


# BMJ Open Neonatal outcomes and indirect consequences following maternal SARS-CoV-2 infection in pregnancy: a systematic review

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## ABSTRACT

**Objectives** To identify the association between maternal SARS-CoV-2 infection in pregnancy and individual neonatal morbidities and outcomes, particularly longer-term outcomes such as neurodevelopment.

**Design** Systematic review of outcomes of neonates born to pregnant women diagnosed with a SARS-CoV-2 infection at any stage during pregnancy, including asymptomatic women.

**Data sources** MEDLINE, Embase, Global Health, WHOLIS and LILACS databases, last searched on 28 July 2021.

**Eligibility criteria** Case-control and cohort studies published after 1 January 2020, including preprint articles were included. Study outcomes included neonatal mortality and morbidity, preterm birth, caesarean delivery, small for gestational age, admission to neonatal intensive care unit, level of respiratory support required, diagnosis of culture-positive sepsis, evidence of brain injury, necrotising enterocolitis, visual or hearing impairment, neurodevelopmental outcomes and feeding method. These were selected according to a core outcome set.

**Data extraction and synthesis** Data were extracted into Microsoft Excel by two researchers, with statistical analysis completed using IBM SPSS (Version 27). Risk of bias was assessed using a modified Newcastle-Ottawa Scale.

**Results** The search returned 3234 papers, from which 204 were included with a total of 45 646 infants born to mothers with SARS-CoV-2 infection during pregnancy across 36 countries. We found limited evidence of an increased risk of some neonatal morbidities, including respiratory disease. There was minimal evidence from low-income settings (1 study) and for neonatal outcomes following first trimester infection (17 studies). Neonatal mortality was very rare. Preterm birth, neonatal unit admission and small for gestational age status were more common in infants born following maternal SARS-CoV-2 infection in pregnancy in most larger studies.

**Conclusions** There are limited data on neonatal morbidity and mortality following maternal SARS-CoV-2 infection, particularly from low-income countries and following early pregnancy infections. Large, representative studies addressing these outcomes are needed to understand the consequences for babies born to women with SARS-CoV-2.

**PROSPERO registration number** CRD42021249818.

## STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ Large sample size both of individual studies and overall number of pregnancies and births included.
- ⇒ Focus on neonatal outcomes and indirect consequences for infants born to mothers with a diagnosis of SARS-CoV-2 during pregnancy, as opposed to purely obstetric outcomes.
- ⇒ Limited data available from low-income and middle-income countries, early pregnancy infections and more granular neonatal outcomes such as neurodevelopmental outcomes.

## INTRODUCTION

Pregnant women have been treated as an 'at risk' group for severe disease during the SARS-CoV-2 pandemic.<sup>1</sup> Initial evidence suggested that infection with SARS-CoV-2 in pregnancy was associated with severe obstetric morbidity,<sup>2</sup> including higher rates of preterm birth, pre-eclampsia and caesarean delivery.<sup>3 4</sup> Early case reports suggested that vertical transmission was possible, although rare.<sup>2 5-9</sup> However, increasingly, research indicates that neonatal infections are mostly mild,<sup>10</sup> suggesting that the risk to neonates from maternal infection is more likely to be as a result of the indirect effects of being born to a mother with SARS-CoV-2 infection, rather than from perinatal or postnatal infection with SARS-CoV-2. Other viral infections, such as Zika virus, in early pregnancy have been associated with adverse neurodevelopmental outcomes<sup>11</sup>; however, the neurodevelopmental impact of maternal SARS-CoV-2 in pregnancy is unclear.

Previous reviews of neonatal outcomes from maternal SARS-CoV-2 infections have been limited by the quality and amount of evidence available, with many studies consisting of case reports and case series or with small sample sizes.<sup>12-14</sup> As larger, population-based

or national studies emerge, an opportunity has arisen to examine neonatal outcomes following maternal infection in greater detail, including longer-term outcomes. In this systematic review, we summarise current evidence on neonatal outcomes after maternal SARS-CoV-2 infection in pregnancy, aiming to quantify the association with specific neonatal morbidities and longer-term outcomes that will be important to families.

## METHODS

The review protocol was preregistered and is available with PROSPERO (17 May 2021, ID CRD42021249818).

### Eligibility criteria

We included peer-reviewed publications of case-control and cohort studies. Preprint articles identified from relevant living systematic reviews were included. We excluded studies of overlapping populations, identified by hospital, date of study period and number of participants. Preprint articles were identified as reporting duplicate populations by the same means. We accepted studies of the babies of pregnant women with a diagnosis of SARS-CoV-2 during pregnancy. A diagnosis of SARS-CoV-2 was defined as positive PCR testing at any stage, lateral flow/rapid antigen testing or locally accepted clinical criteria in order to enable inclusion of studies early in the pandemic or in resource-limited settings where PCR testing may not have been widely available. Studies diagnosing SARS-CoV-2 infection using serology alone were only included if their participants were recruited during the first 9 months of 2020, with the assumption that these participants would mostly have contracted their primary SARS-CoV-2 infection during pregnancy. In case-control studies, we included any study with a comparison group of pregnant women without any diagnosis of SARS-CoV-2 during pregnancy. We allowed studies published after 1 January 2020, although studies published after this date but including data from prior to 1 January 2020 were also included. No language or geographic restrictions were applied.

We included studies describing any of the following infant outcomes: preterm birth (<37 weeks gestation), small for gestational age (<10th centile birth weight for gestational age on appropriate neonatal growth charts), low birth weight (defined as <2500 g), admission and length of stay in neonatal unit, level and duration of respiratory support, diagnosis of culture-positive sepsis during neonatal admission, evidence of brain injury (including seizures, abnormal brain imaging or diagnosis of hypoxic ischaemic encephalopathy),<sup>15</sup> necrotising enterocolitis, other gastrointestinal disease, visual or hearing impairment, quality of life, neurodevelopmental outcomes, exclusive breast feeding and all-cause infant mortality. Selection of neonatal outcomes was informed by a core outcome set developed with health professionals, parents and researchers.<sup>16</sup>

### Search process

MEDLINE, Embase, Global Health, WHOLIS and LILACS databases were searched (see online supplemental appendix 1 for search terms used). The LILACS database was searched for all papers relating to 'SARS-CoV-2', 'covid' and 'coronavirus', owing to its differing search functionality from the other databases. The last search was completed on 28 July 2021.

Results were uploaded to the Rayyan QCRI platform (Rayyan—a web and mobile app for systematic reviews, 2016<sup>17</sup>), and duplicates removed using the duplicate removal tool available on this platform. All titles were screened independently by two reviewers (SS and AS) and subsequently abstracts screened by both. Where there was disagreement, the title/abstract was screened by a third reviewer (CG).

Data were extracted into Microsoft Excel (V.2201) by SS or SA using a proforma with the outcomes described above, study type and dates, location, participant definition and numbers, and method of SARS-CoV-2 diagnosis. Any outcome data not reported was assumed not to have been collected as part of the study. Pregnancies were assumed to be singleton pregnancies unless otherwise specified. A modified Newcastle-Ottawa Scale<sup>18</sup> was used for assessment of study quality, with studies scoring 4 and above (out of a possible 11) deemed as eligible for inclusion. Statistical analysis was completed using Microsoft Excel, SPSS (IBM SPSS Statistics for Macintosh, V.25, 2017)<sup>19</sup> and R (R Studio V.2021.09.01<sup>20</sup>), including calculation of proportion of infants in each study with each outcome, and descriptive statistics of rates of outcomes identified. Weighted means were calculated by dividing the number of infants included in each study by the total number of infants included in the review to find a weighting factor. Each outcome rate was then multiplied by that study's weighting factor, and all the results summed to find the overall weighted mean. Independent sample Kruskal-Wallis tests were used to determine whether there was a significant difference in outcome rates between country income levels as defined by the World Bank.<sup>21</sup> Forest plots were created using R,<sup>20</sup> using a random effects model only. Further meta-analysis was not performed due to heterogeneity in study populations and outcome reporting. Results are reported according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

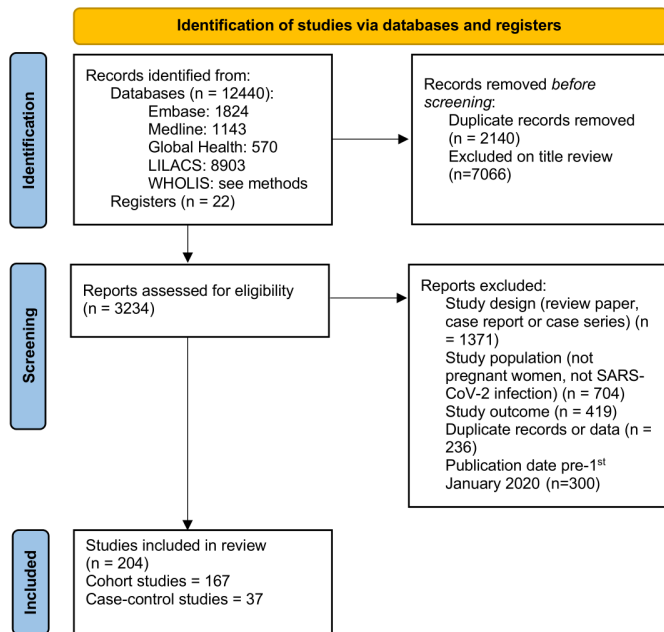
### Patient and public involvement

Patients and the public were not directly involved in the design of this study. However, this study seeks to address some of the knowledge gaps raised by expectant families as part of an online survey of women pregnant or breast feeding during the COVID-19 pandemic.<sup>22</sup>

## RESULTS

### Search results

A total of 3234 papers were identified from the literature search after duplicates were removed. A total of 204 papers were deemed as eligible for inclusion. Of these, 37 papers were case-control studies, and 167 were cohort



**Figure 1** Preferred Reporting Items for Systematic Reviews and Meta-Analyses study selection flow chart.

studies (see figure 1 for PRISMA summary of study selection process). A total of 36 countries were represented, with an additional 6 international papers. Overall, 118 studies were from high-income countries, and only 1 from a low-income country.<sup>23</sup> Study periods ranged from 8 December 2019 to 18 March 2021. Across all studies, a total of 838 743 pregnancies and 786 884 live births were studied, of which 57 059 mothers had received a diagnosis of SARS-CoV-2 infection in pregnancy and had given birth to 45 646 babies. The majority of studies only included women with in their third trimester of pregnancy, with 17 (8.3%) studies including any participants in the second trimester (2%–49% of total participants in each study), and 20 (9.8%) including any first-trimester participants (1%–51% of total participants in each study). Overall, 76% of studies (156) used PCR testing alone to identify cases of SARS-CoV-2. The details of included studies can be found in table 1, and a full results table is available in

		Studies, n	Participants, n
Study type	Case-control	37	793 680
	Cohort	167	45 063
Income group	High	118	809 562
	Upper middle	56	15 027
	Lower middle	24	7174
	Low	1	137
Stages of pregnancy included in study	First trimester included	20	2212
	Second trimester included	17	2141

online supplemental appendix 2. The range of bias assessment scores according to the Newcastle-Ottawa Scale were 4–8, with a median score of 6.

### Neonatal morbidity

Of the included studies, neonatal outcomes were less commonly reported than obstetric outcomes. Need for admission to a neonatal unit was the most frequently reported outcome, with data extracted for 761 489 infants, respectively (97.2% of included infants overall). However, neonatal outcomes such as need for non-invasive respiratory support, neurological disease, sepsis and necrotising enterocolitis were only reported in a minority of infants (<95 000) and studies included in this review.

The weighted mean rate of admission to a neonatal unit for babies born to mothers infected with SARS-CoV-2 was 11%, although it was not clear in some studies how many of these admissions were for isolation purposes as opposed to clinical need. In total, 8 of the 19 case-control studies reporting neonatal unit admission rates found a significant association between neonatal unit admission and maternal infection (including 432 512 infants, in comparison to 306 407 infants included in studies finding no association, see table 2 and figure 2). The need for non-invasive respiratory support among babies born to mothers with SARS-CoV-2 was reported for 6037 infants (weighted mean rate 1%, see table 3). Neurological disease (reported for 3376 SARS-CoV-2 exposed infants, range 0%–7%, weighted mean rate 0.2%), Necrotising enterocolitis (NEC - reported for 2937 SARS-CoV-2 exposed infants, weighted mean rate 0.02%) and confirmed bacterial infection (reported for 4697 SARS-CoV-2 exposed infants, range 0%–7%, weighted mean rate 0.09%) were all reported in a minority of studies. Few case-control studies reported on neonatal morbidity in detail, with only 2 studies of 88 238 infants examining the need for respiratory support, gastrointestinal disease, neurological disease and sepsis. Only 1 small case-control study of 79 infants found maternal SARS-CoV-2 infection to be associated with neurological morbidity (specifically, seizures), affecting 1 (7%) of the exposed infants and none of those non-exposed.<sup>24</sup> One large study of 88 159 infants finding an increased risk of need for respiratory support in babies born to infected mothers found that this association may be explained by prematurity.<sup>25</sup> No study controlled for prematurity in assessing the association between maternal infection and neurological morbidity.

### Birth outcomes

The method of delivery was reported in 184 studies (including 784 395 births), with a weighted mean of 38% of births occurring via caesarean. Of the 28 case-control studies reporting on caesarean delivery as an outcome, 12 studies found a significant association with maternal SARS-CoV-2, although these studies were much larger than those not finding an association (including 651 224 births as compared with 9751 births).

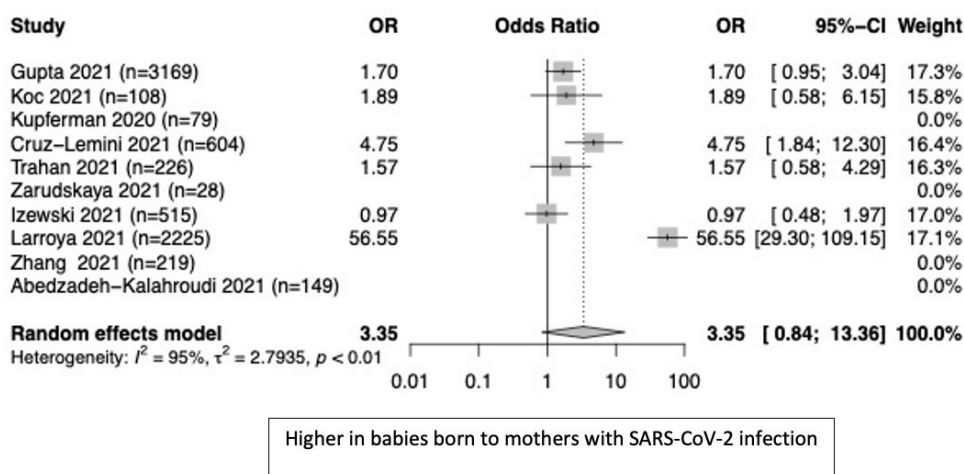
**Table 2** Results of case-control studies

		Studies finding significant association		Studies not finding significant association	
		Studies, n	Participants in studies, n	Studies, n	Participants in studies, n
Birth outcomes	Caesarean delivery	12	651 224	16	9751
	Premature delivery (<37 weeks)	10	648 804	16	9807
	Small for gestational age	1	219	10	648 318
	Low birth weight	1	2130	1	110
Neonatal outcomes	Admission to neonatal care	8	432 512	11	306 407
	Need for non-invasive respiratory support	2	88 238	0	0
	Need for mechanical ventilation	2	88 238	0	0
	Neurological disease	1	79	1	88 159
	Necrotising enterocolitis	0	0	0	0
	Other gastrointestinal disease	0	0	0	0
	Sepsis	0	0	2	88 214
Infant outcomes	Hearing impairment	2	191	0	0
	Developmental outcomes	0	0	0	0
	Any breast feeding (exclusive or mixed feeding)	2	145	2	88 422
	Infant or neonatal death	0	0	10	96 688

Preterm birth (<37 gestational weeks) in SARS-CoV-2-affected pregnancies occurred at weighted mean rate of 14%. The median prematurity rate in SARS-CoV-2 affected pregnancies was 16%, owing to 4 smaller studies finding very high rates of prematurity. Most larger studies reported a higher risk of preterm birth (10 studies including 648 804 births), but several smaller studies did not (10 studies including 9807 births, see [figure 3](#)). Prematurity rates in pregnancies affected by SARS-CoV-2 were not significantly different across income categories, except for rates being significantly

higher in upper-middle-income countries (mean 22.7%) compared with high-income countries (mean 16.3%,  $p=0.043$ ).

A total of 54 studies reported rates of small for gestational age births, including 753 945 infants. The range was 0%–44%, and the weighted mean was 4%. Overall, 25 studies examined the rates of low birth weight. These included only 5108 infants and found a range of low birth weight rates of 0%–50%, with a weighted mean of 1%.

**Figure 2** Forest plot for neonatal intensive care unit admission.

**Table 3** Results from all COVID-19-positive pregnancies (pooled cohort studies and case–control studies)

		Studies reporting, n	SARS-CoV-2 exposed infants included, n	Weighted mean	Range
Birth outcomes	Premature delivery (<37 weeks)	165	42 726	13.8%	0%–81%
	Small for gestational age	55	23 911	4.0%	0%–44%
	Low birth weight	25	3629	1.0%	0%–50%
Neonatal outcomes	Admission to neonatal care	118	31 413	11.0%	0%–100%
	Need for non-invasive respiratory support	27	6037	1.0%	0%–80%
	Need for mechanical ventilation	27	5341	0.4%	0%–20%
	Neurological disease	13	3376	0.2%	0%–7%
	Necrotising enterocolitis	10	2937	0.0%	0%–22%
	Other gastrointestinal disease	6	360	0.0%	0%–5%
	Sepsis	15	4697	0.1%	0%–7%
	Infant outcomes	Hearing impairment	4	197	0.1%
	Developmental outcomes	2	339	0.0%	0%–64%
	Breast feeding	38	7565	12.0%	0%–100%
	Infant or neonatal death	99	23 826	0.4%	0%–18%

### Breast feeding

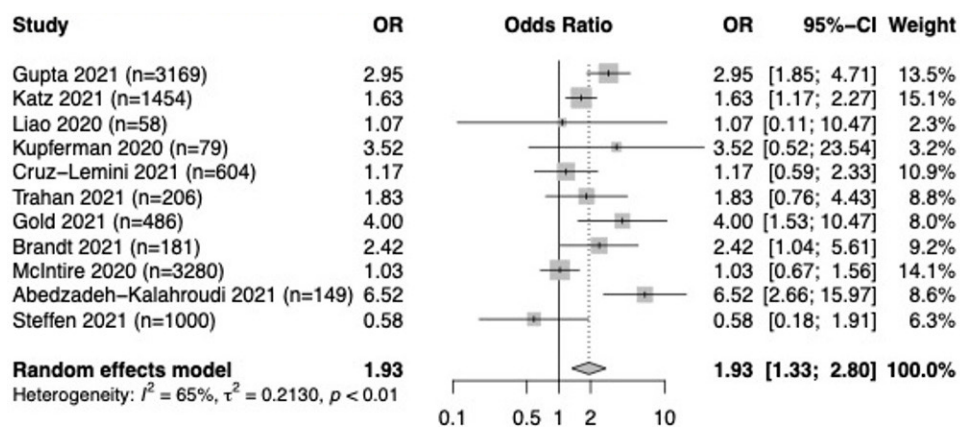
Breastfeeding rates among babies born to mothers with SARS-CoV-2 varied significantly across the 39 studies (96 174 infants) reporting this outcome: 0%–100% (weighted mean 12%). Of the studies reporting breast feeding as an outcome, 11 (28.2%) reported breastfeeding status at hospital discharge and 8 (20.5%) reported breastfeeding status at hospital discharge. The longest follow-up of breast feeding was 2 months, in three studies. In seven studies, it was unclear at what point breastfeeding status was recorded.

Four case–control studies including 88 567 babies examined breast feeding by maternal SARS-CoV-2 infection status: 2 small studies (145 infants) found a significant negative association between maternal SARS-CoV-2 infection and breast feeding,<sup>24 26</sup> whereas 2 other studies (88 422 infants) did not find any significant association

between maternal SARS-CoV-2 and breast feeding. Among studies without a SARS-CoV-2-negative comparator group, one found that asymptomatic mothers were more likely to breast feed than those with symptoms,<sup>27</sup> and one found a significant difference in breastfeeding rates both in hospital and at home between those who were separated (0% in hospital, 12.2% at home) from their babies and those who were not (22.2% in hospital, 27.8% at home).<sup>28</sup>

### Neurodevelopmental outcomes

In total, 2 cohort studies of 339 infants examined developmental outcomes. One study found that psychomotor development was normal at 6 months in all 282 infants born following maternal SARS-CoV-2 infection during pregnancy.<sup>29</sup> A second study examined neurobehavioural development using the Ages and Stages Questionnaire



Higher in babies born to mothers with SARS-CoV-2 infection

**Figure 3** Forest plot for premature delivery.



at 3 months in 57 exposed infants,<sup>30</sup> and found that 28 (63.6%) had concerning features in the social–emotional developmental domain,<sup>30</sup> and that abnormal development was associated with length of mother–baby separation.<sup>30</sup> In total, 2 studies of 191 infants found higher rates of abnormal auditory brainstem response hearing tests (44.9%, 53 vs 23.7%, 28) and poorer otoacoustic emission test results in babies born to mothers infected with SARS-CoV-2.<sup>31 32</sup>

### Mortality

In all studies reporting neonatal or infant mortality, there were 512 deaths reported. A total of 10 case–control studies of 96 688 infants examined neonatal mortality, and none found a significant difference in mortality rate between neonates born to infected mothers and controls. The only study in a low-income country reported no neonatal deaths.<sup>23</sup>

### DISCUSSION

We report the largest systematic review of neonatal and infant outcomes of babies born to women with SARS-CoV-2 in pregnancy, including 57 059 pregnancies and 45 646 babies where mothers had been infected with SARS-CoV-2 during pregnancy from 114 countries. Building on previous studies which concentrated on timing and method of delivery,<sup>3 4</sup> we have examined available data on neonatal morbidity, which may have long-term consequences. Additionally, we included pregnancies with a maternal SARS-CoV-2 infection irrespective of whether the mother was symptomatic or asymptomatic, in contrast to earlier studies focusing on hospitalised or severely unwell mothers. Unfortunately, limited study numbers made it impossible to meta-analyse outcomes in symptomatic women compared with asymptomatic women. The exclusion of case series and case reports reduced the impact of selection bias, and we excluded duplicate populations from our analysis.

### Obstetric outcomes

As in other reviews, we found that maternal infection with SARS-CoV-2 during pregnancy is associated with higher rates of prematurity.<sup>8 33 34</sup> We found that prematurity rates were highest in upper-middle-income countries, although they were similar to those in lower-middle-income countries. This could be due to iatrogenic premature delivery rather than spontaneous preterm labour, but more study will be required to determine the aetiology.

### Neonatal outcomes

We also found some evidence that maternal infection with SARS-CoV-2 is associated with increased rates of admission to the neonatal intensive care unit. The reason for this could be the increase in prematurity, as reported above, but it should be noted that some of these admissions may be for isolation purposes, an observation period, or for the care of a baby whose mother is severely unwell

and unable to care for the baby herself. Additionally, in resource-limited settings, specialist neonatal intensive care may not be available—hence, this is not a generalisable marker for neonatal morbidity in all settings.

Evidence is limited and conflicting as to the association between maternal SARS-CoV-2 in pregnancy and short-term or long-term neonatal morbidity. The strongest evidence supports an association between maternal infection and an increased risk of respiratory disease mediated by preterm birth, but not of neurological or gastrointestinal morbidity.<sup>25</sup> We identified few, small studies that examined longer-term developmental outcomes; these found an apparent association between maternal SARS-CoV-2 infection and adverse outcomes in early infancy (3 months),<sup>29 30</sup> but more studies that follow infants up over a longer time period will be needed to determine the true effect of maternal SARS-CoV-2 infection on development. It is imperative that these concerning findings are examined using standardised and validated neurodevelopmental assessments, and with the same assessment tools throughout multiple studies to allow meta-analysis. These findings also highlight the critical importance of examining neurodevelopment of offspring exposed to SARS-CoV-2 in-utero or in early life definitively through larger studies. Two small studies reported an association between maternal SARS-CoV-2 infection and offspring hearing impairment in healthy newborns without any specific risk factors for hearing impairment,<sup>31 32</sup> further supporting the importance of following up children exposed to SARS-CoV-2 in pregnancy. More recently, a systematic review has also found a potential link between maternal SARS-CoV-2 and hearing impairment, although this association remains controversial.<sup>35</sup>

We were unable to examine the impact by trimester of maternal SARS-CoV-2 infection due to a paucity of studies examining offspring of first or second trimester infection. Other viruses such as Zika virus are known to be harmful to the developing fetus when contracted in the first or second trimester,<sup>36</sup> so there is a reasonable suspicion that this could be true for SARS-CoV-2. Future studies should focus on examining this critical question, particularly as the virus becomes endemic.

Our study did not find clear evidence that maternal SARS-CoV-2 infection is associated with a reduction in breast feeding. Reductions reported in some studies may relate to mother–baby separation or maternal symptoms as opposed to a direct effect of the virus: one study finding lower breastfeeding rates in cases was based in China, which recommended against breast feeding if a lactating woman was infected with SARS-CoV-2.<sup>26</sup> Those findings, no difference were based in Sweden<sup>25</sup> where there were no recommendations to restrict breast feeding, and in the USA,<sup>37</sup> we were unable to verify the exact guidance used by USA-based study hospitals at the time of data collection. We chose not to report vertical transmission of SARS-CoV-2 in this review, as identified studies varied widely in the timing and type of SARS-CoV-2 testing undertaken in

newborns, making a true diagnosis of vertical transmission difficult to accurately report.

Reassuringly, we did not find any evidence of an increased risk of neonatal or infant death with maternal SARS-CoV-2 infection. This is in contrast to other coronaviruses such as MERS, which has been linked with neonatal mortality rates of up to 33%.<sup>4</sup> However, in the studies we identified, it was difficult to determine which neonatal or infant deaths might be attributable specifically to SARS-CoV-2 infection during pregnancy. We elected not to include case reports and case series in this review, but it should be noted that cases of severe SARS-CoV-2 infections in neonates have been reported.<sup>38–40</sup> Although the incidence is likely to be low, this review does not seek to exclude severe neonatal infection with SARS-CoV-2 as a possibility.

### Country income groups

This review identifies a crucial lack of data regarding the consequences for women in lower-income settings. Our findings suggest that some of the adverse perinatal outcomes may be more common in lower-middle-income and upper-middle-income countries than in high-income countries, such as prematurity, but we had insufficient evidence to determine whether this trend continued into low-income countries. Birth rates are consistently higher in lower-income settings,<sup>41</sup> and so many more pregnant women may be affected by SARS-CoV-2 infection in these regions<sup>42</sup> where specialist neonatal care may be limited.

### Limitations

Our study has several limitations. First, we chose to include studies defining SARS-CoV-2 infection by locally accepted clinical criteria as well as by PCR test confirmation. This decision was made as, particularly in lower-resourced settings, the availability and use of PCR testing may have been limited at various points throughout the pandemic and we wanted to ensure data from these settings would be included wherever possible. Although our data may therefore include women with similar, non-COVID-19 illnesses, the majority of included studies did use PCR testing.

Although we identified many studies reporting perinatal outcomes, there was little information reporting neonatal morbidity in depth. Granular detail describing the indirect neonatal consequences of maternal SARS-CoV-2 infection during pregnancy remain unclear. This limitation is particularly pronounced for neurodevelopmental outcomes. With the SARS-CoV-2 declared pandemic 2 years ago, we hope that more information regarding these crucial outcomes will emerge soon; one trial is currently recruiting (the ASPIRE trial) which will follow-up infant outcomes for 1.5 years,<sup>43</sup> and another (the SINEPOST study) will examine development from 18 months onwards.<sup>44</sup>

It should also be acknowledged that given the time taken to accurately extract, synthesise and report outcomes, our search was last updated over a year ago. Furthermore,

we found that studies varied widely on their reporting of severity of maternal disease and maternal symptoms; therefore, we were unable to study the effect of maternal symptomology on neonatal outcomes.

Finally, we found limited evidence from middle-income, and particularly, low-income countries, and little data regarding infections in early pregnancy. These are key research priorities to allow clinicians to adequately inform expectant families.

### CONCLUSION

There is a lack of evidence surrounding neonatal morbidity and longer-term outcomes for babies born to SARS-CoV-2-infected mothers, although there is an association with prematurity, caesarean delivery and admission to the neonatal unit. Neonatal and child health researchers should attempt to address this crucial evidence gap to adequately inform families, healthcare professionals and public health responses.

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**Contributors** The study was designed by SS and SA with input from CG, CB and KLD. Data extraction and analysis was completed by SS and SA, with CG participating where there was disagreement over inclusion of papers. SS prepared the manuscript, which was reviewed and edited by all. SS is responsible for the overall content as guarantor.

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