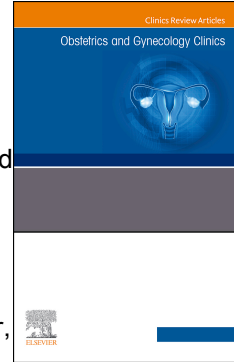


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## Safety and effectiveness of maternal COVID-19 vaccines among pregnant people and infants

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**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.

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**Key words:** COVID-19 vaccine, pregnancy, infants, mRNA vaccines, vaccine effectiveness, vaccine safety, maternal vaccination

### Key points:

- 1) Available evidence demonstrates that COVID-19 vaccination during pregnancy is safe and is not associated with adverse pregnancy or infant outcomes.
- 2) Reactogenicity to COVID-19 vaccines is similar for pregnant people and non-pregnant women of reproductive age for both doses in the primary mRNA vaccine series.
- 3) Effectiveness of mRNA COVID-19 vaccines is similar in pregnant people and non-pregnant women of similar age for prevention of SARS-CoV-2 infection and hospitalizations.
- 4) Maternal COVID-19 vaccination during pregnancy reduces the risk of SARS-CoV-2 infection and COVID-19-associated hospitalization in infants age <6 months.
- 5) 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.
- 6) Everyone, including pregnant people, should stay up to date with recommended COVID-19 vaccines and get the recommended bivalent booster, when eligible.

**Synopsis:**

Evidence has consistently demonstrated that COVID-19 mRNA vaccines are safe when given during pregnancy. COVID-19 mRNA vaccines protect pregnant people and their infants who are too young to receive COVID-19 vaccines. While generally protective, monovalent vaccine effectiveness was lower during SARS-CoV-2 Omicron variant predominance, in part due to changes in the Omicron spike protein. Bivalent vaccines, that combine ancestral strain and Omicron variant, may improve protection against Omicron variants. Everyone, including pregnant people, should stay up to date with recommended COVID-19 vaccines and bivalent booster, when eligible.

**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.<sup>1</sup> Influenza, pertussis, and COVID-19 vaccines are all recommended for pregnant persons.<sup>2-4</sup> Influenza vaccine is recommended for everyone age  $\geq 6$  months, including pregnant people, every influenza season, and maternal influenza vaccination provides protection for the mother during pregnancy and the infant after birth.<sup>2</sup> 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.<sup>4</sup> COVID-19 can cause severe disease in pregnant people. Compared to non-pregnant 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 (ECMO) support.<sup>5</sup> 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.<sup>5</sup> 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;<sup>6</sup> however they were not included in initial clinical trials.<sup>7-10</sup> 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.<sup>11</sup>

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.<sup>12,13</sup> 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.<sup>13</sup> Moreover, infants less than 6 months of age are the only population in the United States not currently eligible for COVID-19 vaccination. Infants may be hospitalized and may become critically ill.<sup>14,15</sup> Among infants less than 6 months of age, COVID-19 causes a similar to higher burden of hospitalizations than influenza,<sup>16</sup> which has long been recognized as a cause of severe respiratory disease in this population.<sup>17</sup>

Because pregnant people were excluded from the COVID-19 vaccine clinical trials, post-authorization studies and surveillance have been important to inform vaccine safety and effectiveness among pregnant people. Several reviews, including three recent reports (of which two were meta-analyses), have covered COVID-19 vaccine safety and effectiveness in pregnancy,<sup>18-20</sup> 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.<sup>3</sup> As of October 12, 2022, people ages 5 years and older are recommended to receive one updated (bivalent) Pfizer-BioNTech or Moderna mRNA booster.<sup>3</sup> Bivalent mRNA boosters contain mRNA encoding both the spike protein from the Omicron (BA.4/BA.5) SARS-CoV-2 variants and from 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.<sup>21</sup> CDC's guidance on staying up to date with COVID-19 vaccines and co-administration with non-COVID-19 vaccines applies to everyone, including pregnant people.<sup>3</sup> 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 are used for the prevention of monkeypox and smallpox); this guidance is available on CDC's website.<sup>3</sup>

Data collected from CDC's National Immunization Survey-Adult COVID-19 Module during August 28-September 30, 2022, indicated that 25.6% (95% confidence interval [CI] 16.6 to 34.5%) of pregnant people had not yet received any COVID-19 vaccine, 72.0% (95% CI 62.9 to 81.1%) had completed a

primary series, and 4.3% (95% CI 0.0 to 8.7%) were up to date with a primary series or bivalent booster, when indicated.<sup>22</sup> In comparison, 16.0% (95% CI 14.6 to 17.3%) of women ages 18-49 years who were not pregnant, trying to become pregnant, or breastfeeding remained unvaccinated, 81.6% (95% CI 80.2 to 83.1%) had completed a primary series, and 3.6% (95% CI 2.9 to 4.3%) were up to date with a primary series or bivalent booster, when indicated.<sup>22</sup> 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 wellbeing of vaccine recipients and trust in regulatory and public health agencies. All vaccines undergo rigorous testing through several phases of clinical trials prior to authorization or approval for use in the general population. However, since 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 pre-authorization vaccine trials.<sup>23</sup> Animal studies did not identify any safety concerns for female fertility or embryonal or fetal development.<sup>24,25</sup> 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.<sup>24,25</sup> Because mRNA vaccines have been the most widely used, most safety data to date in pregnant people come from post-authorization 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<sup>SM</sup> is a smart-phone based active surveillance system developed by CDC to monitor for adverse events and reactogenicity following COVID-19 vaccination.<sup>26</sup> 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 non-male participants. Preliminary findings from 16,982 v-safe participants who identified as pregnant and completed a survey about reactions on post-vaccination 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 to dose 1.<sup>26</sup> The symptoms most commonly reported the day after vaccination included injection-site pain (88.1% post-dose 1, 91.9% post-dose 2), fatigue (29.6% post-dose 1, 71.5% post-dose 2), headache (18.1% post-dose 1, 55.4% post-dose 2), myalgia (11.6% post-dose 1, 54.1% post-dose 2), chills (4.1% post-dose 1, 36.7% post-dose 2), and fever (4.2% post-dose 1, 34.6% post-dose 2). The prevalence of these symptoms and higher reactogenicity after dose 2 were similar to those of non-pregnant women of reproductive age. Systemic reactions were reported more frequently among non-pregnant women of reproductive age except for nausea and vomiting, which was reported more frequently in pregnant people.<sup>26</sup>

Results from other surveillance systems have observed similar reactogenicity profiles for the monovalent mRNA COVID-19 vaccines. In a prospective cohort study of 1,012 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 to BNT162b2.<sup>27</sup> Results from a case-control study of 390 pregnant people and 260 non-pregnant women who all received BNT162b2 in Israel demonstrated that myalgia, arthralgia, and headache occurred more frequently among the non-pregnant control group, but paresthesia (tingling sensation) was more common among pregnant people compared to non-pregnant people post-dose 2 (4.6% vs 1.2%,  $p < 0.001$ ).<sup>28</sup> Incidence of uterine contractions (1.3% for dose 1, 6.4% for dose 2) and vaginal bleeding (0.3% post-dose 1, 1.5% post-dose 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.<sup>28</sup> However, this study did not include unvaccinated pregnant people and could not compare to the baseline risk of these events.<sup>28</sup>

Severe adverse events following vaccination in pregnant people are much less common compared to local and systemic reactions. In a report from the Canadian National Vaccine Safety Network, 226 (4.0%) of 5,597 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.<sup>29</sup> After dose 2, 7.3% reported a significant health event. The most common significant health events were malaise, myalgia, and headache.<sup>29</sup> Fewer than 1% of participants experienced a serious health event, defined as an event resulting in an emergency department or hospital visit.<sup>29</sup> These findings were consistent with electronic health data from the Vaccine Safety Datalink, a collaborative project between CDC and nine integrated



healthcare organizations in the United States to monitor vaccine safety.<sup>30</sup> 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 to non-vaccinated pregnant people.

During December 14, 2020 and October 31, 2021, a total of 3,462 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.<sup>31</sup> 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.<sup>31</sup> 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).<sup>32</sup> Review of VAERS reports did not identify any unexpected reporting of any adverse events compared to other vaccines in VAERS for either the COVID-19 vaccine primary series or the booster dose.<sup>31,32</sup>

### Spontaneous Abortion

Spontaneous abortion (SAB), i.e., pregnancy loss prior to 20 weeks' gestation, is a common pregnancy outcome, affecting 11-22% of all recognized pregnancies.<sup>33,34</sup> 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.<sup>35</sup> To date, no surveillance systems or studies have identified any association between SAB and COVID-19 vaccination.<sup>19,29,36-39</sup>

Participants in CDC's v-safe after vaccination health checker<sup>SM</sup> 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 <20 weeks gestation among a cohort of 2,456 pregnant people who received at least one dose of an mRNA COVID-19 vaccine 30 days prior to their last menstrual period through 19 weeks 6 days gestation.<sup>36</sup> 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.<sup>33,34,36</sup> However, this analysis was limited by several factors, including no control group and a sample that consisted of mostly non-Hispanic White healthcare personnel.

A meta-analysis by Prasad et al.<sup>19</sup> that pooled results from two comparative studies with time-varying exposures<sup>38,39</sup> found no association between COVID-19 vaccine and SAB (odds ratio [OR]: 1.00, 95% CI 0.92-1.09). In another retrospective cohort study, the rate of first trimester SAB among 927 vaccinated pregnant people in Romania was 13.4%.<sup>37</sup> There were no increased odds of first trimester SAB for those who received BNT162b2 (adjusted odds ratio [aOR]: 1.04, 95% CI 0.91-1.12) or mRNA-1273 (aOR: 1.02, 95% CI 0.89-1.08) compared to those not vaccinated.<sup>37</sup> 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 1,000 births in the United States.<sup>40</sup> Recent reports have demonstrated that SARS-CoV-2 infection during pregnancy is associated with an almost two-fold increased risk of stillbirth.<sup>5,41</sup> 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 seven 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).<sup>19</sup> These results were similar to those of another meta-analysis that included five studies (three of which were included in Prasad et al) 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.<sup>20</sup> In a large population-based registry in Norway and Sweden with 28,506 vaccinated singleton pregnancies and 129,015 non-vaccinated 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 0.63-1.17).<sup>42</sup> Similarly, Hui et al. found lower odds of stillbirths among 17,365 mRNA vaccinated singleton pregnancies compared to 15,171 unvaccinated singleton pregnancies in an Australian-based registry (aOR: 0.18, 95% CI 0.09-0.37).<sup>43</sup> 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 appeared to have better access and adherence to prenatal care (with higher rates of receiving gestational diabetes screening) than unvaccinated people.<sup>43</sup>

### Gestational conditions

Development of conditions during pregnancy such as hypertensive disorders or gestational diabetes, have significant implications for the health of both the mother and the fetus. Evidence from four retrospective cohort studies, one 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 to those who were unvaccinated.<sup>19,28,44-47</sup> Dick et al. reported on an Israeli cohort of 5,618 pregnant participants, of which 2,305 participants had received an mRNA COVID-19 vaccine in the second or third trimester.<sup>44</sup> Compared to 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).<sup>44</sup> Similarly, there were no increased odds of pre-eclampsia 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 to 3,486 unvaccinated pregnant people.<sup>47</sup>

Additionally, no studies identified any increased risk of oligohydramnios,<sup>28,47</sup> polyhydramnios,<sup>28,47</sup> non-vertex presentation,<sup>47</sup> thromboembolism,<sup>46</sup> stroke,<sup>46</sup> or antepartum bleeding<sup>48</sup> among vaccinated compared to 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),<sup>49</sup> postpartum hemorrhage,<sup>28,44,46,47,49-51</sup> chorioamnionitis,<sup>50,51</sup> endometritis,<sup>28,51</sup> placental abruption,<sup>28,47</sup> non-reassuring fetal heart tones,<sup>47</sup> vacuum or forceps delivery,<sup>28,47</sup> low 5-minute APGAR score (<7),<sup>49</sup> maternal ICU admission,<sup>46,49,51</sup> or meconium-stained amniotic fluid.<sup>45,47</sup> In a meta-analysis of five studies, receipt of any COVID-19 vaccine during pregnancy was not associated with either Cesarean delivery (OR: 1.05, 95% CI 0.93-1.20) or postpartum hemorrhage (OR: 0.95, 95% CI 0.83-1.07).<sup>20</sup> Meta-analysis of three studies also showed no increased risk for chorioamnionitis among vaccinated pregnant people (OR: 1.06, 95% CI 0.86-1.31).<sup>20</sup> Two studies found a decreased odds of meconium-stained fluid among vaccinated people compared to unvaccinated people (aOR: 0.63, 95% CI: 0.49-0.83; aOR: 0.64, 95% CI: 0.43-0.96)<sup>45,47</sup>, and one study identified decreased odds of non-reassuring fetal heart tones during delivery (aOR: 0.64, 95% CI 0.44, 0.90).<sup>47</sup>

Most of the studies that investigated peripartum outcomes included pregnant people vaccinated during any trimester during pregnancy. Dick et al. compared peripartum outcomes of people vaccinated in the second and third trimesters to 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.<sup>44</sup> Similarly, Rottenstreich et al. 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).<sup>51</sup> Authors reported that receipt of COVID-19 vaccination at >24 weeks' gestation was not associated with the maternal composite adverse outcome (aOR: 0.8, 95% CI 0.61-1.03) compared to no receipt of the COVID-19 vaccine.<sup>51</sup>

#### Placental histopathology

The effect of SARS-CoV-2 infection on placental histopathology is a topic of investigation;<sup>52</sup> 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.<sup>53,54</sup> 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).<sup>53</sup> There was decreased odds of high grade chronic villitis (aOR: 0.31, 95% CI 0.1-0.97).<sup>53</sup> Similarly, Boeling et al. 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.<sup>54</sup> 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).<sup>54</sup> These results suggest that SARS-CoV-2 infection, but not COVID-19 vaccination, affects placental vascular pathology.

#### Preterm birth, Small for Gestational Age (SGA), Neonatal Intensive Care Unit (NICU) admission

Previous studies have suggested that SARS-CoV-2 infection during pregnancy significantly increases the risk of preterm birth (delivery <37 weeks' gestation), SGA (<10% in birth weight for sex), and infant admission to the NICU.<sup>5,55</sup> 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.<sup>19,20</sup> Methodologically, investigation of preterm birth is challenging as analytic techniques to adjust for time-varying exposure must be considered to minimize biased results.<sup>35</sup>

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.<sup>56</sup> 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.<sup>56</sup> 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).<sup>42</sup> Results for SGA and NICU admission were similar in a sensitivity analysis restricting the sample to only term births.<sup>42</sup> Furthermore, in a meta-analysis with six 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).<sup>20</sup> This meta-analysis also pooled results of seven studies that examined preterm birth and six 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).<sup>20</sup>

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.<sup>57</sup> Similarly, Theiler et al. found no significant increase in the prevalence of preterm birth at <24 weeks, 24-<32 weeks, and 32-<37 weeks gestation.<sup>46</sup> 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.<sup>44</sup> However, second trimester vaccination was associated with an increased odds of preterm birth (aOR: 1.49, 95% CI 1.11-2.01); though no preterm births occurred within two weeks after vaccination and the majority 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 authors note that their results may differ from other studies due to their inability to control for several risk factors for preterm birth.<sup>44</sup>

#### 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 (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 to unexposed infants.<sup>57</sup> Additionally, compared to unexposed infants, there was no increased risk for post-neonatal 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).<sup>57</sup> 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 to those who were not exposed to the vaccine (RR: 0.69, 95% CI 0.14-2.41).<sup>57</sup>

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).<sup>58</sup> Among those who received a COVID-19 vaccine during pregnancy, the perinatal mortality rate



was 4.3 (95% CI 2.9-6.4) per 1,000 births compared to 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.<sup>58</sup>

### *Congenital Anomalies*

Few studies have investigated the risk of congenital anomalies among vaccinated pregnant people. Ruderman et al. retrospectively compared the odds of a fetal structural anomaly identified through ultrasonography for 1,149 pregnant people vaccinated with either an mRNA vaccine or Ad26.COVS.2.S (Janssen) vaccine 30 days before conception through 14 weeks' gestation to 2,007 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.<sup>59</sup> 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).<sup>59</sup> Findings were similar even after narrowing the window of exposure to 2-10 weeks gestation (aOR: 0.96, 95% CI 0.63-1.45).<sup>59</sup> 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.<sup>60</sup> However, similar results were reported in two large population-based retrospective cohort studies that evaluated congenital anomalies postnatally among infants born to pregnant people who were vaccinated.<sup>43,57</sup> 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 0.44-1.04) 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=2,021) compared to those unexposed (n=3,580).<sup>57</sup> 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 to those not exposed to a vaccine prenatally (aOR: 0.72, 95% CI 0.56-0.94). However, after restricting the sample to those vaccinated <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).<sup>43</sup> Although reassuring that no increase in congenital anomalies has been detected in infants through one 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 appear to increase the risk for any adverse pregnancy, maternal, or neonatal outcomes. The reactogenicity profile of mRNA vaccines is similar among pregnant people and non-pregnant 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 to unvaccinated pregnant people. Risks of preterm birth, small for gestational age, NICU admission, infant hospitalization, placental pathological findings, and pregnancy and obstetric complications, including gestational diabetes, hypertensive disorders, and non-elective 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 to 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 post-authorization 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 healthcare 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, we review the evidence from studies assessing effectiveness of monovalent mRNA vaccines in pregnant people or infants ages less 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***

##### ***VE 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**),<sup>61-63</sup> and these results were similar to those in the general populations of those countries.<sup>64,65</sup> Goldshtein et al. 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 two BNT162b2 doses for laboratory-confirmed infection was high at  $\geq 28$  days after dose 1 (i.e.,  $>7$  days after dose 2): VE 78% (95% CI 57 to 89%).<sup>61</sup> Another Israeli cohort study by Dagan et al. conducted among pregnant people during December 2020 to June 2021 also demonstrated high VE for two doses of BNT162b2 during days 7-56 after the second dose for laboratory-confirmed infection (VE 96% [95% CI 89 to 100%]), symptomatic COVID-19 (VE 97% [95% CI 91 to 100%]) and hospitalization (VE 89% [95% CI 43 to 100%]).<sup>62</sup> These results were also similar to previously published estimates from the same authors 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 to 95%), symptomatic COVID-19 94% (95% CI 87 to 98%) and hospitalization 87% (95% CI 55 to 100%).<sup>64</sup>

A study by Butt et al. from Qatar, utilizing 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 two 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.<sup>63</sup> Using data from the same study population of pregnant people, Butt et al. estimated that VE for infection was 87.6% (95% CI 44.1 to 97.2%) using a cohort analysis and 86.8% (95% CI 47.5 to 98.5%) using a test-negative, case-control analysis.<sup>63</sup> 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 to 92.3%) and for Beta variant infection was 75.0% (95% CI 70.5 to 78.9%) at 14 or more days after the second dose.<sup>65</sup>

*VE 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.<sup>66,67</sup> Schrag et al. 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.<sup>66</sup> 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 (i.e., doses could be received either before or during pregnancy), and for the same outcomes among non-pregnant women ages 18-45 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 (**Supplementary Table 2**). Although power was more limited to assess VE among pregnant people than non-pregnant women, VE estimates were similar among pregnant people and non-pregnant women ages 18-45 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 to Delta predominance, and VE waned over time after 2 and 3 doses, particularly during Omicron predominance.<sup>66</sup>

The findings from Schrag et al. are similar to those from a preprint by Guedalia et al. 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.<sup>67</sup> VE was assessed for (1) any hospitalization with a positive SARS-CoV-2 test among pregnant people, which the authors 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 >30 breaths per minute, oxygen saturation on room air <94%, ratio of PaO<sub>2</sub> to FiO<sub>2</sub> ratio of <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 (i.e., ≥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 to 69%) at ≥150 days after the second dose, but VE for hospitalization with significant disease and severe disease was high at ≥150 days after the second dose (significant disease VE: 97% [95% CI 92 to 99%], severe disease VE: 96% [95% CI 86 to 99]) and after a booster dose (significant disease VE: 99% [95% CI 93 to 100%], severe disease VE: 99% [95% CI 89 to 100%], **Supplementary Table 2**). However, during Omicron, VE was not significantly different from zero for any of the outcomes at ≥150 days after the second dose. During Omicron, a booster dose increased VE against any hospitalization (likely reflecting VE for infection) to 43% (95% CI 31 to 53%) and against significant and severe disease to 97% (95% CI 72 to 100%) and 94% (95% CI 43 to 99%), respectively. An important caveat to interpreting these results is that VE of two doses was measured at ≥150 days 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.<sup>67</sup>

*Impact of pregnancy on VE*

To address the question of whether pregnancy affected response to vaccine, one study in Norway by Magnus et al. examined the relative effectiveness of monovalent mRNA vaccines for prevention of infection, comparing vaccinated pregnant people to vaccinated non-pregnant women who had been pregnant in the year prior but did not receive their COVID-19 vaccines while pregnant or during the post-partum period.<sup>68</sup> They found no differences in the relative effectiveness of the primary series or booster doses between pregnant and non-pregnant people (**Supplementary Table 3**). During the Omicron predominant period, adjusted hazard ratios were 1.03 (95% CI 0.94 to 1.12) for the comparison of relative effectiveness in pregnant people who received two primary series doses during pregnancy compared to non-pregnant women and 1.24 (95% CI 0.84–1.84) for booster dose receipt during pregnancy compared to non-pregnant people.<sup>68</sup>

*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.<sup>69,70 71,72</sup> Two published analyses from CDC's Overcoming COVID-19 network, both by Halasa et al., assessed effectiveness of a maternal monovalent mRNA primary series given during pregnancy for prevention of COVID-19-associated hospitalization among infants ages less than 6 months. The first analysis utilized data from infants hospitalized during July 2021 to January 2022.<sup>69</sup> In the updated analysis, infants ages less than 6 months were enrolled from 30 pediatric medical centers in 22 U.S. states from July 2021 to March 2022, a period spanning both Delta

and Omicron predominance.<sup>70</sup> As the updated analysis included all data presented in the first analysis, we 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 ages less than 6 months from hospitalization for COVID-19 with an overall VE of 52% (95% CI 33 to 65%) for hospitalization and 70% (95% CI 42 to 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 to 58%]) than during Delta (VE 80% [95% CI 60 to 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 to 87%) for vaccination during the first 20 weeks of pregnancy versus 88% (95% CI 68 to 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 to 56%]), whereas vaccination after 20 weeks was protective (VE 57% [95% CI 25 to 75%]).<sup>70</sup>

Two studies assessed maternal vaccination for prevention of SARS-CoV-2 infection in infants after birth (**Supplementary Table 4**).<sup>71,72</sup> Carlsen et al. 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 2<sup>nd</sup> or 3<sup>rd</sup> trimesters of pregnancy in prevention of SARS-CoV-2 infection in infants from birth through 3 months of age.<sup>71</sup> This study showed that maternal vaccination with 2 doses (with at least the 2<sup>nd</sup> dose given during the 2<sup>nd</sup> or 3<sup>rd</sup> 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 to 81%]) than during Omicron predominance (VE 32% [95% CI 19 to 42%]). During Omicron predominance, receipt of a third (booster) dose during the 2<sup>nd</sup> or 3<sup>rd</sup> trimester increased VE to 78% (95% CI 57 to 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.<sup>71</sup> A preprint by Zerbo et al. used a cohort design to assess effectiveness of  $\geq 2$  doses of monovalent mRNA vaccines for prevention of SARS-CoV-2 infection among infants in northern California at ages less than 2 months, less than 4 months and less than 6 months during Delta and Omicron periods.<sup>72</sup> During Delta predominance (July 1, 2021 to December 20, 2021), VE for infection among infants was 85% (95% CI 67 to 93%) at age less than 2 months, 64% (95% CI 43 to 78%) at age less than 4 months, and 57% (95% CI 36 to 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 30, 2022), maternal vaccination was not protective against infection (i.e., all VE estimates were not significantly different from zero), including among infants ages less than 2, less than 4 or less than 6 months of birth or when stratified by trimester of second dose receipt.<sup>72</sup>

#### 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 non-pregnant 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. Additionally, maternal COVID-19 vaccination during pregnancy protected infants less than 6 months of age 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

which 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,<sup>73</sup> 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 prior to and during pregnancy.

### **Conclusion**

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. Post-authorization 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.

**Note:** 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 current 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 manuscript; the authors are aware that pregnancy is not equated with the decision to parent nor do all parents who give birth identify as mothers.

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