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ORIGINAL ARTICLE

Preliminary Findings of mRNA Covid-19 Vaccine Safety in Pregnant Persons

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Abstract

BACKGROUND

Many pregnant persons in the United States are receiving messenger RNA (mRNA) coronavirus disease 2019 (Covid-19) vaccines, but data are limited on their safety in pregnancy.

METHODS

From December 14, 2020, to February 28, 2021, we used data from the "v-safe after vaccination health checker" surveillance system, the v-safe pregnancy registry, and the Vaccine Adverse Event Reporting System (VAERS) to characterize the initial safety of mRNA Covid-19 vaccines in pregnant persons.

RESULTS

A total of 35,691 v-safe participants 16 to 54 years of age identified as pregnant. Injection-site pain was reported more frequently among pregnant persons than among nonpregnant women, whereas headache, myalgia, chills, and fever were reported less frequently. Among 3958 participants enrolled in the v-safe pregnancy registry, 827 had a completed pregnancy, of which 115 (13.9%) were pregnancy losses and 712 (86.1%) were live births (mostly among participants vaccinated in the third trimester). Adverse neonatal outcomes included preterm birth (in 9.4%) and small size for gestational age (in 3.2%); no neonatal deaths were reported. Although not directly comparable, calculated proportions of adverse pregnancy and neonatal outcomes in persons vaccinated against Covid-19 who had a completed pregnancy were similar to incidences reported in studies involving pregnant women that were conducted before the Covid-19 pandemic. Among 221 pregnancy-related adverse events reported to the VAERS, the most frequently reported event was spontaneous abortion (46 cases).

CONCLUSIONS

Preliminary findings did not show obvious safety signals among pregnant persons who received mRNA Covid-19 vaccines. However, more longitudinal follow-up, including follow-up of large numbers of women vaccinated earlier in pregnancy, is necessary to inform maternal, pregnancy, and infant outcomes.

Introduction

The first coronavirus disease 2019 (Covid-19) vaccines available in the United States were messenger RNA (mRNA) vaccines: BNT162b2 (Pfizer–BioNTech) and mRNA-1273 (Moderna). In December 2020, the vaccines were granted Emergency Use Authorization (EUA) by the Food and Drug Administration (FDA) as a two-dose series, 3 weeks apart for Pfizer–BioNTech and 1 month apart for Moderna, and were recommended for use by the Advisory Committee on Immunization Practices (ACIP).[1-4] Pregnant persons were excluded from preauthorization clinical trials, and only limited human data on safety during pregnancy were available at the time of authorization. However, pregnant persons with Covid-19 are at increased risk for severe illness (e.g., resulting in admission to an intensive care unit, extracorporeal membrane oxygenation, or mechanical ventilation) and death, as compared with nonpregnant persons of reproductive age.[5] Furthermore, pregnant persons with Covid-19 might be at increased risk for adverse pregnancy outcomes, such as preterm birth, as compared with pregnant persons without Covid-19.[6] The Centers for Disease Control and Prevention (CDC) and ACIP, in collaboration with the American College of Obstetricians and Gynecologists and the American Academy of Pediatrics, have issued guidance indicating that Covid-19 vaccines should not be withheld from pregnant persons.[7-9]

Postauthorization monitoring in pregnant persons is necessary to characterize the safety of these new Covid-19 vaccines, which use mRNA, lipid nanoparticles, and state-of-the-art manufacturing processes.

Furthermore, establishing their safety profiles is critical to inform recommendations on maternal vaccination against Covid-19. We report preliminary findings of mRNA Covid-19 vaccine safety in pregnant persons from three U.S. vaccine safety monitoring systems: the "v-safe after vaccination health checker" surveillance system,[10] the v-safe pregnancy registry,[11] and the Vaccine Adverse Event Reporting System (VAERS).[12]

Methods

MONITORING SYSTEMS AND COVERED POPULATIONS

V-safe Surveillance System and Pregnancy Registry

V-safe is a new CDC smartphone-based active-surveillance system developed for the Covid-19 vaccination program; enrollment is voluntary. V-safe sends text messages to participants with weblinks to online surveys that assess for adverse reactions and health status during a postvaccination follow-up period. Follow-up continues 12 months after the final dose of a Covid-19 vaccine. During the first week after vaccination with any dose of a Covid-19 vaccine, participants are prompted to report local and systemic signs and symptoms during daily surveys and rank them as mild, moderate, or severe; surveys at all time points assess for events of adverse health effects. If participants indicate that they required medical care at any time point, they are asked to complete a report to the VAERS through active telephone outreach.

To identify persons who received one or both Covid-19 vaccine doses while pregnant or who became pregnant after Covid-19 vaccination, v-safe surveys include pregnancy questions for persons who do not report their sex as male. Persons who identify as pregnant are then contacted by telephone and, if they meet inclusion criteria, are offered enrollment in the v-safe pregnancy registry. Eligible persons are those who received vaccination during pregnancy or in the periconception period (30 days before the last menstrual period through 14 days after) and are 18 years of age or older. For persons who choose to enroll, the pregnancy registry telephone-based survey collects detailed information about the participant, including medical and obstetric history, pregnancy complications, birth outcomes, and contact information for obstetric and pediatric health care providers to obtain medical records; infants are followed through the first 3 months of life. Details about v-safe and v-safe pregnancy registry methods have been published previously.[10,11]

VAERS

The VAERS is a national spontaneous-reporting (passive-surveillance) system established in 1990 that is administered by the CDC and the FDA.[12] Anyone can submit a report to the VAERS. Health care providers are required to report certain adverse events after vaccination, including pregnancy-related complications resulting in hospitalization and congenital anomalies, under the conditions of the EUAs for Covid-19 vaccines[1,2]; the CDC encourages reporting of any clinically significant maternal and infant adverse events. Signs and symptoms of adverse events are coded with the use of the *Medical Dictionary for Regulatory Activities* (MedDRA), version 23.1.[13] We used a pregnancy-status question in the VAERS form

and a MedDRA code and text-string search to identify reports involving vaccination in pregnant persons.[14]

OUTCOMES

V-safe outcomes included participant-reported local and systemic reactogenicity to the BNT162b2 (Pfizer–BioNTech) vaccine and the mRNA-1273 (Moderna) vaccine on the day after vaccination among all pregnant persons 16 to 54 years of age and among nonpregnant women 16 to 54 years of age as a comparator. For analysis of pregnancy outcomes in the v-safe pregnancy registry, data were restricted to completed pregnancies (i.e., live-born infant, spontaneous abortion, induced abortion, or stillbirth). Participant-reported pregnancy outcomes included pregnancy loss (spontaneous abortion and stillbirth) and neonatal outcomes (preterm birth, congenital anomalies, small size for gestational age, and neonatal death) (Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). In the VAERS, outcomes included non–pregnancy-specific adverse events and pregnancy- and neonatal-specific adverse events.

STATISTICAL ANALYSIS

Demographic information and pregnancy characteristics are described for both v-safe and VAERS participants. Descriptive analyses were performed with the use of v-safe survey data for persons who identified as pregnant through February 28, 2021 (35,691 persons); persons enrolled in the v-safe pregnancy registry who were vaccinated through February 28, 2021 (3958 persons); and VAERS reports involving pregnant women received through February 28, 2021 (221 persons). Local and systemic reactogenicity was compared between persons who identified as pregnant and nonpregnant women. Descriptive analyses were conducted with the use of SAS software, version 9.4 (SAS Institute). All activities were reviewed by the CDC and were conducted in accordance with applicable federal law and CDC policy.

Results

V-SAFE SURVEILLANCE: LOCAL AND SYSTEMIC REACTOGENICITY IN PREGNANT PERSONS

Table 1.

Table 1. Characteristics of Persons Who Identified as Pregnant in the V-safe Surveillance System and Received an mRNA Covid-19 Vaccine.*

Characteristic	Pfizer–BioNTech Vaccine	Moderna Vaccine	Total
	number (percent)		
Total	19,252 (53.9)	16,439 (46.1)	35,691 (100)
Age at first vaccine dose			
16–19 yr	23 (0.1)	36 (0.2)	59 (0.2)
20–24 yr	469 (2.4)	525 (3.2)	994 (2.8)
25–34 yr	11,913 (61.9)	9,960 (60.6)	21,873 (61.3)
35–44 yr	6,002 (31.2)	5,011 (30.5)	11,013 (30.9)
45–54 yr	845 (4.4)	907 (5.5)	1,752 (4.9)
Pregnancy status			
Pregnant at time of vaccination	16,522 (85.8)	14,365 (87.4)	30,887 (86.5)
Positive pregnancy test after vaccination	2,730 (14.2)	2,074 (12.6)	4,804 (13.5)
Race and ethnic group†			
Participants with available data	14,320	13,232	27,552
Non-Hispanic White	10,915 (76.2)	9,982 (75.4)	20,897 (75.8)
Hispanic	1,289 (9.0)	1,364 (10.3)	2,653 (9.6)
Non-Hispanic Asian	972 (6.8)	762 (5.8)	1,734 (6.3)
Non-Hispanic Black	371 (2.6)	338 (2.6)	709 (2.6)
Non-Hispanic multiple races	315 (2.2)	292 (2.2)	607 (2.2)
Non-Hispanic other race	76 (0.5)	56 (0.4)	132 (0.5)
Non-Hispanic American Indian or Alaska Native	40 (0.3)	54 (0.4)	94 (0.3)
Non-Hispanic Native Hawaiian or other Pacific Islander	33 (0.2)	31 (0.2)	64 (0.2)
Unknown race or unknown ethnic group	309 (2.2)	353 (2.7)	662 (2.4)

* Shown are the characteristics of v-safe participants 16 to 54 years of age who identified as pregnant and who received a messenger RNA (mRNA) coronavirus disease 2019 (Covid-19) vaccine — BNT162b2 (Pfizer–BioNTech) or mRNA-1273 (Moderna) — from December 14, 2020, to February 28, 2021. Percentages may not total 100 because of rounding.
† Race and ethnic group were reported by the participants. Questions about race and ethnic group were added to v-safe after launch of the platform; not all pregnancies had recorded race and ethnic group at the time of data analysis. Therefore, data on race and ethnic group were missing for 22.8% of the total number of participants who identified as pregnant (4932 participants receiving the Pfizer–BioNTech vaccine and 3207 receiving the Moderna vaccine).

Characteristics of Persons Who Identified as Pregnant in the V-safe Surveillance System and Received an mRNA Covid-19 Vaccine.

Table 2.

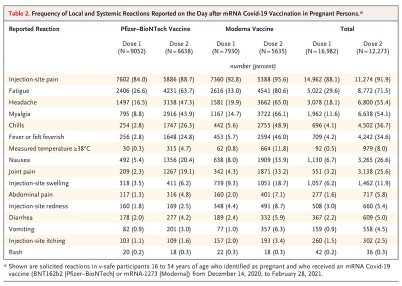


Table 2. Frequency of Local and Systemic Reactions Reported on the Day after mRNA Covid-19 Vaccination in Pregnant Persons.[a]

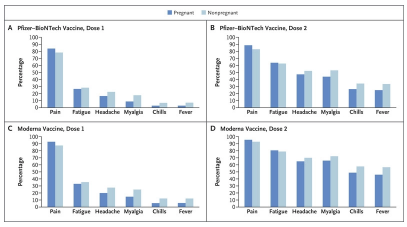
Reported Reaction	Pfizer–BioNTech Vaccine		Moderna Vaccine		Total	
	Dose 1 (N = 9052)	Dose 2 (N = 6638)	Dose 1 (N = 7930)	Dose 2 (N = 5635)	Dose 1 (N = 16,982)	Dose 2 (N = 12,273)
	number (percent)					
Injection-site pain	7602 (84.0)	5886 (88.7)	7360 (92.8)	5388 (95.6)	14,962 (88.1)	11,274 (91.9)
Fatigue	2406 (26.6)	4231 (63.7)	2616 (33.0)	4541 (80.6)	5,022 (29.6)	8,772 (71.5)
Headache	1497 (16.5)	3138 (47.3)	1581 (19.9)	3662 (65.0)	3,078 (18.1)	6,800 (55.4)
Myalgia	795 (8.8)	2916 (43.9)	1167 (14.7)	3722 (66.1)	1,962 (11.6)	6,638 (54.1)
Chills	254 (2.8)	1747 (26.3)	442 (5.6)	2755 (48.9)	696 (4.1)	4,502 (36.7)
Fever or felt feverish	256 (2.8)	1648 (24.8)	453 (5.7)	2594 (46.0)	709 (4.2)	4,242 (34.6)
Measured temperature ≥38°C	30 (0.3)	313 (4.7)	62 (0.8)	664 (11.8)	92 (0.5)	979 (8.0)
Nausea	492 (5.4)	1356 (20.4)	638 (8.0)	1909 (33.9)	1,130 (6.7)	3,265 (26.6)
Joint pain	209 (2.3)	1267 (19.1)	342 (4.3)	1871 (33.2)	551 (3.2)	3,138 (25.6)
Injection-site swelling	318 (3.5)	411 (6.2)	739 (9.3)	1051 (18.7)	1,057 (6.2)	1,462 (11.9)
Abdominal pain	117 (1.3)	316 (4.8)	160 (2.0)	401 (7.1)	277 (1.6)	717 (5.8)
Injection-site redness	160 (1.8)	169 (2.5)	348 (4.4)	491 (8.7)	508 (3.0)	660 (5.4)
Diarrhea	178 (2.0)	277 (4.2)	189 (2.4)	332 (5.9)	367 (2.2)	609 (5.0)
Vomiting	82 (0.9)	201 (3.0)	77 (1.0)	357 (6.3)	159 (0.9)	558 (4.5)
Injection-site itching	103 (1.1)	109 (1.6)	157 (2.0)	193 (3.4)	260 (1.5)	302 (2.5)
Rash	20 (0.2)	18 (0.3)	22 (0.3)	18 (0.3)	42 (0.2)	36 (0.3)

[a] Shown are solicited reactions in v-safe participants 16 to 54 years of age who identified as pregnant and who received an mRNA Covid-19 vaccine (BNT162b2 [Pfizer–BioNTech] or mRNA-1273 [Moderna]) from December 14, 2020, to February 28, 2021.

Frequency of Local and Systemic Reactions Reported on the Day after mRNA Covid-19 Vaccination in Pregnant Persons.

From December 14, 2020, to February 28, 2021, a total of 35,691 v-safe participants identified as pregnant. Age distributions were similar among the participants who received the Pfizer–BioNTech vaccine and those who received the Moderna vaccine, with the majority of the participants being 25 to 34 years of age (61.9% and 60.6% for each vaccine, respectively) and non-Hispanic White (76.2% and 75.4%, respectively); most participants (85.8% and 87.4%, respectively) reported being pregnant at the time of vaccination (Table 1). Solicited reports of injection-site pain, fatigue, headache, and myalgia were the most frequent local and systemic reactions after either dose for both vaccines (Table 2) and were reported more frequently after dose 2 for both vaccines. Participant-measured temperature at or above 38°C was reported by less than 1% of the participants on day 1 after dose 1 and by 8.0% after dose 2 for both vaccines.

Figure 1.



Most Frequent Local and Systemic Reactions Reported in the V-safe Surveillance System on the Day after mRNA Covid-19 Vaccination.

These patterns of reporting, with respect to both most frequently reported solicited reactions and the higher reporting of reactogenicity after dose 2, were similar to patterns observed among nonpregnant women (Figure 1). Small differences in reporting frequency between pregnant persons and nonpregnant women were observed for specific reactions (injection-site pain was reported more frequently among pregnant persons, and other systemic reactions were reported more frequently among nonpregnant women), but the overall reactogenicity profile was similar. Pregnant persons did not report having severe reactions more frequently than nonpregnant women, except for nausea and vomiting, which were reported slightly more frequently only after dose 2 (Table S3).

V-SAFE PREGNANCY REGISTRY: PREGNANCY OUTCOMES AND NEONATAL OUTCOMES

Table 3.

Table 3. Characteristics of V-safe Pregnancy Registry Participants.*

Characteristic	Pfizer–BioNTech Vaccine	Moderna Vaccine	Total
		number (percent)	
Total	2136 (54.0)	1822 (46.0)	3958 (100)
Age at first vaccine dose†			
20–24 yr	17 (0.8)	19 (1.0)	36 (0.9)
25–34 yr	1335 (62.5)	1238 (67.9)	2573 (65.0)
35–44 yr	777 (36.4)	560 (30.7)	1337 (33.8)
45–54 yr	7 (0.3)	5 (0.3)	12 (0.3)
Race and ethnic group‡			
Non-Hispanic White	1663 (77.9)	1463 (80.3)	3126 (79.0)
Hispanic	164 (7.7)	151 (8.3)	315 (8.0)
Non-Hispanic Asian	225 (10.5)	138 (7.6)	363 (9.2)
Non-Hispanic Black	24 (1.1)	26 (1.4)	50 (1.3)
Non-Hispanic multiple races	42 (2.0)	30 (1.6)	72 (1.8)
Non-Hispanic American Indian or Alaskan Native	5 (0.2)	1 (0.1)	6 (0.2)
Non-Hispanic Native Hawaiian or other Pacific Islander	6 (0.3)	3 (0.2)	9 (0.2)
Missing data or participant declined to answer	7 (0.3)	10 (0.5)	17 (0.4)
Timing of first eligible dose			
Periconception: within 30 days before last menstrual period	55 (2.6)	37 (2.0)	92 (2.3)
First trimester: <14 wk	615 (28.8)	517 (28.4)	1132 (28.6)
Second trimester: ≥14 and <28 wk	932 (43.6)	782 (42.9)	1714 (43.3)
Third trimester: ≥28 wk	533 (25.0)	486 (26.7)	1019 (25.7)
Missing data	1 (<0.1)	0	1 (<0.1)
Covid-19 infection during pregnancy			
No Covid-19 infection	2084 (97.6)	1779 (97.6)	3863 (97.6)
Before vaccination	32 (1.5)	24 (1.3)	56 (1.4)
≤14 days after first eligible dose of vaccination	3 (0.1)	7 (0.4)	10 (0.3)
>14 days after first eligible dose of vaccination	9 (0.4)	3 (0.2)	12 (0.3)
Missing data	8 (0.4)	9 (0.5)	17 (0.4)

* Shown are registry participants who received an mRNA Covid-19 vaccine (BNT162b2 [Pfizer–BioNTech] or mRNA-1273 [Moderna]) from December 14, 2020, to February 28, 2021. Percentages may not total 100 because of rounding.
† The v-safe pregnancy registry is only enrolling pregnant persons 18 years of age or older; at the time of this analysis, no participants were younger than 20 years of age.
‡ Race and ethnic group were reported by the participants.

Characteristics of V-safe Pregnancy Registry Participants.

As of March 30, 2021, the v-safe pregnancy registry call center attempted to contact 5230 persons who were vaccinated through February 28, 2021, and who identified during a v-safe survey as pregnant at or shortly after Covid-19 vaccination. Of these, 912 were unreachable, 86 declined to participate, and 274 did not meet inclusion criteria (e.g., were never pregnant, were pregnant but received vaccination more than 30 days before the last menstrual period, or did not provide enough information to determine eligibility). The registry enrolled 3958 participants with vaccination from December 14, 2020, to February 28, 2021, of whom 3719 (94.0%) identified as health care personnel. Among enrolled participants, most were 25 to 44 years of age (98.8%), non-Hispanic White (79.0%), and, at the time of interview, did not report a Covid-19 diagnosis during pregnancy (97.6%) (Table 3). Receipt of a first dose of vaccine meeting registry-eligibility criteria was reported by 92 participants (2.3%) during the periconception period, by 1132 (28.6%) in the first trimester of pregnancy, by 1714 (43.3%) in the second trimester, and by 1019 (25.7%) in the third trimester (1 participant was missing information to determine the timing of vaccination) (Table 3). Among 1040 participants (91.9%) who received a vaccine in the first trimester and 1700 (99.2%) who received a vaccine in the second trimester, initial data had been collected and follow-up scheduled at designated time points approximately 10 to 12 weeks apart; limited follow-up calls had been made at the time of this analysis.

Table 4.

Table 4. Pregnancy Loss and Neonatal Outcomes in Published Studies and V-safe Pregnancy Registry Participants.

Participant-Reported Outcome	Published Incidence*	V-safe Pregnancy Registry†
	%	*no./total no. (%)*
Pregnancy loss among participants with a completed pregnancy		
Spontaneous abortion: <20 wk[15-17]‡	Not applicable	104
Stillbirth: ≥ 20 wk[18,19]	<1	1/725 (0.1)§
Neonatal outcome among live-born infants		
Preterm birth: <37 wk[21,22]	8–15	60/636 (9.4)¶
Small size for gestational age[23,24]‖	3.5	23/724 (3.2)
Congenital anomalies[12,13]	3	16/724 (2.2)
Neonatal death[25]††	<1	0/724

* The populations from which these rates are derived are not matched to the current study population for age, race and ethnic group, or other demographic and clinical factors.
† Data on pregnancy loss are based on 827 participants in the v-safe pregnancy registry who received an mRNA Covid-19 vaccine (BNT162b2 [Pfizer–BioNTech] or mRNA-1273 [Moderna]) from December 14, 2020, to February 28, 2021, and who reported a completed pregnancy. A total of 700 participants (84.6%) received their first eligible dose in the third trimester. Data on neonatal outcomes are based on 724 live-born infants, including 12 sets of multiples.
‡ A total of 96 of 104 spontaneous abortions (92.3%) occurred before 13 weeks of gestation. No denominator was available to calculate a risk estimate for spontaneous abortions, because at the time of this report, follow-up through 20 weeks was not yet available for 905 of the 1224 participants vaccinated within 30 days before the first day of the last menstrual period or in the first trimester. Furthermore, any risk estimate would need to account for gestational week–specific risk of spontaneous abortion.
§ The denominator includes live-born infants and stillbirths.
¶ The denominator includes only participants vaccinated before 37 weeks of gestation.
‖ Small size for gestational age indicates a birthweight below the 10th percentile for gestational age and infant sex according to INTERGROWTH-21st growth standards (http://intergrowth21.ndog.ox.ac.uk). These standards draw from an international sample including both low-income and high-income countries but exclude children with coexisting conditions and malnutrition. They can be used as a standard for healthy children growing under optimal conditions.
** Values include only major congenital anomalies in accordance with the Metropolitan Atlanta Congenital Defects Program 6-Digit Code Defect List (www.cdc.gov/ncbddd/birthdefects/macdp.html); all pregnancies with major congenital anomalies were exposed to Covid-19 vaccines only in the third trimester of pregnancy (i.e., well after the period of organogenesis).
†† Neonatal death indicates death within the first 28 days after delivery.

Pregnancy Loss and Neonatal Outcomes in Published Studies and V-safe Pregnancy Registry Participants.

Among 827 participants who had a completed pregnancy, the pregnancy resulted in a live birth in 712 (86.1%), in a spontaneous abortion in 104 (12.6%), in stillbirth in 1 (0.1%), and in other outcomes (induced abortion and ectopic pregnancy) in 10 (1.2%). A total of 96 of 104 spontaneous abortions (92.3%) occurred before 13 weeks of gestation (Table 4), and 700 of 712 pregnancies that resulted in a live birth (98.3%) were among persons who received their first eligible vaccine dose in the third trimester. Adverse outcomes among 724 live-born infants — including 12 sets of multiple gestation — were preterm birth (60 of 636 among those vaccinated before 37 weeks [9.4%]), small size for gestational age (23 of 724 [3.2%]), and major congenital anomalies (16 of 724 [2.2%]); no neonatal deaths were reported at the time of interview. Among the participants with completed pregnancies who reported congenital anomalies, none had received Covid-19 vaccine in the first trimester or periconception period, and no specific pattern of congenital anomalies was observed. Calculated proportions of pregnancy and neonatal outcomes appeared similar to incidences published in the peer-reviewed literature (Table 4).

ADVERSE-EVENT FINDINGS ON THE VAERS

During the analysis period, the VAERS received and processed 221 reports involving Covid-19 vaccination among pregnant persons; 155 (70.1%) involved nonpregnancy-specific adverse events, and 66 (29.9%) involved pregnancy- or neonatal-specific adverse events (Table S4). The most frequently reported pregnancy-related adverse events were spontaneous abortion (46 cases; 37 in the first trimester, 2 in the second trimester, and 7 in which the trimester was unknown or not reported), followed by stillbirth, premature rupture of membranes, and vaginal bleeding, with 3 reports for each. No congenital anomalies were reported to the VAERS, a requirement under the EUAs.

Discussion

This U.S. surveillance review of the safety of mRNA Covid-19 vaccines during pregnancy and the periconception period indicates that some pregnant persons in the United States are choosing to be vaccinated against Covid-19 in all trimesters of pregnancy. Solicited local and systemic reactions that were reported to the v-safe surveillance system were similar among persons who identified as pregnant and nonpregnant women. Although not directly comparable, the proportions of adverse pregnancy and neonatal outcomes (i.e., preterm birth, small size for gestational age, congenital anomalies, and neonatal death) among participants with completed pregnancies from the v-safe pregnancy registry appear to be similar to the published incidences in pregnant populations studied before the Covid-19 pandemic.[15-26] Many participants in the v-safe pregnancy registry were included in the phase 1a (highest) priority group for Covid-19 vaccination owing to their work as health care personnel.[27] V-safe participation is voluntary, and registration information is not uniformly available at all vaccination locations, although information about the surveillance system is included on the EUA fact sheets for health care providers and patients. Thus, comparisons of the proportions of vaccinated women with these outcomes to previously published estimates are limited by likely differences between these populations in age, ethnic group, and other social, demographic, and clinical characteristics that are

known to be associated with pregnancy and neonatal outcomes. However, such comparisons are helpful to provide a crude sense of whether there are any unexpected safety signals in these early data. At the time of this analysis, just 14.7% of persons who identified as pregnant in the v-safe surveillance system had been contacted to offer enrollment in the pregnancy registry.

Other limitations should also be noted. As with all participant-reported surveillance systems, mistakes in completion of v-safe health surveys can result in misclassification of participants as pregnant; as a result, data for local and systemic reactions that participants reported to the v-safe platform may include some reports from nonpregnant persons. Participants are not required to complete surveys at the same time every day, and our ability to assess onset or duration of adverse events, such as fever, is limited. The registry data are preliminary, are from a small sample, and describe mostly neonatal outcomes from third-trimester vaccination; the findings may change as additional pregnancy outcomes are reported and the sample size increases, which may facilitate detection of rare outcomes. We were unable to evaluate adverse outcomes that might occur in association with exposures earlier in pregnancy, such as congenital anomalies, because no pregnant persons who were vaccinated early in pregnancy have had live births captured in the v-safe pregnancy registry to date; follow-up is ongoing. In addition, the proportion of pregnant persons who reported spontaneous abortion may not reflect true postvaccination proportions because participants might have been vaccinated after the period of greatest risk in the first trimester, and very early pregnancy losses might not be recognized. Whereas some pregnancies with vaccination in the first and early second trimester have been completed, the majority are ongoing, and a direct comparison of outcomes on the basis of timing of vaccination is needed to define the proportion of spontaneous abortions in this cohort. Because of sample-size constraints, both pregnancy and neonatal outcomes were calculated as a proportion instead of a rate.

Our preliminary analysis uses participant-reported data and has limited information on other potential risk factors for adverse pregnancy and neonatal outcomes. The VAERS is subject to the limitations of passive surveillance.[12] Despite EUA mandatory reporting requirements and CDC guidance on VAERS reporting, there is probably substantial underreporting of pregnancy- and neonatal-specific adverse events. We also do not know the total number of Covid-19 vaccine doses administered to pregnant persons, which further limits our ability to estimate rates of reported adverse events from VAERS data. Among pregnancy-specific conditions reported to the VAERS after Covid-19 vaccination, miscarriage was the most common. This is similar to what was observed during the influenza A (H1N1) pandemic in 2009 after the introduction of the 2009 H1N1 inactivated influenza vaccine, where miscarriage was the most common adverse event reported by pregnant persons who received that vaccine.[28]

In addition to vaccination protecting women against Covid-19 and its complications during pregnancy, emerging evidence has shown transplacental transfer of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) antibodies after maternal Covid-19 vaccination during the third trimester, which suggests that maternal vaccination might provide some level of protection to the neonate.[29-32] However, we do not have data on antibody transfer and level of protection relative to the timing of vaccination. The CDC and the FDA are continuing to monitor and disseminate information about the safety of mRNA and additional types of Covid-19 vaccines in pregnant persons.

Early data from the v-safe surveillance system, the v-safe pregnancy registry, and the VAERS do not indicate any obvious safety signals with respect to pregnancy or neonatal outcomes associated with Covid-19 vaccination in the third trimester of pregnancy. Continued monitoring is needed to further assess maternal, pregnancy, neonatal, and childhood outcomes associated with maternal Covid-19 vaccination, including in earlier stages of pregnancy and during the preconception period. Meanwhile, the present data can help inform decision making about vaccination by pregnant persons and their health care providers.

Funding and Disclosures

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

The findings and conclusions in this article are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention (CDC) or the Food and Drug Administration (FDA). Mention of a product or company name is for identification purposes only and does not constitute endorsement by the CDC or the FDA. All authors are U.S. government employees or U.S. government contractors and do not have any material conflicts of interest. Oracle provided in-kind technical support to build and maintain the v-safe after vaccination health checker infrastructure for data capture and messaging to participants.

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A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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The members of the CDC v-safe COVID-19 Pregnancy Registry Team are listed in the Supplementary Appendix, available at NEJM.org.

Supplementary Material

Supplementary Appendix	PDF	234KB
Disclosure Forms	PDF	445KB
Data Sharing Statement	PDF	69KB

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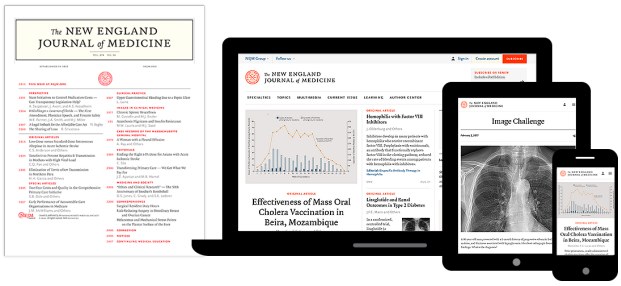

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