The COVID-19 vaccine in pregnancy: risks benefits and recommendations

Irene A. STAFFORD MD, Jacqueline G. PARCHEM MD, Baha M. SIBAI, MD

Department of Obstetrics, Gynecology, and Reproductive Sciences, McGovern Medical School, University of Texas Health Science Center at Houston, Houston, TX

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Correspondence:

Irene A. Stafford, MD

6431 Fannin Ste 3.286

Houston, Texas, 77030

(713) 500-7780

Irene.Stafford@uth.tmc.edu

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Condensation: The COVID-19 vaccine should only be offered to pregnant patients after discussing the lack of safety data and prioritized for women considered at highest risk.

Abstract: The 2019 Coronavirus (COVID-19) has caused over two-million deaths worldwide, with over 412,000 deaths reported in Unites States. To date, at least 57,786 pregnant women in the US have been infected and 71 have died[1-4]. Although pregnant women are at higher risk for severe COVID-19 related illness, clinical trials for the available vaccines excluded pregnant and lactating women. The safety and efficacy of the vaccines for pregnant women, the fetus and the newborn remain unknown. A review of maternal and neonatal COVID-19 morbidity and mortality data along with perinatal vaccine safety considerations are presented to assist providers with shared decision-making regarding vaccine administration for this group, including the health care worker who is pregnant, lactating or considering pregnancy. The COVID-19 vaccine should be offered to pregnant women after discussing lack of safety data, with preferential administration for those at highest risk for severe infection, until safety and efficacy of these novel vaccines are validated.

SARS-CoV-2, vaccine safety, COVID-19, Coronavirus, lactation, COVID-19 vaccine, Severe Acute Respiratory Syndrome Coronavirus 2, mRNA vaccine, maternal immunity, Middle East Respiratory Syndrome, MERS, Severe acute respiratory virus, SARS, Zika, Influenza A H1N1

The COVID-19 vaccine during pregnancy: risks, benefits, and recommendations

The current COVID-19 vaccines

As of January 23, 2021, over ninety-eight million cases of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection have been reported world-wide. In the United States, over twenty-four million people have been infected and at least 400,000 have died[1-4]. The pressing need for therapeutics and vaccines to treat and prevent COVID-19 related illness and its effect on our global economic structure resulted in multiple research studies seeking effective tools to combat this disease[5-12]. With support of the US Department of Health and Human Services (DHHS), multiple researchers and pharmaceutical companies are actively pursuing the development and manufacture of efficacious and timely vaccines against this virus[5-12]. On December 11, 2020, the Federal Drug Administration (FDA) issued the first Emergency Use Authorization (EUA) for Pfizer-BioNTech's mRNA COVID-19 vaccine[13,14]. This allowed the vaccine to be nationally distributed to adults ≥16 years of age using the safety and efficacy data from their global trial[13-16]. Vaccine efficacy was demonstrated to be 95% in preventing symptomatic and lab-confirmed COVID-19 among persons without evidence of prior infection for seven days after the second dose was administered[13-16]. Shortly after, on December 18, 2020, Moderna, Inc. was issued an EUA after the safety and immunogenicity of their mRNA SARS-CoV-2 vaccine data was published and efficacy was demonstrated to be 94.1% against symptomatic and lab-confirmed infection in participants ≥18 years of age without evidence of prior infection for 14 days after completion of the 2-dose series[17-21]. Although not yet approved in the US, the Oxford/AstraZeneca vaccine was approved by the British Department of Health and Social Care in the United Kingdom on December 30, 2020 after the vaccine was shown to have a pooled efficacy of 70.4% in preventing symptomatic and lab confirmed infection 14 days

after completion of the 2-dose series among adults without prior COVID-19[22,23]. Detailed summary data for the approved SARS-CoV-2 vaccines are presented in Table 1. On December 13 and 20, 2020, the Advisory Committee on Immunization Practices (ACIP) branch of the Centers for Disease Control and Prevention (CDC) issued an interim recommendation for use of the Pfizer-BioNTech and Moderna COVID-19 vaccines respectively, after the designated COVID-19 working group reviewed the evidence for vaccine efficacy and safety, and implementation considerations, including offering them to eligible pregnant and lactating women, despite their exclusion from these clinical trials[13-24].

COVID-19 in pregnancy

Mechanical and physiologic alterations in pregnancy increase susceptibility to certain infections[25-27]. The immunologic alterations that occur during pregnancy may be protective to the fetal allograft, but may also create vulnerability to certain viral infections[25-27]. Over 1,600 reports evaluating COVID-19 and pregnancy have been published. Most of these are cohort studies, case series, and metanalyses describing diagnostic challenges, therapeutic options, intrauterine transmission, and perinatal complications among affected pregnancies. Although several studies, including a recent metanalysis with data from over 435 infected pregnant women have suggested that the severity of COVID-19 in pregnant women is similar to non-pregnant adults[28-34], CDC data and other publications indicate an increased risk of intensive care unit (ICU) admission (10.5 vs. 3.9 per 1,000 cases; adjusted risk ratio [aRR], 3.0; 95% confidence interval [CI], 2.6-3.4), mechanical ventilation (2.9 vs. 1.1 per 1,000 cases; aRR, 2.9, 95% CI, 2.2-3.8) and death (1.5 vs. 1.2 per 1,000 cases; aRR, 1.7; 95% CI, 1.2 – 2.4) in pregnant patients with symptomatic COVID-19 infection compared with non-pregnant women after adjusting for age, race, ethnicity and comorbidities, with even higher risk for subgroups of women who are underserved, have

comorbidities or are of advanced maternal age[35-45]. These surveillance data have limitations, however, as over 64.5% of total cases involving women did not have pregnancy status recorded[45]. Additionally, among those with known pregnancy status, race and ethnicity status was missing for 25% of cases, and information on symptoms and underlying conditions was missing for approximately half[45]. A recent publication of morbidity, mortality, and pregnancy outcome of over 400,000 women admitted for delivery with and without COVID-19 collected from an all-payer database of 20% of US hospitals demonstrated similar outcomes, reporting an increased rate of death in women with infection compared to those without COVID-19 (141, 95% CI, 17.95-31.29) versus 5.0 (95% CI, 17.95-31.29 number of deaths per 100,000 women) respectively[46]. Despite limited evidence that the infection increases other adverse pregnancy outcomes, there remains a higher risk of thromboembolic disease, hypertensive disorders, preterm birth and cesarean delivery for infected pregnant women, differentially represented across global regions[28-46]. Although the absolute risk for severe infection is low, the CDC has included pregnancy as a risk factor for severe COVID-19 illness, and this has been echoed by the Society for Maternal Fetal Medicine (SMFM), the American College of Obstetricians and Gynecologists (ACOG) and other women's health organizations[57-63].

Several reports of neonatal transmission and adverse outcomes for infected newborns have been reported as well, however some of these data are confounded by uncertainty surrounding testing and diagnostics for these neonates and other independent neonatal morbidities[47-53]. Collectively, the current available data suggest an approximate 2-3% risk of vertical transmission with a minimal rate of persistent neonatal infection. Consistent with these observations are data showing that SARS-CoV-2 is not routinely detected in amniotic fluid, cord blood or neonatal nasopharyngeal samples associated with affected pregnancies[47-53]. Several studies describe the

detection of viral RNA in breast milk of infected mothers, however there is no evidence to suggest that the ingestion of breastmilk from SAR-CoV-2-positive mothers increases the risk of transmission to their newborns[54-56]. Variable quantities of IgA antibodies were detected in 80% of 18 breast milk samples collected from infected women in one study, however the protective capacity of these antibodies for newborn and infant infection requires further investigation[54-56].

Past pandemics and vaccine safety in pregnant women

Disproportionate rates of maternal morbidity, adverse perinatal outcomes and mortality due to infectious disease have been described in past pandemics as well. During the 2002 severe acute respiratory syndrome (SARS) pandemic, which infected over 8,000 people in 26 countries, maternal case fatality was 25% and miscarriage occurred in 57% of infected pregnant women[64-70]. The Middle East Respiratory Syndrome (MERS), another coronavirus, demonstrated similar pathogenicity, leading to adverse perinatal events in over 90% of infected women in 2012[64-70]. Currently, a safe and efficacious vaccine has not been developed for these pathogens. In 2009, a novel strain of the influenza A virus, termed H1N1, resulted in a global pandemic with an estimated 40 million people infected between April 2009 and 2010, resulting in over 274,304 hospitalizations and 12,469 deaths[64-74]. During the first five months of the H1N1 pandemic, 788 cases were reported in pregnant women. Of these, 30 died, comprising 5% of all reported 2009 Influenza H1N1 deaths during this period[67-74]. Four case reports of suspected H1N1 vertical transmission in newborns have been published, with one reported neonatal demise[75-77-78]. Observational studies demonstrated higher frequencies of maternal infectious morbidity as well, showing higher rates of maternal intensive care unit (ICU) admission and death as a result of H1N1 influenza infection when compared to non-pregnant populations, even more so than the current COVID-19 pandemic[79-80].

153 **Vaccines and reproductive toxicology**

154 Although various vaccine efficacy and safety studies were performed with pregnant and lactating
155 women during the H1N1 pandemic, the COVID-19 vaccine trials have excluded these groups,
156 and therefore critical perinatal safety information remains largely unknown[13-24,81]. The mRNA
157 (Pfizer-BioNTech and Moderna), and viral vector (AstraZeneca), COVID-19 vaccines are novel
158 in design, and to date, are the first mRNA and viral vector vaccine trials to have been
159 comprehensively evaluated for disease prevention in people[13-23,81]. Of note, the Ebola vaccine
160 (rVSVΔG-ZEBOV-G, Merck) was developed using similar viral vector technology and is
161 currently approved for disease prevention in non-pregnant adults[81]. Several preliminary human
162 studies have demonstrated promising safety and immunogenicity data using the mRNA vaccine
163 model with other pathogens, including Influenza, Zika virus and Rabies virus[81-88], but prior
164 efficacy studies evaluating mRNA vaccines during pregnancy are limited to animal studies
165 involving Zika virus, where vaccination resulted in a significant reduction of placental and fetal
166 viral burden[81-88]. Details concerning transplacental vaccine transfer have not been described[81-88].
167 Although disclosed details of the protocols are available for review, the precise formulations of
168 the cationic nanoparticle used for mRNA assembly of the COVID-19 vaccines remain propriety
169 to the manufacturing pharmaceutical companies and preliminary safety data regarding the
170 COVID-19 mRNA vaccines during gestation reference a perinatal/postnatal Reproductive
171 Toxicology study in rats, which demonstrated no safety alerts [13-23,57].

172 Ultimately, the advantage of past and present Influenza vaccine design in comparison is the
173 background benefit of known published protocols and historical experience utilizing inactivated
174 or attenuated virus since 1940, leading to a more expeditious design for safety and efficacy[89-97].
175 These studies were accomplished with fewer challenges compared to the de novo human vaccine

development for the novel SARS-CoV-2 virus[13-23,81]. Typically, vaccines intended for pregnant or breastfeeding women rely on critical review by the scientific community of all observational studies, case reports and series, registries and experimental data regarding the type of vaccine, pathogen placental transfer studies, toxicity and immunogenicity studies, and trimester-specific infection risks. These reviews are conducted through collaborative efforts by the Vaccine Safety Datalink (VSD), a collaborative project between the CDC, and others, including the ACIP Workgroup, National Institutes of Health (NIH), Task Force on Research Specific to Pregnant Women and Lactating Women (PRGLAC), World Health Organization (WHO), and Global Advisory Committee on Vaccine Safety (GACVS)[89-102]. Priority is granted to potential vaccines that meet several key criteria when considered for mass vaccination campaigns[98-110]. The vaccine should demonstrate the potential to reduce morbidity in the pregnant woman and/or her fetus. In addition, there should exist a lack of evidence of adverse pregnancy outcomes or potential harm to the fetus or mother with vaccine exposure[98-110].

Multiple randomized control trials and prospective studies have demonstrated vaccine efficacy against Influenza-related morbidity in the pregnant patient and lab-confirmed infection in their neonates, with an additional 6 months of efficacy during early infancy[89-97]. These safety data also included comprehensive studies and monitoring programs for the adjuvant- and non-adjuvant-containing inactivated trivalent seasonal Influenza vaccine and the H1N1 monovalent vaccines[89-97]. With support from the CDC, the American Academy of Pediatrics, The American Academy of Family Medicine, ACIP, and ACOG, a consensus statement was published recommending that all women receive both the seasonal and 2009 H1N1 inactivated vaccines during pregnancy with FDA approval within six months from the start of the H1N1 pandemic[111-114]. These vaccines, along with known toxoids, have been used to prevent infectious morbidity known to

negatively impact maternal and neonatal health[111-115]. For example, administration of the seasonal and H1N1 Influenza vaccine as well as the tetanus toxoid vaccine (combined with diptheria-pertussis, Tdap) which has resulted in a 92% reported reduction in global pertussis morbidity and mortality [115].

With the disclosure of full intent to perform future research on COVID-19 vaccine safety in this population, the DHHS, companies and researchers prioritized the emergent delivery of a safe and effective vaccine to the public, responding to an emergent call to action, unfortunately with limited time and lower thresholds for evidence prior to implementation for the pregnant and lactating patient[13-24,81].

COVID-19 Vaccine and Pregnancy

Maternal risks and benefits

On December 19, 2020, the CDC and ACIP released a statement supporting the administration of both EUA approved vaccines to prevent COVID-19 in persons ≥ 16 and 18 years of age respectively, starting with prioritization groups outlined by the ACIP[60,62,63]. This strategy includes beginning with health care personnel and long-term care facility residents (Phase 1a), followed by persons aged ≥75 years and non–health care frontline essential workers (1b), and in Phase 1c, the vaccines should be offered to persons aged 65–74 years, persons aged 16–64 years with high-risk medical conditions, and essential workers not included in Phase 1b[60,62,63]. In addition, the CDC, ACOG, SMFM and other agencies support offering vaccination to pregnant and lactating women in these prioritized groups [57-63]. Counseling should include discussion of the risks and benefits for those contemplating vaccination before or during pregnancy, or while breastfeeding with their trusted provider and support network. Mild side effects have been

reported, ranging from a > 80% frequency of pain at injection site, to a 40% rate of systemic complaints, including febrile morbidity, which upon review has been disproven to be teratogenic to the fetus during the first trimester[116,117]. Bell's palsy affected few recipients of both Pfizer-BioNTech and Moderna vaccines, but was not attributed to the vaccination[16,18,21].

Counseling regarding anticipated benefits is clear, as published data reveal between 94 and 95% efficacy in preventing lab-confirmed and mildly symptomatic COVID-19 among people seven to 14 days after completion of the vaccine series, with potential for similar efficacy for the pregnant patient based on similar efficacy observed between pregnant and non-pregnant individuals in other vaccine trials, regardless of pregnancy specifics[13-21,81,98-111].

Major important secondary end points of the BioNTech and Moderna COVID-19 vaccine studies include the efficacy of the vaccine against severe infection related morbidity, defined by the FDA as confirmed COVID-19 with clinical signs that are indicative of severe systemic illness including respiratory failure, evidence of shock, significant acute organ dysfunction, admission to an ICU, or death[14-21]. Although preliminary data report lower hospitalizations among vaccine recipients, these valuable data are not yet available and therefore cannot be fully addressed when counseling the pregnant patient concerned about these more serious outcomes, nor the potential reduction in the long-term sequelae of COVID-19 or risk of continued transmissibility[14-21,] If validated, a reduction in severe COVID-19 would benefit the fetus, given the negative effects maternal illness has on fetal status, which has driven medically indicated and spontaneous preterm birth and associated neonatal sequelae[28-46]. Counseling to this point can include a discussion of the continued pursuit and accumulation of pregnancy specific COVID-19 data worldwide, with current data suggesting that rates of severe morbidity (assisted ventilation, ICU admission and death) are significantly higher among pregnant women with symptomatic

COVID-19 compared to symptomatic non-pregnant cohorts respectively, which equally affect 5% of infected persons[35-46]. However, when examining critical care details and demographic variables of infected pregnant women in large national epidemiologic data, it remains critical to acknowledge that in the largest studies to date, rates of intensive care admission, invasive ventilation and mortality from COVID-19 are 2- 3-fold higher among symptomatic pregnant women over 35 years of age, with comorbidities (obesity, diabetes, cardiovascular disease, chronic lung disease), Black or Asian race or Hispanic ethnicity[35-46]. (Table 2) These findings are further supported by a recent publication analyzing data from a national database encompassing 20% of hospitalizations in the US, including women hospitalized for childbirth between April 1 and November 23, 2020[46]. Women with lab-confirmed COVID-19 along with obesity (BMI > 35, kg/m^2), or diabetes or hypertensive disorders were significantly more likely to require mechanical ventilation or die compared to women without those morbidities (OR, 3.85; [95% CI, 2.05-7.21]), 4.51; [95% CI, 2.10-9.70]), 116.1; [95% CI, 22.91-588.50] respectively). Current data report that over 21% of pregnant women with COVID-19 in the US have been admitted to the hospital, but only 1.6% of women hospitalized for delivery between April 1 and November 23, 2020 were positive for COVID-19[1-4,35-46]. Overall, rates of severe morbidity among pregnant women remain low, with ICU admission approximating 3% and necessity for invasive ventilatory support and death at 1.0 and 0.2% respectively[35-46]. Even when symptomatic for COVID-19 infection, these rates are substantially reduced to 0.9, 0.2 and 0.1% respectively in women less than 35 years of age without complicating health conditions [45]. In fact, according to current CDC surveillance data, mortality rates in persons less than 40 years of age is 0.0063%[1-4].

Fetal risks and benefits

When balancing risks and benefits, it is important to clarify that there are no human trials demonstrating fetal and neonatal safety with the COVID-19 vaccines[14-21]. Thirty-six pregnancies were reported among participants in the Pfizer-BioNTech and Moderna clinical trials combined, including 18 in the vaccine arms[14-21]. All pregnancy variables and outcomes, including any adverse safety events will be recorded, but are currently not available given the temporal relationship of these pregnancies and trial participation[14-21].

Limited unpublished data are currently available from animal developmental and reproductive toxicity (DART) studies which have revealed no safety concerns in over 1,000 rats that received the Moderna COVID-19 vaccine prior to or during gestation with regard to female reproduction, fetal/embryonal, or postnatal development[17,18,57] Although human data surrounding detailed transplacental vaccine transfer, fetal teratogenicity and immunogenicity are lacking, administration of the vaccine does not appear to affect fertility, or miscarriage rate in animal studies [14-21,47,57,81]. Due to the protection of passive immunoglobulins in preventing infectious morbidity for the neonate, certain vaccines are recommended by ACOG, CDC and ACIP for administration during pregnancy and in the third trimester (Influenza, Tdap), a benefit which may or may not be revealed with longitudinal immunogenicity studies for the Pfizer-BioNTech and Moderna vaccines[14-21,57,11-114].

Regarding lactation, it is worth noting that grouping pregnant and lactating women together in discussion of vaccine safety is neither helpful nor logical given that these are phases of reproductive life are physiologically and biologically distinct. Experts (Academy of Breastfeeding Medicine, ACOG, etc) agree that vaccination poses minimal to no potential risk to the newborn, given that vaccine related mRNA has not been detected in early breastmilk studies and no plausible mechanism of neonatal harm has been identified[57-63,81]. Based on the biology of

other vaccines, there is the potential for neonatal benefit if vaccine stimulated immunoglobulin A passes through breastmilk and provides additional protection against SARS-CoV-2 infection[57-63]. Overall, safety for lactating women appears reassuring with no reason to suspect that receipt of the vaccine would lead to any adverse neonatal effects or detrimental changes to lactation[57-63].

Summary

In alignment with the current consensus statements and practice bulletin publications from the CDC, ACOG, SMFM and other women's health organizations, we recognize that pregnant women meet criteria as a prioritized group for administration of the Pfizer-BioNTech and Moderna COVID-19 vaccines, especially for those with high exposure occupations[57-63] Importantly, for pregnant frontline workers currently eligible for the vaccination, efficacy and safety data will not be available in time to inform their decision making. Pregnant women who choose to wait for more data should be supported and updated with evidence by their trusted health care provider. Overall, the benefits of the vaccine are indeed promising. Nevertheless, risks and benefits of the COVID-19 vaccines for pregnant women, the fetus and the newborn must be acknowledged in transparent discussions with our patients[14-21,57-63-21]. Fundamentally, the risks of neonatal transmission and overall infection related morbidity and mortality in the low-risk pregnant patient presenting without symptoms are considerably reduced, but are yet to be fully determined[35-46].

In our expert opinion, we recommend a comprehensive risk-benefit discussion regarding the lack of safety data occur prior to COVID-19 vaccine administration in pregnant women with preferential administration for pregnant women at highest risk for more severe infection related disease, until safety and efficacy of these novel COVID-19 vaccines are ensured[118]. (Table 3)

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Table 1. Summary of Available SARS-CoV-2 vaccines

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Name	Vaccine type	Experimental design	Primary outcome	Secondary	Results
Pfizer-BioNTech	mRNA BNT162b2	Double blinded RCT 1:1 ratio vaccine/placebo 2 doses, 21d apart ≥16 years old N =43,448 Multicenter, international Probability of vaccine efficacy > than 30% 95.0% credible interval for vaccine efficacy Bayesian beta-binomial mode	Efficacy against COVID-19 > 7 d after 2nd dose defined by: a) Symptomatic* with; b) Nucleic acid amplification-based test (NAAT) within 4 days of symptom onset† In persons without prior COVID-19¶	1)Severe COVID-19§ 2)Safety/side effects 3)Efficacy after 1st dose 4)In persons with/without COVID-19	1)Without prior COVID-19: 95.0% efficacy (95% CI, 90.3 to 97.6) 2)With/without prior COVID-19: 94.6% efficacy (95% CI, 89.9 to 97.3) 3)Systemic complaints: 1st dose 52-59% 2nd dose 39-51%
Moderna	mRNA-1273	Observer blinded RCT 1:1 ratio vaccine/placebo 2 doses, 28 d apart ≥18 years old N =30,420 Multicenter US Probability of vaccine efficacy > 30% one-sided O'Brien–Fleming boundary for efficacy. Lan–DeMets alpha-spending for efficacy boundaries	Efficacy against COVID-19 > 14 d after 2nd dose defined by: a) Symptomatic** with; b) Nucleic acid amplification-based test (NAAT) within 4 days of symptom onset†† In persons without prior COVID-19¶	1)Severe COVID-19§ 2)Safety/side effects 3)Efficacy after 1st dose In persons with and without prior COVID-19	1)Without prior COVID-19: 94.1% efficacy (95% CI, 89.3 to 96.8) 2)In persons with prior COVID-19: 93.6% [95% CI, 88.6 to 96.5] 3)Systemic complaints: 1st dose 54.9% 2nd dose 79.4%
Oxford/Astra Zeneca	Adenovirus-vectored vaccine	Single-blind and double blind (1 site) RCT 1:1 ratio vaccine/placebo 28d apart Subset – .5 and full dose 2nd dose ≥18 years old N = 23 848 Multicenter, international Vaccine efficacy Poisson regression model adjusted for age	Efficacy against COVID-19 > 14 d after 2nd dose defined by: a) Symptomatic*** with; b) Nucleic acid amplification-based test (NAAT)††† In persons without prior COVID-19 ¶ Primary: efficacy after 1st dose .5 dose Excluded if NAAT pos within 14 d after 2nd dose	1) Efficacy after both doses full dose 2)Safety/side effects 3)efficacy in patients with prior COVID-19	1)Persons without prior COVID-19: Vaccine efficacy: 90·0% (67·4-97·0) for .5 and full dose 2)vaccine efficacy: 62·1% (95% CI 41·0-75·7) 2 full doses 3)1.6% severe side effects

748 Pfizer * Fever, new or increased cough, new or increased shortness of breath, chills, new or increased muscle pain,
749 new loss of taste or smell, sore throat, diarrhea, or vomiting. †Respiratory specimen obtained during the

750 symptomatic period or within 4 days before or after it that was positive for SARS-CoV-2 by nucleic acid
751 amplification–based testing.

752 Moderna ** Two or > the following symptoms: fever (temperature ≥38°C), chills, myalgia, headache, sore throat, or
753 new olfactory or taste disorder, or as occurring in those who had at least one respiratory sign or symptom (including
754 cough, shortness of breath, or clinical or radiographic evidence of pneumonia). ††One nasopharyngeal (NP) swab,
755 nasal swab, or saliva sample (or respiratory sample, if hospitalized) positive for SARS-CoV-2 by RT-PCR.

756 Astrazeneca *** t >37·8°C, cough, shortness of breath, and anosmia or ageusia. In some sites, the list of qualifying
757 symptoms for swabbing was broader, and additionally included myalgia, chills, sore throat, headache, nasal
758 congestion, diarrhoea, runny nose, fatigue, nausea, vomiting, and loss of appetite. †††One nasopharyngeal (NP)
759 swab, nasal swab positive for SARS-CoV-2 by RT-PCR by home kits using protocol-defined acceptable tests

760 ¶ Participants were assessed for the presence of SARS-CoV-2–binding antibodies specific to the SARS-CoV-2
761 nucleocapsid protein and had a nasopharyngeal swab for SARS-CoV-2 RT-PCR testing using protocol-defined
762 acceptable tests

763 § Severe COVID-19 define by FDA includes severe systemic illness, respiratory failure, evidence of shock,
764 significant acute renal, hepatic, or neurologic dysfunction; admission to an intensive care unit; or death.

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766 Table 2. Intensive care unit (ICU) admissions, invasive ventilation and deaths among
767 symptomatic women of reproductive age with lab-confirmed SARS-CoV-2 (N = 409,462)

Outcome*/Characteristic	Pregnant (n = 23,434)	Nonpregnant (n = 386,028)	Risk ratio (95%CI)
ICU admission¶			
All	**245 (10.5)**	**1,492 (3.9)**	**3.0 (2.6–3.4)**
Age group, yrs			
25–34	118 (9.1)	467 (3.5)	2.4 (2.0–3.0)
35–44	78 (19.4)	781 (6.4)	3.2 (2.5–4.0)
Race/Ethnicity			
Hispanic or Latina	89 (12.8)	429 (5.0)	2.8 (2.2–3.5)
Asian, non-Hispanic	20 (35.7)	52 (6.0)	6.6 (4.0–11.0)
Black, non-Hispanic	46 (13.6)	334 (6.2)	2.8 (2.0–3.8)
White, non-Hispanic	31 (5.6)	348 (2.8)	2.3 (1.6–3.3)
Underlying health conditions			
Diabetes	25 (58.5)	274 (44.8)	1.5 (1.0–2.2)
CVD**	13 (42.8)	247 (32.1)	1.5 (0.9–2.6)
Invasive ventilation††			
All	**67 (2.9)**	**412 (1.1)**	**2.9 (2.2–3.8)**
Age group, yrs			
25–34	30 (2.3)	123 (0.9)	2.5 (1.6–3.7)§§
35–44	26 (6.5)	221 (1.8)	3.6 (2.4–5.4)

Race/Ethnicity			
Hispanic or Latina	33 (4.7)	143 (1.7)	3.0 (2.1–4.5)
Asian, non-Hispanic	4 (7.1)	19 (2.2)	NA
Black, non-Hispanic	10 (3)	86 (1.6)	2.5 (1.3–4.9)
White, non-Hispanic	12 (2.2)	102 (0.8)	3.0 (1.7–5.6)
Underlying health conditions			
Diabetes	10 (23.4)	98 (16.0)	1.7 (0.9–3.3)
CVD**	6 (19.7)	82 (10.6)	1.9 (0.8–4.5)¶¶
Death§§§			
All	**34 (1.5)**	**447 (1.2)**	**1.7 (1.2–2.4)**
Age group, yrs			
25–34	15 (1.2)	125 (0.9)	1.2 (0.7–2.1)
35–44	17 (4.2)	282 (2.3)	2.0 (1.2–3.2)
Race/Ethnicity			
Hispanic or Latina	14 (2.0)	87 (1.0)	2.4 (1.3–4.3)
Asian, non-Hispanic	1 (1.8)	11 (1.3)	NA
Black, non-Hispanic	9 (2.7)	167 (3.1)	1.4 (0.7–2.7)
White, non-Hispanic	3 (0.5)	83 (0.7)	NA
Underlying health conditions			
Diabetes	6 (14.1)	78 (12.7)	1.5 (0.6–3.5)¶¶¶
CVD**	7 (23.0)	89 (11.6)	2.2 (1.0–4.8)****

Data presented by pregnancy status, age, race, ethnicity and comorbidities. Data for Extracorporeal Membrane Oxygenation, multiple or other race, non-Hispanic and unknown were not included in Table 2. Only adjusted risk ratio included.

Abbreviated Data Zambrano LD, Ellington S, Strid P, Galang RR, Oduyebo T, Tong VT, et al. Characteristics of Symptomatic Women of Reproductive Age with Laboratory-Confirmed SARS-CoV-2 Infection by Pregnancy Status — United States, January 22–October 3, 2020. MMWR Morb Mortal Wkly Rep 2020;69:1641–1647

* Percentages calculated among total in pregnancy status group. Adjusted for age, categorical race/ethnicity variable, and dichotomous indicators for diabetes, cardiovascular disease, and chronic lung disease.

¶ A total of 17,007 (72.6%) symptomatic pregnant women and 291,539 (75.5%) symptomatic nonpregnant women were missing information on ICU admission status

** Cardiovascular disease also accounts for presence of hypertension.

†† A total of 17,903 (76.4%) pregnant women and 299,413 (77.6%) nonpregnant women were missing information regarding receipt of invasive ventilation and were assumed to have not received it.

§§ Adjusted for the presence of diabetes, CVD, and chronic lung disease only, and removed race/ethnicity from adjustment set because of model convergence issues.

¶¶ Adjusted for the presence of diabetes and chronic lung disease and age as a continuous covariate only and removed race/ethnicity from adjustment set because of model convergence issues.

§§§ A total of 5,152 (22.0%) pregnant women and 66,346 (17.2%) nonpregnant women were missing information on death and were assumed to have survived.

¶¶¶ Adjusted for the presence of CVD and chronic lung disease and age as a continuous variable.

**** Adjusted for presence of diabetes and chronic lung disease and age as a continuous variable.

Table 3: Recommended criteria for administration of the currently available EUA approved COVID-19 vaccines (BioNTech and Moderna COVID-19 vaccine) during pregnancy if one or more of listed conditions is met using the Interim Clinical Considerations for use of the mRNA COVID-19 vaccines update[118]:

- Heath care providers
- Women ≥ 35 years old
- Multiple gestation
- Cancer
- Chronic Hypertension
- Chronic Kidney Disease
- COPD (chronic obstructive pulmonary disease)
- Heart conditions, such as heart failure, coronary artery disease, or cardiomyopathies
- Immunocompromised state (weakened immune system) from solid organ transplant
- Autoimmune diseases (Systemic Lupus Erythematosus, Rheumatoid Arthritis, Multiple Sclerosis, Inflammatory Bowel Disease, Graves' Disease, Psoriasis/Psoriatic arthritis, Addisons Disease
- Obesity (body mass index [BMI] of 30 kg/m2 or higher)
- Sickle Cell Disease
- Smoking (current or history)
- Type 1 or 2 Diabetes Mellitus

* Contraindications: Severe allergic reaction (e.g., anaphylaxis) after a previous dose of an mRNA COVID-19 vaccine or any of its components

Immediate allergic reaction of any severity to a previous dose of an mRNA COVID-19 vaccine or any of its components (including polyethylene glycol [PEG])*

Immediate allergic reaction of any severity to polysorbate (due to potential cross-reactive hypersensitivity with the vaccine ingredient PEG)*

827 Glossary of Terms

US Department of Health and Human Services	DHHS
National Institutes of Health	NIH
World Health Organization	WHO
Emergency Use Authorization	EUA
Advisory Committee on Immunization Practices	ACIP
Vaccine Safety Datalink	VSD
Global Advisory Committee on Vaccine Safety	GACVS
Developmental and Reproductive Toxicology	DART

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