Published in final edited form as:

Am J Epidemiol. 2023 August 04; 192(8): 1386–1395. doi:10.1093/aje/kwad059.

COVID-19 Vaccine Safety Surveillance in Early Pregnancy in the United States: Design Factors Affecting the Association Between Vaccine and Spontaneous Abortion

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Abstract

In the Vaccine Safety Datalink (VSD), we previously reported no association between coronavirus disease 2019 (COVID-19) vaccination in early pregnancy and spontaneous abortion (SAB). The present study aims to understand how time since vaccine rollout or other methodological factors could affect results. Using a case-control design and generalized estimating equations, we estimated the odds ratios (ORs) of COVID-19 vaccination in the 28 days before a SAB or last date of the surveillance period (index date) in ongoing pregnancies and occurrence of SAB, across cumulative 4-week periods from December 2020 through June 2021. Using data from a single site, we evaluated alternative methodological approaches: increasing the exposure window to 42 days, modifying the index date from the last day to the midpoint of the surveillance period, and constructing a cohort design with a time-dependent exposure model. A protective effect (OR = 0.78, 95% confidence interval: 0.69, 0.89), observed with 3-cumulative periods ending March 8, 2021, was attenuated when surveillance extended to June 28, 2021 (OR = 1.02, 95% confidence interval: 0.96, 1.08). We observed a lower OR for a 42-day window compared with a 28-day window. The time-dependent model showed no association. Timing of the surveillance appears to be an important factor affecting the observed vaccine-SAB association.

Keywords

case-control; COVID-19 vaccines; pregnancy; safety; spontaneous abortion; study design; surveillance

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As of July 25, 2022, over 600 million coronavirus disease 2019 (COVID-19) vaccine doses have been administered in the United States (1). Near real-time surveillance of the safety of these vaccines, conducted by the Vaccine Safety Datalink (VSD) and other groups, began in December 2020 (2). Applying methods for identifying vaccine safety signals from automated health data (3–5), near real-time surveillance of COVID-19 vaccines has demonstrated an overall reassuring safety profile, while also identifying rare vaccine-related adverse events (2, 6).

Pregnant people with COVID-19 infection are at increased risk for severe illness and may be at increased risk for adverse pregnancy outcomes (7–10); as such, COVID-19 vaccines are recommended in pregnancy (11). Pregnant people were excluded from the preauthorization clinical vaccine trials and thus, postauthorization safety surveillance is needed to characterize the safety profile of COVID-19 vaccines in pregnant people. In the United States, early surveillance for spontaneous abortions (SABs) following COVID-19 vaccination was reported through the V-safe Pregnancy Registry and the Vaccine Adverse Event Reporting System (VAERS) (12, 13). However, these systems lack a concurrent comparison group, and events are self-reported. Current methods for near real-time surveillance, such as the Rapid Cycle Analysis (14), which the VSD uses in the general population, are also not appropriate as risks for pregnancy outcomes vary by gestational age (15). Alternative approaches are needed.

As part of the VSD, we have adapted a validated pregnancy algorithm (16) to identify pregnancies in near real time to support surveillance of adverse events after vaccination

in this population. The VSD began surveillance for SAB following COVID-19 vaccination during pregnancy, once the vaccination program was initiated. Results of our initial analyses (not published), including data through March 8, 2021, showed a protective effect. Results including data through June 28, 2021, no longer showed a protective effect (17). It has not been previously described how the timing of the evaluation and methodological choices could affect the observed vaccine-SAB association. In the present study, we extended the scope of the surveillance to identify changes over time in vaccination uptake and delays in the availability of electronic health data that could affect the observed association. In secondary analyses we evaluated how variation in the exposure window length, assignment of the index date for ongoing pregnancies, or epidemiologic design affects the observed vaccine-SAB association.

METHODS

Data source

The VSD is a collaboration of 9 integrated health systems and the Centers for Disease Control and Prevention, with a primary aim to monitor the safety of vaccines in use in the United States. The data for this study come from 8 VSD sites: Denver Health (Colorado); HealthPartners (Minnesota); Colorado, Northern California, Northwest, Southern California, and Washington regions of Kaiser Permanente; and Marshfield Clinic (Wisconsin). The VSD population comprises over 3% of the US population (18), with more than 135,968 pregnancies identified from December 14, 2020, to May 8, 2021, based on pregnancy diagnosis codes (19).

Standardized dynamic data files are produced by participating VSD sites on a weekly basis. These files include data on demographic characteristics, diagnoses, procedures, vaccines, and enrollment. Since August 2018, a pregnancy episode file is created weekly using the dynamic pregnancy episode algorithm (DPA), which identifies completed and ongoing pregnancies. In addition, a monthly mortality file was added in 2021. The DPA is an extension of the pregnancy episode algorithm, which retrospectively identifies completed pregnancies. Both algorithms have been validated (16) and applied in previous studies of vaccine safety and vaccine coverage during pregnancy (19, 20). Pregnancies, pregnancy outcomes (including livebirths, stillbirths, and SABs), and gestational age are identified weekly through *International Statistical Classification of Diseases, Tenth Revision, Clinical Modification* (ICD-10-CM), and Current Procedural Terminology (CPT) codes, using all available electronic health records (EHRs) or claims data indicating health-care visits for pregnancy-related care. For livebirths, delivery dates and gestational age are extracted from birth records when available, and maternal medical records are used to extract last menstrual period (LMP) and expected delivery date (EDD) for ongoing or completed pregnancies. For completed pregnancies, the DPA applies a hierarchical algorithm to determine the pregnancy outcome and date when the outcome occurred based on ICD-10-CM and CPT codes. For ongoing pregnancies, the DPA assigns the expected EDD. Finally, the DPA assigns an estimated pregnancy start date (equivalent to LMP), based on the following hierarchy: gestational age from birth records for livebirths, EDD, gestational week-specific ICD-10-CM diagnoses, LMP, or prenatal care with trimester-specific ICD-10-CM coding (assigning

the median gestational age at prenatal care for each trimester). When no information is available on pregnancy start date, the algorithm uses the median gestational age for each pregnancy outcome (10 weeks for SAB, 28 weeks for stillbirth, 40 weeks for livebirths) or a missing value for ongoing pregnancies. SABs are identified by the DPA using ICD-10-CM code O03* and CPT codes 01965, 59812, 59820, 59821, and 59830, with CPT codes prioritized over diagnoses to identify an outcome date. COVID-19 vaccine administrations are identified through the EHR and supplemented with data from medical and pharmacy claims and bidirectional communication with regional or state immunization information systems (21).

We extracted data from 7 VSD sites on April 14, 2021, and from 8 VSD sites on 3 occasions in 2021 (June 2, July 8, and August 3) with pregnancies identified from December 15, 2020, to 1 day prior to the data extraction date (Web Figure 1, available at https://doi.org/10.1093/aje/kwad059). An additional extraction was performed on September 25, 2021; this final data extraction was limited to a single site where we had access to source data and thus were able to construct the surveillance structure needed to evaluate the impact of methodological design factors on the COVID-19 SAB association, as described below.

Study population

We included people with ongoing pregnancies or pregnancies ending in SAB (fetal demise before 20 weeks' gestation), stillbirth (fetal demise at ≥20 weeks' gestation), or livebirth from December 15, 2020, to July 8, 2021. People with ectopic or molar pregnancies and those with therapeutic abortions were excluded. Enrollment in the health system or insurance plan was not included as a criterion because of delay in availability of these data, while claims and medical encounters were captured in the data files. We excluded ongoing pregnancies with missing start dates. For the secondary analysis, the single-site study population was extended to pregnancies from December 15, 2020, through August 23, 2021.

Study design

To create the surveillance case-control design, we identified SABs (cases) and ongoing pregnancies (controls) in 4-week surveillance periods starting December 15, 2020. A 4-week surveillance period was selected to be consistent with the 28-day exposure window. Web Figure 2 presents an example of SABs and ongoing pregnancies less than 20 weeks' gestation identified in a surveillance period. We excluded surveillance periods where the end date was less than 4 weeks before the date of the data extraction to minimize misclassification due to data lags. For the June 2 extraction, five 4-week surveillance periods were included, ending on May 5, 2021; for the July 8 extraction, six 4-week surveillance periods, ending on May 31, 2021, were included, and for the August 3 extraction, seven 4-weeks surveillance periods, ending on June 28, 2021, were included, respectively (Web Figure 1). We used the last date of each 4-week surveillance period as the index date to select all ongoing pregnancies less than 20 weeks' gestation and collect time-dependent covariates. SABs were identified for each of the 4-week surveillance periods. Mortality data were used to verify that the pregnant people were alive at the index date or SAB. Pregnancies ending in SAB were classified as ongoing pregnancies during 4-week periods

before the period where SAB was identified. A 28-day exposure window before SAB date or index date in ongoing pregnancies was used to evaluate COVID-19 vaccination. This risk window was selected based on the presumed timing of the inflammatory response following vaccination (22).

Strata variables included surveillance period, maternal age at pregnancy start date (16–24, 25–34, or 35–49 years), race/ethnicity (Asian Non-Hispanic, Black Non-Hispanic, Hispanic, White Non-Hispanic, and Non-Hispanic people of other, multiple, or unknown race/ethnicity), gestational age at SAB or index date (6–8, 9–13, or 14–19 weeks), number of prenatal care visits up to the SAB or index date (0–1, 2 or more), and VSD site. COVID-19 vaccine variables included vaccine product and dose. The 4-week surveillance periods of cases and controls could include multiple records per pregnancy.

This study was approved by institutional review boards of all participating sites with a waiver of informed consent and was conducted consistent with federal law and CDC policy (e.g., 45 C.F.R. part 46.102(l) (2), 21 C.F.R. part 56; 42 U.S.C. §241(d); 5 U.S.C. §552a; 44 U.S.C. §3501 et seq). We followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline for case-control designs.

Analysis

We describe the characteristics of the study population by SAB status for the seven 4-week surveillance periods ending June 28, 2021, and the number of pregnancies and vaccinations across the 3 data extractions for the five, six and seven 4-week surveillance periods.
To evaluate the COVID-19 vaccine–SAB association using data from the 8 VSD sites across cumulative surveillance periods, we analyzed the odds of receiving a COVID-19 vaccine in the 28 days before SAB compared with ongoing pregnancies of less than 20 weeks' gestation. We estimated the association using a generalized estimating equation with binomial distribution, logit link, and compound symmetry covariance structure to account for multiple records per pregnancy as well as surveillance period, maternal age, race/ethnicity, gestational age, number of prenatal care visits, and site as main effects. We estimated the associations, adjusted odds ratios (AORs), and 95% confidence intervals (CIs) for cumulative 4-week surveillance periods, starting with the first 3 surveillance periods (ending March 8, 2021), and we compared the results when adding subsequent surveillance periods. We repeated analyses after excluding records for pregnancies with no prenatal care before 20 weeks' gestation (as covariate data may be missing), and those diagnosed SABs that were estimated to have occurred at 20 weeks' gestation or later (as these cases are inconsistent with the definition of an SAB as occurring before 20 weeks' gestation). Secondary analysis of the case-control design choices based on a single site's data included: 1) 28-day window for COVID-19 vaccine administration (base case); 2) applying a 42-day window; 3) adjusting the index date for ongoing pregnancies to the midpoint of the surveillance period; and 4) transforming the data structure to a cohort design.

For the cohort design we included pregnancies with a pregnancy start date after December 15, 2020, to avoid cohort truncation bias due to temporal access to vaccines and truncation of pregnancies when selecting the study period (23, 24). We estimated the hazard ratio and 95% CI using a time-dependent covariate Cox model, with risk sets of 4-weeks' gestation

after 2 weeks from the pregnancy start date. All analyses were performed using SAS/STAT, version 9.4 (SAS Institute, Inc., Cary, North Carolina).

RESULTS

From December 15, 2020, to June 28, 2021, 105,446 pregnant people were identified in the 8 VSD sites. Two maternal deaths, not COVID-19 related, were identified after 20 weeks' gestation in unvaccinated people. COVID-19 vaccination before 20 weeks' gestation or SAB was observed in 14.3%; 4.5% received the first dose or only dose and 10.2% received the second dose before 20 weeks' gestation or SAB; 8.1% received the Pfizer-BioNTech (New York, New York; Mainz, Germany) vaccine (BNT162b2), 6% Moderna (Cambridge, Massachusetts) vaccine (mRNA-1,273), and less than 1% Janssen (Beerse, Belgium) vaccine (Ad26.COV.2.S) (Table 1). Over time, there was an increase in the proportion of pregnant younger people receiving the vaccine in the 28 days before the index date or SAB; 3.0% in the first surveillance period were less than 25 years of age versus 12.9% in the seventh surveillance period. Similarly, there was an increase over time in the proportion of COVID-19-vaccinated pregnant people of Black and Hispanic ethnicity, 3.1% and 18.6% in the first period vs 6.9% and 35.8% the last period, respectively. Among pregnancies of less than 20 weeks' gestation, the gestational age at vaccination did not differ by surveillance period (Table 2). Between the June and July data extractions for the first five 4-week surveillance periods, the number of pregnancies identified increased by 2.3%, and there was an increase of 7.6% of vaccines given before 20 weeks' gestation or SAB (Web Table 1).

COVID-19 vaccination in the 28 days before SAB, compared with ongoing pregnancies, across 7 cumulative 4-week surveillance periods was not associated with increased odds (AOR = 1.02, 95% CI: 0.96, 1.08). Over subsequent data extractions, AORs had overlapping confidence intervals. The early protective effect observed after 3 cumulative surveillance periods, ending on March 8, 2021 (AOR = 0.78, 95% CI: 0.69, 0.89; based on the June 2, 2021, data extraction), gradually attenuated with the inclusion of additional surveillance periods (AOR = 1.02, 95% CI: 0.96, 1.08, for 7 cumulative surveillance periods ending on June 28, 2021, with data extracted on August 3, 2021). When excluding pregnancies with no care visits before 20 weeks' gestation (n = 937 (1%) unique pregnancies), associations did not differ (AOR = 1.01, 95% CI: 0.95, 1.07). Associations also did not differ when 59 SABs with implausible gestational age dating were removed from the analysis (AOR = 1.02, 95% CI: 0.96, 1.08) (Table 3).

Secondary analyses using data from the single site, where we evaluated varying the assigned index date (end or midpoint of the surveillance period) or length of the COVID-19 vaccine exposure window (28 days or 42 days) are in Figure 1 and summarized below. The AOR using 7 periods from December 15, 2021, to June 28, 2021, for the single-site analysis was lower than the overall AOR from the 8-site analysis (single site AOR = 0.79; AOR range across 8 sites: 0.69–1.07). After 9 surveillance periods in the single-site analysis, the AOR was 0.82, 95% CI: 0.64, 1.06. Differing approaches to the epidemiologic design or analyses consistently showed no association, indicating no increased risk of SAB following a COVID-19 vaccination. Assigning ongoing pregnancies with an index date at the midpoint of the surveillance period showed similar results, AOR = 0.85, 95% CI: 0.64, 1.12; and an

exposure window of 42 days resulted in a lower AOR (AOR = 0.76, 95% CI: 0.60, 0.96) compared with a 28-day exposure window. Associations reached a ceiling after including 8 cumulative study periods (Figure 1). After transforming the single-site data to a cohort design, the hazard ratio for SABs following a COVID-19 vaccine exposure showed no association: hazard ratio = 0.97, 95% CI: 0.76, 1.23, based on 4,070 unique pregnancies.

DISCUSSION

Near real-time surveillance is needed to inform vaccine recommendations regarding the safety of COVID-19 vaccines among pregnant people. The present study is, to our knowledge, the first to compare varying approaches for conducting vaccine safety surveillance in early pregnancy. Our study did not identify increased odds of receiving a COVID-19 vaccine in pregnancies ending in SAB compared with ongoing pregnancies. Our results are consistent with findings from Magnus et al. (25). Using a similar study design, they found no increased risk of SAB following COVID-19 vaccination in 5-week and 3-week exposure windows.

When conducting near real-time maternal safety surveillance with EHR and claims data, it is important to consider factors that could threaten the validity of the study findings, including data lags, changes in the composition of the vaccinated population, accuracy of the data, and residual confounding. Similarly, epidemiologic and analytical design decisions may produce different results. Some of these factors may have contributed to the protective effect observed early in the surveillance that was attenuated as more data accumulated.

In near real time, lags between when care encounters occur and when data are available in claims or in EHR repository systems may have an impact on the identification of pregnancies, pregnancy outcome, and dating of the outcome or the pregnancy onset. This is also true for vaccine data, where different sources are optimally needed for complete ascertainment, including vaccines administered through the health-care systems, medical or pharmacy claims data, and regional or state immunization information systems (21). The timing of when these data are captured in the standard VSD dynamic data files can vary by data source and by health system. Covariate ascertainment may also be affected by data lags. We found that 1% of ongoing pregnancies had no prenatal care before 20 weeks' gestation. Although it is possible that some people may have entered prenatal care late, it is also possible that this information was missing because patients received care outside the care system, had gaps in enrollment, or had delays in claims or EHR repository systems resulting in covariate misclassification.

Results from near real-time surveillance may also change over time because of the timing of vaccine availability, evolving recommendations for COVID-19 vaccine administration, differential uptake across diverse populations, and changes over time in the capture of vaccines in the source data. The timing of vaccine availability differed for the 3 COVID-19 vaccines available during the study period. Recommendations by the Advisory Committee on Immunization Practices indicated that pregnant people who were included in phase 1a and 1b allocations could receive COVID-19 vaccination, while pregnancy was indicated as a high-risk category and included in the phase 1c allocation (26). In addition, approaches

to vaccine rollout differed across states, and vaccine uptake differed among pregnant people according to demographic characteristics (19), contributing to changes in the composition of the population analyzed over time. We observed low vaccine uptake during pregnancy in the first surveillance period, a peak in vaccination between March 9, 2021, and April 5, 2021, and a decline thereafter. Similarly, characteristics of the people receiving a COVID-19 vaccine across surveillance periods changed, with younger and more racially and ethnically diverse people accounting for higher proportion of those receiving vaccines in the later surveillance periods. Differences in unmeasured health-related behaviors of those vaccinated early in the vaccine rollout could have contributed to the initial protective effect observed in this study, known as healthy vaccinee bias (27).

Results of maternal vaccine safety studies depend on the accuracy of the data on pregnancy outcome and pregnancy dating. Naleway et al. (16) evaluated the accuracy of pregnancy outcomes, pregnancy outcome dating, and gestational age as captured by the pregnancy episode algorithm and DPA and found adequate validity. They found that for SABs, gestational age was available from automated data for only 69% of the cases; agreement within 30 days for outcome dating was observed in 95% and for gestational age was observed in 77% of the cases using chart-abstractor-identified dates as the gold standard (16). Pregnancy start dating for ongoing pregnancies was not evaluated, but they found that 89% of livebirths identified retrospectively by the pregnancy episode algorithm were identified by the DPA 6 or more months before the outcome date (16). In the present study, for SABs with unknown gestational age, we assigned the SAB as 8 weeks' gestation under the assumption that pregnancies with no prenatal care may correspond to early losses, and reduce potential misclassification on the gestational age strata. Ongoing pregnancies with unknown gestational age were excluded as eligibility of the pregnancy (<20 weeks' gestation) and gestational age at index date could not be assessed. CPT codes for treatment of SAB were used to date the SAB. However, treatment for a missed SAB, including surgical evacuation of the uterus, could occur weeks after the fetal demise (28). In addition, clinical presentation and timing of diagnoses may not always align with the timing of fetal demise. Other factors contributing to outcome misclassification are that early SABs may not be medically attended, while other pregnancy outcomes—including therapeutic abortions, chemical pregnancies, ectopic pregnancies, or molar pregnancies—may be misclassified as SABs. Because of the varied contributing factors, the direction of the bias that results from outcome misclassification is uncertain. In future studies that include clinical review and adjudication of all SAB cases, biases due to outcome misclassification may be minimized.

We selected a case-control design for this near real-time surveillance. A cohort design would have required selecting pregnancies with a pregnancy start date at or after December 15, 2020, to assure that short-gestation pregnancies would not be excluded from the cohort to avoid cohort truncation bias (23, 24). Retrospectively, we constructed a cohort in which all pregnancies could be followed after the second week of gestation to evaluate the association between COVID-19 vaccine and SAB in a time to event approach and found no increased risk. In the case-control approach, we accounted for multiple records per subject as ongoing pregnancies could contribute to the control group in multiple surveillance periods. Ignoring the data structure and strata variables as covariates in the model could lead to biased estimates. Sensitivity analysis, using the midpoint of the surveillance period

compared with the last date, showed associations closer to the null, especially in early cumulative periods, but similar associations were observed with the inclusion of nine 4-week surveillance periods. It is possible that selection of the last date of the surveillance period as the index date in ongoing pregnancies could have introduced a protective effect by allowing the capture of more vaccinations in ongoing pregnancies during periods when vaccination uptake was increasing. We selected a 28-day window before SAB to evaluate the association. Other prior studies of maternal influenza and COVID-19 vaccine safety have used a similar risk window (25, 29, 30), consistent with the presumed timing of the inflammatory response following vaccination (22). We performed a sensitivity analysis with a 42-day window and found lower ORs than that for a 28-day window. Similarly, Magnus et al. (25) found lower ORs when using a 5-week exposure window (AOR = 0.81, 95%CI: 0.79, 1.07) compared with a 3-week exposure window (AOR = 0.91, 95%CI: 0.75, 1.10). Because the biologically plausible risk window between vaccination during pregnancy and spontaneous abortion is unknown, it is important to consider alternative approaches in secondary or sensitivity analyses.

Strengths of this study include the use of a well-established multisite vaccine safety surveillance system, with the availability of structured data files (18). In addition, this work was possible as a result of the development and validation of an automated algorithm that identifies pregnancies in near real time, with adequate accuracy in determining pregnancy outcomes and dating of the pregnancy (16). This algorithm has previously been used to describe receipt of COVID-19 vaccines in pregnant people (19); however, our study is, to our knowledge, the first maternal vaccine safety study conducted as near real-time surveillance. Our study developed an algorithm to extract minimal data for each 4-week surveillance period, which promotes data sharing and facilitates multiple data extractions over time. The findings of the study are based on a population of nearly 1 million pregnancies and were consistent in showing no increased risk for SAB in 3 consecutive data extractions and over 3–7 cumulative surveillance periods, even when vaccine uptake during pregnancy increased, and characteristics of people vaccinated during pregnancy differed across study periods.

Our study is limited because SAB events and dating were not chart confirmed. Health-seeking behaviors, SARS-CoV-2 infection, and high-risk conditions were not incorporated into the analysis. In addition, covariates such as time since the start of the vaccine rollout and maternal age could be modeled with more flexible parametrization to avoid residual confounding, but such measures are difficult to account for when only summary data are shared between sites. While a cohort design may have provided a more accurate measure of association, accounting for immortal time bias, truncation bias due to temporal access to vaccines, and avoiding selecting the length of risk window, our selection of the epidemiologic design was driven by an urgent public health need to accommodate early surveillance after the COVID-19 vaccine approval. The VSD-wide data structure was not sufficiently flexible to perform the analysis on the design features; this analysis was limited to a single site for which we could collect the data.

CONCLUSION

Our case-control study, leveraging automated electronic health data for rapid evidence generation during a public health emergency, did not identify any increased risk for SAB after COVID-19 vaccination in early pregnancy. This approach can be readily adapted to evaluate new vaccines recommended in early pregnancy, including booster doses of the monovalent or bivalent COVID-19 vaccine. However, results available around the time of the vaccine rollout should be interpreted with caution given the potential for healthy vaccinee bias and data lags to impact early estimates of the vaccine-SAB association.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENTS

This work was supported by the Centers for Disease Control and Prevention (contract 200-2012-53526).

External researchers can request deidentified data from the Vaccine Safety Datalink (VSD) for conducting secondary analyses, as described on the VSD website (https://www.cdc.gov/vaccinesafety/ensuringsafety/monitoring/vsd/data-sharing-guidelines.html#access).

We thank the Vaccine Safety Datalink site collaborators for their contributions, and Leslie C. Kuckler for project management.

Presented at the 2022 Health Care Systems Research Network Annual Conference, April 12–13, Pasadena, California. Presented at the 2022 Society for Epidemiologic Research Annual Meeting, June 14–17, Chicago, Illinois. Presented at the 2022 Society for Pediatric and Perinatal Epidemiologic Research, June 13–14, Chicago, Illinois.

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

Conflicts of interest:

G.V.B. has received research support from Sanofi Pasteur and Abbvie for an unrelated study; H.S.L. serves on the Pfizer independent external data monitoring committee for the COVID-19 vaccine; D.G. has received support from the Garfield Memorial Fund, Patient-Centered Outcomes Research Institute (PCORI), HOLOGIC Inc., and Johnson & Johnson for unrelated studies; N.P.K. has received research support from Pfizer for COVID-19 vaccine clinical trials and Merck, GSK, Pfizer, Sanofi Pasteur and Protein Science (now Sanofi Pasteur) for unrelated studies; K.K.V. has received research funding from Pfizer for an unrelated study; J.C.N. has received grant funding from Moderna to participate on COVID-19 vaccine External Safety Advisory Board; and J.D. has received support from Janssen Vaccines and Prevention for an unrelated study. The other authors report no conflicts.

Abbreviations:

AOR	adjusted odds ratios
CI	confidence interval
COVID-19	coronavirus disease 2019
CPT	Current Procedural Terminology
DPA	dynamic pregnancy episode algorithm

EHR	electronic health record
ICD-10-CM	International Statistical Classification of Diseases 10th Tenth Revision, Clinical Modification
OR	odds ratio
SAB	spontaneous abortion
VSD	Vaccine Safety Datalink

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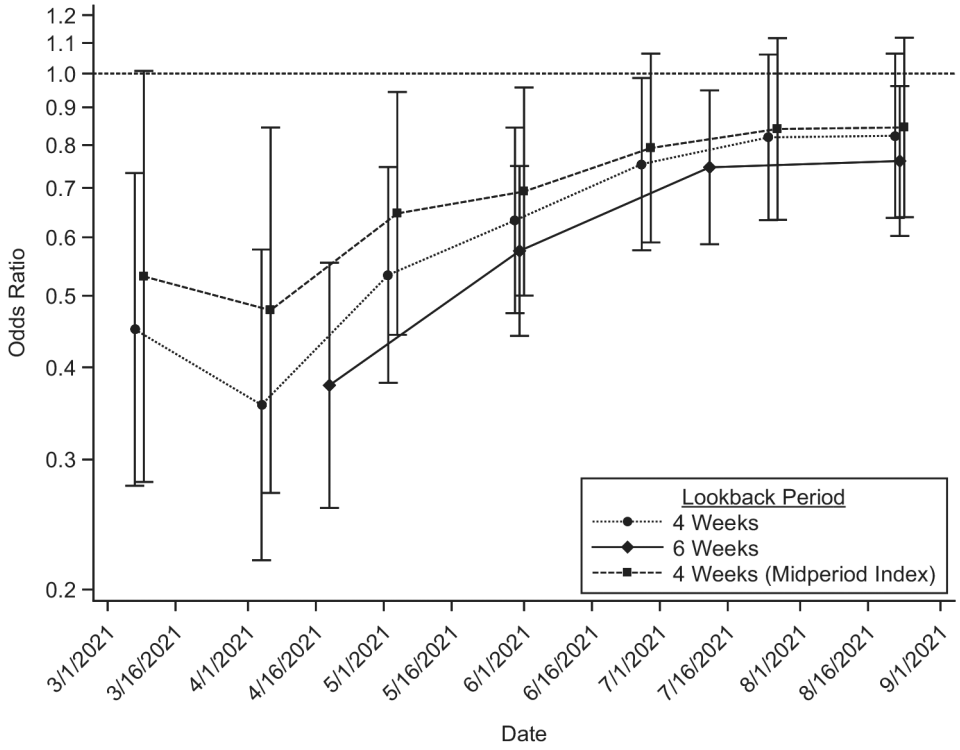

Figure 1.

Adjusted odds ratios and 95% confidence intervals of spontaneous abortion and coronavirus disease 2019 vaccination for 4-week and 6-week cumulative periods with last and midpoint as index date of the surveillance period, Vaccine Safety Datalink single-site analysis, United States, December 15, 2020, to August 23, 2021.

Table 1.

Characteristics of Pregnant People, 8 Vaccine Safety Datalink Sites, United States, December 15, 2020, to June 28, 2021[a]

Characteristic	Ongoing Pregnancies <20 Weeks' Gestation (*n* = 92,286)		Spontaneous Abortions (*n* = 13,160)		All (*n* = 105,446)	
	No.	%	No.	%	No.	%
Site						
1	34,751	37.7	4,985	37.9	39,736	37.7
2	2,967	3.2	415	3.2	3,382	3.2
3	4,573	5.0	757	5.8	5,330	5.1
4	1,534	1.7	215	1.6	1749	1.7
5	4,473	4.8	675	5.1	5,148	4.9
6	2,874	3.1	272	2.1	3,146	3.0
7	36,548	39.6	5,143	39.1	41,691	39.5
8	4,566	4.9	698	5.3	5,264	5.0
Age group, years						
16–24	13,823	15.0	1,433	10.9	15,256	14.5
25–34	57,858	62.7	6,640	50.5	64,498	61.2
35–49	20,605	22.3	5,087	38.7	25,692	24.4
Race/ethnicity						
Asian[b]	13,228	14.3	2028	15.4	15,256	14.5
Black[b]	6,887	7.5	1,079	8.2	7,966	7.6
Hispanic	31,684	34.3	4,346	33.0	36,030	34.2
Unknown/other[b]	10,255	11.1	1,435	10.9	11,690	11.1
White[b]	30,232	32.8	4,272	32.5	34,504	32.7
Not vaccinated prior to 20 weeks' gestation or SAB	78,705	85.3	11,633	88.4	90,338	85.7
Vaccine product received during <20 weeks' gestation or SAB						
Janssen[c]	480	0.5	48	0.4	528	0.5
Moderna[c]	5,638	6.1	675	5.1	6,313	6.0
Pfizer-BioNTech[c]	7,463	8.1	804	6.1	8,267	7.8
Vaccine dose received during <20 weeks' gestation or SAB						
First dose or only dose	4,139	4.5	631	4.8	4,770	4.5

Characteristic	Ongoing Pregnancies <20 Weeks' Gestation (*n* = 92,286)		Spontaneous Abortions (*n* = 13,160)		All (*n* = 105,446)	
	No.	%	No.	%	No.	%
Second dose	9,442	10.2	896	6.8	10,338	9.8

Abbreviation: SAB, spontaneous abortion.

[a] July 8, 2021, data extraction.

[b] Non-Hispanic ethnic groups.

[c] Pfizer-BioNTech (New York, New York; Mainz, Germany); Moderna (Cambridge, Massachusetts), and Janssen (Beerse, Belgium).

Table 2.

Characteristics of Pregnant People Receiving COVID-19 Vaccine During 28 Days Before Spontaneous Abortion or Index Date[a], 8 Vaccine Safety Datalink Sites and 7 Surveillance Periods, United States, December 15, 2020, to June 28, 2021[b]

Characteristic	Period 1 (*n* = 732)		Period 2 (*n* = 1,330)		Period 3 (*n* = 1,816)		Period 4 (*n* = 4,247)		Period 5 (*n* = 3,984)		Period 6 (*n* = 2,133)		Period 7 (*n* = 866)	
	12/15/20–1/11/21		1/12/21–2/8/21		2/9/21–3/8/21		3/9/21–4/5/21		4/6/21–5/3/21		5/4/21–5/31/21		6/1/21–6/28/21	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Gestational age, weeks														
6–8	215	29.4	584	43.9	677	37.3	1,262	29.7	1,477	37.1	943	44.2	325	37.5
9–13	232	31.7	368	27.7	526	29.0	1,241	29.2	1,171	29.4	501	23.5	189	21.8
14–19	285	38.9	378	28.4	613	33.8	1,744	41.1	1,336	33.5	689	32.3	352	40.7
Site														
1	269	36.8	513	38.6	743	40.9	1,844	43.4	1779	44.7	920	43.1	361	41.7
2	34	4.6	52	3.9	118	6.5	169	4.0	147	3.7	57	2.7	32	3.7
3	71	9.7	119	9.0	112	6.2	196	4.6	232	5.8	97	4.6	24	2.8
4	4	0.6	17	1.4	13	0.7	22	0.5	24	0.6	8	0.4	4	0.5
5	45	6.2	121	9.1	91	5.0	187	4.4	178	4.5	126	5.9	48	5.5
6	19	2.6	12	0.9	16	0.9	61	1.4	69	1.7	72	3.4	42	4.9
7	254	34.7	425	31.9	606	33.4	1,479	34.8	1,298	32.6	714	33.5	306	35.3
8	36	4.9	71	5.3	117	6.4	289	6.8	257	6.5	139	6.5	49	5.7
Age group, years														
16–24	22	3.0	50	3.8	64	3.5	221	5.2	299	7.5	234	11.0	112	12.9
25–34	425	58.1	822	61.8	1,142	62.9	2,602	61.3	2,440	61.2	1,284	60.2	536	61.9
35–49	285	38.9	458	34.4	610	33.6	1,424	33.5	1,245	31.3	615	28.8	218	25.2
Race/ethnicity														
Asian[c]	204	27.9	304	22.9	337	18.6	829	19.5	970	24.4	520	24.4	154	17.8
Black[c]	23	3.1	45	3.4	59	3.3	119	2.8	133	3.3	106	5.0	60	6.9
Hispanic	136	18.6	320	24.1	450	24.5	1,084	25.5	1,059	26.6	656	30.8	310	35.8
Other/unknown[c]	60	8.2	140	10.5	162	8.9	472	11.1	460	11.6	251	11.8	106	12.2
White[c]	309	42.2	521	39.2	808	44.5	1743	41.0	1,362	34.2	600	28.1	236	27.3
No. of prenatal care visits														

Characteristic	Period 1 (*n* = 732)		Period 2 (*n* = 1,330)		Period 3 (*n* = 1,816)		Period 4 (*n* = 4,247)		Period 5 (*n* = 3,984)		Period 6 (*n* = 2,133)		Period 7 (*n* = 866)	
	12/15/20–1/11/21		1/12/21–2/8/21		2/9/21–3/8/21		3/9/21–4/5/21		4/6/21–5/3/21		5/4/21–5/31/21		6/1/21–6/28/21	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
≤1	313	42.8	639	48.1	740	40.8	1,417	33.4	1,654	41.5	1,003	47.0	356	41.1
≥2	419	57.2	691	51.9	1,076	59.3	2,830	66.6	2,330	58.5	1,130	53.0	510	58.9

Abbreviation: COVID-19, coronavirus disease 2019.

[a] Index date is the last date of the 4-week surveillance period and serves to assess the gestational week at SAB or index date and number of prenatal care visits.

[b] July 8, 2021, data extraction.

[c] Non-Hispanic ethnic groups.

Table 3.

Adjusted Odds Ratios and for Spontaneous Abortion and COVID-19 Vaccination in the 28-Day Window for Cumulative Surveillance Periods and Data Extractions Using Data From 8 Vaccine Safety Datalink Sites, United States, December 15, 2020, to June 28, 2021

Cumulative Surveillance Period or Restriction	Last Index Date	June 2, 2021, Extraction		July 8, 2021, Extraction		August 3, 2021, Extraction	
		AOR[a]	95% CI	AOR[a]	95% CI	AOR[a]	95% CI
3	3/8/21	0.78	0.69, 0.89	0.72	0.63, 0.81	0.66	0.58, 0.75
4	4/5/21	0.76	0.69, 0.83	0.73	0.66, 0.80	0.68	0.62, 0.75
5	5/3/21	0.87	0.81, 0.94	0.88	0.82, 0.94	0.82	0.77, 0.89
6	5/31/21			0.99	0.93, 1.06	0.94	0.89, 1.00
7	6/28/21					1.02	0.96, 1.08
Restriction to pregnancies with at least 1 care visit by 19 weeks' gestation[b]						1.01	0.95, 1.07
Restriction to pregnancies with at least 1 care visit and plausible SAB dating[c]						1.02	0.96, 1.08

Abbreviations: AOR, adjusted odds ratio; CI, confidence interval; COVID-19, coronavirus disease 2019; SAB, spontaneous abortion.

[a]Odds ratios were adjusted for maternal age, race/ethnicity, gestational age at SAB or index date, prenatal care encounters, surveillance period, and site.

[b]937 (1%) unique pregnancies had no recorded care visits before 20 weeks.

[c]59 SABs had a gestational age of 20 weeks or more.