI, body mass index; GA, gestational age.

Table 3 Absolute and relative risk of adverse health outcomes comparing pregnant women with and without SARS-CoV-2 infection

Outcomes	Studies (n)	Included studies*†	Confirmed COVID-19 case		COVID-19-negative comparison		Relative risk (95% CI)¶	I^2% (P value)
			Events/total	Pooled risk (95% CI)§	Events/total	Pooled risk (95% CI)§		
Critical care indicators								
ICU admission	8	c d e1* e2 f h j k	78/1299	0.03 (0.00 to 0.09)	17/5361	0.00 (0.00 to 0.01)	**3.81 (2.03 to 7.17)**	0 (0.67)
Ventilation	7	c d e1* e2 f h j	21/796	0.02 (0.01 to 0.04)	0/4091	0.00 (0.00 to 0.00)	**15.23 (4.32 to 53.71)**	0 (0.81)
Any critical care	7	c d e1* e2 f h j*	73/771	0.04 (0.00 to 0.13)	10/3964	0.00 (0.00 to 0.01)	**5.48 (2.57 to 11.72)**	0 (0.73)
Pneumonia	6	c e1* e2 f h j*	124/711	0.18 (0.05 to 0.37)	13/3862	0.01 (0.00 to 0.02)	**23.46 (3.03 to 181.39)**	91 (0)
Maternal mortality and morbidity								
Maternal death	10	a* c* d* e1* e2* f* g h i j*	38/368	0.07 (0.00 to 0.22)	3/1122	0.00 (0.00 to 0.02)	**7.68 (1.70 to 34.61)**	30.49 (0.24)
Haemorrhage	6	a c g h i k	109/1136	0.08 (0.04 to 0.14)	795/7273	0.07 (0.03 to 0.13)	1.22 (0.76 to 1.98)	68.35 (0.01)
Placental abruption	5	a f h j k	15/928	0.01 (0.00 to 0.03)	56/4258	0.01 (0.00 to 0.02)	1.55 (0.75 to 3.21)	0 (0.55)
Hypertensive disorders of pregnancy (diagnosed at or after COVID-19)	3	a b j	24/255	0.08 (0.01 to 0.20)	254/3396	0.06 (0.01 to 0.14)	1.33 (0.89 to 1.98)	0 (0.8)
Hypertensive disorders of pregnancy (diagnosed at any time)	10	a b c e1 e2 g h i j k	178/1570	0.09 (0.05 to 0.14)	497/9902	0.06 (0.04 to 0.09)	**1.25 (1.04 to 1.50)**	0 (0.87)
Pre-eclampsia	9	a b d e1 e2 f i j k	100/1360	0.06 (0.04 to 0.08)	324/7417	0.04 (0.02 to 0.06)	**1.42 (1.13 to 1.78)**	0 (0.62)
Eclampsia	7	a* b* e1* e2* i j* k*	0/133	–	2/613	0.00 (0.00 to 0.01)	0.92 (0.04 to 19.04)	0 (0)
Pre-eclampsia or eclampsia	10	a b c e1 e2 g h i j k	138/1570	0.07 (0.04 to 0.11)	399/9902	0.04 (0.02 to 0.05)	**1.46 (1.17 to 1.81)**	0 (0.57)
Thromboembolic disease	8	a c d* e1* e2* g* i* j*	2/265	0.01 (0.00 to 0.02)	7/4881	0.00 (0.00 to 0.00)	**5.50 (1.12 to 27.12)**	0 (0.46)
Preterm labour	6	c e1* e2 g i j	33/508	0.06 (0.03 to 0.10)	190/4674	0.04 (0.02 to 0.05)	1.59 (0.87 to 2.89)	43.18 (0.13)
Preterm labour—COVID onset <37 weeks	4	c g i j	17/223	0.07 (0.03 to 0.12)	114/3546	0.03 (0.02 to 0.04)	**2.47 (1.28 to 4.79)**	17.31 (0.3)
C-section	10	a c d e1 e2 g h i j k	499/1505	0.34 (0.28 to 0.40)	2609/9066	0.30 (0.25 to 0.36)	**1.10 (1.01 to 1.20)**	0 (0.88)
Intrapartum C-section	8	a c e1* e2 g h i j	166/792	0.22 (0.14 to 0.30)	1053/7095	0.17 (0.12 to 0.23)	1.14 (0.97 to 1.34)	0 (0.66)
Fetal and neonatal mortality and morbidity								
Stillbirth**	12	a b c d* e1 e2 f g h i j* k	14/1602	0.01 (0.00 to 0.02)	64/10 060	0.01 (0.00 to 0.01)	1.08 (0.53 to 2.16)	0 (0.97)
Perinatal death††	9	a c d e1 e2 f g i j*	7/931	0.00 (0.00 to 0.01)	48/8078	0.01 (0.00 to 0.01)	1.23 (0.58 to 2.61)	0 (0.93)
Early neonatal death††	9	a c d e1 e2 f g i j*	1/928	0.00 (0.00 to 0.00)	23/8071	0.00 (0.00 to 0.00)	1.37 (0.47 to 4.01)	0 (0.85)
Neonatal death††	10	a c d e1 e2 f g h i j*	4/1064	0.00 (0.00 to 0.01)	30/8118	0.00 (0.00 to 0.00)	1.71 (0.71 to 4.12)	0 (0.8)
NICU admission at birth‡‡	7	a c d e2 f g j	110/661	0.21 (0.06 to 0.41)	472/6976	0.07 (0.05 to 0.08)	**1.86 (1.12 to 3.08)**	73.78 (0)
Adverse birth outcomes								
Very low birth weight (<1500 g)	12	a b c d e1 e2 f g h i j* k	30/1646	0.01 (0.01 to 0.03)	169/10 129	0.01 (0.01 to 0.02)	1.12 (0.74 to 1.71)	0 (0.99)
Low birth weight (<2500 g)	12	a b c d e1 e2 f g h i j k	198/1670	0.12 (0.08 to 0.16)	926/10 260	0.09 (0.07 to 0.11)	**1.19 (1.02 to 1.40)**	0 (0.6)
Small for gestational age (3rd centile)	12	a b c d e1 e2 f g h i j k	48/1670	0.03 (0.01 to 0.05)	293/10 260	0.03 (0.02 to 0.05)	1.05 (0.77 to 1.43)	0 (0.67)

Continued

Table 3 Continued

Outcomes	Studies (n)	Included studies*†	Confirmed COVID-19 case		COVID-19-negative comparison		Relative risk (95% CI)¶	I^2% (P value)
			Events/total	Pooled risk (95% CI)§	Events/total	Pooled risk (95% CI)§		
Small for gestational age (10th centile)	12	a b c d e1 e2 f g h i j k	136/1670	0.08 (0.05 to 0.12)	885/10 260	0.09 (0.07 to 0.12)	0.96 (0.80 to 1.15)	0 (0.56)
Moderate preterm birth (<34 weeks)	12	a b c d e1 e2 f g h i j k	80/1666	0.05 (0.03 to 0.07)	354/10 218	0.03 (0.02 to 0.04)	**1.37 (1.05 to 1.79)**	0 (0.84)
Moderate preterm birth (<34 weeks)—COVID onset <34 weeks‡	7	b c d g i j k	48/448	0.12 (0.04 to 0.23)	241/5623	0.04 (0.02 to 0.06)	**2.92 (1.88 to 4.54)**	34.74 (0.16)
Preterm birth (<37 weeks)	12	a b c d e1 e2 f g h i j k	234/1666	0.14 (0.10 to 0.19)	1054/10 218	0.10 (0.08 to 0.14)	**1.27 (1.07 to 1.49)**	11.96 (0.33)
Preterm birth (<37 weeks)—COVID onset <37 weeks‡	7	b c d g i j k	129/610	0.24 (0.15 to 0.35)	742/5623	0.12 (0.08 to 0.17)	**1.71 (1.28 to 2.29)**	50.31 (0.06)

*Included studies for each estimate are categorised as follows: (a) Ahlberg *et al*, Sweden[19]; (b) Akelo and Tippett Barr (2021), Kenya; (c) Bevilacqua and Laurita Longo (2020), Italy; (d) Brandt (2020), New Brunswick, USA; (e1) Crovetto (2020), Spain, Cohort I; (e2) Crovetto (2020), Spain, Cohort II; (f) Kalafat *et al*, Turkey[22]; (g) Le Doare (2021), Uganda; (h) Nachega (2021), Multi-country Africa; (i) Nunes (2021), South Africa; (j) Poon (2021), China-Hong Kong; (k) Sakowicz (2021), Chicago, USA.
†Asterisks indicate there is zero total outcome event for a given study. These studies are not included in the 'Events/Total' and pooled risk estimates.
‡These outcomes (preterm labour, very preterm birth before 34 weeks' gestation and preterm birth before 37 weeks' gestation) were included in the sensitivity analyses where we restrict confirmed COVID-19 cases to those with confirmed COVID-19 onset prior to 37 weeks' gestation (or 34 weeks for moderate preterm birth). The full comparison group is used for each of the sensitivity analyses.
§Pooled absolute risks are calculated using Freeman-Tukey transformed proportions, pooled from all participating studies with at least one adverse event for the given outcome, using a DerSimonian-Laird random-effects inverse-variance model meta-analysis.
¶Relative risks are calculated by pooling unadjusted relative risks from all participating studies with at least one adverse event for the given outcome using a DerSimonian-Laird random-effects model meta-analysis. For any study with zero event in one arm (COVID-19 cases or COVID-negative comparisons), we used a continuity correction of 0.5.
**The outcome presented here is stillbirth occurring at or after 28 weeks' gestational age per WHO definition.
††The outcome 'neonatal death' is reported by nine participating studies. However, most studies were not designed to follow-up neonates until 28 days after birth. The count of neonatal deaths is likely an underestimate.
‡‡The outcome 'NICU Admission at Birth' is defined as admission to the neonatal intensive care unit or the equivalent for all studies except for Crovetto (2020), Spain, Cohort II, where the outcome also includes 'admission to high-dependency care unit'.
C-section, caesarean section; ICU, intensive care unit; NICU, neonatal intensive care unit.

95% CI 1.07 to 1.49) and moderate preterm (12 studies; 11 884 live births; RR 1.37, 95% CI 1.05 to 1.79). A sensitivity analysis restricted to the seven studies recording the date of COVID-19 onset and preterm birth found a similar, although strengthened, link between SARS-CoV-2 infection and moderate preterm and preterm births. Infection during pregnancy was linked to a nearly threefold increased risk of moderate preterm birth (RR 2.92, 95% CI 1.88 to 4.54) and a near doubling of the risk in preterm birth (RR 1.71, 95% CI 1.28 to 2.29) (table 3). Infants born to women with SARS-CoV-2 infection during pregnancy were also more likely to be low birth weight (<2500 g) (12 studies; 11 930 neonates; RR 1.19, 95% CI 1.02 to 1.40).

Secondary analysis (symptomatic COVID-19 cases)

We conducted a secondary analysis restricted to only symptomatic infections as compared with SARS-CoV-2 uninfected pregnant women; asymptomatic infections were excluded from this analysis. Similar to the primary analysis, we found that pregnant women with symptomatic infections were more likely than uninfected pregnant women to be admitted to the ICU, require ventilation or receive critical care. The risk of maternal death was also significantly higher. They were also more likely to be diagnosed with pneumonia, hypertensive disorders of pregnancy, pre-eclampsia, pre-eclampsia or eclampsia, or thromboembolic disease. They were more likely to experience preterm labour and to have a caesarean delivery or require an intrapartum caesarean delivery. Infants born to women with symptomatic SARS-CoV-2 during pregnancy were more likely to be born very low birth weight, low birth weight, moderate preterm and preterm; they were also more likely to be admitted to the NICU as compared with infants born to women without COVID-19 during pregnancy (table 4).

Additional sensitivity analyses comparing the results of this meta-analysis to results of eligible studies in the PregCOV-19 Living Systematic Review and comparing pooled estimates among PMA studies using different definitions of stillbirth are presented in the online supplemental tables S4 and S5, respectively.

We found the majority of included studies and outcomes to be at low risk of bias (table 5). Three studies received a star for all domains for all outcomes, indicating the lowest risk of bias; the majority of other studies had only one domain where a higher risk of bias was a concern. The most common reason a study was considered at higher risk of bias was related to selection of the exposed group (SARS-CoV-2 infection); in seven studies, more than half of the SARS-CoV-2-infected women were identified in a way that was potentially not representative of the general pregnant population in the community, such as testing based on recent travel or clinical concern, or clinical diagnosis of probable COVID-19 based on symptoms (online supplemental table S6). Three studies were deemed at higher risk of bias because more than 10% of women had incomplete information about the pregnancy outcome, and three studies were deemed at higher risk of bias because more than 10% of participants were missing a particular outcome (online supplemental tables S7 and S8).

DISCUSSION

Our IPD meta-analysis confirms findings from a growing body of published literature that SARS-CoV-2 infection during pregnancy increases the risk of maternal death and imparts an increased risk for adverse health outcomes for both pregnant women and their fetuses and neonates.

Compared with a contemporaneous group of pregnant women who tested negative for SARS-COV-2 infection, those with infection at any time during pregnancy had a higher risk for all critical care indicators, maternal mortality and several morbidity outcomes such as hypertensive disorders of pregnancy, pre-eclampsia or eclampsia, preterm labour and thromboembolic disease. Our findings are consistent with a living systematic review that included studies using concurrent or historical controls which found that women with COVID-19 during pregnancy had an increased risk of ICU admission and all-cause mortality.[1] A recent multinational cohort study (the INTERCOVID study) including data from 706 SARS-CoV-2-infected pregnancies and 1424 pregnancies without a known diagnosis from 43 institutions in 18 countries found similar increased risks of ICU admission and all-cause mortality linked with COVID-19 during pregnancy. The INTERCOVID study additionally found women with COVID-19 were at higher risk for pre-eclampsia or eclampsia and severe infections (RR 3.38; 95% CI 1.63 to 7.01).[4] Other studies have also reported that COVID-19 is linked with pre-eclampsia or eclampsia.[4 5 26]

There is widespread disagreement about the biological plausibility that SARS-CoV-2 infection can induce hypertensive disorders of pregnancy, including pre-eclampsia. Some have hypothesised that altered ACE2 expression linked to COVID-19, or the systemic inflammation and hypercoagulable state common in COVID-19, may increase the risk of pre-eclampsia.[27] While others have suggested that SARS-CoV-2 infection may lead to a pre-eclampsia-like syndrome that will resolve along with the infection (rather than delivery),[28] clinicians do not commonly measure angiogenic factors such as the soluble fms-like tyrosine kinase-1/placental growth factor that can differentiate between true pre-eclampsia and pre-eclampsia-like symptoms.[29 30] Others have suggested the link between COVID-19 and hypertensive disorders of pregnancy is driven by screening bias.[31] In general, people who face increased risks of SARS-CoV-2 infection are also at higher risk for other comorbidities such as hypertension, obesity, diabetes and pregnancy complications such as pre-eclampsia. Hence, associations between infection and adverse outcomes may be the result of residual confounding. We attempted to address whether people with hypertensive disorders of pregnancy

Table 4 Relative risk of outcomes comparing COVID-19 cases (symptomatic cases only) versus COVID-negative pregnancies

Outcome	Studies (n)	Included studies*†	Symptomatic RR (95% CI)
ICU admission	8	c d e1* e2 f h j k	**4.88 (2.57 to 9.27)**
Ventilation	7	c d e1* e2 f h j	**24.09 (6.85 to 84.77)**
Critical care	7	c d e1* e2 f h j*	**8.47 (3.37 to 21.28)**
Pneumonia	6	c e1* e2 f h j*	**34.58 (3.36 to 356.13)**
Maternal death	10	a* c* d* e1* e2* f* g h i j*	**8.48 (1.70 to 42.21)**
Haemorrhage	6	a c g h i k	1.30 (0.81 to 2.10)
Placental abruption	5	a f h j* k	2.08 (0.95 to 4.53)
Hypertensive disorders of pregnancy (diagnosed at or after COVID-19)		a b j	**1.74 (1.01 to 3.00)**
Hypertensive disorders of pregnancy (diagnosed at any time)	10	a b c e1 e2 g h i j k	**1.28 (1.03 to 1.59)**
Pre-eclampsia	9	a b d e1 e2 f i j k	**1.58 (1.20 to 2.08)**
Eclampsia	7	a* b* e1* e2* i j* k*	1.07 (0.05 to 22.17)
Pre-eclampsia or eclampsia	10	a b c e1 e2 g h i j k	**1.63 (1.26 to 2.11)**
Thromboembolic disease	8	a c d* e1* e2* g* i* j*	**9.64 (1.69 to 54.97)**
Preterm labour	6	c e1* e2 g i j	**1.87 (1.06 to 3.32)**
Preterm labour (COVID-19 onset <37 weeks)	4	c g i j	**2.71 (1.25 to 5.85)**
Caesarean section	10	a c d e1 e2 g h i j k	**1.16 (1.04 to 1.29)**
Intrapartum C-section	8	a c e1* e2 g h i j	**1.27 (1.06 to 1.52)**
Stillbirth	12	a b c d* e1 e2 f g h i j* k	1.35 (0.62 to 2.96)
Perinatal death	9	a c d e1 e2 f g i j*	1.45 (0.62 to 3.43)
Early neonatal death	9	a c d e1 e2* f g i j*	1.89 (0.61 to 5.9)
Neonatal death	10	a c d e1 e2* f g h i j*	1.93 (0.71 to 5.25)
NICU admission at birth	7	a c d e2 f g j	**2.12 (1.31 to 3.43)**
Very low birth weight (<1500 g)	12	a b c d e1 e2 f g h i j* k	**1.67 (1.07 to 2.62)**
Low birth weight (<2500 g)	12	a b c d e1 e2 f g h i j k	**1.32 (1.09 to 1.59)**
Small for gestational age (3rd)	12	a b c d e1 e2 f g h i j k	1.22 (0.86 to 1.71)
Small for gestational age (10th)	12	a b c d e1 e2 f g h i j k	1.05 (0.85 to 1.30)
Moderate preterm birth (<34 weeks)	12	a b c d e1 e2 f g h i j k	**1.62 (1.20 to 2.17)**
Moderate preterm birth (<34 weeks) (COVID-19 onset <34 weeks)‡	7	b c d g i j k	**3.12 (1.94 to 5.02)**
Preterm birth (<37 weeks)	12	a b c d e1 e2 f g h i j k	**1.41 (1.15 to 1.73)**
Preterm birth (<37 weeks) (COVID-19 onset <37 weeks)‡	7	b c d g i j k	**1.70 (1.22 to 2.36)**

*Included studies for each estimate are categorised as follows: (a) Ahlberg *et al*, Sweden[19]; (b) Akelo and Tippett Barr (2021), Kenya; (c) Bevilacqua and Laurita Longo (2020), Italy; (d) Brandt (2020), New Brunswick, USA; (e1) Crovetto (2020), Spain, Cohort I; (e2) Crovetto (2020), Spain, Cohort II; (f) Kalafat *et al*, Turkey[22]; (g) Le Doare (2021), Uganda; (h) Nachega (2021), Multi-country Africa; (i) Nunes (2021), South Africa; (j) Poon (2021), China-Hong Kong; (k) Sakowicz (2021), Chicago, USA.
†Asterisks indicate there is zero total event for a given study. These studies are not included in the 'Events/Total' and pooled risk estimates.
‡These outcomes (preterm labour, moderate preterm birth before 34 weeks' gestation and preterm birth before 37 weeks' gestation) were included in the sensitivity analyses where we restrict COVID-19 cases to those with confirmed onset prior to 37 weeks' gestation (or 34 weeks for moderate preterm birth). The full comparison group is used for each of the sensitivity analyses.
C-section, caesarean section; ICU, intensive care unit; NICU, neonatal intensive care unit; RR, relative risk.

were more likely to be screened, and thus test positive, through our sensitivity analysis including only diagnoses that occurred at or after the SARS-CoV-2 test positive date; the effect estimate was similar to primary analysis, although the CI was much wider given that only three studies contributed data to the sensitivity analysis. Determining whether a true causal link exists and elucidating the potential pathophysiology of hypertensive disorders of pregnancy among women with COVID-19 is needed to strengthen patient care and management. However, the higher risks reported here are similar to those reported by other studies[4 5 26] and are consistent with the practice of prompt, precautionary monitoring of hypertensive women with SARS-CoV-2 infection.

Table 5 Summary of risk of bias assessment for individual studies based on an adapted Newcastle-Ottawa Scale

	Exposure*				Outcome†				
	Representativeness of exposed cohort	Selection of non-exposed cohort	Ascertainment of exposure (SARS-CoV-2 infection)	Ascertainment of control (SARS-CoV-2 negative)	Outcome assessment data source	Adequacy pregnancy follow-up		Data completeness‡	Total stars
Akelo and Tippett Barr (2021)	*	*	*	*	*	§	(a) Critical care	N/A	N/A
							(b) Maternal mortality and morbidity	*	6/7
							(c) Fetal and neonatal mortality	N/A	N/A
							(d) Adverse birth outcomes	¶	5/7
Le Doare (2021)	**	*	††	*	*	*	(a) Critical care	N/A	N/A
							(b) Maternal mortality and morbidity	*	5/7
							(c) Fetal and neonatal mortality	*	5/7
							(d) Adverse birth outcomes	*	5/7
Crovetto (2020), Cohort I	*	*	*	*	*	§	(a) Critical care	*	6/6
							(b) Maternal mortality and morbidity	*	6/7
							(c) Fetal and neonatal mortality	*	6/7
							(d) Adverse birth outcomes	*	6/7
Poon (2021)	**	*	*	*	*	*	(a) Critical care	*	5/6
							(b) Maternal mortality and morbidity	*	6/7
							(c) Fetal and neonatal mortality	*	6/7
							(d) Adverse birth outcomes	*	6/7
Crovetto (2020), Cohort II	*	*	*	*	*	*	(a) Critical care	*	6/6
							(b) Maternal mortality and morbidity	*	7/7
							(c) Fetal and neonatal mortality	*	7/7
							(d) Adverse birth outcomes	*	7/7

Continued

Table 5 Continued

	Exposure*				Outcome†				
	Representativeness of exposed cohort	Selection of non-exposed cohort	Ascertainment of exposure (SARS-CoV-2 infection)	Ascertainment of control (SARS-CoV-2 negative)	Outcome assessment data source	Adequacy pregnancy follow-up		Data completeness‡	Total stars
Bevilacqua and Laurita Longo (2020)	**	*	*	*	*	*	(a) Critical care	*	5/6
							(b) Maternal mortality and morbidity	*	6/7
							(c) Fetal and neonatal mortality	*	6/7
							(d) Adverse birth outcomes	*	6/7
Nachega (2021)	**	*	*	*	*	§	(a) Critical care	¶	4/6
							(b) Maternal mortality and morbidity	¶	4/7
							(c) Fetal and neonatal mortality	*	5/7
							(d) Adverse birth outcomes	¶	4/7
Nunes (2021)	**	*	*	*	*	*	(a) Critical care	N/A	N/A
							(b) Maternal mortality and morbidity	*	6/7
							(c) Fetal and neonatal mortality	*	6/7
							(d) Adverse birth outcomes	*	6/7
Sakowicz *et al*[23]	**	*	*	*	*	*	(a) Critical care	*	5/6
							(b) Maternal mortality and morbidity	*	6/7
							(c) Fetal and neonatal mortality	¶	5/7
							(d) Adverse birth outcomes	*	6/7
Ahlberg *et al*[19]	*	*	*	*	*	*	(a) Critical care	N/A	N/A
							(b) Maternal mortality and morbidity	*	7/7
							(c) Fetal and neonatal mortality	*	7/7
							(d) Adverse birth outcomes	*	7/7

Continued

Table 5 Continued

	Exposure*			Outcome†				
	Representativeness of exposed cohort	Selection of non-exposed cohort	Ascertainment of exposure (SARS-CoV-2 infection)	Ascertainment of control (SARS-CoV-2 negative)	Outcome assessment data source	Adequacy pregnancy follow-up	Data completeness‡	Total stars
Kalafat *et al*[22]	**	*	*	*	*	*	(a) Critical care *	5/6
							(b) Maternal mortality and morbidity *	6/7
							(c) Fetal and neonatal mortality *	6/7
							(d) Adverse birth outcomes *	6/7
Brandt (2020)	*	*	*	*	*	*	(a) Critical care *	6/6
							(b) Maternal mortality and morbidity *	7/7
							(c) Fetal and neonatal mortality *	7/7
							(d) Adverse birth outcomes *	7/7

Stars (*) indicate a study is at lower risk of bias in a given domain.
*See online supplemental table S6 for detailed risk of bias assessment related to selection of the exposed and unexposed cohorts for individual studies.
†See online supplemental table S6 for detailed risk of bias assessment related to outcome assessment for individual studies.
‡See online supplemental table S8 for a description of follow-up by study and review of missing data by outcome.
§Pregnancy follow-up domain deemed at higher risk of bias because <90% of pregnancy outcomes had been ascertained at the time of data transfer.
¶Data completeness domain deemed at higher risk of bias because one or more outcomes in this category had missing data for 11%–25% of participants.
**Representativeness of the exposed cohort domain deemed at higher risk of bias because 50% or more of the cases were identified using a method that was only somewhat representative of all SARS-CoV-2-infected pregnant women in the community (eg, pregnant women tested at antenatal care of delivery based on symptoms or travel; pregnant women tested for antibodies during routine screening; medical records of pregnant women hospitalised for any reason, excluding delivery).
††Ascertainment of exposure (SARS-CoV-2 infection) domain deemed at higher risk of bias because a proportion of COVID-19-positive cases were identified through clinical diagnosis or radiography consistent with WHO case definitions of probable and suspected cases.
N/A, not available.

Our analysis also revealed that neonates born to women with a SARS-CoV-2 infection had a significantly higher risk for a moderately preterm (<34 weeks) or preterm (<37 weeks) birth, though we did not distinguish between spontaneous and iatrogenic preterm births. These findings are consistent with other studies. Based on 18 studies in the living systematic review, COVID-19 during pregnancy is linked with a 47% increased risk of preterm birth; SARS-CoV-2 infected women in the INTERCOVID study had a similar increased risk of preterm birth and 97% increased risk of having a medically indicated preterm birth.[1 4] Notably, we did not find any link between SARS-CoV-2 infection during pregnancy and being born small for gestational age. The INTERCOVID study, one of the few published studies to examine a similar suite of outcomes, has similar findings.[4] Taken together, these findings suggest no association between SARS-CoV-2 infection during pregnancy and intrauterine growth restriction, although the question should be examined in more detail considering the timing and severity of infection during pregnancy.

We did not find a link between SARS-CoV-2 infection during pregnancy and an increased *risk of stillbirth* at or beyond 28 weeks' gestation, based on analysis of 78 cases of stillbirth (14 in the COVID-19 group). This is in contrast with the living systematic review that reported that women with COVID-19 had 2.84 times the risk of stillbirth as compared with their uninfected peers, although this was based on only 35 stillbirths (nine in the COVID-19 group).[1] A national study of more than 340 000 pregnancies in England also found a higher risk of stillbirth (adjusted OR 2.17, 95% CI 1.96 to 2.42).[5] These inconsistent findings may be partly due to analytical choices. For example, we defined stillbirth as fetal death at or beyond 28 weeks' gestational age[32] while other studies used an earlier cut-off; even so, we did not find a significant difference within the PMA studies using different definitions of stillbirth (online supplemental table S5). We also excluded studies with historical controls from our analysis, and we did not use a continuity correction for zero total event study in our meta-analysis because this can cause bias when the exposed and unexposed groups are not equal in size.[33] The design of included studies may also influence our findings. A study in Sweden compared estimates for facilities that had universal screening at ANC or delivery versus those obtained from facilities with non-universal testing policies; they found no link between SARS-CoV-2 infection and stillbirth in the universal screening analysis, but a strong relationship between infection and increased risk of stillbirth in the non-universal screening analysis.[6] Finally, a recent report by the US Centers for Disease Control and Prevention suggests that the Delta variant is associated with a higher risk for stillbirth than earlier SARS-CoV-2 variants.[34] Given stillbirth is a rare outcome, additional data are needed to understand the potential risk and whether risk varies based on the timing and severity of SARS-CoV-2 infection.

Our study is intended to provide robust and high-quality estimates of the impacts of SARS-CoV-2 infection during pregnancy as compared with uninfected pregnancies. The IPD meta-analysis includes both unpublished and previously published data that were uniformly processed and analysed using a harmonised set of outcomes. We also included an expanded set of maternal morbidity outcomes that have not been extensively studied. The unpublished data include information from five countries in sub-Saharan Africa; no data from sub-Saharan Africa were previously available for inclusion in the current living systematic review.[1] Further, the IPD meta-analysis includes newer data (through July 2021) and some study designs at lower risk of potential bias. For example, the data from Akelo and Tippett Barr in Kenya, Le Doare in Uganda and Crovetto Cohort I study in Spain include data from prospective pregnancy cohorts with repeated testing throughout pregnancy. The data from Poon in China-Hong Kong and the Crovetto Cohort II study in Spain include a large control group that is antibody negative throughout pregnancy. Together, these studies provide a large comparison group that likely never had a SARS-CoV-2 infection during pregnancy. In the remaining studies, the comparison group includes pregnancies that were confirmed PCR negative at a single time point. These studies nonetheless offer an improvement over others that use a comparison group defined by the absence of a positive test, rather than a confirmed negative test. Several newer studies also included study sites with universal screening at ANC or delivery which makes these cohorts better representative of the general pregnant population; they identify cases at all gestational ages and address some concerns regarding bias that is introduced when only symptomatic women or those with severe morbidities are more likely to receive a test.

Our study is not without limitations. The possibility of selection bias remains, given that selection of pregnant women with a COVID-19 diagnosis depended on when and how the participants were tested for SARS-CoV-2; this changed over time across sites along with the availability of test kits. However, our risk of bias assessment carefully documents the methods for recruiting exposed and unexposed study participants and suggests that most participants across most studies were sampled in a representative way. Further, this analysis does not consider the differential impact of SARS-CoV-2 variants that have emerged since the onset of the pandemic because sequencing data was not available for individual patients in this study . Additionally, the majority of studies included in this analysis conducted recruitment only during a time period where a single variant was dominant at the national level (online supplemental figure S1). Another serious concern is related to incomplete follow-up for some outcomes such as maternal mortality through 42 days post partum and neonatal mortality through 28 days following birth. Most of the studies had partial follow-up, likely causing undercounting of events. Another potential limitation is the use of site-specific definitions of critical

care indicators, which might introduce misclassification bias. However, it is reassuring that our findings regarding critical care indicators are not substantively different from our findings regarding maternal, fetal and neonatal mortality, which were defined using WHO criteria.

CONCLUSION

Taken together, this analysis of 12 studies including 13 136 pregnant women from 12 countries indicates that SARS-CoV-2 infection at any time during pregnancy increases the risk of maternal mortality, severe maternal morbidities and adverse newborn outcomes. These findings underscore the need for global efforts to prevent COVID-19 during pregnancy through targeted administration of vaccines and non-pharmaceutical interventions. Further efforts are needed to advance our understanding of the best clinical care and management strategies for SARS-CoV-2-infected pregnant women and their newborns. As more data become available, we will update these findings as per the published protocol.

Author affiliations
[1]Department of Global Health, The George Washington University Milken Institute School of Public Health, Washington, DC, USA
[2]Division of Maternal Fetal Medicine, University of California Los Angeles, Los Angeles, California, USA
[3]Department of Medicine, Solna, Clinical Epidemiology Division, Karolinska Institute, Stockholm, Sweden
[4]Division of Maternal-Fetal Medicine, The George Washington University School of Medicine and Health Sciences, Washington, DC, USA
[5]Office of the Director, US Centers for Disease Control and Prevention, Kisumu, Kenya
[6]Department of Pediatrics, University of California Los Angeles, Los Angeles, California, USA
[7]Department of Women and Child Health, Women Health Area, Fondazione Policlinico Universitario Agostino Gemelli, IRCCS, Roma, Italy
[8]Division of Maternal-Fetal Medicine, Department of Obstetrics, Gynecology, and Reproductive Sciences, Rutgers Robert Wood Johnson Medical School, New Brunswick, New Jersey, USA
[9]Department of Sexual and Reproductive Health and Research, World Health Organization, Geneve, Switzerland
[10]Department of Obstetrics and Gynecology, Hospital Universitario de Torrejón, Madrid, Spain
[11]Departamento de Obstetricia y Ginecologia, Universidad del Desarrollo Facultad de Medicina Clinica Alemana, Santiago, Chile
[12]The Biostatistics Center, The George Washington University Milken Institute School of Public Health, Rockville, Maryland, USA
[13]International Federation of Gynecology and Obstetrics, London, UK
[14]Department of Women's and Children's Health, University of Padua, Padova, Italy
[15]Department of Maternal-Fetal Medicine, BCNatal, Barcelona Center for Maternal-Fetal and Neonatal Medicine, Hospital Sant Joan de Déu and Hospital Clínic, Universitat de Barcelona, Barcelona, Spain
[16]Surveillance for Emerging Threats to Mothers and Babies, Puerto Rico Department of Health, San Juan, Puerto Rico
[17]Asian Research and Training Institute for Skill Transfer (ARTIST), Bengaluru, India
[18]Center for Vaccine Development, University of Maryland School of Medicine, Baltimore, Maryland, USA
[19]Materno-Fetal and Obstetrics Research Unit, Department 'Femme-Mère-Enfant', Lausanne University Hospital, Lausanne, Switzerland
[20]Department of Pediatrics, University of California San Francisco, San Francisco, California, USA
[21]Neonatal Medicine, School of Public Health, Imperial College London Faculty of Medicine, London, UK
[22]Gynecology and Obstetrics, Felix Bulnes Hospital and RedSalud Clinic, Santiago, Chile
[23]South African Medical Research Council, Vaccines and Infectious Diseases Analytics Research Unit, University of the Witwatersrand Faculty of Health Sciences, Johannesburg, South Africa
[24]Department of Obstetrics and Gynecology, Koç University School of Medicine, Istanbul, Turkey
[25]Center for Global Health Research, Kenya Medical Research Institute, Kisumu, Kenya
[26]Nuffield Department of Population Health, University of Oxford, Oxford, UK
[27]Department of Pediatrics, University of Maryland School of Medicine, Baltimore, Maryland, USA
[28]Uganda Virus Institute and the London School of Hygiene & Tropical Medicine, Entebbe, Uganda
[29]Pediatric Infectious Diseases Research Group, St George's University of London, London, UK
[30]Department of Metabolism, Digestion and Reproduction, Imperial College London, London, UK
[31]Department of Obstetrics and Gynecology, University of Washington School of Medicine, Seattle, Washington, USA
[32]Institute of Obstetrics and Gynecology Clinic, Catholic University of Sacred Heart, Rome, Italy
[33]Department of Women and Children's Health, School of Life Course and Population Sciences, King's College London, London, UK
[34]Clinical Research Division, National Institute of Perinatology, Mexico City, Mexico
[35]RTI International, Research Triangle Park, North Carolina, USA
[36]Departments of Obstetrics and Gynecology, University of Utah Health Sciences Center, Salt Lake, Utah, USA
[37]Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, Northwestern University Feinberg School of Medicine, Chicago, Illinois, USA
[38]Department of Obstetrics and Gynecology, The University of British Columbia, Vancouver, British Columbia, Canada
[39]Department of Obstetrics and Gynecology, The Chinese University of Hong Kong, Hong Kong, Hong Kong
[40]Department of Epidemiology, University of Pittsburgh Graduate School of Public Health, Pittsburgh, Pennsylvania, USA
[41]Kisumu County Department of Health, Kisumu, Kenya
[42]Institute of Primary Health Care (BIHAM), University of Bern, Bern, Switzerland
[43]Pediatric Growth and Nutrition Branch, National Institute of Health, Bethesda, Maryland, USA
[44]Universidad Pontificia Bolivariana, Medellin, Antioquia, Colombia
[45]Centre of Excellence in Women and Child Health, Aga Khan University, Nairobi, Kenya
[46]Department of Obstetrics and Gynecology, St Luke's University Health Network, Bethlehem, Pennsylvania, USA
[47]Centre for Trials Research, Cardiff University, Cardiff, UK
[48]Children with Special Medical Needs Division, Puerto Rico Department of Health, San Juan, Puerto Rico
[49]Department of Women and Children's Health, King's College London Faculty of Life Sciences and Medicine, London, UK
[50]Department of Maternal-Fetal Medicine, The Royal Women's Hospital, University of Melbourne, Parkville, Victoria, Australia
[51]Department of Obstetrics and Gynecology, Sancaktepe Sehit Prof Dr Ilhan Varank Training and Research Hospital, Istanbul, Turkey

Twitter Emily R Smith @DrEmilyRSmith, Irene Fernández Buhigas @IreneFB80, Jeanne Conry @ConryJeanne and Shabir A Madhi @ShabirMadh

Collaborators Perinatal COVID PMA Study Collaborators: AFRHealth Study (Nachega et al., 2021): Eduard Langenegger, MBChB, PhD, Department of Obstetrics and Gynecology, Tygerberg Teaching Hospital and Faculty of Medicine and Health Sciences, Stellenbosch University, Cape Town, South Africa; Nadia A. Sam-Agudu, MD, International Research Center of Excellence, Institute of Human Virology Nigeria, Abuja, Nigeria; Onesmus W. Gachuno, MBChB, Department of Obstetrics and Gynaecology, University of Nairobi, Nairobi, Kenya; Musa Sekikubo, MBChB, Department of Obstetrics and Gynaecology, School of Medicine, College of Health Sciences, Makerere University, Kampala, Uganda; Denis M. Mukwege, MD, PhD, Gynaecology and General Surgery, Panzi General Referral Hospital, Bukavu, and Université Evangelique en Afrique (UEA), Bukavu, Democratic Republic of the Congo.Adverse Pregnancy Outcomes Associated with COVID-19 Infection (ANCOV) Kenya Study (Akelo, Tippett Barr, et al., 2021): Richard Omore, ANCOV

Kenya; Gregory Ouma, Kenya Medical Research Institute, Centre for Global Health Research; Clayton Onyango, Kenya Medical Research Institute, Centre for Global Health Research; Kephas Otieno, Kenya Medical Research Institute, Centre for Global Health Research; Zacchaeus Abaja Were, Kenya Medical Research Institute, Centre for Global Health Research; Joyce Were, Kenya Medical Research Institute, Centre for Global Health Research. Koc University Hospital (Kalafat 2020): Pinar Birol İlter, Kartal Dr. Lutfi Kirdar Hospital, Istanbul, Turkey. PREPARE Uganda (periCOVID) Study (Le Doare, et al., 2021): Robert Mboizi, PREPARE Uganda; Lauren Hookham, PREPARE Uganda. Rome Hospital Study (Bevilacqua, Laurita Longo, et al., 2020): Federica Meli, Department of Women's and Child Health Sciences and Public Health, IRCCS A. Gemelli University Polyclinic Foundation, Rome, Italy; Giulia Bonanni, Department of Women's and Child Health Sciences and Public Health, IRCCS A. Gemelli University Polyclinic Foundation, Rome, Italy; Federica Romanzi, Department of Women's and Child Health Sciences and Public Health, IRCCS A. Gemelli University Polyclinic Foundation, Rome, Italy; Eleonora Torcia, Department of Women's and Child Health Sciences and Public Health, IRCCS A. Gemelli University Polyclinic Foundation, Rome, Italy; Chiara di Ilio, Department of Women's and Child Health Sciences and Public Health, IRCCS A. Gemelli University Polyclinic Foundation, Rome, Italy. Rutgers Robert Wood Johnson Medical School (Brandt, et al., 2020): Cande V. Ananth, PhD, Division of Maternal-Fetal Medicine, Department of Obstetrics, Gynecology, and Reproductive Sciences, Rutgers Robert Wood Johnson Medical School, New Brunswick, NJ, USA; Jennifer Hill, MD, Division of Maternal-Fetal Medicine, Department of Obstetrics, Gynecology, and Reproductive Sciences, Rutgers Robert Wood Johnson Medical School, New Brunswick, NJ, USA; Ajay Reddy, MD, Division of Maternal-Fetal Medicine, Department of Obstetrics, Gynecology, and Reproductive Sciences, Rutgers Robert Wood Johnson Medical School, New Brunswick, NJ, USA; Haylea Sweat Patrick, MD, Division of Maternal-Fetal Medicine, Department of Obstetrics, Gynecology, and Reproductive Sciences, Rutgers Robert Wood Johnson Medical School, New Brunswick, NJ, USA. University of the Witwatersrand Study (Nunes et al., 2021): Vuyelwa Baba, University of the Witwatersrand, Johannesburg, South Africa; Mary Adam, University of the Witwatersrand, Johannesburg, South Africa; Philiswa Mlandu, University of the Witwatersrand, Johannesburg, South Africa; Yasmin Adam, University of the Witwatersrand, Johannesburg, South Africa; Renate Strehlau, University of the Witwatersrand, Johannesburg, South Africa.

Contributors Conceptualisation: ERS, EO, JT. Data curation: ERS, EO. Formal analysis: ERS, EO, GWG, KF, FF, GR, JS. Funding acquisition: ERS. Investigation: ERS, YA, MA, HA, VA, GA, BATB, OH, EB, JSB, NB, IFB, JCa, RC, JCo, EC, FCri, FCro, CD-L, HD, AJD, GF, VJF, CG, MMG, SLG, EG, SJ, EK, SK, MK, KK, AL, KLD, CL, EL, EML, VLL, LAM, RJM-P, EMM, TDM, ESM, DM, SM, EM, JBN, MCN, DO, AP, LCP, DR, GR, DS, AS, JS-B, JS, OS, MT, AT, JET, JT, MV-P, SV, PvD, KAW, CW, MY. Methodology: ERS, EO, FF, JT. Project administration: KF, EO, GWG. Supervision: ERS, JT. Visualisation: ERS, FF, EO. Writing—original draft preparation: ERS, GWG, EO, KF, JT. Writing—review and editing: all authors. ERS is responsible for the overall content.

Funding Funded by the Bill & Melinda Gates Foundation grant to ERS (INV-022057).

Competing interests CW declares a relationship with Ferring Pharmaceuticals COVID-19 Investigational Grant and NHMRC Fellowship (salary support). AP declares the following research grants to her institution: 'H2020-Grant—Consortium member of Innovative medicine initiative call 13 topic 9 «ConcePTION», Efficacy and safety studies on Medicines EMA/2017/09/PE/11, Lot 4, WP 2 lead, Safety monitoring of COVID-19 vaccines in the EU—Reopening of competition no. 20 under a framework contract following procurement procedure EMA/2017/09/PE (Lot 3) (Euro 110,000), Federal Office of Public Health (207,000 CHF)'. EM declares a relationship with the National Institute for Health Research (project grant for PAN COVID study). DM declares a relationship with the Canadian Institutes of Health Research (payments to institution only), Public Health Agency of Canada (payments to institution only), BC Women's Foundation (payments to institution only) and is a member of the COVID-19 Immunity Task Force sponsored by the Canadian government. TDM declares a relationship with Pfizer (site principal investigator for SARS-CoV-2 vaccination in pregnancy study, money paid to institution and member of Medical Advisory Board for SARS-CoV-2 vaccination in pregnancy study, money paid to TDM), NICHD (subcommittee chair for the NICHD Maternal-Fetal Medicine Units Network Gestational Research Assessments of COVID-19 (GRAVID) study) and Society for Maternal-Fetal Medicine (board member). EL declares a relationship with the US NIH (paid institution) and is an employee of AbbVie, but was employed at the University of Washington at the time of the study. KK declares a relationship with the Bill & Melinda Gates Foundation. VJF declares a relationship with the Bill & Melinda Gates Foundation (payments to institution), Yellow Chair Foundation (payments to institution), Robert Woods Johnson Foundation (payments to institution), CDC Foundation, California Health Care Foundation (payments to institution), Tara Health Foundation (payments to institution), UCSF Women's Health Center of Excellence (payments to institution) and California Department of Health Care Services (payments made to institution). JS-B declares a relationship with the Ferring Pharmaceuticals, which gave a grant ($10 000) for the expenses of RECOGEST trial and is a part of the Columbian Federation of Perinatology. YA declares a relationship with the Bill & Melinda Gates Foundation (payments made to institution), CDC Foundation (payments made to institution), Robert Woods Johnson Foundation (payments made to institution) and UCLA Dean's Office COVID-19 research (payments made to institution). RC declares a relationship with the NIH HD36801 (MFMU Network DCC). MCN declares a relationship with the BMGF (project grant made to institution), EDCTP, Sanofi, AstraZeneca, Pfizer (research grants made to institution), Sanofi Pasteur (payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events) and Sanofi Pasteur and Pfizer (payment for expert testimony). ESM declares a relationship with Pfizer (site principal investigator for phase 2/3 RCT of COVID vaccine during pregnancy). OS declares a relationship with the NordForsk Funding (Nordic research funding grant number: 105545), the Swedish Medical Products Agency (funding for reports on COVID-19 vaccines and pregnancy) and Karolinska Institutet (funding for COVID research and pregnancy: 2020-01567). EG declares a relationship with the Stavros Niarchos Foundation, Santander Foundation and 'La Caixa' Foundation (payments made to institution). SAM declares a relationship with BMGF (funded study in South Africa).

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement No data are available. Individual patient data should be requested from the original or parent study investigators.

ORCID iDs
Emily R Smith http://orcid.org/0000-0001-5715-9459
Irene Fernández Buhigas http://orcid.org/0000-0003-4354-5273
Camille Delgado-López http://orcid.org/0000-0003-3231-6942
Chris Gale http://orcid.org/0000-0003-0707-876X
Sammy Khagayi http://orcid.org/0000-0002-2470-1851
Raigam Jafet Martinez-Portilla http://orcid.org/0000-0003-4711-3857
Peter von Dadelszen http://orcid.org/0000-0003-4136-3070

REFERENCES

1 Allotey J, Stallings E, Bonet M, *et al*. Clinical manifestations, risk factors, and maternal and perinatal outcomes of coronavirus disease 2019 in pregnancy: living systematic review and meta-analysis. *BMJ* 2020;370:m3320.
2 Chinn J, Sedighim S, Kirby KA, *et al*. Characteristics and outcomes of women with COVID-19 giving birth at US academic centers during the COVID-19 pandemic. *JAMA Netw Open* 2021;4:e2120456.
3 Metz TD, Clifton RG, Hughes BL, *et al*. Disease severity and perinatal outcomes of pregnant patients with coronavirus disease 2019 (COVID-19). *Obstet Gynecol* 2021;137:571–80.
4 Villar J, Ariff S, Gunier RB, *et al*. Maternal and neonatal morbidity and mortality among pregnant women with and without COVID-19 infection: the INTERCOVID multinational cohort study. *JAMA Pediatr* 2021;175:817–26.

5 Gurol-Urganci I, Jardine JE, Carroll F, *et al*. Maternal and perinatal outcomes of pregnant women with SARS-CoV-2 infection at the time of birth in England: national cohort study. *Am J Obstet Gynecol* 2021;225:522.e1–522.e11.
6 Stephansson O, Pasternak B, Ahlberg M, *et al*. SARS-CoV-2 and pregnancy outcomes under universal and non-universal testing in Sweden: register-based nationwide cohort study. *BJOG* 2022;129:282-290.
7 Vousden N, Bunch K, Morris E, *et al*. The incidence, characteristics and outcomes of pregnant women hospitalized with symptomatic and asymptomatic SARS-CoV-2 infection in the UK from March to September 2020: a national cohort study using the UK obstetric surveillance system (UKOSS). *PLoS One* 2021;16:e0251123.
8 Smith ER, He S, Oakley EM, *et al*. Protocol for a sequential, prospective meta-analysis to describe COVID-19 in pregnancy and newborn periods. medRxiv published online first, 2020. Available: https://www.medrxiv.org/content/10.1101/2020.11.08.20228056v1.abstract
9 WHO. WHO COVID-19 case definition. World Health organization, 2022. Available: https://www.who.int/publications/i/item/WHO-2019-nCoV-Surveillance_Case_Definition-2022.1 [Accessed 10 Aug 2022].
10 Wells GA, Shea B, O'Connell D, *et al*. The Newcastle-Ottawa scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. The Ottawa Hospital research Institute, 2014. Available: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp [Accessed 25 Apr 2022].
11 World Health Organization. Maternal deaths. the global health Observatory: indicator metadata registry list. Available: https://www.who.int/data/gho/indicator-metadata-registry/imr-details/4622 [Accessed 25 Apr 2022].
12 Tavares Da Silva F, Gonik B, McMillan M, *et al*. Stillbirth: case definition and guidelines for data collection, analysis, and presentation of maternal immunization safety data. *Vaccine* 2016;34:6057–68.
13 Barfield WD. Committee on fetus and newborn. standard terminology for fetal, infant, and perinatal deaths. *Pediatrics* 2016;137.
14 Pathirana J, Muñoz FM, Abbing-Karahagopian V, *et al*. Neonatal death: Case definition & guidelines for data collection, analysis, and presentation of immunization safety data. *Vaccine* 2016;34:6027–37.
15 Villar J, Cheikh Ismail L, Victora CG, *et al*. International standards for newborn weight, length, and head circumference by gestational age and sex: the newborn cross-sectional study of the INTERGROWTH-21st project. *Lancet* 2014;384:857–68.
16 Freeman MF, Tukey JW. Transformations related to the angular and the square root. *Ann Math Statist.* 1950;21:607–11.
17 Clopper CJ, Pearson ES. The use of confidence or FIDUCIAL limits illustrated in the case of the binomial. *Biometrika* 1934;26:404–13.
18 DerSimonian R, Laird N. Meta-Analysis in clinical trials. *Control Clin Trials* 1986;7:177–88.
19 Ahlberg M, Neovius M, Saltvedt S, *et al*. Association of SARS-CoV-2 test status and pregnancy outcomes. *JAMA* 2020;324:1782–5.
20 Brandt JS, Hill J, Reddy A, *et al*. Epidemiology of coronavirus disease 2019 in pregnancy: risk factors and associations with adverse maternal and neonatal outcomes. *Am J Obstet Gynecol* 2021;224:389.e1–389.e9.
21 Crovetto F, Crispi F, Llurba E. Impact of SARS-CoV-2 infection on pregnancy outcomes: a population-based study. *Clin Infect Dis* 2021.
22 Kalafat E, Yassa M, Koc A, *et al*. Utility of lung ultrasound assessment for probable SARS-CoV-2 infection during pregnancy and universal screening of asymptomatic individuals. *Ultrasound Obstet Gynecol* 2020;56:624–6.
23 Sakowicz A, Ayala AE, Ukeje CC, *et al*. Risk factors for severe acute respiratory syndrome coronavirus 2 infection in pregnant women. *Am J Obstet Gynecol MFM* 2020;2:100198.
24 Hadfield J, Megill C, Bell SM, *et al*. Nextstrain: real-time tracking of pathogen evolution. *Bioinformatics* 2018;34:4121–3.
25 Sagulenko P, Puller V, Neher RA. TreeTime: maximum-likelihood phylodynamic analysis. *Virus Evol* 2018;4:vex042.
26 Wei SQ, Bilodeau-Bertrand M, Liu S, *et al*. The impact of COVID-19 on pregnancy outcomes: a systematic review and meta-analysis. *CMAJ* 2021;193:E540–8.
27 Coronado-Arroyo JC, Concepción-Zavaleta MJ, Zavaleta-Gutiérrez FE, *et al*. Is COVID-19 a risk factor for severe preeclampsia? Hospital experience in a developing country. *Eur J Obstet Gynecol Reprod Biol* 2021;256:502–3.
28 Mendoza M, Garcia-Ruiz I, Carreras E, *et al*. Authors' reply re: Pre-eclampsia-like syndrome induced by severe COVID-19: a prospective observational study. *BJOG* 2020;127:1576–7.
29 Espino-Y-Sosa S, Martinez-Portilla RJ, Torres-Torres J, *et al*. Novel ratio soluble FMS-like tyrosine Kinase-1/Angiotensin-II (sFlt-1/ANG-II) in pregnant women is associated with critical illness in COVID-19. *Viruses* 2021;13. doi:10.3390/v13101906. [Epub ahead of print: 23 09 2021].
30 Torres-Torres J, Espino-Y-Sosa S, Poon LC, *et al*. Increased levels of soluble fms-like tyrosine kinase-1 are associated with adverse outcome in pregnant women with COVID-19. *Ultrasound Obstet Gynecol* 2022;59:202–8.
31 Knight M, Draper E, Kurinczuk JJ. Misclassification bias and unnecessary anxiety. *Am J Obstet Gynecol* 2021;225:584.
32 Stillbirth. World Health Organization. Available: https://www.who.int/health-topics/stillbirth [Accessed 11 Apr 2022].
33 Deeks JJ, Higgins J, Altman D. Cochrane Handbook for systematic reviews of interventions version. vol. 10. Cochrane, 2022. Available: https://training.cochrane.org/handbook/current
34 DeSisto CL, Wallace B, Simeone RM, *et al*. Risk for Stillbirth Among Women With and Without COVID-19 at Delivery Hospitalization - United States, March 2020-September 2021. *MMWR Morb Mortal Wkly Rep* 2021;70:1640–5.

Supplementary Material

Table of Contents

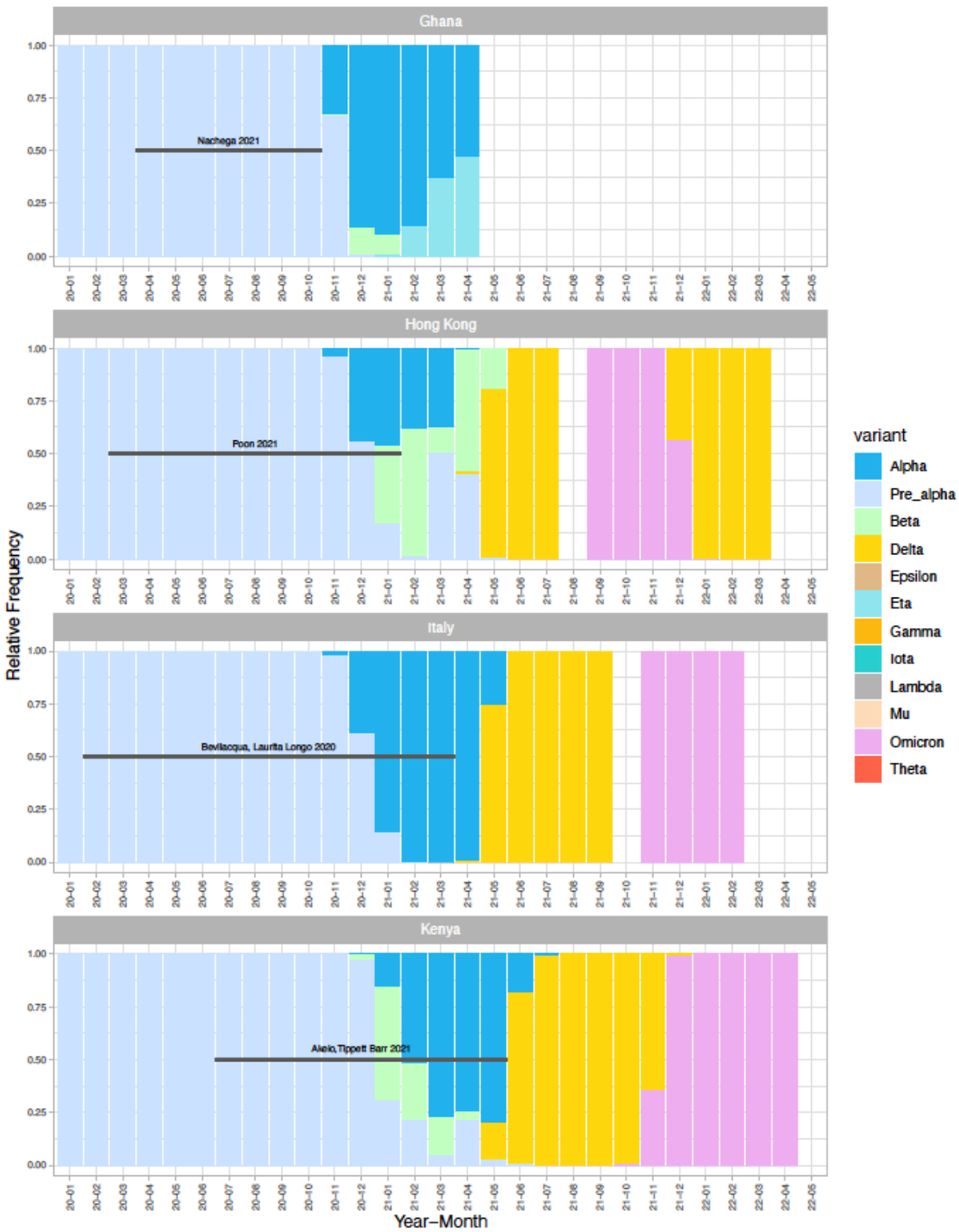
Table S1: Description of differences between prior publications and data contributed to the PMA

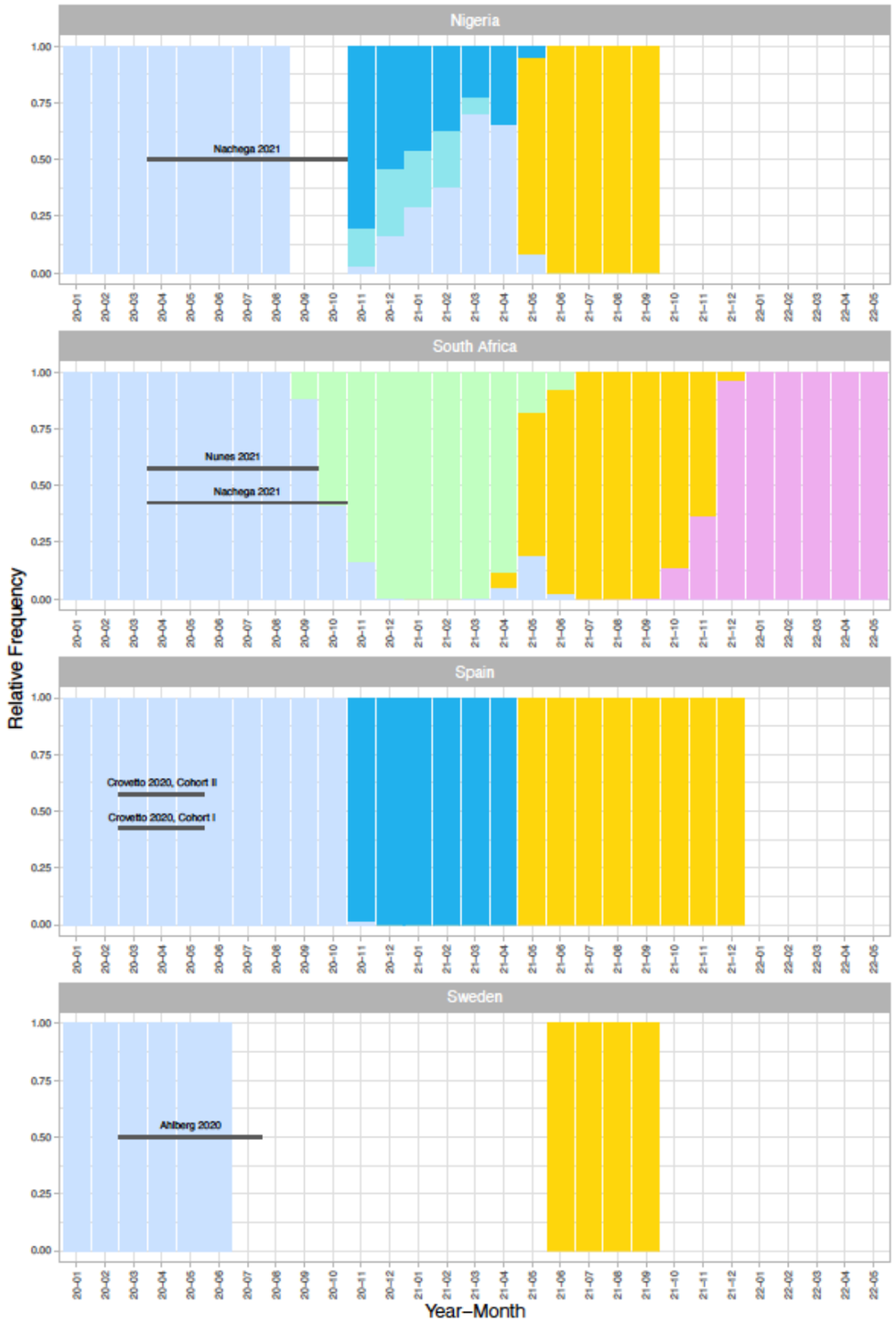
PMA Data Contributor	***Description of Re-analysis of Published Data***	***Citation***
Ahlberg et al, 2020 (Sweden)	The data submitted to the PMA by Ahlberg et al are published in the research letter by Ahlberg et al (2020). For this analysis, we collaborated with investigators to re-analyze the data submitted according to the PMA protocol. The original analysis conducted in this study focused on a smaller sample size (n= 759) after the investigators used propensity score matching to match COVID-negative controls with COVID-positive cases. For the PMA, we use the full sample of patients presenting at labor and delivery at Karolinska University Hospital between March 25 and July 24 2020 (n=2,682).	Ahlberg, M, Neovius, M, Saltvedt, S, Söderling, J, Pettersson, K, Brandkvist, C, Stephansson, O. Association of SARS-CoV-2 Test Stattus and Pregnancy Outcomes. *JAMA*. 2020 Sept; 324(17): 1782-1785. Available from: doi: 10.1001/jama.2021.5775
Bevilacqua et al, 2020 (Italy)	The data submitted to the PMA by Bevilacqua et al are also published as a subset of the data in the PregOuTCOV Study, an international multicenter retrospective cohort in Europe (Badr et al, 2021). For this analysis, we re-analyze the data submitted by Bevilacqua et al according to the PMA protocol. Further, this analysis excludes 728 observations collected in the original study that were asymptomatic and *not* tested for COVID-19, resulting in a sample size of n=2465 for this study.	Badr, DA, Picone, O, Bevilacqua, E, Carlin, A, Meli, F, Sibiude, J, et al. Severe Acute Respiratory Syndrome Coronavisu 2 and Pregnancy Outcomes According to Gestational Age at Time of Infection. *Emerging Infectious Diseases*. 2021 Oct; 27(10): 2535-2543. Available from: https://dx.doi.org/10.3201%2Feid2710.211394
Brandt, 2020 (USA - New Brunswick)	The data submitted to the PMA by Brandt are published in the study Brandt et al (2021). For this analysis, we re-analyze the data submitted according to the PMA protocol. Further, this analysis excludes 21 observations collected in the original study including: 1 COVID-positive observation where COVID-19 onset was more than 1 week after the pregnancy outcome; 20 COVID-negative observations that were assumed negative for COVID-19 but did not receive a PCR test due to recruitment for the study early in the pandemic before testing was widely available (March - early April 2020). This results in a sample size of n=162 for this contributing study in the PMA.	Brandt, JS, Hill, J, Reddy, A, Schuster, M, Patrick, HS, Rosen, T, et al. Epidemiology of coronavirus disease 2019 in pregnancy: risk factors and associations with adverse maternal and neonatal outcomes. *American Journal of Obstetric Gynecology*. 2021 Apr; 224(4): 389.e1-389.e9. Available from: doi: 10.1016/j.ajog.2020.09.043
Crovetto et al, 2020 (Spain)	The data submitted to the PMA by Crovetto et al are published in the study Crovetto et al (2020). For this analysis, we re-analyze the data submitted according to the PMA protocol. Further, for this analysis, Crovetto et al identified 32 additional COVID-positive observations among those who were initially identified as COVID-negative at early pregnancy screening and then tested positive during follow-up PCR testing at labor and delivery (Crovetto et al follow-up study forthcoming). For the PMA, we consider the Crovetto et al study as two separate cohort studies based on the distinct study designs for each cohort, with a sample size of n=921 for Cohort I and n=1,304 for Cohort II.	Crovetto, F, Crispi, F, Llurba, E, Pascal, R, Larroya, M, Trilla, C, et al. Impact of SARS-CoV-2 infection on pregnancy outcomes: A population-based study. *Clinical Infectious Diseases*. 2021 Feb; 73(10): 1768-1775. Available from: https://doi.org/10.1093/cid/ciab104
Kalafat 2020 (Turkey)	The data submitted to the PMA by Kalafat are also published as a subset of the data in the previously published study Kalafat, Yassa, Koc, Tug, and the TULIP Collaboration, 2020. For this analysis, we re-analyze the data submitted by Kalafat according to the PMA protocol, with a sample size n=362 (collected in Istanbul, Turkey).	Kalafat, E, Yassa, M, Koc, A, Tug, N, the TULIP collaboration. Utility of lung ultrasound assessment for probable SARS-CoV-2 infection during pregnancy and universal screening of asymptomatic individuals. *Ultrasound in Obstetrics & Gynecology*. 2020 Sept; 56(4): 624-626. Available from: https://doi.org/10.1002/uog.23099
Sakowicz et al, 2021 (USA – Chicago)	A subset of the data submitted to the PMA by Sakowicz et al are published in the study Sakowicz et al, 2020. The overlapping data include all COVID-negative pregnancies submitted to the PMA (n=1,270) and all COVID-positive pregnancies delivered prior to May 31, 2020 (n=101). Sakowicz et al also submitted additional COVID-positive cases to the PMA delivered on or after June 1, 2020 (n=402) that are not included in this original publication. For this analysis, we re-analyzed the data according to the PMA protocol, retaining all observations submitted by Sakowicz et al (n=1773).	Sakowicz, A, Ayala, AE, Ukeje, CC, Witting, CS, Grobman, WA, Miller, ES. Risk factors for severe acute respiratory syndrome coronavirus 2 infection in pregnant women. *American Journal of Obstetrics and Gynecology MFM.* 2020 Nov; 2(4): 100198. Available from: doi: 10.1016/j.ajogmf.2020.100198

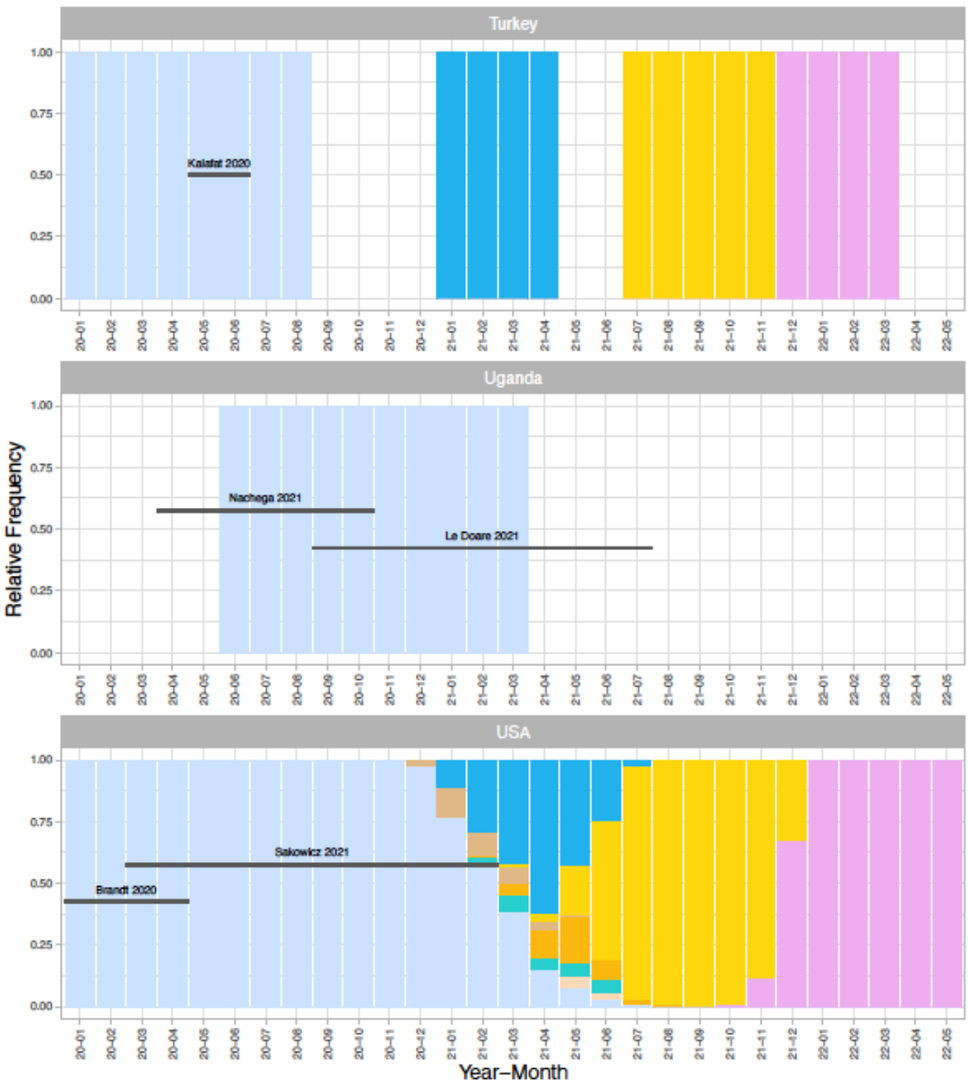
Table S2: Description of the adapted Newcastle Ottawa Scale for assessing risk of bias

	Participant Selection				Outcome Assessment	
	Representativeness of the exposed cohort (Confirmed COVID-19 cases)	**Selection of the non-exposed cohort (COVID-negative comparisons)**	**Ascertainment of exposure (COVID-19 Cases)**	**Ascertainment of control (COVID-negative comparison group)**	**Adequacy of follow up for pregnancy outcome**	**Adequacy of data completeness (by outcome group)**
Lower risk of bias (earns a quality star in the Newcastle Ottawa Scale)	a) At least 50% of the cases were identified using a method truly representative of the COVID-exposed (confirmed/suspected) pregnant women in the community (e.g., pregnant women universally tested when presenting for delivery at the hospital; pregnant women universally tested during antenatal care visits as part of routine screening)	a) Drawn from the same community and same time (e.g., calendar time or gestational age) as the exposed cohort	a) Viral test indicating active infection (e.g., PCR test, antigen test) b) Serology/antibody test with confirmed onset during pregnancy based on date of pandemic and gestational age	a) Viral test indicating the absence of an active infection at a single or multiple times points (e.g., PCR test, antigen test) b) Serology/antibody test indicating no infection during pregnancy	a) >90% of pregnancy outcomes ascertained	a) Complete follow up: data available for ≥99% of participants b) Subjects lost to follow up unlikely to introduce bias (<10% of participants with missing data)
Higher risk of bias	b) 50% or more of the cases were identified using a method a somewhat representative of the COVID-19-infected pregnant persons in the community (e.g., pregnant women tested at antenatal care of delivery based on symptoms or travel; pregnant women tested for antibodies during routine screening; medical records of pregnant women hospitalized for any reason, excluding delivery). c) selected group of pregnancies (e.g., nurses, volunteers)	b) Drawn from a different sampling frame or time (e.g., calendar time or gestational age)	c) Clinical diagnosis or radiography consistent with WHO case definitions of probably and suspected cases d) Self report	c) Absence of a positive test (subject is excluded from this analysis)	b) 75-90% of pregnancy outcomes ascertained c) <75% of pregnancy outcomes ascertained	c) Data missing for 11-25% of participants d) > 25% of participants are missing data (outcome is excluded from this analysis)

Figure S1. Timeline of recruitment by study compared to dominant SARS-CoV-2 variant data [1,2,3]




Nigeria
Nachega 2021
South Africa
Nunes 2021
Nachega 2021
Spain
Crovetto 2020, Cohort II
Crovetto 2020, Cohort I
Sweden
Ahlberg 2020
Relative Frequency
Year–Month



[1] Variant profile over the months for each country was generated using publicly available data from Nextstrain.org
[2] Democratic Republic of Congo variant data not available publicly
[3] White space on individual facets indicate lack of variant data by month availability at Nextstrain.org

Table S3: Comparison of selected demographic characteristics of pregnant women with and without Covid-19 diagnosis

	Mean age (SD)		% Obese	
Study Author Year, Country	COVID-19 Cases	COVID-19 Negative Comparison	COVID-19 Cases	COVID-19 Negative Comparison
Akelo, Tippett Barr 2021, Kenya	26.5 (5.2)	25.6 (5.4) [1]	--	--
Le Doare, 2021, Uganda	27.3 (5.8)	25.7 (5.7)	--	--
Crovetto 2020, Spain - Cohort I	32.7 (5.4)	33.3 (5.3)	11.6%	9.1%
Poon 2021, China-Hong Kong	33.7 (5.4)	32.9 (4.4)	--	--
Crovetto 2020, Spain - Cohort II	32.0 (6.2)	31.9 (5.7)	13.6%	11.2%
Bevilacqua, Laurita Longo 2020, Italy	32.6 (5.7)	33.8 (5.4)	19.3%	15.2%
Nachega 2021, Afrehealth	30.7 (5.8) [2]	30.1 (5.5)	--	--
Nunes 2021, South Africa	31.8 (6.6)	30.7 (6.8)	--	--
Sakowicz, 2021, USA	30.8 (5.8)	32.8 (4.7)	--	--
Ahlberg, 2020, Sweden [3]	32.1 (4.8)	32.3 (5.1)	25.0%	15.0%
Kalafat 2020, Turkey	28.0 (5.9)	26.9 (5.5)	--	--
Brandt 2020, USA	30.3 (6.5)	31.2 (6.3)	--	--

[1] n=12 observations missing age data
[2] n=2 observations missing age data
[3] n=100 observations had missing data on BMI (across the two groups)

Table S4. Sensitivity analysis comparing pooled PMA results to pooled results of eligible studies not recruited from the PregCOV-19 Living Systematic Review

	PMA Studies			PregCOV-19 Studies[1]			Overall Results		
Outcomes	N Studies	Relative Risk[2] (95% CI)	I^2% (p value)	N Studies	Relative Risk[2] (95% CI)	I^2% (p value)	N Studies	Relative Risk[2] (95% CI)	I^2% (p value)
ICU admission	8	**3.81 (2.03, 7.17)**	0 (0.67)	19	**4.56 (3.04, 6.84)**	57.7 (0.001)	27	**4.47 (3.16, 6.32)**	48.6 (0.004)
All-cause mortality	10	**7.68 (1.70, 34.61)**	30.5 (0.24)	18	**5.57 (1.46, 21.22)**	81.7 (0)	28	**6.53 (2.42, 17.62)**	72.4 (0.001)
C-section	10	**1.10 (1.01, 1.20)**	0 (0.88)	40	1.03 (0.96, 1.10)	40.1 (0.005)	50	1.05 (0.99, 1.10)	30.6 (0.02)
Stillbirth [3]	12	1.08 (0.53, 2.16)	0 (0.97)	18	**1.66 (1.26, 2.20)**	0 (0.73)	30	**1.57 (1.21, 2.03)**	0 (0.93)
Neonatal death [4]	10	1.71 (0.71, 4.12)	0 (0.8)	17	1.95 (0.89, 4.29)	0 (0.83)	27	**1.84 (1.02, 3.31)**	0 (0.81)
Admission to neonatal unit at birth [5]	7	**1.86 (1.12, 3.08)**	73.8 (0)	22	**1.57 (1.12, 2.20)**	83.3 (0)	29	**1.64 (1.24, 2.17)**	81.2 (0)
Preterm birth (<37 weeks)	12	**1.27 (1.07, 1.49)**	12.0 (0.33)	35	**1.35 (1.20, 1.52)**	29.5 (0.05)	47	**1.32 (1.20, 1.45)**	24.3 (0.07)

Notes: The table above presents pooled estimates for the PMA studies alongside studies included in the most recently-published PregCOV-19 Living Systematic Review (May 2022) that meet eligibility criteria for the PMA study comparing pregnant people with and without SARS-CoV-2 infection but that were not successfully recruited to the PMA. We present these results for 7 common outcomes for this comparison group across the two studies: Intensive care unit admission; all-cause mortality; caesarean delivery; stillbirth; neonatal death; admission to a neonatal unit at birth; and preterm birth before 37 weeks gestation. These meta-analysis results follow the same methods described for the PMA.

1 PregCOV-19 Living Systematic Review studies incorporated in this analysis include those that 1) recruited a minimum of 25 cases of SARS-CoV-2 infection during pregnancy, 2) recruited a concurrent comparison group of uninfected pregnancies (i.e., excluding historical comparison cohorts, and 3) were not included in the PMA study analysis. These 53 studies include the following: Abedzadeh-Kalahroudi, 2021, Iran; Adhikari, 2020, USA; Afshar, 2020, USA; Anuk, 2021, Turkey; Beharier, 2021, Israel; Campbell, 2020, USA; Cardona-Pérez, 2021, Mexico; Celik, 2021, Turkey; Cuñarro-López, 2020, Spain; Debelenko, 2021, USA; Diaz-Corvillon, 2020, Chile; Dotters-Katz, 2020, USA; Edlow, 2020, USA; Egerup, 2020, Denmark; Elenga, 2021, French Guiana; Erol Koc, 2020, Turkey; Flaherman, 2020, USA; Gold, 2021, USA; Hcini, 2020, French Guiana; Izewski, 2021, USA; Jaiswala, 2021, India; Janssen, 2020, USA; Jering, 2021, USA; Levitan, 2021, USA; Liu, 2020, China; Liu, 2021, USA; Martinez-Perez, 2020, Spain; Maru, 2020, USA; McLaren, 2021, USA; Molenaar, 2021, USA; Money, 2021, Canada; Nayak, 2020, India; Ona, 2021, USA; Patberg, 2020, USA; Pineles, 2020, USA; Pirjani, 2020, Iran; Prabhu, 2020, USA; Rios-Silva, 2020, Mexico; Rosenbloom, 2021, USA; Ruggiero, 2020, Italy; Smithgall, 2020, USA; Soto-Torres, 2021, USA; Steffen, 2021, USA; Trahan, 2021, Canada; Tsatsaris, 2020, France; Vielma, 2020, Chile; Villar, 2021, multi-country study (includes 18 countries); Vouga, 2020, multi-country study (includes 16 countries); Wang, 2020, USA; Yadav, 2020, India; Yang, 2020, China; Zhang, 2020, USA; Zhang, 2021, USA.

2 Relative risks are calculated by pooling unadjusted relative risks from all participating studies with at least 1 adverse event for the given outcome using a DerSimonian-Laird random effects model meta-analysis. For any study with zero events in one arm (COVID-19 cases or COVID-negative comparisons), we used a continuity correction of 0.5.

3 The PMA outcome presented here is stillbirths occurring at or after 28 weeks gestational age per the WHO definition. For PregCOV-19 Studies, the estimates presented are as-reported by the study site and may span multiple different definitions of stillbirth (20-28 weeks).

4 The outcome "neonatal death" is reported by 9 participating studies in the PMA. However, most studies included in the PMA were not designed to follow-up neonates until 28 days after birth. The count of neonatal deaths is likely an underestimate.

5 The PMA outcome "NICU Admission at Birth" is defined as admission to the neonatal intensive care unit or the equivalent for all studies except for Crovetto, 2020, Spain, Cohort II, where the outcome also includes "admission to high-dependency care unit." The outcome for PregCOV-19 presented is defined as "admission to neonatal unit at birth."

Table S5. Sensitivity analysis comparing pooled absolute and relative risk of adverse outcomes using multiple definitions of stillbirth[1]

			Confirmed COVID-19 Case		COVID-19 Negative Comparison			
Outcomes	**N Studies**	**Included studies [2,3]**	**Events/Total**	**Pooled Risk[4] (95% CI)**	**Events/Total**	**Pooled Risk[4] (95% CI)**	**Relative Risk[5] (95% CI)**	**I^2% (p value)**
Stillbirths at or after 28 weeks gestation [6]	12	a b c d* e1 e2 f g h i j* k	14 / 1602	0.01 (0.00, 0.02)	64 / 10060	0.01 (0.00, 0.01)	1.08 (0.53, 2.16)	0 (0.97)
Stillbirths at or after 24 weeks gestation [7]	12	a b c d* e1 e2 f g h i j* k	21 / 1609	0.01 (0.0, 0.2)	84 / 10080	0.01 (0.0, 0.01)	0.92 (0.53, 1.59)	0 (0.99)
Stillbirths at or after 22 weeks gestation [8]	12	a b c d* e1 e2 f g h i j* k	24 / 1612	0.01 (0.0, 0.02)	99 / 10095	0.01 (0.01, 0.02)	0.89 (0.52, 1.51)	0 (0.99)
Stillbirths at or after 20 weeks gestation [9]	11	b c d e1 e2 f g h i j* k	25 / 1516	0.01 (0.00, 0.03)	94 / 7670	0.01 (0.01, 0.02)	0.88 (0.51, 1.50)	0 (0.97)

1 This analysis presents pooled absolute and relative risk of stillbirth based on four separate definitions by gestational age (at or after 28, 24, 22, or 20 weeks gestation). The fourth estimate (20 weeks gestation) does not Ahlberg et al. (2020, Sweden) because the study draws from a registry that does not include miscarriages (i.e., pregnancy loss before 22 weeks gestational age per the local definition).
2 Included studies for each estimate are categorized as follows: a) Ahlberg, 2020, Sweden; b) Akelo, Tippett Barr, 2021, Kenya; c) Bevilacqua, Laurita Longo 2020, Italy; d) Brandt, 2020, New Brunswick, USA; e1) Crovetto, 2020, Spain, Cohort I; e2) Crovetto, 2020, Spain, Cohort II; f) Kalafat, 2020, Turkey; g) Le Doare, 2021, Uganda; h) Nachega, 2021, Multi-country Africa; i) Nunes, 2021, South Africa; j) Poon, 2021, China-Hong Kong; k) Sakowicz, 2021, Chicago, USA
3 Asterisks (*) indicate there are zero total outcome events for a given study. These studies are not included in the "Events/Total" and pooled risk estimates.
4 Pooled absolute risks are calculated using Freeman-Tukey transformed proportions, pooled from all participating studies with at least 1 adverse event for the given outcome, using a DerSimonian-Laird random-effects inverse-variance model meta-analysis.
5 Relative risks are calculated by pooling unadjusted relative risks from all participating studies with at least 1 adverse event for the given outcome using a DerSimonian-Laird random effects model meta-analysis. For any study with zero events in one arm (COVID-19 cases or COVID-negative comparisons), we used a continuity correction of 0.5.
6 The outcome presented here is the definition used throughout the PMA study: stillbirths occurring at or after 28 weeks gestational age per the WHO definition.
7 The outcome presented here is stillbirths occurring at or after 24 weeks gestational age per the definition used by the UK National Health Service.
8 The outcome presented here is stillbirths occurring at or after 22 weeks gestational age per the definition used by the European Medicines Agency.
9 The outcome presented here is stillbirths occurring at or after 20 weeks gestational age per the definition used by the US Centers for Disease Control and Prevention.

Table S6. Detailed risk of bias assessment related to selection of the exposed and unexposed cohorts for individual studies

Study	Selection			
	Representativeness of the exposed cohort	**Selection of the non-exposed cohort**	**Ascertainment of exposure (COVID-19 Cases)**	**Ascertainment of control (COVID-negative comparison group)**
Akelo 2021	Population-based pregnancy surveillance Universal screening at antenatal care, after enrollment (50 cases, 47.17%) Universal screening at delivery (11 cases, 10.38%) Universal screening at enrollment (32 cases, 30.19%) Hospitalized for COVID-19 (1 cases diagnosed while hospitalized and 11 hospitalized for COVID-19 management, 11.32%) Other COVID-19 testing for clinical concern (1 case, 0.94%)	Same cohort as exposed cohort	positive PCR test result	negative PCR test result
Le Doare 2021	Clinic-based pregnancy surveillance: PCR screening at recruitment in early pregnancy (19 cases, 27.5%, includes 1 patient hospitalized for COVID-19) Diagnosed with probable COVID-19 during pregnancy (50 cases, 72.5% includes 1 patient hospitalized for COVID-19)	Drawn from the same cohort of pregnancies as the exposed group, all non-exposed observations received a negative test during PCR screening at recruitment. These cases were followed up through clinic-based pregnancy surveillance, although repeated PCR testing was generally not available.	Positive PCR test result or meeting criteria for probable COVID-19 as per the WHO	Negative PCR and/or negative antibody test at recruitment **AND** did not meet WHO criteria for probable COVID-19 infection during pregnancy follow-up visits.
Crovetto 2020, Cohort I	Phase 1 (Initial recruitment from March-May 2020): Pregnant women at 10-16 weeks of gestation who provided blood sample for Down's syndrome screening were tested for SARS- CoV-2 antibodies (141 cases, 81.5%) Phase 2: Follow-up testing at labor and delivery for all phase 1 participants using PCR; 32 cases, 18.5%)	Same cohort as exposed cohort	Tested positive for SARS-CoV-2 antibodies in early pregnancy **OR** PCR positive at delivery	Tested negative for SARS-CoV-2 antibodies in early pregnancy **AND** negative PCR test at delivery
Poon 2021	Testing for "clinical concern" Universal testing for admission to the Labor & Delivery Universal testing for any hospital admission	The first 2 patients who delivered following a confirmed COVID-19 case; if none, deliveries from the preceding day were selected.	positive PCR test result	negative serology test during routine Down syndrome screening (11-13 weeks' gestation) and again at delivery
Crovetto 2020, Cohort II	Universal testing at Labor & Delivery (Apr-May 2020): Universal testing (antibody testing for all, PCR testing for some) at Labor & Delivery Tested positive with PCR test only: 3 cases (1.7%) Tested positive for antibody test only: 138 cases (78.4%) Tested positive with both PCR and antibody test: 35 cases (19.9%)	Same cohort as exposed cohort	PCR positive test result, positive antibody test result, or positive PCR and antibody test at delivery	Negative antibody test at delivery or negative PCR and antibody test at delivery
Bevilacqua 2020	Testing for "clinical concern" (50 cases, 45.87%) Universal testing for admission to the Labor & Delivery (19 cases, 17.43%) Universal testing for hospital admission other than Labor & delivery, including pregnancy-related admission pre-term (40 cases, 36.70%)	Same cohort as exposed cohort	positive PCR test result	negative PCR test result

Nachega 2021	Symptomatic hospitalized women	Symptomatic hospitalized women	positive PCR test result	negative PCR test result
Nunes 2021	All women presenting for antenatal care (or admitted during pregnancy) with COVID-like symptoms (119 cases, 85.6%) Screening of 10 asymptomatic women per day (19 cases, 13.7%) Retested at labor & delivery after initial recruitment during antenatal care (1 case, 0.7%)	Same cohort as exposed cohort	positive PCR test result	PCR confirmed negative result
Sakowicz 2020	(March 2020-Feb2021): Testing for "clinical concern" (357 cases, 71%) (Mar 2020-Feb 2021): Universal testing for admission to the Labor & Delivery (146 cases, 29%)	(April 2020 to May 2020): Universal testing for admission to the Labor & Delivery	Electronic health records (EHRs) indicating PCR positive test results	Electronic health records (EHRs) indicating negative PCR test result
Ahlberg 2020	Universal PCR testing for admission to the Labor & Delivery (142 cases, 91.02%) Record of PCR or antibody positive test during antenatal care (14 cases, 8.97%) Positive during pregnancy but negative upon admission (11 cases, 7.05%) Positive antibody test not tested upon delivery (3 cases, 1.92%)	Universal PCR testing for admission to the Labor & Delivery	positive PCR test result Record of PCR or antibody positive test during antenatal care	negative PCR test upon admission for delivery (no previous positive test)
Kalafat 2020	Asymptomatic pregnant women admitted for delivery (19 cases, 24.7%) Symptomatic pregnant women evaluated for probable SARS-CoV-2 infection (58 cases, 75.3%)	Same cohort as exposed cohort	positive PCR test result	negative PCR test result
Brandt 2020	(Mar-Apr 2020): Testing for "clinical concern", recent travel, or exposure to known case (10 cases, 16.7%) (Apr-Jun 2020): Universal testing for admission to the Labor & Delivery (50 cases, 83.3%)	Each COVID-19 case was matched to 2 controls by delivery date. Before April 10, controls were selected as the first 2 patients who delivered between 16.0- and 41.6-weeks' gestation on the same date as the cases if they were asymptomatic or had a negative COVID-19 test result. After April 10, controls were selected if they had a negative COVID-19 test result and delivered on the same date as the cases. On days with 2 or more cases, we identified the next 2 eligible controls as potential matches.	positive PCR test result	negative PCR test result

Table S7. Detailed risk of bias assessment related to outcome assessment for individual studies

Study	Outcome		
	Assessment of outcome	**Adequacy of follow up of cohorts for pregnancy outcome**	**Adequacy of data completeness[1]**
Akelo 2021	Clinical data were routinely collected in real time based on clinic and home visits	Number of pregnancies with pregnancy outcome known: 817 (52.4%) Note: This is an ongoing cohort study and some missing pregnancy outcomes are because women have not yet delivered. The percentage of pregnancies with a recorded endpoint among those with expected due dates 4 weeks or more before the date data was shared is 83%.	a) Critical Care Indicators: Data excluded due to missingness >25% b) Maternal Mortality & Morbidity: 0% Missing c) Fetal & Neonatal Mortality & Morbidity: Neonatal follow up in progress still and thus excluded d) Adverse Birth Outcomes: Missing 7% preterm, 9% birthweight, 21% SGA
Le Doare 2021	Clinical data were routinely collected in real time based on clinic visits	Number of pregnancies with pregnancy outcome known: 516 (97.0%)	a) Critical Care Indicators: Data not available b) Maternal Mortality & Morbidity: <1% missing c) Fetal & Neonatal Mortality & Morbidity: <1% missing d) Adverse Birth Outcomes: < 2% missing
Crovetto 2020, Cohort I	All patient data were abstracted from the electronic medical records or hospital records	Number of pregnancies with pregnancy outcome known: 790 (85.8%)	a) Critical Care Indicators: 0% missing b) Maternal Mortality & Morbidity: <4% missing for all, except PROM (excluded due to 36.5% missing outcome data) c) Fetal & Neonatal Mortality & Morbidity: <1% missing, except NICU (excluded due to 39.4% missing outcome data) d) Adverse Birth Outcomes: <3% missing
Poon 2021	Electronic health records and clinical report	Number of pregnancies with pregnancy outcome known: 152 (100%)	a) Critical Care Indicators: 0% missing b) Maternal Mortality & Morbidity: 0% missing c) Fetal & Neonatal Mortality & Morbidity: 0% missing d) Adverse Birth Outcomes: 0% missing
Crovetto 2020, Cohort II	All patient data were abstracted from the electronic medical records or hospital records	Number of pregnancies with pregnancy outcome known: 1,304 (100%)	a) Critical Care Indicators: 0% missing b) Maternal Mortality & Morbidity: 0% missing c) Fetal & Neonatal Mortality & Morbidity: ≤ 2% missing d) Adverse Birth Outcomes: < 1% missing
Bevilacqua 2020	Clinical data were routinely collected in real time in the patient's electronic medical records.	Number of pregnancies with pregnancy outcome known: 2464 (100%)	a) Critical Care Indicators: 0% missing b) Maternal Mortality & Morbidity: 0% missing, except c-section (1.1%) c) Fetal & Neonatal Mortality & Morbidity: 0% missing d) Adverse Birth Outcomes: <1% missing

Nachega 2021	All patient data were abstracted from the patient hospital charts and logbooks	Number of pregnancies with pregnancy outcome known: 228 (51.6%)	a) Critical Care Indicators: <3%, except pneumonia (21.9%) b) Maternal Mortality & Morbidity: <8%, except c-section (23%) c) Fetal & Neonatal Mortality & Morbidity: <2% d) Adverse Birth Outcomes: <20%
Nunes 2021	All patient data were abstracted from the hospital records or telephonic contact	Number of pregnancies with pregnancy outcome known: 746 (95.5%)	a) Critical Care Indicators: Data not available b) Maternal Mortality & Morbidity: <1% missing; except placental abruption (> 99% missing, excluded) c) Fetal & Neonatal Mortality & Morbidity: <1% missing (NICU admission not available) d) Adverse Birth Outcomes: ≤5.2% missing
Sakowicz 2020	Electronic health records (EHRs) were reviewed for all pregnant women identified to have a SARS-CoV-2 test performed	Number of pregnancies with pregnancy outcome known: 1773 (100%)	a) Critical Care Indicators: <1% missing b) Maternal Mortality & Morbidity: <1% missing c) Fetal & Neonatal Mortality & Morbidity: 21.6% missing NICU, neonatal death (excluded due to high differential missingness between the exposed and non-exposed cohorts) d) Adverse Birth Outcomes: <1% missing
Ahlberg 2020	Maternal and neonatal data were collected from the Swedish Pregnancy Register2 and medical records.	Number of pregnancies with pregnancy outcome known: 2682 (100%)	a) Critical Care Indicators: Data not available b) Maternal Mortality & Morbidity: 0% missing, except haemorrhage (4.6%) c) Fetal & Neonatal Mortality & Morbidity: 0% missing during observed period, but 28 day follow not part of study d) Adverse Birth Outcomes: <1% missing
Kalafat 2020	All patient data were abstracted from the patient hospital charts, logbooks and electronic patient records.	Number of pregnancies with pregnancy outcome known: 351 (97.0%)	a) Critical Care Indicators: 0% missing b) Maternal Mortality & Morbidity: 0% missing c) Fetal & Neonatal Mortality & Morbidity: <1% missing d) Adverse Birth Outcomes: <1 missing
Brandt 2020	All patient data were abstracted from the electronic medical records	Number of pregnancies with pregnancy outcome known: 162 (100%)	a) Critical Care Indicators: 0% missing b) Maternal Mortality & Morbidity: 0% missing c) Fetal & Neonatal Mortality & Morbidity: 0% missing d) Adverse Birth Outcomes: <1% missing

1 Additional information on adequacy of data completeness for each individual outcome is presented in Table S8.

Table S8: Description of Follow-up by Study and Review of Missing Data by Outcome [1]

Study (Author Year, Site)	Overall Follow-up		Missing Data by Outcome: among all pregnancies			
	Number of pregnancies identified	Number of pregnancies with a recorded endpoint (%)	ICU admission	Ventilation	Critical care	Pneumonia
Akelo, Tippett Barr 2021, Kenya [2]	1560	817 (52.4%) [2]	99.4%*	99.4%*	99.4%*	99.4%*
Le Doare, 2021, Uganda [3]	532	516 (97.0%)[3]	--	--	--	--
Crovetto 2020, Spain, Cohort I	921	790 (85.8%)	0.0%	0.0%	0.0%	0.0%
Poon 2021, China-Hong Kong	152	152 (100%)	0.0%	0.0%	0.0%	0.0%
Crovetto 2020, Spain, Cohort II	1,304	1,304 (100%)	0.0%	0.0%	0.0%	0.0%
Bevilacqua, Laurita Longo 2020, Italy	2465	2464 (100%)	0.0%	0.0%	0.0%	0.0%
Nachega 2021, Afrehealth	442	228 (51.6%)	0.0%	2.7%	2.0%	21.9%
Nunes 2021, South Africa	781	746 (95.5%)	--	--	--	--
Sakowicz, 2021, USA [4]	1773	1773 (100%)	0.4%	--	--	--
Ahlberg, 2020, Sweden	2682	2682 (100%)	--	--	--	--
Kalafat 2020, Turkey	362	351 (97.0%)	0.0%	0.0%	0.0%	0.0%
Brandt 2020, USA	162	162 (100%)	0.0%	0.0%	0.00%	--

[1] For each outcome, this table shows the percentage of missing data for each outcome. For our meta-analysis, we excluded any outcome that was more than 25% missing. These excluded outcomes are indicated with an asterisk. Outcomes that were not collected for a study are noted using the "--" symbol.

[2] The ANCOV Kenya study (Akelo, Barr, 2021) is an ongoing cohort study conducting population-level surveillance and some missing pregnancy outcomes can be accounted for by pregnant women who have been identified for the study but have not yet delivered. Among the 885 pregnancies with an expected due date 4 weeks or more before the date data was shared (August 19, 2021), 83% have completed pregnancy follow up.

[3] The PREPARE Uganda study (Le Doare 2021) is an ongoing cohort study and some missing pregnancy outcomes can be accounted for by pregnant women who have been identified for the study but have not yet delivered. The percentage of pregnancies with a recorded endpoint among those with expected due dates 4 weeks or more before the date data was most recently updated (October 31, 2021) is 97.4%, with 16 observations missing pregnancy outcome out of 530 pregnancies.

[4] We excluded the Sakowicz study (2021, USA) from the pooled estimates for NICU admission and neonatal death because of differential missingness across the COVID-19 cases in pregnancy and COVID-negative comparison group. Neonatal death was 68% missing for COVID-19 cases in pregnancy, but only 3% missing for COVID-negative pregnancies. NICU Admission was 68% missing for COVID-19 cases in pregnancy, but only 2% missing for COVID-negative comparison pregnancies.

Table S8: Description of Follow-up by Study and Review of Missing Data by Outcome [1], continued

Study (Author Year, Site)	Missing Data by Outcome: among all completed pregnancies (with a recorded pregnancy endpoint)										
					Hypertensive disorders of pregnancy						
	Maternal death	PROM	Haemorrhage	Placental abruption	Diagnosed at or after COVID-19	Diagnosed at any time	Preeclampsia or Eclampsia	Thromboembolic disease	Preterm labor	Preterm labor - COVID onset <37w	Cesarian section
Akelo, Tippett Barr 2021, Kenya [2]	--	--	--	--	0.0%	0.0%	0.0%	--	--	--	--
Le Doare, 2021, Uganda [3]	0.0%	0.0%	0.0%	--	--	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
Crovetto 2020, Spain, Cohort I	0.0%	36.5%*	--	--	--	0.0%	0.0%	0.0%	3.9%	--	0.8%
Poon 2021, China-Hong Kong	0.0%	0.0%	--	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
Crovetto 2020, Spain, Cohort II	0.0%	0.0%	--	--	--	0.0%	0.0%	0.0%	0.0%	--	0.0%
Bevilacqua, Laurita Longo 2020, Italy	0.0%	--	0.0%	--	--	0.0%	0.0%	0.0%	0.0%	0.0%	1.1%
Nachega 2021, Afrehealth	0.4%	7.5%	7.0%	6.6%	--	3.5%	5.7%	--	26.3%*	6.9%	22.9%
Nunes 2021, South Africa	0.7%	0.0%	0.0%	99.5%*	--	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%
Sakowicz, 2021, USA [4]	--	--	0.2%	0.0%	--	0.4%	0.4%	--	--	--	0.0%
Ahlberg, 2020, Sweden	0.0%	0.0%	4.4%	0.0%	0.0%	0.0%	0.0%	0.0%	--	--	0.0%
Kalafat 2020, Turkey	0.0%	--	--	0.0%	--	--	--	--	--	--	--
Brandt 2020, USA	0.0%	--	--	--	--	--	--	0.0%	--	--	0.0%

[1] For each outcome, this table shows the percentage of missing data for each outcome. For our meta-analysis, we excluded any outcome that was more than 25% missing. These excluded outcomes are indicated with an asterisk. Outcomes that were not collected for a study are noted using the "--" symbol.

[2] The ANCOV Kenya study (Akelo, Barr, 2021) is an ongoing cohort study conducting population-level surveillance and some missing pregnancy outcomes can be accounted for by pregnant women who have been identified for the study but have not yet delivered. Among the 885 pregnancies with an expected due date 4 weeks or more before the date data was shared (August 19, 2021), 83% have completed pregnancy follow up.

[3] The PREPARE Uganda study (Le Doare 2021) is an ongoing cohort study and some missing pregnancy outcomes can be accounted for by pregnant women who have been identified for the study but have not yet delivered. The percentage of pregnancies with a recorded endpoint among those with expected due dates 4 weeks or more before the date data was most recently updated (October 31, 2021) is 97.4%, with 16 observations missing pregnancy outcome out of 530 pregnancies.

[4] We excluded the Sakowicz study (2021, USA) from the pooled estimates for NICU admission and neonatal death because of differential missingness across the COVID-19 cases in pregnancy and COVID-negative comparison group. Neonatal death was 68% missing for COVID-19 cases in pregnancy, but only 3% missing for COVID-negative pregnancies. NICU Admission was 68% missing for COVID-19 cases in pregnancy, but only 2% missing for COVID-negative comparison pregnancies.

Table S8: Description of Follow-up by Study and Review of Missing Data by Outcome [1], continued

Study (Author Year, Site)	Missing Data by Outcome: among all births or livebirths (with a recorded pregnancy endpoint)							
	Stillbirth	**Perinatal death**	**Neonatal death**	**NICU Admission at birth**	**Low birthweight (<2500g)**	**Small for gestational age (10th)**	**Preterm birth (<37 weeks)**	**Preterm birth (<37 weeks) - COVID onset <37w**
Akelo, Tipett Barr 2021, Kenya [2]	0.1%	26%*	26.5%*	--	8.7%	20.9%	7.1%	6.7%
Le Doare, 2021, Uganda [3]	0.2%	0.4%	0.0%	0.2%	0.0%	1.7%	0.8%	0.8%
Crovetto 2020, Spain, Cohort I	0.0%	0.4%	0.4%	39.4%*	1.3%	2.9%	1.2%	--
Poon 2021, China-Hong Kong	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
Crovetto 2020, Spain, Cohort II	0.0%	0.0%	0.0%	2.0%	0.0%	0.3%	0.0%	--
Bevilacqua, Laurita Longo 2020, Italy	0.0%	0.0%	0.0%	0.0%	0.1%	0.2%	0.0%	0.0%
Nachega 2021, Afrehealth	1.5%	--	0.0%	--	14.2%	19.1%	12.6%	14.9%
Nunes 2021, South Africa	0.1%	0.5%	0.4%	--	3.0%	5.2%	0.4%	0.4%
Sakowicz, 2021, USA [4]	0.0%	--	21.6%[4]	21.0% [4]	0.1%	0.3%	0.1%	0.0%
Ahlberg, 2020, Sweden	0.0%	0.0%	0.0%	0.0%	0.4%	0.7%	0.0%	--
Kalafat 2020, Turkey	0.0%	0.3%	0.3%	0.6%	0.0%	0.0%	0.0%	0.0%
Brandt 2020, USA	0.0%	0.0%	0.0%	0.0%	0.0%	0.6%	0.0%	0.0%

[1] For each outcome, this table shows the percentage of missing data for each outcome. For our meta-analysis, we excluded any outcome that was more than 25% missing. These excluded outcomes are indicated with an asterisk. Outcomes that were not collected for a study are noted using the "--" symbol.

[2] The ANCOV Kenya study (Akelo, Barr, 2021) is an ongoing cohort study conducting population-level surveillance and some missing pregnancy outcomes can be accounted for by pregnant women who have been identified for the study but have not yet delivered. Among the 885 pregnancies with an expected due date 4 weeks or more before the date data was shared (August 19, 2021), 83% have completed pregnancy follow up.

[3] The PREPARE Uganda study (Le Doare 2021) is an ongoing cohort study and some missing pregnancy outcomes can be accounted for by pregnant women who have been identified for the study but have not yet delivered. The percentage of pregnancies with a recorded endpoint among those with expected due dates 4 weeks or more before the date data was most recently updated (October 31, 2021) is 97.4%, with 16 observations missing pregnancy outcome out of 530 pregnancies.

[4] We excluded the Sakowicz study (2021, USA) from the pooled estimates for NICU admission and neonatal death because of differential missingness across the COVID-19 cases in pregnancy and COVID-negative comparison group. Neonatal death was 68% missing for COVID-19 cases in pregnancy, but only 3% missing for COVID-negative pregnancies. NICU Admission was 68% missing for COVID-19 cases in pregnancy, but only 2% missing for COVID-negative comparison pregnancies.

COVID-19 infection at any time during pregnancy boosts mother's risk of death

And is associated with serious illness in mothers and newborns
Findings reinforce need for targeted interventions, including vaccination, say researchers

COVID-19 infection at any time during pregnancy boosts the mother's risk of death and is associated with serious illness in both mothers and their newborns, finds a pooled data analysis of international evidence, published in the open access journal ***BMJ Global Health***.

The findings reinforce the need for global efforts to minimise these infection risks during pregnancy through targeted vaccination campaigns and other protective measures, say the researchers.

There's a vast and growing body of research on COVID-19 infection during pregnancy. But extensive differences in study design, methods, and comparison groups make it difficult to reach any firm conclusions, added to which few studies have been done in low income countries, say the researchers.

The researchers formed an international consortium in April 2020 to obtain high quality prospective data from relevant studies being carried out in several countries and applied a uniform analytical approach to avoid the issues associated with previous research.

The current research, which comprises the results of the first individual level pooled data analysis of those studies, assesses the risks of ill health and death among pregnant women with or without confirmed or probable COVID-19 infection.

The analysis is based on participants in 12 studies involving 13,136 pregnant women in Ghana, China-Hong Kong, Italy, Kenya, Nigeria, South Africa, Spain, Sweden, the Democratic Republic of Congo, Turkey, Uganda, and the USA.

It shows that pregnant women infected with SARS-CoV-2, the virus responsible for COVID-19 infection, were nearly 8 times as likely to die as their uninfected peers.

And they were nearly 4 times as likely to require intensive care; 15 times as likely to require mechanical ventilation; and more than 5 times as likely to need any type of critical care.

They were also more than 23 times as likely to be diagnosed with pneumonia and more than 5 times as likely to have serious blood clots.

Babies born to women with COVID-19 infection were nearly twice as likely to be admitted to a neonatal care unit; nearly 3 times as likely to be born moderately premature (before 34 weeks); and 19% more likely to be underweight at birth than babies born to uninfected women.

But unlike the findings of previous reviews, COVID-19 Infection wasn't linked to a heightened risk of stillbirth at or beyond 28 weeks of pregnancy, nor restricted growth.

The researchers point to some limitations of their study. The selection of pregnant women with COVID-19 depended on when and how they were tested for SARS-CoV-2; this changed over time across sites along with the availability of test kits. The analysis didn't consider the differential impact of SARS-CoV-2 variants that have emerged since the pandemic started. Some outcomes weren't monitored for a clinically meaningful period either.

Notwithstanding these caveats, "These findings underscore the need for global efforts to prevent COVID-19 during pregnancy through targeted administration of vaccines and non-pharmaceutical interventions," say the researchers.

This is particularly important as: "Global guidance has been equivocal on the potential risks of infection and benefits and safety of vaccination, and more than 80 countries do not currently recommend that all pregnant and lactating women should be vaccinated," they point out.