Received: 17 September 2020 | Revised: 16 October 2020 | Accepted: 20 October 2020

DOI: 10.1002/jmv.26622

REVIEW

JOURNAL OF MEDICAL VIROLOGY WILEY

Possible vertical transmission and antibodies against SARS-CoV-2 among infants born to mothers with COVID-19: A living systematic review

George M. Bwire[1] | Belinda J. Njiro[2] | Dorkasi L. Mwakawanga[3] | Deodatus Sabas[4] | Bruno F. Sunguya[5]

[1]School of Pharmacy, Muhimbili University of Health and Allied Sciences, Dar es Salaam, Tanzania

[2]School of Medicine, Muhimbili University of Health and Allied Sciences, Dar es Salaam, Tanzania

[3]School of Nursing, Muhimbili University of Health and Allied Sciences, Dar es Salaam, Tanzania

[4]Directorate of Library Services, Muhimbili University of Health and Allied Sciences, Dar es Salaam, Tanzania

[5]School of Public Health and Social Sciences, Muhimbili University of Health and Allied Sciences, Dar es Salaam, Tanzania

Correspondence
George M. Bwire, School of Pharmacy, Muhimbili University of Health and Allied Sciences, P.O. Box 65001, Dar es Salaam, Tanzania.
Email: georgebwire@gmail.com

Abstract

Current evidence suggests that coronavirus disease 2019 (COVID-19), caused by severe respiratory syndrome coronavirus 2 (SARS-CoV-2), is predominantly transmitted from human-to-human. However, evidence on vertical transmission and natural passive immunity among the newborns exposed to COVID-19 is scanty and varies. This poses a challenge on preventive interventions for the newborns. We conducted a systematic review to first, determine the likelihood of vertical transmission among COVID-19 exposed infants and second, determine whether antibodies against SARS-CoV-2 were generated among COVID-19 vertically exposed but negative infants. This review registered in PROSPERO searched evidence from PubMed/MEDLINE and Google Scholar, among others. About 517 studies were pooled, where 33 articles (5.8%) met the inclusion criteria such as infection prevention and control measures at birth. A total of 205 infants born to COVID-19 positive mothers were studied. Overall, 6.3% (13/205; 95% CI: 3.0%–9.7%) of the infants tested positive for COVID-19 virus at birth. Of 33 eligible studies, six studies (18.8%) reported about immunoglobulin G/M (IgG/IgM) against SARS-CoV-2. IgG/IgM were detected in 90% infants (10/11; 95% CI: 73.9%–107.9%) who tested negative for COVID-19 virus. The median antibody levels detected were 75.49 AU/ml (range, 7.25–140.32 AU/ml) and 3.79 AU/ml (range, 0.16–45.83 AU/ml), $p = .0041$ for IgG and IgM, respectively. In conclusion, the current evidence revealed a low possibility of vertical transmission of COVID-19 and antibodies against SARS-CoV-2 were detected among vertically exposed but negative infants. Further studies on transplacental transmission and the magnitude of natural passive immunity in infants born to mothers with COVID-19 are warranted.

KEYWORDS
antibodies, COVID-19, SARS-CoV-2, vertical transmission

1 | INTRODUCTION

Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)/COVID-19 virus and spread from person-to-person[1] was first reported from Wuhan, China in late December 2019.[2] Since then, there has been a rapid increase in the number of new cases and deaths from the disease, and overall changing in the disease landscape.[3] Like other viral infectious diseases,[4,5] pregnant women continue to be vulnerable to COVID-19.[6–8] The literature has reported the possible potential implications of COVID-19 in pregnancy but the debate on a possible vertical transmission is still ongoing.[9,10] Few studies have associated the potential influence of COVID-19 infection from an infected pregnant woman to her fetus or newborn, these include the possibility of miscarriages, preterm delivery, and neonatal infections.[11,12] The previous epidemic from severe acute respiratory syndrome coronavirus 1 (SARS-CoV) reported no prenatal transmission of SARS. This was confirmed through testing of amniotic fluid and umbilical cord blood obtained during cesarean section together with throat swab of the newborn.[13,14]

Evidence has started to show the likelihood of mother to child transmission of COVID-19 infection among the confirmed neonatal infections.[15–17] On the other hand, the detection of immunoglobulin (IgM/IgG) against SARS-CoV-2 IgG and IgM among infants born COVID-19 confirmed mothers but themselves tested COVID-19 negative have been reported.[18–23] This serological evidence raises more concern about the possible mother to child transmission of antibodies against SARS-CoV-2.[13,14] However, evidence seems to be scant and varying with regard to both vertical transmission and antibodies against COVID-19 virus among the exposed newborns. To address this scientific gap of clinical and policy implication, we conducted this systematic review to first, pull evidence to examine the likelihood of vertical transmission and antibodies against SARS-CoV-2 among newborns exposed to COVID-19.

2 | MATERIALS AND METHODS

2.1 | Design

This systematic review was conducted to address the following question, *"Is there a vertical transmission and antibody responses against SARS-CoV-2 in infants born to mothers with COVID-19?"* A systematic review protocol was developed following Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) guidelines[24] and registered in the International Prospective Register of Systematic Reviews (https://www.crd.york.ac.uk/prospero/: PROSPERO database registration number: CRD42020185362).

To ensure that current evidence and updated information are available to the research communities and final users, a living systematic review will be conducted using rapidly emerging and new research evidence generated through a continual literature search approach as previously described elsewhere.[25] Standard method of reporting living systematic reviews[26] were used and will be used every time when the new COVID-19 research evidence become available.

2.2 | Search strategy

Articles were retrieved using online search engines and library sources, including PubMed/MEDLINE and Google Scholar. In addition, websites of key healthcare organizations such as World Health Organization (WHO), Centre for Disease Prevention and Control (CDC), standard alone journals/publishers such as JAMA, NEJM, Wiley online library, Springer Nature, Elsevier, BMJ, Lancet, Cells, Nature, Science, and BMJ were searched with the help of Google. We also searched articles from pre-print servers, that is, Research Square and medRxiv. Data from December 1, 2019 to May 18, 2020 conducted in human beings, and published in the English language were included. The strategy was developed for PubMed/MEDLINE (Additional file 1) using keywords and MeSH (MEDLINE) then adapted to other databases. To be as inclusive as possible, the search strategy included the terms covering the concept of immunity and infection among infants born to mothers with COVID-19. Keywords such as "vertical transmission," "antibody," "immunoglobulin," "pregnant mother," "pregnancy," "child," "infant," "newborn," "SARS-CoV-2," and "COVID-19" were used.

2.3 | Eligibility criteria and study selection

To exclude irrelevant studies, two reviewers (GMB and BJN) independently screened the titles and abstracts, and a full-text articles were assessed for further consideration for inclusion. Disagreements on study eligibility were resolved by consensus, and/or a third reviewer was consulted if necessary. If the information on eligibility was unavailable and/or unclear, study authors were contacted to clarify. The selected studies were included based on laboratory-confirmed COVID-19 infection using quantitative real-time reverse transcription polymerase chain reaction (qRT-PCR) or dual fluorescence PCR and immunoassay such as enzyme-linked immunosorbent assay, patient pregnant on admission, infant's COVID-19 status soon after birth and infection control and prevention (IPC) measures during and after delivery, that is, mother wore N-95 during delivery, personnel protective equipment wore by healthcare workers, infants immediately separated with her mother to a negative pressure room and infants did not breastfeed before samples were taken. This review included, letter to the editor, correspondence, editorial, research article (case report, case series, cross-sectional, clinical trial, cohort, and case-control study) and so forth, however, articles that reported on the secondary data and reviews were excluded.

2.4 | Data management

All article citations retrieved from database searches were exported into EndNote software version X7 (Thomson Reuters, 2015) where

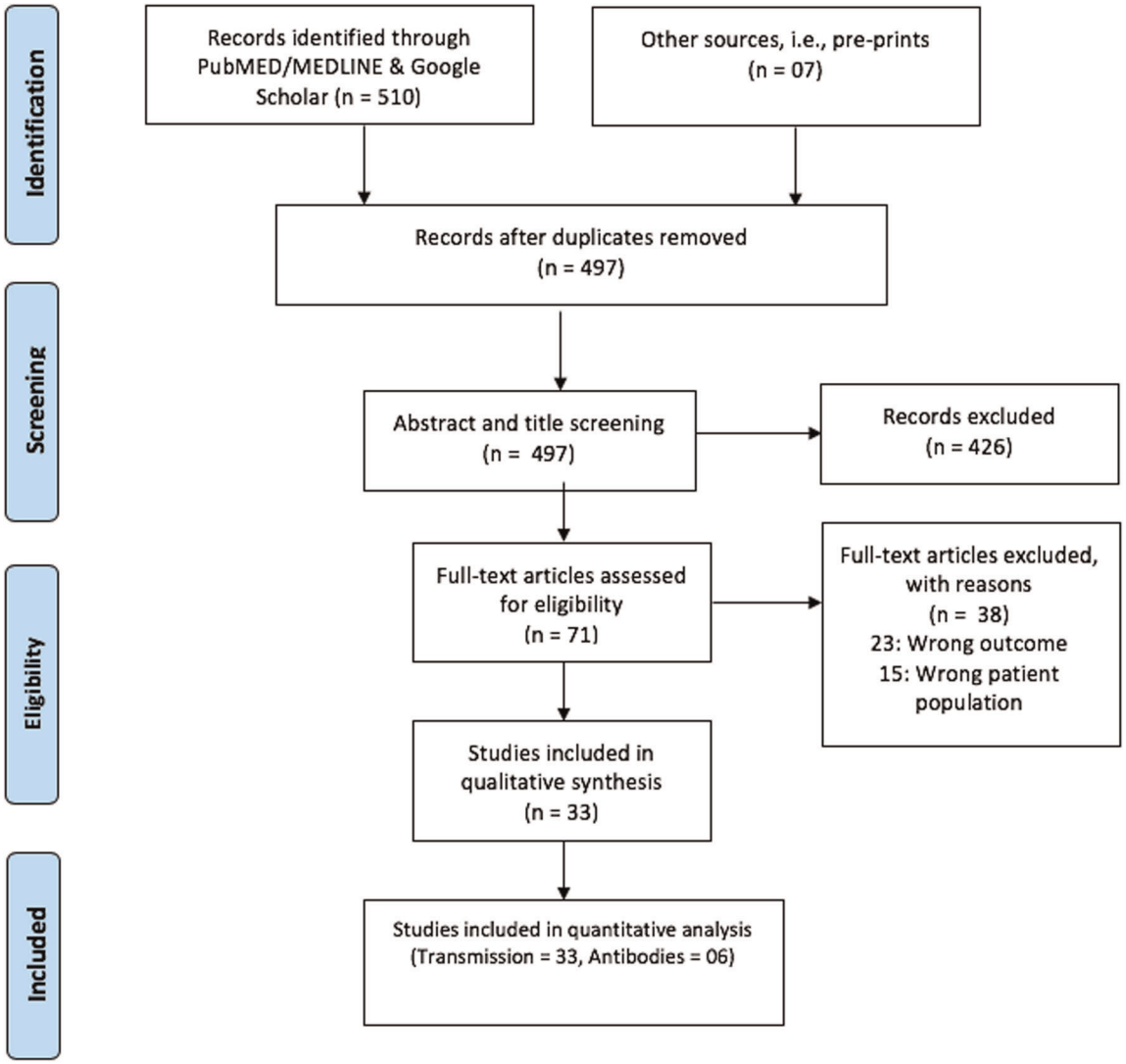

FIGURE 1 PRISMA diagram showing flow of article search and screening

duplicates were identified and removed. Identified publication(s) were analyzed using criteria based on vertical transmission and/or IgG/IgM against SARS-CoV-2 and maximum correspondence with inclusion criteria (Figure 1).

2.5 | Data extraction and quality assessment

The reviewers independently extracted the variables of interest from the selected studies using data extraction. Data extraction form was developed in Excel spreadsheet 2010 (Microsoft Corporation), pre-tested on three eligible articles and adjusted accordingly (Table 1). The primary endpoints were COVID-19 infection and IgG/M against SARS-CoV-2 from the samples taken at birth. PRISMA-P guideline[24] recommends a quality assessment of the included literature, but given the time from the first report of COVID-19 (December 31, 2019), most of the extracted studies were case reports with a very small number of participants (mostly one participant) per study. In this regard, the authors decided not to perform the risk assessment,[27] publication bias, heterogeneity, and meta-analysis.

2.6 | Summary measures and synthesis of results

A summary estimate of proportions for COVID-19 virus positive and IgG/IgM against SARS-CoV-2 among infants born to mothers with COVID-19 were determined using Open Meta Analyst software.[52] The statistical measures included along with 95% confidence interval (95% CI) for continuous variables. We performed a two-tailed nonparametric Mann–Whitney test to determine and compare the median antibody levels using Prism 7 (GraphPad Software). The narrative was written by the lead reviewer (GMB) and then checked independently by two reviewers (BJN and DLM). The variables that were missing from included articles were recorded as not reported (NR). No statistical test was applied in handling missing data. However, available information was used in recalculating some variables using the Open Meta Analyst calculator.

TABLE 1 Characteristics of the included studies

Author	Country	Design	Mode of delivery	Gestation period	COVID-19 (positive cases/total)	IgM/IgG against SARS-CoV-2 (detected/total)	IgM/IgG levels against SARS-CoV-2 in newborns	
							IgG (AU/ml)	IgM (AU/ml)
Al-kuraishy et al.[28]	Iraq	CR	Vaginal	Preterm	0/1.0	NR	NR	NR
Alzamora et al.[18]	Peru	CR	Cesarean	Preterm	1.0/1.0	0/1.0	ND	ND
Baud et al.[29]	Switzerland	CR	Vaginal	Preterm	1.0/1.0	NR	NR	NR
Buonsenso et al.[19]	Italy	CR	Cesarean	Full term	0/1.0	1.0/1.0	Weakly positive	ND
	Italy	CR	Cesarean	Preterm	0/1.0	NR	NR	NR
Chen et al.[30]	China	CR	Cesarean	Full term	0/3.0	NR	NR	NR
De Socio et al.[20]	Italy	CR	Vaginal	Full term	0/1.0	1.0/1.0	Strongly positive	Weakly detected
Díaz et al.[31]	Spain	CR	Cesarean	Full term	0/1.0	NR	NR	NR
Fan et al.[32]	China	CR	Cesarean	Full term	0/1.0			
	China	CR	Cesarean	Preterm	0/1.0			
Lee et al.[23]	Korea	CR	Cesarean	Full term	0/1.0			
Li al.[33]	China	CR	Cesarean	Preterm	0/1/0			
Liu et al.[34]	China	RT	NA	Full term	0/10			
Ferrazzi et al.[35]	Italy	RT	Vaginal	NA	2.0/24			
	Italy	RT	Cesarean	NA	0/18			
Lowe et al.[36]	Australia	CR	Vaginal	Full term	0/1.0			
Lu al.[37]	China	CR	Cesarean	Full term	0/1.0			
Lyra et al.[38]	Portugal	CR	Cesarean	Full term	0/1/0			
Zhu et al.[39]	China	RT	NA	Full term,	0/4			
	China	RT	NA	Preterm	0/6			
Zeng et al.[17]	China	PR	NA	Full term	2.0/29			
	China	PR	NA	Preterm	1/4.0			
Zeng et al.[21]	China	RT	Cesarean	Full term	0/6	6.0/6.0	125.5	39.6
							113.91	16.25
							75.49	3.79
							73.19	1.9
							51.38	0.96
							7.25	0.16
Zamaniyan et al.[40]	Iran	CR	Cesarean	Preterm	1/1.0	NR	NR	NR
Yu et al.[41]	China	RT	Cesarean	Full term	1/3.0			
Yin et al.[42]	China	RT	NA	Full term	0/12			
	China	RT	NA	Preterm	0/5			
Yang et al.[32]	China	PR	Cesarean	Full term	0/3			
	China	PR	Cesarean	Preterm	0/4			
Yan et al.[43]	China	RT	Cesarean	Full term	0/4			
	China	RT	Cesarean	Preterm	0/1			
Xiong et al.[22]	China	CR	Vaginal	Full term	0/1	0/1	ND	ND
Wang et al.[44]	China	CR	Cesarean	Preterm	0/1	NR	NR	NR

TABLE 1 (Continued)

Author	Country	Design	Mode of delivery	Gestation period	COVID-19 (positive cases/total)	IgM/IgG against SARS-CoV-2 (detected/total)	IgM/IgG levels against SARS-CoV-2 in newborns	
							IgG (AU/ml)	IgM (AU/ml)
Wang et al.[45]	China	CR	Cesarean	Preterm	1/1.0			
Sun et al.[46]	China	CR	Cesarean	Full term	1/1.0			
	china	CR	Cesarean	Preterm	1/2.0			
Sun et al.[47]	China	RT	NR	Full term	0/13			
Qiancheng et al.[48]	China	RT	NR	Full term	0/22			
	China	RT	NR	Preterm	0/1.0			
Peng et al.[49]	China	CR	Cesarean	preterm	0/1			
Chen et al.[50]	China	RT	Cesarean	Full term	0/5			
	China	RT	Cesarean	Preterm	0/4			
Dong et al.[7]	China	CR	Cesarean	Preterm	0/1	1/1	140.32	45.83
Vivant et al.[51]	France	CR	Cesarean	Preterm	1/1	NR	NR	NR

Note: Babies born before 37 weeks were termed as "preterm."

Abbbreviations: COVID-19, coronavirus disease 2019; CR, case report; NA, not applicable; ND, not detected; NR, not reported; PR, prospective study; RT, retrospective study; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

3 | RESULTS

3.1 | Characteristics of the studies included

A total of 517 studies were pooled from a systematic search, where only 33 articles (5.8%) were eligible for final analysis. Of 33 included studies, 21 were case reports (65.6%), 10 retrospective studies (28.1%), and two (6.3%) prospective studies. From 33 articles, a total of 205 infants were born to COVID-19 virus-positive mothers. All articles reported on COVID-19 transmission, but only six studies (18.8%) reported about IgG/IgM against SARS-CoV-2 among infants born to COVID-19 virus-positive mothers. Two articles had quantified (reported the metric values) IgG/IgM levels[7,21] whereas two articles reported unquantified detection of IgG/IgM.[19,20] Some pooled studies reported that no IgG/IgM was detected from the newborns' samples tested.[18,22] Most of the studies, 19 (59.4%) were conducted in China. Twenty-three studies (71.9%), reported that mothers delivered through a cesarean route with preterm delivery in the majority of the studies, 20 (62.5%). Except for retrospective studies where not applicable (NA) status was assigned in this review because of the limited information, all the remained studies implemented IPC measures during and after delivery (Table 1).

3.2 | The proportions of possible vertical transmission of SARS-CoV-2

Thirty-three studies were analyzed to determine the possible vertical transmission of among infants born to COVID-19 virus-positive mothers. A total of 205 infants were born to COVID-19 virus-positive mothers, where only 6.3% (13/205; 95% CI: 3.0%–9.7%) of the infants tested positive for COVID-19 virus at birth. Of 33 included studies, 21 were case reports (65.6%), 10 retrospective studies (28.1%), and 2 (6.3%) prospective studies. The proportions of the infants who contracted COVID-19 vertically from their mother were 22.2% (6/27; 95% CI: 6.5%–37.9%), 2.1% (3/141; 95% CI: −0.3% to 4.5%), 7.5% (3/40; 95% CI: −0.7% to 15.7%) for case reports, retrospective and prospective study, respectively.

A total of 19 studies (59.4%) were reported to be conducted in China and the remained from the rest part of the world. China reported 4.2% of infants vertically contracted COVID-19 from their mothers (7/167; 95% CI: 1.2%–7.2%) where those who were reported outside China were 10.5% (6/57; 2.6%–18.5%). Twenty-three studies (71.9%) reported about mothers who delivered through cesarean while six (18.7%) studies were vaginal delivery route. The remained studies did not report about the mode of delivery. Cesarean mode of delivery found 10% positive infants (7/70: 95% CI: 3.0%–17.0%) while for vaginal delivery route was 10.3% (3/29; −0.7% to 21.4%).

Twenty-one studies (63.6%) reported IPC were in place, other studies IPC were difficult to assess since they were retrospective study with no clear mention of IPC in place, hence assigned NA except two studies where IPC was NR. In the rest of the studies, IPC was not clearly reported. For those with IPC measures in place, 12.3% (9/73; 95% CI: 4.8%–19.9%) of the infants tested positive for COVID-19 at birth. A total of 20 studies (62.5%) reported preterm delivery while 12 (37.5%) were full-term delivery. Two studies gestation period was NR. In the group of full term, 3.2% (4/124; 95%CI: 0.1%–6.3%) infants tested COVID-19 virus positive while for preterm, 18.4% (7/38; 95% CI: 6.1%–30.7%) of infants born to COVID-19 virus-positive mothers were positive.

3.3 | IgG/IgM against SARS-CoV-2 among infants born to mothers with COVID-19

Of 33 included studies, only six studies (18.8%) reported about IgG/IgM against SARS-CoV-2 among infants born to COVID-19 virus-positive mothers. Antibodies were quantified in 11 infants, where 10 out of 11 infants (90.9%; 95% CI: 73.9%–107.9%) had IgG/IgM against SARS-CoV-2. Among 10 infants with detected antibodies against SARS-CoV-2, only one infant (10%; −8.6% to 28.6%) tested COVID-19 virus positive. Furthermore, one infant whose antibodies against SARS-CoV-2 were not detected tested positive for COVID-19. The median antibody levels detected in COVID-19 exposed newborns who tested negative for the virus after delivery but were born to mothers with COVID-19 were 75.49 AU/ml (range, 7.25–140.32 AU/ml) and 3.79 AU/ml (range, 0.16–45.83 AU/ml), $p = .0041$ for anti-SARS-CoV-2 IgG and IgM, respectively.

4 | DISCUSSION

This review summarizes findings for 205 infants born to mothers with COVID-19. The review aimed to determine the possible vertical transmission of COVID-19 and determine whether antibodies responses against COVID-19 virus were generated among vertically exposed but negative infants. It was found that 6.3% of infants born to COVID-19 mothers were infected. This finding correlates to those reported from the systematic review by Kotlyar et al.[8] In the current review, the transmission was reported both in preterm[18,29,30,40,51] and full-term born infants[30,46] and even where the infection prevention and control measures were in place.[18,29,51]

Furthermore, the vertical transmission was reported regardless of the mode of delivery, vaginal[29,35] or cesarean route.[18,30,40,46,51] Based on negative samples from amniotic fluid, cord blood, vaginal discharge, neonatal throat swabs, or breastmilk, WHO reported no evidence on mother-to-child transmission when infection manifests in the third trimester.[53] However, the recent case report conducted in France, reported the case of transplacental transmission of a male neonate who was delivered through a cesarean section with a gestational age of 35^{+5} weeks. A baby was delivered under a well infection prevention and control settings, amniotic fluid, blood and nonbronchoscopic, nasopharyngeal, rectal swabs, and bronchoalveolar lavage fluid samples were collected for RT-PCR and all were positive for the E and S genes of SARS-CoV-2.[51]

Findings from the current review were contrary to those reported by Gatta et al.,[12] from their review which involved 51 pregnant women, where three pregnancies were ongoing, among 48 remained pregnancies, 46 gave birth by cesarean delivery, and two gave birth vaginally, there was no evidence of vertical transmission recorded in all reported births. In this study, all studies were retrospective and conducted in the same country, China. In the current study, about 40% of the reported cases were reported outside China. However, the study reported a high number of preterm birth and cesarean delivery route similar to the findings of the current review where 71.9% were delivered by the cesarean route and 62.5% by preterm birth. Another rapid review conducted in 32 pregnant women affected with COVID-19 found no evidence of vertical transmission, the study reported 27 cesarean section, two vaginal delivery, and 47% delivered preterm.[11] A small sample size ($n = 32$) used in this rapid review may have contributed to the differences in detecting the number of infected infants compared with the current review ($n = 205$).

On the other hand, this review has revealed evidence for antibodies (IgG/IgM) against SARS-CoV-2 among infants tested negative for COVID-19 but born to COVID-19 mothers. Antibodies were quantified in 11 infants,[18–23] where 10 out of 11 infants (90.9%) had IgG/IgM against SARS-CoV-2. One infant whose antibodies were not detected tested positive for COVID-19.[18] In this study,[18] negative serology was found both in mother and neonate on the day of birth, and later seroconversion of the mother occurred. The delayed serological conversion curve can be explained in the studies conducted elsewhere in which IgM seroconverts after Day 5 from symptom onset.[54] In the study by Zeng et al.,[21] three infants were reported to have elevated IgG levels but normal IgM levels. However, virus-specific IgG/IgM was detected in all six neonatal blood sera samples. The IgG concentrations were elevated in five infants. IgG elevation is explained by the fact that IgG is passively transferred across the placenta from mother to fetus at the beginning of 20th gestational week and become more elevated at the time of birth.[55] But, IgM, which was detected in two infants,[21] is unlikely to be transferred from mother to fetus due to large molecular structure.[56]

The presence of this specific antibody IgG/IgM for the infants who tested negative, and were born to mothers with COVID-19 indicated the possibility of transplacental immunity (natural passive immunity) while the one who had COVID-19 developed antibodies against SARS-CoV-2 following exposure to the virus (natural active immunity). Using the reference range of less than 10 AU/ml,[21] this study found high levels of antibodies (75.49 AU/ml) for IgG and low levels (3.79 AU/ml) of IgM against SARS-CoV-2 among the exposed but negative newborns. Generally, IgM is highly expressed as the first line antibodies during the time when the disease is active whereas IgG detection usually indicates the long-time infection or recovery from the past infection.[57] Furthermore, IgM is large in molecular structure making them unlikely to cross the placenta.[56] However, there were studies,[7,20,21] which reported the detection of SARS-CoV2-IgM among uninfected infants but born to COVID-19 positive mothers.

Immunological experience form other respiratory infections such as influenza indicated that natural transplacental influenza antibodies protect infants during the first few months of life.[58] In addition, artificial maternal influenza antibodies significantly reduced the rate of laboratory-confirmed influenza in infants.[59] That experience can be employed to further study the generated IgG/IgM against SARS-CoV-2 and find out their protective effect to the newborns.

This study is limited by the small number of participants obtained from the extracted studies, type of the study (low-quality study designs, i.e., retrospective studies) included, and limited

samples from amniotic fluid and cord blood. Nevertheless, this is the first review with more than 200 infants born to mothers with COVID-19 where IPC measures before samples were taken were assessed before considering an article for final analysis. Findings from this review are important for understanding the transmission likelihood and immunological characteristics of infants whose mothers were infected by SARS-CoV-2.

5 | CONCLUSION

Currently, there is low possibility of vertical transmission in infants born to COVID-19 virus-positive mothers. In addition, antibodies against SARS-CoV-2 were detected among infants who tested COVID-19 negative. Further studies on transplacental transmission and the magnitude of natural passive immunity in infants born to mothers with COVID-19 are warranted.

ACKNOWLEDGMENTS

Authors (GMB and BJN) acknowledge the training support received from Muhimbili University of Health and Allied Sciences through Systematic Review and Meta-analysis workshop funded by Swedish International Development Cooperation Agency (Sida), Sweden.

CONFLICT OF INTERESTS

The authors declare that they have no competing interests.

AUTHOR CONTRIBUTIONS

George M. Bwire designed the study protocol, conducted data extraction and synthesis, and drafted the narrative synthesis. Belinda J. Njiro designed the study protocol, conducted data extraction, and synthesis. Deodatus Sabas designed the protocol and performed data search. Dorkasi L. Mwakawanga revised the narrative synthesis. Bruno F. Sunguya participated in protocol development and revised the narrative synthesis. All authors have read and approved the final version of this manuscript.

DATA AVAILABILITY STATEMENT

A data sets used and/or analyzed in this review are provided in the main manuscript and its supplementary material (Additional file 1).

REFERENCES

1. Adnan M, Khan S, Kazmi A, Bashir N, Siddique R. COVID-19 infection: origin, transmission, and characteristics of human coronaviruses. *J Adv Res*. 2020;24:91-98. https://doi.org/10.1016/j.jare.2020.03.005
2. Sohrabi C, Alsafi Z, O'Neill N, et al. World Health Organization declares global emergency: A review of the 2019 novel coronavirus (COVID-19). *Int J Surg*. 2020;76:71-76. https://doi.org/10.1016/j.ijsu.2020.02.034
3. Rothan HA, Byrareddy SN. The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak. *J Autoimmun*. 2020;109:102433. https://doi.org/10.1016/j.jaut.2020.102433
4. Mertz D, Geraci J, Winkup J, Gessner BD, Ortiz JR, Loeb M. Pregnancy as a risk factor for severe outcomes from influenza virus infection: A systematic review and meta-analysis of observational studies. *Vaccine*. 2017;35:521-528. https://doi.org/10.1016/j.vaccine.2016.12.012
5. Chibueze EC, Tirado V, Lopes KS, et al. Zika virus infection in pregnancy: a systematic review of disease course and complications. *Reprod Health*. 2017;14:28. https://doi.org/10.1186/s12978-017-0285-6
6. Lamouroux A, Attie-Bitach T, Martinovic J, Ville Y. Evidence for and against vertical transmission for severe acute respiratory syndrome coronavirus 2. *Am J Obstet Gynecol*. 2020;223(1):91.e1-91.e4.
7. Dong L, Tian J, He S, et al. Vertical transmission of SARS-CoV-2 from and infectd mother to her newborn. *Public Health Ethics*. 2020;323(18):phw039. https://doi.org/10.1093/phe/phw039
8. Kotlyar AM, Grechukhina O, Chen A, et al. Systematic review vertical transmission of coronavirus disease 2019: a systematic review and meta-analysis [published online ahead of print July 31, 2020]. *Am J Obstet Gynecol*. 2020. https://doi.org/10.1016/j.ajog.2020.07.049
9. Tseng J-Y. Potential implications of SARS-CoV-2 on pregnancy. *Taiwan J Obstet Gynecol*. 2020;59(3):464-465. https://doi.org/10.1016/j.tjog.2020.03.025
10. Nunzia A, Gatta D, Rizzo R, Pilu G, Simonazzi G. Systematic review coronavirus disease 2019 during pregnancy: a systematic review of reported cases. *Am J Obstet Gynecol*. 2020;223:1-6. https://doi.org/10.1016/j.ajog.2020.04.013
11. Mullins E, Evans D, Viner RM, O'Brien P, Morris E. Coronavirus in pregnancy and delivery: rapid review. *Ultrasound Obstet Gynecol*. 2020:586-592. https://doi.org/10.1002/uog.22014
12. Della Gatta AN, Rizzo R, Pilu G, Simonazzi G. COVID19 during pregnancy: a systematic review of reported cases. *Am J Obstet Gynecol*. 2020;223:1-6. https://doi.org/10.1016/j.ajog.2020.04.013
13. Hospital PM, Kong H, Wai F, Cheng T, Peiris JSM, Lee KH. Infants born to mothers with severe acute respiratory syndrome. *Pediatrics*. 2003;112(4):e254. https://doi.org/10.1542/peds.112.4.e254
14. Wong SF, Chow KM, Leung TN, et al. Pregnancy and perinatal outcomes of women with severe acute respiratory syndrome. *Am J Obstet Gynecol*. 2004;191:292-297. https://doi.org/10.1016/j.ajog.2003.11.019
15. Yu N, Li W, Kang Q, et al. Clinical features and obstetric and neonatal outcomes of pregnant patients with COVID-19 in Wuhan, China: a retrospective, single-centre, descriptive study. *Lancet Infect Dis*. 2020;20(5):559-564. https://doi.org/10.1016/S1473-3099(20)30176-6
16. Zeng H, Xu C, Fan J, et al. Antibodies in infants born to mothers with COVID-19 pneumonia. *JAMA*, 323(18):1848-1849. https://doi.org/10.1038/2101070a0
17. Zeng L, Xia S, Yuan W, et al. Neonatal early-onset infection With SARS-CoV-2 in 33 neonates born to mothers with COVID-19 in Wuhan, China. *JAMA Pediatr*. 2020;174(7):722-725. https://doi.org/10.1001/jamapediatrics.2020.0878
18. Alzamora MC, Paredes T, Caceres D, et al. Severe COVID-19 during pregnancy and possible vertical transmission. *Am J Perinatol*. 2020;1(212):861-865. https://doi.org/10.1055/s-0040-1710050
19. Buonsenso D, Costa S, Sanguinetti M, et al. Neonatal late onset infection with severe acute respiratory syndrome coronavirus 2. *Am J Perinatol*. 2020;1(212):869-872. https://doi.org/10.1055/s-0040-1710541
20. De Socio GV, Malincarne L, Arena S, et al. Delivery in asymptomatic Italian woman with SARS-CoV-2 infection. *Mediterr J Hematol Infect Dis*. 2020;12(1):e2020033. https://doi.org/10.4084/MJHID.2020.033
21. Zeng Hui, Xu Chen, Fan Junli, et al. In infants born to mothers with COVID-19 pneumonia tests. *JAMA*. 2000;210:1070-1071. https://doi.org/10.1038/2101070a0

22. Xiong X, Wei H, Zhang Z, et al. Vaginal delivery report of a healthy neonate born to a convalescent mother with COVID19. *J Med Virol*. 2020;92(9):1657-1659. https://doi.org/10.1002/jmv.25857
23. Lee DH, Lee J, Kim E, Woo K, Park HY, An J. Emergency cesarean section on severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) confirmed patient. *Korean J Anesthesiol*. 2020;73:347-351. https://doi.org/10.4097/kja.20116
24. Shamseer L, Moher D, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (prisma-p) 2015: elaboration and explanation. *BMJ*. 2015;349:1-25. https://doi.org/10.1136/bmj.g7647
25. Centeno-Tablante E, Medina-Rivera M, Finkelstein JL, et al. Transmission of SARS-CoV-2 through breast milk and breastfeeding: a living systematic review [published online ahead of print August 28, 2020]. *Ann NY Acad Sci*. 2020:1-23. https://doi.org/10.1111/nyas.14477
26. Elliott JH, Turner T, Clavisi O, et al. Living systematic reviews: an emerging opportunity to narrow the evidence-practice gap. *Plos Med*. 2014;11(2):1-6. https://doi.org/10.1371/journal.pmed.1001603
27. Zaigham M, Andersson O. Maternal and perinatal outcomes with COVID-19: A systematic review of 108 pregnancies. *Acta Obstet Gynecol Scand*. 2020;99(7):823-829. https://doi.org/10.1111/aogs.13867
28. Al-kuraishy H, Al-Maiahy T, Al-Gareeb A, Musa R, Ali Z. COVID-19 pneumonia in an Iraqi pregnant woman with preterm delivery [published online ahead of print October 24, 2020]. *Asian Pacific J Reprod*. 2020. https://doi.org/10.4103/2305-0500.282984
29. Baud D, Greub G, Favre G, et al. Second-trimester miscarriage in a pregnant woman with SARS-CoV-2 infection. *JAMA*. 2020;323:1-3. https://doi.org/10.1001/jama.2020.7233
30. Chen Y, Peng H, Wang L, et al. Infants born to mothers with a new coronavirus (COVID-19). *Front Pediatr*. 2020;8:1-5. https://doi.org/10.3389/fped.2020.00104
31. Díaz CA, Maestro ML, Pumarega TMM, Antón BF, Alonso CRP. Primer caso de infección neonatal por SARS-CoV-2 en España (First case of neonatal infection due to COVID 19 in Spain). *An Pediatr (Barc)*. 2020;92(4):237-238. https://doi.org/10.1016/j.anpedi.2020.03.002
32. Fan C, Lei D, Fang C, Li C, Wang M, Yuling L. Perinatal transmission of COVID-19 associated SARS-CoV-2: should we worry? *Foreign Aff*. 2012;91(5):287. https://doi.org/10.1017/CBO9781107415324.004
33. Li Y, Zhao R, Zheng S, et al. Lack of vertical transmission of severe acute respiratory syndrome coronavirus 2, China. *Emerg Infect Dis*. 2020;26(6):200287-201336. https://doi.org/10.3201/eid2606.200287
34. Liu W, Wang J, Li W, Zhou Z, Liu S, Rong Z. Clinical characteristics of 19 neonates born to mothers with COVID-19. *Front Med*. 2020;14(2):193-198. https://doi.org/10.1007/s11684-020-0772-y
35. Ferrazzi E, Frigerio L, Savasi V, et al. Vaginal delivery in SARS-CoV-2 infected pregnant women in Northern Italy: a retrospective analysis. *BJOG*. 2020;127:0-1. https://doi.org/10.1111/1471-0528.16278
36. Lowe B, Bopp B. COVID-19 vaginal delivery - a case report. *Aust New Zeal J Obstet Gynaecol*. 2020;60:465-466. https://doi.org/10.1111/ajo.13173
37. Lu D, Sang L, Du S, Li T, Chang Y, Yang X. Asymptomatic COVID-19 infection in late pregnancy indicated no vertical transmission [published online ahead of print April 24, 2020]. *J Med Virol*. 2020:1-5. https://doi.org/10.1002/jmv.25927
38. Lyra J, Valente R, Rosario M, Guimaraes M. Cesarean section in a pregnant woman with COVID-19: first case in Portugal. *Acta Med Port*. 2020;33:1-3. https://doi.org/10.20344/amp.13883
39. Zhu H, Wang L, Fang C, et al. Clinical analysis of 10 neonates born to mothers with 2019-nCoV pneumonia. *Transl Pediatr*. 2020;9(1):51-60. https://doi.org/10.21037/tp.2020.02.06
40. Zamaniyan M, Ebadi A, Aghajanpoor Mir S, Rahmani Z, Haghshenas M, Azizi S. Preterm delivery in pregnant woman with critical COVID -19 pneumonia and vertical transmission [published online ahead of print April 17, 2020]. *Prenat Diagn*. 2020. https://doi.org/10.1002/pd.5713
41. Yu N, Li W, Kang Q, Zeng W, Feng L, Wu J. No SARS-CoV-2 detected in amniotic fluid in mid-pregnancy. *Lancet Infect Dis*. 2020;3099(20):19-20. https://doi.org/10.1016/S1473-3099(20)30320-0
42. Yin M, Zhang L, Deng G, et al. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection during pregnancy in China: a retrospective cohort study [published online ahead of print April 11, 2020]. *medRxiv*. 2020. https://doi.org/10.1101/2020.04.07.20053744
43. Yan J, Guo J, Fan C, et al. Coronavirus disease 2019 (COVID-19) in pregnant women: a report based on 116 cases. *Am J Obstet Gynecol*. 2020;223(1):111.e1-111.e14. https://doi.org/10.1016/j.ajog.2020.04.014
44. Wang X, Zhou Z, Zhang J, Zhu F, Tang Y, Shen X. A case of 2019 novel coronavirus in a pregnant woman with preterm delivery. *Clin Infect Dis*. 2020;71(15):844-846. https://doi.org/10.1093/cid/ciaa200
45. Wang S, Guo L, Chen L, et al. A case report of neonatal COVID-19 infection in China. *Clin Infect Dis*. 2020;71(15):853-857. https://doi.org/10.1093/cid/ciaa225
46. Sun M, Xu G, Yang Y, et al. Evidence of mother-newborn infection with COVID-19. *Br J Anaesth*. 2020;125(2):e245-e247. https://doi.org/10.1016/j.bja.2020.04.066
47. Yang H, Sun G, Tang F, et al. Clinical features and outcomes of pregnant women suspected of coronavirus disease 2019. *J Infect*. 2020;81(1):e40-e44. https://doi.org/10.1016/j.jinf.2020.04.003
48. Qiancheng X, Jian S, Lingling P, et al. Coronavirus disease 2019 in pregnancy. *Int J Infect Dis*. 2020;95:376-383. https://doi.org/10.1016/j.ijid.2020.04.065
49. Peng Z, Wang J, Mo Y, et al. Unlikely SARS-CoV-2 vertical transmission from mother to child: a case report. *J Infect Public Health*. 2020;13(5):818-820. https://doi.org/10.1016/j.jiph.2020.04.004
50. Chen H, Guo J, Wang C, et al. Clinical characteristics and intrauterine vertical transmission potential of COVID-19 infection in nine pregnant women: a retrospective review of medical records. *Lancet*. 2020;395(10226):809-815. https://doi.org/10.1016/S0140-6736(20)30360-3
51. Vivanti A, Vauloup-Fellous C, Prevot S, et al. Transplacental transmission of SARS-CoV-2 infection. *Nat Commun*, 11:3572. https://doi.org/10.21203/rs.3.rs-28884/v1
52. Wallace BC, Schmid CH, Lau J, Trikalinos TA. Meta-Analyst: software for meta-analysis of binary, continuous and diagnostic data. *BMC Med Res Methodol*. 2009;9(1):1-12. https://doi.org/10.1186/1471-2288-9-80
53. World Health Organization. WHO Clinical management of severe acute respiratory infection (SARI) when COVID-19 disease is suspected (WHO, March 12, 2019). 2020. https://www.who.int/internal-publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-(ncov)-infection-is-suspected%0A, http://apps.who.int/iris/bitstream/10665/178529/1/WHO_MERS_Clinical_15.1_eng.pdf
54. Melville JM, Moss TJM. The immune consequences of preterm birth. *Front Neurosci*. 2013;7:79. https://doi.org/10.3389/fnins.2013.00079
55. Kohler PFFR. Elevation of cord over maternal IgG immunoglobulin: evidence for an active placental IgG transport. *Nature*. 1966;210(5040):1070-1071. https://doi.org/10.1038/2101070a0
56. Ng WF, Wong SF, Lam A, et al. The placentas of patients with severe acute respiratory syndrome: a pathophysiological

evaluation. *Pathology*. 2006;38(3):210-218. https://doi.org/10.1080/00313020600696280
57. Li Z, Yi Y, Luo X, et al. Development and clinical application of a rapid IgM-IgG combined antibody test for SARS-CoV-2 infection diagnosis. *J Med Virol*. 2020;92:1518-1524. https://doi.org/10.1002/jmv.25727
58. Puck JM, Glezen WP, Frank AL, Six HR. Protection of infants from infection with influenza A virus by transplacentally acquired antibody. *J Infect Dis*. 1980;142(6):844-849.
59. Zaman K, Roy E, Arifeen SE, et al. Effectiveness of maternal influenza immunization in mothers and infants. *N Engl J Med*. 2008;359(15):1555-1564. https://doi.org/10.1056/NEJMoa0708630

SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

How to cite this article: Bwire GM, Njiro BJ, Mwakawanga DL, Sabas D, Sunguya BF. Possible vertical transmission and antibodies against SARS-CoV-2 among infants born to mothers with COVID-19: A living systematic review. *J Med Virol*. 2021;93:1361–1369. https://doi.org/10.1002/jmv.26622