RESEARCH LETTER

Durability of Anti-Spike Antibodies in Infants After Maternal COVID-19 Vaccination or Natural Infection

COVID-19 vaccination in pregnancy generates functional anti-spike (anti-S) IgG antibodies in maternal circulation that are detectable in umbilical cord blood at birth and can protect the newborn and infant from COVID-19.[1-4] Anti-S IgG titers in the umbilical cord are correlated with maternal titers and are highest after late second and early third trimester vaccination.[2-4] We characterized the persistence of vaccine-induced maternal anti-S IgG in infant blood and compared persistence of infant anti-S IgG after maternal vaccination vs natural infection.

Supplemental content

Methods | The study included individuals who had received an mRNA COVID-19 vaccine in pregnancy or were infected with SARS-CoV-2 at 20 to 32 weeks' gestation, had enrolled in a prospective study at 2 academic medical centers in Boston, and had enrolled their infants in this follow-up study conducted from July 21, 2021, to October 22, 2021. Individuals vaccinated or infected at 20 to 32 weeks' gestation were enrolled because previous studies have demonstrated superior transplacental transfer of antibodies during this window compared with vaccination closer to delivery.[4,5] Those infected before vaccination were excluded. Matched maternal and umbilical cord serum samples were collected at birth. Infant capillary serum samples were collected via microneedle device at 2 months after birth for infants of vaccinated mothers and at 6 months for infants of mothers who

Table. Demographic and Clinical Data for Participants Vaccinated Against COVID-19 vs Those With Natural COVID-19 Infection

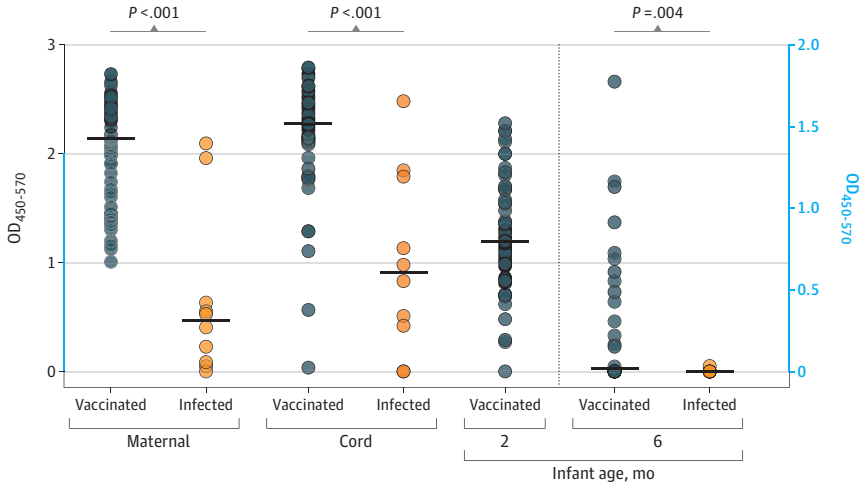
	COVID-19, No. (%)		
	Vaccination (n = 77)	Infection (n = 12)	*P* value
Maternal age, median (IQR), y	34 (32-36)	35 (31-37)	.95
Parity, median (IQR)	1 (0-1)	1 (1-2)	.07
Prepregnancy BMI, median (IQR)	23.7 (21.6-25.3)	24.3 (23.6-26.4)	.29
Gestational age at delivery, median (IQR), completed wk	39 (38-40)	38 (38-39)	.06
Weeks of gestation at vaccination or SARS-CoV-2 infection, median (IQR)	27 (21-32)	27 (25-32)	.84
Days from first vaccine dose to delivery, mean (SD)	85 (46)		
SARS-CoV-2 infection			
Days from SARS-CoV-2 positive test to delivery, mean (SD)		71 (28)	
Disease severity			
Mild		8 (67)	
Moderate		3 (25)	
Severe		1 (8)	
Vaccine platform			
mRNA-1273	25 (32)		
BNT162b2	52 (68)		
Neonatal sex			
Female	40 (52)	7 (58)	.76
Birthweight, median (IQR), g	3330 (3000-3675)	3076 (2668-3504)	.14
Days from birth to serum collection, mean (SD)			
At 2 mo	71 (11)		
At 6 mo	170 (23)	207 (40)	.002
Titers at birth, mean (SD), $OD_{450-570}$			
Maternal	2.03 (0.47)	0.65 (0.76)	<.001
Umbilical cord	2.17 (0.50)	1.00 (0.83)	<.001
Infant titer, mean (SD), $OD_{450-570}$			
At 2 mo[a]	1.29 (0.53)		
At 6 mo[b]	0.33 (0.46)	0 (0.01)	.004
Infants with detectable antibody			
At 2 mo	48/49 (98)		
At 6 mo	16/28 (57)	1/12 (8)	.005

Abbreviations: BMI, body mass index, calculated as weight in kilograms divided by height in meters squared; $OD_{450-570}$, phosphate-buffered saline corrected optical density at 450 nm corrected from a reference wavelength of 570 nm.

[a] Due to the timing of COVID-19 cases relative to the study period, infants born to mothers infected with COVID-19 during pregnancy were older than 2 months at sample collection. Thus, the 2-month time point includes only infants of vaccinated mothers.

[b] The 6-month time point includes both infants born to vaccinated mothers and infants born to unvaccinated mothers with COVID-19.

Figure. Persistence of Antibody in Infants After Maternal COVID-19 Vaccination or Infection



Black lines represent the median for each group at each time point. Differences in titer between groups at birth and the 6-month time points were assessed by Mann-Whitney *U* test. Due to the timing of COVID-19 cases relative to the study period, infants born to mothers infected with COVID-19 during pregnancy were older than 2 months at sample collection (see eMethods in the Supplement). $OD_{450\text{-}570}$ indicates optical density (OD) at 450 nm corrected from a reference wavelength of 570 nm. Detectable anti-Spike IgG was defined as any value greater than the sum of the mean value of assay negative controls (SARS-CoV-2 negative, unvaccinated samples) and 3 × the standard deviation of those samples.

were vaccinated and mothers who had been infected with SARS-CoV-2. Antibody titers against the SARS-CoV-2 spike protein were quantified using an enzyme-linked immunosorbent assay (eMethods in the Supplement). Differences in titers between vaccinated and infected groups at delivery and 6-month infant age were assessed by the Mann-Whitney *U* test. Differences in proportions of infants with detectable antibodies at 6 months were assessed by the Fisher exact test. Correlation between delivery titers and infant antibody was assessed via the Spearman rank test. Analyses were conducted using Prism version 9.0. Significance was defined as a 2-sided $P < .05$. The study was approved by the Mass General Brigham institutional review board, and all participants provided written informed consent.

Results | Seventy-seven vaccinated pregnant mothers and 12 with symptomatic SARS-CoV-2 infection in pregnancy were included (**Table**). At 2 months, capillary serum samples were collected from 49 infants of vaccinated mothers; at 6 months, serum samples were collected from 28 infants of vaccinated mothers (mean, 170 days after birth) and 12 infants of infected mothers (mean, 207 days after birth).

Vaccinated mothers had significantly higher titers at delivery with a mean (SD) of 2.03 (0.47) optical density ($OD_{450\text{-}570}$) compared with mothers after infection with a mean (SD) of 0.65 (0.76) $OD_{450\text{-}570}$ ($P < .001$). Similarly, the respective mean (SD) cord titers were higher after vaccination vs natural infection: 2.17 (0.50) $OD_{450\text{-}570}$ vs 1.00 (0.83) $OD_{450\text{-}570}$ ($P < .001$; **Figure**). Among infants of vaccinated mothers at 2 months, 98% (48 of 49) had detectable anti-S IgG. The mean (SD) titer at 2 months was 1.29 (0.53) $OD_{450\text{-}570}$, which was correlated with both maternal ($r = 0.55$, $P < .001$) and cord titers ($r = 0.43$, $P = .01$) at delivery.

Vaccination resulted in significantly greater antibody persistence in infants than infection. At 6 months, 57% (16 of 28) of infants born to vaccinated mothers had detectable antibodies (Table) compared with 8% (1 of 12) of infants born to infected mothers ($P = .005$). Titers were a mean (SD) of 0.33 (0.46) $OD_{450\text{-}570}$ among infants of vaccinated mothers and 0 (0.01) $OD_{450\text{-}570}$ among infants of infected mothers ($P = .004$, Figure). Neither maternal ($P = .23$) nor cord ($P = .05$) titers were significantly correlated with infant anti-S titers at 6 months, largely because 43% of infants had no detectable titer at that time.

Discussion | This study found that the majority of infants born to COVID-vaccinated mothers had persistent anti-S antibodies at 6 months, compared with infants born to mothers with SARS-CoV-2 infection. Understanding the persistence of maternal antibody levels in infants is important because COVID-19 infections in this age group account for a disproportionate burden of pediatric SARS-CoV-2–associated morbidity[6] and because COVID-19 vaccines are not currently planned for administration to infants younger than 6 months. Study limitations include the small number of infants, the longer mean time to follow-up in the infected group (due to pragmatic constraints related to timing of COVID-19 surges in Boston and the availability of participants for timely follow-up), and the reporting of antibody titers rather than clinical outcomes. Although the antibody titer known to be protective against COVID-19 in infants is unknown, these findings provide further incentive for pregnant individuals to pursue COVID-19 vaccination.

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