Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Safety and Effectiveness of Maternal COVID-19 Vaccines Among Pregnant People and Infants

Katherine E. Fleming-Dutra, MD[a,*,1], Lauren Head Zauche, PhD, MSN[b,1], Lauren E. Roper, MPH[a], Sascha R. Ellington, PhD[c], Christine K. Olson, MD[b,d], Andrea J. Sharma, PhD[b,d], Kate R. Woodworth, MD[e], Naomi Tepper, MD[d,e], Fiona Havers, MD[a,d], Sara E. Oliver, MD[a,d], Evelyn Twentyman, MD[a], Tara C. Jatlaoui, MD[d,f]

KEYWORDS

• COVID-19 vaccine • Pregnancy • Infants • mRNA vaccines • Vaccine effectiveness • Vaccine safety • Maternal vaccination

KEY POINTS

- Available evidence demonstrates that COVID-19 vaccination during pregnancy is safe and is not associated with adverse pregnancy or infant outcomes.
- Reactogenicity to COVID-19 vaccines is similar for pregnant people and nonpregnant women of reproductive age for both doses in the primary messenger RNA (mRNA) vaccine series.
- Effectiveness of mRNA COVID-19 vaccines is similar in pregnant people and nonpregnant women of similar age for prevention of SARS-CoV-2 infection and hospitalizations.
- Maternal COVID-19 vaccination during pregnancy reduces the risk of SARS-CoV-2 infection and COVID-19–associated hospitalization in infants younger than 6 months.

Continued

[a] National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, 1600 Clifton Road NE, Mailstop H24-9 Atlanta, GA 30329, USA; [b] Division of Healthcare Quality Promotion, National Center for Emerging and Zoonotic Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, GA, USA; [c] Division of Reproductive Health, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, Atlanta, GA, USA; [d] U.S. Public Health Service Commissioned Corps, Atlanta, GA, USA; [e] Division of Birth Defects and Infant Disorders, National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention, Atlanta, GA, USA; [f] Immunization Services Division, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, Atlanta, GA, USA
[1] Drs K.E. Fleming-Dutra and L.H. Zauche contributed equally to this article.
* Corresponding author.
E-mail address: ftu2@cdc.gov

Obstet Gynecol Clin N Am 50 (2023) 279–297
https://doi.org/10.1016/j.ogc.2023.02.003
0889-8545/23/Published by Elsevier Inc.
obgyn.theclinics.com

Continued

- The effectiveness of maternal monovalent mRNA COVID-19 vaccination was lower for infections and hospitalizations in both pregnant people and infants during predominance of the Omicron variant than during predominance of prior SARS-CoV-2 variants.

INTRODUCTION

Maternal vaccination is a safe and effective strategy to prevent morbidity and mortality from vaccine-preventable diseases both among pregnant people and through transplacental transfer of antibodies, among infants after birth.[1] Influenza, pertussis, and COVID-19 vaccines are all recommended for pregnant persons.[2–4] Influenza vaccine is recommended for everyone age 6 months and older, including pregnant people, every influenza season, and maternal influenza vaccination provides protection for the mother during pregnancy and the infant after birth.[2] In comparison, acellular pertussis vaccine (Tdap) is recommended for pregnant people during every pregnancy, optimally between 27 and 36 weeks gestation, with the goal of maximizing protection for the infant in the first few months after birth.[4] COVID-19 can cause severe disease in pregnant people. Compared with nonpregnant women of similar age, pregnant people with COVID-19 are at increased risk for admission to the intensive care unit (ICU) and for requiring mechanical ventilation and extracorporeal membrane oxygen support.[5] COVID-19 during pregnancy also increases the risk of adverse pregnancy outcomes, including preterm birth, stillbirth, infant neonatal ICU admission, and rarely, maternal and neonatal death.[5] Pregnant people have been eligible for COVID-19 vaccination in the United States since the initial Emergency Use Authorizations (EUA) in December 2020 and were initially given the option of vaccination[6]; however, they were not included in initial clinical trials.[7–10] Based on accumulating data on COVID-19 safety and effectiveness, in August 2021, the Centers for Disease Control and Prevention (CDC) strengthened its recommendations for COVID-19 vaccination of all pregnant people.[11]

COVID-19 vaccination during pregnancy, regardless of trimester of exposure, is associated with detectable antibodies in maternal sera, umbilical cord blood, and infant sera at delivery that may provide protection to infants against COVID-19.[12,13] Antibodies after vaccination in maternal and cord blood at delivery demonstrate neutralizing responses, and antibodies in infant sera can persist through early infancy, with one study detecting antibodies to at least 12 weeks of age.[13] Moreover, infants younger than 6 months are the only population in the United States not currently eligible for COVID-19 vaccination. Infants may be hospitalized and may become critically ill.[14,15] Among infants younger than 6 months, COVID-19 causes a similar to higher burden of hospitalizations than influenza,[16] which has long been recognized as a cause of severe respiratory disease in this population.[17]

Because pregnant people were excluded from the COVID-19 vaccine clinical trials, postauthorization studies and surveillance have been important to inform vaccine safety and effectiveness among pregnant people. Several reviews, including 3 recent reports (of which 2 were meta-analyses), have covered COVID-19 vaccine safety and effectiveness in pregnancy,[18–20] and recently new evidence has emerged on the vaccine effectiveness of monovalent COVID-19 booster doses among pregnant people and the effects of maternal COVID-19 vaccination among infants. The objective of this review is to provide an update on COVID-19 vaccination coverage among

pregnant people and an overview of the evidence on COVID-19 vaccine safety and effectiveness in pregnant people for vaccines authorized or approved for use in the United States, with further discussion of booster doses and potential benefits in infants.

COVID-19 VACCINE RECOMMENDATIONS AND COVERAGE IN PREGNANT PEOPLE IN THE UNITED STATES

CDC recommends everyone ages 6 months and older, including pregnant people, stay up to date with COVID-19 vaccines recommended for their age group.[3] As of October 12, 2022, people ages 5 years and older are recommended to receive one updated (bivalent) Pfizer-BioNTech or Moderna messenger RNA (mRNA) booster.[3] Bivalent mRNA boosters contain mRNA encoding the spike protein from both the Omicron (BA.4/BA.5) SARS-CoV-2 variants and the ancestral (or original) SARS-CoV-2 strain, whereas the original (monovalent) mRNA vaccines only contain mRNA encoding the ancestral strain spike protein. The bivalent booster dose should be administered at least 2 months after completion of the primary series or the last monovalent booster dose. For those ages 18 years and older who have completed a primary series but not a booster, Novavax monovalent COVID-19 vaccine is available as an alternative for those who cannot or will not pursue bivalent booster vaccination.[21] CDC's guidance on staying up to date with COVID-19 vaccines and coadministration with non-COVID-19 vaccines applies to everyone, including pregnant people.[3] COVID-19 vaccines may be administered without regard to timing of other vaccines, and this includes simultaneous administration of COVID-19 vaccine and other vaccines, such as influenza and Tdap vaccines, on the same day. However, there are additional considerations if administering an orthopoxvirus vaccine (which is used for the prevention of monkeypox and smallpox); this guidance is available on CDC's Web site.[3]

Data collected from CDC's National Immunization Survey-Adult COVID-19 Module during August 28 to September 30, 2022 indicated that 25.6% (95% confidence interval [CI] 16.6%–34.5%) of pregnant people had not yet received any COVID-19 vaccine, 72.0% (95% CI 62.9%–81.1%) had completed a primary series, and 4.3% (95% CI 0.0%–8.7%) were up to date with a primary series or bivalent booster, when indicated.[22] In comparison, 16.0% (95% CI 14.6%–17.3%) of women ages 18 to 49 years who were not pregnant, trying to become pregnant, or breastfeeding remained unvaccinated, 81.6% (95% CI 80.2%–83.1%) had completed a primary series, and 3.6% (95% CI 2.9%–4.3%) were up to date with a primary series or bivalent booster, when indicated.[22] These data indicate that opportunities remain to increase primary series COVID-19 vaccination and bivalent booster uptake among pregnant people.

SAFETY OF COVID-19 VACCINES IN PREGNANT PEOPLE AND THEIR INFANTS

Vaccine safety is essential to ensure the well-being of vaccine recipients and trust in regulatory and public health agencies. All vaccines undergo rigorous testing through several phases of clinical trials before authorization or approval for use in the general population. However, because pregnant people were excluded from initial trials, initial safety data came from developmental and reproductive toxicity animal studies and from a very small sample of participants who became pregnant during the preauthorization vaccine trials.[23] Animal studies did not identify any safety concerns for female fertility or embryonal or fetal development.[24,25] No safety concerns were identified in the 23 participants who became pregnant in the monovalent Pfizer-BioNTech mRNA COVID-19 vaccine (BNT162b2) trial or the 12 participants who became pregnant in the

monovalent Moderna mRNA COVID-19 vaccine (mRNA-1273) trial.[24,25] Because mRNA vaccines have been the most widely used, most safety data to date in pregnant people come from postauthorization safety monitoring and observational studies examining monovalent mRNA vaccines, specifically primary series vaccination. Included studies are detailed in Supplementary Table 1.

Local and Systemic Reactions

Monitoring the reactogenicity to vaccination is important for establishing and understanding a vaccine's safety profile. Because vaccines stimulate an immune response, it is common for individuals to experience local adverse events following vaccination such as pain, redness, rash, or swelling around the injection site, as well as systemic adverse events, such as fever, myalgia, arthralgia, headache, and nausea or vomiting.

The v-safe after vaccination health checker is a smartphone–based active surveillance system developed by CDC to monitor for adverse events and reactogenicity following COVID-19 vaccination.[26] Vaccinated individuals voluntarily enroll in v-safe and receive text messages with weblinks to online surveys that assess for adverse events, severity of symptoms, and health impact of symptoms. To identify people who received a COVID-19 vaccine while pregnant, v-safe surveys include a question inquiring about pregnancy status for nonmale participants. Preliminary findings from 16,982 v-safe participants who identified as pregnant and completed a survey about reactions on postvaccination day 1 during December 14, 2020 and February 28, 2021 demonstrated that local and systemic reactions following vaccination with BNT162b2 and mRNA-1273 vaccines were common after each dose but were more frequently reported after dose 2 compared with dose 1.[26] The symptoms most commonly reported the day after vaccination included injection-site pain (88.1% postdose 1, 91.9% postdose 2), fatigue (29.6% postdose 1, 71.5% postdose 2), headache (18.1% postdose 1, 55.4% postdose 2), myalgia (11.6% postdose 1, 54.1% postdose 2), chills (4.1% postdose 1, 36.7% postdose 2), and fever (4.2% postdose 1, 34.6% postdose 2). The prevalence of these symptoms and higher reactogenicity after dose 2 were similar to those of nonpregnant women of reproductive age. Systemic reactions were reported more frequently among nonpregnant women of reproductive age except for nausea and vomiting, which was reported more frequently in pregnant people.[26]

Results from other surveillance systems have observed similar reactogenicity profiles for the monovalent mRNA COVID-19 vaccines. In a prospective cohort study of 1012 pregnant people from the Swiss COVI-PREG registry, 35.3% and 67.3% reported a systemic reaction after dose 1 and dose 2, respectively; systemic reactions were primarily fatigue, headache, and myalgia and were more common with mRNA-1273 compared with BNT162b2.[27] Results from a case-control study of 390 pregnant people and 260 nonpregnant women who all received BNT162b2 in Israel demonstrated that myalgia, arthralgia, and headache occurred more frequently among the nonpregnant control group, but paresthesia (tingling sensation) was more common among pregnant people compared with nonpregnant people postdose 2 (4.6% vs 1.2%, $P < .001$).[28] Incidence of uterine contractions (1.3% for dose 1, 6.4% for dose 2) and vaginal bleeding (0.3% postdose 1, 1.5% postdose 2) were low but were more common after dose 2; uterine contractions did not result in preterm birth for any pregnant people in the study.[28] However, this study did not include unvaccinated pregnant people and could not compare with the baseline risk of these events.[28]

Severe adverse events following vaccination in pregnant people are much less common compared with local and systemic reactions. In a report from the Canadian National Vaccine Safety Network, 226 (4.0%) of 5597 vaccinated pregnant people

reported a significant health event, which was defined as a new or worsening health event sufficient to cause work or school absenteeism, medical consultation, or to prevent normal daily activities after dose 1 of an mRNA COVID-19 vaccine.[29] After dose 2, 7.3% reported a significant health event. The most common significant health events were malaise, myalgia, and headache.[29] Fewer than 1% of participants experienced a serious health event, defined as an event resulting in an emergency department or hospital visit.[29] These findings were consistent with electronic health data from the Vaccine Safety Datalink, a collaborative project between CDC and 9 integrated health care organizations in the United States to monitor vaccine safety.[30] Of 45,232 pregnant people who had received a COVID-19 vaccine immediately before or during pregnancy, fewer than 1% experienced symptoms for which they needed to seek medical care. Serious acute adverse events, including cerebral venous sinus thrombosis, encephalitis or myelitis, Guillain-Barré syndrome, myocarditis, pericarditis, or pulmonary embolism, did not occur more frequently in vaccinated pregnant people compared with nonvaccinated pregnant people.

During December 14, 2020 and October 31, 2021, a total of 3462 reports of adverse events in pregnant people who received a COVID-19 primary series dose (91.8% received an mRNA vaccine, 7.9% received Ad26.COV2.S [Janssen] vaccine) were submitted to the Vaccine Adverse Event Reporting System (VAERS), a passive surveillance system in the United States.[31] A total of 621 reports (17.9%) were categorized as serious, including 8 maternal deaths and 12 neonatal deaths. Medical record review for cases in which records could be obtained did not identify any concerning patterns for cause or probable cause of death that could be attributed to vaccination.[31] VAERS also received 323 reports of adverse events in pregnant people who received a monovalent mRNA vaccine booster dose from September 22, 2021 through March 24, 2022; 72 (22.3%) were coded as serious, most of which were spontaneous abortions (n = 56).[32] Review of VAERS reports did not identify any unexpected reporting of any adverse events compared with other vaccines in VAERS for either the COVID-19 vaccine primary series or the booster dose.[31,32]

Spontaneous Abortion

Spontaneous abortion (SAB), that is, pregnancy loss before 20 weeks gestation, is a common pregnancy outcome, affecting 11% to 22% of all recognized pregnancies.[33,34] Concern about the risk of SAB may be a barrier to early maternal vaccination. Because the underlying risk of SAB varies by week of pregnancy, it is essential that time-varying exposure methods be considered to minimize bias in studies assessing SAB after vaccination.[35] To date, no surveillance systems or studies have identified any association between SAB and COVID-19 vaccination.[19,29,36–39]

Participants in CDC's v-safe after vaccination health checker[SM] who reported they were pregnant at the time of vaccination or shortly thereafter were invited to participate in CDC's COVID-19 Vaccine Pregnancy Registry. The pregnancy registry reported a 14.1% (95% CI 12.1%–16.1%) cumulative risk of SAB from 6 to less than 20 weeks gestation among a cohort of 2456 pregnant people who received at least one dose of an mRNA COVID-19 vaccine 30 days before their last menstrual period through 19 weeks 6 days gestation.[36] After age-standardization with a reference population, the cumulative risk of SAB was 12.8% (95% CI 10.8%–14.8%), consistent with published estimates of underlying risk of SAB in reference populations.[33,34,36] However, this analysis was limited by several factors, including no control group and a sample that consisted of mostly non-Hispanic White health care personnel.

A meta-analysis by Prasad and colleagues[19] that pooled results from 2 comparative studies with time-varying exposures[38,39] found no association between COVID-19

vaccine and SAB (odds ratio [OR]: 1.00, 95% CI 0.92 to 1.09). In another retrospective cohort study, the rate of first trimester SAB among 927 vaccinated pregnant people in Romania was 13.4%.[37] There were no increased odds of first trimester SAB for those who received BNT162b2 (adjusted odds ratio [aOR]: 1.04, 95% CI 0.91 to 1.12) or mRNA-1273 (aOR: 1.02, 95% CI 0.89–1.08) compared with those not vaccinated.[37] These results taken together suggest that COVID-19 vaccination does not increase the risk of SAB.

Stillbirth

Stillbirth, or intrauterine fetal demise occurring at or after 20 weeks gestation, is a devastating pregnancy outcome that occurs in approximately 5.7 per 1000 births in the United States.[40] Recent reports have demonstrated that SARS-CoV-2 infection during pregnancy is associated with an almost 2-fold increased risk of stillbirth.[5,41] In contrast, studies assessing COVID-19 vaccination during pregnancy have not identified an increased risk of stillbirth following vaccination.

In a systematic review and meta-analysis that included 7 studies of 66,067 vaccinated and 425,624 unvaccinated pregnant people, receipt of an mRNA COVID-19 vaccination during pregnancy was associated with a 15% reduction in the odds of stillbirth (OR: 0.85, 95% CI 0.73–0.99).[19] These results were similar to those of another meta-analysis that included 5 studies (3 of which were included in Prasad and colleagues) of 31,796 vaccinated and 135,652 unvaccinated pregnant people and identified a 27% reduction in the odds of stillbirth among those vaccinated with any COVID-19 vaccine (OR: 0.73, 95% CI 0.57–0.94), although it is important to note that the definition of stillbirth varied among the studies included in the meta-analysis.[20] In a large population-based registry in Norway and Sweden with 28,506 vaccinated singleton pregnancies and 129,015 nonvaccinated singleton pregnancies, the rate of stillbirths after vaccination was 2.1 per 100,000 pregnancy days, whereas the rate of stillbirths was 2.4 per 100,000 pregnancy days among those unvaccinated (adjusted hazard ratio [aHR]: 0.86, 95% CI 0.63 to 1.17).[42] Similarly, Hui and colleagues found lower odds of stillbirths among 17,365 mRNA-vaccinated singleton pregnancies compared with 15,171 unvaccinated singleton pregnancies in an Australian-based registry (aOR: 0.18, 95% CI 0.09–0.37).[43] The protective effect of vaccination is likely partially due to the prevention of severe COVID-19 illness, which is associated with stillbirth, but it is also possible that this result may in part be due to confounding. Vaccinated people in this study may have been healthier overall and seemed to have better access and adherence to prenatal care (with higher rates of receiving gestational diabetes screening) than unvaccinated people.[43]

Gestational Conditions

Development of conditions during pregnancy such as hypertensive disorders or gestational diabetes has significant implications for the health of both the mother and the fetus. Evidence from 4 retrospective cohort studies, 1 case-control study, and a meta-analysis suggests no increased risk of hypertensive disorders of pregnancy or gestational diabetes among those who received a COVID-19 vaccine during pregnancy compared with those who were unvaccinated.[19,28,44–47] Dick and colleagues reported on an Israeli cohort of 5618 pregnant participants, of which 2305 participants had received an mRNA COVID-19 vaccine in the second or third trimester.[44] Compared with unvaccinated participants, those vaccinated had no increased odds of a hypertensive disorder of pregnancy (aOR: 0.71, 95% CI 0.33–1.54 for second trimester vaccination; aOR: 0.83, 95% CI 0.45–1.55 for third trimester vaccination) or gestational diabetes (aOR: 1.21, 95% CI 0.93–1.58 for second trimester

vaccination; aOR: 0.99, 95% CI: 0.77–1.27 for third trimester vaccination).[44] Similarly, there were no increased odds of preeclampsia or eclampsia (aOR: 1.17, 95% CI 0.84–1.61) among a cohort of 913 pregnant people who received a BNT162b2 vaccine during pregnancy compared with 3486 unvaccinated pregnant people.[47]

In addition, no studies identified any increased risk of oligohydramnios,[28,47] polyhydramnios,[28,47] nonvertex presentation,[47] thromboembolism,[46] stroke,[46] or antepartum bleeding[48] among vaccinated compared with unvaccinated pregnant people.

Delivery Complications

COVID-19 vaccination during pregnancy has not been associated with increased risk of any adverse peripartum outcomes compared with unvaccinated pregnant people, including cesarean delivery (overall and emergency),[49] postpartum hemorrhage,[28,44,46,47,49–51] chorioamnionitis,[50,51] endometritis,[28,51] placental abruption,[28,47] nonreassuring fetal heart tones,[47] vacuum or forceps delivery,[28,47] low 5-min APGAR score (<7),[49] maternal ICU admission,[46,49,51] or meconium-stained amniotic fluid.[45,47] In a meta-analysis of 5 studies, receipt of any COVID-19 vaccine during pregnancy was not associated with either cesarean delivery (OR: 1.05, 95% CI 0.93–0.1.20) or postpartum hemorrhage (OR: 0.95, 95% CI 0.83–1.07).[20] Meta-analysis of 3 studies also showed no increased risk for chorioamnionitis among vaccinated pregnant people (OR: 1.06, 95% CI 0.86–1.31).[20] Two studies found a decreased odds of meconium-stained fluid among vaccinated people compared with unvaccinated people (aOR: 0.63, 95% CI: 0.49–0.83; aOR: 0.64, 95% CI: 0.43–0.96),[45,47] and one study identified decreased odds of nonreassuring fetal heart tones during delivery (aOR: 0.64, 95% CI 0.44, 0.90).[47]

Most of the studies that investigated peripartum outcomes included pregnant people vaccinated during any trimester during pregnancy. Dick and colleagues compared peripartum outcomes of people vaccinated in the second and third trimesters with unvaccinated pregnant people and found no significant differences in the odds of low APGAR score (<7) at 5 minutes, cesarean delivery, or postpartum hemorrhage by trimester of vaccination.[44] Similarly, Rottenstreich and colleagues investigated adverse peripartum outcomes in pregnant people vaccinated in the third trimester by creating a composite adverse maternal outcome variable, defined as experiencing at least one of the following: chorioamnionitis, postpartum hemorrhage, endometritis, blood transfusion, cesarean delivery, ICU admission, or extended length of stay (>5 days for vaginal delivery or >7 days for cesarean).[51] The investigators reported that receipt of COVID-19 vaccination at greater than 24 weeks gestation was not associated with the maternal composite adverse outcome (aOR: 0.8, 95% CI 0.61–1.03) compared with no receipt of the COVID-19 vaccine.[51]

Placental Histopathology

The effect of SARS-CoV-2 infection on placental histopathology is a topic of investigation[52]; it remains unknown whether the COVID-19 vaccine affects the placenta. Two studies were identified that compared placental histopathology of pregnant people who had been vaccinated with a COVID-19 vaccine and unvaccinated pregnant people in the United States.[53,54] In a cross-sectional study of 200 pregnant people, of which 84 people received a COVID-19 vaccine during pregnancy, there was no increased odds of decidual arteriopathy (aOR: 0.75, 95% CI 0.3–1.9), fetal vascular malperfusion (aOR: 0.85, 95% CI 0.27–2.7), or low-grade chronic villitis (aOR: 1.6, 95% CI 0.62–4.2).[53] There was decreased odds of high-grade chronic villitis (aOR: 0.31, 95% CI 0.1–0.97).[53] Similarly, Boelig and colleagues reported no significant differences in the odds of placental maternal vascular malperfusion (aOR: 0.61, 95% CI

0.22–1.68) comparing 49 vaccinated pregnant people with 198 unvaccinated pregnant people in a retrospective cohort study.[54] However, in this same study, those who were unvaccinated but had COVID-19 in pregnancy (n = 59) had significantly higher odds of placental maternal vascular malperfusion than those without COVID-19 (aOR: 2.34, 95% CI 1.16–4.73).[54] These results suggest that SARS-CoV-2 infection, but not COVID-19 vaccination, affects placental vascular pathology.

Preterm birth, small for gestational age, neonatal intensive care unit admission

Previous studies have suggested that SARS-CoV-2 infection during pregnancy significantly increases the risk of preterm birth (delivery <37 weeks gestation), small for gestational age (SGA) (<10% in birth weight for sex), and infant admission to the neonatal intensive care unit (NICU).[5,55] Although multiple studies have examined the risk of preterm birth, SGA, and NICU admission following receipt of COVID-19 vaccination in pregnancy, none have detected any increased risks.[19,20] Methodologically, investigation of preterm birth is challenging, as analytical techniques to adjust for time-varying exposure must be considered to minimize biased results.[35]

In a retrospective cohort study from the Vaccine Safety Datalink, risks for preterm birth and SGA at birth among 10,064 vaccinated and 36,015 unvaccinated pregnant people were compared, accounting for time-dependent vaccine exposures and propensity to be vaccinated based on maternal age, race and ethnicity, adequacy of prenatal care, comorbidities, neighborhood poverty rate, state-level percentage of positive COVID-19 test results, and site.[56] COVID-19 vaccination during pregnancy was not associated with either preterm birth (aHR: 0.91, 95% CI 0.82–1.01) or SGA (aHR: 0.95 95% CI 0.87–1.03). After stratifying by second and third trimester vaccination, results consistently showed no increased risk.[56] A large population-based retrospective study in Norway and Sweden that accounted for time-varying exposure also found no increased risk of preterm birth (aHR: 0.98, 95% CI 0.91–1.05) or increased odds of SGA (aOR: 0.97, 95% CI 0.90–1.04) or NICU admission (aOR: 0.97, 95% CI 0.86, 1.10).[42] Results for SGA and NICU admission were similar in a sensitivity analysis restricting the sample to only term births.[42] Furthermore, in a meta-analysis with 6 studies, receipt of a COVID-19 vaccine in pregnancy was associated with a 12% reduction in the odds of infant NICU admission (OR: 0.88, 95% CI 0.80–0.97).[20] This meta-analysis also pooled results of 7 studies that examined preterm birth and 6 studies that examined SGA; COVID-19 vaccination was not significantly associated with either preterm birth (OR: 0.89, 95% CI 0.76–1.04) or SGA (OR: 0.99, 95% CI 0.94–1.04).[20]

Some studies restricted analyses to investigate risk of preterm birth or SGA based on trimester of first vaccine receipt. First trimester vaccination exposure did not increase risk of preterm birth (RR: 0.87, 95% CI 0.67–1.12) or SGA (RR: 1.14, 95% CI 0.92–1.40) in a retrospective cohort study from Israel; no significant differences for early preterm or moderately preterm births were detected.[57] Similarly, Theiler and colleagues found no significant increase in the prevalence of preterm birth at less than 24 weeks, 24 to less than 32 weeks, and 32 to less than 37 weeks gestation.[46] Second or third trimester vaccination exposure was also not associated with increased odds of SGA at birth (aOR: 0.73, 95% CI 0.52–1.03 for second trimester; aOR: 0.85, 95% CI 0.64–1.13 for third trimester) in another retrospective cohort study from Israel.[44] However, second trimester vaccination was associated with increased odds of preterm birth (aOR: 1.49, 95% CI 1.11–2.01); though no preterm births occurred within 2 weeks after vaccination and most of these births were after 35 weeks gestation. In this same study, third trimester vaccination was associated with decreased odds of preterm birth (aOR: 0.49, 95% CI 0.34–0.71); the study investigators note that their results

may differ from other studies due to their inability to control for several risk factors for preterm birth.[44]

Infant Hospitalization and Infant Mortality

All-cause infant hospitalization and infant mortality are important outcomes to monitor in infants of people vaccinated during pregnancy. To date, there are limited studies available that have investigated these outcomes. In a population-based retrospective cohort study of 24,288 infants in Israel, risk of neonatal hospitalization was not significantly different among infants prenatally exposed to BNT162b2 in the first trimester (risk ratio [RR]: 0.86, 95% CI 0.67–1.09) or during any trimester in pregnancy (RR: 0.99, 95% CI 0.88–1.12) compared with unexposed infants.[57] In addition, compared with unexposed infants, there was no increased risk for postneonatal hospitalization for either prenatal exposure in the first trimester (RR: 0.95, 95% CI 0.84–1.07) or any trimester in pregnancy (RR: 0.78, 95% CI 0.54–1.09).[57] Infant mortality rates were low for both infants exposed prenatally to BNT162b2 and for infants unexposed prenatally (0.1% in both groups); no difference was observed in mortality for infants exposed in the first trimester to the vaccine compared with those who were not exposed to the vaccine (RR: 0.69, 95% CI 0.14–2.41).[57]

Perinatal mortality, which is inclusive of both stillbirths and neonatal deaths, was compared between pregnant people in Scotland who received any COVID-19 vaccine during pregnancy (regardless of infection status) and those who had SARS-CoV-2 infection during pregnancy (regardless of vaccination status).[58] Among those who received a COVID-19 vaccine during pregnancy, the perinatal mortality rate was 4.3 (95% CI 2.9–6.4) per 1000 births compared with 8.0 (95% CI 5.0–12.8) and 22.6 (95% CI 12.9–38.5) among those who had SARS-CoV-2 infection (regardless of vaccination status) during pregnancy or within 28 days of delivery, respectively; all perinatal deaths occurring after SARS-CoV-2 infection occurred in pregnant people who were unvaccinated.[58]

Congenital Anomalies

Few studies have investigated the risk of congenital anomalies among vaccinated pregnant people. Ruderman and colleagues retrospectively compared the odds of a fetal structural anomaly identified through ultrasonography for 1149 pregnant people vaccinated with either an mRNA vaccine or Ad26.COV2.S (Janssen) vaccine 30 days before conception through 14 weeks gestation with 2007 pregnant people who were either unvaccinated or received a COVID-19 vaccine after 14 weeks gestation; the first trimester (<14 weeks gestation) is a period of organogenesis when impacts of exposures on the development of structural birth defects would be more likely to occur.[59] COVID-19 vaccination ($\geq$1 dose of any COVID-19 vaccine) was not associated with the presence of a fetal structural defect identified on ultrasonography (aOR: 1.05; 95% CI 0.72–1.54).[59] Findings were similar even after narrowing the window of exposure to 2 to 10 weeks gestation (aOR: 0.96, 95% CI 0.63–1.45).[59] A limitation of this analysis is that birth defect surveillance typically relies on postnatal confirmation and collection of data through the first year of life rather than ultrasonography.[60] However, similar results were reported in 2 large population-based retrospective cohort studies that evaluated congenital anomalies postnatally among infants born to pregnant people who were vaccinated.[43,57] Data from a large population-based study conducted in Israel found no increased risk of overall congenital anomalies (adjusted risk ratio [aRR]: 0.69, 95% CI 0.44 to 1.04) and a decreased risk of a major congenital heart anomaly (aRR: 0.46, 95% CI 0.24–0.82) diagnosed in the first month of life among infants who were exposed to BNT162b2 in the first trimester (n = 2021) compared with those unexposed (n = 3580).[57] In an Australian registry of 17,365 singleton infants

exposed to mRNA vaccines prenatally, the odds of a congenital anomaly diagnosed at birth were lower compared with those not exposed to a vaccine prenatally (aOR: 0.72, 95% CI 0.56–0.94). However, after restricting the sample to those vaccinated less than 20 weeks gestation, the odds of a congenital anomaly were the same among pregnant people who did and did not receive a COVID-19 vaccine (aOR: 0.80, 95% CI 0.57–1.13).[43] Although reassuring that no increase in congenital anomalies has been detected in infants through 1 month of age, birth defect surveillance typically goes through 1 year of life, so additional follow-up will be needed to confirm these findings.

Safety Summary

COVID-19 vaccination during pregnancy does not seem to increase the risk for any adverse pregnancy, maternal, or neonatal outcomes. The reactogenicity profile of mRNA vaccines is similar among pregnant people and nonpregnant women of reproductive age, although there was a lower incidence of systemic effects following vaccination among pregnant people. Data from national registries and observational cohort studies suggest no increased risk of spontaneous abortion and a decreased risk of stillbirth following COVID-19 vaccination in pregnancy. Furthermore, evidence suggests no increased risk of congenital anomalies among those vaccinated in the first trimester compared with unvaccinated pregnant people. Risks of preterm birth, SGA, NICU admission, infant hospitalization, placental pathologic findings, and pregnancy and obstetric complications, including gestational diabetes, hypertensive disorders, and nonelective cesarean delivery, were similar between vaccinated and unvaccinated pregnant people. Risk of perinatal mortality was higher among people who had COVID-19 during pregnancy compared with those who were vaccinated and did not have COVID-19 during pregnancy. Overall, these results on maternal and neonatal outcomes were observed consistently across studies regardless of type of vaccine and timing of vaccine exposure. These postauthorization safety data on a variety of pregnancy, maternal, and neonatal outcomes support recommendations for COVID-19 vaccination during pregnancy and provide reassurance to pregnant people and their health care providers that COVID-19 vaccines are safe.

EFFECTIVENESS OF MATERNAL COVID-19 VACCINATION

Data regarding effectiveness of COVID-19 vaccines for the prevention of infection and disease among pregnant people and their infants are only available from observational studies conducted after vaccine introduction, and data remain limited. For vaccines currently authorized or approved in the United States, vaccine effectiveness (VE) data among pregnant people and infants are currently only available for the monovalent mRNA COVID-19 vaccines. Here, the authors review the evidence from studies assessing effectiveness of monovalent mRNA vaccines in pregnant people or infants younger than 6 months against laboratory-confirmed SARS-CoV-2 infection, symptomatic or medically attended COVID-19, COVID-19-associated hospitalization, and severe or critical COVID-19. Studies estimating the effect of COVID-19 vaccines on adverse pregnancy outcomes have done so primarily to assess vaccine safety and thus are covered in the safety section of this review. Studies assessing VE against death among pregnant people and young infants are not available due to the rarity of this outcome.

For Outcomes Occurring Among Pregnant People

Vaccine effectiveness for SARS-COV-2 infection

Two studies from Israel and one from Qatar conducted soon after COVID-19 vaccine rollout examined effectiveness of 2 doses of mRNA vaccines in pregnant people and

showed high VE against SARS-CoV-2 infection (Supplementary Table 2),[61–63] and these results were similar to those in the general populations of those countries.[64,65] Goldshtein and colleagues conducted an observational cohort study among pregnant people in Israel during the first 4 months of vaccine rollout (December 19, 2020 to April 11, 2021) and found effectiveness of 2 BNT162b2 doses for laboratory-confirmed infection was high at 28 days or more after dose 1 (ie, >7 days after dose 2): VE 78% (95% CI 57%–89%).[61] Another Israeli cohort study by Dagan and colleagues conducted among pregnant people during December 2020 to June 2021 also demonstrated high VE for 2 doses of BNT162b2 during days 7 to 56 after the second dose for laboratory-confirmed infection (VE 96% [95% CI 89%–100%]), symptomatic COVID-19 (VE 97% [95% CI 91%–100%]), and hospitalization (VE 89% [95% CI 43%–100%]).[62] These results were also similar to previously published estimates from the same investigators among the general Israeli population ages 16 years or older during a similar time frame (December 20, 2020 to February 1, 2021), in which VE for laboratory-confirmed infection was 92% (95% CI 88%–95%), symptomatic COVID-19 94% (95% CI 87%–98%), and hospitalization 87% (95% CI 55%–100%).[64]

A study by Butt and colleagues from Qatar, using data from December 30, 2020 to May 30, 2021 and conducted during circulation of the SARS-CoV-2 Alpha and Beta variants, also found that VE of 2 doses of mRNA vaccines (including both BNT162b2 and mRNA-1273) for infection in pregnant people was high at 14 or more days after the second dose.[63] Using data from the same study population of pregnant people, Butt and colleagues estimated that VE for infection was 87.6% (95% CI 44.1%–97.2%) using a cohort analysis and 86.8% (95% CI 47.5%–98.5%) using a test-negative, case-control analysis.[63] These results were also similar to results among the general population of Qatar in which VE for laboratory-confirmed infection with the Alpha variant was 89.5% (95% CI 85.9%–92.3%) and for Beta variant infection was 75.0% (95% CI 70.5%–78.9%) at 14 or more days after the second dose.[65]

Vaccine effectiveness for COVID-19–associated emergency department and urgent care visits and hospitalizations

Two studies, one from the United States and another from Israel, have assessed VE for medically attended COVID-19, including COVID-19–associated emergency department and urgent care visits and hospitalizations occurring among pregnant people.[66,67] Schrag and colleagues used a test-negative design in CDC's VISION Network to assess effectiveness of monovalent mRNA vaccines for prevention of emergency department and urgent care visits and COVID-19–associated hospitalization occurring during pregnancy.[66] VE was estimated among pregnant people who received at least one dose during pregnancy, pregnant people regardless of whether any doses were received during pregnancy (ie, doses could be received either before or during pregnancy), and for the same outcomes among nonpregnant women ages 18 to 45 years, allowing for comparison of VE estimates among these groups. VE was also stratified by total number of doses received, days since last dose, and by Delta and Omicron variant predominant periods (see Supplementary Table 2). Although power was more limited to assess VE among pregnant people than nonpregnant women, VE estimates were similar among pregnant people and nonpregnant women ages 18 to 45 years, and VE was similar among pregnant people when stratified by doses given during pregnancy versus doses given before or during pregnancy. Furthermore, VE was higher against hospitalization, a more severe outcome, than against emergency department and urgent care visits, a milder outcome. VE was lower during Omicron predominance compared with Delta predominance, and VE waned over time after 2 and 3 doses, particularly during Omicron predominance.[66]

The findings from Schrag and colleagues are similar to those from a publication by Guedalia and colleagues that assessed VE of BNT162b2 for prevention of hospitalization using a population-based cohort study including all pregnant people in Israel who delivered between August 1, 2021 and March 22, 2022.[67] VE was assessed for (1) any hospitalization with a positive SARS-CoV-2 test among pregnant people, which the investigators noted likely reflected VE for infection, as testing was near universal among hospitalized pregnant people; (2) hospitalization with significant disease, defined as having COVID-19 pneumonia; and (3) hospitalization with severe or critical disease, defined as resting respiratory rate greater than 30 breaths per minute, oxygen saturation on room air less than 94%, Pa_{O_2} to Fi_{O_2} ratio of less than 300, mechanical ventilation, clinically severe organ failure, or death. VE was assessed among pregnant people who had received a booster (third) dose and among pregnant people who were eligible for but had yet not received a booster dose (ie, $\geq$150 days after the second dose). They found that among pregnant people in Israel, during Delta variant predominance, VE for any hospitalization (likely reflecting VE for infection) was moderate at 61% (95% CI 51%–69%) at 150 days or more after the second dose, but VE for hospitalization with significant disease and severe disease was high at 150 days or more after the second dose (significant disease VE: 97% [95% CI 92%–99%], severe disease VE: 96% [95% CI 86–99]) and after a booster dose (significant disease VE: 99% [95% CI 93%–100%], severe disease VE: 99% [95% CI 89%–100%], see Supplementary Table 2). However, during Omicron, VE was not significantly different from zero for any of the outcomes at 150 days or more after the second dose. During Omicron, a booster dose increased VE against any hospitalization (likely reflecting VE for infection) to 43% (95% CI 31%–53%) and against significant and severe disease to 97% (95% CI 72%–100%) and 94% (95% CI 43%–99%), respectively. An important caveat to interpreting these results is that VE of 2 doses was measured at 150 days or more after the second dose and thus is reflective of waning, whereas the timing of assessment of VE after the booster dose was not specified but likely reflects a period soon after the booster dose.[67]

Impact of Pregnancy on Vaccine Effectiveness

To address the question of whether pregnancy affected response to vaccine, one study in Norway by Magnus and colleagues examined the relative effectiveness of monovalent mRNA vaccines for prevention of infection, comparing vaccinated pregnant people with vaccinated nonpregnant women who had been pregnant in the year prior but did not receive their COVID-19 vaccines while pregnant or during the postpartum period.[68] They found no differences in the relative effectiveness of the primary series or booster doses between pregnant and nonpregnant people (Supplementary Table 3). During the Omicron predominant period, aHR were 1.03 (95% CI 0.94–1.12) for the comparison of relative effectiveness in pregnant people who received 2 primary series doses during pregnancy compared with nonpregnant women and 1.24 (95% CI 0.84–1.84) for booster dose receipt during pregnancy compared with nonpregnant people.[68]

For Outcomes Occurring Among Infants After Birth

Three studies with four publications have assessed effectiveness of a maternal COVID-19 vaccination for outcomes occurring among infants after birth.[69–72] Two published analyses from CDC's Overcoming COVID-19 network, both by Halasa and colleagues, assessed effectiveness of a maternal monovalent mRNA primary series given during pregnancy for prevention of COVID-19–associated hospitalization among infants younger than 6 months. The first analysis used data from infants hospitalized during July 2021 to January 2022.[69] In the updated analysis, infants younger

than 6 months were enrolled from 30 pediatric medical centers in 22 US states from July 2021 to March 2022, a period spanning both Delta and Omicron predominance.[70] As the updated analysis included all data presented in the first analysis, the authors only included results from the updated analysis using data through March 2022. Results from the updated analysis showed that maternal receipt of COVID-19 primary series during pregnancy protected infants younger than 6 months from hospitalization for COVID-19 with an overall VE of 52% (95% CI 33%–65%) for hospitalization and 70% (95% CI 42%–85%) for admission to the ICU (Supplementary Table 4). Among infants, VE for hospitalization was also lower during Omicron predominance (VE 38% [95% CI 8%–58%]) than during Delta (VE 80% [95% CI 60%–90%]). When VE was stratified by timing of vaccination during pregnancy, VE estimates for hospitalization during Delta were not significantly different: 68% (95% CI 19%–87%) for vaccination during the first 20 weeks of pregnancy versus 88% (95% CI 68%–96%) for vaccination after 20 weeks. However, during Omicron predominance, vaccination in the first 20 weeks did not show effectiveness in prevention of hospitalization among infants: (VE 25% [95% CI -26%–56%]), whereas vaccination after 20 weeks was protective (VE 57% [95% CI 25%–75%]).[70]

Two studies assessed maternal vaccination for prevention of SARS-CoV-2 infection in infants after birth (see Supplementary Table 4).[71,72] Carlsen and colleagues used a cohort study including all liveborn infants in Norway from September 1, 2021 to February 28, 2022 to assess effectiveness of maternal COVID-19 vaccination (BNT162b2, mRNA-1273, and ChAdOx1 nCoV-19 [AstraZeneca]) given during the second or third trimesters of pregnancy in prevention of SARS-CoV-2 infection in infants from birth through 3 months of age.[71] This study showed that maternal vaccination with 2 doses (with at least the second dose given during the second or third trimester) provided protection against SARS-CoV-2 infection in infants age up through 3 months, and VE was higher during Delta predominance (VE 71%, [95% CI 56%–81%]) than during Omicron predominance (VE 30% [95% CI 17%–41%]). During Omicron predominance, receipt of a third (booster) dose during the second or third trimester increased VE to 78% (95% CI 57%–88%), but VE estimates were not stratified by time since last dose. Thus, the VE for a third dose may have reflected a shorter time frame after the dose than the VE of a second dose.[71] A publication by Zerbo and colleagues used a cohort design to assess effectiveness of 2 or more doses of monovalent mRNA vaccines for prevention of SARS-CoV-2 infection among infants in northern California younger than 2 months, younger than 4 months, and younger than 6 months during Delta and Omicron periods.[72] During Delta predominance (July 1, 2021 to December 20, 2021), VE for infection among infants was 84% (95% CI 66%–93%) at age less than 2 months, 62% (95% CI 39%–77%) at age less than 4 months, and 56% (95% CI 34%–71%) at age less than 6 months. When stratified by trimester of receipt of the second dose, VE was significant when the second dose was given in the second or third trimester but not during the first trimester. However, during Omicron predominance (December 21, 2021 to May 31, 2022), maternal vaccination was not protective against infection (ie, all VE estimates were not significantly different from zero), including among infants younger than 2 months, younger than 4 months, or younger than 6 months of birth or when stratified by trimester of second dose receipt.[72]

Vaccine Effectiveness Summary

Taken together, results of these studies indicate that effectiveness of mRNA COVID-19 vaccines for prevention of infection and hospitalizations are similar in pregnant people and nonpregnant women of similar age. For these outcomes, time since the last vaccine dose likely affects VE more than whether the vaccine was received during

pregnancy. In addition, maternal COVID-19 vaccination during pregnancy protected infants younger than 6 months from infection and hospitalization for COVID-19. The effectiveness of maternal monovalent mRNA COVID-19 vaccines is lower for infections and hospitalizations in both pregnant people and infants during predominance of the Omicron variant than during predominance of prior SARS-CoV-2 variants. The lower VE seen during Omicron predominant time periods is likely due to a combination of factors, including changes in the Omicron spike protein that allowed for immune escape from antibody made against the ancestral strain in the vaccine and a higher prevalence of infection-induced immunity in the population overall during Omicron predominance,[73] which reduces the ability to measure VE. Data on vaccine effectiveness of bivalent boosters among pregnant people and infants are lacking at this time but are needed to inform COVID-19 vaccine policy recommendations. Data are also needed regarding the effectiveness among infants by timing of maternal vaccination, including for doses given before and during pregnancy.

SUMMARY

In conclusion, pregnant people are at increased risk of severe disease and adverse pregnancy outcomes from COVID-19, but initial COVID-19 vaccine clinical trials excluded pregnant people. Postauthorization studies have been important to fill evidence gaps regarding COVID-19 vaccine safety and effectiveness in pregnant people and infants, and lessons learned from the COVID-19 pandemic include the importance of including pregnant people in clinical trials when possible. Evidence has consistently demonstrated that COVID-19 mRNA vaccines are safe when given during pregnancy for both pregnant people and infants, and COVID-19 mRNA vaccines protect pregnant people and their infants who are too young to receive COVID-19 vaccines. Monovalent vaccine effectiveness was lower during Omicron predominance, and bivalent vaccines may improve protection against Omicron variants. Everyone, including people who are pregnant, breastfeeding, trying to get pregnant now, or might become pregnant in the future, should stay up to date with recommended COVID-19 vaccines and get the recommended bivalent booster, when eligible.

CLINICS CARE POINTS

- Everyone, including pregnant people, should stay up to date with recommended COVID-19 vaccines and get the recommended bivalent booster, when eligible.

DISCLAIMER

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention. Mention of a product or company name is for identification purposes only and does not constitute endorsement by CDC.

DISCLOSURES

None of the authors have conflicts of interest.

FUNDING

This work was funded by the Centers for Disease Control and Prevention.

ACKNOWLEDGMENTS

The authors acknowledge that not every person who can become pregnant identifies as a woman. Although we try to use gender-neutral language as often as possible, much of the research available currently refers only to "women" when discussing the ability to become pregnant. When citing research, we refer to the language used in the study. In these cases, "woman" refers to someone who was assigned female at birth. For clarity in terminology, "maternal' is used to identify the person who is pregnant or postpartum throughout this article; the authors are aware that pregnancy is not equated with the decision to parent nor do all parents who give birth identify as mothers.

SUPPLEMENTARY DATA

Supplementary data related to this article can be found online at https://doi.org/10.1016/j.ogc.2023.02.003.

REFERENCES

1. Omer SB. Maternal Immunization. N Engl J Med 2017;376(13):1256–67.
2. Grohskopf LA, Blanton LH, Ferdinands JM, et al. Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices - United States, 2022-23 Influenza Season. MMWR Recomm Rep (Morb Mortal Wkly Rep) 2022;71(1):1–28.
3. Centers for Disease Control and Prevention. Use of COVID-19 Vaccines in the United States: Interim Clinical Considerations. 2022. Available at: https://www.cdc.gov/vaccines/covid-19/clinical-considerations/covid-19-vaccines-us.html#:~:text=The%20CDC%20Interim%20Clinical%20Considerations%20are%20informed%20by,currently%20approved%20or%20authorized%20in%20the%20United%20States. Accessed October 19, 2022.
4. Liang JL, Tiwari T, Moro P, et al. Prevention of Pertussis, Tetanus, and Diphtheria with Vaccines in the United States: Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep (Morb Mortal Wkly Rep) 2018;67(2):1–44.
5. Allotey J, Stallings E, Bonet M, et al. Clinical manifestations, risk factors, and maternal and perinatal outcomes of coronavirus disease 2019 in pregnancy: living systematic review and meta-analysis. BMJ 2020;370:m3320. https://doi.org/10.1136/bmj.m3320.
6. Dooling K, Marin M, Wallace M, et al. The Advisory Committee on Immunization Practices' Updated Interim Recommendation for Allocation of COVID-19 Vaccine - United States, December 2020. MMWR Morb Mortal Wkly Rep 2021;69(5152):1657–60.
7. Dunkle LM, Kotloff KL, Gay CL, et al. Efficacy and Safety of NVX-CoV2373 in Adults in the United States and Mexico. N Engl J Med 2021;386(6):531–43.
8. El Sahly HM, Baden LR, Essink B, et al. Efficacy of the mRNA-1273 SARS-CoV-2 Vaccine at Completion of Blinded Phase. N Engl J Med 2021. https://doi.org/10.1056/NEJMoa2113017.
9. Polack FP, Thomas SJ, Kitchin N, et al. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. N Engl J Med 2020;383(27):2603–15.
10. Sadoff J, Gray G, Vandebosch A, et al. Safety and Efficacy of Single-Dose Ad26.COV2.S Vaccine against Covid-19. N Engl J Med 2021;384(23):2187–201.

11. Centers for Disease Control and Prevention. New CDC Data: COVID-19 Vaccination Safe for Pregnant People. Available at: https://www.cdc.gov/media/releases/2021/s0811-vaccine-safe-pregnant.html. Accessed October 26, 2022.
12. Atyeo CG, Shook LL, Brigida S, et al. Maternal immune response and placental antibody transfer after COVID-19 vaccination across trimester and platforms. Nat Commun 2022/06/28 2022;13(1):3571.
13. Prahl M, Golan Y, Cassidy AG, et al. Evaluation of transplacental transfer of mRNA vaccine products and functional antibodies during pregnancy and infancy. Nat Commun 2022/07/30 2022;13(1):4422.
14. 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(11):429–36.
15. Hamid S, Woodworth K, Pham H, et al. COVID-19-Associated Hospitalizations Among U.S. Infants Aged <6 Months - COVID-NET, 13 States, June 2021-August 2022. MMWR Morb Mortal Wkly Rep 2022;71(45):1442–8.
16. Delahoy MJ, Ujamaa D, Taylor CA, et al. Comparison of influenza and COVID-19-associated hospitalizations among children < 18 years old in the United States-FluSurv-NET (October-April 2017-2021) and COVID-NET (October 2020-September 2021). Clin Infect Dis 2022. https://doi.org/10.1093/cid/ciac388.
17. Chaves SS, Perez A, Farley MM, et al. The burden of influenza hospitalizations in infants from 2003 to 2012, United States. *Pediatr Infect Dis J*. Sep 2014;33(9):912–9.
18. Badell ML, Dude CM, Rasmussen SA, et al. Covid-19 vaccination in pregnancy. BMJ 2022;378:e069741.
19. Prasad S, Kalafat E, Blakeway H, et al. Systematic review and meta-analysis of the effectiveness and perinatal outcomes of COVID-19 vaccination in pregnancy. Nat Commun 2022;13(1):2414.
20. Watanabe A, Yasuhara J, Iwagami M, et al. Peripartum Outcomes Associated With COVID-19 Vaccination During Pregnancy: A Systematic Review and Meta-analysis. JAMA Pediatr 2022.
21. Rosenblum HG, Wallace M, Godfrey M, et al. Interim Recommendations from the Advisory Committee on Immunization Practices for the Use of Bivalent Booster Doses of COVID-19 Vaccines - United States, October 2022. MMWR Morb Mortal Wkly Rep 2022;71(45):1436–41.
22. Centers for Disease Control and Prevention. COVID-19 Vaccination Coverage and Vaccine Confidence Among Adults: COVIDVaxView. Available at: https://www.cdc.gov/vaccines/imz-managers/coverage/covidvaxview/interactive/adults.html. Accessed November 14, 2022.
23. Rasmussen SA, Kelley CF, Horton JP, et al. Coronavirus Disease 2019 (COVID-19) Vaccines and Pregnancy: What Obstetricians Need to Know. Obstet Gynecol 2021;137(3):408–14.
24. Food and Drug Administration VaRBPAC. FDA briefing document: Moderna COVID-19 Vaccine; Vaccines and related biological products Advisory committee meeting December. 2020. https://www.fda.gov/media/144434/download.
25. Food and Drug Administration VaRBPAC, FDA briefing document: Pfizer-BioNTech COVID-19 Vaccine: Vaccines and Related Biological Products Advisory Committee meeting December 10, 2020, Available at: https://www.fda.gov/media/144245/download, 2020. Accessed November 15, 2022.
26. 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(24):2273–82.

27. Favre G, Maisonneuve E, Pomar L, et al. COVID-19 mRNA vaccine in pregnancy: Results of the Swiss COVI-PREG registry, an observational prospective cohort study. Lancet Reg Health Eur. Jul 2022;18:100410.
28. Bookstein Peretz S, Regev N, Novick L, et al. Short-term outcome of pregnant women vaccinated with BNT162b2 mRNA COVID-19 vaccine. Ultrasound Obstet Gynecol 2021;58(3):450–6.
29. Sadarangani M, Soe P, Shulha HP, et al. Safety of COVID-19 vaccines in pregnancy: a Canadian National Vaccine Safety (CANVAS) network cohort study. Lancet Infect Dis. Aug 2022;11:11. https://doi.org/10.1016/S1473-3099(22)00426-1.
30. DeSilva M, Haapala J, Vazquez-Benitez G, et al. Evaluation of Acute Adverse Events after Covid-19 Vaccination during Pregnancy. N Engl J Med 2022; 387(2):187–9.
31. Moro PL, Olson CK, Clark E, et al. Post-authorization surveillance of adverse events following COVID-19 vaccines in pregnant persons in the vaccine adverse event reporting system (VAERS), 2020 - 2021. Vaccine 2022;40(24):3389–94.
32. Moro PL, Olson CK, Zhang B, et al. Safety of Booster Doses of Coronavirus Disease 2019 (COVID-19) Vaccine in Pregnancy in the Vaccine Adverse Event Reporting System. Obstet Gynecol 2022;140(3):421–7.
33. Mukherjee S, Velez Edwards DR, Baird DD, et al. Risk of miscarriage among black women and white women in a U.S. Prospective Cohort Study. Am J Epidemiol 2013;177(11):1271–8.
34. Goldhaber MK, Fireman BH. The fetal life table revisited: spontaneous abortion rates in three Kaiser Permanente cohorts. Epidemiology 1991;2(1):33–9.
35. Xu R, Luo Y, Chambers C. Assessing the effect of vaccine on spontaneous abortion using time-dependent covariates Cox models. Pharmacoepidemiol Drug Saf 2012;21(8):844–50.
36. 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(16):1533–5.
37. Citu IM, Citu C, Gorun F, et al. The Risk of Spontaneous Abortion Does Not Increase Following First Trimester mRNA COVID-19 Vaccination. J Clin Med 2022;11(6):18.
38. Kharbanda EO, Haapala J, DeSilva M, et al. Spontaneous Abortion Following COVID-19 Vaccination During Pregnancy. JAMA 2021;326(16):1629–31.
39. Magnus MC, Gjessing HK, Eide HN, et al. Covid-19 Vaccination during Pregnancy and First-Trimester Miscarriage. N Engl J Med 2021;385(21):2008–10.
40. Gregory ECW VC, Hoyert DL. Fetal mortality: United States, 2020. Natl Vital Stat Rep 2022;71.
41. 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(47):1640–5.
42. Magnus MC, Ortqvist AK, Dahlqwist E, et al. Association of SARS-CoV-2 Vaccination During Pregnancy With Pregnancy Outcomes. JAMA 2022;327(15):1469–77.
43. Hui L, Marzan MB, Rolnik DL, et al. Reductions in stillbirths and preterm birth in COVID-19 vaccinated women: a multi-center cohort study of vaccination uptake and perinatal outcomes. Am J Obstet Gynecol 2022. https://doi.org/10.1016/j.ajog.2022.10.040.
44. Dick A, Rosenbloom JI, Gutman-Ido E, et al. Safety of SARS-CoV-2 vaccination during pregnancy- obstetric outcomes from a large cohort study. BMC Pregnancy Childbirth 2022;22(1):166.

45. Peretz-Machluf R, Hirsh-Yechezkel G, Zaslavsky-Paltiel I, et al. Obstetric and Neonatal Outcomes following COVID-19 Vaccination in Pregnancy. J Clin Med 2022;11(9):30.
46. Theiler RN, Wick M, Mehta R, et al. Pregnancy and birth outcomes after SARS-CoV-2 vaccination in pregnancy. Am J Obstet Gynecol MFM 2021;3(6):100467.
47. Wainstock T, Yoles I, Sergienko R, et al. Prenatal maternal COVID-19 vaccination and pregnancy outcomes. Vaccine 2021;39(41):6037–40.
48. Bleicher I, Kadour-Peero E, Sagi-Dain L, et al. Early exploration of COVID-19 vaccination safety and effectiveness during pregnancy: interim descriptive data from a prospective observational study. Vaccine 2021;39(44):6535–8.
49. Blakeway H, Prasad S, Kalafat E, et al. COVID-19 vaccination during pregnancy: coverage and safety. Am J Obstet Gynecol 2022;226(2):236 e1–e236 e14.
50. Fell DB, Dhinsa T, Alton GD, et al. Association of COVID-19 Vaccination in Pregnancy With Adverse Peripartum Outcomes. JAMA 2022;327(15):1478–87.
51. Rottenstreich M, Sela HY, Rotem R, et al. Covid-19 vaccination during the third trimester of pregnancy: rate of vaccination and maternal and neonatal outcomes, a multicentre retrospective cohort study. BJOG 2022;129(2):248–55.
52. Di Girolamo R, Khalil A, Alameddine S, et al. Placental histopathology after SARS-CoV-2 infection in pregnancy: a systematic review and meta-analysis. Am J Obstet Gynecol MFM 2021;3(6):100468.
53. Shanes ED, Otero S, Mithal LB, et al. Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Vaccination in Pregnancy: Measures of Immunity and Placental Histopathology. Obstet Gynecol 2021;138(2):281–3.
54. Boelig RC, Aghai ZH, Chaudhury S, et al. Impact of COVID-19 disease and COVID-19 vaccination on maternal or fetal inflammatory response, placental pathology, and perinatal outcomes. Am J Obstet Gynecol 2022;227(4):652–6.
55. Neelam V, Reeves EL, Woodworth KR, et al. Pregnancy and infant outcomes by trimester of SARS-CoV-2 infection in pregnancy–SET-NET, 22 jurisdictions. Birth Defects Research 2020. https://doi.org/10.1002/bdr2.2081.
56. 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 7 2022;71(1):26–30.
57. Goldshtein I, Steinberg DM, Kuint J, et al. Association of BNT162b2 COVID-19 Vaccination During Pregnancy With Neonatal and Early Infant Outcomes. JAMA Pediatr 2022;176(5):470–7.
58. Stock SJ, Carruthers J, Calvert C, et al. SARS-CoV-2 infection and COVID-19 vaccination rates in pregnant women in Scotland. Nat Med 2022;28(3):504–12.
59. Ruderman RS, Mormol J, Trawick E, et al. Association of COVID-19 Vaccination During Early Pregnancy With Risk of Congenital Fetal Anomalies. JAMA Pediatr 2022;176(7):717–9.
60. Mai CT, Isenburg JL, Canfield MA, et al. National population-based estimates for major birth defects, 2010–2014. Birth Defects Research 2019;111(18):1420–35.
61. Goldshtein I, Nevo D, Steinberg DM, et al. Association Between BNT162b2 Vaccination and Incidence of SARS-CoV-2 Infection in Pregnant Women. JAMA 2021;326(8):728–35.
62. Dagan N, Barda N, Biron-Shental T, et al. Effectiveness of the BNT162b2 mRNA COVID-19 vaccine in pregnancy. Nat Med 2021/10/01 2021;27(10):1693–5.
63. Butt AA, Chemaitelly H, Al Khal A, et al. SARS-CoV-2 vaccine effectiveness in preventing confirmed infection in pregnant women. J Clin Investig 2021;131(23).

64. Dagan N, Barda N, Kepten E, et al. BNT162b2 mRNA Covid-19 Vaccine in a Nationwide Mass Vaccination Setting. N Engl J Med 2021;384(15):1412–23.
65. Abu-Raddad LJ, Chemaitelly H, Butt AA. Effectiveness of the BNT162b2 Covid-19 Vaccine against the B.1.1.7 and B.1.351 Variants. N Engl J Med 2021; 385(2):187–9.
66. Schrag SJ, Verani JR, Dixon BE, et al. Estimation of COVID-19 mRNA Vaccine Effectiveness Against Medically Attended COVID-19 in Pregnancy During Periods of Delta and Omicron Variant Predominance in the United States. JAMA Netw Open 2022;5(9):e2233273.
67. Guedalia J, Lipschuetz M, Calderon-Margalit R, et al. Effectiveness of a third BNT162b2 mRNA COVID-19 vaccination during pregnancy: a national observational study in Israel. Nat Commun 2022;13:6961. https://doi.org/10.1038/s41467-022-34605-x.
68. Magnus MC, Håberg SE, Carlsen EØ, et al. Pregnancy status at the time of COVID-19 vaccination and incidence of SARS-CoV-2 infection. Clin Infect Dis 2022. https://doi.org/10.1093/cid/ciac739.
69. 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(7):264–70.
70. Halasa NB, Olson SM, Staat MA, et al. Maternal Vaccination and Risk of Hospitalization for Covid-19 among Infants. N Engl J Med 2022;387(2):109–19.
71. Carlsen EO, 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;182(8):825–31.
72. Zerbo O, Ray GT, Fireman B, et al. Maternal SARS-CoV-2 Vaccination and Infant Protection Against SARS-CoV-2 During the First Six Months of Life. Nat Commun 2023;14(894). https://doi.org/10.1038/s41467-023-36547-4.
73. Clarke KEN, Jones JM, Deng Y, et al. Seroprevalence of Infection-Induced SARS-CoV-2 Antibodies - United States, September 2021-February 2022. MMWR Morb Mortal Wkly Rep 2022;71(17):606–8.