ORIGINAL ARTICLE

Maternal Vaccination and Risk of Hospitalization for Covid-19 among Infants

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ABSTRACT

BACKGROUND

Infants younger than 6 months of age are at high risk for complications of coronavirus disease 2019 (Covid-19) and are not eligible for vaccination. Transplacental transfer of antibodies against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) after maternal Covid-19 vaccination may confer protection against Covid-19 in infants.

METHODS

We used a case–control test-negative design to assess the effectiveness of maternal vaccination during pregnancy against hospitalization for Covid-19 among infants younger than 6 months of age. Between July 1, 2021, and March 8, 2022, we enrolled infants hospitalized for Covid-19 (case infants) and infants hospitalized without Covid-19 (control infants) at 30 hospitals in 22 states. We estimated vaccine effectiveness by comparing the odds of full maternal vaccination (two doses of mRNA vaccine) among case infants and control infants during circulation of the B.1.617.2 (delta) variant (July 1, 2021, to December 18, 2021) and the B.1.1.259 (omicron) variant (December 19, 2021, to March 8, 2022).

RESULTS

A total of 537 case infants (181 of whom had been admitted to a hospital during the delta period and 356 during the omicron period; median age, 2 months) and 512 control infants were enrolled and included in the analyses; 16% of the case infants and 29% of the control infants had been born to mothers who had been fully vaccinated against Covid-19 during pregnancy. Among the case infants, 113 (21%) received intensive care (64 [12%] received mechanical ventilation or vasoactive infusions). Two case infants died from Covid-19; neither infant's mother had been vaccinated during pregnancy. The effectiveness of maternal vaccination against hospitalization for Covid-19 among infants was 52% (95% confidence interval [CI], 33 to 65) overall, 80% (95% CI, 60 to 90) during the delta period, and 38% (95% CI, 8 to 58) during the omicron period. Effectiveness was 69% (95% CI, 50 to 80) when maternal vaccination occurred after 20 weeks of pregnancy and 38% (95% CI, 3 to 60) during the first 20 weeks of pregnancy.

CONCLUSIONS

Maternal vaccination with two doses of mRNA vaccine was associated with a reduced risk of hospitalization for Covid-19, including for critical illness, among infants younger than 6 months of age. (Funded by the Centers for Disease Control and Prevention.)

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*A list of the Overcoming Covid-19 Investigators is provided in the Supplementary Appendix, available at NEJM.org.

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Coronavirus disease 2019 (COVID-19) during pregnancy is associated with severe illness, hospitalization, and death[1] as well as an increased risk of adverse pregnancy outcomes and neonatal complications.[2] Many complications of Covid-19 in the general population are preventable through vaccination. Studies have shown that the mRNA vaccines (BNT162b2 [Pfizer–BioNTech] and mRNA-1273 [Moderna]) have been highly effective in preventing severe Covid-19 during pregnancy.[3,4] Data also support the safety of Covid-19 vaccination during pregnancy, and the Centers for Disease Control and Prevention (CDC) recommends Covid-19 vaccination, including boosters when eligible, for persons who are pregnant or plan to become pregnant.[5-9]

Maternal vaccination may have dual benefits; vaccination provides pregnant persons with protection and may also provide the added benefit of protecting their infants, who would not be eligible for vaccination.[10-14] Covid-19 vaccination during pregnancy leads to the presence of detectable maternal antibodies in cord blood, breast milk, and serum specimens obtained from infants, findings that indicate the transfer of maternal antibodies to infants; antibody titers among infants are highest when maternal vaccination occurs late in the second trimester or early in the third trimester of pregnancy.[15-22] Moreover, the anti-spike antibodies against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) persist through the first 6 months of life, and these antibody levels are higher among infants born to mothers who were vaccinated during pregnancy than among infants whose mothers had antibodies induced by natural SARS-CoV-2 infection during pregnancy.[23] These findings are reassuring because Covid-19 is associated with severe illness and hospitalization in infants.[24,25] During the peak period of circulation of the B.1.1.259 (omicron) variant of SARS-CoV-2, hospitalization rates among infants younger than 6 months of age who had SARS-CoV-2 infection were six times as high as the rates during the B.1.617.2 (delta) variant peak, and Covid-19 was the primary reason for admission in 85% of such infants; infants in this age group accounted for 44% of Covid-19–related hospitalizations among children 4 years of age or younger.[24]

We previously reported a 61% reduced risk of hospitalization for Covid-19 among infants younger than 6 months of age in association with maternal vaccination with two doses of an mRNA Covid-19 vaccine during pregnancy.[13] The data obtained during that study were from infants who were hospitalized predominantly during circulation of the delta variant. The current report assesses associations between maternal Covid-19 vaccination and hospitalization for Covid-19 among infants in a larger population that comprised an additional 361 case infants and 309 controls, including infants who were enrolled after omicron became the predominant circulating variant. The enrollment of these additional infants also provided more statistical power to assess the associations between the gestational timing of vaccination and hospitalization for Covid-19 among infants and between vaccination and Covid-19 leading to admission to an intensive care unit (ICU) or the receipt of life-supporting interventions.

Methods

Study Design

We used a case–control, test-negative design to assess the effectiveness of maternal vaccination against hospitalization for Covid-19 among infants younger than 6 months of age. Vaccine effectiveness was estimated by comparing the odds of full maternal vaccination (i.e., receipt of two doses of mRNA vaccine) during pregnancy among symptomatic infants younger than 6 months of age who were hospitalized for Covid-19 (case infants) and infants younger than 6 months of age who were hospitalized without Covid-19 (control infants).[26-30] The protocol was reviewed by the CDC and other participating institutions and was determined to be public health surveillance and thus not subject to informed-consent requirements.[31] The first and last two authors vouch for the accuracy and completeness of the data and for the fidelity of the study to the protocol.

Study Population

Infants younger than 6 months of age who were included in this study were identified between July 1, 2021 (when maternal vaccination coverage was suspected to approach 20%), and March 8, 2022, with the use of active ongoing surveillance for Covid-19–associated hospitalizations in 30 pediatric hospitals across 22 states in the CDC-funded Overcoming Covid-19 Network.[29,30,32] Site personnel attempted to identify all cases that met

inclusion criteria during the site surveillance period, and case infants and control infants were enrolled independently of information on maternal vaccination status.

Case infants were identified through review of hospital admission logs or electronic medical records and included infants hospitalized with Covid-19 as the primary reason for admission or with a clinical syndrome that was consistent with acute Covid-19 (see Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). This syndrome was defined by the presence of one or more of the following: fever, cough, shortness of breath, gastrointestinal symptoms, use of respiratory support (high-flow oxygen through a nasal cannula or new invasive or noninvasive ventilation) for the acute illness, or new pulmonary findings on chest imaging that were consistent with pneumonia. All the case infants were to have had a positive SARS-CoV-2 reverse-transcriptase–polymerase-chain-reaction (RT-PCR) or antigen test within 10 days after the onset of symptoms or within 72 hours after hospital admission.

The control infants were hospitalized infants younger than 6 months of age who were to have had a negative SARS-CoV-2 RT-PCR or antigen test, with or without Covid-19–associated symptoms (Table S2). To achieve a balance between case infants and control infants with respect to the hospital and the calendar period, site personnel attempted to enroll one eligible control infant for every case infant, with a date of hospital admission that was within 4 weeks before or after the date of admission of the case infant. Further details are provided in the Supplementary Appendix.

We excluded infants who underwent testing for SARS-CoV-2 more than 10 days after illness onset or more than 72 hours after the admission date. We also excluded case infants who had a positive SARS-CoV-2 test but were admitted for reasons unrelated to Covid-19.

VACCINATION STATUS

Maternal vaccination (full vaccination) was defined as completion of a two-dose series of either the BNT162b2 or mRNA-1273 vaccine during pregnancy. Women who received the first dose before pregnancy and the second dose during pregnancy were included.[13] To isolate the effects of full vaccination during pregnancy and inform decisions regarding vaccination during pregnancy, we excluded infants born to mothers who had been partially vaccinated during pregnancy (i.e., received one dose during pregnancy and no dose before pregnancy) or who had been fully vaccinated before pregnancy or after delivery.[13] Because protective immunity is not achieved until approximately 2 weeks after vaccination, we excluded case infants born to mothers who had been vaccinated less than 14 days before delivery. We also excluded infants born to mothers who had received a third dose of an mRNA vaccine (29 infants) or had received a non-mRNA vaccine (i.e., Ad26.COV2.S [Johnson & Johnson–Janssen]; 13 infants) because of the small number of pregnant persons in both of these categories. Data on maternal history of SARS-CoV-2 infection were not collected.

DATA COLLECTION

Demographic characteristics, clinical information about the current illness, and SARS-CoV-2 testing history were obtained through interviews with the infants' parents or guardians and through review of electronic medical records. Parents or guardians were asked about Covid-19 maternal vaccination history, including vaccination dates, the number of doses received, whether a dose had been received during pregnancy, the location where vaccination occurred, the vaccine manufacturer, and the availability of a Covid-19 vaccination card. Study personnel searched state immunization information systems or electronic medical records to verify vaccination status.

We collected data on outcomes of Covid-19–associated hospitalization, admission to an ICU, and critical illness leading to the receipt of life-supporting interventions or to death (also referred to as critical Covid-19). Life-supporting interventions included noninvasive mechanical ventilation (bilevel positive airway pressure or continuous positive airway pressure), invasive mechanical ventilation, extracorporeal membrane oxygenation, and vasoactive infusions.[25,29,30]

STATISTICAL ANALYSIS

The effectiveness of maternal vaccination against Covid-19–associated hospitalization among infants was estimated with the use of logistic regression, whereby the odds of maternal vaccination were compared among case infants and control infants with the following equation:

vaccine effectiveness = 100% × (1 − adjusted odds ratio). Models were adjusted a priori for infant age (continuous variable), sex, race and ethnic group, U.S. Census region, and calendar date of admission (biweekly intervals).[29,33] We used the change-in-estimate approach to assess other potential confounding factors (the presence of underlying health conditions in the infants, the score on the Social Vulnerability Index, and the occurrence of preterm birth at less than 37 weeks of gestation). The final models did not include these other factors because they did not change the odds ratio for vaccination by more than 5%; variables with substantial missingness, including breast-feeding (status missing for 38% of infants) and day-care attendance (status missing for 42% of infants), were also not included (Tables S3 to S6 and Fig. S1). To evaluate clustering according to hospital, we calculated the conditional and marginal odds ratio with hospital as a cluster variable. In a subgroup analysis, we evaluated vaccine effectiveness according to disease severity (ICU admission) and according to delta-predominant and omicron-predominant periods. In the latter analysis, we used proxy time periods of circulation of predominantly the delta variant (defined as the period in which infants were admitted between July 1, 2021, and December 18, 2021) as compared with circulation of predominantly the omicron variant (defined as the period in which infants were admitted between December 19, 2021, and March 8, 2022).[34] In the analysis of vaccine effectiveness according to disease severity, control infants represented all hospitalized control infants. We evaluated the effectiveness of receipt of the second dose of Covid-19 vaccine early in pregnancy (within the first 20 weeks) and late in pregnancy (after 20 weeks).[15-17] The widths of the confidence intervals were not adjusted for multiplicity, so the intervals should not be used in place of a hypothesis test. Analyses were performed with the use of SAS software, version 9.4 (SAS Institute).

RESULTS

PARTICIPANTS

A total of 1327 case infants and control infants younger than 6 months of age were enrolled at 30 hospitals between July 1, 2021, and March 8, 2022 (Table S7). After analytic exclusion criteria were applied, a total of 278 of these infants (21%) were excluded from the analytic data set (Fig. 1). Most of the excluded case infants and control infants had been born to mothers who had been vaccinated before pregnancy, after delivery, or within 13 days before delivery (172 of 278 infants [62%]). Our analysis included 537 case infants (181 of whom had been admitted to a hospital during the delta-predominant period and 356 during the omicron-predominant period) and 512 control infants. The median age of both the case infants and the control infants was 2 months; 19% of the case infants and 24% of the control infants had at least one underlying health condition (Table 1). A lower percentage of case infants than control infants was non-Hispanic White (34% vs. 44%), a finding that is consistent with the broader population of infants with Covid-19 in the United States (Table S8). Among 234 infants whose mothers had been fully vaccinated during pregnancy, documented dates of vaccination were obtained for 218 (93%). A total of 87 of the 537 case infants (16%) had been born to mothers who were fully vaccinated during pregnancy, as compared with 147 of the 512 control infants (29%).

CLINICAL SEVERITY OF COVID-19 AMONG CASE INFANTS

Among the 537 case infants, a total of 113 (21%) were admitted to an ICU, including 64 infants (12%) who received mechanical ventilation or vasoactive infusions. As compared with case infants whose mothers had not been fully vaccinated during pregnancy (450 infants), case infants whose mothers had been fully vaccinated during pregnancy (87 infants) had a lower incidence of ICU admission (23% vs. 13%), critical Covid-19 (12% vs. 9%), receipt of invasive mechanical ventilation (7% vs. 3%), receipt of noninvasive mechanical ventilation (8% vs. 6%), and receipt of vasoactive infusions (3% vs. 1%) (Fig. 2). Two case infants died from Covid-19, and 2 case infants received extracorporeal membrane oxygenation; none of the 4 infants' mothers had been vaccinated during pregnancy.

VACCINE EFFECTIVENESS

Overall, the effectiveness of maternal vaccination against Covid-19–associated hospitalization among infants younger than 6 months of age was

52% (95% confidence interval [CI], 33 to 65) (Fig. 3). Alternative models that were used to assess the conditional and marginal effects of potential clustering by site did not substantively alter the results (Table S9). Effectiveness was 70% (95% CI, 42 to 85) against admission to an ICU for Covid-19 and 47% (95% CI, 25 to 62) against non-ICU hospitalization. Effectiveness was 80% (95% CI, 60 to 90) during the period of delta predominance, as compared with 38% (95% CI, 8 to 58) during the period of omicron predominance.

Effectiveness against Covid-19–associated hospitalization for either variant among infants was 69% (95% CI, 50 to 80) when maternal vaccination occurred after 20 weeks of pregnancy, as compared with 38% (95% CI, 3 to 60) when maternal vaccination occurred during the first 20 weeks of pregnancy. Similarly, during both the delta-predominant period and the omicron-predominant period, point estimates were higher when maternal vaccination occurred after 20 weeks of pregnancy than when vaccination occurred during the first 20 weeks of pregnancy. Post hoc sensitivity analyses that were based on person-reported vaccination status or that included infants born to mothers who had been fully vaccinated before pregnancy were consistent with the overall results (Table S10).

DISCUSSION

We found that maternal vaccination during pregnancy was associated with a reduced risk of hospitalization for Covid-19 among infants younger than 6 months of age; the risk was reduced by 80% (95% CI, 60 to 90) during the period of circulation of the delta variant and by 38% (95% CI, 8 to 58) during circulation of the omicron variant. The infants whose data were included in this multicenter network had severe Covid-19 (i.e., Covid-19 resulting in hospitalization); among these infants, 21% were admitted to an ICU and 12% had critical Covid-19. Vaccine effectiveness against admission to an ICU for Covid-19 was 70% overall; most of the infants admitted to an ICU for Covid-19 (90%) had been born to unvaccinated mothers. The finding that the risk of hospitalization, and in particular, hospitalization in an ICU, was reduced among infants whose mothers had been fully vaccinated during pregnancy provides evidence of additional benefits of

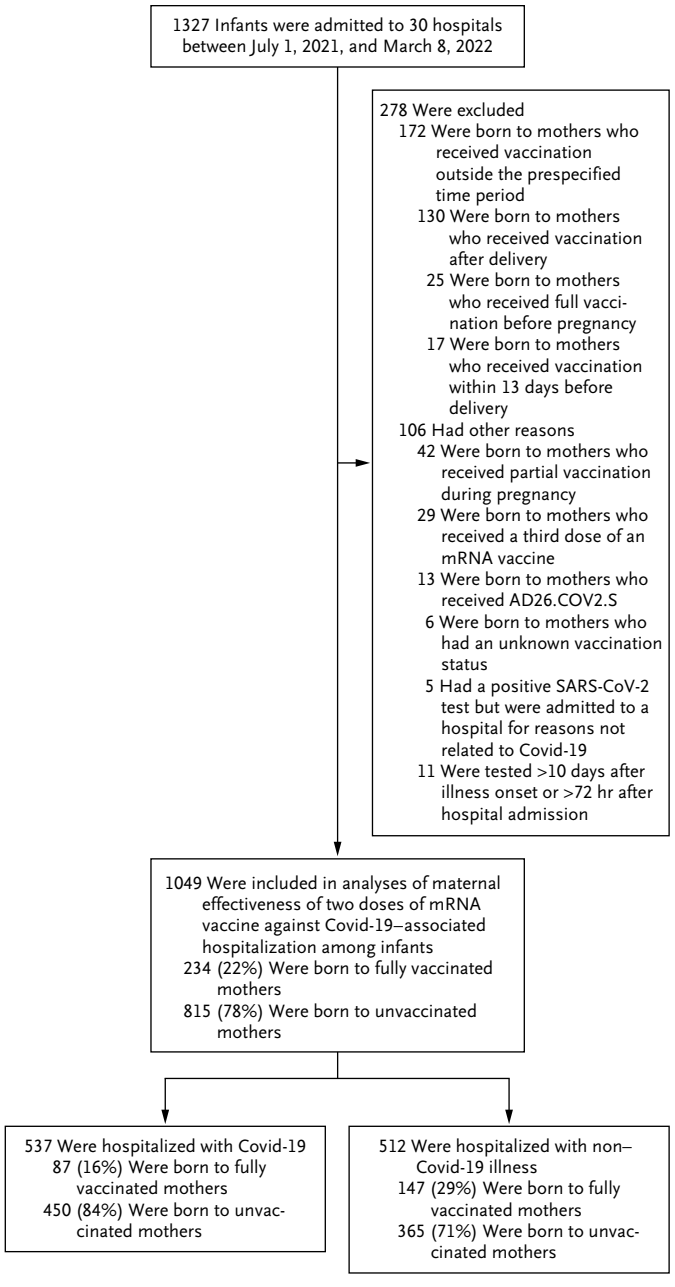


Figure 1. Study Enrollment and Outcomes (July 1, 2021–March 8, 2022).
Women were considered to be fully vaccinated if they had completed a two-dose series of either the BNT162b2 or mRNA-1273 vaccine during pregnancy; women could have received the first dose before pregnancy and the second dose during pregnancy. Women were considered to be partially vaccinated if they had received one dose of vaccine during pregnancy and no dose before pregnancy. Women were considered to be unvaccinated if they had not received vaccine doses during pregnancy and before their infant's hospitalization. Covid-19 denotes coronavirus disease 2019, and SARS-CoV-2 severe acute respiratory syndrome coronavirus 2.

Table 1. Characteristics of Case Infants and Control Infants from 30 Pediatric Hospitals in 22 States, July 2021–March 2022.*

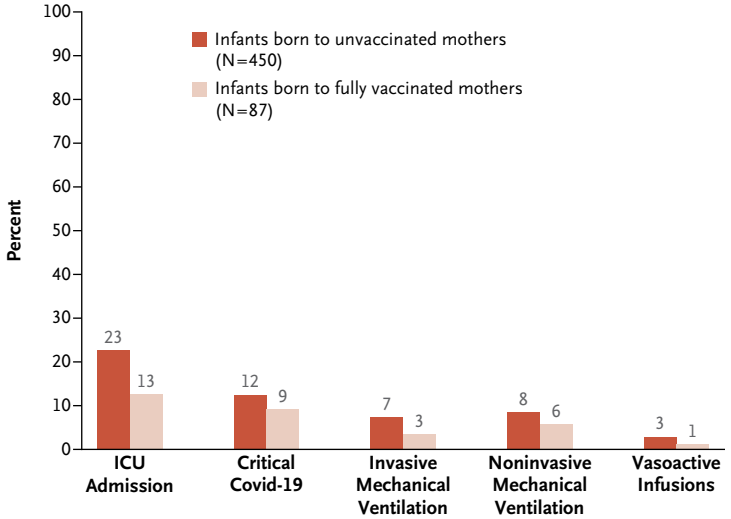
Characteristic	Case Group		Maternal Vaccination Status	
	Case Infants (N=537)	Control Infants (N=512)	Fully Vaccinated (N=234)	Unvaccinated (N=815)
Median age (IQR) — mo	2 (1–3)	2 (1–3)	2 (1–3)	2 (1–3)
Age group — no. (%)				
0–2 mo	386 (72)	371 (72)	176 (75)	581 (71)
3–5 mo	151 (28)	141 (28)	58 (25)	234 (29)
Female sex — no. (%)	235 (44)	219 (43)	94 (40)	360 (44)
Race and ethnic group — no. (%)†				
White, non-Hispanic	185 (34)	226 (44)	115 (49)	296 (36)
Black, non-Hispanic	108 (20)	76 (15)	22 (9)	162 (20)
Hispanic, any race	162 (30)	140 (27)	71 (30)	231 (28)
Other, non-Hispanic	31 (6)	36 (7)	19 (8)	48 (6)
Unknown	51 (9)	34 (7)	7 (3)	78 (10)
Median Social Vulnerability Index (IQR)‡	0.7 (0.4–0.9)	0.6 (0.3–0.8)	0.5 (0.2–0.8)	0.7 (0.4–0.9)
U.S. Census region — no. (%)				
Northeast	70 (13)	69 (13)	54 (23)	85 (10)
Midwest	127 (24)	120 (23)	27 (12)	220 (27)
South	200 (37)	180 (35)	63 (27)	317 (39)
West	140 (26)	143 (28)	90 (38)	193 (24)
Predominant variant on the basis of hospital admission date — no. (%)				
Delta: July 1, 2021, to December 18, 2021	181 (34)	216 (42)	75 (32)	322 (40)
Omicron: December 19, 2021, to March 8, 2022	356 (66)	296 (58)	159 (68)	493 (60)
Underlying health conditions among infants — no./total no. (%)				
At least one underlying condition	100/537 (19)	121/511 (24)	52/233 (22)	169/815 (21)
Respiratory	31/537 (6)	27/511 (5)	9/233 (4)	49/815 (6)
Cardiovascular	44/537 (8)	49/511 (10)	16/233 (7)	77/815 (9)
Neurologic or neuromuscular	13/537 (2)	18/511 (4)	5/233 (2)	26/815 (3)
Other chronic conditions§	55/537 (10)	75/511 (15)	32/233 (14)	98/815 (12)
Preterm birth (born at <37 wk of gestation) — no./total no. (%)	113/491 (23)	104/487 (21)	40/231 (17)	177/747 (24)
Maternal vaccination status — no. (%)¶				
Unvaccinated	450 (84)	365 (71)	—	—
Fully vaccinated	87 (16)	147 (29)	—	—
Timing of maternal vaccination — no./total no. (%)‖				
During first 20 wk of pregnancy	46/77 (60)	62/141 (44)	108/218 (50)	—
After 20 wk of pregnancy	31/77 (40)	79/141 (56)	110/218 (50)	—

* Percentages may not total 100 because of rounding. IQR denotes interquartile range.
† Race and ethnic group were reported by the infants' parents or guardians or were extracted from the medical record.
‡ Data were missing for 4 infants (3 case infants and 1 control infant). Scores on the Social Vulnerability Index range from 0 to 1.0, with higher scores indicating greater social vulnerability. Details regarding this index are available at https://www.atsdr.cdc.gov/placeandhealth/svi/index.html. The median scores on the Social Vulnerability Index were based on 2018 data.
§ Other chronic conditions included immunosuppression, rheumatologic or autoimmune disorder, hematologic disorder, renal or urologic dysfunction, gastrointestinal or hepatic disorder, metabolic or confirmed or suspected genetic disorder, and atopic or allergic condition.
¶ Women were considered to be unvaccinated if they had not received vaccine doses during pregnancy and before their infant's hospitalization. Women were considered to be fully vaccinated if they had completed a two-dose primary mRNA vaccination series during pregnancy and 14 or more days before delivery. Women who received the first dose before pregnancy and the second dose during pregnancy were considered to be fully vaccinated.
‖ The timing of vaccination was based on the date of receipt of the second dose of a two-dose series of an mRNA Covid-19 vaccine during pregnancy.

maternal vaccination beyond those previously reported for the mother.[3,4]

Several lines of evidence support a causal link between maternal vaccination and protection against Covid-19–related hospitalization among infants. First, many studies have shown that maternally derived anti–SARS-CoV-2 antibodies from vaccination or from previous infection are efficiently transferred to the infant.[15-23,35] A recent report showed that infants whose mothers had been vaccinated during pregnancy had higher levels of these antibodies, and were more likely to have persistent antibodies, at 6 months of age than infants whose mothers had had SARS-CoV-2 infection during pregnancy.[23] These findings of transplacentally acquired SARS-CoV-2 antibodies in infants, which correlate with protection, are consistent with our observation of a reduced risk of Covid-19–related hospitalization among infants in association with maternal vaccination. Second, studies have shown that antibody titers in umbilical-cord blood are highest after Covid-19 vaccination during the late second or early third trimester of pregnancy.[15,16,20] Although our sample size was limited with respect to evaluating effectiveness by trimester, we observed higher point estimates of effectiveness among infants whose mothers had been fully vaccinated after 20 weeks of gestation than among those whose mothers had been fully vaccinated during the first 20 weeks of gestation. Third, we observed higher protection against Covid-19–associated hospitalization among infants during the delta period than during the omicron period, a finding that is consistent with the lesser degree of protection observed against omicron-associated hospitalization than delta-associated hospitalization among vaccinated children and adults.[36,37] Fourth, benefits of maternal vaccination with respect to illness among infants during the first 6 months of life have previously been shown for other vaccine-preventable diseases, such as pertussis and influenza.[10-12]

Vaccination has been shown to provide strong protection against Covid-19 during pregnancy, similar to that observed among nonpregnant



	ICU Admission	Critical Covid-19	Invasive Mechanical Ventilation	Noninvasive Mechanical Ventilation	Vasoactive Infusions
Infants Born to Unvaccinated Mothers — no./total no. (%)	102/450 (23)	56/450 (12)	33/450 (7)	38/449 (8)	13/448 (3)
Infants Born to Fully Vaccinated Mothers — no./total no. (%)	11/87 (13)	8/87 (9)	3/87 (3)	5/87 (6)	1/87 (1)

Figure 2. Clinical Severity of Covid-19 as Indicated by Outcomes among Case Infants, According to Maternal Vaccination Status.

Critical Covid-19 was defined as Covid-19 leading to life-supporting interventions (i.e., noninvasive mechanical ventilation [bilevel positive airway pressure or continuous positive airway pressure], invasive mechanical ventilation, vasoactive infusions, or extracorporeal membrane oxygenation) or to death. An infant could have been included in more than one outcome category. Two infants who had been born to unvaccinated mothers (2 of 450 infants [<1%]) received extracorporeal membrane oxygenation. An additional 2 infants who had been born to unvaccinated mothers (2 of 442 infants [<1%]) died; among the 450 infants who had been born to unvaccinated mothers, 8 had mothers for whom data on hospital discharge were not available. ICU denotes intensive care unit.

persons.[3,4] Furthermore, studies have shown that Covid-19 vaccination is safe during pregnancy, with no increased risk of preterm birth or delivery of a small-for-gestational-age infant.[5-8] Infants younger than 6 months of age are at high risk for complications of Covid-19, including severe respiratory failure and death, and account for a disproportionately high percentage of hospitalizations among children 0 to 4 years of age.[24,25] Despite the known benefits and safety of vaccination during pregnancy, only 29% of the control infants had been born to mothers who had been fully vaccinated during pregnancy, a percentage similar to that reported by the CDC among pregnant women in the United States.[38]

We observed that maternal vaccination was associated with lower protection against Covid-19–related hospitalization among infants during the omicron period than during the delta period. This is consistent with the results of a recently published maternal Covid-19 vaccination study from Norway[14] and with data from effectiveness studies involving children and adults that showed that the omicron variant can evade neutralizing antibodies induced by mRNA vaccination.[36,39,40] However, maternal vaccination was still associated with a moderate (38%) reduction in the risk of hospitalization during the omicron period among infants younger than 6 months of age, a group for whom vaccines are not likely to be licensed in the foreseeable future. Although we did not address booster vaccination during pregnancy, previous studies have shown that booster doses can improve protection against omicron in the general population and are also recommended during pregnancy. As booster coverage increases, investigation of rates of severe Covid-19 among infants in association with maternal booster vaccination may further inform strategies to control Covid-19 in this population.

Although point estimates of vaccine effectiveness were higher when vaccination occurred after 20 weeks of gestation, the appropriate timing of maternal vaccination for the transfer of antibodies to protect the infant is currently uncertain. In some studies, SARS-CoV-2 anti–spike protein antibody titers in cord blood were higher when maternal vaccination occurred during the late sec-

Subgroup	Case Infants	Control Infants	Effectiveness of Maternal Vaccination
	no. of vaccinated mothers/total no. (%)		*% (95% CI)*
Overall effectiveness of maternal vaccination	87/537 (16)	147/512 (29)	52 (33 to 65)
Timing of vaccination			
During first 20 wk of pregnancy	46/496 (9)	62/427 (15)	38 (3 to 60)
After 20 wk of pregnancy	31/481 (6)	79/444 (18)	69 (50 to 80)
Delta-predominant period	14/181 (8)	61/216 (28)	80 (60 to 90)
Vaccinated during first 20 wk of pregnancy	8/175 (5)	22/177 (12)	68 (19 to 87)
Vaccinated after 20 wk of pregnancy	5/172 (3)	37/192 (19)	88 (68 to 96)
Omicron-predominant period	73/356 (21)	86/296 (29)	38 (8 to 58)
Vaccinated during first 20 wk of pregnancy	38/321 (12)	40/250 (16)	25 (−26 to 56)
Vaccinated after 20 wk of pregnancy	26/309 (8)	42/252 (17)	57 (25 to 75)
Type of hospital admission			
ICU	11/113 (10)	147/512 (29)	70 (42 to 85)
Non-ICU	76/424 (18)	147/512 (29)	47 (25 to 62)

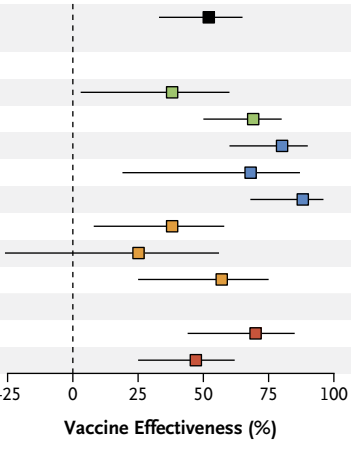


Figure 3. Effectiveness of Maternal Two-Dose mRNA Vaccination against Hospitalization for Covid-19 among Infants, Stratified According to Vaccination Timing, Variant, and Type of Admission.

The delta-predominant period was defined as July 1, 2021, to December 18, 2021. The omicron-predominant period was defined as December 19, 2021, to March 8, 2022. The timing of maternal vaccination was based on the date of receipt of the second dose of a two-dose series of an mRNA Covid-19 vaccine during pregnancy. Gestational age was missing for 3 infants who had been born to vaccinated mothers with known timing of the second dose; for these infants, classification of vaccination timing was based on a gestational age of 40 weeks. For 16 infants who had been born to mothers who had been fully vaccinated during pregnancy, dates of vaccination were not available to determine the vaccination timing during pregnancy. Vaccine effectiveness was calculated as (1 − adjusted odds ratio) x 100, where the odds ratio is the odds of maternal vaccination among mothers of case infants as compared with control infants. The widths of the confidence intervals have not been adjusted for multiplicity and should not be used in place of a hypothesis test.

ond or early third trimester than when vaccination occurred earlier in pregnancy.[15,16,20] However, the difference was small, and titers have been detectable among infants born to persons who were fully vaccinated at any time during pregnancy. Studies of vaccination against influenza and pertussis have shown that many factors beyond the timing of vaccination can influence antibody titers in infants.[10] Some potential gains achieved by vaccinating later in pregnancy might be offset by missed opportunities to complete vaccination or receive boosters, and vaccination is recommended as soon as possible during pregnancy to provide direct protection against severe complications, death, and adverse birth outcomes associated with Covid-19.[9]

Our report has some limitations. First, we could not assess potential biases related to natural SARS-CoV-2 infection before or during pregnancy. If previous maternal infection offers protection against subsequent infection and is correlated with not being vaccinated, this would attenuate estimates of vaccine effectiveness. Second, the possibility of residual confounding resulting from differences between case infants and control infants cannot be excluded. Such confounding could be related to differences in demographic characteristics, exposures to the specific variant causing Covid-19, history of breast-feeding, and history of day-care attendance or differences in behaviors between vaccinated and unvaccinated pregnant persons that might have affected the risk of infection among the infants. Third, the findings from this study might not apply to less severe Covid-19 or to other variants. Fourth, we were unable to verify the person-reported maternal vaccination status for 2% (12 of 537) of the case infants and 2% (8 of 512) of the control infants. Fifth, we were unable to assess the effectiveness of a maternal booster dose received during pregnancy or the effectiveness of non-mRNA vaccination.

In this real-world evaluation, maternal vaccination with mRNA vaccines was associated with a substantial reduction in the risk of Covid-19–related hospitalization and critical illness among young infants, although reductions were less pronounced when the omicron variant was predominant. These findings provide additional support for the current recommendations regarding Covid-19 vaccination during pregnancy.

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APPENDIX

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REFERENCES

1. Zambrano LD, Ellington S, Strid P, et al. Update: characteristics of symptomatic women of reproductive age with laboratory-confirmed SARS-CoV-2 infection by pregnancy status — United States, January 22–October 3, 2020. MMWR Morb Mortal Wkly Rep 2020;69:1641-7.
2. DeSisto CL, Wallace B, Simeone RM, et al. Risk for stillbirth among women with and without COVID-19 at delivery hospitalization — United States, March 2020–September 2021. MMWR Morb Mortal Wkly Rep 2021;70:1640-5.
3. Butt AA, Chemaitelly H, Al Khal A, et al. SARS-CoV-2 vaccine effectiveness in preventing confirmed infection in pregnant women. J Clin Invest 2021;131(23): e153662.
4. Dagan N, Barda N, Biron-Shental T, et al. Effectiveness of the BNT162b2 mRNA COVID-19 vaccine in pregnancy. Nat Med 2021;27:1693-5
5. Lipkind HS, Vazquez-Benitez G, DeSilva M, et al. Receipt of COVID-19 vaccine during pregnancy and preterm or small-for-gestational-age at birth — eight integrated health care organizations, United States, December 15, 2020–July 22, 2021. MMWR Morb Mortal Wkly Rep 2022;71:26-30.
6. Shimabukuro TT, Kim SY, Myers TR, et al. Preliminary findings of mRNA Covid-19 vaccine safety in pregnant persons. N Engl J Med 2021;384:2273-82.
7. Zauche LH, Wallace B, Smoots AN, et al. Receipt of mRNA Covid-19 vaccines and risk of spontaneous abortion. N Engl J Med 2021;385:1533-5.
8. Magnus MC, Gjessing HK, Eide HN, Wilcox AJ, Fell DB, Håberg SE. Covid-19 Vaccination during pregnancy and first-trimester miscarriage. N Engl J Med 2021; 385:2008-10.
9. Centers for Disease Control and Prevention. COVID-19 vaccines while pregnant or breastfeeding (https://www.cdc.gov/coronavirus/2019-ncov/vaccines/recommendations/pregnancy.html).
10. Abu Raya B, Edwards KM, Scheifele DW, Halperin SA. Pertussis and influenza immunisation during pregnancy: a landscape review. Lancet Infect Dis 2017; 17(7):e209-e222.
11. Azziz-Baumgartner E, Grohskopf L, Patel M. Realizing the potential of maternal influenza vaccination. JAMA 2021; 325:2257-9.
12. Omer SB. Maternal immunization. N Engl J Med 2017;376:1256-67.
13. Halasa NB, Olson SM, Staat MA, et al. Effectiveness of maternal vaccination with mRNA COVID-19 vaccine during pregnancy against COVID-19-associated hospitalization in infants aged <6 months — 17 states, July 2021–January 2022. MMWR Morb Mortal Wkly Rep 2022;71: 264-70.
14. Carlsen EØ, Magnus MC, Oakley L, et al. Association of COVID-19 vaccination during pregnancy with incidence of SARS-CoV-2 infection in infants. JAMA Intern Med 2022 June 1 (Epub ahead of print).
15. Mithal LB, Otero S, Shanes ED, Goldstein JA, Miller ES. Cord blood antibodies following maternal coronavirus disease 2019 vaccination during pregnancy. Am J Obstet Gynecol 2021;225:192-4.
16. Beharier O, Plitman Mayo R, Raz T, et al. Efficient maternal to neonatal transfer of antibodies against SARS-CoV-2 and BNT162b2 mRNA COVID-19 vaccine. J Clin Invest 2021;131:150319.
17. Prabhu M, Murphy EA, Sukhu AC, et al. Antibody response to coronavirus disease 2019 (COVID-19) messenger RNA vaccination in pregnant women and transplacental passage into cord blood. Obstet Gynecol 2021;138:278-80.
18. Perl SH, Uzan-Yulzari A, Klainer H, et al. SARS-CoV-2-specific antibodies in breast milk after COVID-19 vaccination of breastfeeding women. JAMA 2021;325: 2013-4.
19. Baird JK, Jensen SM, Urba WJ, Fox BA, Baird JR. SARS-CoV-2 antibodies detected in mother's milk post-vaccination. J Hum Lact 2021;37:492-8.
20. Yang YJ, Murphy EA, Singh S, et al. Association of gestational age at coronavirus disease 2019 (COVID-19) vaccination, history of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, and a vaccine booster dose with maternal and umbilical cord antibody levels at delivery. Obstet Gynecol 2022;139: 373-80.
21. Trostle ME, Aguero-Rosenfeld ME, Roman AS, Lighter JL. High antibody levels in cord blood from pregnant women vaccinated against COVID-19. Am J Obstet Gynecol MFM 2021;3:100481.
22. Nir O, Schwartz A, Toussia-Cohen S, et al. Maternal-neonatal transfer of SARS-CoV-2 immunoglobulin G antibodies among parturient women treated with BNT162b2 messenger RNA vaccine during pregnancy. Am J Obstet Gynecol MFM 2022;4:100492.
23. Shook LL, Atyeo CG, Yonker LM, et al. Durability of anti-spike antibodies in infants after maternal COVID-19 vaccination or natural infection. JAMA 2022;327: 1087-9.
24. Marks KJ, Whitaker M, Agathis NT, et al. Hospitalization of infants and children aged 0-4 years with laboratory-confirmed COVID-19 — COVID-NET, 14 states, March 2020–February 2022. MMWR Morb Mortal Wkly Rep 2022;71:429-36.
25. Hobbs CV, Woodworth K, Young CC, et al. Frequency, characteristics and complications of COVID-19 in hospitalized infants. Pediatr Infect Dis J 2022;41(3): e81-e86.
26. Mølgaard-Nielsen D, Fischer TK, Krause TG, Hviid A. Effectiveness of maternal immunization with trivalent inactivated influenza vaccine in pregnant women and their infants. J Intern Med 2019; 286:469-80.
27. Olson SM, Newhams MM, Halasa NB, et al. Vaccine effectiveness against life-threatening influenza illness in US Children. Clin Infect Dis 2022 January 13 (Epub ahead of print).
28. Chua H, Feng S, Lewnard JA, et al. The use of test-negative controls to monitor vaccine effectiveness: a systematic review of methodology. Epidemiology 2020; 31:43-64.
29. Olson SM, Newhams MM, Halasa NB, et al. Effectiveness of BNT162b2 vaccine

against Critical Covid-19 in adolescents. N Engl J Med 2022;386:713-23.
30. Olson SM, Newhams MM, Halasa NB, et al. Effectiveness of Pfizer-BioNTech mRNA vaccination against COVID-19 hospitalization among persons aged 12-18 years — United States, June–September 2021. MMWR Morb Mortal Wkly Rep 2021;70:1483-8.
31. Office of the Federal Register. Code of federal regulations: a point in time eCFR system. Title 45 (https://www.ecfr.gov/cgi-bin/text-idx?SID=fc043bd2812f0775fa80066558a6bbcf&mc=true&node=pt45.1.46&rgn=div5#se45.1.46_1102).
32. Razzaghi H, Meghani M, Pingali C, et al. COVID-19 vaccination coverage among pregnant women during pregnancy — eight integrated health care organizations, United States, December 14, 2020–May 8, 2021. MMWR Morb Mortal Wkly Rep 2021;70:895-9.
33. Patel MK, Bergeri I, Bresee JS, et al. Evaluation of post-introduction COVID-19 vaccine effectiveness: summary of interim guidance of the World Health Organization. Vaccine 2021;39:4013-24.
34. Centers for Disease Control and Prevention. COVID data tracker: variant proportions (https://covid.cdc.gov/covid-data-tracker/#variant-proportions).
35. Gray KJ, Bordt EA, Atyeo C, et al. Coronavirus disease 2019 vaccine response in pregnant and lactating women: a cohort study. Am J Obstet Gynecol 2021;225(3):303.e1-303.e17.
36. Klein NP, Stockwell MS, Demarco M, et al. Effectiveness of COVID-19 Pfizer-BioNTech BNT162b2 mRNA vaccination in preventing COVID-19-associated emergency department and urgent care encounters and hospitalizations among nonimmunocompromised children and adolescents aged 5-17 years — VISION Network, 10 States, April 2021–January 2022. MMWR Morb Mortal Wkly Rep 2022;71:352-8.
37. Lauring AS, Tenforde MW, Chappell JD, et al. Clinical severity of, and effectiveness of mRNA vaccines against, Covid-19 from omicron, delta, and alpha SARS-CoV-2 variants in the United States: prospective observational study. BMJ 2022;376:e069761.
38. Centers for Disease Control and Prevention. Archived cumulative data: percent of pregnant people aged 18-49 years receiving at least one dose of a COVID-19 vaccine during pregnancy overall, by race/ethnicity, and date reported to CDC-Vaccine Safety Datalink*, United States | December 20, 2020–January 20, 2022 (https://data.cdc.gov/Vaccinations/Cumulative-Data-Percent-of-Pregnant-People-aged-18/4ht3-nbmd/data).
39. Nemet I, Kliker L, Lustig Y, et al. Third BNT162b2 vaccination neutralization of SARS-CoV-2 omicron infection. N Engl J Med 2022;386:492-4.
40. Thompson MG, Natarajan K, Irving SA, et al. Effectiveness of a third dose of mRNA vaccines against COVID-19-associated emergency department and urgent care encounters and hospitalizations among adults during periods of delta and omicron variant predominance — VISION Network, 10 States, August 2021–January 2022. MMWR Morb Mortal Wkly Rep 2022;71:139-45.