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RESEARCH ARTICLE

COVID-19 antibody positivity over time and pregnancy outcomes in seven low-and-middle-income countries: A prospective, observational study of the Global Network for Women's and Children's Health Research

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Abstract

Objectives: To determine COVID-19 antibody positivity rates over time and relationships to pregnancy outcomes in low- and middle-income countries (LMICs).

Design: With COVID-19 antibody positivity at delivery as the exposure, we performed a prospective, observational cohort study in seven LMICs during the early COVID-19 pandemic.

Setting: The study was conducted among women in the Global Network for Women's and Children's Health's Maternal and Newborn Health Registry (MNHR), a prospective, population-based study in Kenya, Zambia, the Democratic Republic of the Congo (DRC), Bangladesh, Pakistan, India (two sites), and Guatemala.

Population: Pregnant women enrolled in an ongoing pregnancy registry at study sites.

Methods: From October 2020 to October 2021, standardised COVID-19 antibody testing was performed at delivery among women enrolled in MNHR. Trained staff masked to COVID-19 status obtained pregnancy outcomes, which were then compared with COVID-19 antibody results.

Main Outcome Measures: Antibody status, stillbirth, neonatal mortality, maternal mortality and morbidity.

Results: At delivery, 26.0% of women were COVID-19 antibody positive. Positivity increased over the four time periods across all sites: 13.8%, 15.4%, 21.0% and 40.9%. In the final period, positivity rates were: DRC 27.0%, Kenya 33.1%, Pakistan 32.8%, Guatemala 37.0%, Zambia 37.8%, Bangladesh 47.2%, Nagpur, India 57.4% and Belagavi, India 62.4%. Adjusting for site and maternal characteristics, stillbirth, neonatal mortality, low birthweight and preterm birth were not significantly associated with COVID-19. The adjusted relative risk (aRR) for stillbirth was 1.27 (95% CI 0.95–1.69). Postpartum haemorrhage was associated with antibody positivity (aRR 1.44; 95% CI 1.01–2.07).

Conclusions: In pregnant populations in LMICs, COVID-19 antibody positivity has increased. However, most adverse pregnancy outcomes were not significantly associated with antibody positivity.

KEYWORDS
developing countries, obstetrics and gynaecology

1 | INTRODUCTION

The World Health Organization (WHO) declared COVID-19 to be a worldwide pandemic in February 2020.[1] With several important variants emerging, COVID-19 has continued to spread and cause death and morbidity in people of both sexes and all ages in all countries to the present time.[2] However, far less is known regarding the extent of the pandemic or its outcomes among pregnant women or their offspring. The initial COVID-19 research largely originated from high-income countries,[3–8] although studies from low- and middle-income countries (LMIC) have also been published.[9,10] Studies from the USA and European countries suggest that pregnancy outcomes may be worse among pregnant women with severe COVID-19 during pregnancy, but few population-based studies have been carried out.[11,12] Preterm birth, caesarean delivery and maternal morbidity have all been reported to be increased in association with COVID-19. The research published to date suggests that these adverse outcomes are more commonly associated with women who have existing co-morbidities such as diabetes, hypertensive disease or obesity, or have severe COVID-19 disease.[12,13] However, few studies have evaluated the impact of COVID-19 in geographic-based populations during pregnancy on maternal, fetal and neonatal outcomes in LMICs.

To better understand the impact of the pandemic on pregnant women and their offspring, we sought to determine the population-based prevalence of COVID-19 using antibody testing on serum samples drawn at delivery among pregnant women in eight sites in seven LMICs before the widespread availability of vaccination. Specifically, we aimed to determine the rates of positive antibody tests over time, to determine demographic factors associated with a positive test, and to determine the risk of adverse outcomes in women who were antibody positive. This is a sub-study of a pregnancy registry conducted in the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Global Network for Women's and Children's Health Research (Global Network).[14,15]

2 | METHODS

The Global Network's Maternal and Newborn Health Registry (MNHR) is a prospective, population-based observational study initiated in 2009. All pregnant women in defined geographic communities are identified by the

registry administrators, and if consented, are enrolled. Pregnancies are included whether the deliveries took place in a hospital, in a clinic or at home. Because of differences in the gestational ages of individual women's registration, and sensitivity to reporting abortions, pregnancy outcomes that occur at less than 20 weeks of gestation are not uniformly collected across sites. The Global Network includes sites in western Kenya, Zambia (Kafue and Chongwe), the DRC (North and South Ubangi Provinces), Bangladesh (Tangail district), Pakistan (Thatta in Sindh Provence), India (Belagavi and Nagpur) and Guatemala (Chimaltenango). The registry administrators completed data collection at three main points for each pregnant woman. The first was at her enrolment in prenatal care, the second was completed soon after delivery and is focused on the pregnancy outcome, and the third, for both the mother and infant, was completed 42 days after delivery.

The MNHR, including the sites conducting the study, and the definitions for the terms and outcomes have previously been described.[14,15] Stillbirth was defined as the birth of a baby at 20 weeks or more of gestation with no sign of life including respiration, a heartbeat or movement. A neonatal death was defined as the death of a live-born infant in the first 28 days of life. A preterm birth was defined as a birth at less than 37 weeks of gestation, and low birthweight as a baby with a birthweight less than 2500 g. Antepartum and postpartum haemorrhage were based on mother's reports.

The COVID-19 antibody study, embedded within the MNHR, included a sub-set of women who were approached at delivery and enrolled. The COVID-19 antibody study starting date varied by site (October 2020 for Pakistan; in November 2020, for the DRC, Bangladesh, Guatemala and Nagpur, India; in December 2020, for Kenya and Belagavi, India; and in February 2021 for Zambia). We collected a serum sample at or near delivery for each mother who was approached and consented. The antibody test results for all specimens collected in those sites were analysed and linked to data in the MNHR. For this study, participants with samples collected through to 31 October 2021 were included as several sites started to introduce vaccination of pregnant women around this time.

Because of our desire to track positivity rates over time, an assumption that the pandemic would wane over time, and because of resource constraints, each site was asked to enrol a maximum of 170 women per month in the COVID-19 antibody study. Therefore, each month, most sites ended enrolment in the antibody study once the target of 170 enrolees was reached. For various reasons, some sites did not reach the goal of 170 women per month. Therefore, although we nearly reached our original goal of about 16 000 participants, the enrolments by site and by month were varied.

2.1 | Sensitivity analyses

We also performed several sensitivity analyses. These included an analysis of outcomes of approximately 2400 pregnancies in four sites (Pakistan, Bangladesh, Guatemala and Nagpur, India) where specimens collected at prenatal care and at delivery in the same women were available. As we had information about COVID-19 vaccination status at delivery, we also performed an analysis only in the women who had not been vaccinated.

2.2 | COVID-19 antibody testing methods

2.2.1 | Blood collection and serum separation

Whole blood samples were collected from the mothers by venepuncture. After preparation, serum samples were stored at a central location at each site at −20°C or less. The serum samples were later processed for serology testing.

2.2.2 | Antibody assessment

A serology test was performed to identify the presence of antibodies against SARS-CoV-2 using Zeus's SARS-CoV-2 IgG Test System (Zeus Scientific), which received an Emergency Use Authorization by the US Food and Drug Administration. The test is an enzyme-linked immunosorbent assay, which was designed to specifically target IgG antibodies to the S1 receptor binding domain of the spike protein and a nucleoprotein.

The assay was performed by laboratory staff at each of the international sites according to the manufacturer's protocol. Quality control assessments were performed for all assays as recommended by the manufacturer to validate the runs. If all requirements were satisfied, the assay was considered valid. For invalid assays, the samples were re-analysed using a new kit. For valid assays, the sample optical densities and the cutoff optical density were used to calculate an index value for each sample, which provided negative, indeterminate/equivocal or positive results. Interpretation of the results is shown in Figure S1.

Samples with indeterminate/equivocal results after the initial screen were re-assayed in duplicate. The quality control assessment and the sample index values for valid assays were executed as described above. Final determination (negative, positive or indeterminate) for each repeated indeterminate sample was made by assessing the results of the first and the repeat assays.

2.3 | Statistical analyses

We originally designed the study to occur for a 12-month period to meet the main study objectives: (1) to determine the COVID-19 antibody prevalence over time, and (2) to detect the outcomes of interest, including stillbirth and neonatal death. At that time, we assumed a COVID-19 positivity rate of at least 8%. Assuming 80% power, we estimated that we needed 16 000 participants overall to detect a relative risk

(RR) of 1.5 if the underlying antibody positivity rate was at least 8% and baseline prevalence of the outcome of interest was 3%. Because of our interest in tracking over time, each of the eight sites targeted 170 participants per month and at least 2000 over the study period.

This analysis included those women who delivered at 20 weeks of gestation or more and had a COVID-19 antibody test at delivery completed on samples collected from October 2020 through October 2021. Because we analysed data over a 13-month period, for the time trend analyses, we used blocks as follows: October to December 2020, January to March 2021, April to June 2021 and July to October 2021.

We calculated the prevalence of antibody positivity. In addition, adjusted relative risks (aRRs) and 95% confidence intervals (CIs) were obtained from generalised linear models with a Poisson distribution and a log link adjusting for COVID-19 sample result, site, maternal education, maternal age, parity, antenatal care visits, delivery location, socioeconomic status, antepartum haemorrhage, postpartum haemorrhage and hypertensive disorders of pregnancy. All analyses were conducted in SAS v. 9.4 (SAS Institute, Cary, NC, USA).

3 | RESULTS

Figure 1 summarises enrolment in the Global Network antibody study carried out between 1 October 2020 and 31 October 2021. Across the sites, of the 31 514 women enrolled in the MNHR who had a delivery at 20 weeks of gestation or later, 14 351 were approached for the COVID-19 antibody study and of those, 14 224 consented (99.1%) and 14 015 had results available. The number of samples collected and

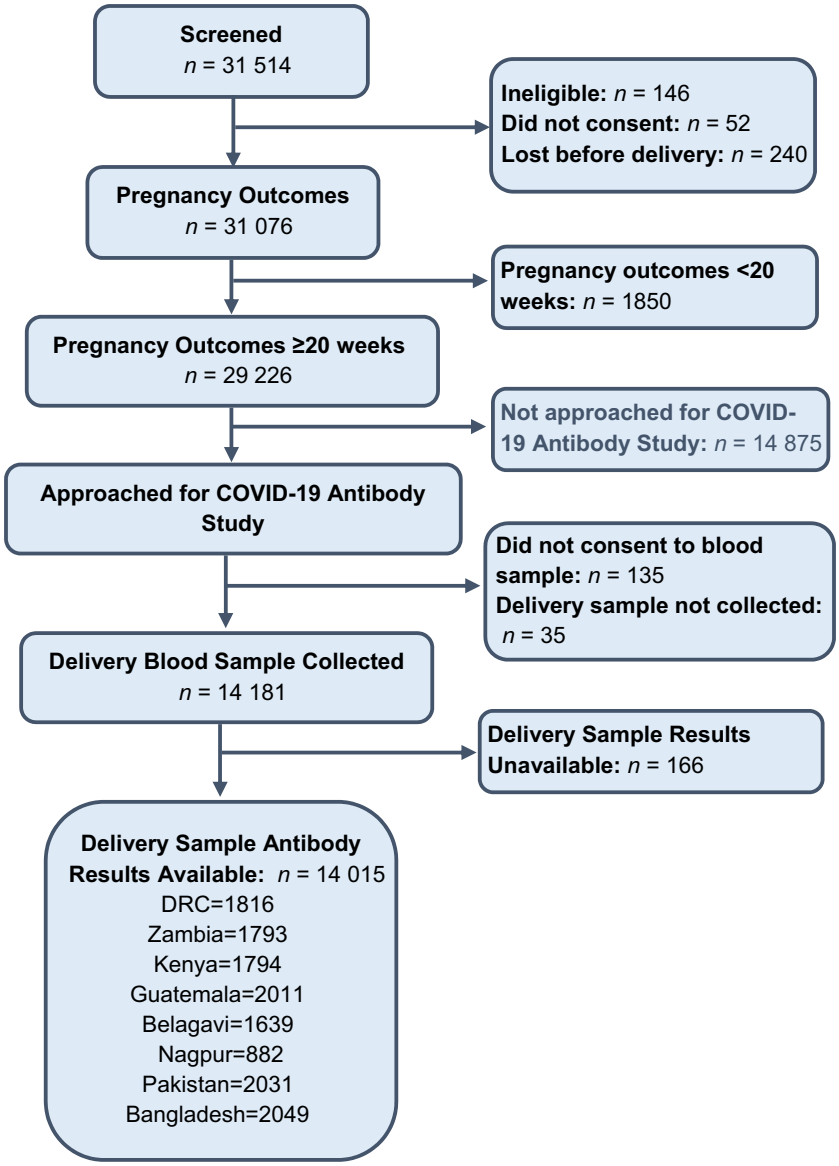


FIGURE 1 Enrolment in the Global Network COVID-19 Antibody Study, October 2020 to October 2021

TABLE 1 Maternal characteristics of women in the COVID-19 antibody study

Variable	Overall, *n* (%)	DRC, *n* (%)	Zambia, *n* (%)	Kenya, *n* (%)	Guatemala, *n* (%)	Belagavi, *n* (%)	Nagpur, *n* (%)	Pakistan, *n* (%)	Bangladesh, *n* (%)
Women with COVID-19 delivery sample results available	14 015	1816	1793	1794	2011	1639	882	2031	2049
Education	14 014	1816	1793	1793	2011	1639	882	2031	2049
No schooling	2815 (20.1)	565 (31.1)	159 (8.9)	18 (1.0)	146 (7.3)	76 (4.6)	13 (1.5)	1692 (83.3)	146 (7.1)
1–6 years	2773 (19.8)	679 (37.4)	216 (12.0)	211 (11.8)	802 (39.9)	116 (7.1)	21 (2.4)	146 (7.2)	582 (28.4)
7–12 years	7474 (53.3)	566 (31.2)	1364 (76.1)	1433 (79.9)	893 (44.4)	1202 (73.3)	660 (74.8)	177 (8.7)	1179 (57.5)
≥13 years	952 (6.8)	6 (0.3)	54 (3.0)	131 (7.3)	170 (8.5)	245 (14.9)	188 (21.3)	16 (0.8)	142 (6.9)
Age (years)	14 013	1816	1793	1792	2011	1639	882	2031	2049
<20	2313 (16.5)	470 (25.9)	369 (20.6)	385 (21.5)	360 (17.9)	127 (7.7)	20 (2.3)	59 (2.9)	523 (25.5)
20–35	10 899 (77.8)	1206 (66.4)	1276 (71.2)	1298 (72.4)	1482 (73.7)	1505 (91.8)	855 (96.9)	1841 (90.6)	1436 (70.1)
>35	801 (5.7)	140 (7.7)	148 (8.3)	109 (6.1)	169 (8.4)	7 (0.4)	7 (0.8)	131 (6.5)	90 (4.4)
Parity	14 015	1816	1793	1794	2011	1639	882	2031	2049
0	4464 (31.9)	419 (23.1)	527 (29.4)	598 (33.3)	730 (36.3)	589 (35.9)	426 (48.3)	379 (18.7)	796 (38.8)
1–2	6236 (44.5)	549 (30.2)	789 (44.0)	714 (39.8)	875 (43.5)	950 (58.0)	441 (50.0)	780 (38.4)	1138 (55.5)
>2	3315 (23.7)	848 (46.7)	477 (26.6)	482 (26.9)	406 (20.2)	100 (6.1)	15 (1.7)	872 (42.9)	115 (5.6)
Delivery location	14 015	1816	1793	1794	2011	1639	882	2031	2049
Facility	11 627 (83.0)	1741 (95.9)	1587 (88.5)	1509 (84.1)	1271 (63.2)	1625 (99.1)	881 (99.9)	1622 (79.9)	1391 (67.9)
Home/other	2388 (17.0)	75 (4.1)	206 (11.5)	285 (15.9)	740 (36.8)	14 (0.9)	1 (0.1)	409 (20.1)	658 (32.1)

included in this analysis ranged from 2049 in the Bangladeshi site to 882 in the Nagpur, India site.

Table 1 summarises the demographic characteristics of the 14 015 participants overall and by site. Overall, 20.1% had no formal schooling with about half (53.3%) having 7–12 years of school. Only 16.5% were younger than 20 years of age with the majority (77.8%) being 20–35 years of age. Of the participants, 31.9% were primiparas, 44.5% were of parity 1–2, and 23.7% were of parity 3 or more; 83.0% of the mothers delivered in a health facility. There were substantial variations in the study participants' demographic characteristics by site.

Overall, 26.6% of the 14 015 samples tested were antibody positive, 71.4% were negative and 2.0% were indeterminate (Table 2). The percent positive ranged from 17.2% in Guatemala to 39.1% and 44.8% in Belagavi and Nagpur, India, respectively. The three African sites had positivity rates of 24.2% in Kenya, 27.8% in Zambia and 29.1% in the DRC, whereas the site in Pakistan had a positivity rate of 20.5% and the Bangladeshi site had a positivity rate of 22.5%.

Figure 2 shows the rates of antibody positivity by time-period overall and by site. The overall rate of positivity increased from 13.8% in the first 3 months (October through December 2020) to 15.4% in the second 3 months (January through March 2021), to 21.0% in the third 3 months (April through June 2021), to 40.9% in the last period (July through October 2021). Generally, in each site, the antibody positivity rates at delivery increased over time. In the last period, in increasing order of prevalence, the positivity rate for the DRC site was 27.0%, for the Pakistani site 32.8%, for the Kenyan site 33.1%, for the Guatemalan site 37.0%, for the Zambian site 37.8%, for the Bangladeshi site 47.2%, for the Nagpur, Indian site 57.4%, and for the Belagavi, Indian site 62.4%.

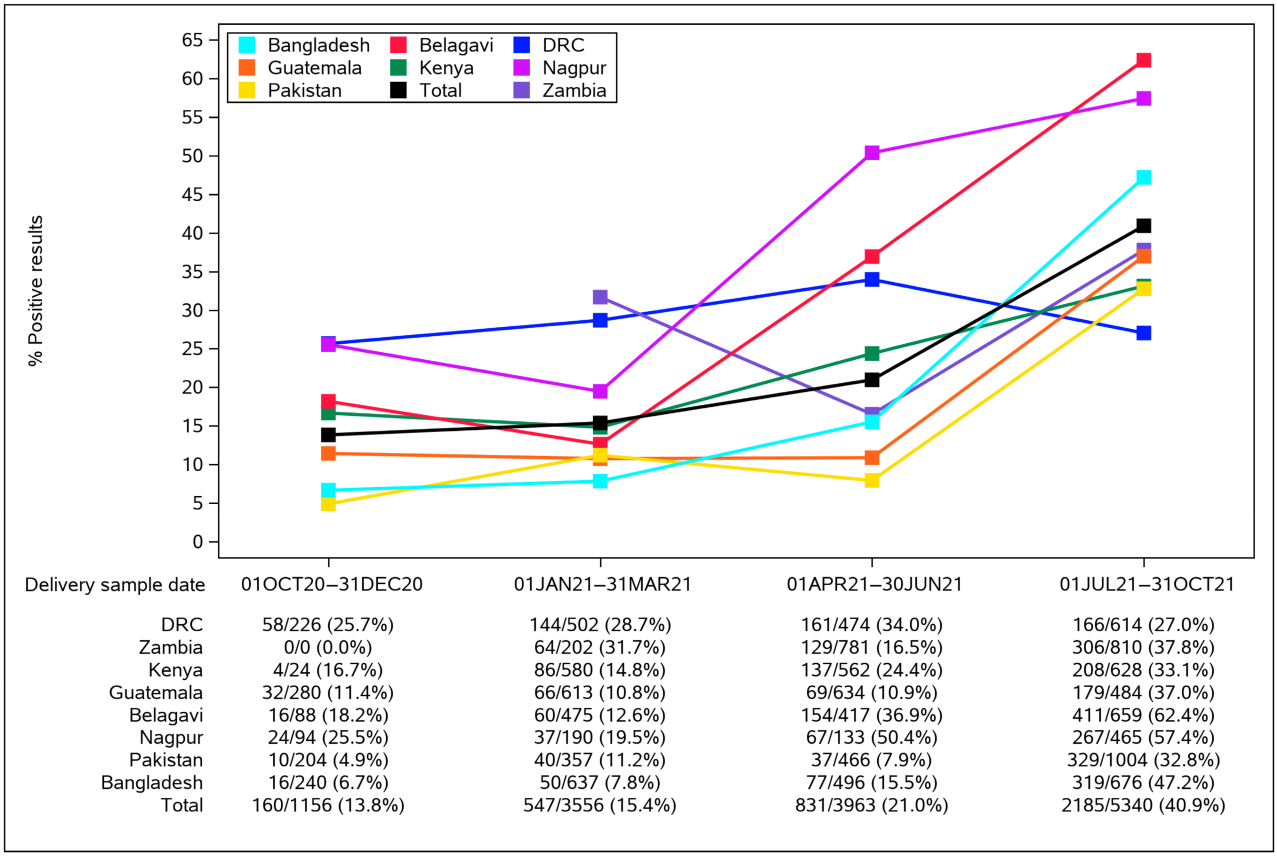
Table 3 shows for the entire study population, the maternal characteristics associated with a positive antibody test, adjusted by study site. Women with a positive test were more likely to have more education, were more likely to be older and were more likely to deliver in a facility.

Because samples were collected for approximately half (48.5%) of all deliveries that occurred during the study period, we evaluated potential selection bias. First, we assessed whether the characteristics of the populations for which samples were and were not collected were similar. The maternal demographic characteristics of women who provided samples and those who did not were generally similar (Table S1). We also assessed the maternal and delivery outcomes of those with and without samples (Table S2). For the outcomes of low birthweight, preterm birth and small for gestational age, we had approximately a similar percentage of samples with and without that outcome. However, for women with a stillbirth (18.2% versus 35.0%), a neonatal death (17.5% versus 29.3%), and a maternal death, a smaller percentage of samples were collected from women with the outcome. The pattern in the sites mirrored the overall pattern in that for all the sites but one, there were fewer enrolees for pregnancies with stillbirths, or neonatal and maternal deaths than there were for pregnancies without those conditions.

TABLE 2 COVID-19 antibody positivity at delivery, overall and by study site

Variable	Overall, *n* (%)	DRC, *n* (%)	Zambia, *n* (%)	Kenya, *n* (%)	Guatemala, *n* (%)	Belagavi, *n* (%)	Nagpur, *n* (%)	Pakistan, *n* (%)	Bangladesh, *n* (%)
COVID-19 delivery sample results	14 015	1816	1793	1794	2011	1639	882	2031	2049
Positive	3723 (26.6)	529 (29.1)	499 (27.8)	435 (24.2)	346 (17.2)	641 (39.1)	395 (44.8)	416 (20.5)	462 (22.5)
Negative	10 010 (71.4)	1228 (67.6)	1287 (71.8)	1294 (72.1)	1630 (81.1)	951 (58.0)	462 (52.4)	1596 (78.6)	1562 (76.2)
Indeterminate	282 (2.0)	59 (3.2)	7 (0.4)	65 (3.6)	35 (1.7)	47 (2.9)	25 (2.8)	19 (0.9)	25 (1.2)

Note: Date first delivery sample collected: Pakistan – 20 October 2020, Bangladesh – 5 November 2020, DRC/Guatemala – 7 November 2020, Nagpur – 24 November 2020, Kenya – 14 December 2020, Belagavi – 15 December 2020, Zambia – 24 February 2021.



Delivery sample date	01OCT20–31DEC20	01JAN21–31MAR21	01APR21–30JUN21	01JUL21–31OCT21
DRC	58/226 (25.7%)	144/502 (28.7%)	161/474 (34.0%)	166/614 (27.0%)
Zambia	0/0 (0.0%)	64/202 (31.7%)	129/781 (16.5%)	306/810 (37.8%)
Kenya	4/24 (16.7%)	86/580 (14.8%)	137/562 (24.4%)	208/628 (33.1%)
Guatemala	32/280 (11.4%)	66/613 (10.8%)	69/634 (10.9%)	179/484 (37.0%)
Belagavi	16/88 (18.2%)	60/475 (12.6%)	154/417 (36.9%)	411/659 (62.4%)
Nagpur	24/94 (25.5%)	37/190 (19.5%)	67/133 (50.4%)	267/465 (57.4%)
Pakistan	10/204 (4.9%)	40/357 (11.2%)	37/466 (7.9%)	329/1004 (32.8%)
Bangladesh	16/240 (6.7%)	50/637 (7.8%)	77/496 (15.5%)	319/676 (47.2%)
Total	160/1156 (13.8%)	547/3556 (15.4%)	831/3963 (21.0%)	2185/5340 (40.9%)

FIGURE 2 Positivity of maternal COVID-19 serum samples over time by study site

We assessed the antibody positivity rates by maternal, fetal and newborn outcomes, including hypertensive disease, antepartum haemorrhage and postpartum haemorrhage as well as stillbirth, preterm birth, low birthweight and neonatal death (Table 4). Overall, 26.6% of the samples were antibody positive, as were 26.6% of the samples in women with live births, Among the conditions evaluated, the COVID-19 antibody positivity rate was 25.8% in women with preterm births, 25.1% in women with neonatal deaths, 27.6% in women with stillbirths, 27.8% in women with low birthweight births, 25.7% in women with hypertension, 28.4% in women with antepartum haemorrhage and 31.1% in women with postpartum haemorrhage.

We next evaluated the association between COVID-19 antibody positivity and pregnancy outcomes (Table 5). After adjusting for co-variates including site, maternal demographics, antenatal care visits, delivery location, labor induction and pregnancy complications, among the maternal outcomes only postpartum haemorrhage was significantly associated with antibody positivity (aRR 1.44, 95% CI 1.01–2.07). The number of maternal deaths in women with antibody data was too small to assess (three maternal deaths total; two women who died were COVID-19 antibody negative and one woman was positive). Among the fetal/neonatal outcomes, none of the outcomes were statistically significant for antibody positivity. The aRR for low birthweight was 1.09 (95% CI 0.99–1.19) and for stillbirth it was 1.27 (95% CI 0.95–1.69).

Because we did not know whether women who were positive at delivery had acquired the infection during the pregnancy, we performed a sensitivity analysis among women in four sites who were tested early in pregnancy and then were tested again at delivery. In this sample of 2400 pregnancies, postpartum haemorrhage was significantly associated with antibody positivity (aRR 2.43, 95% CI 1.29–4.57) (Table S2). However, none of the fetal/neonatal outcomes evaluated had a significant relationship with antibody status. We had evidence that 257 women (2%) in this population were vaccinated by delivery, so we also carried out a sensitivity analysis on the women who were not vaccinated by delivery. In this adjusted analysis, postpartum haemorrhage remained significantly associated with antibody positivity (aRR 1.47, 95% CI 1.00–2.15) and low birthweight was also significantly associated with antibody positivity (aRR 1.10, 95% CI 1.00–1.22) (data not shown).

4 | DISCUSSION

4.1 | Main findings

Across the eight Global Network sites, evaluating 14 015 women, COVID-19 antibody positivity in mothers at delivery increased over time from 13.8% to 40.9% from July to October 2021. The rate of positive tests varied by site, and in the final

TABLE 3 Maternal characteristics by COVID-19 antibody status at delivery

Variable	Sample results		
	Positive, *n* (%)	Negative, *n* (%)	*p* Value[a]
Delivery sample results, *n* (row %)	3723 (27.1)	10 010 (72.9)	
Education	3723	10 009	<0.001
No schooling	604 (16.2)	2171 (21.7)	
1–6 years	633 (17.0)	2073 (20.7)	
7–12 years	2184 (58.7)	5140 (51.4)	
≥13 years	302 (8.1)	625 (6.2)	
Age (years)	3723	10 008	0.044
<20	537 (14.4)	1725 (17.2)	
20–35	2997 (80.5)	7686 (76.8)	
>35	189 (5.1)	597 (6.0)	
Parity	3723	10 010	0.657
0	1202 (32.3)	3173 (31.7)	
1–2	1711 (46.0)	4396 (43.9)	
>2	810 (21.8)	2441 (24.4)	
Delivery location	3723	10 010	0.048
Facility	3243 (87.1)	8139 (81.3)	
Home/other	480 (12.9)	1871 (18.7)	

[a]Generalised linear models fit separately for each characteristic containing terms for site and sample results (positive or negative). Indeterminate results are excluded.

TABLE 4 Percent COVID-19 antibody positivity among women with various maternal and fetal/neonatal outcomes

Variable	*n*/*N*[a]	% (95% CI)
Women ≥20 weeks pregnant with sample collected	14 015	
Fetuses/babies among deliveries ≥20 weeks of gestation with sample collected	14 144	
Positive delivery sample among those in the following groups		
All women	3723/14 015	26.6 (25.8–27.3)
Evidence of hypertensive disease/severe pre-eclampsia/eclampsia	78/303	25.7 (20.8–30.7)
Antepartum haemorrhage	25/88	28.4 (19.0–37.8)
Postpartum haemorrhage	46/148	31.1 (23.6–38.5)
All births	3759/14 144	26.6 (25.8–27.3)
Live births	3688/13 887	26.6 (25.8–27.3)
Stillbirths[a]	71/257	27.6 (22.2–33.1)
Preterm births	571/2210	25.8 (24.0–27.7)
Low-birthweight births	666/2400	27.8 (26.0–29.5)
Neonatal deaths <28 days[b]	61/243	25.1 (19.7–30.6)

[a]The denominator is the number of women with each condition tested while the numerator is the number of women with that condition tested who were positive. The percent is the numerator divided by the denominator.

[b]Reported as rate/1000.

period ranged from 27.0% in the DRC to 62.4% in Belagavi, India. Overall, the Indian sites had the highest rates of antibody positivity and Guatemala the lowest. Based on the adjusted analyses, women who had more education, who were older and who delivered in a facility were more likely to be antibody positive. Overall, 26.6% of the samples were antibody positive. Among the conditions evaluated, the COVID-19 antibody positivity rate ranged from 25.8% in preterm births to 31.1% among those with postpartum haemorrhage. In the adjusted analyses, none of the fetal/neonatal outcomes were significantly associated with antibody positivity when adjusted for maternal characteristics including socioeconomic status, number of antenatal care visits, delivery location and labor induction, and pregnancy complications. Among the maternal outcomes, only postpartum haemorrhage was significantly associated with antibody positivity.

4.2 | Interpretation

We have considered why the differences in several adverse pregnancy outcomes between those women who were antibody positive and those who were antibody negative were either non-existent or relatively small. First, most previous reports of the impact of COVID-19 on pregnancy outcomes were usually based on outcomes among women who were antigen positive and symptomatic,[12,13] and few or none report population-based outcomes. As many or most women with COVID-19 are asymptomatic and most pregnancies involving COVID-19 are not associated with a stillbirth or neonatal death, our population-based results based on antibody positivity are plausible.[16–23]

Our findings regarding an increase in postpartum haemorrhage in antibody-positive women is also plausible because a very large meta-analysis noted this relationship as well.[24] Although we do not know the origin of this relationship, that COVID-19 can be associated with various placental malperfusion and inflammatory lesions, and both types of lesions are associated with haemorrhage,[25] the relationship is plausible as well.

We should emphasise that due to resource constraints, the sites were instructed to recruit a maximum of 170 women per month. In retrospect, for a number of reasons, there were fewer women among those sampled who had a serious adverse outcome of stillbirth or neonatal and maternal death. We believe that by using an adjusted analysis, we could estimate the number of stillbirths and neonatal deaths with and without antibody positivity. However, because of the limited number of maternal deaths with antibody testing, we could not perform a similar adjusted analysis for maternal mortality.

4.3 | Strengths and limitations

Among the strengths of this study were the large sample size, population-based data from eight sites in seven LMICs on

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TABLE 5 Risk of adverse maternal and fetal/neonatal outcomes by COVID-19 antibody test results adjusted for maternal characteristics

Variable	Overall, %, *n*/*N*	Positive, %, *n*/*N*	Negative, %, *n*/*N*	Model, *N*	Adjusted[a] RR (95% CI)	*p* Value
Maternal outcomes						
Maternal deaths <42 days[b]	22, 3/13 724	27, 1/3719	20, 2/10 005			
Evidence of hypertensive disease/severe pre-eclampsia/eclampsia	2.1, 295/13 733	2.1, 78/3723	2.2, 217/10 010	13 205	0.96 (0.73–1.26)	0.7690
Antepartum haemorrhage	0.6, 86/13 732	0.7, 25/3722	0.6, 61/10 010	13 205	1.15 (0.70–1.87)	0.5864
Postpartum haemorrhage	1.0, 144/13 729	1.2, 46/3722	1.0, 98/10 007	13 201	1.44 (1.01–2.07)	0.0457
Fetal/neonatal outcomes						
Stillbirths[c]	18.3, 253/13 860	18.9, 71/3759	18.0, 182/10 101	13 075	1.27 (0.95–1.69)	0.1022
Preterm births	15.7, 2170/13 796	15.2, 571/3749	15.9, 1599/10 047	13 021	1.03 (0.93–1.14)	0.5504
Low birthweight	17.0, 2361/13 849	17.7, 666/3757	16.8, 1695/10 092	13 064	1.09 (0.99–1.19)	0.0872
Neonatal deaths <28 days[c]	17.6, 239/13 596	16.6, 61/3684	18.0, 178/9912	12 820	1.11 (0.82–1.50)	0.5045

[a]Relative risks and 95% confidence intervals are obtained from generalised linear models with a Poisson distribution and a log link adjusting for COVID-19 sample result, site, maternal education, maternal age, parity, antenatal care visits, delivery location and socioeconomics. Fetal/neonatal outcomes also adjust for severe antepartum haemorrhage, hypertensive disorders of pregnancy, severe infection and induction. Indeterminate results are excluded.

[b]Reported as rate/100 000.

[c]Reported as rate/1000.

three continents, the use of the same product for antibody testing in all sites, quality oversight provided by a central source, and standard demographic and outcome data across all sites collected with identical forms and using standard definitions. Another strength is the lack of bias among data collectors, as the staff performing the antibody testing were masked to the study outcomes, which were collected and analysed independently. Weaknesses include that we did not collect specimens for antibody tests for all deliveries in the sites over the study period and hence the women who were tested at delivery were not completely representative. Specifically, the women who had a stillbirth, a neonatal death, or a maternal death were less likely to be tested for COVID-19. We, therefore, used multivariate techniques to account for differences in stillbirth and neonatal deaths among the women who had samples collected and those who did not. Our inability to predict the severity of the epidemic in terms of the proportion of the population infected or determine when women were infected was a potential weakness. However, because the rate of COVID-19 and extended time of the epidemic was larger than expected, we had improved power to determine whether there were relationships between COVID-19 and rarer outcomes, such as stillbirth or neonatal death. Another weakness is that using antibodies as a measure of infection did not allow us to determine whether the infection was active during pregnancy. To address this issue, we performed sensitivity analyses restricted to women who tested negative early in pregnancy and became positive at delivery, as well as among women who were unvaccinated, with little difference in results. Finally, we did not test for type of COVID-19 variants or try to describe the context of the disease in each site, in part because comparable country data on variants was generally not available for pregnant women.

5 | CONCLUSIONS

In the pregnant populations in eight sites in seven LMICs, as documented by the presence of COVID-19 antibodies at delivery, COVID-19 became increasingly common. There were substantial differences in the rates of antibody positivity across the sites, with the Indian sites having the highest rates of positivity. Surprisingly, among fetal/infant outcomes, most adverse outcomes, including preterm birth, stillbirth and neonatal death, were apparently not increased significantly in women who were antibody positive. Among maternal outcomes, only postpartum haemorrhage was significantly associated with antibody positivity. Hence, although COVID-19 in pregnancy as documented by antigen positivity in symptomatic high-risk women is associated with major complications,[12,13] it appears that on a population basis, as documented by a positive COVID-19 antibody test at delivery, COVID-19 in pregnancy do not cause a significant increase in most adverse outcomes for either the mother or the fetus/neonate. As the pandemic evolves, further population-based evaluations in LMIC of COVID-19 during pregnancy are indicated.

AUTHOR CONTRIBUTIONS

RLG, SS, SkMB, EMM, PLH, JK, TLN, ALG and NFK conceived the study with input from SSG, EC, RJD, AP, WAP, CLB, MB, WAC, EAL and MK-T. JK, JLM and TLN performed statistical analyses. JK, NKG, AA, MS, WIE, SE, MD, BH and SSi oversaw the laboratory analyses. RH, LF, AL, AT, SSG, AK, FE, MMw, EC, AP, PD and MM, oversaw implementation. All authors reviewed and approved the final manuscript.

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CONFLICT OF INTERESTS

None declared. Completed disclosure of interests form available to view online as supporting information.

DATA AVAILABILITY STATEMENT

The data will be uploaded in the NICHD Data and Specimen Hub (NDASH).

ETHICS APPROVAL

This study was reviewed and approved by the institutional review boards and ethics review committees of the participating institutions as follows: University of Kinshasa School of Public Health, Kinshasa, DRC; University of North Carolina at Chapel Hill, Chapel Hill, NC; University of Alabama at Birmingham, Birmingham, AL; University of Zambia, Lusaka, ZM; University of Colorado at Denver, Denver, CO; University Francisco Marroquin, Guatemala City, Guatemala; icddr,b, Dhaka Bangladesh; University of Virginia, Charlottesville, VA; KLE Academy of Higher Education, Belagavi, India; Thomas Jefferson University, Philadelphia, PA; Aga Khan University, Karachi, Pakistan; Columbia University, New York, NY; Lata Medical Research Foundation, Nagpur, India; Boston University, Boston, MA; Moi University, Eldoret, Kenya; Indiana University, Indianapolis, IN and RTI International, Durham, NC.

DETAILS OF PATIENT'S CONSENT

All participants provided informed written consent before participation in the study.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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