Infant Antibodies After Maternal COVID-19 Vaccination During Pregnancy or Postpartum

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abstract

BACKGROUND AND OBJECTIVE: We describe the kinetics of maternally derived antibodies in infants in the first 6 months of life following 2- or 3-dose maternal vaccination during pregnancy or postpartum.

METHODS: This prospective, multicenter cohort study enrolled infants born to mothers vaccinated with 2- (n = 280) or 3-dose (boosted) monovalent messenger RNA vaccines in pregnancy (n = 202) or to mothers vaccinated postpartum (n = 36) from July 2021 to January 2022. Binding (immunoglobulin G to S and receptor-binding domain), pseudovirus, and live neutralizing antibody (nAb) geometric mean titers (GMTs) to vaccine and Omicron BA.1/BA.5 strains were measured at birth and 2 and 6 months of age. Antibody half-life and the effect of maternal or infant COVID-19 infection were assessed.

RESULTS: Significantly higher GMTs of binding antibody and nAb to all antigens were present at birth and 2 months in infants of boosted mothers ($P < .01$) and higher titers to the vaccine strain, but not Omicron BA.1 and BA.5, persisted up to 6 months of age in infants of boosted mothers compared with the other groups ($P < .01$). Higher infant antibody titers at delivery and 6 months of age were associated with a booster dose during pregnancy and maternal prenatal and infant COVID-19 infection. Maternal infection status or vaccine regimen did not influence the half-life of infant antibodies.

CONCLUSIONS: A maternal COVID-19 booster in pregnancy results in significantly higher functional antibody titers in infants compared with 2 doses in pregnancy or postpartum. High titers at birth and maternal hybrid immunity result in persistently elevated titers in infants for 6 months.

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WHAT'S KNOWN ON THIS SUBJECT: COVID-19 vaccines recommended in pregnancy protect mothers directly and the neonate via transplacental antibodies. The kinetics and duration of maternally derived antibodies in infants by neutralizing activity and by maternal infection and vaccination status remain poorly characterized.

WHAT THIS STUDY ADDS: A COVID-19 booster in pregnancy significantly increases functional antibodies in infants compared with 2 doses in pregnancy or postpartum. Despite a rapid decline, high titers at birth and maternal hybrid immunity result in persistently elevated titers in infants for 6 months.

To cite: Munoz FM, Parameswaran L, Gundacker H, et al. Infant Antibodies After Maternal COVID-19 Vaccination During Pregnancy or Postpartum. *Pediatrics.* 2025;156(1): e2024070175

INTRODUCTION

COVID-19 in early infancy can result in severe illness and complications, including hospitalization and death.[1] Since Omicron variants have predominated, COVID-19 hospitalization rates for infants aged younger than 6 months have been the highest among all pediatric age groups, often among infants with no underlying medical conditions, and they continue to remain at the greatest risk for hospitalization in 2024.[2–4]

Infants aged younger than 6 months are not eligible for COVID-19 vaccination,[5] which makes maternal vaccination during pregnancy of paramount importance given the potential for infant protection through passively transferred antibodies. During the Delta and Omicron periods in the United States, maternal vaccination with 2 doses of original messenger RNA (mRNA) monovalent vaccine was associated with a decreased risk of hospitalization and critical illness among infants aged younger than 6 months.[6] In a more recent analysis, these findings were sustained, especially for infants aged younger than 3 months.[7] Furthermore, a third dose or booster vaccination during pregnancy results in additional protection against COVID-19 hospitalization in infants when compared with 2 doses or no maternal vaccination.[8] Vaccine effectiveness may vary with emerging variants, with decreasing protection from vaccination with the original monovalent vaccines noted against Omicron variants.[9] We previously reported that a booster dose of mRNA vaccine during pregnancy and higher titers of binding and nAbs at birth substantially reduced the risk of infant symptomatic COVID-19 infection in the first 2 to 6 months of life during a period of Omicron predominance.[10,11] Here, we describe the kinetics of binding and nAbs in infants after maternal COVID-19 mRNA vaccination during pregnancy or postpartum and evaluate the effect of a booster dose of vaccine during pregnancy on the durability of infant antibody titers from birth to 6 months of age. We also assess the potential effect of maternal and infant COVID-19 infection and of breastfeeding on infant antibody titers over time.

METHODS

Clinical Study Design

A prospective cohort study of pregnant individuals and their infants was conducted across 9 United States academic sites with enrollment from July 6, 2021, until January 31st, 2022, and maternal and infant follow-up for 12 months after delivery (ClinicalTrials.gov ID NCT05031468). The study protocol has been previously described.[12] This report of the Multisite Observational Maternal and Infant Study for COVID-19 describes the antibody kinetics in infants through 6 months of age after maternal vaccination during pregnancy or postpartum. Three study groups are included: (1) infants of mothers who received a primary 2-dose series of the original monovalent BNT162b2 Pfizer-BioNTech (Pfizer) or mRNA-1273 Moderna (Moderna) vaccine (results shown as combined mRNA vaccine) during pregnancy, with the last dose at least 2 weeks prior to delivery; (2) infants of mothers who received a third or booster dose of either mRNA vaccine during pregnancy and at least 2 weeks prior to delivery with receipt of first 2 doses during or shortly before pregnancy; and (3) infants of mothers who received a primary 2-dose mRNA series within 2 months postpartum (no vaccine doses prior to or during pregnancy), with the last dose at least 2 weeks prior to the 2-month study visit. Race and ethnicity are described to allow readers to understand the characteristics of the study population. Serum from peripheral blood was collected from mothers at delivery and in infants at birth from cord blood and from venous blood sampling at 2 and 6 months of age. Reported maternal COVID-19 infection up to 6 months prior to delivery, infant COVID-19 illness, and breastfeeding status through 6 months of age were collected. Most reported symptomatic maternal and infant illnesses were confirmed by at-home testing or by clinical providers at the time of the conduct of this study.[10]

Immunogenicity

Total serum immunoglobulin G (IgG) to SARS-CoV-2 nucleocapsid (N) protein, spike protein (S), and S1 receptor-binding domain (RBD) were evaluated with commercial Meso Scale Discovery (MSD) V-PLEX SARS-CoV-2 panel 2 assay (MSD #K15383U). IgG values are reported here as binding antibody units after conversion of MSD values with World Health Organization International Standard controls (National Institute for Biological Standards and Control code: 20/136).[13–16] Assay protocols were followed directly for serum (see Supplemental Information). nAb titers against SARS-CoV-2 were evaluated by a pseudovirus neutralizing assay using a replication-incompetent lentivirus expressing luciferase and containing the SARS-CoV-2 spike protein (Wuhan-Hu-1) in the viral envelope. Neutralization is reported here as a half-maximum inhibitory concentration, wherein the sample antibody titer dilution is observed inhibiting viral entry and replication by 50%.[17] Complementary live virus focus reduction neutralization titer assay with viruses representing SARS-CoV-2 spike mutation D614G and Omicron BA.1.1.529 (BA.1) and BA.5 (BA.5) variants is also reported as the serum inhibitory dilution required to achieve 50% neutralization (see Supplemental Information).[18] Transplacental transfer ratios were calculated comparing infant antibody titers in cord blood with maternal titers at the time of delivery. Reported SARS-CoV-2 infection in participants, both mothers and infants, was confirmed by the presence of serum N-protein antibodies using the MSD assay.

Statistical Analysis

Maternal and infant characteristics were summarized using descriptive statistics: median with IQR and/or range for continuous variables and number with percentages for categorical variables. Geometric mean titers (GMTs) across time points were calculated. Titers reported as below the lower limit of quantitation (LLOQ) were imputed with a value equivalent to half the assay LLOQ.

Titers of SARS-CoV-2 binding IgG and nAb were compared across vaccine groups using linear regression controlled for time since last vaccine dose and COVID-19 infection (reported infection or N-protein–positive IgG at the specified time point).

Univariable and multivariable linear regression models were used to assess the association of prenatal maternal vaccine dosing with infant log-10–transformed antibody titer levels at birth and 6 months of age adjusted for potential confounders, including prenatal characteristics (3 vs 2 maternal doses, weeks between last maternal dose and delivery, maternal prenatal infection) and infant postnatal infection. Because infant titers at delivery were a priori expected to capture all maternal dosing and prenatal characteristics, multivariate models for 6-month titers were built with and without infant titers at delivery to assess this assumption. To illustrate the effect of number of prenatal doses on infant titers over time, trajectories of titers over time were plotted excluding measurements taken post–infant infection.

To estimate the half-life of antibody titers, we calculated the differences between the log-2–transformed values of antibody measure at birth and 2 months divided by the time between those time points, subsetted to those infants who antibody levels were measurable at birth and 2 months, did not have evidence of infection between the 2 time points and did not have an increase in antibody measure between the 2 time points. The half-life and its corresponding 95% CI are the inverse of the means of these transformed values and their corresponding 95% CIs.[19]

All analyses were generated using SAS (version 9.4) and R software (version 4.3.1).

RESULTS

Study Population

Among 571 infants enrolled in the study, 518 had laboratory results available for inclusion in this analysis (Figure S1, consort diagram). The study population includes 280 infants born to 276 mothers who received a primary 2-dose mRNA vaccine series during pregnancy, 202 infants born to 197 mothers who received a 2-dose series followed by a third dose booster vaccination administered during pregnancy, and 36 infants whose mothers were only vaccinated postpartum (no prenatal doses). Maternal and infant characteristics are shown in Table 1.

Maternal age, infant gestational age at delivery, birth weight, and sex were similar among the groups. Most infants (88.9%–92.5%) were born at term (Table 1). In general, the primary 2-dose vaccination series was completed in the second trimester of gestation with a median interval between vaccination and delivery of 22.1 weeks (IQR, 16.3–26.9), whereas the third dose booster vaccination was received later in pregnancy, with a median interval from booster to delivery of 14.9 weeks (IQR, 9.1–21.4). Most infants were breastfed in the first 2 weeks and 2 months of life in all groups (ranges of 97.5%–100% and 87.9%–94.5%, respectively). By 6 months, the proportion of breastfed infants dropped to 68.6% in the 2-dose primary series group, 80.8% in the booster, and 90% in the postpartum vaccine group.

COVID-19 infection confirmed by report or N-protein positivity within 6 months prior to delivery occurred in 12.3%, 20.3%, and 8.3% in the 2-dose, booster, and postpartum vaccine recipients, respectively. The proportion of maternal participants with COVID-19 infection increased by 6 months postdelivery in all groups. Among infants, the proportion with COVID-19 infection was small at 2 months (2.8%–4.0%) and increased from 2 to 6 months of age, with 25% to 30.7% of infants in all groups becoming infected by 6 months. We previously reported that symptoms of infection in our infant population were generally mild, with no hospitalizations or deaths occurring during the period of follow-up, when Omicron BA.1 and BA.5 were the predominant circulating strains.[10]

Transplacental Antibody Transfer

Transplacental transfer of IgG binding antibody and nAb to all antigens ranged from a mean ratio of 1.13 to 3.93 after a 2-dose series and between 1.68 and 2.78 after booster vaccination (Table 2). Transfer ratios were significantly higher after booster vaccination compared with the 2-dose series for live nAb to D614G and Omicron BA.1 and BA.5 antibodies after adjusting for days from last vaccination to delivery and maternal COVID-19 infection prior to delivery.

Proportion of Infants With Detectable Antibodies

The proportion of infants without maternal or infant infection that had detectable binding IgG and nAb to each of the antigens evaluated is shown in Figure 1. Overall, 100% of infants had detectable binding antibodies to S and RBD at delivery and 2 and 6 months when mothers received a booster in pregnancy. The proportion of infants with binding antibodies at 6 months was greater than 90% and was significantly higher after 2-dose or booster vaccination in pregnancy than with postpartum maternal vaccination (Figure 1, Table S1). nAbs (pseudovirus and live) were detected in a higher proportion of infants from birth to 6 months when mothers received a booster dose of monovalent vaccine (Figure 1, Table S2). A significantly higher

TABLE 1. Maternal and Infant Characteristics by Study Group

	Two Doses of mRNA Vaccine	Three Doses of mRNA Vaccine	No Prenatal Doses of mRNA Vaccine
Maternal, n	276	197	36
Age, median (range; IQR), y	34 (19–51; 31–37)	34 (22–46; 31–37)	32 (24–42; 30–34)
Race (self-reported), % (n)			
American Indian/Alaska Native	1.1 (3)	0.5 (1)	0 (0)
Asian	8.7 (24)	7.1 (14)	2.8 (1)
Black/African American	15.2 (42)	2.5 (5)	25.0 (9)
White	69.6 (192)	84.8 (167)	69.4 (25)
Other	5.4 (15)	5.1 (10)	2.8 (1)
Hispanic or Latino, % (n)	15.6 (43)	8.6 (17)	5.6 (2)
Weeks between last prenatal dose and postvaccination visit, median (IQR)[a]	17 (8–22)	5.9 (3.3–8.4)	–
Weeks between last prenatal dose and delivery, median (IQR)[a]	22.1 (16.3–26.9)	14.9 (9.1–21.4)	–
Gestational week of last prenatal dose, median (IQR)[a]	17.1 (12.4–24.1)	25.1 (18.1–31.1)	–
Postpartum week of first vaccine dose, median (IQR)	–	–	2.1 (0.6–3.9)
Weeks between last prenatal dose and month 2 visit, median (IQR)[a]	31 (24.6–35.6)	22.4 (16.6–28.9)	–
Weeks between last prenatal dose and month 6 visit, median (IQR)[a]	47.6 (41.7–52.4)	40.1 (34.1–46.9)	–
Breastfeeding at 2 wk, % (n)	97.3 (248/255)	98.4 (184/187)	100.0 (9/9)
Breastfeeding at 2 mo, % (n)	87.9 (218/248)	94.5 (172/182)	93.9 (31/33)
Breastfeeding at 6 mo, % (n)	68.6 (164/239)	80.8 (139/172)	90.0 (27/30)
Prenatal SARS-Cov-2 infection, % (n)[b]	12.3 (34)	20.3 (40)	8.3 (3)
Protein positive at delivery, % (n)[c]	10.5 (28/266)	14.5 (28/193)	–
Protein positive at 2 mo, % (n)[c]	17.0 (43/253)	22.5 (43/191)	8.3 (3)
Protein positive at 6 mo, % (n)[c]	37.2 (89/239)	41.7 (70/168)	26.5 (9/34)
Infant, n	280	202	36
Race, % (n)			
Asian	4.6 (13)	5.9 (12)	5.6 (2)
Black/African American	15.0 (42)	1.5 (3)	27.8 (10)
White	60.4 (169)	86.6 (175)	61.1 (22)
Other	20.0 (56)	5.9 (12)	5.6 (2)
Hispanic or Latino, % (n)	15.7 (44)	9.4 (19)	13.9 (5)
Gestational age at delivery, % (n)			
Full-term birth (≥37 wk)	92.5 (259)	89.6 (181)	88.9 (32)
Preterm birth (<37 wk)	7.5 (21)	10.4 (21)	11.1 (4)
Gestational wk at delivery, median (range)	39.3 (25.1–42.6)	39.3 (29.9–41.6)	39.0 (27.3–41.4)
Among preterm birth (<37 wk)	35.6 (25.1–36.9)	35.7 (29.9–36.9)	32.0 (27.3–36.9)
Median birthweight, kg (range)	3.4 (1.7–4.9)	3.4 (1.0–5.2)	3.3(0.9–4.5)
Female sex, % (n)	51.1 (143)	54.0 (109)	47.2 (17)
Infant infection			
SARS-CoV-2 infection up to month 2 visit, % (n)[d]	3.2 (9)	4.0 (8)	2.8 (1)
Evidence of seroconversion, n[e]	6	5	0
Self-report, n[e]	4	5	1
SARS-CoV-2 infection up to month 6 visit, % (n)[d]	26.4 (74)	30.7 (62)	25.0 (9)
Evidence of seroconversion, n[e]	60	45	7
Self-report, n[e]	48	43	7

(Continued on next page)

TABLE 1. Maternal and Infant Characteristics by Study Group (Continued)

	Two Doses of mRNA Vaccine	Three Doses of mRNA Vaccine	No Prenatal Doses of mRNA Vaccine
Infant retention			
Attendance at month 6 visit, % (n)	91.4 (256)	92.6 (187)	94.4 (34)
Lab results at month 6 visit, % (n)[f]	79.3 (222)	75.7 (153)	86.1 (31)
Reported vaccination prior to 6-mo visit, % (n)	0 (0)	5.0 (10)[g]	0 (0)

Abbreviations: anti-N, anti-nucleocapsid; BAU/mL, binding antibody unit; IgG, immunoglobulin G; mRNA, messenger RNA.
[a] The last prenatal dose refers to the second dose in the 2-dose mRNA vaccine group and the third dose in the 3-dose mRNA vaccine group.
[c] "N protein positive" is defined as anti-N IgG >11.8 BAU/mL for mothers and >6.88 BAU/mL for infants.
[b] For mothers, prenatal SARS-CoV-2 infection is defined as either a self-reported COVID-19 diagnosis within 180 d prior to delivery or being "N protein positive" at the time of delivery for the two-thirds dose group. For the "no prenatal doses of mRNA vaccine" group, "N protein positive" at the earliest collected result postdelivery was used.
[d] For infants, SARS-CoV-2 infection is defined as either being "N protein positive" with an increased level from the previous visit or based on self-report. For "no prenatal doses of mRNA vaccine" group, the earliest collected anti-N IgG measurement postdelivery and self-report were used to determine infection status.
[e] The numbers in the "Evidence of seroconversion" and "Self-report" rows do not necessarily add up to the total number of SARS-CoV-2 infections because an infant can have both evidence of seroconversion and a self-reported COVID-19 infection.
[f] Represents the percentage of infants with available laboratory results at the 6-month visit, specifically including data from binding and nAb tests.
[g] The 6-month measurement of 10 infants has been excluded from the analysis.

proportion of infants of boosted mothers had nAb to Omicron BA.1 and BA.5 at delivery and at 2 months, but by 6 months, the CIs overlapped between all vaccine groups.

GMTs and Kinetics of Binding and Neutralizing Antibodies in Infants

The GMTs and kinetics of vaccine-induced binding antibody and nAb were evaluated in infants who were never infected with COVID-19 up to 6 months of age and whose mothers were not infected with COVID-19 prior to delivery (Figure 2 and Supplemental Information Tables S1, S2, and S3). Although a substantial and rapid decline in GMTs was observed from birth to 2 months regardless of pregnancy vaccine regimen, significantly higher GMTs of binding, pseudovirus, and live nAb were present at birth and 2 months in infants of mothers who received a booster in pregnancy vs a 2-dose series or no vaccine in pregnancy (all P values <.01) (Table S3). At 6 months, significantly higher GMTs of binding, pseudovirus, and live nAb against D614G were present in infants of mothers who received a booster in pregnancy vs a 2-dose series or no vaccine in pregnancy ($P < .01$), but live nAbs against Omicron BA.1 and BA.5 were not significantly different at this time point (Table S3).

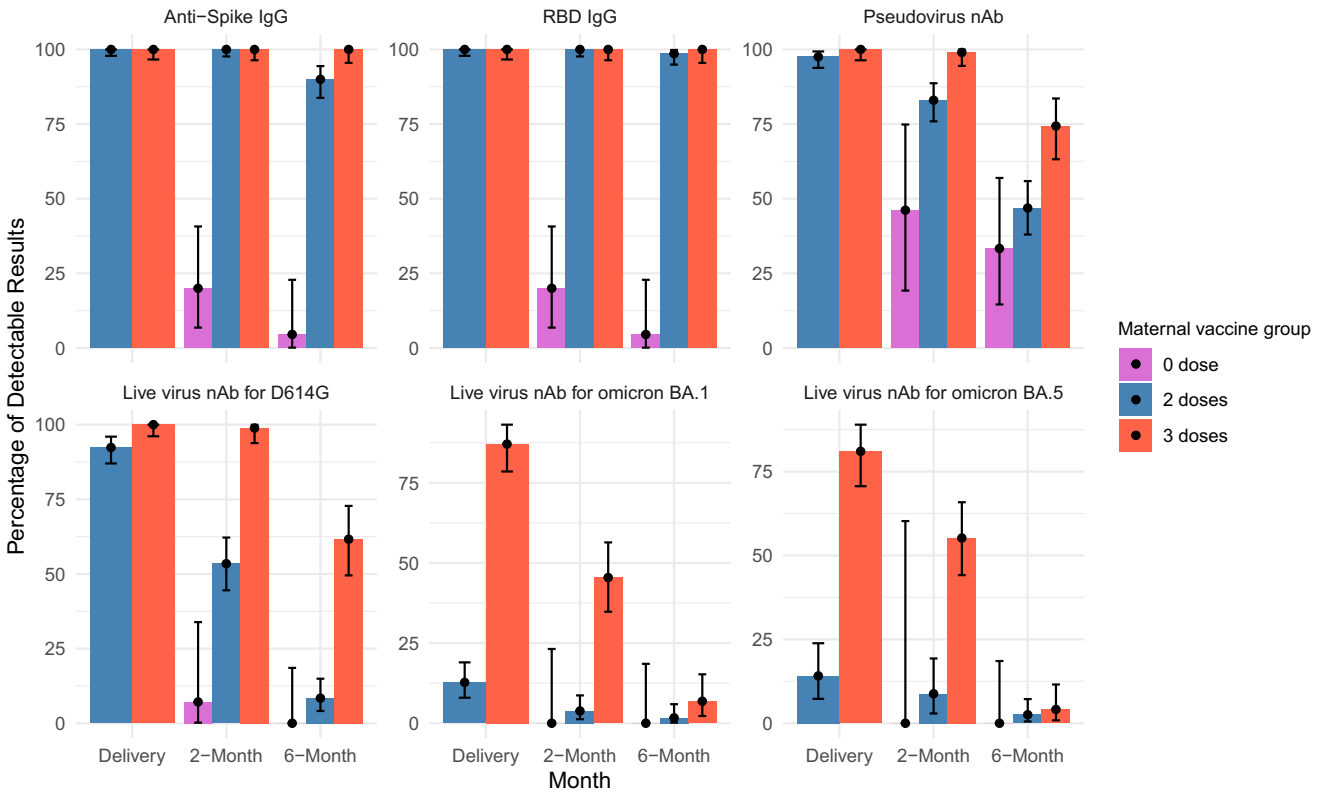
Factors Contributing to Infant Antibody Titers at Delivery and at 6 Months of Age

Factors significantly associated with infant binding, pseudovirus, and live nAb titers at delivery included maternal prenatal receipt of 3 vs 2 COVID-19 vaccine doses and maternal prenatal infection (all $P \leq .01$; Table 3A), whereas a shorter

TABLE 2. Binding and Neutralizing Antibody Transfer Ratios by Antigen and Maternal Vaccine Regimen

Lab Assay	Group (n)	Transfer Ratio Mean (95% CI)	Cord Blood GMT (95% CI)	Maternal Serum GMT (95% CI)	*P* Value[a]
Anti-spike IgG	Two doses of mRNA vaccine (245)	1.86 (1.77–1.96)	568.79 (492.91–656.36)	340.2 (291.18–397.47)	–
Anti-spike IgG	Three doses of mRNA vaccine (172)	1.68 (1.59–1.77)	2916.98 (2531.14–3361.64)	1880.36 (1608.04–2198.8)	.1898
RBD IgG	Two doses of mRNA vaccine (245)	1.88 (1.78–1.97)	799.62 (685.46–932.81)	479.9 (406.16–567.02)	–
RBD IgG	Three doses of mRNA vaccine (172)	1.71 (1.61–1.82)	4722.52 (4083.58–5461.44)	3026.36 (2570.62–3562.91)	.3900
Pseudotyped WT nAb	Two doses of mRNA vaccine (240)	3.93 (3.21–4.66)	189.4 (162.37–220.92)	88.22 (75.68–102.83)	–
Pseudotyped WT nAb	Three doses of mRNA vaccine (171)	2.78 (2.21–3.36)	594.99 (493–718.09)	339.07 (278.69–412.52)	.0792
D614G spike nAb	Two doses of mRNA vaccine (229)	1.73 (1.59–1.87)	105.8 (89.4–125.21)	75.77 (61.53–93.31)	–
D614G spike nAb	Three doses of mRNA vaccine (154)	1.85 (1.66–2.04)	729.13 (618.88–859.03)	479.24 (396.52–579.21)	.0024
B.1.1.529 (Omicron) nAb	Two doses of mRNA vaccine (229)	1.2 (1.09–1.32)	14.54 (13.06–16.2)	13.73 (12.29–15.34)	–
B.1.1.529 (Omicron) nAb	Three doses of mRNA vaccine (154)	1.89 (1.69–2.09)	92.3 (74.79–113.91)	61.02 (48.23–77.2)	<.0001
BA.5 (Omicron) nAb	Two doses of mRNA vaccine (117)	1.13 (1–1.25)	14.9 (12.84–17.29)	14.62 (12.51–17.08)	–
BA.5 (Omicron) nAb	Three doses of mRNA vaccine (130)	1.76 (1.56–1.97)	61.52 (49.9–75.83)	41.79 (33.56–52.04)	<.0001

Abbreviations: GMT, geometric mean titer; IgG, immunoglobulin G; mRNA, messenger RNA; nAb, neutralizing antibody; RBD, receptor-binding domain; WT, wild type.
[a] *P* value from linear regression comparing transfer ratio between 2-dose group and 3-dose group adjusted for days since last prenatal vaccination and prenatal maternal COVID-19 infection.



*Excludes infants diagnosed with COVID−19 by 6 months of age or with prenatal maternal SARS−CoV−2 infection, defined by self−reported infection within 180 days prior to delivery or Anti−N IgG >11.8 BAU/ml at delivery.For the 'no prenatal dose' group, earliest collected Anti−N IgG was used.

FIGURE 1.
Proportion of infants with detectable binding and nAbs by maternal vaccine group.
Abbreviations: anti-N, anti-nucleocapsid; BAU/mL, binding antibody unit; IgG, immunoglobulin G; nAb, neutralizing antibody; RBD, receptor-binding domain.

interval between maternal vaccination and delivery was also associated with higher binding and pseudovirus nAb titers at delivery (all $P < .01$).

Factors significantly associated with infant titers by 6 months of age included infant titers at delivery and infection within the first 6 months of life (Table 3B). When infant titers at delivery was removed from the models, several other variables significantly contributed to infant titers at 6 months of age, including the number of maternal prenatal vaccine doses (3 vs 2), timing of maternal vaccination during pregnancy, and mother's prenatal infection, indicating that infant titers at delivery is a proxy for maternal prenatal factors that influence persistence of titers by 6 months of age.

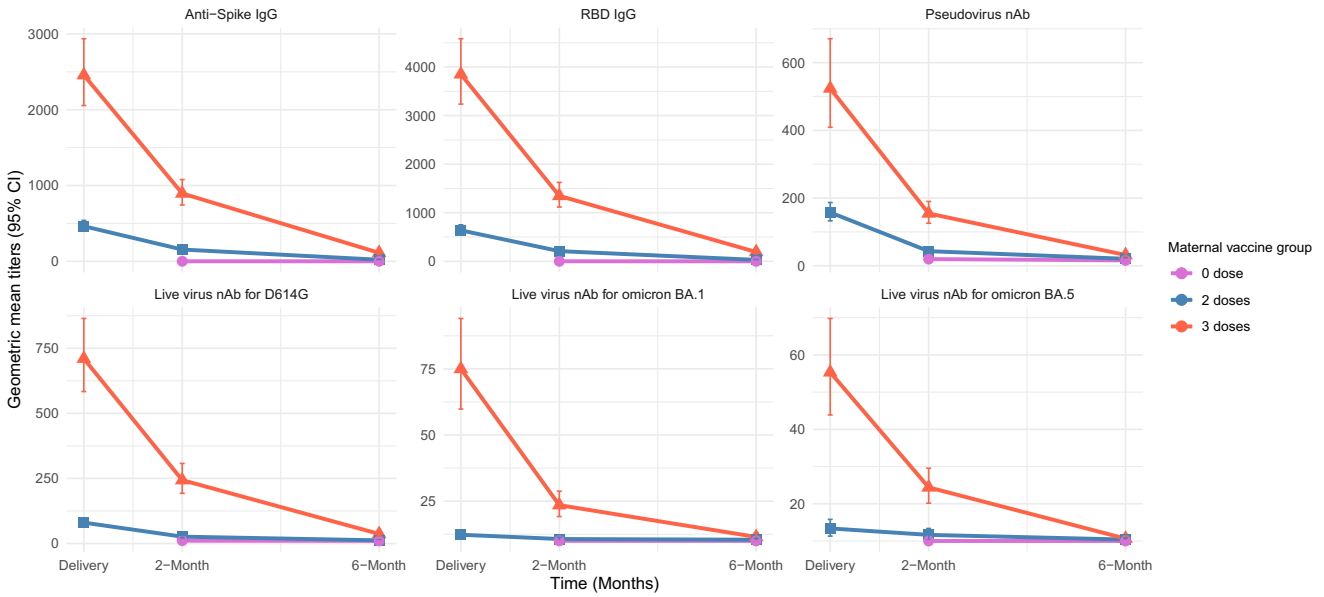
Overall, in regression models examining factors influencing infant titers at delivery and 6 months of age for all antibody types, the number of prenatal vaccine doses (3 vs 2) as well as maternal prenatal and infant infection status were the most consistently identified variables that contributed significantly to infant titers (Tables 3A and 3B). Only infant infection was significantly associated with the presence of high nAb titers to vaccine strain, D614G, BA.1, and BA.5 in infants at 6 months (Table 3B).

Half-Life of Vaccine-Induced Maternally Derived Antibodies in Infants

The calculated half-life of vaccine-induced binding antibodies to spike and RBD in infants was 36.4 (95% CI, 36.5–37.3) and 35.3 (95% CI, 34.5–36.2) days overall, with no substantial differences noted by maternal vaccine regimen or by maternal infection status (Figure 3). Although the calculated half-life of nAb measured by pseudovirus assay was slightly shorter, 28.2 (95% CI, 26.4–30.2) days, the half-life for live nAb, was overall similar to that of binding antibodies for D614G (37.6 days; 95% CI, 35.6–39.8), Omicron BA.1 (37.3 days; 95% CI, 33.9–41.4), and Omicron BA.5 (40.3 days; 95% CI, 36.8–44.6) nAb, with greater variability noted in the Omicron analysis because it included a smaller number of results. Assay variability is expected because of a number of factors, including the dynamic range of the assay, virus variants, entry vs spread-based assays, and others.[20,21]

Effect of Infant or Maternal COVID-19 Infection on Infant Antibody Responses

Infants who were infected with COVID-19 between 2 and 6 months had binding and pseudovirus nAb titers that



*Excludes infants diagnosed with COVID−19 by 6 months of age or with prenatal maternal SARS−CoV−2 infection, defined by self−reported infection within 180 days prior to delivery or Anti−N IgG >11.8 BAU/ml at delivery. For the 'no prenatal dose' group, earliest collected Anti−N IgG was used.

FIGURE 2.
Geometric mean titer of binding and nAbs in infants at delivery, 2 and 6 months of age, by maternal vaccine group.
Abbreviations: anti-N, anti-nucleocapsid; BAU/mL, binding antibody unit; IgG, immunoglobulin G; nAb, neutralizing antibody; RBD, receptor-binding domain.

TABLE 3A. Factors Contributing to Infant Antibody Titers at Delivery

Assay	Covariate	Univariable[a]		Multivariable[a]	
		Estimate (95% CI)	*P* Value	Estimate (95% CI)	*P* Value
Spike IgG	3 vs 2 prenatal doses	0.70 (0.62–0.79)	<.001	0.53 (−0.45 to 0.60)	<.001
	Weeks between last dose and delivery (per 1 wk increase)	−0.03 (−0.04 to −0.03)	<.001	−0.02 (−0.03 to −0.02)	<.001
	Mother's prenatal infection vs no prenatal infection	0.59 (0.45–0.73)	<.001	0.56 (0.47–0.66)	<.001
RBD IgG	3 vs 2 prenatal doses	0.76 (0.67–0.85)	<.001	0.58 (0.50–0.66)	<.001
	Weeks between last dose and delivery (per 1 wk increase)	−0.03 (−0.04 to −0.03)	<.001	−0.02 (−0.03 to −0.02)	<.001
	Mother's prenatal infection vs no prenatal infection	0.66 (0.51–0.80)	<.001	0.62 (0.51–0.72)	<.001
Pseudovirus nAb	3 vs 2 prenatal doses	0.51 (0.40–0.61)	<.001	0.35 (0.25–0.45)	<.001
	Weeks between last dose and delivery (per 1 wk increase)	−0.02 (−0.03 to −0.02)	<.001	−0.02 (−0.03 to −0.01)	<.001
	Mother's prenatal infection vs no prenatal infection	0.56 (0.42–0.70)	<.001	0.55 (0.42–0.67)	<.001
Live virus D614G	3 vs 2 prenatal doses	0.81 (0.33–1.29)	.002	0.75 (0.29–1.21)	.002
	Weeks between last dose and delivery (per 1 wk increase)	−0.01 (−0.04 to 0.02)	.41	0.00 (−0.02 to 0.02)	.94
	Mother's prenatal infection vs no prenatal infection	0.82 (0.16–1.47)	.018	0.71 (0.18–1.24)	.012
Omicron BA.1	3 vs 2 prenatal doses	0.86 (0.37–1.36)	.002	0.81 (0.37–1.24)	.001
	Weeks between last dose and delivery (per 1 wk increase)	−0.01 (−0.04 to 0.02)	.47	0.00 (−0.02 to 0.02)	.81
	Mother's prenatal infection vs no prenatal infection	0.97 (0.31–1.62)	.006	0.85 (0.34–1.36)	.002
Omicron BA.5	3 vs 2 prenatal doses	0.62 (0.09–1.14)	.024	0.37 (−0.05 to 0.78)	.078
	Weeks between last dose and delivery (per 1 wk increase)	−0.01 (−0.04 to 0.02)	.46	−0.00 (−0.02 to 0.01)	.80
	Mother's prenatal infection vs no prenatal infection	1.06 (0.60–1.52)	<.001	0.93 (0.48–1.38)	<.001

Abbreviations: IgG, immunoglobulin G; nAb, neutralizing antibody; RBD, receptor-binding domain.
[a] Coefficients from linear regression models.

TABLE 3B. Factors Contributing to Infant Antibody Titers by 6 mo of Age

Assay	Covariate	Univariable[a]		Multivariable[a]		Multivariable Without Delivery Titers[a]	
		Estimate (95% CI)	*P* Value	Estimate (95% CI)	*P* Value	Estimate (95% CI)	*P* Value
Spike IgG	3 vs 2 prenatal doses	0.59 (0.49 to 0.70)	<.001	0.01 (−0.08 to 0.10)	.82	0.42 (0.33–0.52)	<.001
	Weeks between last dose and delivery (per 1 wk increase)	−0.03 (−0.03 to −0.02)	<.001	−0.00 (−0.01 to 0.00)	.58	−0.02 (−0.03 to −0.02)	<.001
	Infant titers (log10) at delivery	0.82 (0.76–0.88)	<.001	0.79 (0.70–0.88)	<.001	–	–
	Mother's prenatal infection vs no prenatal infection	0.50 (0.34–0.66)	<.001	0.04 (−0.07 to 0.15)	.46	0.46 (0.33–0.59)	<.001
	Infant infection vs no infection	0.32 (0.19–0.44)	<.001	0.32 (0.25–0.39)	<.001	0.30 (0.21–0.40)	<.001
RBD IgG	3 vs 2 prenatal doses	0.69 (0.58–0.79)	<.001	0.04 (−0.05 to 0.13)	.35	0.51 (0.41–0.62)	<.001
	Weeks between last dose and delivery (per 1 wk increase)	−0.03 (−0.04 to −0.02)	<.001	−0.00 (−0.01 to 0.00)	.74	−0.02 (−0.03 to −0.02)	<.001
	Infant titers (log10) at delivery	0.85 (0.80–0.91)	<.001	0.81 (0.73–0.90)	<.001	–	–
	Mother's prenatal infection vs no prenatal infection	0.57 (0.40–0.74)	<.001	0.04 (−0.07 to 0.15)	.49	0.52 (0.38–0.65)	<.001
	Infant infection vs no infection	0.22 (0.08–0.35)	.002	0.21 (0.14–0.28)	<.001	0.20 (0.10–0.30)	<.001
Pseudovirus nAb	3 vs 2 prenatal doses	0.17 (0.10–0.24)	<.001	0.06 (−0.02 to 0.14)	.13	0.13 (0.06–0.20)	<.001
	Weeks between last dose and delivery (per 1 wk increase)	−0.01 (−0.01 to −0.00)	.008	−0.00 (−0.01 to 0.01)	.83	−0.00 (−0.01 to 0.00)	.053
	Infant titers (log10) at delivery	0.25 (0.19–0.31)	<.001	0.09 (−0.02 to 0.19)	.11	–	–
	Mother's prenatal infection vs no prenatal infection	0.21 (0.11–0.31)	<.001	0.09 (−0.02 to 0.19)	.11	0.19 (0.09–0.29)	<.001
	Infant infection vs no infection	0.14 (0.06–0.22)	<.001	0.15 (0.07–0.22)	<.001	0.13 (0.06–0.20)	<.001
Live virus D614G	3 vs 2 prenatal doses	0.41 (0.31–0.51)	<.001	−0.26 (−0.89 to 0.37)	.38	0.33 (0.24–0.43)	<.001
	Weeks between last dose and delivery (per 1 wk increase)	−0.01 (−0.02 to −0.01)	<.001	0.01 (−0.01 to 0.04)	.26	−0.01 (−0.02 to −0.00)	.002
	Infant titers (log10) at delivery	0.59 (0.27–0.91)	.002	0.74 (0.24–1.25)	.009	–	–
	Mother's prenatal infection vs no prenatal infection	0.45 (0.30–0.59)	<.001	−0.06 (−0.73 to 0.60)	.84	0.43 (0.29–0.56)	<.001
	Infant infection vs no infection	0.12 (0.00–0.23)	.049	0.25 (−0.28 to 0.78)	.31	0.09 (−0.01 to 0.19)	.065
Omicron BA.1	3 vs 2 prenatal doses	−0.06 (−0.17 to 0.04)	.24	−0.19 (−0.84 to 0.47)	.53	−0.11 (−0.19 to −0.03)	.007
	Weeks between last dose and delivery (per 1 wk increase)	−0.00 (−0.01 to 0.01)	.76	−0.01 (−0.03 to 0.02)	.46	−0.01 (−0.01 to −0.00)	.029
	Infant titers (log10) at delivery	0.29 (−0.15 to 0.74)	.17	0.37 (−0.14 to 0.88)	.13	–	–
	Mother's prenatal infection vs no prenatal infection	0.16 (0.01–0.31)	.04	0.31 (−0.34 to 0.97)	.30	0.12 (0.01–0.23)	.034
	Infant infection vs no infection	0.70 (0.62–0.78)	<.001	0.81 (0.28–1.34)	.007	0.70 (0.62–0.78)	<.001
Omicron BA.5	3 vs 2 prenatal doses	0.15 (0.06–0.24)	.002	0.07 (−0.40 to 0.54)	.73	0.13 (0.07–0.20)	<.001
	Weeks between last dose and delivery (per 1 wk increase)	0.00 (−0.00 to 0.01)	.75	0.00 (−0.02 to 0.03)	.76	0.00 (−0.00 to 0.00)	.64
	Infant titers (log10) at delivery	−0.22 (0.98–0.53)	.52	−0.19 (−0.77 to 0.40)	.45	–	–
	Mother's prenatal infection vs no prenatal infection	0.30 (0.17–0.43)	<.001	0.51 (−0.23 to 1.25)	.14	0.22 (0.13–0.31)	<.001
	Infant infection vs no infection	0.68 (0.61–0.75)	<.001	0.88 (0.45–1.31)	.003	0.66 (0.60–0.73)	<.001

Abbreviations: IgG, immunoglobulin G; nAb, neutralizing antibody; RBD, receptor-binding domain.
[a] Coefficients from linear regression models.

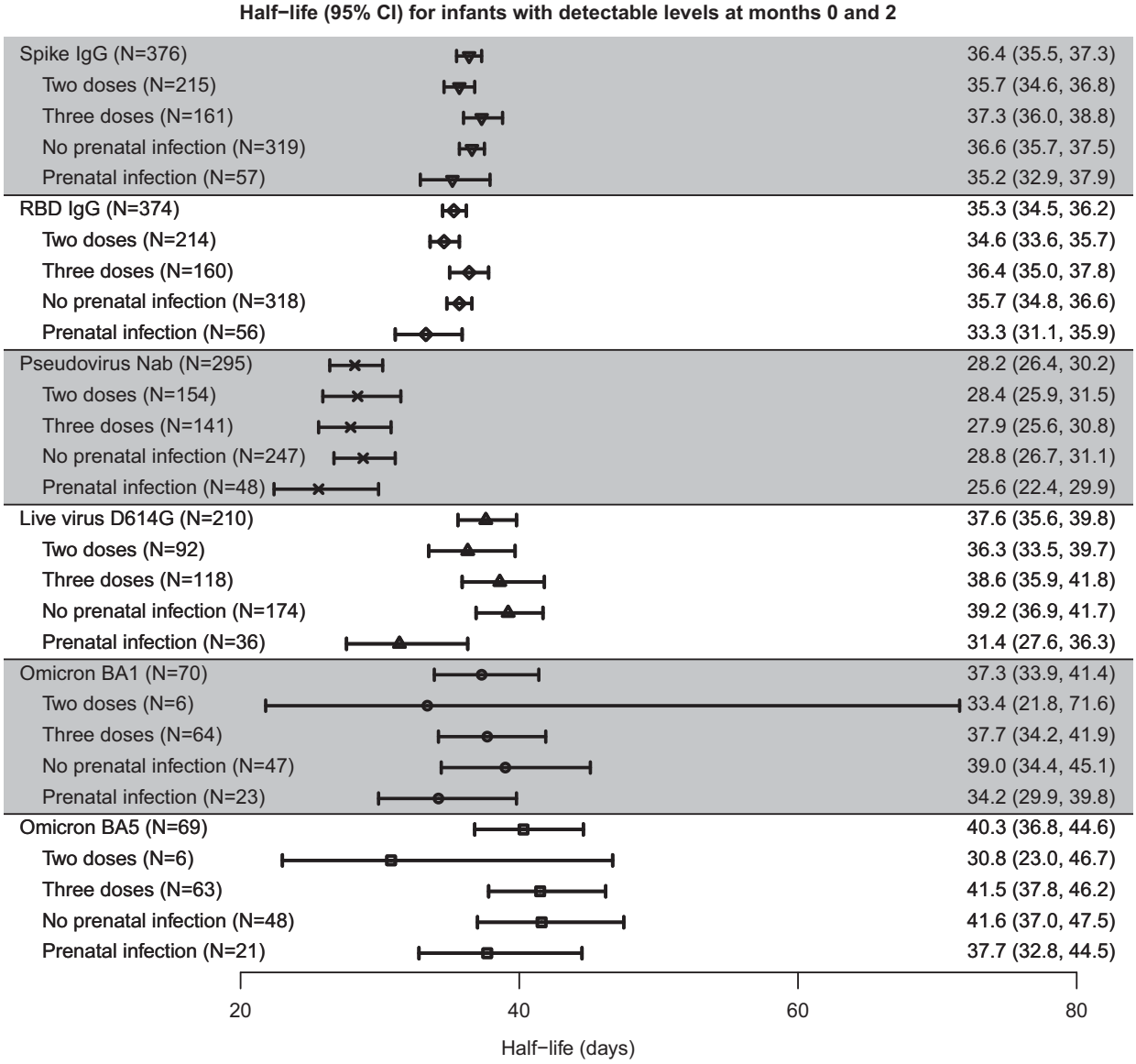


FIGURE 3.
Half-life (95% CI) for infants with detectable levels at months 0 and 2.
Abbreviations: IgG, immunoglobulin G; nAb, neutralizing antibody; RBD, receptor-binding domain.

increased more prominently for those in the 2-dose vaccine group as compared with the 3-dose vaccine group (Figure S2). However, infants infected between 2 and 6 months had Omicron BA.1 and BA.5 nAb increase substantially in both 2-dose and 3-dose vaccine groups, consistent with predominantly circulating strains at the time. Infant immune responses to infection were observed in all groups, regardless of maternal vaccine regimen.

Maternal COVID-19 infection during pregnancy in both 2- and 3-dose vaccine groups resulted in higher titers of antibodies in infants at all time points, indicating that hybrid immunity increases antibody persistence in the first 6 months of the infant's life (Figure S3).

Effect of Breastfeeding on Infant Titers

No significant effect on infant serum GMTs at different time points was observed when comparing infants who were breastfed and infants who were not (Figure S4).

DISCUSSION

We conducted an observational cohort study during the early phases of the COVID-19 pandemic, spanning Delta and Omicron BA.4/BA.5 circulation, when preventive strategies included routine vaccination during pregnancy and testing to confirm infection was prevalent.

Infants of mothers who received a third dose booster during pregnancy had significantly higher binding antibody and nAb titers against vaccine and Omicron variants at birth and 2 months of age compared with infants of mothers who received only 2 doses or were vaccinated postpartum. At 6 months, findings were similar, with the exception of live nAbs against Omicron BA.1 and BA.5 that were not significantly different at this time point. Two doses of vaccine during pregnancy were also able to achieve significantly higher binding and pseudovirus nAb titers at birth and 2 months compared with no prenatal vaccination but not by 6 months, and 2 prenatal doses were not able to achieve higher tigers against Omicron BA.1 or BA.5 at 2 or 6 months compared with no vaccination in pregnancy. Additionally, antibody concentrations in infants of mothers who received 2 prenatal doses were substantially lower than those of infants of boosted mothers. These findings were sustained after adjusting the confounding effect of maternal and infant infection during the study period.

The most important factors contributing to high infant antibody titers at birth were maternal receipt of a booster dose of vaccine in pregnancy, a shorter interval from maternal vaccination to delivery, and maternal COVID-19 infection in pregnancy. The most influential factors in achieving persistently high antibody titers at 6 months of age were infant titers at delivery (determined by maternal vaccination and infection status) and infant infection. Our findings suggest that a booster vaccination in pregnancy and hybrid immunity (vaccination in mothers with prior infection) provide the potential for longer infant protection.

Primary maternal vaccination in the second trimester of gestation was shown early in the pandemic to result in robust maternal responses and efficient transplacental passage of antibodies to the neonate.[22,23] However, consistent with our findings, higher concentrations of antibodies are achieved in infants born to mothers who had antenatal vaccination during the third trimester compared with the second trimester.[24,25] In a prospective cohort study conducted from 2021 to 2023, women who received 3 doses of vaccine before delivery had 10-fold higher cord anti–spike antibody titers compared with 2-dose recipients.[25] When term and preterm deliveries were compared, maternal antibody titers were more influential to achieve high cord antibody concentrations than gestational age at birth, and the authors concluded that individuals at risk for preterm delivery could benefit from additional doses of COVID-19 vaccine in pregnancy. In a multicenter observational immunogenicity study conducted by the Centers for Disease Control and Prevention in women vaccinated in 2021, cord-blood GMTs of nAb to D614G-like viruses were 5-fold higher if women were vaccinated in the third vs the first trimester of pregnancy and were also higher when vaccination occurred closer to delivery, with titers waning over time so that most infants had no detectable nAbs by 6 months of age.[26]

Furthermore, booster vaccination in pregnancy with mRNA vaccines has been shown to induce a strong anti–spike antibody response, including to Omicron strains.

COVID-19 antibodies after maternal vaccination can persist through 6 months of life in infants,[27] and early studies suggested that vaccine-induced antibodies persist longer than antibodies derived from maternal infection.[27–30] In our study, we demonstrated high antibody transplacental transfer ratios (>1) of binding and nAbs after mRNA COVID-19 vaccination in pregnancy, particularly after a booster dose administration in the third trimester of gestation. Overall, the calculated half-life of vaccine-induced maternally derived IgG binding and nAb in infants ranged from 33 to 40 days and was not affected by maternal vaccine regimen or by maternal infection status. However, maternal COVID-19 infection during pregnancy in both 2- and 3-dose vaccine groups resulted in higher titers of antibodies in infants at all time points, indicating that hybrid immunity increases antibody persistence in the first 6 months of the infant's life. Although the protective effectiveness of hybrid immunity against severe COVID-19 and specifically Omicron variant disease has been described numerous times in adult studies,[31–34] the effect of hybrid maternal immunity on infant antibody titers at birth and in the first 6 months of life is less well characterized. One study conducted in Seoul, South Korea evaluated the maternal and neonatal serum-neutralizing activity against SARS-CoV2 ancestral stain in vaccinated pregnant individuals who were later infected and their newborns, demonstrating 6-fold and 32-fold higher nAb in mothers and newborns, respectively, compared with individuals who were infected only or vaccinated only.[35] Although the neutralizing activity was lower for Omicron BA.5 strain in this study, the favorable effect of hybrid immunity remained.

As expected, postpartum maternal vaccination or breastfeeding did not affect infant antibody titers and kinetics.[22] Although maternal vaccination postpartum does not provide direct protection to infants at risk, breastfeeding may reduce the risk of respiratory infections in general.[36]

The role of maternally derived antibodies in protecting infants from COVID-19 symptomatic and severe disease has been previously described. Although an antibody correlate of protection has not been identified, data previously reported from our study cohort showed that higher transplacental binding and nAb titers at birth substantially reduced the risk of COVID-19 symptomatic infection in infants in the first 2 months of life and a third booster dose amplified this protection so that with each 10-fold rise in anti–S-IgG titer at delivery, the risk of acquiring infection by infant was reduced by 47%.[10] In a large study with more than 30 000 infants during the Delta variant period, receipt of at least 2 doses of maternal COVID-19 vaccination was protective for the infants against both infection with SARS-CoV-2 and hospitalization for the first 6 months.[9]

This effect was observed during the Omicron variant period as well, particularly if the third or booster dose was given during pregnancy,[37] with the dose enhancing the protection from the more infectious Omicron variant.[38] Given that the incidence of severe COVID-19 in pregnancy has decreased as the pandemic evolved, with less frequent hospitalization and adverse obstetric outcomes compared with early and Delta pandemic periods, a key objective for maternal vaccination is the protection of infants too young to be vaccinated, who continue to have substantial morbidity and mortality from COVID-19.[39] During 2022–2024, COVID-19 vaccination in pregnancy dropped from 18% to less than 5%, yet the COVID-19–Associated Hospitalization Network reported the highest hospitalization rates in pediatrics to be in infants aged younger than 6 months (≤23.0 per 100 000 infants and similar to those of adults 65–74 years old), with 1 in 5 infants hospitalized with COVID-19 requiring admission to the intensive care unit, 1 in 20 requiring mechanical ventilation, and 9 dying during their COVID-19–associated hospitalization.[4] Of particular concern in this report is that, among hospitalized infants with known maternal vaccination status, 87.5% of mothers had no documentation of COVID-19 vaccination during pregnancy, and all infants who died were born to unvaccinated mothers. Our study results strongly support antenatal maternal COVID-19 vaccination in previously vaccinated or infected mothers to increase potentially protective antibody titers in the infant from birth through 6 months.

LIMITATIONS

This study was limited by its observational design in that vaccination of participants occurred at different times during pregnancy and postpartum as per contemporary recommendations, which resulted in various intervals between doses of vaccine and from last vaccination and delivery. Also, the study was conducted during the time of the emergence of Omicron, a strain not included in the available vaccines. However, close follow-up and high compliance with study visits allowed for the assessment of factors contributing to infant antibody titers at delivery and persistence up to 6 months of age, including maternal and infant infection, which were confirmed by laboratory testing. This study was not designed to estimate the protection against infection in infants from breastfeeding, and we were unable to evaluate the effects of Omicron containing vaccines or additional boosters in mothers.

CONCLUSION

A maternal COVID-19 booster in pregnancy resulted in significantly higher binding antibody and nAb in infants from birth to 6 months than 2 doses in pregnancy or postpartum vaccination. Although transplacentally derived antibody titers decline rapidly in the first 6 months of life, higher concentrations at birth may confer longer duration of protection until vaccination of infants when they become age eligible. Maternal receipt of a booster dose of vaccine in pregnancy and maternal infection independently and together (hybrid immunity) resulted in higher titers for a longer duration in infants. Infants aged 0 to 6 months remain at high risk for severe disease and hospitalization from COVID-19. This study supports COVID-19 vaccination during pregnancy in previously vaccinated or infected mothers to optimize antibody titers and protection of infants from birth through 6 months.

ABBREVIATIONS

BAU/mL: binding antibody unit
GMT: geometric mean titer
IgG: immunoglobulin G
LLOQ: lower limit of quantitation
mRNA: messenger RNA
MSD: Meso Scale Discovery
N: nucleocapsid protein
nAb: neutralizing antibody
RBD: receptor-binding domain
S: spike protein

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Drs Munoz, Cardemil, Beigi, and Neuzil conceptualized and designed the study, designed the data collection instruments, coordinated and supervised data collection, drafted the initial manuscript, and critically reviewed and revised the manuscript for important intellectual content. Drs Badell, Bunge, Mulligan, Parameswaran, Olson-Chen, Novak, Brady, DeFranco, Gerber, and Piper collected data and critically reviewed and revised the manuscript. Drs Posavad, Pasetti, Shriver, Coler, Larsen, Suthar, and Moreno coordinated and supervised data collection, performed laboratory testing, and critically reviewed and revised the manuscript. Drs Richardson and Brown and Ms Gundacker and Ms Sui designed and carried out the analyses and critically reviewed and revised the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work. Data collected for the study will be made available to others as a deidentified patient dataset after finalization of clinical study report at the discretion of the Infectious Diseases Clinical Research Consortium. Analyses of data, including data from staged analyses, will be available for presentation at scientific meetings and publication to inform the scientific community. If preliminary analyses are considered of public health importance or relevant to inform research, development, and implementation

of SARS-CoV-2 vaccine in pregnancy, results may be shared with public health officials and partners to inform the global scientific community. The study will be conducted in accordance with the National Institutes of Health Public Access Policy publication and data-sharing policies and regulations. To request study data once complete, contact Dr Flor Munoz (florm@bcm.edu).

CONFLICT OF INTEREST DISCLOSURES: Dr Munoz is an investigator of pediatric studies of COVID-19 vaccines for Pfizer and for a pediatric remdesivir study conducted by Gilead Sciences, Inc; serves as investigator on projects supported by a National Institutes of Health contract for a Vaccine Treatment and Evaluation Unit and the Centers for Disease Control and Prevention New Vaccine Surveillance Network, serves as member of the data safety monitoring board for clinical trials conducted by Pfizer, Moderna, Meissa Vaccines, Virometix, and the National Institutes of Health; and is a member of the American Academy of Pediatrics Section of Infectious Diseases, member of the Immunization Expert Group of the American College of Obstetrics and Gynecology, and Chair of the Coalition for Epidemic Preparedness Innovations Safety Platform for Emergency vACcines Special Populations Work Package. Dr Parameswaran receives clinical trial contractual support as principal investigator and sub-intern from Pfizer and Sanofi as well as salary support from the Robert A. Winn Diversity in Clinical Trials Training Program. Dr Badell conducts laboratory research and clinical trials with contract funding for vaccines or monoclonal antibodies vs SARS-CoV-2 with Lilly, Pfizer, and Sanofi and receives personal fees for scientific advisory board service from Merck, Meissa Vaccines, Inc, and Pfizer. Dr Novak is a paid advisor to Gilead and an investigator on National Institutes of Health–funded trials of Moderna, Pfizer, and Janssen vaccines. Dr Brady receives research grant support for clinical trials from PATH, Astra Zeneca, and Pfizer, on which she serves as co-investigator. Dr Suthar served as an advisor for Moderna (ended December 2021) and is currently serving as an advisor for Ocugen, Inc. Dr Richardson currently holds a position on a data safety and monitoring board for clinical trials at Gilead Sciences, Inc. Dr Neuzil is a member of the World Health Organization Strategic Advisory Group of Experts on Immunization. Dr Neuzil currently serves as Director at the Fogarty International Center of the National Institutes of Health. Dr Brown serves on data safety and monitoring board for studies funded by the National Institutes of Health and Bill & Melinda Gates Foundation (ongoing) as well as Merck (past). The other authors have no relevant conflicts to disclose.

FUNDING: This study is supported by the Infectious Diseases Clinical Research Consortium through the National Institute of Allergy and Infectious Diseases, part of the National Institutes of Health, under award numbers UM1AI148684, UM1AI148575, UM1AI148372, UM1AI148452, UM1AI148576, UM1AI148574, UM1AI148450, UM1AI148685, UM1AI148689, and UM1AI148373. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

CLINICAL TRIAL REGISTRATION: This paper reflects protocol version 5.0, December 13, 2021—Division of Microbiology and Infectious Diseases 21–0004, ClinicalTrials.gov number NCT05031468. Recruitment began on July 6, 2021, and completed on January 31, 2022.

Accepted for Publication Date: February 14, 2025

https://doi.org/10.1542/peds.2024-070175

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