Maternal COVID-19 Vaccination and Prevention of Symptomatic Infection in Infants

Cristina V. Cardemil, MD, MPH,[a] Yi Cao, PhD,[b] Christine M. Posavad, PhD,[b] Martina L. Badell, MD,[c] Katherine Bunge, MD,[d] Mark J. Mulligan, MD,[e] Lalitha Parameswaran, MD,[e] Courtney Olson-Chen, MD,[f] Richard M. Novak, MD,[g] Rebecca C. Brady, MD,[h] Emily DeFranco, DO,[h] Jeffrey S. Gerber, MD, PhD,[i] Marcela Pasetti, PhD,[j] Mallory Shriver, MSc,[j] Rhea Coler, PhD,[k] Bryan Berube, PhD,[k] Mehul S. Suthar, PhD,[l] Alberto Moreno, MD,[l] Fei Gao, PhD,[b] Barbra A. Richardson, PhD,[m] Richard Beigi, MD, MSc,[d] Elizabeth Brown, ScD,[m] Kathleen M. Neuzil, MD, MPH,[j] Flor M. Munoz, MD,[n] on behalf of the MOMI-Vax Study Group

abstract

BACKGROUND AND OBJECTIVES: Maternal vaccination may prevent infant coronavirus disease 2019 (COVID-19). We aimed to quantify protection against infection from maternally derived vaccine-induced antibodies in the first 6 months of an infant's life.

METHODS: Infants born to mothers vaccinated during pregnancy with 2 or 3 doses of a messenger RNA COVID-19 vaccine (nonboosted or boosted, respectively) had full-length spike (Spike) immunoglobulin G (IgG), pseudovirus 614D, and live virus D614G, and omicron BA.1 and BA.5 neutralizing antibody (nAb) titers measured at delivery. Infant severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection was determined by verified maternal-report and laboratory confirmation through prospective follow-up to 6 months of age between December 2021 and July 2022. The risk reduction for infection by dose group and antibody titer level was estimated in separate models.

RESULTS: Infants of boosted mothers ($n = 204$) had significantly higher Spike IgG, pseudovirus, and live nAb titers at delivery than infants of nonboosted mothers ($n = 271$), and were 56% less likely to acquire infection in the first 6 months ($P = .03$). Irrespective of boost, for each 10-fold increase in Spike IgG titer at delivery, the infant's risk of acquiring infection was reduced by 47% (95% confidence interval 8%–70%; $P = .02$). Similarly, a 10-fold increase in pseudovirus titers against Wuhan Spike, and live virus nAb titers against D614G, and omicron BA.1 and BA.5 at delivery were associated with a 30%, 46%, 56%, and 60% risk reduction, respectively.

CONCLUSIONS: Higher transplacental binding and nAb titers substantially reduced the risk of SARS-CoV-2 infection in infants, and a booster dose amplified protection during a period of omicron predominance. Until infants are age-eligible for vaccination, maternal vaccination provides passive protection against symptomatic infection during early infancy.

[a]*National Institute of Allergy and Infectious Diseases, National Institutes of Health, Rockville, Maryland;* [b]*Vaccine and Infectious Disease Division, Fred Hutchinson Cancer Center, Department of Laboratory Medicine and Pathology, University of Washington, Seattle, Washington;* [c]*Division of Maternal Fetal Medicine, Department of Gynecology and Obstetrics, Emory University Hospital Midtown Perinatal Center, Atlanta, Georgia;* [d]*Department of Obstetrics, Gynecology, and Reproductive Sciences, Magee-Women's Hospital, Pittsburgh, Pennsylvania;* [e]*New York University Langone Vaccine Center, and Division of Infectious Diseases and Immunology, Department of Medicine, New York University Grossman School of Medicine, New York, New York;* [f]*Department of Obstetrics and Gynecology, University of Rochester, Rochester, New York;* [g]*Division of Infectious Diseases, University of Illinois, Chicago, Illinois;* [h]*Division of Infectious Diseases, Cincinnati Children's Hospital Medical Center, University of Cincinnati College of Medicine, Cincinnati, Ohio;* [i]*Division of Infectious Diseases, Children's Hospital of Philadelphia, University of Pennsylvania Perelman School of Medicine, Philadelphia, Pennsylvania;* [j]*Center for Vaccine Development and Global Health, University of Maryland School of Medicine, Baltimore, Maryland;* [k]*Seattle Children's Research Institute, Center for Global Infectious Disease Research, Seattle, Washington;* [l]*Emory Vaccine Center, Emory School of Medicine, Emory University, Atlanta, Georgia;* [m]*Departments of Biostatistics and Global Health, University of Washington, Divisions of Vaccine and Infectious Disease and Public Health Sciences, Fred Hutchinson Cancer Center, Seattle, Washington; and* [n]*Departments of Pediatrics and Molecular Virology & Microbiology, Baylor College of Medicine, and Texas Children's Hospital, Houston, Texas*

WHAT'S KNOWN ON THIS SUBJECT: Emerging evidence indicates that maternal COVID-19 vaccination reduces the risk of disease in infancy. Yet, the degree and durability of protection that SARS-CoV-2 vaccine-induced antibodies provide for infants, and the role of a booster dose, are not well defined.

WHAT THIS STUDY ADDS: After maternal COVID-19 vaccination, higher binding and neutralizing SARS-CoV-2 antibody titers at birth substantially reduced the risk of symptomatic infection for infants <6 months old. Compared with primary series vaccination, a maternal booster dose significantly increased protection for infants.

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Coronavirus disease 2019 (COVID-19) is a leading cause of death in children in the United States, and infants <1 year old have the highest COVID-19 death rate in pediatrics.[1] In contrast to the first 2 years of the pandemic when the burden of disease was highest in adults, hospitalization rates in infants <6 months old in the United States surged during the omicron period in 2022, and this age group currently has a COVID-19 hospitalization rate on par with adults 65 to 74 years old.[2,3] Among infants who are hospitalized with COVID-19, more than half are previously healthy without underlying comorbidities. Although COVID-19 vaccines are an important tool for prevention and widely available for children 6 months of age and older, the youngest remain ineligible for vaccination.

Maternal COVID-19 vaccination, analogous to established immunization recommendations during pregnancy to protect the infant against pertussis and influenza,[4,5] is a promising strategy to prevent COVID-19 in early infancy. Emerging vaccine effectiveness (VE) studies indicate that maternal immunization provides protection in early infancy.[6–10] However, antibody decay and waning immunity 2 to 6 months after primary series or booster dose have been observed.[7,9,11] Additionally, VE is lower against widely circulating omicron variants.[9,10]

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) neutralizing antibodies (nAbs) after maternal vaccination are present in infant cord blood at delivery,[12–14] suggesting protection in the neonatal period and beyond through passive immunity.[15] Yet, the degree and durability of protection that maternally derived, vaccine-specific SARS-CoV-2 binding and nAbs provide to infants is not well defined. In this multisite, prospective, longitudinal cohort study of maternal–infant dyads after maternal COVID-19 vaccination during pregnancy,[16] our objective was to determine the association between SARS-CoV-2 anti–full-length spike (Spike) immunoglobulin G (IgG), pseudovirus neutralizing, and live virus nAb titers in the infant at birth and the risk of SARS-CoV-2 infection in the first 6 months of life. We also aimed to determine if a maternal booster dose increased protection for infants.

METHODS

Study Population

Launched in 2021, the MOMI-Vax longitudinal cohort includes mother and infant pairs followed actively from pregnancy until the infant's first birthday.[16] Participants were recruited from 9 US academic sites, before or after maternal COVID-19 primary series or booster dose vaccination. Infants were eligible for inclusion in this analysis if they were born to individuals vaccinated during pregnancy with 2 or 3 doses of a monovalent messenger RNA COVID-19 vaccine (no boost or boosted group, respectively), and were followed prospectively from birth up to 6 months of age. Infant blood for sera was collected at delivery, and anti-Spike IgG, pseudovirus nAb against the ancestral Wuhan strain (614D), and live virus nAb levels against the D614G and omicron BA.1 and BA.5 variants were measured at this time point. Infants were tested for nucleocapsid (N) protein IgG antibodies at birth, 2 months, and 6 months of life.

Case Definitions

The primary case definition for infant SARS-CoV-2 infection included SARS-CoV-2 infections by verified maternal-report. Infant cases were first identified by maternal interview at in-person visits at prespecified time points at birth, 2, and 6 months of age to determine presence of signs and symptoms and date of infection, and verified through review of documentation of laboratory testing (antigen testing or polymerase chain reaction) and health care utilization. The secondary case definition included both infant cases that were determined by verified maternal-report as in the primary case definition, as well as the addition of infant cases that were identified by seroconversion of N protein between time points.

Immunogenicity

Serum-binding IgG against SARS-CoV-2 Spike protein and N protein was measured using the Meso Scale Discovery V-PLEX SARS-CoV-2 Panel 2 assay (Meso Scale Discovery #K15383U), bridged to international standards and reported as binding antibody units.[17] SARS-CoV-2 nAb titers were evaluated by a pseudovirus neutralizing assay using a replication-incompetent lentivirus coding for luciferase and containing the SARS-CoV-2 Spike protein (Wuhan-Hu-1) in the viral envelope (expressed as an IC50 value indicating the sample antibody titer capable of inhibiting viral entry and replication by 50%),[18] and a live virus focus reduction neutralization titer assay with viruses representing SARS-CoV-2 Spike mutation D614G, and omicron BA.1 and BA.5 variants (expressed as the serum inhibitory dilution required to achieve 50% neutralization).[19] Detailed assay methods are described elsewhere.[13]

Statistical Analysis

To ensure valid comparisons between exposures of interest and potential confounders including calendar-time and infant age, we calculated the amount of person-time of follow-up per calendar month in the study and defined the analysis period to include calendar months with >0.8 person-years of follow-up (~10 infants in follow-up for the entire month) in both the 2- and 3-dose exposure groups and by age groups 0 to <2 and 2 to 6 months. This resulted in an analysis period from December 2021 to July 2022.

Incidence rates per 100 person-years with 95% confidence intervals (CIs) were calculated by exposure group

using the normal approximation. The risk reduction for COVID-19 infection in infants by booster status and antibody titers at delivery was estimated using separate calendar-time Cox regression models stratified by site. Covariates (including vaccine type, maternal age, race, ethnicity, number of maternal comorbidities, and trimester of infection) were assessed for inclusion in the models on the basis of their association with:

1. risk of SARS-CoV-2 acquisition in the infant as assessed univariably by Cox regression, adjusting for each of the immune markers and boosting status, respectively; and
2. antibody level in the risk model using linear regression models.

Variables significant at $P < .10$ in either the outcome or exposure assessment were included in the final regression model for that exposure. The primary end point was defined as time to the primary case definition (verified maternal-report of infant infection), and the secondary end point defined as time to the secondary case definition (verified maternal-report or seroconversion), with censoring at infant's first infection date up to 194 days. Infants whose parents did not report infection but transitioned from negative to positive N protein between time points did not have a date of infection to include as an end point in the model. The date of infection between 0 to <2 months and 2 to 6 months old was imputed for these infants on the basis of the observed data from infants who had an infection reported by parents and also transitioned from negative to positive. The association between immune markers at delivery and time from last maternal dose to delivery was examined visually using locally estimated scatterplot smoothing splines. All analyses were conducted in R Version 4.2.2.[20]

RESULTS

In total, 475 infants completed at least 1 follow-up visit after delivery and were eligible for analysis; this included 204 infants of boosted mothers and 271 infants of nonboosted mothers (Table 1; Supplemental Fig 4). By parental report, 76% of infants were white, 10.2% Black or African American, 8.1% Asian American, and 11.9% Hispanic or Latino. Most infants were born term (>89%) and had a normal birth weight (>82%). Retention by 6 months was >90%. Although all follow-up was during the omicron variant period, more infants were born before the first omicron wave in the nonboosted group (83.4%), reflecting the timing of the rollout of primary series vaccine implementation and booster dose recommendation for adults in the United States during 2021.

For the primary end point, 71 cases were reported in infants between birth and 6 months of life (41% in infants of boosted mothers, and 59% in infants of nonboosted mothers). For the secondary end point, 19 additional cases were identified for a total of 90 cases reported by either verified maternal report or seroconversion. The majority of infant cases in the primary end point group were laboratory confirmed by polymerase chain reaction or antigen testing (61 of 71; 85.9%) and were symptomatic (100% in infants of boosted, and 93.5% in infants of nonboosted mothers), with 70.0% reporting rhinorrhea, 55.2% reporting fever, and 55.2% cough, and the median duration of symptoms was 5 days. No infants in this analysis cohort were hospitalized.

Incidence Rates by Age and Maternal Booster Status, and Reduction in Risk After Maternal Boost

The majority of COVID-19 infections in infants occurred between 2 and 6 months of age ($n = 61$ of 71; 85.9%) (Fig 1A). Infants 2 to 6 months old had higher COVID-19 incidence rates by calendar month and overall (56.8 per 100 person-years [95% CI 44.2–73.0]) as compared with infants 0 to <2 months of age (21.6 per 100 person-years [95% CI 11.6–40.1]).

Infants of nonboosted mothers had a higher overall COVID-19 incidence rate (52.1 per 100 person-years [95% CI 38.5–70.6]) compared with infants of boosted mothers (39.6 per 100 person-years [95% CI 27.5–57.0]) (Fig 1B). In the multivariable regression model examining the effect of 3 vs 2 maternal COVID-19 vaccine doses for infant protection, boosting during pregnancy reduced the infant's risk of acquiring COVID-19 in the first 6 months by 56% (95% CI 8%–79%, $P = .03$) relative to no boosting (Table 2).

Spike IgG, Pseudovirus, and Live Virus Neutralizing Antibody Titers at Delivery and Reduction in Risk of Infection

Infants whose mothers were boosted in pregnancy had higher mean Spike IgG, pseudovirus nAb, and live nAb titers at delivery compared with the nonboosted group (Spike: 4433 vs 1093 binding antibody units per mL, $P < .001$; pseudovirus nAb: 1282 vs 410 IC50, $P < .001$; live virus D614G: 1194 vs 254, $P < .001$; live virus omicron BA.1: 226 vs 26, $P < .001$; live virus omicron BA.5: 122 vs 24, $P < .001$) (Table 1, Fig 2A–D boxplots).

In the multivariable regression model for the primary end point, a 10-fold increase in Spike IgG titer (unit change in the log10 scale) measured at delivery was associated with a 47% (95% CI 8%–70%, $P = .02$) reduction in the infant's risk of acquiring COVID-19 in the first 6 months of life (Table 2). A similar reduction in risk with higher delivery titers was observed for each of the pseudovirus and live virus nAb models. A 10-fold increase in pseudovirus nAb against Wuhan Spike, and live virus nAb against D614G, and omicron BA.1 and BA.5 variants at delivery was associated with a 30% (95% CI

TABLE 1 Maternal and Infant Characteristics by Maternal COVID-19 Vaccination Status		
	Maternal Boost (3 mRNA Vaccine Doses During Pregnancy) (*N* = 204)	**No Maternal Boost (2 mRNA Vaccine Doses During Pregnancy) (*N* = 271)**
Maternal characteristics at enrollment		
Age, median (IQR)	34.0 (24)	34.0 (32)
Race, *N* (%)		
White	172 (84.3%)	189 (69.7%)
Black or African American	6 (2.9%)	42 (15.5%)
Asian American	14 (6.9%)	24 (8.9%)
Other	12 (5.9%)	15 (5.5%)
Hispanic/Latino ethnicity, *N* (%)	18 (8.8%)	38 (14.4%)
Number of comorbidities, mean (SD)	0.33 (0.57)	0.38 (0.73)
Health care worker, *N* (%)	96 (47.1%)	51 (19.2%)
Primary series vaccine type, *N* (%)		
Moderna	55 (27.0%)	93 (34.3%)
Pfizer	149 (73.0%)	178 (65.7)
Booster type, *N* (%)		
Moderna homologous boost	50 (24.5%)	—
Pfizer homologous boost	140 (68.6%)	—
Heterologous boost	14 (6.9%)	—
Risk factors at delivery		
Epidemic phase at delivery, *N* (%)		
Before omicron wave (before December 2021)	13 (6.4%)	226 (83.4%)
During omicron wave (December 2021–February 2022)	105 (51.5%)	39 (14.4%)
After omicron wave (March 2022 and beyond)	86 (42.1%)	6 (2.2%)
Wk between last dose to delivery, mean (SD)	13.3 (8.01)	18.9 (8.42)
Gestational wk at delivery, mean (SD)	38.8 (1.80)	39.0 (1.91)
Maternal COVID-19 infection, *N* (%)		
Self-report before second trimester	13 (6.4%)	22 (8.1%)
Self-report during second–third trimesters	26 (12.7%)	12 (4.5%)
Maternal N protein IgG-positive at delivery	27 (13.2%)	27 (10.0%)
Infant characteristics at delivery		
Anti-Spike IgG level (BAU per mL) at delivery, mean		
Overall	4433.4 (5066.5)	1092.8 (2063.3)
Heel stick (*N* = 27)	3217.0 (3050.7)	471.1 (289.8)
Cord blood (*N* = 404)	4511.6 (5165.4)	1134.9 (2124.5)
Pseudovirus nAbs GMT for Wuhan Spike (614D), mean	1282.1 (2239.3)	409.8 (739.5)
Live virus nAb GMT for variant, mean		
D614G	1194.2 (1258.2)	254.3 (463.3)
Omicron BA.1 (B.1.1.529)	225.8 (376.2)	25.9 (75.7)
Omicron BA.5	121.9 (158.1)	24.2 (51.2)
Male, *N* (%)	94 (46.1%)	130 (50.0%)
Race, *N* (%)		
White	176 (86.3%)	164 (60.5%)
Black or African American	4 (2.0%)	41 (15.1%)
Asian American	12 (5.9%)	13 (4.8%)
Other	12 (5.9%)	53 (19.6%)
Hispanic/Latino ethnicity, *N* (%)	19 (9.3%)	40 (14.8%)
Gestational age, *N* (%)		
Preterm (<37)	22 (10.8%)	19 (7.0%)
Term (≥37)	182 (89.2%)	248 (93.0%)
Birth weight, *N* (%)		
High birth weight: 4000 g or more	16 (7.8%)	25 (9.3%)
Normal weight: 2500 g–<4000 g (8.8 lb)	169 (82.8%)	223 (83.4%)
Low birth weight: 1500 g–<2500 g (5.5 lb)	19 (9.3%)	20 (7.4%)

TABLE 1 Continued

	Maternal Boost (3 mRNA Vaccine Doses During Pregnancy) (*N* = 204)	No Maternal Boost (2 mRNA Vaccine Doses During Pregnancy) (*N* = 271)
Infant is breastfeeding, *N* (%)	185 (90.7%)	247 (92.2%)
Follow-up characteristics		
Infants who completed 2-mo visit, *N* (%)	198 (97.1%)	267 (99.6%)
Infants who completed 6-mo visit, *N* (%)	179 (90.7%)	249 (94.5%)
Infant infections in first 6 mo of life,[a] *N* (%)	29 (14.2%)	42 (15.5%)
Any symptoms reported, *n* (%)	29 (100%)	40 (93.5%)
Rhinorrhea	20 (70.0%)	30 (75.0%)
Fever	16 (55.2%)	22 (55.0%)
Cough	16 (55.2%)	23 (57.5%)
Laboratory positive by any test,[b] (%)	25 (86.2%)	36 (87.8%)
RT-PCR	8 (32.0%)	14 (38.9%)
Antigen	3 (12.0%)	6 (16.7%)
Antibody	0 (0%)	1 (2.8%)
Home antigen test	4 (16.0%)	1 (2.8%)
N protein seroconversion	15 (60%)	25 (69.4%)
Unknown	0 (0%)	3 (8.3%)
Total person-years of follow-up	72	75
Average follow-up, wk	18	15
Infants breastfeeding at 2 mo, *N* (%)	189 (92.6%)	250 (92.3%)
Infants breastfeeding at 6 mo, *N* (%)	171 (83.8%)	236 (87.1%)

BAU, binding antibody units; GMT, Geometric Mean Titer; IQR, interquartile range; mRNA, messenger RNA; RT-PCR, reverse transcription polymerase chain reaction. —, Participants in the 2 mRNA Vaccine Doses During Pregnancy Group did not receive a booster dose.

[a] Verified by maternal-report as per primary end point definition.

[b] Laboratory positive by any test includes reverse transcription polymerase chain reaction, antigen, antibody, home antigen test, or N protein seroconversion.

−15% to 57%; $P = .16$), 46% (95% CI 6%–69%, $P = .03$), 56% (95% CI 1%–80%, $P = .05$), and 60% (95% CI −15% to 86%; $P = .09$) reduction in risk for the infant in the first 6 months of life, respectively. Regression models for the secondary end point showed a similar or higher reduction in risk with higher delivery titers (all P values $<.05$) for all analysis sets (Table 2).

In sensitivity analyses that subset the Spike IgG, pseudovirus, and live virus nAb models to either boosted or nonboosted cohorts, a trend toward risk reduction was identified with increase in delivery titer only in the boosted cohorts (Supplemental Tables 3–8). Although not statistically significant, this trend suggests that the maternal boost during pregnancy and resulting higher titers was likely the main contributor to the infant's reduction in risk.

Infant Titers at Delivery by Week Since Last Dose of Maternal Vaccine, and Gestational Age at Boost

Regardless of the number of weeks between the last COVID-19 vaccine dose during pregnancy and delivery, infants of boosted mothers had higher Spike IgG, pseudovirus, and live virus nAb titers than infants of nonboosted mothers at delivery (Figs 2A–E). Delivery titers increased for the prenatally boosted group as the number of weeks to delivery decreased, until ∼4 to 5 weeks before delivery, when they began to decline precipitously to match titers from the nonboosted group. For the boosted group, peak Spike IgG, pseudovirus, and live virus nAb titers were observed ∼6 to 12 weeks before delivery.

By gestational age, infant Spike IgG levels at delivery were lowest if mothers were boosted in the first trimester of pregnancy (≤13 weeks), increased by week gestation when mothers were boosted in the second trimester (14–26 weeks), reached peak titers at delivery when mothers were boosted between 28 and 34 weeks, and then declined slightly if mothers were boosted after ∼34 weeks (Fig 3A). Similarly, infant pseudovirus nAb titers at delivery were highest if mothers were vaccinated in the early third trimester (Fig 3B). Despite declining levels in the late third trimester, titers among those boosted in the third trimester remained at or above those of participants boosted in the first and early second trimesters.

DISCUSSION

In this multisite, prospective, longitudinal cohort study of mother–infant dyads enrolled after maternal COVID-19 vaccination, higher antibody titers at birth were associated with substantially increased infant protection from infection in the first 6 months of life. Maternal boost during pregnancy resulted in notably higher infant binding and nAbs versus primary series alone, with peak delivery titers after third trimester maternal boost,

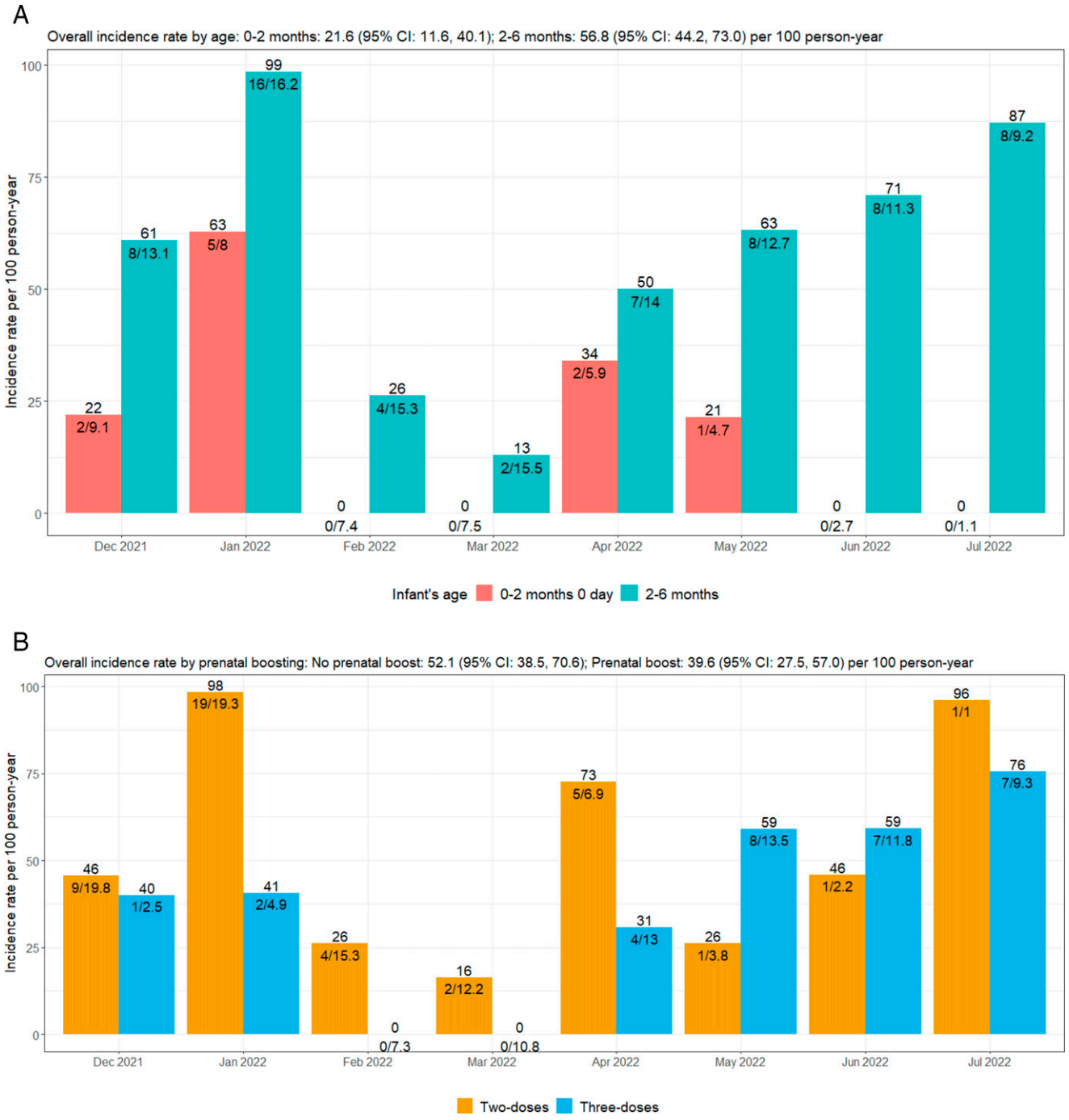

FIGURE 1

COVID-19 incidence rate per 100 person-years within a calendar month (above each bar) and overall (top of each panel) from December 2021 to July 2022 stratified by infant's age (A) and maternal COVID-19 boost (B). Within each bar, the number of incident infections in that month is listed, separated by a slash (/) next to the total person-years at risk within that month.

and booster receipt was associated with a strong reduction in risk of infant infection. Additionally, after combining boosted and nonboosted groups, increased protection was also demonstrated with higher delivery titers for Spike IgG, pseudovirus nAb against Wuhan, and live virus nAb to D614G, and omicron BA.1 and BA.5 variants, indicating consistency across the breadth of the humoral immune response and highlighting the predictive value of neutralization antibody as it relates to disease outcomes.

TABLE 2 Univariable and Multivariable Cox Regression Models Estimating Relative Risk Reduction of SARS-CoV-2 Infection in the Infant's First 6 Months of Life, After Maternal COVID-19 Booster Dose or Primary Series Vaccination

			Univariable			Multivariable		
Exposure of Interest	***N***	**# Cases**	**RRR**	**95% CI**	***P***	**RRR**	**95% CI**	***P***
Primary case definition: Verified maternal report of infection								
Number of vaccine doses								
Boosted by delivery (3 vs 2 maternal COVID-19 doses)	475	71	42%	−14% to 71%	.11	56%	8%–79%	.03
Infant titers at delivery								
10-fold increase in Spike IgG titer	434	68	44%	8%–66%	.02	47%	8%–70%	.02
10-fold increase in Pseudovirus nAb titer	423	64	33%	−5% to 57%	.08	30%	−15% to 57%	.16
10-fold increase in live virus D614G[a] nAb titer	392	64	52%	20%–71%	.005	46%	6%–69%	.03
10-fold increase in live virus omicron BA.1 (B.1.1.529) nAb titer	392	42	62%	22%–81%	.008	56%	1%–80%	.05
10-fold increase in live virus omicron BA.5 nAb titer	260	29	58%	−4% to 83%	.06	60%	−15% to 86%	.09
Secondary case definition: Verified maternal report of infection, or seroconversion by 6 mo								
Number of vaccine doses								
Boosted by delivery (3 vs 2 maternal COVID-19 doses)	401	90	69%	45%–88%	<0.001	75%	53%–87%	<.001
Infant titers at delivery								
10-fold increase in Spike IgG titer	363	83	37%	2%–59%	0.04	50%	18%–70%	.01
10-fold increase in pseudovirus nAb titer	356	83	29%	−5% to 52%	0.09	28%	5%–60%	.03
10-fold increase in Live virus D614G[a] nAb titer	332	78	46%	16%–66%	0.006	52%	22%–71%	.003
10-fold increase in live virus omicron BA.1 (B.1.1.529) nAb titer	332	78	58%	23%–77%	0.004	63%	26%–81%	.004
10-fold increase in live virus omicron BA.5 nAb titer	221	54	61%	13%–83%	0.02	73%	33%–89%	.005

RRR, relative risk reduction.
[a] Lower limit of quantification, log10(20).

Achieving optimal protection from SARS-CoV-2 infection during early infancy has been elusive, in part because of the unavailability of COVID-19 vaccines for infants <6 months old. After maternal 2-dose primary-series vaccination, 1 previous study showed that higher infant anti-Spike cord blood levels were associated with longer disease-free intervals after birth, but lacked the sample size or booster dose data to measure the degree of protection and compare titers by number of doses.[15] Our study is unique in estimating the substantial reductions for infants because of higher antibody titers at delivery, as well as quantifying the additional protection that a maternal COVID-19 booster dose affords in early infancy. This is consistent with findings from a recent study of adults in Japan[21] that found that higher anti-Spike antibody titers after 3-dose vaccine series were associated with higher protection against omicron BA.5 infection. Our results are also complementary to VE studies of maternal vaccination for pregnant persons with a booster dose,[22] as well as studies that have examined VE in infants after maternal vaccination.[6–9,23,24]

Higher delivery titers for Spike IgG, pseudovirus, and live virus nAb were associated with substantial reductions in risk in our infant cohort, indicating that both binding and functional antibodies of the humoral immune response correlate with protection from infection. As compared with antibody levels against D614G, lower omicron BA.1 and BA.5 titers were noted at delivery in both boosted and nonboosted groups, and BA.1 and BA.5 titers at delivery were much lower in the nonboosted cohort, in line with previous studies.[13] Yet, importantly, all live virus models were strongly supportive of infant protection. Therefore, these data indicate that maternal booster vaccination with ancestral strains provided functional antibodies that protected against infection in infants during early infancy, at a time when omicron variants were circulating widely. These results are critically important, because some VE studies in children and after maternal vaccination for infants have shown lower effectiveness during periods of omicron predominance, with some estimates crossing 0.[23] Because infection-induced immunity has increased since the start of the pandemic, with seroprevalence ranging widely by age and geographic location from 11% to 92% in children <5 years old,[25–27] the ability to measure VE has become more challenging, making direct measurement of antibody titers a crucial piece of the puzzle to understand the beneficial impact of maternal immunization.

Nationally, infants <6 months old were hospitalized at increasing rates during and after the widespread takeover of omicron BA.1 and BA.5 throughout the United States, coinciding with the COVID-19 cases in our analysis cohort. During this time of omicron predominance, the hospitalization rate in infants <6 months old surged above 70 per 100 000, reaching similar rates to those in older adults aged 65 to 75 years.[2] As a result, maternal booster vaccination during pregnancy is an increasingly important strategy to decrease the burden of disease in this young, vulnerable population. A number of studies

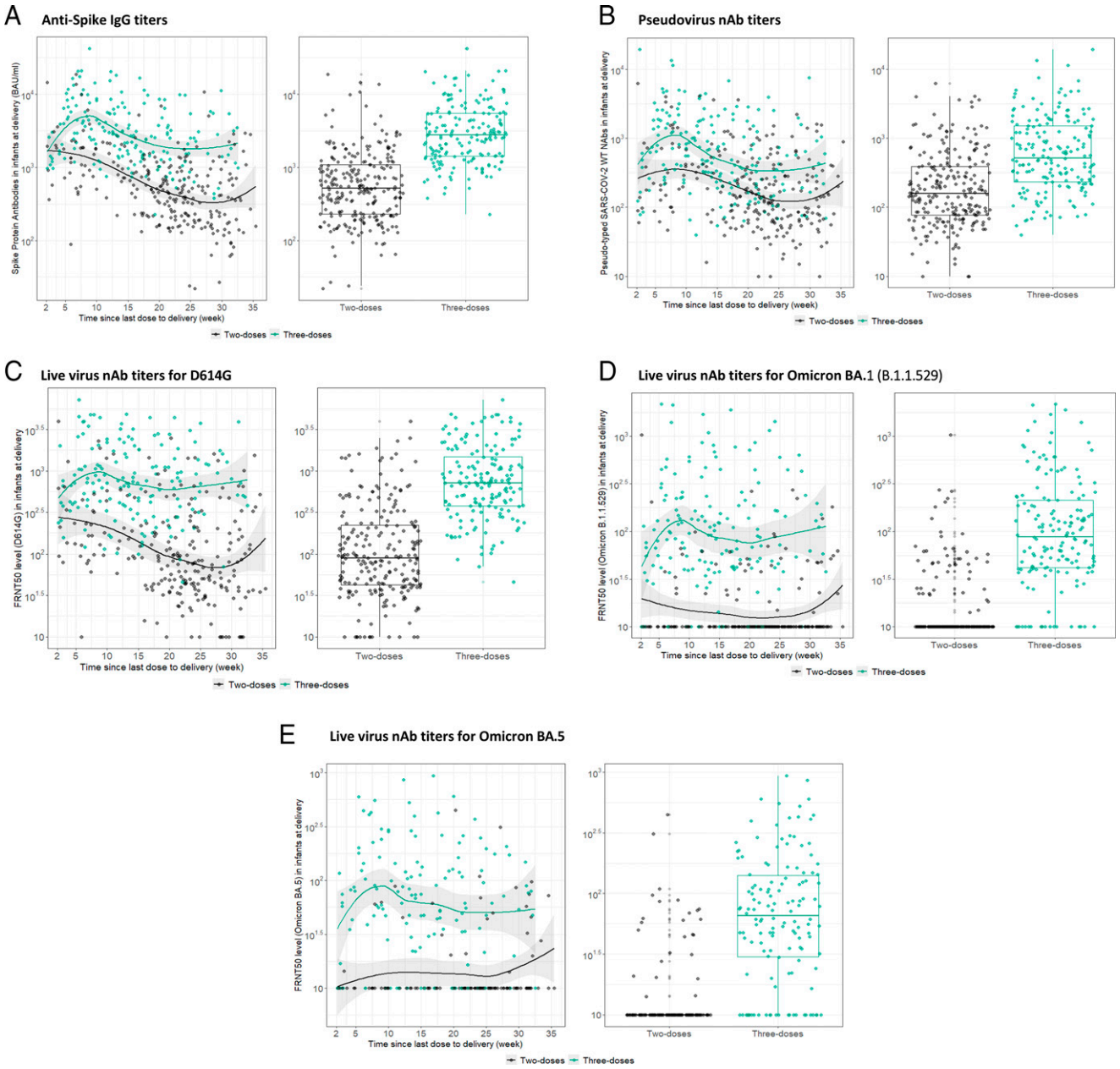

FIGURE 2

Smoothed estimate of the relationship between time since last COVID-19 vaccine dose and infant antibody titer at delivery by maternal boost status (left panel), and a boxplot of infant antibody titers at delivery stratified by maternal boost status (right panel). (A) anti-Spike IgG titers, (B) pseudovirus nAb titers, (C) live virus nAb titers for D614G, (D) live virus nAb for omicron BA.1, and (E) live virus nAb for omicron BA.5. The lower limit of quantitation (LLOQ) for the live virus neutralization assay (focus reduction neutralization titer) is 20; samples that do not neutralize at the limit of quantitation are assigned a value that is 1/2 of the LLOQ or 10. Samples with titers <20 are interpreted as not detected.

have sought to understand the optimal timing of maternal immunization during pregnancy for infant protection, with some indicating that vaccination in the second or early third trimesters provides better protection for infants,[8,9,28,29] whereas others have signaled that vaccination at any point during pregnancy is likely to be beneficial.[30] Although our study was not specifically designed to assess infection risk by timing of maternal vaccination, evaluation of both binding IgG and nAb delivery titers by week gestation of vaccination during pregnancy indicates that higher antibodies at delivery were achieved if maternal vaccination, and particularly a booster dose, was received during the early third trimester of pregnancy. Peak titers were observed after maternal booster dose if given ~6 to 12 weeks before delivery, corresponding with 28 to 34 weeks' gestation during pregnancy. However, despite this variation in

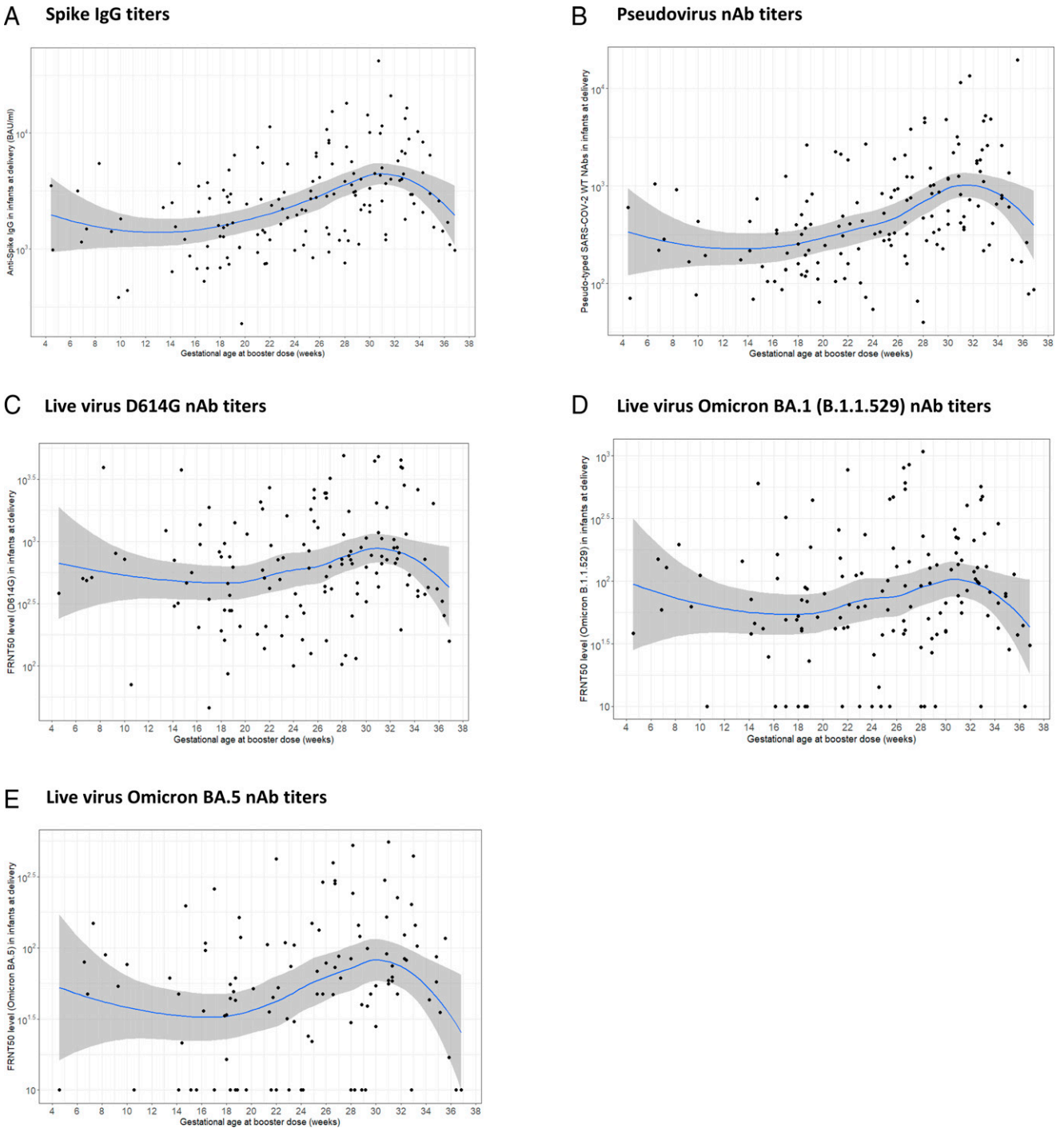

FIGURE 3

Antibody titers in infants at delivery after maternal COVID-19 booster dose during pregnancy, by maternal gestational age at booster dose in weeks. Cohort is limited to mothers without SARS-CoV-2 infection during pregnancy and who completed a booster at least 14 days before delivery. (A) Anti-Spike IgG titers, (B) pseudovirus nAb titers, (C) live virus nAb titers for D614G, (D) live virus nAb for omicron BA.1, and (E) live virus nAb for omicron BA.5. The lower limit of quantitation (LLOQ) for the live virus neutralization assay (focus reduction neutralization titer) is 20; samples that do not neutralize at the limit of quantitation are assigned a value that is 1/2 of the LLOQ or 10. Samples with titers <20 are interpreted as not detected.

titer by timing of vaccination, the most striking difference in infant delivery titer for all binding and functional antibody analysis data sets was between the boosted and nonboosted groups, reinforcing the importance of booster dose receipt at any time during pregnancy for infant protection. Ultimately, recommendations on timing of vaccination will need to balance the benefits in providing protection to the pregnant person and the infant.

Our study has limitations. First, the differential timing of enrollment of boosted and nonboosted mothers of the infants in our analysis made comparisons between groups challenging, because national immunization recommendations evolved to add booster doses concurrent with the emergence of new variants throughout the United States. To account for this, we purposefully restricted the analysis to include sufficient follow-up time by dose exposure group and infant age, and our regression analyses controlled for calendar-time. Nonetheless, unmeasured confounders could remain. Second, because of no hospitalized cases, we were unable to distinguish if higher antibodies or maternal boost afforded more protection against severe disease; at the same time, few moderate to severe cases in an entirely vaccinated cohort are consistent with the known effectiveness of messenger RNA COVID-19 vaccines. Third, our study did not have enough power to examine relative risk by both infant age and booster status simultaneously. Yet, the higher COVID-19 incidence in older infants (2–6 months versus 0–<2 months old) is consistent with other studies that have demonstrated higher VE for infants within a shorter time frame after maternal vaccination.

Our study also had notable strengths. First, we designed a large prospective cohort study early in the pandemic that met participant targets and resulted in robust comparisons by vaccine group. Second, a multicenter study with racial and ethnic diversity reflective of recruitment at participating sites increases the generalizability of our findings. Third, our high retention rates at follow-up time points minimize bias. Fourth, we were able to conduct extensive, centralized laboratory testing for each of the 3 antibody assays including neutralization and paired these results with case data in young infants, allowing for increased understanding of the breadth and function of the immune response in an understudied population after maternal COVID-19 immunization.

CONCLUSIONS

This study provides strong evidence of the robust immune response after maternal booster COVID-19 vaccination that protects infants against SARS-CoV-2 infection, and adds to the growing evidence base of effectiveness of maternal COVID-19 vaccination for both mothers and their infants.[31] Specifically, we show that a monovalent booster dose during pregnancy leads to higher binding and nAb titers at delivery that are effective against omicron, for an age group that has the highest COVID-19–associated hospitalization rate in pediatrics since the emergence and ubiquitous spread of omicron variants. Currently, infants are not eligible for COVID-19 vaccination until they reach 6 months of age. Until they are, maternal booster vaccination during pregnancy is an effective strategy that provides transplacentally transferred passive binding and neutralizing SARS-CoV-2 antibodies that protect effectively against infection during early infancy.

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ABBREVIATIONS

CI: confidence interval
COVID-19: coronavirus disease 2019
IgG: immunoglobulin G
LLOQ: lower limit of quantification
N: nucleocapsid
nAb: neutralizing antibody
SARS-CoV-2: severe acute respiratory syndrome coronavirus 2
Spike: full-length spike
VE: vaccine effectiveness

Drs Cardemil, Munoz, 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 Beigi collected data and critically reviewed and revised the manuscript; Drs Posavad, Pasetti, Coler, Berube, Suthar, and Moreno, and Ms Shriver coordinated and supervised data collection, performed laboratory testing, and critically reviewed and revised the manuscript; Drs Cao, Gao, Richardson, and Brown designed and conducted the analyses and critically reviewed and revised the manuscript; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

A complete list of group members appears in the Supplemental Information.

This article reflects Protocol Version 5.0, December 13, 2021; DMID 21-0004, ClinicalTrials.gov NCT05031468. Recruitment began on July 6, 2021, and was completed on January 31, 2022. Data collected for the study will be made available to others as a deidentified patient data set 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 severe acute respiratory syndrome coronavirus 2 (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 Cardemil at cristina.cardemil@nih.gov.

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Address correspondence to Cristina V. Cardemil, MD, MPH, National Institute of Allergy and Infectious Diseases, National Institutes of Health, 5601 Fishers Lane, Rockville, MD, 20852. E-mail: cristina.cardemil@nih.gov

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