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COVID-19 vaccination during or just prior to pregnancy and hypertensive disorders of pregnancy

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ABSTRACT

Hypertensive disorders of pregnancy (HDP) are leading causes of maternal and fetal morbidity/mortality. To identify potential safety concerns, we evaluated whether COVID-19 vaccination during pregnancy or within 30 days of last menstrual period was associated with self-reported HDP. We also evaluated HDP risk associated with COVID-19 illness during pregnancy.

We conducted a matched cohort study using data from the Centers for Disease Control and Prevention's COVID-19 Vaccine Pregnancy Registry (C19VPR; vaccinated) and Pregnancy Risk Assessment Monitoring System (PRAMS; unvaccinated). Participants included nulliparous women with singleton pregnancies ending in livebirth (C19VPR, December 2020–March 2022; PRAMS, 2019–2021). Participants were matched by age group, race/ethnicity, and gestational age at delivery. We estimated relative risk (RR) for self-reported HDP by vaccination status using Poisson regression, adjusting for confounders. We tested for effect modification by vaccine manufacturer and vaccination timing (<20 or ≥ 20 weeks' gestation). Among matched pairs with data on self-reported COVID-19 illness in pregnancy, we estimated risk of HDP by illness status.

Of 8030 eligible C19VPR participants, 8024 (99.9%) were matched to a PRAMS participant. Most C19VPR participants delivered in 2021 (98.9%); PRAMS participants delivered predominantly in 2020 (54.5%) and 2019 (17.4%). Adjusted RR for HDP was 1.24 (95% confidence interval [CI]: 1.08, 1.43) among C19VPR versus PRAMS participants. We observed no effect modification. Results of an analysis restricted to matched pairs who delivered in 2021 ($n = 2231$) were similar. Among matched pairs ($n = 4039$) with data on COVID-19 illness in pregnancy, adjusted RR for HDP was 1.28 (95%CI: 1.02, 1.60) for those reporting illness compared with no illness.

Risk of HDP was higher among COVID-19 vaccinated compared to unvaccinated women; however, the two groups were sampled from different cohorts. Risk was similar to those who reported COVID-19 illness. Given cohort differences, the associations observed cannot be considered causal; updated assessments of HDP risks after illness and vaccination would be useful.

1. Introduction

COVID-19 illness during pregnancy has been associated with adverse maternal and pregnancy outcomes [1]. Due to the increased risk of severe illness and complications, including stillbirth, from SARS-CoV-2 infection during pregnancy, COVID-19 vaccines were recommended

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for all pregnant women [2]. Pregnant women were not included in randomized clinical trials of COVID-19 vaccines. To monitor vaccine safety during pregnancy nationally, the Centers for Disease Control and Prevention (CDC) established the COVID-19 Vaccine Pregnancy Registry (C19VPR) in January 2021 [3].

Affecting nearly 16% of U.S. women at delivery [4], hypertensive disorders of pregnancy (HDP) encompass a spectrum of diagnoses varying in severity and implications, including prepregnancy (chronic) hypertension, gestational hypertension, preeclampsia, and eclampsia. HDP are an important public health concern due to their association with maternal and fetal/neonatal morbidity and mortality [5], and represent an important outcome to monitor in vaccine safety surveillance. Among published studies investigating the risk of HDP following COVID-19 vaccination, three were conducted in the United States. Two large, retrospective studies using electronic health record (EHR) data found no differences in clinical subcategories of HDP (gestational hypertension, preeclampsia, or eclampsia) between pregnant women who had received ≥1 dose of an mRNA COVID-19 vaccine during pregnancy compared to propensity-score-matched unvaccinated pregnant women [6,7]. Neither study examined HDP as a composite indicator. A smaller retrospective study, also using EHR data, found no association between HDP and receipt of a primary series mRNA COVID-19 vaccine; however, most participants received a first dose during the third trimester [8]. Meta-analyses including these and Israeli studies reported no association between COVID-19 vaccination and HDP [9–11]. However, several studies in the meta-analyses did not control for confounders such as demographic, clinical, lifestyle, or geographic factors [8,12–14]; few included participants who were vaccinated early in pregnancy [7,15–17].

To monitor for risk of HDP following receipt of ≥1 COVID-19 vaccine dose during or just prior to pregnancy, we compared the proportion of C19VPR participants who self-reported HDP after vaccination with a matched cohort unvaccinated during pregnancy. We also assessed whether any associations were modified by vaccine manufacturer, timing of vaccination during pregnancy, or COVID-19 illness in pregnancy. As a secondary objective, we evaluated risk of HDP among a subset of matched pairs with data on COVID-19 illness during pregnancy.

2. Methods

2.1. Study design and data sources

We conducted a matched cohort study using data from the C19VPR and the CDC Pregnancy Risk Assessment Monitoring System (PRAMS). A complete description of the C19VPR is available elsewhere [3]. Briefly, C19VPR participants reported into CDC's V-safe system the receipt of at least one dose of an initial monovalent COVID-19 vaccine up to 30 days prior to their last menstrual period (LMP) or during pregnancy from December 2020 through mid-June 2021. Given the timing of C19VPR enrollment eligibility and COVID-19 vaccine availability, for 97% of participants, the vaccine dose conferring registry eligibility was also the first dose. C19VPR included 23,249 participants aged 18–54 years; 16 participants had two registry-eligible pregnancies for a total of 23,265 pregnancies. C19VPR participants completed phone surveys on gestational health, pregnancy outcomes, delivery and postpartum complications, health history, and demographics.

Because all C19VPR participants received a COVID-19 vaccination, we matched them to unvaccinated women who participated in PRAMS during 2019, 2020, or 2021. PRAMS is an ongoing, cross-sectional state-based surveillance system supported by the CDC [18]. The PRAMS questionnaire assessed pregnancy-related behaviors and experiences, and data were linked to select demographic and medical information available through National Vital Statistics System (NVSS) birth certificate files. PRAMS participants with live births in 2019 and 2020 were assumed unvaccinated, as nearly all gave birth prior to public availability of COVID-19 vaccines on December 14, 2020 [19]. For 2021, PRAMS jurisdictions could include a question on COVID-19 vaccination during pregnancy [18]. PRAMS participants from the 22 jurisdictions that included the vaccination question and reported receiving no COVID-19 vaccine during pregnancy were eligible for matching.

The C19VPR was reviewed by CDC and conducted consistent with applicable federal law and CDC policy; the activity met requirements of public health surveillance defined in 45 CFR 46.102.[1] The PRAMS protocol, including survey supplements, was reviewed and approved by the institutional review boards of each participating jurisdiction and CDC. For C19VPR and PRAMS participants who completed interviews by telephone, participants verbally consented. For PRAMS participants who completed mailed surveys, written consent was not required; consent was implied if a survey was completed. PRAMS jurisdictions included in the study approved the analysis plan and met response rate thresholds [18].

2.2. Study cohort

Nulliparous C19VPR and PRAMS participants with singleton live births were eligible for matching (Fig. 1). Parous participants were excluded because history of a HDP is a risk factor for hypertension in subsequent pregnancies [20], and we did not have data on prior HDP. We excluded participants aged <18 years and those with unknown age, race and ethnicity, or gestational age at delivery, as these variables were used in matching. Because we were assessing risk of HDP associated with vaccination during pregnancy, we excluded participants reporting chronic hypertension before pregnancy ("Have you ever been diagnosed with high blood pressure prior to your current pregnancy?"), missing data on HDP for the current pregnancy, or reporting onset of HDP before receipt of first COVID-19 vaccination. To make exposure groups comparable at baseline, we matched 1:1 on categories of age (18–24, 25–29, 30–34, 35–39, ≥40 years), race and ethnicity (Non-Hispanic [NH] Black, NH-White, Hispanic, NH-American Indian or Alaska Native, NH-Native Hawaiian or Pacific Islander, NH-Asian), and gestational age at delivery (≤27, 28–33, 34–36, 37–42 weeks). We matched on gestational age at delivery to reduce potential selection bias, as preterm deliveries are overrepresented in PRAMS, though reasons for preterm delivery are not known. Without matching on gestational age at delivery, the unvaccinated group (PRAMS) would have had more preterm deliveries than the vaccinated group (C19VPR), introducing selection bias in two ways. First, HDP can lead to preterm delivery, overrepresenting HDP in PRAMS. Second, for preterm deliveries not due to HDP, opportunity to develop and diagnose is limited because HDP increase with gestational age; this could underrepresent HDP in PRAMS. We preferentially matched 2021 PRAMS participants, as their pregnancies were closer in time to those of C19VPR participants, followed by 2020 PRAMS and then 2019 PRAMS. Had 2019 PRAMS participants not been included, we would have been unable to match approximately 1400 C19VPR participants.

2.3. Outcome

The primary outcome, HDP, was defined by response to survey questions asking about a diagnosis of high blood pressure that started during pregnancy or pre-eclampsia, regardless of gestational age (Supplemental Table 1). The PRAMS questionnaire served as the model for C19VPR hypertension questions; thus, ascertainment of HDP was self-reported and defined similarly. C19VPR participants were also asked to report the date or gestational age of their initial HDP diagnosis.

[1] § See e.g., 45C.F.R. part 46.102(l)(2), 21C.F.R. part 56; 42 U.S.C. §241(d); 5 U.S.C. §552a; 44 U.S.C. §3501 et seq.

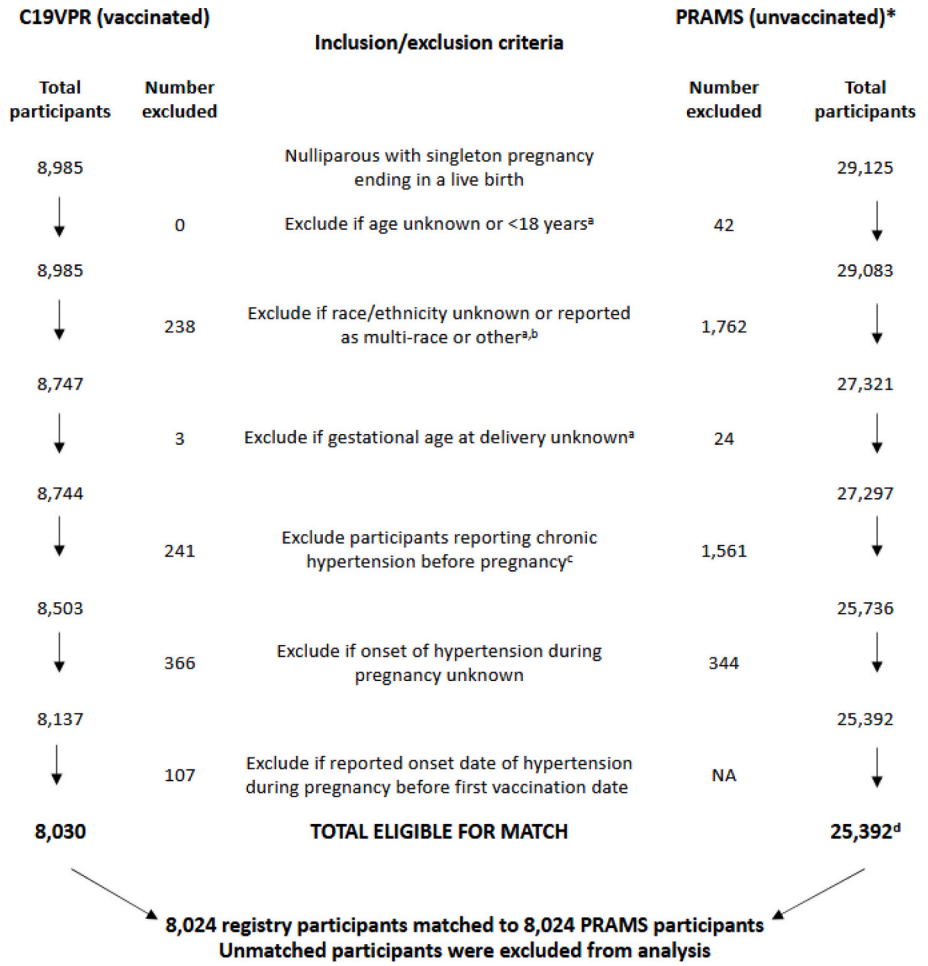

Fig. 1. Consort diagram describing study inclusion and exclusion criteria and the number of participants eligible for the match between the CDC COVID-19 Vaccine Pregnancy Registry (C19VPR; vaccinated; December 2020–March 2022) and Pregnancy Risk Assessment Monitoring System (PRAMS; unvaccinated; 2019–2021). Abbreviations: NA, not applicable *All PRAMS participants from 2019 and 2020 were assumed unvaccinated as deliveries occurred prior to large-scale distribution of the COVID-19 vaccine. Only 2021 PRAMS participants who reported that they did not receive any COVD-19 vaccine during pregnancy were eligible for the match.
[a] Age, race/ethnicity, and gestational age at delivery were required for matching PRAMS participants to registry participants.
[b] For 127 PRAMS participants, Hispanic ethnicity was unknown; these were assumed to be non-Hispanic and categorized according to their reported race. In the final sample eligible for the match, 116 participants remained.
[c] Chronic hypertension was unknown for 208 PRAMS and 97 registry participants, respectively. Given the low prevalence of chronic hypertension (<6% PRAMS, <3% registry) and thus small probability of misclassification, these participants were assumed to have no chronic hypertension and retained in this step. In the final sample eligible for the match, 183 PRAMS and 17 registry participants remained.
[d] Of the records eligible for matching; 11,794 were from PRAMS 2019, 10,436 from PRAMS 2020, and 3162 from PRAMS 2021. Matching was conducted using PRAMS 2021 participants first, unmatched C19VPR participants were then matched to PRAMS 2020 participants, any remaining unmatched C19VPR participants were then matched to PRAMS 2019 participants.

2.4. Covariates

Participant age in years at the time of delivery was calculated using dates of birth and delivery. For PRAMS, gestational age at delivery was based on the obstetric estimate reported by the delivery facility; if missing, it was calculated from the self-reported LMP and delivery date. For C19VPR, gestational age at delivery was calculated preferentially from the self-reported estimated date of delivery (EDD) and the actual date of delivery. If the EDD was missing, gestational age at delivery was used; if this was also missing, the calculation was based on LMP and the date of delivery. For analysis, gestational age at delivery was categorized as preterm (<37 weeks) or term. Pre-pregnancy body mass index (BMI) categories were calculated from self-reported pre-pregnancy weight and height. Race, ethnicity, diabetes mellitus in the current pregnancy (i.e., preexisting Type 1 or 2, or gestational), and manufacturer of the first registry-eligible COVID-19 vaccine received (i.e., Pfizer-BioNTech, Moderna, or Janssen) were self-reported. For analyses, the race and ethnicity categories of NH-American Indian or Alaska Native and NH-Native Hawaiian or Pacific Islander were combined. State of residence was included in PRAMS data and based on zip code for C19VPR participants. State was included in analyses as a proxy indicator of potential unmeasured confounding associated with differences in healthcare access or SARS-CoV-2 exposure during the study period. HDP has increased annually in the United States [4,21]; thus, year of delivery was included in models to account for possible confounding associated with time. Fewer than 150 participants in PRAMS and C19VPR were missing data on BMI, pre-existing diabetes, or gestational diabetes mellitus (GDM). Missing data were determined to be not missing at random, and therefore, responses were imputed using regression methods prior to matching (Table 1 footnote) [22].

COVID-19 illness during pregnancy has been associated with hypertension [23]. C19VPR participants were asked if they had COVID-19 illness during pregnancy, and the date or gestational age at illness onset. PRAMS participants were asked whether a healthcare provider told

Table 1
Characteristics of the study cohort: CDC COVID-19 Vaccine Pregnancy Registry (C19VPR; vaccinated) participants (December 2020–March 2022) matched to Pregnancy Risk and Monitoring System (PRAMS; unvaccinated) participants (2019–2021).

	C19VPR (vaccinated)		PRAMS (unvaccinated)		p-value[a]
	n = 8024	%	n = 8024	%	
Hypertensive disorders of pregnancy					<0.0001
No	6817	85.0	7065	88.0	
Yes	1207	15.0	959	12.0	
Maternal age at delivery (years)					1
18–24	166	2.1	166	2.1	
25–29	1589	19.8	1589	19.8	
30–34	4281	53.4	4281	53.4	
35–39	1701	21.2	1701	21.2	
≥40	286	3.6	286	3.6	
Maternal race/ethnicity					1
NH-Black	133	1.8	133	1.7	
NH-White	6528	87.7	6528	87.7	
Hispanic	764	10.3	764	10.3	
NH-American Indian or Alaska Native	13	0.2	13	0.2	
NH-Native Hawaiian or Pacific Islander	3	0.0	3	0.0	
NH-Asian	583	7.8	583	7.8	
Gestational age at delivery (weeks)					1
≤27	15	0.2	15	0.2	
28–33	126	1.6	126	1.6	
34–36	442	5.5	442	5.5	
37–42	7441	92.7	7441	92.7	
Pre-pregnancy BMI (kg/m^2)[b]					<0.0001
<18.5 (underweight)	171	2.1	294	3.7	
18.5–24.9 (healthy weight)	4483	55.9	3525	43.9	
25.0–29.9 (overweight)	1955	24.4	2115	26.4	
30.0–34.9 (obesity, class I)	858	10.7	1147	14.3	
35.0–39.9 (obesity, class II)	351	4.4	552	6.9	
≥40 (obesity, class III)	206	2.6	391	4.9	
Diabetes mellitus (preexisting or GDM)[c]					<0.0001
No	7272	90.6	7099	88.5	
Yes	752	9.4	925	11.5	
Year of delivery					<0.0001
2019	0	0.0	1398	17.4	
2020	15	0.2	4372	54.5	
2021	7938	98.9	2254	28.1	
2022	71	0.9	0	0.0	
COVID-19 illness during pregnancy					<0.0001
Yes	275	3.4	231	2.9	
No	7759	96.6	3808	47.5	
Unknown	0	0.0	3985	49.7	
COVID-19 vaccine manufacturer[d]					NA
Pfizer-BioNTech	4843	60.4	0	0.0	
Moderna	2993	37.3	0	0.0	
Janssen	187	2.3	0	0.0	
Timing of first COVID-19 vaccination[e]					NA
<20 weeks' gestation	4166	51.9	0	0.0	
≥20 weeks' gestation	3857	48.1	0	0.0	

Abbreviations: BMI, body mass index; GDM, gestational diabetes mellitus; NA, not applicable; NH, Non-Hispanic.

[a] Chi Square used to assess the difference in distributions between PRAMS and C19VPR. Maternal age, race/ethnicity, and gestational age at delivery were matching variables, thus distributions are completely concordant.

[b] BMI was imputed for 127 C19VPR participants.

[c] Diabetes mellitus (preexisting or GDM) was imputed for 65 C19VPR participants and 20 PRAMS participants.

[d] COVID-19 vaccine manufacturer is classified by manufacturer of first registry-eligible dose received.

[e] Timing of first COVID-19 vaccination is based on the participant's earliest registry-eligible dose (up to 30 days prior to last menstrual period), <3% participants received a dose prior to their registry-eligible dose.

them they had COVID-19 illness during pregnancy. For PRAMS, this question was only included in 29 jurisdictions in 2020 and 17 jurisdictions in 2021; missing responses were coded as unknown. For the 2019 PRAMS, COVID-19 illness during pregnancy was coded as 'no' [22].

2.5. Validation of self-reported HDP

To assess validity of self-reported HDP among C19VPR participants, we compared self-reports of HDP to medical record documentation, when available. Among participants consenting to medical record release, records were requested from both outpatient prenatal care and delivery facilities for participants who reported HDP ($n = 1054$) and for a subsample of participants who did not report HDP ($n = 1443$); medical records were received for 81.5% and 86.6%, respectively (Supplemental Fig. 1). Abstracted information included: diagnosis of hypertension prior to pregnancy; diagnosis of hypertension during pregnancy; earliest date of diagnosis; and types of records received.

Comprehensiveness of medical records received varied. Obstetric subject-matter experts (C.K.O. and A.M.) determined that prenatal and delivery discharge summary records would most reliably include diagnosis of HDP. Thus, the primary validation analysis included only participants for whom both prenatal and delivery discharge summary records were received ($n = 1276$). We conducted a sensitivity analysis using less strict record requirements as described in Supplemental Table 2.

2.6. Statistical analysis

We compared characteristics of the matched C19VPR (vaccinated) and PRAMS (unvaccinated) cohorts and examined covariates of HDP. Poisson regression models with robust variance (accounting for matched pairs as clusters) were used to estimate crude and adjusted relative risk (aRR) and 95% confidence intervals (CIs) of HDP among C19VPR participants compared with PRAMS participants [24,25]. Adjusted models included available covariates associated with both vaccination status and HDP (confounders), including pre-pregnancy BMI, diabetes, state, and year of delivery. Age and race and ethnicity were also included as these variables were not conditionally independent of vaccination status [26]. We adjusted for COVID-19 illness during pregnancy in an additional model. Because the year of delivery was highly correlated with vaccination status (Spearman $r = 0.73$, $p < 0.001$), we assessed associations with and without adjusting for year. To further assess the risk, we conducted a sensitivity analysis that limited the study sample to the 2231 matched pairs who delivered in 2021. Because the associations between vaccination, HDP and gestational age at delivery are complex, we also conducted a sensitivity analysis restricted to matched pairs who delivered at or after 37 weeks' gestation (full-term). We tested for evidence of effect modification by vaccine manufacturer and timing of first vaccination during pregnancy (i.e., <20 or ≥ 20 weeks' gestation). We assessed the risk of HDP associated with having COVID-19 illness in pregnancy among the subset of 4039 matched pairs with data on COVID-19 illness during pregnancy. Using this subset, we assessed whether reported COVID-19 illness during pregnancy modified the association between vaccination and HDP. Validity of self-reported HDP was assessed through comparison to medical record documentation using percent agreement, Cohen's kappa statistic, sensitivity, and specificity. Cohen's kappa was used as a more robust measure as it accounted for agreement expected to occur by chance. Kappa values 0.40 or less were considered poor-to-fair agreement, 0.41–0.60 moderate, 0.61–0.80 good, and 0.81–1.00 very good agreement [27]. SAS (version 9.4; SAS Institute, Cary, North Carolina, USA) was used for analyses. Statistical significance was defined by p-values <0.05 for main effects and < 0.15

for interactions.

3. Results

Of the 8030 C19VPR participants eligible for the study, 8024 (99.9%) were matched to a PRAMS participant on age, race and ethnicity, and gestational age at delivery (Fig. 1). Six C19VPR participants were unable to be matched due to few PRAMS participants identifying as NH-Native Hawaiian or Pacific Islander or NH-American Indian and Alaska Native; unmatched participants were not included in analyses.

There were significant differences (p-values <0.0001) in the distributions of HDP, BMI, and diabetes by vaccination status (Table 1). Compared to PRAMS participants, more C19VPR participants had self-reported HDP (15.0% vs 12.0%) and normal weight (55.9% vs 43.9%); fewer were underweight (BMI ≤18.5 kg/m^2; 2.1% vs 3.7%), overweight (BMI 25.0–29.9 kg/m^2; 24.4% vs 26.4%), or obese (BMI ≥ 30 kg/m^2; 17.6% vs 26.1%). Fewer C19VPR participants reported diabetes during pregnancy compared to PRAMS participants (9.4% vs 11.5%). C19VPR participants delivered their infants predominately in 2021 (98.9%) whereas PRAMS participants delivered in 2019 (17.4%), 2020 (54.5%), and 2021 (28.1%). Fig. 2 displays the onset of the COVID-19 pandemic, timing of availability of vaccines, and month of delivery for C19VPR and PRAMS participants. Among matched pairs, PRAMS pregnancies ended an average of 11.4 calendar months (standard deviation 8.9) before C19VPR pregnancies. Among C19VPR participants, 3.4% reported COVID-19 illness during pregnancy compared to 2.9% of PRAMS participants; however, status was unknown for 49.7% of PRAMS participants, as not all states in 2020 and 2021 collected this data. Among C19VPR participants, 60.4%, 37.3%, and 2.3% reported Pfizer-BioNTech, Moderna, and Janssen, respectively, as the manufacturer of their first COVID-19 vaccine dose. About half (51.9%) of C19VPR participants received their first registry-eligible dose prior to 20 weeks' gestation; median gestational age of first vaccination within this group was 11.1 weeks. C19VPR participants resided in all 50 states, the District of Columbia, and the U.S. Virgin Islands; PRAMS participants resided in the District of Columbia, Puerto Rico, and all states except California, Idaho, Indiana, Nevada, Ohio, South Carolina, Texas, and Vermont (data not shown).

HDP was associated with each of the covariates listed in Table 2. HDP generally increased with age, with 18.4% of those aged 40+ years reporting HDP. HDP was highest among participants identifying as NH-Black (19.5%) and lowest among NH-Asian (7.5%). HDP was highest among participants with obesity class I (BMI 30–34.9 kg/m^2), II (BMI 35.0–39.9 kg/m^2), and III (BMI ≥40.0 kg/m^2) (20.5%, 26.7%, 32.3%, respectively), diabetes (20.8%), and COVID-19 illness during pregnancy (16.4%). HDP substantially increased with year of delivery; 9.3% of participants who delivered in 2019 reported HDP compared to 14.6% of those who delivered in 2021 (Table 2). This pattern was similar among both C19VPR and PRAMS participants (Supplemental Fig. 2).

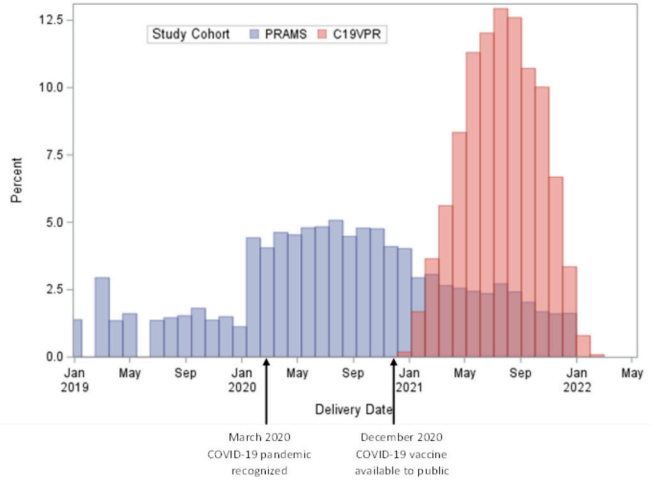

Fig. 2. Distribution of delivery month and year for matched CDC COVID-19 Vaccine Pregnancy Registry (C19VPR; vaccinated) participants (December 2020–March 2022) and CDC Pregnancy Risk Assessment Monitoring System (PRAMS; unvaccinated) participants (2019–2021).

Table 2
Bivariate associations between hypertensive disorders of pregnancy (HDP) and covariates among study participants of CDC COVID-19 Vaccine Pregnancy Registry (C19VPR; vaccinated; December 2020—March 2022) and Pregnancy Risk and Monitoring System (PRAMS; unvaccinated;2019–2021).

	Hypertensive Disorders of Pregnancy				p-value[a]
	No		Yes		
	n = 13,882	% (Row)	n = 2166	% (Row)	
Maternal age at delivery (years)					0.001
18–24	286	86.1	46	13.9	
25–29	2762	86.9	416	13.1	
30–34	7459	87.1	1103	12.9	
35–39	2908	85.4	496	14.6	
40+	467	81.6	105	18.4	
Maternal race/ethnicity[b]					<0.0001
NH-Black	214	80.5	52	19.5	
NH-White	11,222	86.0	1834	14.0	
Hispanic	1342	87.8	186	12.2	
NH-American Indian, Alaskan Native, Hawaiian or Pacific Islander	26	81.3	6	18.8	
NH-Asian	1078	92.5	88	7.5	
Gestational age at delivery (weeks)[c]					<0.0001
<37 (preterm)	798	68.4	368	31.6	
37–42 (term)	13,084	87.9	1798	12.1	
Pre-pregnancy BMI (kg/m^2)[d]					<0.0001
<18.5 (underweight)	438	94.2	27	5.8	
18.5–24.9 (healthy weight)	7304	91.2	704	8.8	
25.0–29.9 (overweight)	3480	85.5	590	14.5	
30.0–34.9 (obesity, class I)	1594	79.5	411	20.5	
35.0–39.9 (obesity, class II)	662	73.3	241	26.7	
≥40 (obesity, class III)	404	67.7	193	32.3	
Diabetes mellitus (preexisting or GDM)[e]					<0.0001
No	12,553	87.3	1818	12.7	
Yes	1329	79.2	348	20.8	
COVID-19 illness during pregnancy					0.03
Yes	423	83.6	83	16.4	
No	9975	86.3	1582	13.7	
Unknown	3484	87.4	501	12.6	
Year of delivery					<0.0001
2019	1268	90.7	130	9.3	
2020	3853	87.8	534	12.2	
2021	8700	85.4	1492	14.6	
2022	61	85.9	10	14.1	

Abbreviations: BMI, body mass index; GDM, gestational diabetes mellitus; NH, non-Hispanic.

[a] Chi Square used to assess the difference in distributions between hypertensive disorders in pregnancy: yes vs no.

[b] Due to small cell sizes, the race and ethnicity categories NH-American Indian or Alaska Native and NH-Native Hawaiian or Pacific Islander were combined.

[c] Due to small cell sizes, gestational age at delivery was grouped into preterm (<37 weeks' gestation), yes or no.

[d] BMI was imputed for 127 C19VPR participants.

[e] Diabetes mellitus (preexisting or GDM) was imputed for 65 C19VPR participants and 25 PRAMS participants.

COVID-19 vaccination and HDP.

Risk of HDP was higher among the C19VPR participants (vaccinated) relative to the PRAMS participants (unvaccinated) (Fig. 3). After

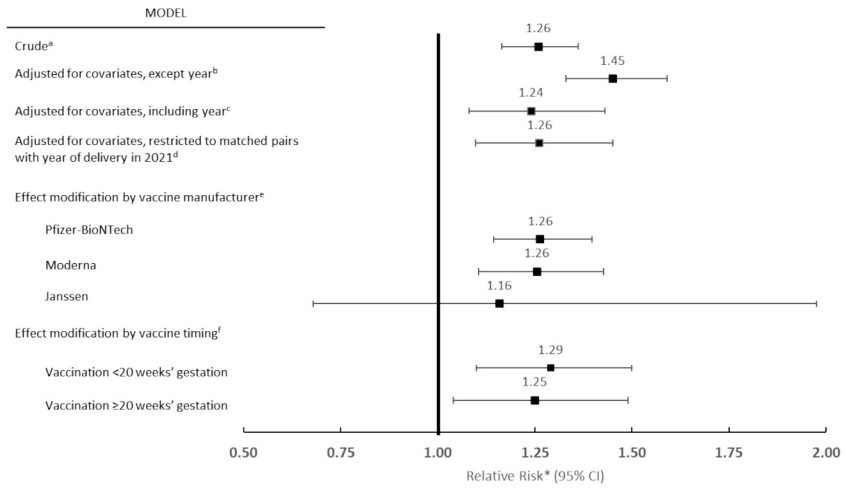

Fig. 3. Risk of hypertensive disorders of pregnancy among CDC COVID-19 Vaccine Pregnancy Registry (C19VPR; vaccinated) participants (December 2020–March 2022) compared with matched Pregnancy Risk and Monitoring System (PRAMS; unvaccinated) participants (2019–2021).
Abbreviations: CI confidence interval.
*Referent group is unvaccinated matched participants in PRAMS; where sample size is equal to the number of C19VPR participants in the model (i.e., matched pairs are retained in stratified models).
[a] No covariates included.
[b] Covariates: age, race/ethnicity, gestational age at delivery, body mass index category, state of residence, diabetes mellitus (preexisting or gestational).
[c] Covariates: age, race/ethnicity, gestational age at delivery, body mass index category, state of residence, diabetes mellitus (preexisting or gestational), year of delivery.
[d] Covariates: age, race/ethnicity, gestational age at delivery, body mass index category, state of residence, diabetes mellitus (preexisting or gestational), year of delivery, COVID-19 illness during pregnancy.
[e] Covariates: age, race/ethnicity, gestational age at delivery, body mass index category, state of residence, diabetes mellitus (preexisting or gestational); restricted to the 2231 matched pairs where year of delivery was in 2021.
[f] p-value for interaction = 0.89; Model testing for interaction adjusted for all covariates. Stratified models not adjusted for covariates due to model instability.
[g] *p*-value for interaction = 0.66; Model testing for interaction adjusted for all covariates. Stratified models adjusted only for all covariates except state of residence due to model instability. Timing of first COVID-19 vaccination is based on the participant's earliest registry-eligible dose (up to 30 days prior to last menstrual period). The first COVID-19 vaccine dose ever received was the registry-eligible dose for 97.1% of participants.

adjusting for covariates, risk of HDP among C19VPR participants was 1.24 (95%CI 1.08, 1.43) times as high as that of PRAMS participants. Risk of HDP among C19VPR participants compared to PRAMS participants remained similar when adjusting for covariates and COVID-19 illness during pregnancy (aRR: 1.20, 95%CI 1.03, 1.41) and when restricting to matched pairs who delivered in 2021 (aRR: 1.26, 95%CI 1.10, 1.45). Restricting to matched pairs who delivered full-term yielded similar results (aRR: 1.37, 95%CI 1.20, 1.57). There was no evidence for effect modification by vaccine manufacturer (*p*-value for interaction = 0.94) or timing of vaccination during pregnancy (p-value for interaction = 0.66).

COVID-19 illness and HDP.

Among the subset of matched pairs with data on COVID-19 illness during pregnancy, 3.5% (141 of 4039) and 5.7% (n = 230 of 4039) of C19VPR and PRAMS participants, respectively, reported COVID-19 illness during pregnancy. Among C19VPR participants reporting COVID-19 illness during pregnancy, 60.3% reported having the illness prior to completing the primary vaccine series (one-dose for Janssen vaccine; 2 doses for mRNA vaccines). Adjusted RR of HDP was 1.28 (95%CI 1.02, 1.60) among those reporting COVID-19 illness compared to those reporting no COVID-19 illness, adjusting for vaccination status and covariates. Among the subset of matched pairs, relative risk of HDP among C19VPR compared to PRAMS participants was similar to that for the full study sample (aRR 1.19, 95%CI 1.01, 1.39). We did not find that COVID-19 illness during pregnancy modified the association between COVID-19 vaccination and HDP (*p*-value for interaction = 0.31). Due to the small sample size, we were unable to explore whether HDP risk differed by the timing of illness relative to vaccination.

Validation of self-reported HDP.

Among C19VPR participants with self-report and medical record data, prenatal and delivery discharge summary records were available for 58.9% reporting HDP and 61.7% reporting no HDP (Supplemental Fig. 1). Self-report of HDP agreed with medical record data among 87% of participants (Supplemental Table 2). Among those with HDP reported in the medical record, 80% were identified by self-report (sensitivity), while 91% of participants without HDP in the medical record were correctly reported by participants (specificity). Cohen's kappa was 72%, indicating good agreement between self-report of HDP and medical records. Additionally, the sensitivity analysis, which included participants with alternative record types, did not yield different results (Supplemental Table 2). Fewer than 10 participants included in validation analyses had medical records identifying chronic hypertension prior to pregnancy, indicating >99% agreement that those with preexisting hypertension were excluded from analysis (data not shown).

4. Discussion

In this matched cohort study, we compared self-reported HDP diagnoses among pregnancy registry participants who received a COVID-19 vaccine just prior to or during pregnancy to those of a matched, unvaccinated cohort. We found a 24% higher risk of reporting HDP, defined as high blood pressure that started during this pregnancy or preeclampsia, in the registry cohort. Risk did not differ by vaccine manufacturer or gestational age at time of vaccination. Among the matched pairs with COVID-19 illness during pregnancy data available, we also observed a 28% increase in the risk of HDP among participants reporting COVID-19 illness in pregnancy compared with those reporting no COVID-19 illness in pregnancy.

Most previous studies have not reported statistically significant risks of HDP among women who received the COVID-19 vaccine during pregnancy compared to pregnant women who did not receive the COVID-19 vaccine [6–17,28,29]; however, point estimates in several

studies were elevated. [7,9,10,14,29] For example, the Vaccine Safety Datalink evaluated 39,201 pregnant women (21.8% vaccinated) across eight integrated healthcare centers in the United States. Odds of gestational hypertension or preeclampsia were 1.08 (95%CI: 0.96, 1.22) and 1.10 (95%CI: 0.97, 1.24), respectively, among women who received the COVID-19 vaccine in pregnancy compared to those who did not [7]. Similarly, in the International INTERCOVID-2022 prospective cohort study, the risk ratio of HDP among 1478 women receiving their first COVID-19 vaccine during pregnancy compared to 1420 unvaccinated pregnant women was 1.30 (95%CI: 0.94, 1.80) [29]. Two studies reported a statistically significant increase (p-values <0.05) in the risk of HDP associated with periconceptional vaccination. [30,31] In a study of 3911 women undergoing assisted reproduction in China, those who received an inactivated COVID-19 vaccine before embryo transfer had a higher HDP risk (RR: 1.45, 95%CI: 1.10, 1.92), while women vaccinated with a recombinant COVID-19 vaccine prior to embryo transfer did not. [31] In a study of 80,253 pregnancies in Ontario, Canada, those receiving any COVID-19 vaccine in the periconceptional period or in the first trimester had a slightly higher risk of HDP (adjusted hazard ratio: 1.10, 95%CI: 1.03, 1.17) compared to unvaccinated pregnancies [30]. Therefore, our study is not the first to identify a higher risk of HDP among COVID-19-vaccinated pregnant women. However, specific types of COVID-19 vaccines received, the time interval between receipt of vaccination and pregnancy, and the ability to account for potential confounding differed by study.

Several methodological differences between our study and previous studies may contribute to the modestly different findings. First, C19VPR included participants vaccinated prior to pregnancy and in the first trimester, whereas the majority of previous studies included mostly women vaccinated in the second and third trimesters [6,8,12–14,28]. Although we found no statistically significant difference in risk by timing of vaccination, earlier vaccination allowed more time for hypertension to develop and opportunities to be diagnosed with vaccination occurring earlier in pregnancy. Second, most of the previously published studies were conducted outside the United States among populations differing in demographics, access to healthcare, and stressors experienced during the pandemic. Such differences may affect underlying risk or diagnosis of HDP. Third, the three prior U.S.-based studies [6–8] relied on electronic medical records to ascertain HDP diagnosis, whereas we used self-reported data, which may be subject to higher rates of misclassification. Fourth, the question asked of participants in this study (whether they had high blood pressure that started during pregnancy or pre-eclampsia) did not allow us to differentiate participants' HDP diagnoses by severity. In contrast, other studies have examined clinical subcategories of HDP to assess associations based on diagnostic severity. For example, Vesco et al. analyzed gestational hypertension (less severe) separately from the combined outcome of preeclampsia, eclampsia, and HELLP (hemolysis, elevated liver enzymes, and low platelet count) syndrome (more severe) [7]. While a large sample size increased our sensitivity to detect any association between COVID-19 vaccination and any HDP, our results may have more limited clinical implications because worse pregnancy outcomes (e.g., maternal seizure or stroke, preterm birth) are correlated with HDP severity. C19VPR data have not shown an association between COVID-19 vaccination during pregnancy and an increased risk of adverse outcomes that are often associated with severe HDP, including preterm birth or perinatal mortality (Madni et al., *under review*), which suggests the severity of HDP in this cohort may have been relatively low. Finally, the American College of Obstetricians and Gynecologists classifies hypertension diagnosed prior to 20 weeks' gestation as chronic hypertension [32]. We included C19VPR participants with hypertension diagnosed after vaccination, even if diagnosed prior to 20 weeks, as it was consistent with our study objective. Furthermore, the timing of hypertension diagnosis was not available in PRAMS. Thus, we could not exclude those diagnosed with hypertension prior to 20 weeks. In contrast, other studies of COVID-19 vaccination either excluded all participants with hypertension diagnosed prior to 20 weeks' gestation, categorized them as chronic hypertension even if identified after early vaccination, or only included participants with chronic hypertension who were diagnosed with superimposed preeclampsia, eclampsia, or HELLP syndrome [6–8,30]. If COVID-19 vaccination is associated with HDP, it is possible that exclusion of participants vaccinated early in pregnancy with subsequent hypertension onset prior to 20 weeks in these other studies could have underestimated the risk of HDP.

The etiology of HDP is complex and likely multifactorial given the heterogeneity of the disease [33]. There are at least two biological mechanisms that have been proposed that may support the observations in our study. First, the SARS-CoV-2 virus spike protein binds to the angiotensinogen-converting enzyme-2 (ACE2) receptors on host cells, including endothelial and placental cells. As a result, ACE2 receptors are downregulated, disrupting the renin-angiotensin system (RAS) that maintains blood pressure homeostasis, potentially leading to increased blood pressure [34,35]. Because COVID-19 mRNA vaccines encode the SARS-CoV-2 virus spike protein, elevations in blood pressure following vaccination may occur through the same proposed pathway [36,37]. Second, vaccines activate the release of pro-inflammatory cytokines as part of the body's immune response; the level of inflammation varies by the recipient's genetic background and previous level of immunity [38]. It is possible that elevations in blood pressure are due to an exaggerated systemic inflammatory response [39]. Imbalances between immune response and inflammation early in pregnancy may alter placental vascularity, leading to reduced blood flow through the placenta and to the fetus, contributing to the development of HDP [40,41]. Among non-pregnant populations, increased blood pressure following COVID-19 vaccination has been observed to affect fewer than 5% of vaccinees and generally was transient, with duration up to several weeks [42,43]. Whether increased blood pressure after vaccination during pregnancy would be sustained or substantial enough to lead to a diagnosis of HDP is unclear. The complexity of the pathophysiology of HDP and the lack of an association between the timing of vaccine receipt and HDP diagnosis in our study make interpretation challenging. However, given the association of HDP with adverse pregnancy outcomes as well as the relationship between HDP and increased cardiovascular risk later in life, the possible short- and long-term physiologic effects of COVID-19 vaccination on blood pressure merit further investigation, particularly in populations no longer immunologically naïve [44,45].

This study had the ability to validate self-report of HDP by C19VPR participants but is also subject to multiple limitations. All data are self-reported and subject to misclassification. We found high absolute agreement (87%) between self-report of HDP by C19VPR participants and medical record documentation. Compared with two validation studies of HDP conducted in three PRAMS jurisdictions [46,47], our sensitivity estimate (80%) fell within the reported ranges (66.7% in Maryland, 76.7% in New York City, and 85.1% in Vermont), while our specificity estimate (91%) was slightly lower than those reported in New York City (96.1%) and Vermont (93.7%). Participants were asked about HDP using similar questions in C19VPR and PRAMS surveys to reduce potential differential misclassification. However, an important limitation of our study is that nearly half of C19VPR participants reported working in healthcare [3]. During the pandemic, stress was notably high among healthcare personnel [48]. This high proportion of healthcare workers likely introduced unmeasured differences in education level between C19VPR and PRAMS participants. In addition, healthcare workers may differ from non-healthcare workers in health-seeking behaviors or willingness to report adverse health effects, potentially introducing reporting bias that may overestimate HDP risk given a good sensitivity and slightly lower specificity.

Exposure status (i.e., vaccinated vs. unvaccinated) and date of vaccination was likely correct for C19VPR participants as vaccination status was reported to V-safe and subsequently confirmed during enrollment into the C19VPR. Nearly 75% of PRAMS participants were pregnant prior to the availability of COVID-19 vaccines. Among the

remaining 25% of PRAMS unvaccinated participants, it is possible that some may have been vaccinated prior to pregnancy or vaccine status was misreported, biasing results toward the null.

All pregnancies in the C19VPR started after mid-March 2020, when COVID-19 was declared a pandemic, whereas about one-third of PRAMS participants had already delivered prior to the pandemic. Being pregnant during the COVID-19 pandemic may have increased the risk for HDP [49,50], contributing to the higher incidence of HDP observed among C19VPR participants. The pandemic was associated with a wide array of disruptions and stressors that differed by location and changed over time (e.g., shutdowns, virus burden) [51–53] The pandemic altered access to healthcare and clinical practice, including for example, blood pressure surveillance. Increased medical scrutiny may have led to more diagnoses, while reduced in-person care may have led to underdiagnosis. If reporting accuracy differed over time, this could bias relative risk estimates in unpredictable directions. Similarly, over the six-month eligibility window, the availability of the COVID-19 vaccine by manufacturer varied during the study period, and the choice of manufacturer differed periodically by localities. Analyses assessing effect modification by vaccine manufacturer or gestational age at vaccination may reflect temporal or contextual differences rather than biological effects.

Furthermore, rates of HDP have been increasing annually for decades [4,54]. Data from the U.S. National Vital Statistics System show an average annual increase in HDP of 3.6% each year from 1989 through 2020 [21]. We observed increases in HDP over time with a higher percentage of participants reporting HDP in 2021 and 2022 compared to 2019 and 2020. Because PRAMS participants delivered on average 11 months earlier than C19VPR participants, some of the difference in HDP risk may be attributable to temporal trends. C19VPR and PRAMS also differ by participant recruitment methods, the modes of data collection, and timing of survey completion relative to the end of pregnancy, which may have contributed to reporting and recall biases affecting relative risk estimates in unpredictable directions.

Other limitations of our analyses include the inability to adjust for potential confounding factors such as alcohol use, smoking, use of assisted reproductive technologies, medical history, gestational weight gain, socioeconomic status, and urban residence, to name a few, as these data were not collected by both C19VPR and PRAMS. A substantial majority (93%) of C19VPR participants reported urban residence [3], which has been associated with HDP [54]. Similarly, we had limited ability to examine the influence of COVID-19 illness in pregnancy, as not all PRAMS jurisdictions collected this data; illness may also be underreported and those who chose to provide data on illness history may differ from those who chose to leave the question unanswered (i.e., missing data not random). While the overall study population was large, results from some stratified models had wide CIs because of relatively smaller sample sizes. For those diagnosed with HDP, the time interval between vaccination and HDP onset could not be meaningfully evaluated because the onset date of HDP, often initially asymptomatic, is directly related to opportunities for routine blood pressure screening during prenatal visits, which typically occur in the course of a standardized gestational age-based appointment schedule. Therefore, it is possible that some C19VPR participants with undiagnosed HDP prior to vaccination were included in analyses, which would overestimate HDP risk. Our study findings may have limited generalizability. Our study population consisted of nulliparous pregnant women who were predominantly NH-White, older than the U.S. average age at delivery, and likely SARS-CoV-2-infection-naïve at the time of vaccination. The current U.S. population is no longer immunologically naïve; previous COVID-19 illness, COVID-19 vaccination, or both are common [55]. The vaccines received by C19VPR participants were the first available COVID-19 vaccines based on the native SARS-CoV-2 virus rather than subsequent circulating variants.

Our findings suggest that early in the pandemic, relative risk of HDP was similar among women who experienced COVID-19 illness during pregnancy and women who enrolled in V-safe and received a COVID-19 vaccine during, or just prior to, pregnancy. Previous studies have documented small, but not statistically significant (p-values >0.05), increased risk of HDP following COVID-19 vaccination. In contrast, an increased risk of HDP associated with SARS-CoV-2 infection has been well-documented and of a larger magnitude [23,56]. A 2022 meta-analysis of 26 studies showed that SARS-CoV-2 infection during pregnancy was associated with higher odds of developing preeclampsia (62%), preeclampsia with severe features (76%), eclampsia (97%), and HELLP (110%); a dose-response was also noted, with more severe COVID-19 symptoms related to higher odds of more severe HDP [56]. One prospective, population-based cohort study following over 312,000 pregnancies reported no association with SARS-CoV-2 infection at any time during pregnancy and HDP after 20 weeks' gestation. [57]

During the COVID-19 pandemic, vaccination was recommended at any time during pregnancy because of the demonstrated increased risks of severe illness and pregnancy complications in unvaccinated pregnant women with COVID-19 [1]. One important consideration after the pandemic is that many studies evaluating risks of SARS-CoV-2 infection or COVID-19 vaccination were conducted among populations that were largely immunologically naïve to SARS-CoV-2. In 2025, women of childbearing age have varying degrees of vaccine- and infection-induced immunity. Therefore, findings from the early period of the COVID-19 pandemic are of uncertain significance for pregnant women in the post-pandemic era.

5. Conclusion

We found an increased risk of HDP after COVID-19 vaccination in the C19VPR cohort; however, our findings are subject to multiple limitations. These findings do not represent causal associations. Updated risk estimates of HDP associated with SARS-CoV-2 infection and continued safety monitoring of COVID-19 vaccines, are needed to update risk-benefit comparisons and inform decision-making. Vaccine studies that include data on the timing of vaccine receipt, the time interval between vaccination and initial HDP diagnosis, and COVID-19 illness and timing during pregnancy would provide important additional insights.

CRediT authorship contribution statement

Andrea J. Sharma: Writing – review & editing, Writing – original draft, Validation, Supervision, Methodology, Investigation, Formal analysis, Conceptualization. **Ashley N. Smoots:** Writing – review & editing, Formal analysis. **Sabrina A. Madni:** Writing – review & editing, Writing – original draft, Methodology, Data curation, Conceptualization. **Lauren Head Zauche:** Writing – review & editing, Writing – original draft, Data curation, Conceptualization. **Ansley Waters:** Writing – review & editing, Project administration, Data curation. **Aliza Machefsky:** Writing – review & editing, Writing – original draft, Data curation, Conceptualization. **David K. Shay:** Writing – review & editing, Validation, Supervision. **Cameron Hinrichsen:** Writing – review & editing, Data curation. **Jenna Chambless:** Writing – review & editing, Data curation. **Kendra Norris:** Writing – review & editing, Data curation. **Sarah A. Thompson:** Writing – review & editing, Data curation. **Tara Johnson:** Writing – review & editing, Project administration. **Sascha Ellington:** Writing – review & editing, Supervision, Conceptualization. **Christine K. Olson:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Conceptualization.

Disclaimer

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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 data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2026.128268.

Data availability

Data will be made available on request.

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