



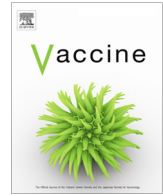
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Post-authorization surveillance of adverse events following COVID-19 vaccines in pregnant persons in the vaccine adverse event reporting system (VAERS), December 2020 – October 2021



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ABSTRACT

Background: Pregnant persons are at increased risk of severe illness from COVID-19 infection, including intensive care unit admission, mechanical ventilation, and death compared with non-pregnant persons of reproductive age. Limited data are available on the safety of COVID-19 vaccines administered during and around the time of pregnancy.

Objective: To evaluate and summarize reports to the Vaccine Adverse Event Reporting System (VAERS), a national spontaneous reporting system, in pregnant persons who received a COVID-19 vaccine to assess for potential vaccine safety problems.

Methods: We searched VAERS for US reports of adverse events (AEs) in pregnant persons who received a COVID-19 vaccine from 12/14/2020–10/31/2021. Clinicians reviewed reports and available medical records. Crude reporting rates for selected AEs were calculated, and disproportional reporting was assessed using data mining methods.

Results: VAERS received 3,462 reports of AEs in pregnant persons who received a COVID-19 vaccine; 1,831 (52.9%) after BNT162b2, 1,350 (38.9%) after mRNA-1273, and 275 (7.9%) after Ad26.COV2.S. Eight maternal deaths and 12 neonatal deaths were reported. Six-hundred twenty-one (17.9%) reports were serious. Pregnancy-specific outcomes included: 878 spontaneous abortions (<20 weeks), 101 episodes of vaginal bleeding, 76 preterm deliveries (<37 weeks), 62 stillbirths (≥20 weeks), and 33 outcomes with birth defects. Crude reporting rates for preterm deliveries and stillbirths, as well as maternal and neonatal mortality rates were below background rates from published sources. No disproportional reporting for any AE was observed.

Conclusions: Review of reports to VAERS following COVID-19 vaccines in pregnant persons did not identify any concerning patterns of maternal or infant-fetal outcomes.

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1. Introduction

Pregnant and recently pregnant persons with coronavirus disease 2019 (COVID-19) have an increased risk of severe illness that

results in intensive care unit admission, mechanical ventilation, and death compared with non-pregnant women of reproductive age [1–4]. Pregnant persons with COVID-19 are at increased risk of preterm birth and may be at risk of other adverse pregnancy outcomes compared with pregnant persons without COVID-19. Three COVID-19 vaccines were authorized for emergency use in the United States (U.S.) by the Food and Drug Administration (FDA) during the study period, with two of these vaccines receiving full FDA approval since the end of the study period. Two COVID-19

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vaccines are messenger ribonucleic acid (mRNA) based and were authorized in December 2020: BNT162b2 from Pfizer Inc/BioNTech and mRNA-1273 from Moderna [5,6]. Ad26.COV2.S from Janssen Pharmaceuticals Companies of Johnson & Johnson uses a recombinant replication-incompetent adenovirus type 26 (Ad26) vector to stimulate an immune response and was authorized for emergency use at the end of February 2021 [7]. Data on safety of these vaccines in pregnancy were limited because pregnant persons were excluded from pre-authorization clinical trial enrollment and were not eligible to receive additional doses of the vaccine if found to be pregnant during the studies [8,9]. The Centers for Disease Control and Prevention's (CDC) Advisory Committee on Immunization Practices (ACIP) COVID-19 vaccine initial allocation guidance stated that pregnant people may choose to get vaccinated [10–12]. In August 2021, CDC updated its interim clinical considerations for use of COVID-19 vaccines to recommend COVID-19 vaccination during pregnancy [13]. The CDC and the FDA leveraged existing and implemented new vaccine safety monitoring systems to capture information about vaccination during pregnancy to better understand the safety profiles of COVID-19 vaccines in pregnancy.

A study of the safety of mRNA COVID-19 vaccines in pregnant persons during the first two months of the vaccination program found no safety concerns for these vaccines [14]. This preliminary analysis included data from three systems: v-safe [15] the v-safe COVID-19 Vaccine Pregnancy Registry, and the Vaccine Adverse Event Reporting System (VAERS) [16]. During the time since that initial publication, additional reports of adverse events among pregnant persons have been submitted to VAERS. This manuscript describes VAERS reports for pregnant persons who received any of the three authorized COVID-19 vaccines since the start of the U.S. vaccination program in December 2020.

2. Material and methods

2.1. Vaccine adverse events reporting system (VAERS)

VAERS is a national passive vaccine safety surveillance system, implemented in 1990 and co-administered by the CDC and the FDA that receives spontaneous reports of adverse events (AEs) from healthcare providers, vaccine recipients, manufacturers, and other reporters following vaccination [16]. Vaccine manufacturers are required, by law, to report AEs that come to their attention, and healthcare providers are required to report AEs that are considered a contraindication to further doses of vaccine and those specified in the VAERS table of reportable events following vaccination [16]. VAERS data are monitored in real time to detect new, unusual, or rare vaccine AEs as well as increases in known AEs.

Signs and symptoms of AEs reported to VAERS are coded by trained personnel and entered into a database using the Medical Dictionary for Regulatory Activities (MedDRA), a clinically validated, internationally standardized medical terminology [17]. A VAERS report may be assigned one or more MedDRA preferred terms (PT). A PT is a distinct descriptor for a symptom, sign, disease, diagnosis, therapeutic indication, investigation, surgical, or medical procedure, or medical, social, or family history characteristic [17]. Reports are further classified as serious as per the U.S. Code of Federal Regulations if one of the following is reported: death, life-threatening illness, hospitalization or prolongation of hospitalization, permanent disability, or a congenital anomaly [18]. Methods used to analyze and categorize pregnancy reports in VAERS have been described previously [19].

2.2. Review of reports

We identified U.S. reports of pregnant persons who received COVID-19 vaccine and who reported an AE to VAERS by using a

pregnancy-status question in the VAERS form, specific MedDRA codes, and a text-string search of the symptom field in the VAERS form. Medical records were requested for all serious reports. Physicians (PM, CO) manually reviewed all VAERS reports to distinguish pregnancy from non-pregnancy reports. Obstetricians reviewed medical records of case-reports containing more specialized pregnancy information (CO, EC). Reports indicating that COVID-19 vaccination was administered prior to the last menstrual period or during the post-partum period were excluded. When more than one AE was reported for the same person, we selected what we believed was the primary clinical event of concern after medical review. If the report described an AE in the pregnant person and their fetus or infant, we considered this a single report but treated AEs as separate. AEs were classified as pregnancy-specific (e.g., spontaneous abortion, stillbirth), non-pregnancy specific (e.g., local or systemic reaction), infant or neonatal (e.g., birth defect), or as certain pre-specified conditions of special interest (e.g., anaphylaxis, SARS-CoV-2 infection after COVID-19 vaccination).

2.3. Analysis

We calculated frequencies of the most common MedDRA coding terms, demographic and selected pregnancy and fetal outcomes, and reporting rates for selected outcomes using SAS version 9.3 (SAS Institute, Cary, NC).

We used empirical Bayesian (EB) data mining to identify AEs that were reported more frequently than expected following COVID-19 vaccines compared to other vaccines in VAERS. We also identified COVID-19 vaccine-adverse event combinations that were reported more frequently than expected among pregnant women aged 16–54 years [20]. We conducted the analyses using the Multi-Item Gamma Poisson Shrinker (MGPS) algorithm [20,21] in Oracle's Empirica™ Signal System. The main statistical scores computed were EBG, EB05, EB95, representing the empirical Bayes geometric mean and the 90% confidence interval. We used published criteria to identify AEs that were reported at least twice as frequently as would be expected following a COVID-19 vaccine (i.e., lower bound of the 90% confidence interval surrounding the EB geometric mean [EB05] > 2) [21].

2.4. Reporting rates

We used national vital statistics data on monthly live births and fetal deaths to calculate rates. To account for the study period of interest, we applied a proportion of 0.58 to December birth and fetal death values as vaccines were only available for a portion of December. To estimate the number of live births, we used national provisional counts by month for 2020 and 2021 [22]. We estimate 3,173,387 live births occurred in the United States during our study period. Fetal death microdata from 2019 was used to determine monthly fetal deaths [23]. Consistent with National Center for Health Statistic methods [24] we included fetal deaths of 20 weeks' gestation or more as determined by obstetric estimate, among women 15–44 years, excluding foreign residents, for December 2020 through October 2021. Approximately 18,945 stillbirths occurred during the study period. We then applied COVID-19 vaccination coverage rates for women receiving vaccination during pregnancy by month. A vaccination coverage of 2.6% was applied to monthly live births and stillbirths for December 2020, January 2021, and February 2021 as only cumulative data were available [25]. Based on weekly vaccination coverage data available for April through October 2021, a monthly average was applied to live births and stillbirths occurring these months providing the number of live births and stillbirths that occurred where a COVID-19 vaccine may have been received during pregnancy [25]. The rate of stillbirths was calculated monthly by dividing the number of still-

births observed by the total number of stillbirths and live births that occurred where a vaccine may have been received during pregnancy. The rate of preterm births was calculated by dividing the number of preterm births observed by live births where a vaccine may have been received. Similarly, the maternal and infant mortality rate after COVID-19 vaccination was calculated by dividing the number of maternal or infant deaths observed by live birth. See [supplementary material](#)

2.5. Ethics

Because VAERS is a routine public health surveillance program that does not meet the definition of research, it is not subject to Institutional Review Board review and informed consent requirements.

3. Results

From December 14, 2020 through October 31, 2021, VAERS received a total of 603,786 reports after receipt of any COVID-19 vaccine; 3,462 of these reports involved pregnant persons: 1,831 (52.9%) after BNT162b2, 1,350 (39.0%) after mRNA-1273, 275 (7.9%) after Ad26.COV2.S and 6 had unknown manufacturer. Medical records were obtained for 713 (20.6%) of 3,462 reports. Characteristics of pregnancy reports into VAERS can be seen in [Table 1](#). Six-hundred twenty-one (17.9%) reports were coded as serious, including eight maternal deaths. Most COVID-19 vaccines were reported as administered during the first (1,040; 45.5%) or second trimester of pregnancy (727; 31.8%). The most frequent pregnancy-specific AEs reported following any COVID-19 vaccine administration ([Table 2](#)) were spontaneous abortion (SAB) in 878 women (25.4%), vaginal bleeding in 101 (2.9%), premature delivery in 76 (2.2%) and stillbirth in 62 (1.8%). Most (81.3%; 490/603) SABs with gestational age data were reported to occur at < 12 weeks' gestation and in 338/859 (39.3%) the pregnant person was 35 years of age or older. Among 849 SAB reports with onset interval information (onset interval is the period of time from vaccination to presentation of symptoms/signs of the adverse event), the onset interval was 0–3 days in 26.4%, 4–7 days in 12.0%, 8–14 days in 15.5%, and ≥ 15 days in 46.1%

Eight maternal deaths were reported. Cause of death could be ascertained through medical record review in four reports: pulmonary embolism (case 1), amniotic fluid embolism (case 2), eclampsia with peripartum cardiomyopathy (case 3), and acute cerebellar intraparenchymal hemorrhage secondary to severe persistent thrombocytopenia due to acute myelogenous leukemia (case 4). In two other cases (cases #5–#6) the patients experienced sudden clinical deterioration leading to death and in one of them, amniotic fluid embolism, a rare but acute life-threatening complication of childbirth [26], was suspected as the event leading to death. No medical records were available for two reports (cases #7–#8), and the information in the VAERS reports was very limited. A brief description of each report is available in supplementary Table S1.

The most common non-pregnancy specific AEs were injection site and systemic reactions ([Table 3](#)), irrespective of type of vaccine or brand. Among pre-specified conditions of interest, 17 reports of Bell's palsy or facial paralysis were reported but only two could be verified through medical record review. Eleven were after BNT162b2 and 6 after mRNA-1273. Median onset interval was 7 days (range, 0–70 days). Three reports were serious. One report of Guillain Barré Syndrome – Miller Fisher variant was reported and verified in a woman at 27 weeks' gestation expecting her first child, 3 weeks after receiving the Ad26.COV2.S vaccine. This patient was hospitalized for 5 days and by the time of discharge she was significantly improved and fetal surveillance did not show findings of concern. A second report of Guillain Barre Syndrome (GBS) after mRNA-1273 was reported but could not be verified as no medical records were available. Ten reports of anaphylaxis or possible anaphylaxis were reported. Two were verified by review of medical records. Eight patients had recovered but no information was available for other two. Four reports of myocarditis and one report of pericarditis that met CDC's case definition for myopericarditis [27] were reported to VAERS. For myocarditis, two reports were after BNT162b2, one report after mRNA-1273 and one after Ad26.COV2.S. The one report of pericarditis was after mRNA-1273. All 5 patients recovered.

Fifty-eight reports of SARS-CoV-2 infection after COVID-19 vaccination in pregnant persons were reported to VAERS. Fourteen were coded as serious but for reasons unrelated to COVID-19 infec-

Table 1
Characteristics of VAERS reports received following COVID-19 vaccines in pregnant persons, United States, December 14, 2020–October 31, 2021.

Characteristic	All vaccines ^a	<u>BNT162b2</u> Vaccine	<u>mRNA-1273</u> Vaccine	Ad26.COV2.S Vaccine
Total reports	3,462	1,831	1,350	275
Maternal age in years, median (IQR) ^b	33 (30–36)	33 (30–36)	33 (30–36)	33 (30–36)
Reports with maternal, age ≥ 35 years ^b , n (%)	1,233 (36.3)	660 (36.0)	477 (35.3)	95 (34.5)
Interval from vaccination to adverse event in days, median (IQR) ^c	2 (0–15)	2 (0–17)	2 (0–14)	1 (0–11)
Gestational age in weeks at time of vaccination, median (IQR) ^d	15.0 (7–26)	16 (6–27)	14 (7–25)	18 (9–28)
Reports of serious adverse events, n (%) ^e	621 (17.9)	359 (19.6)	217 (16.1)	42 (15.3)
Type of reporter, N (%)				
Patient/parent	2,213 (63.9)	1,116 (61.0)	920 (68.1)	176 (64.0)
Provider	747 (21.6)	401 (21.9)	296 (21.9)	46 (16.7)
Other	157 (4.5)	83 (4.5)	60 (4.4)	14 (5.1)
Manufacturer	345 (10.0)	231 (12.6)	74 (5.5)	39 (14.2)
Trimester of pregnancy at time of vaccination, N (%)				
First (0 – 13 weeks)	1,040 (45.5)	567 (44.7)	413 (48.5)	60 (35.9)
Second (14 – 27 weeks)	727 (31.8)	396 (31.2)	271 (31.8)	59 (35.3)
Third (>= 28 weeks)	520 (22.7)	304 (24.0)	167 (19.6)	48 (28.7)

IQR (interquartile range).

^a Brand unknown in 6 reports;

^b Maternal age unknown in 69 reports.

^c Onset interval unknown for 106 reports with adverse events

^d Gestational age at time of vaccination is unknown for 1,174 reports.

^e A report is defined as serious when one of the following is reported: death, life-threatening illness, hospitalization or prolongation of hospitalization, permanent disability, a congenital anomaly[12]

Table 2
Reported pregnancy-specific and infant adverse events (AEs)[†] in pregnant persons following receipt of COVID-19 vaccines, VAERS, December 2020–October 2021.

Adverse events [‡]	All vaccines	BNT162b2 Vaccine	mRNA-1273 Vaccine	Ad26.COVS.2 Vaccine
Total reports	3,462	1,831	1,350	275
	N (%)			
Pregnancy specific[‡]	1,377 (39.8)	783 (42.8)	506 (37.5)	84 (30.5)
Spontaneous abortion (<20 weeks gestation)	878 (25.4)	479 (26.2)	341 (25.3)	55 (20.0)
Vaginal bleeding	101 (2.9)	59 (3.2)	36 (2.7)	6 (2.2)
Preterm delivery (<37 weeks)	76 (2.2)	48 (2.6)	25 (1.9)	3 (1.1)
Stillbirth (≥20 weeks gestation) [‡]	62 (1.8)	38 (2.1)	20 (1.5)	4 (1.5)
Premature rupture of membranes	25 (0.7)	17 (0.9)	8 (0.6)	0
Placental abnormalities	34 (1.0)	17 (0.9)	13(1.0)	4 (1.5)
Preeclampsia/gestational hypertension	43 (1.2)	20 (1.1)	13 (1.0)	9 (3.3)
Ectopic/molar pregnancy	17 (0.5)	9 (0.5)	6 (0.4)	2 (0.7)
Gestational diabetes	15 (0.4)	10 (0.5)	4 (0.3)	1 (0.4)
Maternal deaths	8 (0.2)	6 (0.3)	2 (0.1)	0
Other ^a	91 (2.6)	59 (3.2)	27 (2.0)	5 (1.8)
Infant[‡]	108 (3.1)	64 (3.5)	40 (3.0)	4 (1.5)
Neonatal death	12 (0.3)	9 (0.5)	1 (0.07)	2 (0.7)
Birth defects	26 (0.8)	11 (0.6)	15 (1.1)	0
Infant in intensive care unit (diverse abnormalities)	21 (0.6)	10 (0.5)	10 (0.7)	1 (0.4)
^b Other infant conditions	49 (1.4)	34 (1.9)	14 (1.0)	1 (0.4)

[†]Adverse events are not mutually exclusive; [‡]Percentages for pregnancy and infant conditions calculated using total pregnancy reports. ^aFor other pregnancy-specific: Delivery (29), contractions (18), fetal growth restriction (11), amniotic fluid anomalies/polyhydramnios (9), decreased fetal movement (7), elective ab (5), subchorionic hematoma/hemorrhage (7), chromosomal abnormalities (7), unviable pregnancy (3), bleeding (2), and one each report of: shortened cervix, gestational thrombocytopenia/fever/chills/fetal heart rate deceleration, fetal loss, cervical insufficiency, umbilical cord prolapse, facial numbness/thrombus in placenta, fetal tachycardia, HCG testing, rupture of membranes, twin pregnancy, increased fetal movement, chorioamnionitis, postpartum, small for gestational age, fetal hypokinesia, rash/urticaria/vaginal birth of normal infant, postpartum hemorrhage, single umbilical artery, induced high blood pressure, conjoined twins, irregular heartbeat, fetal death/high blood pressure, twin pregnancy, fetal development disorder, prelabor rupture of membranes/breech presentation/post-partum hemorrhage, hydrops/termination of pregnancy, rupture of membranes, meconium stained fluid, uncomplicated pregnancy/term infant, false labor/fetal evaluation, term baby, uterine inversion/ mastitis/ endometriosis, marginal cord insertion

^bOther infant conditions include: preterm infant (5), low birth weight (4), fetal hydrops (3), premature closure of ductus arteriosus (2), healthy infant (2), large for gestational age, preterm infant/injured brain tissue, fetal tachycardia, infant seizures/ischemic brain injury, eroded skin lower legs, sub-amniotic hematoma/neonatal pneumonia, stopped lactating, laryngomalacia, baby brain not developing well, hypoxic-ischemic encephalopathy, fetal arrhythmia, hypoglycemia in infant, small for gestational age, respiratory distress/suspected spontaneous gastrointestinal perforation, cardiac abnormalities, normal delivery, LBW/infant with low blood glucose/high bilirubin, seizure, jaundice, neonatal disorder, bell's palsy infant, brain hemorrhage in fetus, platelet disorder in infant-bruise easily, hypertension/unilateral auditory neuropathy, pleural effusion in fetus, nummular eczema in infant

Table 3
Most common MedDRA codes after COVID-19 vaccines, combined and by brand, among non-pregnancy specific reports (1,611), VAERS, December 2020 – October 2021[†]

All vaccine brands (N = 2,002)	n	BNT162b2 vaccine (N = 1,006)	n	mRNA-1273 vaccine (N = 809)	n	Ad26.COVS.2 vaccine (N = 185)	n
Headache	434 (21.7)	Headache	211 21.0%	Headache	160 (19.8)	Pyrexia	77 (41.6)
Fatigue	422 (21.1)	Fatigue	209 20.8%	Fatigue	155 (19.2)	Chills	70 (37.8)
Pyrexia	381 (19.0)	Chills	159 15.8%	Chills	152 (18.8)	Headache	63 (34.1)
Chills	369 (18.4)	Pain	153 15.2%	Pain	145 (17.9)	Fatigue	58 (31.4)
Pain	342 (17.1)	Pyrexia	152 15.1%	Chills	139 (17.2)	Pain	43 (23.2)
Nausea	299 (14.9)	Nausea	143 14.2%	Pain in extremity	123 (15.2)	Nausea	36 (19.4)
Pain in extremity	266 (13.3)	Dizziness	122 12.1%	Nausea	120 (14.8)	Myalgia	24 (12.9)
Dizziness	225 (11.2)	Pain in extremity	122 12.1%	Injection site erythema	88 (10.9)	Pain in extremity	21 (11.4)
Injection site pain	186 (9.3)	Vomiting	85 8.5%	Injection site pain	87 (10.8)	Vomiting	18 (9.7)
Vomiting	165 (8.2)	Injection site pain	84 8.4%	Dizziness	86 (10.6)	Dizziness	17 (9.2)

[†] MedDRA codes are not mutually exclusive meaning one report may have several MedDRA codes
872 reports from vaccine manufacturers (not included in tables above) were received in large batches over a short period of time and were not manually reviewed. Automated analysis revealed the most common adverse events from this group were: pain in extremity (83;9.5%), headache (58;6.7%), fatigue (50; 5.7%), chills (38; 4.4%), injection site pain (38;4.4%), myalgia (38; 4.4%), fever (37; 4.2%), pain (34; 3.9%) nausea (27; 3.1%), dizziness (19; 2.2%), and spontaneous abortion (18; 2.1%)

tion (e.g., elevated blood pressure, scheduled cesarean section). Twenty were asymptomatic, 25 were symptomatic and 13 did not indicate if the patient presented symptoms. Thirty-eight SARS CoV-2 infections were after BNT162b2, twelve after mRNA-1273, 7 after Ad26.COVS.2 vaccine, and one of unknown brand.

One hundred seven infant conditions were reported which included 12 neonatal deaths (Table S2). Medical records noting the cause of death were available for three reports which included prematurity. One of these reports has been described before [14]. Thirty-three reports described a major birth defect or chromosomal abnormality. Eighteen and fifteen infants with birth defects

were reported for BNT162b2 and mRNA-1273 vaccines, respectively. In 16 reports the vaccine was administered during the first trimester. Supplementary table S3 shows the specific birth defects by brand of COVID-19 vaccine.

3.1. Data mining

Disproportionality analysis of COVID-19 vaccines did not reveal an elevated EB05 (>2) for any MedDRA PTs among pregnancy reports reported to VAERS.

Crude reporting rates

Using published [25] vaccination coverage data for COVID-19 vaccines, we estimated that the crude reporting rate of stillbirths is 17.3 reports per 100,000 stillbirths and live births, for preterm deliveries 21.4 reports per 100,000 live births, for maternal deaths 2.3 per 100,000 live births, and for neonatal deaths 3.4 per 100,000 live births (Table S4). All crude reporting rates were below published background rates for these conditions [28–30].

4. Discussion

During December 14, 2020 through October 31, 2021, VAERS has received and processed 603,786 reports of AEs after any COVID-19 vaccine. Of these, 3,462 (0.5%) were reports of pregnant persons. An initial assessment of pregnancy reports after the mRNA vaccines during the first two months of vaccine roll-out [14] did not identify unexpected or unusual increased reporting of any adverse event. In the following months since this initial report, we have monitored pregnancy reports received by VAERS for any unexpected increase in adverse events, particularly pregnancy specific conditions. We did not find disproportional reporting of any adverse event nor increased reporting rates for certain pregnancy-specific conditions compared to their background rates. A small number of maternal and neonatal deaths were reported but the mortality rates estimated from them were below published statistics on maternal and neonatal mortality [28,29].

The most common pregnancy-specific AE reported was SAB which accounted for a quarter of all reports submitted. The one common risk factor for 39% of them was an advanced age of ≥ 35 years. SAB are relatively common during pregnancy and their rates increase with increasing age with rates as high as 80% at 45 years of age [30]. We did not find disproportional reporting for any MedDRA PT for SAB in data mining analysis. Stillbirths (≥ 20 weeks gestation) were reported much less frequently than expected with 62 reports overall and an estimated reporting rate of 17.3 reports per 100,000 stillbirths and live births, which is well below the background rate of 595 per 100,000 live births and fetal death [30]. The reporting rate to VAERS for stillbirths may be due to underreporting, which is a limitation in VAERS. Our findings in VAERS for SAB reports and other pregnancy-specific conditions after the COVID-19 vaccines did not show any safety concern but given the limitations of VAERS any finding needs to be interpreted carefully. A recent study from the v-safe pregnancy registry found a cumulative risk of spontaneous abortion after a mRNA COVID-19 vaccine of 13%, consistent with background rates of this condition [31]. Another study in the Vaccine Safety Datalink found that among women with spontaneous abortions, the odds of COVID-19 vaccine exposure were not increased in the prior 28 days compared with women with ongoing pregnancies [32]. Preterm delivery is a pregnancy outcome of interest which in 2020 occurred at a rate of 10.1% [33]. Many studies on the effect of vaccination and preterm delivery have been done with the seasonal or 2009 H1N1 influenza vaccines [33]. Most studies have either shown a protective association between influenza vaccine and preterm delivery or no effect. A few showed a slight increased risk [34]. COVID-19 vaccines are different from influenza vaccines, which are conventional inactivated viral subunit vaccines. However, we did not observe increased reporting or a concerning reporting rate for preterm births following COVID-19 vaccination.

Among 33 infants/fetuses with birth defects or chromosomal abnormalities reported to VAERS, we did not observe unusual clustering of birth defects (Table S3). For reports describing non-pregnancy specific AEs the most common conditions reported were local and systemic reactions which was consistent with findings from pre-authorization studies in non-pregnant persons [5–7]

and from pregnant persons enrolled in the v-safe pregnancy registry [15].

Other pre-specified conditions identified during pregnancy included 17 reports of Bell's palsy or facial paralysis. One verified report of Guillain Barré Syndrome (GBS) was reported in a pregnant person after the Ad26.COV2.S vaccine. GBS is an acute, immune-mediated paralytic disorder of the peripheral nervous system [35] which has been found to be associated with administration of the Ad26.COV2.S vaccine [36]. Ten reports of anaphylaxis or possible anaphylaxis were reported but only two could be confirmed as anaphylaxis. COVID-19 infections following vaccination were reported in 58 pregnant persons. Consistent with increased reporting of myopericarditis reports in the VAERS database, we noted a small number of these reports in pregnant persons that met case definition for this condition [37].

VAERS is a national surveillance system used to detect signals of potential adverse events following vaccination. During the post-authorization monitoring of AEs after the COVID-19 vaccines, VAERS has fulfilled its mission by being able to identify rare AEs although no disproportional reporting was observed for pregnancy-specific events [16]. For example, increased reports in VAERS of myocarditis following receipt of a second dose of mRNA COVID-19 vaccines, prompted changes in the emergency use authorization provider information sheets [37]. Passive surveillance systems such as VAERS have a number of important limitations and their data cannot be compared directly with findings from randomized or observational studies; findings therefore need to be interpreted with caution. VAERS may be prone to biased reporting (over- or under-reporting) and inconsistency in the quality and completeness of reports. VAERS also generally cannot determine whether a vaccine caused an AE [16]. Stimulated reporting can occur following publicity around a potential AE and AEs occurring closer to vaccination or those more serious in nature may be reported more frequently [16]. VAERS does not collect data on the number of vaccinees and generally it is not possible to calculate rates of adverse events. However, during the COVID-19 vaccination program, CDC collected data on the number of COVID-19 vaccines administered. Vaccination coverage data for pregnant women from the Vaccine Safety Datalink allowed for calculation of crude reporting rates in this study [25].

5. Conclusions

The earliest data on the safety of COVID-19 vaccines came from the v-safe pregnancy registry and VAERS [14] and filled a gap in knowledge on the safety of the COVID-19 vaccines in pregnant persons. As more pregnant people get vaccinated and pregnancies come to completion, more complete data will be available and signal detection for rare events may be possible. Furthermore, large, linked database systems such as the Vaccine Safety Datalink can evaluate rates and risks for specific adverse events, including those initially detected in surveillance systems. Together these systems work to rapidly and comprehensively study the safety of COVID-19 vaccines among pregnant persons.

Our review of pregnancy-related safety for the COVID-19 vaccines from VAERS identified no disproportionate reporting of any pregnancy specific condition. Moreover, reporting rates for important conditions were well below background rates. CDC and FDA will continue to closely monitor the safety of COVID-19 vaccines in pregnant persons in VAERS complementing the safety data from other systems. Timely results from enhanced maternal safety monitoring following COVID-19 vaccination has informed federal agencies, healthcare providers, domestic immunization partners, and the public on the safety of these new vaccines in pregnant persons.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.vaccine.2022.04.031>.

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