OBSTETRICS

Maternal vaccination against COVID-19 and neonatal outcomes during Omicron: INTERCOVID-2022 study

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BACKGROUND: In early 2023, when Omicron was the variant of concern, we showed that vaccinating pregnant women decreased the risk for severe COVID-19—related complications and maternal morbidity and mortality.

OBJECTIVE: This study aimed to analyze the impact of COVID-19 during pregnancy on newborns and the effects of maternal COVID-19 vaccination on neonatal outcomes when Omicron was the variant of concern.

STUDY DESIGN: INTERCOVID-2022 was a large, prospective, observational study, conducted in 40 hospitals across 18 countries, from November 27, 2021 (the day after the World Health Organization declared Omicron the variant of concern) to June 30, 2022, to assess the effect of COVID-19 in pregnancy on maternal and neonatal outcomes and to assess vaccine effectiveness. Women diagnosed with laboratory-confirmed COVID-19 during pregnancy were compared with 2 nondiagnosed, unmatched women recruited concomitantly and consecutively during pregnancy or at delivery. Mother-newborn dyads were followed until hospital discharge. The primary outcomes were a neonatal positive test for COVID-19, severe neonatal morbidity index, severe perinatal morbidity and mortality index, preterm birth, neonatal death, referral to neonatal intensive care unit, and diseases during the neonatal period. Vaccine effectiveness was estimated with adjustment for maternal risk profile.

RESULTS: We enrolled 4707 neonates born to 1577 (33.5%) mothers diagnosed with COVID-19 and 3130 (66.5%) nondiagnosed mothers. Among the diagnosed mothers, 642 (40.7%) were not vaccinated, 147 (9.3%) were partially vaccinated, 551 (34.9%) were completely vaccinated, and 237 (15.0%) also had a booster vaccine. Neonates of booster-vaccinated mothers had less than half (relative risk, 0.46; 95% confidence interval, 0.23—0.91) the risk of being diagnosed with COVID-19 when compared with those of unvaccinated mothers; they also had the lowest rates of preterm birth, medically indicated preterm birth, respiratory distress syndrome, and number of days in the neonatal intensive care unit. Newborns of unvaccinated mothers had double the risk for neonatal death (relative risk, 2.06; 95% confidence interval, 1.06—4.00) when compared with those of nondiagnosed mothers. Vaccination was not associated with any congenital malformations. Although all vaccines provided protection against neonatal test positivity, newborns of booster-vaccinated mothers had the highest vaccine effectiveness (64%; 95% confidence interval, 10%—86%). Vaccine effectiveness was not as high for messenger RNA vaccines only. Vaccine effectiveness against moderate or severe neonatal outcomes was much lower, namely 13% in the booster-vaccinated group (all vaccines) and 25% and 28% in the completely and booster-vaccinated groups, respectively (messenger RNA vaccines only). Vaccines were fairly effective in protecting neonates when given to pregnant women $\leq$100 days (14 weeks) before birth; thereafter, the risk increased and was much higher after 200 days (29 weeks). Finally, none of the neonatal practices studied, including skin-to-skin contact and direct breastfeeding, increased the risk for infecting newborns.

CONCLUSION: When Omicron was the variant of concern, newborns of unvaccinated mothers had an increased risk for neonatal death. Neonates of vaccinated mothers had a decreased risk for preterm birth and adverse neonatal outcomes. Because the protective effect of COVID-19 vaccination decreases with time, to ensure that newborns are maximally protected against COVID-19, mothers should receive a vaccine or booster dose no more than 14 weeks before the expected date of delivery.

Key words: COVID-19, COVID-19 vaccination, morbidity, mortality, multicenter study, neonatal health, neonatal intensive care admission, neonatal outcomes, neurologic outcomes, newborn, perinatal practices, pregnancy, preterm birth, respiratory support, respiratory symptoms, SARS-CoV-2, SARS-CoV-2 exposure, skin-to-skin

Introduction

In 2022, we reported the results of the INTERCOVID multinational study, which showed that neonates born to women with COVID-19 between March 2, 2020, and March 18, 2021, that is, when the original wild type was predominant, were at increased risk for

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AJOG at a Glance

Why was this study conducted?

We aimed to study the effects of (1) COVID-19 during pregnancy on newborns and (2) maternal vaccination on neonatal outcomes when Omicron was the variant of concern.

Key findings

Neonates of booster-vaccinated mothers had less than half the risk of being diagnosed with COVID-19 than those of unvaccinated mothers; they also had the lowest rates of preterm birth, medically-indicated preterm birth, respiratory distress syndrome, and number of days in the neonatal intensive care unit. All vaccines provided protection against neonatal test positivity, but vaccine effectiveness was highest among newborns of booster-vaccinated mothers. Vaccines were fairly effective in protecting neonates when given to pregnant women ≤100 days (14 weeks) before birth; thereafter, the risk increased and was much higher after 200 days (29 weeks). None of the neonatal practices studied, including skin-to-skin contact and direct breastfeeding, increased the risk of infecting neonates.

What does this add to what is known?

At a time when Omicron was the variant of concern, neonates of unvaccinated mothers died twice as frequently as those of vaccinated mothers. Vaccines protected against preterm birth and adverse neonatal outcomes. To ensure that newborns are maximally protected against COVID-19, women should receive a vaccine or booster dose no more than 14 weeks before the expected date of delivery.

neonatal complications.[1] Moreover, neonates of infected women delivered by cesarean delivery were more likely to become infected than those born vaginally.

We then published, in early 2023, the first results of the INTERCOVID-2022 study that described the health outcomes of women who gave birth between November 27, 2021, and June 30, 2022, that is, during the period that Omicron was the variant of concern. We reported that when compared with vaccinated women, unvaccinated women who were infected had a greater risk for severe COVID-19 symptoms, referral to higher level of care, intensive care unit (ICU) admission, and death. Specifically, a complete vaccine regimen provided 74% protection against these outcomes, and an additional booster gave 91% protection.[2]

Recent publications have dealt with the consequences of COVID-19 infection among pregnant women and the fetus or newborn[3–5] and the effects of the COVID-19 vaccines on pregnant women and their newborns and infants, including antibody response and transplacental transfer of antibodies.[6–13]

One recent meta-analysis, conducted before the emergence of the Omicron variant, found that neonates of mothers who were infected were more likely to be born prematurely and to be admitted to a neonatal ICU (NICU) than those born to mothers who were not infected.[14] Another meta-analysis found that infants whose mothers received a messenger RNA (mRNA) vaccine during pregnancy were 15% less likely to be born prematurely and 20% less likely to be admitted to a NICU than infants of unvaccinated mothers.[15] A subgroup analysis based on different SARS-CoV-2 variant periods showed that maternal vaccination reduced the risk for infection by 70% by 2, 4, and 6 months of life in the Delta period, but the risk increased by 78% during the Omicron period.

A nationwide Norwegian registry-based cohort study[16] found that infants whose mothers received an mRNA vaccine had a substantially lower risk for testing positive for SARS-CoV-2 during the first 4 months of life than infants of unvaccinated mothers. This reduction was noted during the periods when the Delta and Omicron variants were predominant, although vaccine effectiveness (VE) seemed greater when Delta predominated. The possible protective effect of vaccination on the risk for other adverse neonatal outcomes was not evaluated.

In this study, we report on the effects of COVID-19 during pregnancy on neonatal outcomes during the Omicron period in the INTERCOVID-2022 study. We specifically aimed to determine if maternal vaccination protected against neonatal infection with SARS-CoV-2, severe neonatal complications, NICU admission, and death.

Materials and Methods

Study design and participants

This was a prospective, observational cohort study involving 40 hospitals in 18 countries (Argentina, Brazil, Egypt, France, Indonesia, Israel, Italy, Japan, Mexico, Nigeria, North Macedonia, Pakistan, Spain, Switzerland, Turkey, the United Kingdom, Uruguay, and the United States). Participating hospitals were part of the Oxford Maternal and Perinatal Health Institute worldwide network of research institutions that provide routine care to several thousand women and neonates every year according to standardized protocols (wrh.ox.ac.uk/research/omphi). These hospitals were not selected to represent the underlying populations but rather to enable us to enroll the maximum number of diagnosed and concomitant non-diagnosed pregnant women in the shortest possible time. We conducted an a priori power analysis to determine the required sample size for our study. To estimate relative risks, we used 50% of the relative risk from our previous COVID-19 study.[17] The largest estimated sample size for COVID-19–exposed pregnant women was 1041 to obtain 80% power for neonatal morbidity with an estimated relative risk of 1.8.

The protocol has been described previously.[2] Women with a documented, laboratory-confirmed diagnosis of COVID-19 (real-time polymerase chain reaction [PCR] or rapid test) who delivered between September 10, 2021, and June 23, 2022, were enrolled at any time during pregnancy or delivery at the participating hospitals. Live and stillborn singleton and multiple births and those with congenital anomalies were included. Mothers and their live newborns were followed until hospital discharge.

After each COVID-19 diagnosed woman was enrolled, to minimize the risk of bias, 2 unmatched COVID-19 nondiagnosed women, as representative of the pregnant population at each study site, were enrolled concomitantly and consecutively, that is, at delivery or at the same level of care (if identified antenatally). If a nondiagnosed woman did not agree to participate, the next woman was approached until 2 nondiagnosed women were enrolled per diagnosed woman. If a nondiagnosed woman reported or had a documented COVID-19 diagnosis before the index pregnancy (n=9), she was counted as nondiagnosed for the risk analyses but considered immunologically exposed for the VE analyses.

The Oxford Tropical Research Ethics Committee and all local ethics committees approved the study, which did not interfere with clinical management. Informed consent (oral or written) was obtained from study participants according to local requirements, except when a local committee granted waiver or exemption. We adhered to the Declaration of Helsinki and Good Clinical Practice guidelines. The study protocol, including the laboratory tests used, has been published previously.[1]

Procedures

During the study period, universal screening for COVID-19 was implemented in 28 (70%) of the 40 maternity hospitals; thus, 3615 (78.3%) of the 4618 pregnant women enrolled were tested at the time of admission, including at delivery. The other 1003 (21.7%) women were tested if they were symptomatic or if they were asymptomatic but had had direct contact with cases or family members of cases or if they were healthcare providers, schoolteachers, frontline public workers or patients at high risk according to local protocols. If women were test-positive but asymptomatic, they were analyzed under the asymptomatic strata. We obtained ecological-level information on the predominant variant during the study period from official monthly reports from catchment areas of each participating hospital.

For consistency, we used the same procedures, documentation, and data management system as in the original INTERCOVID study.[17] Maternal and pregnancy history, delivery mode, indication for cesarean delivery, newborn outcomes, and feeding practices were collected using standardized The International Fetal and Newborn Growth Consortium for the 21st Century (INTERGROWTH-21st) forms (The Global Health Network). All data were obtained from the medical records that were collected on neonatal and mother care forms during hospital stay and at discharge.

Gestational age estimation was based on ultrasound measurements of the fetal crown-rump length (<14 weeks' gestation) against the international INTERGROWTH-21st standard[18] or, if an early ultrasound was not carried out, the best obstetrical estimate was used (based on all clinical and ultrasonography data available at the time of delivery). Newborn weight, length, and head circumference at birth were assessed against the international INTERGROWTH-21st standards.[19] Measurement instruments were regularly calibrated and used by trained staff. In addition, we recorded data on the mother's health and condition at admission, perinatal management, in-hospital baby practices including immediate skin-to-skin contact, rooming-in, and maternal isolation from newborns, and the practice by mothers and hospital staff of using masks and hand washing before touching newborns. Detailed data regarding feeding were recorded and included the type of feeding, that is, any breastfeeding (defined as exclusive or partial breastfeeding) and no breastfeeding (defined as exclusive formula or only parenteral nutrition), and mode of feeding, that is, direct breastfeeding, bottle feeding, or tube feeding.

Vaccination history was obtained from the medical records, vaccination registries, primary care records, maternal vaccination cards, maternal oral report, or any other documentation or registration system. If none of these methods provided evidence of vaccination, women were considered unvaccinated.

For stratified a priori determined analyses, we documented the type of vaccine, number of doses, and time between the last dose received and the first post-vaccination COVID-19 positive laboratory test. We categorized women as boosted if they received 3 doses of any vaccine or 2 doses of a Janssen or Johnson & Johnson vaccine; as completely vaccinated if they received 2 doses of any vaccine or 1 dose of a Janssen or Johnson & Johnson vaccine; as partially vaccinated if they received 1 dose of any vaccine other than Janssen or Johnson & Johnson or if they indicated they were vaccinated but did not provide further information; and as unvaccinated if they received no doses or if the vaccination status was missing (n=19). We grouped vaccinated women according to the type of vaccine administered, namely mRNA (Moderna or Pfizer-BioNTech), inactivated virus (Cansino, Coronovac, Covaxin, Sinopharm, or SinoVac), and viral vector (AstraZeneca, Covishield, Janssen, Johnson & Johnson, or Sputnik). For 4 women, we imputed the type of vaccine based on the vaccine offered to pregnant women in the hospital's catchment area at the time of the study.

Outcomes

The analytical strategy was based on 3 sets of comparisons, namely (1) between neonates of mothers exposed and those not exposed to COVID-19, (2) between neonates of diagnosed mothers not exposed to vaccination and those who were partially, completely, or booster vaccinated, and (3) between neonates of

diagnosed mothers stratified by vaccination status (unvaccinated, partially, completely or booster vaccinated) and those not exposed to COVID-19. The primary outcomes were (1) severe neonatal morbidity index (SNMI), including at least 1 morbidity (bronchopulmonary dysplasia, hypoxic-ischemic encephalopathy, sepsis, anemia requiring transfusion, patent ductus arteriosus, intraventricular hemorrhage, necrotizing enterocolitis, and retinopathy of prematurity), and (2) severe perinatal morbidity and mortality index (SPMMI), including any of the morbidities listed in the SNMI, intrauterine or neonatal death, or a NICU stay $\geq$7 days. Secondary outcomes were each component of the above indices considered separately.

The maternal symptom severity score was defined as a continuous variable that was made up of the sum of preset values attributed to each maternal COVID-19−related symptom according to the severity of the symptom.

Cesarean delivery indications were grouped into those potentially COVID-19−related vs all others. We included the following in the potentially COVID-19−related indications: pregnancy-induced hypertension (PIH), pre-eclampsia and eclampsia, fetal distress, small for gestational age, premature rupture of membranes, and infections.

Information on the neonatal health outcomes, diagnostics, and treatments were collected in detail and then presented as the following categories: (1) neurologic problems including seizures, hydrocephalus, neurologic disorders, hypoxic-ischemic encephalopathy, and periventricular hemorrhage or leukomalacia; (2) gastrointestinal conditions including no enteral feeding for >24 hours, necrotizing enterocolitis, stoppage of enteral feeding for more than 3 consecutive days, gastro-esophago-pharyngeal reflux, persistent vomiting, and diarrhea; (3) infections including sepsis, hypotension requiring inotropic drugs and/or steroids, and pneumonia or acute respiratory infections; and (4) respiratory conditions including pneumonia or bronchiolitis, apnea of prematurity, bronchopulmonary dysplasia (BPD), and corticosteroids for BPD.

We compared newborns of mothers with and those without a COVID-19 diagnosis by vaccination status (all women and unvaccinated) and by maternal COVID-19 symptoms (asymptomatic or related symptoms, moderate symptoms, and severe symptoms). We evaluated VE against a neonatal laboratory-confirmed COVID-19 diagnosis and moderate or severe symptomatic COVID-19 or complications (NICU admission or death). We also used a composite variable of disease severity and neonatal complications for the VE analyses, which included the presence of severe COVID-19 symptoms or NICU admission or death.

Statistical analysis

We described the baseline characteristics (number and percentage or mean±standard deviation [SD]) for non-diagnosed and diagnosed women according to vaccination status. We used chi-square tests for proportions and *t* tests for continuous variables to compare the maternal baseline characteristics, birth characteristics, and perinatal outcomes between neonates born to non-diagnosed mothers and those born to diagnosed mothers.

We used Poisson regression models with a log link function to calculate the relative risks (RRs) and 95% confidence intervals (CIs) for all analyses. We calculated the unadjusted RRs for test-positive neonates among all neonates and for those with diagnosed mothers by vaccination status and using unvaccinated mothers as the reference group. We calculated the RRs and 95% CIs for neonatal outcomes among all neonates born to diagnosed mothers and used those born to nondiagnosed mothers as the reference group. We then stratified the group of neonates born to diagnosed mothers by maternal vaccination status (unvaccinated, partially vaccinated, completely vaccinated, and booster vaccinated) and again using neonates born to nondiagnosed mothers as the reference group. We adjusted for the following covariates that represented the maternal risk profile and that were selected using directed acyclic graphs: maternal age, tobacco use, parity, history of preterm birth, and previous maternal morbidity (including diabetes, thyroid, and other endocrine disorders; cardiac disease; hypertension; chronic respiratory disease; kidney disease; or tuberculosis).

VE was defined as the proportionate reduction in COVID-19 diagnoses among neonates born to vaccinated mother in comparison with those born to unvaccinated mothers (1−RR; 95% CI). We evaluated VE by vaccination status for all vaccines and for mRNA vaccines separately against a laboratory-confirmed neonatal COVID-19 diagnosis and moderate or severe neonatal outcomes (including neurologic conditions, anemia requiring transfusion, fever, gastrointestinal issues, infections, antibiotics, respiratory conditions, respiratory support, intermediate or special care, NICU stay $\geq$7 days, and death).

Because the raw data from our non-randomized observational design increased the risk of selection bias owing to the behavior and risk profile of the women who accepted vaccination, we evaluated VE by adjusting the RR (95% CI) for maternal age, overweight status (body mass index >25 kg/m^2), and preexisting maternal morbidities. To evaluate VE over time, we plotted Kaplan-Meier curves with the percentage of neonates diagnosed with COVID-19 and the time of their mother's last vaccine dose according to vaccination status (partial, complete, and boosted).

In sensitivity analyses, we excluded women diagnosed with COVID-19 before the index pregnancy and evaluated VE for women with any or moderate COVID-19 symptoms. We also ran models adjusted for maternal educational level (data available for 86.7% women) and maternal work outside the home (data available for 92.5% women). In addition, we conducted sensitivity analyses with exclusion of women who delivered during the study period but who were diagnosed before January 1, 2022, because the Omicron variant became dominant around this date.

Among neonates born to diagnosed mothers, we investigated whether factors during and after delivery were related to the neonate testing positive by

calculating RRs and 95% CIs for test positivity based on these factors. Finally, we calculated RRs and 95% CIs for neonates who tested positive, stratified by the number of days between maternal diagnosis and birth.

Results

Between November 27, 2021, and June 30, 2022, we enrolled 1545 pregnant women who were diagnosed with COVID-19 (reverse transcriptase−PCR, 80%; rapid tests, 20%) and 3073 nondiagnosed women, enrolled concomitantly and consecutively at the same level of care without a positive test during their pregnancy. The 4618 women gave birth to 4707 neonates (3130/4707 [66.5%] born to nondiagnosed mothers and 1577/4707 [33.5%] born to diagnosed mothers). Among those in the diagnosed group, the mothers of 642 of the 1577 (40.7%) newborns were not vaccinated, those of 147 of the 1577 (9.3%) newborns were partially vaccinated, 551 of 1577 (34.9%) were completely vaccinated, and 237 of 1577 (15.0%) also had a booster vaccine. The numbers and percentages of mothers and neonates who tested positive for COVID-19 by country are provided in Supplemental Table 1. The percentage of neonates who tested positive varied significantly by country ($P<.001$)

Table 1 shows that the maternal and pregnancy characteristics of the nondiagnosed and diagnosed women were similar. However, among the diagnosed women, those who had received a booster dose (when compared with unvaccinated and partially or completely vaccinated women) were older, less often smokers, had lower rates of gestational diabetes and premature rupture of membranes, and were less often treated with prophylactic antenatal corticosteroids.

Neonatal outcomes for mothers diagnosed and not diagnosed with COVID-19

Table 2 shows that the birth characteristics and perinatal outcomes of the neonates of nondiagnosed and diagnosed mothers were similar. However, the newborns of diagnosed mothers were more often tested (36.1% vs 3.8%) and more likely to have a positive test themselves (4.4%) than the tested newborns of nondiagnosed mothers (0.5%).

Neonatal outcomes of mothers diagnosed with COVID-19 by vaccination status

Table 2 also presents crude, nonadjusted analyses showing that neonates of booster-vaccinated mothers had the lowest rates of preterm birth, medically indicated preterm birth, respiratory distress syndrome, and number of days in the NICU (when compared with those of unvaccinated and partially or completely vaccinated mothers).

Figure 1 shows the RRs of being diagnosed with COVID-19 for newborns whose mothers were vaccinated in comparison with those whose mothers were not vaccinated. Neonates of all mothers who had received a booster dose

TABLE 1
Maternal and pregnancy characteristics according to COVID-19 diagnosis and vaccination status, the INTERCOVID-22 study

		Mothers with COVID-19 diagnosis				
	Mothers without COVID-19 diagnosis (n=3073)	All diagnosed (n=1545)	Unvaccinated (n=631)	Partially vaccinated (n=145)	Completely vaccinated (n=535)	Booster vaccinated (n=233)
Characteristics[a]	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Maternal age (mean±SD)	31.5±6.0	31.2±6.0	30.6±6.1	30.1±6.2	31.1±5.7	33.7±5.2
Maternal smoking	116 (7.6)	177 (5.8)	59 (9.4)	19 (13.1)	36 (6.8)	2 (0.9)
Previous preterm birth	152 (5.0)	66 (4.3)	28 (4.4)	6 (4.1)	23 (4.3)	9 (3.9)
Previous low birth weight	185 (6.1)	71 (4.6)	32 (5.1)	10 (6.9)	21 (3.9)	8 (3.4)
Previous neonatal death	70 (2.3)	41 (2.7)	16 (2.5)	4 (2.8)	17 (3.2)	4 (1.7)
Prenatal multivitamins or minerals	1619 (52.9)	790 (51.5)	336 (53.9)	65 (44.8)	259 (48.4)	130 (56.0)
Gestational diabetes mellitus	353 (11.8)	185 (12.3)	80 (13.2)	19 (13.2)	69 (13.2)	17 (7.4)
Maternal hypertension, preeclampsia, or eclampsia	267 (8.9)	139 (9.2)	55 (9.1)	9 (6.3)	54 (10.3)	21 (9.1)
Premature rupture of membranes	602 (20.2)	281 (18.7)	121 (20.0)	31 (21.7)	96 (18.3)	33 (14.4)
Prophylactic corticosteroids	229 (7.7)	106 (7.1)	44 (7.3)	12 (8.3)	41 (7.8)	9 (3.9)
Cesarean delivery	1156 (38.0)	616 (40.4)	254 (40.8)	55 (38.2)	216 (41.0)	91 (39.2)
Induced labor	758 (25.0)	375 (24.6)	145 (23.4)	30 (21.0)	141 (26.6)	59 (25.4)

SD, standard deviation.

[a] The number of missing values ranged from 18 (previous preterm birth) to 138 (premature rupture of membranes).

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TABLE 2
Birth characteristics, perinatal outcomes, and COVID-19 testing according to maternal COVID-19 diagnosis and vaccination status in the INTERCOVID-22 study

		Mothers with COVID-19 diagnosis				
Characteristics[a]	Mother without COVID-19 diagnosis (n=3130)	All (n=1577)	Mother unvaccinated (n=642)	Mother partially vaccinated (n=147)	Mother completely vaccinated (n=551)	Mother booster vaccinated (n=237)
Birth characteristics	Mean±SD or n (%)	Mean±SD or n (%)	Mean±SD or n (%)	Mean±SD or n (%)	Mean±SD or n (%)	Mean±SD or n (%)
Male sex	1564 (50.4)	779 (49.8)	322 (50.7)	71 (48.6)	267 (48.9)	119 (50.2)
Birth weight	3135±633	3135±635	3120±656	3101±630	3113±646	3245±541
Birth length	48.3±6.6	48.2±6.7	48.5±5.8	47.8±6.9	48.5±5.4	47.2±10.6
Head circumference at birth	33.8±3.5	33.9±3.0	33.9±2.6	33.6±4.5	34.0±2.5	33.9±3.8
5-min Apgar score <7	91 (2.9)	53 (3.4)	29 (4.6)	5 (3.5)	15 (2.8)	4 (1.7)
Perinatal outcomes						
Fetal distress	53 (1.7)	32 (2.0)	19 (3.0)	2 (1.4)	8 (1.5)	3 (1.3)
Meconium aspiration	17 (0.5)	11 (0.7)	4 (0.6)	0 (0.0)	7 (1.3)	0 (0.0)
Preterm birth	436 (14.0)	234 (14.9)	107 (16.8)	28 (19.2)	80 (14.6)	19 (8.0)
Medically indicated preterm birth	311 (10.0)	165 (10.5)	75 (11.8)	19 (13.0)	60 (10.9)	11 (4.6)
Gestational age at delivery (mean ± SD)	38.6±2.7	38.5±2.9	38.5±2.9	38.4±2.7	38.3±3.2	39.1±1.9
NICU admission	352 (11.3)	196 (12.4)	81 (12.6)	19 (12.9)	69 (12.5)	27 (11.4)
Days in NICU	14.6±19.3	15.3±21.1	17.0±24.1	17.1±17.4	15.4±21.1	9.3±11.7
Respiratory distress syndrome	166 (5.3)	81 (5.1)	48 (7.5)	6 (4.1)	24 (4.4)	3 (1.3)
COVID-19 testing						
COVID-19 positive test	17 (0.5)	70 (4.4)	38 (5.9)	5 (3.4)	22 (4.0)	5 (2.1)
Neonate tested	120 (3.8)	570 (36.1)	270 (42.1)	47 (32.0)	194 (35.2)	59 (24.9)
COVID-19 positive among tested	17 (14.2)	70 (12.3)	38 (14.1)	5 (10.6)	22 (11.3)	5 (8.5)
Testing within 24 h after birth	44 (1.4)	332 (21.1)	157 (24.5)	25 (17.0)	113 (20.5)	37 (15.6)
Testing within 48 h after birth	58 (1.9)	495 (31.4)	231 (36.0)	41 (27.9)	170 (30.9)	53 (22.4)

NICU, neonatal intensive care unit; *SD*, standard deviation.

[a] Number of missing values ranged from 20 (gestational age at delivery) to 60 (Apgar score).

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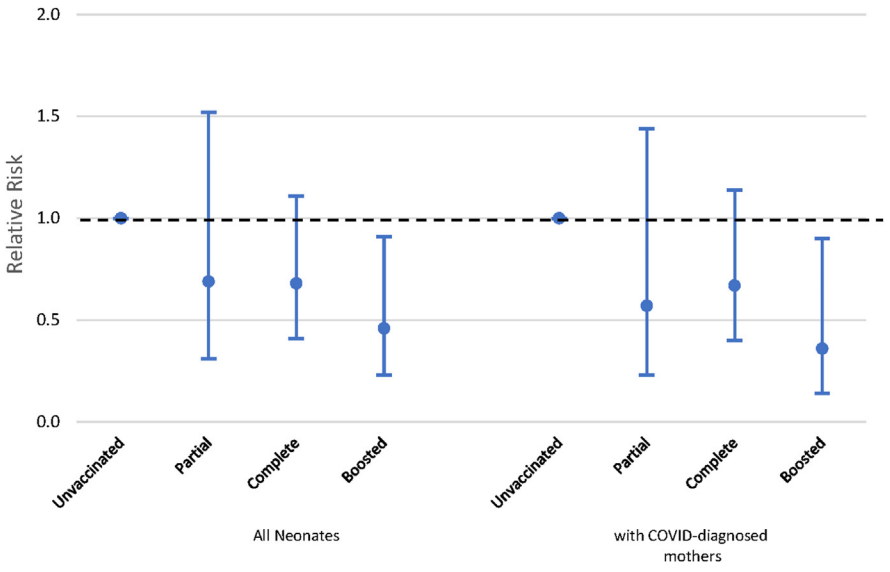
FIGURE 1
COVID-19 diagnosis in neonates by maternal vaccination status and diagnosis



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(when compared with unvaccinated mothers) had less than half (RR, 0.46; 95% CI, 0.23−0.91) the risk of receiving a COVID-19 diagnosis; the effect was even greater when neonates of diagnosed mothers were evaluated (RR, 0.36; 95% CI, 0.1−0.90). There was a lower but not statistically significant risk for neonates whose mothers were only partially or completely vaccinated (Figure 1 and Supplemental Table 2).

Table 3 presents the adjusted RRs for neonatal outcomes for newborns of diagnosed mothers, stratified by vaccination status, with newborns of nondiagnosed mothers as the reference group. Neonates of booster-vaccinated mothers were significantly less likely to be born prematurely (RR, 0.60; 95% CI, 0.39−0.93) and to have a medically indicated preterm birth (RR, 0.46; 95% CI, 0.26−0.84). Neonates of unvaccinated mothers had a greater risk for infections (RR, 1.52; 95% CI, 1.16−1.98), antibiotic treatment (RR, 1.47; 95% CI, 1.09−1.97), respiratory support for >48 hours (RR, 1.65; 95% CI, 1.11−2.47), and neonatal death (RR, 2.06; 95% CI, 1.06−4.00). Importantly, the risk for congenital malformations was not increased among neonates of diagnosed mothers, irrespective of their vaccination status. Newborns of completely vaccinated mothers had a lower risk for malformations (RR, 0.46; 95% CI, 0.22−0.94), but this was not observed among neonates of booster-vaccinated mothers. There were no differences in the SNMI and SPMNI between the groups analyzed.

VE levels (analyzed by all vaccine types and mRNA vaccines separately) against neonate test positivity and against moderate or severe neonatal outcomes are shown in Table 4. Although all vaccines combined gave protection, newborns of booster-vaccinated mothers had the highest significant VE (64%; 95% CI, 10%−86%); VE was not as high for mRNA vaccines. VE against moderate or severe neonatal outcomes was much lower, namely 13% in the booster-vaccinated group (all vaccines) and 25% and 28% in the completely and booster-vaccinated groups, respectively (mRNA vaccines).

In Figure 2, VE against neonate test positivity was plotted against the time in days since the last maternal vaccine dose. The log rank test showed no difference among the partial, complete, and booster vaccination groups (P=.80) with vaccines being fairly effective in protecting neonates when given 100 days (14 weeks) or less before birth; thereafter, the risk started to increase and was much higher after 200 days (29 weeks). The VE for mRNA vaccines only over time against neonate test positivity was very similar to that for all vaccines combined.

The time between maternal diagnosis and delivery was also important. The risk for neonates testing positive was 2.1 times greater when more than 14 days had elapsed between maternal diagnosis and delivery (Supplemental Table 3). Finally, Table 5 shows different aspects of neonatal care among diagnosed mothers. None of the practices studied, including skin-to-skin contact and direct breastfeeding, increased the risk for infecting newborns. Although neonatal care practices differed by time between maternal diagnosis and delivery in the expected directions (ie, more recent infections led to more isolation and masking and to less skin-to-skin contact), the risk for COVID-19 infection among newborns did not vary significantly in stratified analyses.

In sensitivity analyses when excluding mothers infected with SARS-CoV-2 before the index pregnancy or those who delivered during the study period but were diagnosed before January 1, 2022, the results did not change, nor did adjusting for maternal education level or maternal work outside the home change the results. Similarly, when we evaluated VE among mothers with any or moderate COVID-19 symptoms, the results did not change substantially.

Comment

Principal findings

In the original INTERCOVID study, when compared with nondiagnosed pregnant women, there was an increased risk for maternal morbidity and mortality, referral to a higher level of care and ICU admission, and perinatal morbidity and mortality among women diagnosed with COVID-19 with moderate or severe symptoms during pregnancy.[17]

TABLE 3

Adjusted[a] relative risks for neonatal outcomes for newborns of mothers with a COVID-19 diagnosis according to maternal COVID-19 vaccination status in comparison with newborns of nondiagnosed mothers in the INTERCOVID-22 study

	All COVID-19 diagnosed mothers (n=1544)		Unvaccinated (n=631)		Partially vaccinated (n=145)		Completely vaccinated (n=535)		Booster vaccinated (n=233)	
Outcome	n	RR (95% CI)	n	RR (95% CI)	n	RR (95% CI)	n	RR (95% CI)	n	RR (95% CI)
Preterm birth	234	1.07 (0.92–1.25)	107	1.20 (0.98–1.47)[b]	28	1.40 (0.97–2.01)[b]	80	1.05 (0.82–1.34)	19	0.60 (0.39–0.93)[c]
Medically indicated preterm birth	165	1.08 (0.89–1.31)	75	1.23 (0.95–1.58)	19	1.40 (0.87–2.24)	60	1.11 (0.82–1.51)	11	0.46 (0.26–0.84)[c]
Congenital malformation	45	0.90 (0.63–1.28)	24	1.20 (0.76–1.90)	2	0.43 (0.11–1.75)	8	0.46 (0.22–0.94)[c]	11	1.36 (0.74–2.50)
Neurologic conditions	21	1.57 (0.88–2.80)	6	1.12 (0.46–2.73)	5	3.98 (1.49–10.66)[c]	8	1.72 (0.78–3.77)	2	0.98 (0.24–4.10)
Anemia requiring transfusion	15	1.97 (0.97–4.04)[b]	6	2.02 (0.77–5.31)	2	2.98 (0.70–12.72)	5	1.83 (0.66–5.03)	2	1.66 (0.39–7.02)
Fever	7	1.96 (0.66–5.82)	4	2.90 (0.79–10.69)	1	3.19 (0.40–25.22)	2	1.50 (0.30–7.60)	0	NA
Gastrointestinal conditions	11	1.02 (0.49–2.12)	3	0.69 (0.20–2.38)	1	0.97 (0.13–7.37)	5	1.33 (0.51–3.43)	2	1.23 (0.29–5.24)
Infections	155	1.39 (1.14–1.70)[c]	68	1.52 (1.16–1.98)[c]	13	1.27 (0.74–2.18)	54	1.39 (1.03–1.87)[c]	20	1.15 (0.74–1.78)
Antibiotics	130	1.37 (1.09–1.70)[c]	56	1.47 (1.09–1.97)[c]	12	1.34 (0.76–2.36)	45	1.35 (0.97–1.87)[b]	17	1.16 (0.72–1.86)
Respiratory conditions	144	1.09 (0.89–1.33)	68	1.28 (0.98–1.66)[b]	13	1.09 (0.64–1.87)	49	1.07 (0.78–1.45)	14	0.67 (0.40–1.13)
Respiratory support ≤48 h	71	0.86 (0.65–1.14)	32	0.96 (0.65–1.41)	5	0.68 (0.28–1.64)	26	0.93 (0.61–1.41)	8	0.60 (0.30–1.21)
Respiratory support >48 h	59	1.26 (0.91–1.74)	31	1.65 (1.11–2.47)[c]	8	1.90 (0.94–3.84)[b]	18	1.08 (0.64–1.82)	2	0.28 (0.07–1.12)[b]
Intermediate or special care	97	1.07 (0.83–1.38)	44	1.25 (0.89–1.75)	80	1.00 (0.50–1.97)	33	0.99 (0.68–1.46)	12	0.87 (0.49–1.55)
NICU ≥7 d	111	1.24 (0.97–1.58)[b]	48	1.32 (0.95–1.83)[b]	13	1.61 (0.95–2.73)[b]	35	1.13 (0.76–1.68)	15	1.08 (0.65–1.80)
Death	21	1.35 (0.76–2.39)	13	2.06 (1.06–4.00)[c]	2	1.38 (0.32–5.97)	5	0.92 (0.36–2.37)	1	0.43 (0.06–3.16)
SNMI	52	1.25 (0.88–1.76)	16	0.96 (0.56–1.64)	10	2.56 (1.35–4.85)[c]	19	1.29 (0.79–2.12)	7	1.08 (0.51–2.32)
SPMMI	150	1.22 (1.00–1.50)[b]	65	1.30 (0.99–1.71)[b]	16	1.43 (0.89–2.29)	48	1.12 (0.81–1.55)	21	1.12 (0.73–1.71)

CI, confidence interval; *NA*, not applicable; *NICU*, neonatal intensive care unit; *RR*, relative risk; *SNMI*, severe neonatal morbidity index; *SPMMI*, severe perinatal morbidity and mortality index.

[a] Models adjusted for maternal age, previous morbidity, smoking, previous birth, and history of preterm birth. Reference group was nondiagnosed mothers (n=3130); [b] Indicates $P<.1$; [c] Indicates $P<.05$.

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TABLE 4
Vaccine effectiveness[a] (%) for neonatal COVID-19 diagnosis and moderate or severe neonatal outcomes among all neonates born to diagnosed mothers according to maternal vaccination status in the INTERCOVID-22 study

	Vaccine effectiveness against COVID-19 positivity in neonates		Vaccine effectiveness against moderate or severe neonatal outcomes[b]	
Vaccination status	n	VE (95% CI)	n	VE (95% CI)
All neonates and vaccines				
Unvaccinated	642	0 (ref)	119	0 (ref)
Partially vaccinated	147	43% (0–77)	25	4% (0–36)
Completely vaccinated	551	34% (0–60)	94	7% (0–28)
Booster vaccinated	237	64% (10–86)[c]	37	13% (0–38)
mRNA vaccines				
Unvaccinated	642	0 (ref)	119	0 (ref)
Partially vaccinated	84	61% (0–90)	14	7% (0–44)
Completely vaccinated	358	8% (0–47)	50	25% (0–46)
Booster vaccinated	156	41% (0–77)	20	28% (0–54)

CI, confidence interval; *mRNA*, messenger RNA; *VE*, vaccine effectiveness.

[a] Models adjusted for maternal age at birth, preexisting maternal morbidities, and maternal overweight status; [b] Moderate or severe neonatal outcomes include neurologic conditions, anemia requiring transfusion, fever, gastrointestinal issues, infections, antibiotics, respiratory conditions, respiratory support, intermediate or special care, neonatal intensive care unit stay ≥7 days, and death; [c] $P<.05$.

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Subsequently, in our first report from the INTERCOVID-2022 study, when the Omicron variant was predominant, we showed that vaccination was highly effective at protecting pregnant women against severe COVID-19 symptoms, referral to higher care, ICU admission, and death.[2]

In this second report from the INTERCOVID-2022 study, we showed that maternal vaccination protected newborn infants against SARS-CoV-2 infection with VE reaching 64% among those neonates whose mothers received a booster dose. However, VE decreased with time from the last vaccination and was lower when given more than 100 days (14 weeks) before delivery and much lower when given 200 days (29 weeks) before delivery. Therefore, our data indicate that, to ensure newborns are maximally protected against COVID-19, mothers should receive a vaccine or booster dose no more than 14 weeks before the expected date of delivery. It is important to note that, for their full protection, mothers should have received a COVID-19 vaccine dose before pregnancy, and if this was not the case, they should be vaccinated early in pregnancy.

Maternal vaccination conferred other important health advantages. Newborns of booster-vaccinated mothers were less likely to be born prematurely, develop respiratory distress syndrome, and spend ≥7 days in the NICU. Conversely, neonates of unvaccinated diagnosed mothers had twice the risk of dying when compared with those of nondiagnosed mothers.

Maternal vaccination has previously been associated with a decreased risk for preterm birth,[15,20] and a retrospective cohort study showed that mRNA vaccines had a protective effect against preterm birth, stillbirth, and low birthweight and that booster vaccination conferring further protection.[21] In addition, in line with our findings, a recent study showed that booster mRNA vaccines during pregnancy elicited a strong antibody response against the ancestral and Omicron SARS-CoV-2 strains, which were detected in umbilical cord blood.[10]

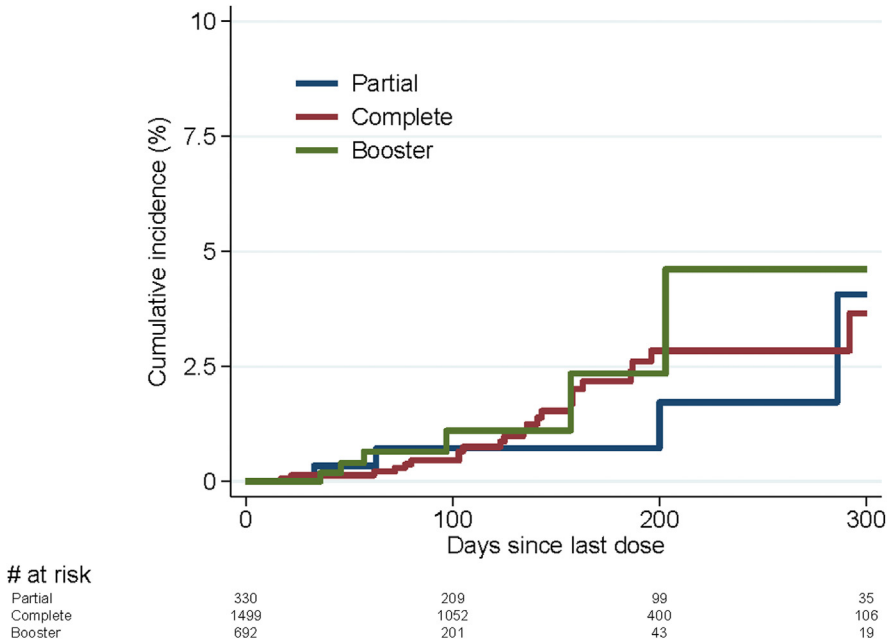
Our results also align with an Israel cohort study that showed that booster vaccination protected infants from COVID-19–related hospitalizations up to the age of 4 months with a VE of 46%. Administering the third dose closer to delivery enhanced protection, highlighting the importance of maternal booster vaccinations in preventing infant COVID-19 hospitalizations in the Delta and Omicron periods.[22]

Another of our findings that may help in setting health policies was that neonates of diagnosed mothers did not have an increased risk for being infected when applying practices such as skin-to-skin contact and direct breastfeeding. Moreover, none of the neonates of vaccinated mothers had a congenital malformation.

Results in the context of what is known and clinical implications

On May 5, 2023, the World Health Organization (WHO) declared that COVID-19 "no longer constitutes a public health emergency of international concern," which may be contributing to decreasing vaccine uptake, fueled by the

FIGURE 2
Vaccine effectiveness against neonatal COVID-19 positive by maternal vaccination status



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action of anti-vaccine groups. At least in the United States, vaccine hesitancy is higher among pregnant women than in the general population.[23]

A meta-analysis of studies conducted in the second half of 2021 found that 38% of pregnant women had vaccine hesitancy, which was mainly a consequence of a lack of information about the vaccine, a fear that the vaccine is unsafe, and a fear for side effects.[24] A more recent meta-analysis found that 26% to 57% of pregnant women were hesitant for similar reasons.[25] Our study demonstrated the clear benefits of vaccination for pregnant women and their infants; hence, public health and medical communities must work to ensure that pregnant women are properly immunized.

Strengths and limitations

One strong aspect of our study is that it was based on a clear research strategy. Between November 27, 2021, (immediately after WHO recognized Omicron as a variant of concern) and June 30, 2022, we compared a large international cohort of pregnant women diagnosed with COVID-19 with a concomitantly recruited reference group of pregnant women without a COVID-19 diagnosis. We used the same study sites, research methodology, and analytical strategy of our previous reports on the effect of the wild-type virus during pregnancy,[1,17,26,27] but as widely recommended, we added estimates of VE according to the doses and type of vaccine received. We believe that the degree of standardization in both periods of data collection makes our results sufficiently robust to inform patient care, health education, and public health programs.

Study limitations include the need to interpret the associations between severe symptoms of COVID-19 and some results with caution because of the small sample size and wide CIs. The profiles of the women who were vaccinated suggests some selection bias, not because of the study design, but because the eligibility criteria for being vaccinated changed during the study period. Once the risks for COVID-19 during pregnancy were recognized, pregnant women were no longer considered a low-risk group because of their age and were started to be vaccinated because they were pregnant. Consequently, we adjusted the VE analyses for possible confounding factors, such as medical risk profile, overweight and obesity, and maternal age.

We did not collect material for viral genotyping; instead, the association with Omicron was based on the period when this was the variant of concern. Thus, because it is possible that some other variants could have caused infections in December 2021, we performed sensitivity analyses and excluded women who were enrolled before January 1, 2022, and found that there were no substantial changes to the results.

We could not include sub-Saharan sites in our sample, despite all our best efforts; this is an important limitation that reduces the external validity of our findings.

We avoided the use of definitions of COVID-19 clinical severity, because pregnancy is a unique physiological state and a meta-analysis showed considerable heterogeneity in how disease severity is reported.[28] Instead, we decided to use substantive clinical events, such as NICU admission. Lastly, we did not collect any further information about the infants after hospital discharge because of a lack of funding.

Conclusion

We found that immunizing mothers against COVID-19 protected their neonates from acquiring the disease, and booster vaccination decreased their risk of being born prematurely, developing respiratory distress syndrome, and staying in the NICU for long time periods. The newborn infants of unvaccinated mothers were twice as likely to die in the neonatal period than those of vaccinated mothers. However, the protective effects of maternal vaccination diminished with time; hence, pregnant women should receive a vaccine or booster dose no more than 14 weeks before the expected date of delivery. Infants of diagnosed mothers who were being breastfed

TABLE 5
Characteristics of neonatal care among newborns that tested negative and positive for COVID-19 born to diagnosed mothers in the INTERCOVID-22 study

	Mother with COVID-19 diagnosis					
		Neonate COVID-19 negative		Neonate COVID-19 positive		
Characteristic	Total no.	No.	n (%)	No.	n (%)	Relative risk (95% CI)
Immediate skin-to skin contact	527	461	321 (69.6)	66	39 (59.1)	0.67 (0.42–1.07)
Newborn isolated from mother	526	461	131 (28.4)	65	20 (30.8)	1.10 (0.67–1.81)
Mother wore a mask	516	451	340 (75.4)	65	46 (70.8)	0.82 (0.49–1.35)
Mother washed hands before touching newborn	522	457	398 (87.1)	65	56 (86.2)	0.93 (0.48–1.80)
Hospital policy of staff wearing mask and gloves	525	459	435 (94.8)	66	64 (97.0)	1.67 (0.43–6.45)
Relatives with COVID-19	516	451	57 (12.6)	65	12 (18.5)	1.47 (0.82–2.62)
Direct breastfeeding	570	500	420 (84.0)	70	56 (80.0)	0.79 (0.45–1.40)
Breast milk, no breastfeeding	498	435	26 (6.0)	63	4 (6.4)	1.06 (0.41–2.72)
Oral feeding, no breast milk	498	435	33 (7.6)	63	8 (12.7)	1.62 (0.78–3.37)

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directly or kept in skin-to-skin contact were not at increased risk for infection, which should influence policy making for postnatal care.

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SUPPLEMENTAL TABLE 1

Mothers and neonates who tested COVID-19 positive by country in the INTERCOVID-22 study

Country enrolled	Mothers COVID-19 positive n (%)	Neonates COVID-19 positive[a] n (%)
Argentina	224 (14.5)	0 (0.0)
Brazil	24 (1.6)	0 (0.0)
France	101 (6.5)	2 (2.0)
Indonesia	15 (1.0)	1 (6.7)
Israel	15 (1.0)	0 (0.0)
Italy	375 (24.3)	17 (4.4)
Japan	17 (1.1)	0 (0.0)
Macedonia	4 (0.3)	0 (0.0)
Mexico	53 (3.4)	12 (22.2)
Middle East	29 (1.9)	0 (0.0)
Nigeria	4 (0.3)	0 (0.0)
Pakistan	81 (5.2)	0 (0.0)
Spain	117 (7.6)	19 (16.0)
Switzerland	61 (4.0)	3 (4.8)
Turkey	72 (4.7)	3 (4.0)
United Kingdom	152 (9.8)	2 (1.3)
United States	151 (9.8)	4 (2.6)
Uruguay	50 (3.2)	7 (13.5)
Total	1545 (100.0)	70 (4.4)

[a] Percentage is of all neonates (n=1577). The percentage of COVID-19 positive infants varied significantly by country ($P<.001$).

Barros. Maternal vaccinations against COVID-19 and neonatal outcomes. Am J Obstet Gynecol 2024.

SUPPLEMENTAL TABLE 2

Relative risk of COVID-19 diagnosis in newborns according to maternal vaccination status and COVID-19 diagnosis in the INTERCOVID-22 study

	All neonates			Neonates with COVID-19 diagnosed mother		
Vaccination Status of Mother	No.	COVID-19 positive n (%)	COVID-19 positive RR (95% CI)	No.	COVID-19 positive n (%)	COVID-19 positive RR (95% CI)
All	4707	87 (1.9)	NA	1577	70 (4.4)	NA
Unvaccinated	1761	43 (2.4)	Ref	642	38 (5.9)	Ref
Partially vaccinated	417	7 (1.7)	0.69 (0.31–1.52)	147	5 (3.4)	0.57 (0.23–1.44)
Completely vaccinated	1632	27 (1.7)	0.68 (0.41–1.11)	551	22 (4.0)	0.67 (0.40–1.14)
Booster vaccinated	897	10 (1.1)	0.46 (0.23–0.91)[a]	237	5 (2.1)	0.36 (0.14–0.90)[a]

CI, confidence interval; *NA*, not applicable; *RR*, relative risk.

[a] Indicates $P<.05$.

Barros. Maternal vaccinations against COVID-19 and neonatal outcomes. Am J Obstet Gynecol 2024.

SUPPLEMENTARY TABLE 3

Relative risks and 95% confidence intervals for neonates who tested COVID-19 positive, stratified by time between maternal COVID-19 diagnosis and delivery in the INTERCOVID-22 study

Days between maternal COVID-19 diagnosis and delivery	Relative risk (95% CI)	*P* value
>1 d	0.84 (0.54–1.31)	.44
>3 d	0.82 (0.50–1.35)	.43
>7 d	1.36 (0.79–2.33)	.27
>10 d	1.60 (0.89–2.88)	.12
>14 d	2.13 (1.17–3.86)	.01

CI, confidence interval.

Barros. Maternal vaccinations against COVID-19 and neonatal outcomes. Am J Obstet Gynecol 2024.