CMS should consider restricting coverage for aducanumab to populations meeting trial eligibility criteria and requiring additional evidence on clinical outcomes in groups excluded from the trials.

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1. Alexander GC, Emerson S, Kesselheim AS. Evaluation of aducanumab for Alzheimer disease: scientific evidence and regulatory review involving efficacy, safety, and futility. *JAMA*. 2021;325(17):1717-1718. doi:10.1001/jama.2021.3854

2. Centers for Medicare & Medicaid Services. Chronic Conditions Data Warehouse. Accessed July 10, 2021. https://www2.ccwdata.org/web/guest/condition-categories

3. ClinicalTrials.gov. 221AD302 Phase 3 Study of Aducanumab (BIIB037) in Early Alzheimer's Disease (EMERGE). Accessed July 10, 2021. https://clinicaltrials.gov/ct2/show/NCT02484547

4. ClinicalTrials.gov. 221AD301 Phase 3 Study of Aducanumab (BIIB037) in Early Alzheimer's Disease (ENGAGE). Accessed July 10, 2021. https://clinicaltrials.gov/ct2/show/NCT02477800

5. US Food and Drug Administration. Aducanumab (marketed as Aduhelm) information. Accessed July 14, 2021. https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/aducanumab-marketed-aduhelm-information

6. Lee E, Gatz M, Tseng C, et al. Evaluation of Medicare claims data as a tool to identify dementia. *J Alzheimers Dis*. 2019;67(2):769-778. doi:10.3233/JAD-181005

Spontaneous Abortion Following COVID-19 Vaccination During Pregnancy

COVID-19 infection during pregnancy can be associated with severe maternal morbidity.[1] In the United States, 1 COVID-19 vaccine has been approved and 2 have been authorized for use for pregnant women. To date, data on maternal COVID-19 vaccine safety come primarily from passive surveillance, and studies lack an unvaccinated comparison group.[2,3] Spontaneous abortion has been identified as a priority outcome in studies of maternal vaccine safety,[4] and concerns regarding risks of spontaneous abortion may be a barrier to vaccination during pregnancy. We present findings from case-control surveillance of COVID-19 vaccination during pregnancy and spontaneous abortion.

Supplemental content

Methods | The Vaccine Safety Datalink is a collaboration between the Centers for Disease Control and Prevention and 9 health systems, representing approximately 3% of the US population.[5] We applied a validated pregnancy algorithm, which incorporates diagnostic and procedure codes and electronic health record (EHR) data, to identify and assign gestational ages for spontaneous abortions and ongoing pregnancies.[6] Data from 8 health systems (Kaiser Permanente: Washington, Northwest, Northern California, Southern California, and Colorado; Denver Health; HealthPartners; and Marshfield Clinic, Wisconsin) over seven 4-week surveillance periods from December 15, 2020, through June 28, 2021, were included. Ongoing pregnancies between 6 and 19 weeks' gestation were identified on the last day of each 4-week surveillance period (index date) and contributed data to 1 or more surveillance periods. Spontaneous abortions were assigned to a 4-week surveillance period based on their outcome date; these spontaneous abortions could have been included in the ongoing pregnancy categories during prior periods (eFigure in the Supplement). Vaccination data came from EHRs, medical and pharmacy claims, and regional or state immunization information systems.

We analyzed the odds of receiving a COVID-19 vaccine in the 28 days prior to spontaneous abortion compared with the odds of receiving a COVID-19 vaccine in the 28 days prior to index dates for ongoing pregnancies. Both spontaneous abortions and ongoing pregnancies were assigned to gestational age groups (6-8, 9-13, and 14-19 weeks), surveillance periods, site, maternal age groups (16-24, 25-34, and 35-49 years), number of antenatal visits (≤1 or ≥2), and race and ethnicity. Generalized estimating equations with binomial distribution and logit link were used to account for repeated ongoing pregnancies across surveillance periods. Analyses by manufacturer and gestational age group were also conducted. Analysis was performed using SAS/STAT software version 9.4 (SAS Institute Inc).

This surveillance was approved by the institutional review boards of all participating sites with a waiver of informed consent.

Table 1. Receipt of COVID-19 Vaccine in Prior 28-Day Window, by Baseline Characteristics and Surveillance Period, December 15, 2020, Through June 28, 2021

	Ongoing pregnancy periods[a]		Spontaneous abortions	
	No.	COVID-19 vaccine, No. (%)	No.	COVID-19 vaccine, No. (%)
All	250 944	20 139 (8.0)	13 160	1128 (8.6)
Maternal age group, y				
16-24	37 210	1325 (3.6)	1433	69 (4.8)
25-34	156 166	12 451 (8.0)	6640	493 (7.4)
35-49	57 568	6363 (11.1)	5087	566 (11.1)
Race and ethnicity[b]				
Asian	35 938	4433 (12.3)	2028	262 (12.9)
Black, non-Hispanic	18 790	715 (3.8)	1079	48 (4.4)
Hispanic	86 108	5207 (6.0)	4346	322 (7.4)
White, non-Hispanic	81 834	7571 (9.3)	4272	373 (8.7)
Unknown/other	28 274	2213 (7.8)	1435	123 (8.6)
Gestational age group, wk				
6-8	57 355	5196 (9.1)	5238	482 (9.2)
9-13	88 982	6067 (6.8)	6652	528 (7.9)
14-19	104 607	8876 (8.5)	1270	118 (9.3)
Antenatal visits				
≥1	89 913	6850 (7.6)	3203	244 (7.6)
≥2	161 031	13 289 (8.3)	9957	884 (8.9)
Surveillance periods				
December 15, 2020-January 11, 2021	36 964	711 (1.9)	1767	21 (1.2)
January 12-February 8, 2021	36 981	1696 (4.6)	2097	68 (3.2)
February 9-March 8, 2021	37 030	2322 (6.3)	1871	97 (5.2)
March 9-April 5, 2021	37 144	4934 (13.3)	1903	204 (10.7)
April 6-May 3, 2021	36 191	5654 (15.6)	1864	330 (17.7)
May 4-May 31, 2021	34 545	3485 (10.1)	1811	272 (15.0)
June 1-June 28, 2021	32 089	1337 (4.2)	1847	136 (7.4)

[a] Four-week surveillance periods included December 15, 2020, through January 11, 2021; January 12 through February 8, 2021; February 9 through March 8, 2021; March 9 through April 5, 2021; April 6 through May 3, 2021; May 4 through May 31, 2021; and June 1 through 28, 2021. Unique ongoing pregnancies may be counted in more than one 4-week surveillance period and were identified at the last date of the 4-week period.

[b] Race and ethnicity came from electronic health data, based on self-report. Race and ethnicity are included because both COVID-19 vaccine uptake and rates of spontaneous abortion vary by race and ethnicity.

Table 2. Adjusted Odds Ratios for Receipt of COVID-19 Vaccine Within 28 Days Prior to a Spontaneous Abortion, December 15, 2020, Through June 28, 2021, Across 8 Vaccine Safety Datalink Sites and Among 264 104 Pregnancy Periods[a]

	Adjusted odds ratio (95% CI)[b]
Full population	1.02 (0.96-1.08)
By gestational age, wk	
6-8	0.94 (0.86-1.03)
9-13	1.07 (0.99-1.17)
14-19	1.08 (0.89-1.29)
By vaccine type[c]	
mRNA-1273 (Moderna)	1.03 (0.94-1.11)
BNT162b2 (Pfizer-BioNTech)	1.03 (0.95-1.11)

[a] See Table 1 footnote a for 4-week pregnancy periods. Unique ongoing pregnancies may be counted in more than 1 surveillance period.

[b] Generalized estimating equation models included gestational age group, surveillance period, maternal age group, number of antenatal visits, site, and race and ethnicity factors and accounted for repeated ongoing pregnancies across surveillance periods.

[c] The Ad26.COV.2.S vaccine is not included due to the small number of exposures.

Results | Of 105 446 unique pregnancies, 13 160 spontaneous abortions and 92 286 ongoing pregnancies were identified. Overall, 7.8% of women received 1 or more BNT162b2 (Pfizer-BioNTech) vaccines; 6.0% received 1 or more mRNA-1273 (Moderna) vaccines; and 0.5% received an Ad26.COV.2.S (Janssen) vaccine during pregnancy and before 20 weeks' gestation. The proportion of women aged 35 through 49 years with spontaneous abortions was higher (38.7%) than with ongoing pregnancies (22.3%). A COVID-19 vaccine was received within 28 days prior to an index date among 8.0% of ongoing pregnancy periods vs 8.6% of spontaneous abortions (**Table 1**). Spontaneous abortions did not have an increased odds of exposure to a COVID-19 vaccination in the prior 28 days compared with ongoing pregnancies (adjusted odds ratio, 1.02; 95% CI, 0.96-1.08). Results were consistent for mRNA-1273 and BNT162b2 and by gestational age group (**Table 2**).

Discussion | 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. Strengths of this surveillance include the availability of a multisite diverse population with robust data capture. Several limitations should be noted. First, gestational age of spontaneous abortions and ongoing pregnancies were not chart confirmed; pregnancy dating may be inaccurate early in pregnancy. Second, although vaccination status was identified using multiple data sources, the COVID-19 vaccine

rollout has been complex and some vaccines may have been missed, potentially biasing findings to the null. Third, data on important confounders, such as prior pregnancy history, were not available. Fourth, it was not possible to assess risks specific to the Ad26.COV.2.S vaccine given the small number of exposures. Despite limitations, these data can be used to inform vaccine recommendations and to counsel patients.

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1. Ko JY, DeSisto CL, Simeone RM, et al. Adverse pregnancy outcomes, maternal complications, and severe illness among US delivery hospitalizations with and without a coronavirus disease 2019 (COVID-19) diagnosis. *Clin Infect Dis*. 2021; 73(suppl 1):S24-S31. doi:10.1093/cid/ciab344

2. Shimabukuro TT, Kim SY, Myers TR, et al; CDC v-safe COVID-19 Pregnancy Registry Team. Preliminary findings of mRNA COVID-19 vaccine safety in pregnant persons. *N Engl J Med*. 2021;384(24):2273-2282. doi:10.1056/NEJMoa2104983

3. Kadali RAK, Janagama R, Peruru SR, et al. Adverse effects of COVID-19 messenger RNA vaccines among pregnant women: a cross-sectional study on healthcare workers with detailed self-reported symptoms. *Am J Obstet Gynecol*. Published online Juen 9, 2021. doi:10.1016/j.ajog.2021.06.007

4. Rouse CE, Eckert LO, Babarinsa I, et al; Global Alignment of Immunization Safety in Pregnancy (GAIA) Abortion Work Group; Brighton Collaboration Abortion Working Group. Spontaneous abortion and ectopic pregnancy: case definition & guidelines for data collection, analysis, and presentation of maternal immunization safety data. *Vaccine*. 2017;35(48 pt A):6563-6574. doi: 10.1016/j.vaccine.2017.01.047

5. Baggs J, Gee J, Lewis E, et al. The Vaccine Safety Datalink: a model for monitoring immunization safety. *Pediatrics*. 2011;127(suppl 1):S45-S53. doi:10.1542/peds.2010-1722H

6. Naleway AL, Crane B, Irving SA, et al. Vaccine Safety Datalink infrastructure enhancements for evaluating the safety of maternal vaccination. *Ther Adv Drug Saf*. 2021;12:20420986211021233. doi:10.1177/20420986211021233

Trends in Mortality Among Pregnant and Recently Pregnant Women in the US, 2015-2019

Maternal mortality involving deaths due to pregnancy-specific causes is higher in the US than in most other developed nations.[1,2] Trends in maternal mortality rates have been challenging to assess because of staggered implementation of the pregnancy checkbox on death certificates between 2003 and 2017,[3] although by 2015 all but 2 states (Alabama and West Virginia) had adopted it. Additionally, reports on maternal mortality due to causes of death other than pregnancy are limited. Herein, we report mortality rates and annual percentage changes (APCs) for pregnancy-related and other causes among pregnant and recently pregnant women from 2015 to 2019, and provide a comparison with cause-specific mortality rates within the total female population of childbearing age.

Supplemental content

Methods | Deidentified individual-level Multiple Cause of Death files were obtained from the National Center for Health Statistics (2015-2019).[4] Live birth counts were obtained from the Centers for Disease Control and Prevention's WONDER database,[5] as were age-adjusted mortality rates for the total female population of childbearing age. We defined recently pregnant women based on the death certificate pregnancy checkbox[3] as either (1) pregnant at time of death or (2) having died within 1 year of the end of pregnancy, consistent with Pregnancy Mortality Surveillance System definitions.[6] Age groups for death counts, live births, and total female population of childbearing age included standard 10-year groupings (5-14, 15-24, 25-34, 35-44, and 45-54 years; the 5- to 14-year-old group was included because births and deaths occur among girls in the older ages of this grouping). Underlying cause-of-death *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* codes were used to define causes of death as pregnancy related, drug/alcohol poisoning, motor vehicle