Journal Pre-proof

Maternal Vaccination Against COVID-19 and Neonatal Outcomes During Omicron: INTERCOVID-2022 Study

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Short title: Maternal Vaccination Against COVID-19 and Neonatal Outcomes

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

OBJECTIVES: 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 is 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, as well as vaccine effectiveness (VE). Women diagnosed with laboratory-confirmed COVID-19 in pregnancy were compared with two 'non-diagnosed', unmatched women recruited concomitantly and consecutively in pregnancy or at delivery. Mother/newborn dyads were followed until hospital discharge. Primary outcomes were a neonatal positive test for COVID-19, severe neonatal morbidity index

(SNMI), severe perinatal morbidity and mortality index (SPMMI), preterm birth, neonatal death, referral to neonatal intensive care unit (NICU), and diseases during the neonatal period. VE was estimated adjusted by maternal risk profile.

RESULTS: We enrolled 4707 neonates born to 1577 (33.5%) mothers diagnosed with COVID-19 and 3130 (66.5%) non-diagnosed mothers. Amongst 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 (RR=0.46; 95%CI=0.23, 0.91) the risk of being diagnosed with COVID-19 compared to 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 NICU.

Newborns of unvaccinated mothers had double the risk of neonatal death (RR=2.06; 95% CI=1.06, 4.00) compared to those of non-diagnosed 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 significantly highest VE (64%; 95% CI=10-86%); VE was not as high for mRNA vaccines only. VE against moderate/severe neonatal outcomes was much lower: 13% in the booster-vaccinated group (all vaccines), and 25% and 28% in the completely and booster-vaccinated groups, respectively (mRNA vaccines only). Vaccines were fairly effective in protecting neonates when given to pregnant women 100 days (14 weeks) or less 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 of infecting newborns.

CONCLUSION: When Omicron was the variant of concern, newborns of unvaccinated mothers had an increased risk of neonatal death. Neonates of vaccinated mothers had a decreased risk of preterm birth and adverse neonatal outcomes. As 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, SARS-CoV-2, SARS-CoV-2 exposure, pregnancy, neonatal health, morbidity, mortality, multicenter study, neonatal intensive care admission, neonatal outcomes, preterm birth, respiratory support, respiratory symptoms, newborn, neurologic outcomes, skin-to-skin, perinatal practices,

Tweetable statement

INTERCOVID 2022: Neonates of booster-vaccinated mothers had less than half the risk of being infected with COVID-19 compared to those of unvaccinated mothers; and the lowest rates of preterm birth, respiratory distress syndrome and days in NICU.

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 compared to 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 NICU. All vaccines provided protection against neonatal test positivity, but vaccine effectiveness was highest in newborns of booster-vaccinated mothers. Vaccines were fairly effective in protecting neonates when given to pregnant women 100 days (14 weeks) or less 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.

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, i.e. when the original wild type was predominant, were at increased risk of neonatal complications.[1] Moreover, neonates of infected women delivered by Cesarean section were more likely to become infected than those born vaginally.

We then published, in early 2023, the first results of the INTERCOVID-2022 study describing the health outcomes of women who gave birth between November 27, 2021 and June 30, 2022, i.e. during the period when Omicron was the variant of concern. We reported that, compared to vaccinated women, infected unvaccinated women had a greater risk of 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 on pregnant women and the fetus/newborn,[3-5] and the effects on pregnant women and their newborns and infants of the COVID-19 vaccines, 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 infected mothers were more likely to be born preterm and admitted to a neonatal ICU (NICU) than those born to uninfected mothers.[14] Another meta-analysis found that infants whose mothers received an mRNA vaccine during pregnancy were 15% less likely to be born preterm and 20% less likely to be admitted to a NICU compared to infants of unvaccinated mothers.[15] Subgroup analysis based on different SARS-CoV-2 variant periods showed that maternal vaccination reduced the risk of 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 Norwegian nationwide registry-based cohort study [16] found that infants whose mothers received an mRNA vaccine had a substantially lower risk of testing positive for SARS-CoV-2 during the first 4 months of life compared with 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 of other adverse neonatal outcomes was not evaluated.

Here, 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 whether 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, UK, Uruguay and the USA). Participating hospitals are part of the Oxford Maternal and Perinatal Health

Institute (OMPHI) worldwide network of research institutions that provide routine care to several thousand women and neonates every year following standardized protocols (wrh.ox.ac.uk/research/omphi). These hospitals were not selected to represent the underlying populations, rather to enable us to enroll the maximum number of 'diagnosed', and concomitant 'non-diagnosed' pregnant women in the shortest possible time. We conducted 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 (Villar et al. 2021). 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 previously described.[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 minimise risk of bias, two unmatched COVID-19 non-diagnosed women, as representative of the pregnant population at each study site, were enrolled concomitantly and consecutively, i.e., at delivery or at the same level of care (if identified antenatally). If a non-diagnosed woman did not agree to participate, the next woman was approached until two non-diagnosed women were enrolled per diagnosed woman. If a non-diagnosed woman reported or had a documented COVID-19 diagnosis before the index pregnancy (n=9), she was counted as non-diagnosed 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/exemption. We adhered to the Declaration of Helsinki and Good Clinical Practice guidelines. The study protocol, including the laboratory tests used, has been previously published.[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 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 were health care providers, schoolteachers, front-line 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 our original INTERCOVID Study.[17] Maternal and pregnancy history, delivery mode, indication for Cesarean section, newborn outcomes, and feeding practices were collected using standardized INTERGROWTH-21st forms (The Global Health Network). All data were obtained from the medical records, collected on neonatal and mother care forms during hospital stay and at discharge.

Gestational age estimation was based on ultrasound measurement of fetal crown-rump length (<14 weeks' gestation) against the international INTERGROWTH-21st standard [18], or if early ultrasound was not carried out, the "best obstetric estimate" was used (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 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, i.e., any breastfeeding (defined as exclusive or partial breastfeeding) and no breastfeeding (defined as exclusive formula or only parenteral nutrition); mode of feeding, i.e., 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* determinate 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 three doses of any vaccine or two doses of a Janssen or Johnson & Johnson vaccine; *completely vaccinated* if they received two doses of any vaccine or one dose of a Janssen or Johnson & Johnson vaccine; *partially vaccinated* if they received one dose of any vaccine other than Janssen or Johnson & Johnson, or if they indicated they were vaccinated but did not provide further information; and *unvaccinated* if they received no doses or vaccination status was missing (n=19). We grouped vaccinated women according to the type of vaccine administered: mRNA (Moderna or Pfizer-BioNTech), inactivated virus (Cansino, Coronovac, Covaxin, Sinopharm or SinoVac), and viral vector (AstraZeneca, Covishield, Janssen, Johnson & Johnson or Sputnik). For four 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 two sets of comparisons: 1) between neonates of mothers exposed and those not exposed to COVID-19, 2) between neonates of diagnosed mothers not exposed to vaccination compared to those partially, completely or booster vaccinated, and 3) between neonates of diagnosed mothers stratified by vaccination status (unvaccinated, partially, completely or booster vaccinated) comparison to those not exposed to COVID-19. The primary outcomes were: a) Severe neonatal morbidity index (SNMI), including at least one morbidity (bronchopulmonary dysplasia, hypoxic-ischemic encephalopathy, sepsis, anemia requiring transfusion, patent ductus arteriosus, intraventricular hemorrhage, necrotizing enterocolitis, and retinopathy of prematurity), and b) Severe perinatal morbidity and mortality index (SPMMI), including any of the morbidities listed in the SNMI, intrauterine or neonatal death, or a NICU stay ≥7 days. Secondary outcomes were each component of the above indices considered separately.

The maternal symptoms severity score was defined as a continuous variable made up of the sum of pre-set values attributed to each maternal COVID-19-related symptom, according to the severity of the symptom.

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

Neonatal health outcomes, diagnostics and treatments were collected in detail and then presented as categories: 1) Neurologic problems including seizures, hydrocephalus, neurologic disorders, hypoxic-ischemic encephalopathy and periventricular hemorrhage/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; 4) Respiratory conditions including pneumonia/bronchiolitis, apnea of prematurity, bronchopulmonary dysplasia (BPD) and corticosteroids for BPD.

We compared newborns of mothers with and without a COVID-19 diagnosis according to vaccination status (all women and unvaccinated) and maternal COVID-19 symptoms (asymptomatic, and 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 COVID-19 severe symptoms or NICU admission or death.

Statistical analysis

We described 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 maternal baseline characteristics, birth characteristics and perinatal outcomes between neonates born to non-diagnosed and diagnosed mothers.

We used Poisson regression models with a log link function to calculate relative risks (RR) and 95% Confidence Intervals (CI) for all analyses. We calculated unadjusted RRs for test-positive neonates among all neonates and those with diagnosed mothers by vaccination status with unvaccinated mothers as the reference group. We calculated RRs and 95% CIs for neonatal outcomes among all neonates born to diagnosed mothers with those born to non-diagnosed 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), again with neonates born to non-diagnosed mothers as the reference group. We adjusted for the following covariates, representing the maternal risk profile, 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 in neonates among those born to vaccinated relative 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/special care, NICU stay ≥ 7 days and death).

As the raw data from our non-randomized, observational design increased the risk of selection bias due to the behavior and risk profile of the women that accepted vaccination, we evaluated VE adjusting RR (95% CI) for maternal age, overweight status (body mass index > 25 kg/m^2) and pre-existing 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 booster).

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 excluding women who delivered during the study period but were diagnosed prior to January 1, 2022, since 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 testing 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 diagnosed with COVID-19 (RT-PCR = 80%, rapid tests = 20%) and 3073 non-diagnosed 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 non-diagnosed mothers and 1577/4707 (33.5%) to diagnosed mothers. Amongst the diagnosed group, the mothers of 642/1577 (40.7%) newborns were not vaccinated, 147/1577 (9.3%) partially vaccinated, 551/1577 (34.9%) completely vaccinated, and 237/1577 (15.0%) had also had a booster vaccine. The numbers and percentages of mothers and neonates testing COVID-19 positive by country are provided in Supplementary Table 1. The percentage of neonates testing positive varied significantly by country (p<0.001)

Table 1 shows that the maternal and pregnancy characteristics of the non-diagnosed and diagnosed women were similar. However, amongst the diagnosed women, those who had received a booster dose (compared to 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 non-diagnosed 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 non-diagnosed mothers (0.5%).

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

Table 2 also presents crude, non-adjusted 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 NICU (compared to those of unvaccinated and partially or completely vaccinated mothers).

Figure 1 shows the relative risks of being diagnosed with COVID-19 for newborns whose mothers were vaccinated, compared to those not vaccinated. Neonates of all mothers who had received a booster dose (compared to unvaccinated mothers) had less than half (RR=0.46; 95%CI=0.23, 0.91) the risk of a COVID-19 diagnosis; the effect was even greater for neonates of diagnosed mothers (RR=0.36; 95%CI=0.14, 0.90). There was a lower, but not statistically significant, risk for neonates whose mothers were only partially or completely vaccinated (Figure 1 and Supplementary Table 2).

Table 3 presents adjusted relative risks for neonatal outcomes among newborns of diagnosed mothers, stratified by vaccination status, compared with newborns of non-diagnosed mothers as the reference group. Neonates of booster-vaccinated mothers were significantly less likely to be born preterm (RR=0.60; 95%CI=0.39, 0.93) and have a medically-indicated preterm birth (RR=0.46; 95%CI=0.26, 0.84). Neonates of unvaccinated mothers had a greater risk of 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 of congenital malformations was not increased in neonates of diagnosed mothers, irrespective of their vaccination status. Newborns of completely vaccinated mothers had a lower risk of 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 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/severe neonatal outcomes, are shown in Table 4. Although all vaccines combined gave protection, newborns of booster-vaccinated mothers had the significantly highest VE (64%; 95% CI=10-86%); VE was not as high for mRNA vaccines. VE against moderate/severe neonatal outcomes was much lower: 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 is plotted against the time in days since the last maternal vaccine dose. The log rank test showed no difference between partial, complete and booster vaccination groups (p=0.80), 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 of neonates testing positive was 2.1 times greater when more than 14 days had elapsed between maternal diagnosis and delivery (Supplementary Table 3). Finally, Table 5 shows different aspects of neonatal care amongst diagnosed mothers: none of the practices studied, including skin-to-skin contact and direct breastfeeding, increased the risk of infecting newborns. Although neonatal care practices differed by the time between maternal diagnosis and delivery in the expected directions (i.e. more recent infections led to more isolation and masking and less skin-to-skin contact), the risk of COVID-19 infection newborns did not vary significantly in stratified analyses.

In sensitivity analyses, 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, did not change the results, nor did adjusting for maternal education level or maternal work outside the home. 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, we reported an increased risk of maternal morbidity and mortality, referral to a higher level of care and ICU admission, and perinatal morbidity and mortality, in COVID-19-diagnosed women with moderate/severe symptoms during pregnancy compared to non-diagnosed pregnant women.[17]

Then, 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 from severe COVID-19 symptoms, referral to higher care, ICU admission and death.[2]

In this second report from the INTERCOVID-2022 Study, we show that maternal vaccination protected newborn infants from SARS-CoV-2 infection, with VE reaching 64% in those neonates whose mothers had received a booster dose. However, VE decreased with time since the last vaccine, being lower when given after 100 days (14 weeks) before delivery and much lower after 200 days (29 weeks). 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 preterm, develop respiratory distress syndrome, and spend ≥ 7 days in NICU. Conversely, neonates of unvaccinated diagnosed mothers had twice the risk of dying compared to those of non-diagnosed mothers.

Maternal vaccination has previously been associated with decreased risk of preterm birth[15,20], and a retrospective cohort study showed a protective effect of mRNA vaccination against preterm birth, stillbirth and low birthweight, with booster vaccination conferring further protection.[21] In addition, in line with our findings, a recent study showed that booster mRNA vaccines during pregnancy elicit a strong antibody response against the ancestral and Omicron SARS-CoV-2 strains, which were detected in umbilical cord blood.[22]

Our results also align with an Israel cohort study, showing that booster vaccination protects infants from COVID-19-related hospitalizations up to the age of four months, with vaccine effectiveness 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.[23]

Another of our findings that may help in setting health policies was that neonates of diagnosed mothers did not have an increased risk of being infected with 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 action of anti-vaccine groups. At least in the USA, vaccine hesitancy is higher among pregnant women than in the general population.[24]

A meta-analysis of studies conducted in the second half of 2021 found that 38% of pregnant women had vaccine hesitancy, produced mainly by lack of information about the vaccine, fear that the vaccine is unsafe, and fear of side-effects.[25] A more recent meta-analysis found that 26% to 57% or pregnant women were hesitant for similar reasons.[26] Our study demonstrates 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 is 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 utilized the same study sites, research methodology, and analytical strategy of our previous reports on the effect of the wild-type virus during pregnancy[1,17,27,28] but, as widely recommended, we added estimates of VE according to the doses and type of vaccine. We believe 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 due to the small sample size and wide confidence intervals. The profiles of the women who were vaccinated suggests some selection bias, not due to the study design, but because the eligibility criteria for being vaccinated changed during the study period. Once the risks of COVID-19 during pregnancy were recognized, pregnant women were no longer considered a low-risk group due to their age, and started being vaccinated because they were pregnant. Consequently, we adjusted the VE analyses for possible confounding factors such as medical risk profile, overweight/obesity, and maternal age.

We did not collect material for viral genotyping; the association with Omicron was based instead on the period when this was the variant of concern. Thus, as it is possible that some other variants could have caused infections in December 2021, we performed sensitivity analyses, excluding women 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.[29] 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.

Conclusions

We found that immunizing mothers against COVID-19 protects their neonates from acquiring the disease and booster vaccination decreases their risk of being born preterm, developing respiratory distress syndrome and staying long periods in NICU. Unvaccinated mothers have newborn infants that are twice as likely to die in the neonatal period as those of vaccinated mothers. However, the protective effects of maternal vaccination diminish 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 directly breastfed or kept in skin-to-skin contact were not at increased risk of infection, which should influence policy making for postnatal care.

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Table 1. Maternal and pregnancy characteristics according to COVID-19 diagnosis and vaccination status, the INTERCOVID-22 Study.

Characteristics[a]	Mothers without COVID-19 Diagnosis (n=3073)	Mothers with COVID-19 Diagnosis				
		All Diagnosed (n=1545)	Unvaccinated (n=631)	Partially Vaccinated (n=145)	Completely Vaccinated (n=535)	Booster Vaccinated (n=233)
	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 birthweight	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/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)

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

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

Characteristics[a]	Mother without COVID-19 Diagnosis (n=3130)	Mothers with COVID-19 Diagnosis				
		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)
Birthweight	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-minute 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 24h 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)

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

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 compared to newborns of 'non-diagnosed' mothers in the INTERCOVID-22 Study.

Outcome	All COVID-19 Diagnosed Mothers (n=1544)		Unvaccinated (n=631)		Partially Vaccinated (n=145)		Completely Vaccinated (n=535)		Booster Vaccinated (n=233)	
	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)#	28	1.40 (0.97, 2.01)#	80	1.05 (0.82, 1.34)	19	0.60 (0.39, 0.93)*
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)*
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)*	11	1.36 (0.74, 2.50)
Neurological conditions	21	1.57 (0.88, 2.80)	6	1.12 (0.46, 2.73)	5	3.98 (1.49, 10.66)*	8	1.72 (0.78, 3.77)	2	0.98 (0.24, 4.10)
Anemia requiring transfusion	15	1.97 (0.97, 4.04)#	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)*	68	1.52 (1.16, 1.98)*	13	1.27 (0.74, 2.18)	54	1.39 (1.03, 1.87)*	20	1.15 (0.74, 1.78)
Antibiotics	130	1.37 (1.09, 1.70)*	56	1.47 (1.09, 1.97)*	12	1.34 (0.76, 2.36)	45	1.35 (0.97, 1.87)#	17	1.16 (0.72, 1.86)
Respiratory conditions	144	1.09 (0.89, 1.33)	68	1.28 (0.98, 1.66)#	13	1.09 (0.64, 1.87)	49	1.07 (0.78, 1.45)	14	0.67 (0.40, 1.13)
Respiratory support ≤ 48h	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 > 48h	59	1.26 (0.91, 1.74)	31	1.65 (1.11, 2.47)*	8	1.90 (0.94, 3.84)#	18	1.08 (0.64, 1.82)	2	0.28 (0.07, 1.12)#
Intermediate/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 days	111	1.24 (0.97, 1.58)#	48	1.32 (0.95, 1.83)#	13	1.61 (0.95, 2.73)#	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)*	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)*	19	1.29 (0.79, 2.12)	7	1.08 (0.51, 2.32)
SPMMI	150	1.22 (1.00, 1.50)#	65	1.30 (0.99, 1.71)#	16	1.43 (0.89, 2.29)	48	1.12 (0.81, 1.55)_	21	1.12 (0.73, 1.71)

[a] Models adjusted for maternal age, previous morbidity, smoking, previous birth and history of preterm birth. Reference group is non-diagnosed mothers (n=3130).

*p<0.05; #p<0.1   NICU= Neonatal Intensive Care Unit

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

Vaccination Status	Vaccine effectiveness against COVID-19 positivity in neonates		Vaccine effectiveness against moderate/severe neonatal outcomes[b]	
	N	VE (95% CI)	N	VE (95% CI)
All neonates/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)*	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)

[a] Models adjusted for maternal age at birth, maternal pre-existing morbidities and maternal overweight status.
[b] Moderate/severe neonatal outcomes include neurologic conditions, anemia requiring transfusion, fever, gastrointestinal issues, infections, antibiotics, respiratory conditions, respiratory support, intermediate/special care, NICU ≥7 days and death.

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 N	N	n (%)	N	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)

Supplementary Table 1. Mothers and neonates testing 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)
UK	152 (9.8)	2 (1.3)
USA	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<0.001).

Supplementary Table 2. Relative risk of COVID-19 diagnosis in newborns according to maternal vaccination status and COVID-19 diagnosis in the INTERCOVID-22 Study.

Vaccination Status of Mother	All neonates			Neonates with COVID-19 diagnosed mother		
	N	COVID-19 Positive N (%)	COVID-19 Positive RR (95% CI)	N	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)*	237	5 (2.1)	0.36 (0.14, 0.90)*

RR= relative risk; *p<0.05.

Supplementary Table 3. Relative risks and 95% Confidence Intervals for neonates testing 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 day	0.84 (0.54, 1.31)	0.44
> 3 days	0.82 (0.50, 1.35)	0.43
> 7 days	1.36 (0.79, 2.33)	0.27
> 10 days	1.60 (0.89, 2.88)	0.12
> 14 days	2.13 (1.17, 3.86)	0.01

Figure legends

Figure 1. COVID-19 diagnosis in neonates according to maternal vaccination status and COVID-19 diagnosis in the INTERCOVID-22 Study.

Figure 2. Vaccine effectiveness against neonatal COVID-19 positive test according to partial, complete and booster doses for newborns of mothers diagnosed with COVID-19 in the INTERCOVID-22 Study.

Appendix: Contributors and Members of the International Study on the Effects of Covid-19 in pregnancy on maternal and newborn outcomes (The INTERCOVID-2022 Study)

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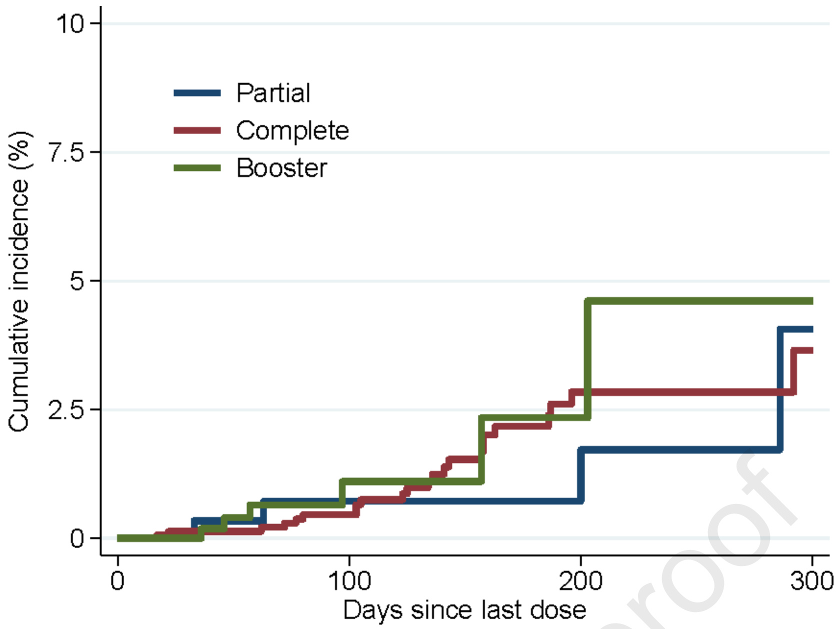
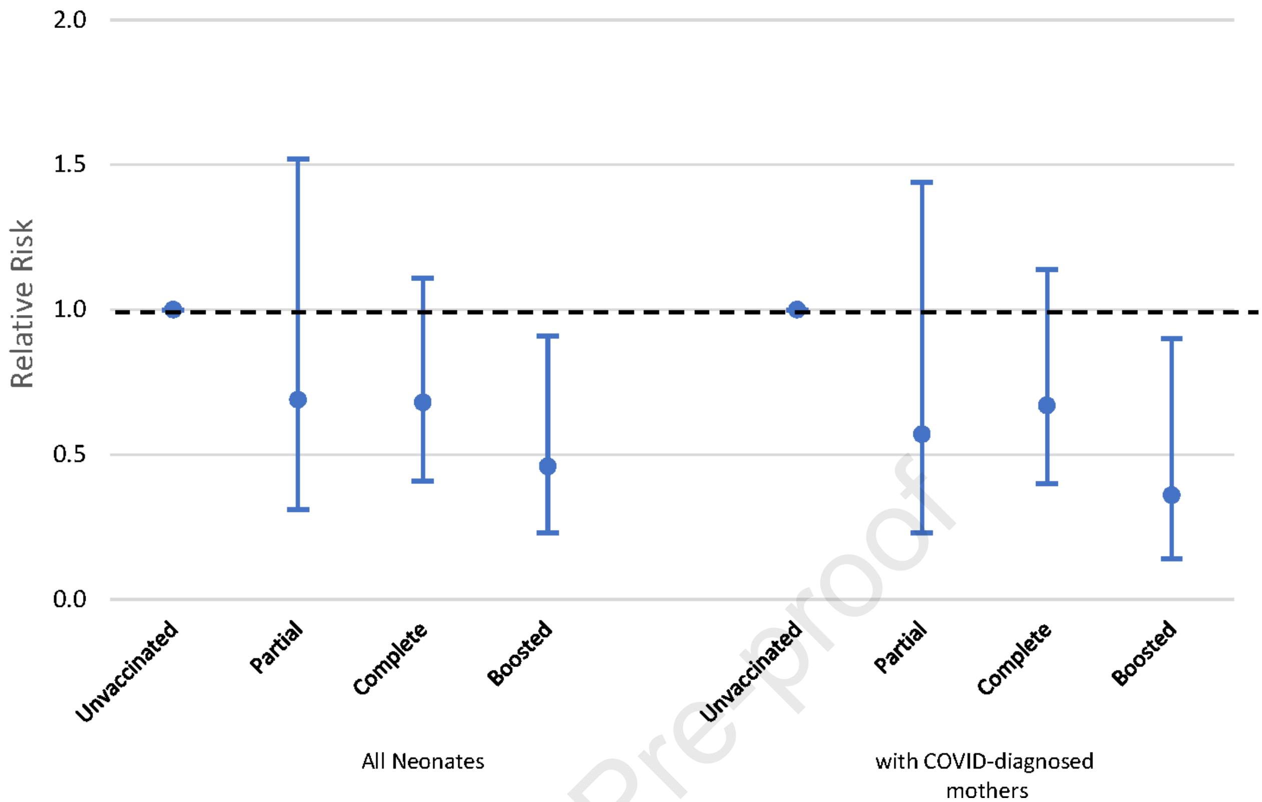


at risk

Partial	330	209	99	35
Complete	1499	1052	400	106
Booster	692	201	43	19


2.0
1.5
1.0
0.5
0.0
Relative Risk
Unvaccinated
Partial
Complete
Boosted
Unvaccinated
Partial
Complete
Boosted
All Neonates
with COVID-diagnosed mothers