PROTOCOL

COVID-19 Vaccine Safety Evaluation in Pregnant Women and their Infants

VSD #1351

Version 1.0

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SURVEILLANCE FOR ADVERSE PREGNANCY AND BIRTH OUTCOMES FOLLOWING
COVID-19 VACCINE EXPOSURES DURING PREGNANCY

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Protocol Change History

Version	Date	Change
1.0	6/17/2021	N/A – Original protocol

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LIST OF ABBREVIATIONS

APNCU = adequacy of prenatal care utilization index

CDC = U.S. Centers for Disease Control and Prevention

CPT® = Common Procedural Terminology

DMD = distributed data model

DPA = dynamic pregnancy algorithm

EDD = estimated delivery date

EHR = electronic health record

ICD-10-CM = International Classification of Diseases, Tenth Revision, Clinical Modification

LMP = last menstrual period

SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2

SES = socioeconomic status

VAERS = Vaccine Adverse Event Reporting System

VSD = Vaccine Safety Datalink

Abstract

Pregnant women were excluded from the initial COVID-19 vaccine clinical trials and thus, to date there is limited data to date on the safety of COVID-19 vaccines in pregnancy. Two COVID-19 mRNA vaccines and one adenovirus vector vaccine have been approved under emergency use authorization (EUA) in the United States. Pregnancy is *not* a contraindication for these three vaccines and pregnant women have been designated as at increased risk for severe COVID-19 infections. As such there is an urgent need for data on pregnancy and birth outcomes following use of COVID-19 vaccines in pregnant populations. This protocol is the second phase of the COVID-19 vaccine safety surveillance in pregnant women and their infants. In this phase, we describe our approach for evaluating risks for selected pregnancy and birth outcomes among women with live births who received one or more COVID-19 vaccine doses during pregnancy. Surveillance will be conducted for pregnancies with pregnancy start dates May 1, 2020, or later, and vaccines administered from December 15, 2020 through December 14, 2021. We are planning for an initial exploration of the data on pregnancy and birth outcomes to be conducted in August 2021, including live births that have occurred as of June 30, 2021.

Introduction

Human infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes COVID-19, was first described in Wuhan, China in December 2019.[1] The first U.S. COVID-19 case was described in January 2020 in Seattle, WA. Given lack of pre-existing immunity to the virus, asymptomatic transmission of the virus through very fine respiratory droplets and aerosol particles, along with other challenges in containment, there has been exponential spread of infection across the globe. In March 2020, the World Health Organization designated COVID-19 as a global pandemic. Worldwide, as of May 17, 2021 about 164 million people have contracted COVID-19 and there have been nearly 3.4 million deaths due to COVID-19. To date, approximately one-fifth of reported COVID-19 cases and deaths have occurred in the U.S.[2]

The COVID-19 pandemic profoundly impacted our economy, education, and nearly all aspects of day-to-day life. Even with the rapid spread of COVID-19, most countries, states and regions are still far from achieving herd immunity.[3] As such, protection from COVID-19 infection through vaccination will be necessary to fully re-open society without continued widespread outbreaks. Since the SARS-CoV-2 genome sequence was first published, the race to develop and test a vaccine has been underway. Results from the phase 2/3 portion of the Pfizer-BioNTech COVID-19 (BNT162b2) vaccine trial demonstrated that the two-dose regimen was 95% effective in preventing symptomatic COVID-19 disease.[4] Additionally, the BNT162b2 had a similar incidence of serious adverse events compared to the placebo group (0.6% and 0.5%, respectively); overall reactogenicity was generally mild or moderate. Similarly, the Moderna mRNA COVID-19, (mRNA-1273) vaccine was reported to have 94% efficacy for preventing COVID-19 disease with an overall favorable safety profile.[5] Given the ongoing pandemic, the benefits of these COVID-19 vaccines were presumed to far outweigh the risks and on December 11, 2020, the Pfizer-BioNTech COVID-19 vaccine was granted Emergency Use Authorization (EUA) by the FDA for use in the United States.[6] On December 12, 2020, the Advisory Committee on Immunization Practices (ACIP) issued recommendations regarding use of the BNT162b2 vaccine in individuals 16 years and older.[7] Subsequently, on December 18, 2020 the FDA issued an EUA for the Moderna vaccine

for use in adults 18 years and older in the United States. On February 27, 2021, the FDA approved a third COVID-19 vaccine for adults 18 and older, developed by Janssen and using an adenoviral vector, known as Ad26.COV2.S. The Moderna, Pfizer, and Janssen vaccines are recommended by ACIP, without a stated preference.[8] Additional COVID-19 vaccines are currently in Phase III trials in the United States and may be licensed and recommended in the future.

In February 2021, Pfizer launched a Phase II/III randomized, placebo-controlled clinical trial to assess the safety and efficacy of BNT162b2 in pregnancy, aiming to enroll about 700 pregnant women.[9] In March 2021, Janssen launched a Phase II open-label clinical trial of Ad26.COV2.S in 400 pregnant women.[10] Results from these trials are not expected for many months. Furthermore, the sample sizes for these trials will be insufficient to assess many important safety outcomes. In addition, the population enrolled, healthy and at low risk for adverse birth outcomes, may not be generalizable to real-world pregnant populations. Prior clinical trials of COVID-19 vaccines have been limited to non-pregnant adults where pregnancy testing was conducted prior to each vaccine dose. Thus, vaccine exposures in pregnant women were uncommon and occurred pre-pregnancy or very early in pregnancy, prior to a positive pregnancy test. At the time of the EUA submission, Pfizer-BioNTech reported to FDA on 23 pregnancies in the Phase II/III pivotal trial. Of these, 12 were in the vaccine group and 11 in the placebo group. Among the vaccine group, 4 were vaccinated prior to their last menstrual period (LMP) (pre-pregnancy), 4 within 30 days after their LMP, and none were vaccinated later in pregnancy. One spontaneous abortion was reported in the placebo group and no other pregnancy outcomes have been reported among the remaining 22 pregnancies. The EUA Prescribing Information states, "Available data on Pfizer-BioNTech COVID-19 vaccine administered to pregnant women are insufficient to inform vaccine-associated risks in pregnancy." In the Moderna Phase II/III trial, 13 pregnancies were reported, 6 in the vaccine group and 7 in the placebo group. Of these, there was one spontaneous abortion, one therapeutic abortion and one pregnant subject was lost to follow-up, all in the placebo group. The remaining pregnancies were ongoing at the time of EUA submission. At the time of EUA submission for Ad26.COV2.S, there were 8 pregnancies reported. For all three COVID-19 vaccines now in use in the U.S. under an EUA, pregnancy is *not* a contraindication to vaccination.[8,11]

Evidence to date demonstrates the potential for SARS-CoV-2 infections during pregnancy to increase risks for morbidity in pregnant women and adverse birth outcomes in their infants.[12-14] There is also growing evidence regarding the benefits of vaccination, including specifically the immunogenicity of mRNA Covid-19 vaccines in pregnant and lactating women.[15] Despite the lack of comprehensive data on COVID-19 vaccine safety in pregnancy, the known risks of COVID-19 infection are likely to outweigh the unknown risks associated with COVID-19 vaccination. The American College of Obstetrics and Gynecology broadly supports that COVID-19 vaccines be available for use in pregnant women and that pregnant women not be denied vaccination.[16,17]

As of June 2021, only one publication has described the safety of the COVID-19 mRNA vaccines in pregnant women, based on passive reports to the Vaccine Adverse Event Reporting System (VAERS) and the v-safe pregnancy registry. In this preliminary report, among 827 completed pregnancies following COVID-19 vaccination, there were 712 (86%) live births. Among live births, 9.4% were preterm and 3.2% were small-for-gestational age.[18] These rates were consistent with expected background rates and thus reassuring. Nevertheless, additional data in larger cohorts and with longer follow-up are needed. The VSD, established in 1990, is a collaboration between

the U.S. Centers for Disease Control and Prevention (CDC) Immunization Safety Office and eight large health care organizations in the United States.[19] With data on approximately 3% of the U.S. population, automated identification of pregnant women, and linkages to infant records, and validated vaccine files, the VSD provides a robust infrastructure for monitoring maternal and infant outcomes following COVID-19 vaccination in pregnancy. As of May 8, 2021, over 22,000 women in the VSD have received one or more COVID-19 vaccine doses during pregnancy.[20] However, as vaccination may occur early in pregnancy, there could be a lag of 7 months or greater between the date when vaccination occurred and when birth outcomes following vaccination can be assessed. As such, in the first phase of VSD surveillance of COVID-19 vaccine safety in pregnancy (VSD #1345) we are evaluating acute adverse events, occurring within 21 or 42 days of vaccination. This protocol is for our second phase of surveillance on COVID-19 vaccine safety in pregnancy - evaluating maternal and birth outcomes following COVID-19 vaccination. In a future, third phase, we will evaluate infant outcomes in the first year of life.

Objectives

1. Objective 1: (Primary) Among women with live births, to evaluate risks for selected maternal and peripartum complications (hypertensive disorders in pregnancy, gestational diabetes, postpartum hemorrhage, thrombotic events, thrombocytopenia, and myocarditis) following COVID-19 vaccination during pregnancy, comparing women exposed to one or more COVID-19 vaccine doses during pregnancy to unexposed pregnant women.

2. Objective 2: (Primary) Among women with live births, to evaluate risks for selected adverse birth outcomes (preterm birth and small-for-gestational-age birth) following COVID-19 vaccination during pregnancy, comparing births among women exposed to one or more COVID-19 vaccine doses during pregnancy to those among unexposed pregnant women.

3. Objective 3: (Primary) To compare maternal complications and adverse birth outcomes in women with live births by vaccine type (mRNA and viral vector) and by number of COVID-19 vaccine doses during pregnancy.

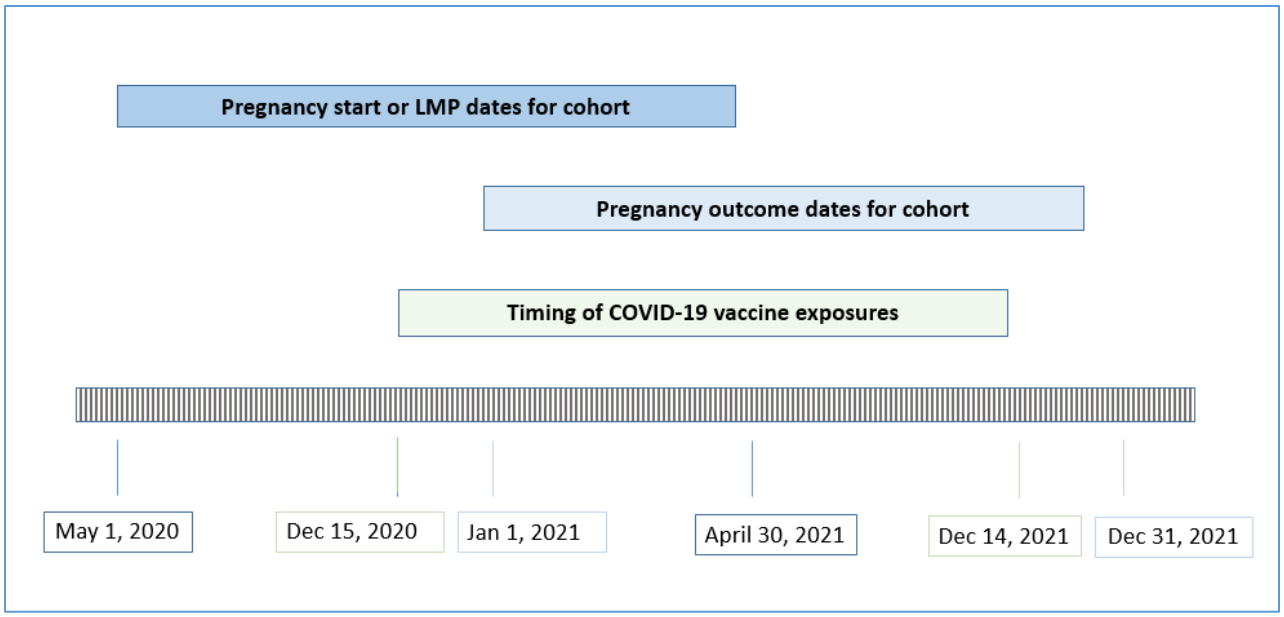
4. Objective 4: (Secondary) To compare maternal complications and adverse birth outcomes in women with live births who received one or more COVID-19 vaccines during pregnancy to those who received one or more doses 4 or more weeks prior to LMP or pregnancy start, and no COVID-19 vaccine doses during pregnancy.

Design

We will use a retrospective observational cohort of pregnant women in the VSD population with estimated pregnancy start dates (or LMP) from May 1, 2020 – April 30, 2021, as shown in Figure 1, below. We have defined the cohort by pregnancy start dates in order to include women with access to COVID-19 vaccination during pregnancy and sufficient observation time for live births to occur, without biasing the sample to select shorter gestations or preterm births at the end of the study period or longer gestations at the beginning of the study period. For the primary objectives, rates of maternal complications and adverse birth outcomes in women exposed to one more COVID-19 vaccine doses during pregnancy, from December 15, 2020–December 14, 2021, will be

compared to rates for these outcomes in women with pregnancies during the same time period who did not receive a COVID-19 vaccine during pregnancy. Maternal complications will be assessed at any interval following vaccination and prior to delivery. Birth outcomes will be assessed for pregnancies ending from January 1, 2021 – December 31, 2021. We are planning an interim data pull in August 2021, and will provide interim analyses for live births that have occurred as of June 15, 2021. In secondary analyses, women who received a COVID-19 vaccine during pregnancy will be compared to women who received one or more COVID-19 vaccine doses in the period 4 or more weeks prior to LMP or pregnancy start, and no doses administered during pregnancy for the full study period.

Figure 1. Characteristics of cohort, timing of pregnancy start dates, pregnancy outcome dates and COVID-19 vaccine exposure dates



Population

The source population for this surveillance evaluation will be pregnant women 16–49 years of age at 8 VSD sites: Kaiser Washington, Kaiser Permanente Northwest, Kaiser Permanente Northern California, Kaiser Permanente Southern California, HealthPartners, Marshfield Clinic, Denver Health, and Kaiser Permanente Colorado.

Inclusion criteria

- Women with estimated pregnancy start date as of May 1, 2020 – April 30, 2021 (May 2020 - November 2020 for interim analysis)
- Women with at least one prenatal care visit in a VSD health system and a pregnancy ending in a singleton live birth.

Exclusion criteria

- Pregnancies with the following outcomes: ectopic pregnancy, therapeutic abortion, spontaneous abortion, stillbirth, gestational trophoblastic disease, or unknown pregnancy outcome
- Multiple gestation pregnancies
- Pregnancies that are ongoing at the time of each data pull.

Pregnancy identification and dating

- Pregnancies are identified using a validated algorithm.[21] Dating uses gestational age at delivery based on birth records, estimated delivery date (EDD), gestational age-specific ICD-10-CM diagnoses, or last menstrual period (LMP).

Exposure and comparator

Exposure: The primary exposure is receipt of a COVID-19 vaccine during pregnancy, for vaccines administered from December 15, 2020 – December 14, 2021. Vaccines will be identified from standardized DDF Vaccine files, where vaccines are coded using CVX Codes. The Vaccine files also include vaccines identified by sites through CPT® or GPI codes, or through bi-directional communication with state immunization registries. Exposure windows will be defined based on the outcome of interest. For end of pregnancy outcomes, (postpartum hemorrhage, preterm birth and small-for-gestational age birth) and for outcomes that can occur at any time during pregnancy (myocarditis/pericarditis and thrombotic events) receipt of one or more COVID-19 vaccines at any time from LMP to 2 days prior to delivery will be included. Vaccines administered within 2 days of delivery will not be included to reduce the misclassification of postpartum vaccines as occurring during pregnancy, and to reduce the identification of outcomes with onset prior to vaccination. For outcomes that are likely to occur at 24 weeks' gestation or later, or peripartum, (hypertensive disorders of pregnancy, thrombocytopenia, and gestational diabetes) in order to reduce the likelihood of event onset occurring prior to vaccination, receipt of one or more COVID-19 vaccines at any time from LMP to 24 weeks' gestation will be included. Vaccine exposures will be classified by timing of vaccination: first trimester, second trimester, or third trimester. We will stratify by type of vaccine, (mRNA, viral vector), by vaccine dose (first or second) and by number of vaccine doses during pregnancy (one or two).

Comparator: The primary comparator is no history of a COVID-19 vaccine administered during pregnancy. In secondary analyses the comparator will be women who received one or more COVID-19 vaccines 4 or more weeks prior to pregnancy, and no COVID-19 vaccines during pregnancy.

Outcomes

Specific maternal and birth outcomes have been selected based on biologic plausibility, data from the COVID-19 vaccine clinical trials as reported to the FDA, and reporting to the Vaccine Adverse Event Reporting System (VAERS).[18,22,23] In addition, outcome selection has been informed by the need to provide evidence to help guide pregnant women, who were excluded from the initial vaccine clinical trials and are now considering whether to be vaccinated, balancing the need for outcome inclusion versus risks for Type 1 error. Many of the selected maternal complications and birth outcomes are prioritized outcomes as part of the Global alignment of immunization

assessment (GAIA project).[24] Potential adverse events will be identified using ICD-10-CM codes assigned at inpatient, outpatient, or emergency department clinical encounters, or from birth records. In addition, procedure codes may be requested. Relevant diagnostic settings (e.g., inpatient, outpatient, or emergency department) and outcome specific exclusions are also listed in Table 1. We will define preterm birth as occurring before 37 weeks' gestation and based on birth records, EHR data, or ICD-10-CM codes. Small-for-gestational-age birth will be defined as having weight for gestational age <10th percentile based on a U.S. reference population, as described by Talge et al.[25] Expected timing of outcomes in pregnancy and planned comparisons by outcome are in Table 2.

Table 1. Outcome definitions				
Maternal Complications		**ICD-10-CM codes in maternal record**	**Setting**	**Exclusions**
Thrombotic events		I26.*, I82.210, I82.220, I82.290, I82.3 I82.4*, I82.6*, I82.A1*, I82.B1*, I82.C1*, I82.81*, I82.890, I82.90, O22.3*, O22.8*	Inpatient or ED	-
Myocarditis / pericarditis		B33.22, B33.23, I30.*, I40.*	Inpatient, ED, or Outpatient	-
Hypertensive disorders in pregnancy: gestational hypertension / preeclampsia/ eclampsia/ HELLP	Gestational hypertension	O13.1, O13.2, O13.3, O13.4, O13.5, O13.9, O16.1, O16.2, O16.3, O16.4, O16.5, O16.9	Inpatient, ED, or Outpatient	-
	Preeclampsia	O11.1, O11.2, O11.3, O11.4, O11.5, O11.9, O14.00, O14.02, O14.03, O14.04, O14.05, O14.10, O14.12, O14.13, O14.14, O14.15,	Inpatient (use first diagnosis in any setting for onset date)	
	Eclampsia / HELLP	O14.20, O14.22, O14.23, O13.24, O14.25, O14.90, O14.92, O14.93, O14.94, O14.95, O15.*	Inpatient	
Gestational diabetes		O24.4* (2 diagnoses required, onset based on date of first diagnosis)	Inpatient, ED, or Outpatient;	T1DM or T2DM;
Thrombocytopenia: gestational thrombocytopenia/ ITP / HELLP / DIC	Gestational thrombocytopenia / ITP	D69.0, D69.3, O99.11*, or platelet <100,000	Inpatient, ED, or Outpatient	-
	HELLP / DIC	O14.20, O14.22, O14.23, O14.25, D65, O67.0, O72.3	Inpatient	
Hemorrhage: intrapartum hemorrhage / postpartum hemorrhage / placental abruption		O67.*, O72.*, O45.* or 36430 or internal codes for blood transfusion	Inpatient	Coagulopathy: D67, D68.0, D68.1, D68.2, D68.3*
Birth outcomes		**ICD-10-CM codes in infant record**		
Preterm birth (<37 weeks' gestation)		Birth records/EHR data or O60.1* or Z3A.22 – Z38.36 at delivery date	Inpatient or Outpatient (birthing center)	-
Small-for-gestational age birth (<10th)		Birth records/ EHR data	NA	-

No chart reviews are planned *a priori.* However, we may request chart reviews to confirm

diagnoses for selected outcomes if observed rates far exceed expected background rates. Chart reviews may also be requested to evaluate any potential signals. If these additional chart reviews are needed, the protocol will be amended to include these forms.

Covariates

We will pull additional data to characterize the population and to identify potential confounders. These include: age, site, race/ethnicity, prenatal care during pregnancy (adequacy of prenatal care utilization index or APNCU) and receipt of other vaccines, and presence of comorbidities associated with increased propensity to receive a COVID-19 vaccine during pregnancy or with increased risk for maternal complications or adverse birth outcomes (Table 2).

Table 2. Maternal Comorbidities
Diabetes
Obesity
Cancer
Sickle cell disease and other hematologic disorders
Lupus and other autoimmune disorders
Cirrhosis and other liver disease
Organ transplant
Renal failure / dialysis
Hypertension and other cardiovascular disease – cardiomyopathy, heart failure
Pulmonary disease – persistent asthma, cystic fibrosis
Smoking / nicotine dependence
Covid infection during or prior to pregnancy
Trauma (for thrombotic events)

If feasible based on the timing of data pulls and availability of cycle file data, we will also incorporate supplemental data such as census tract level as a proxy for neighborhood socioeconomic status (SES), obstetric status characteristics (gravida, parity), and other potential risk behaviors and conditions (i.e., smoking status, pre-pregnancy weight and height) available in the PREG file. If feasible, we would collect some of these variables in an ancillary file together with birth outcomes.

Additionally we will collect weekly county SARS-CoV-2 positivity rates from public health records through the HHS protects public data hub.

Methods for confounding adjustment

To account for confounding we will use inverse probability weighting approach by estimating propensity scores to receive Covid-19 vaccine and applying weights in the regression models.

Identification of potential confounders

We will tabulate characteristics of pregnant women who are exposed and unexposed to COVID-19 vaccine during pregnancy and estimate the standardized differences. We will calculate the standardized differences for each covariate by dividing the mean difference between the two groups by the estimate of the common standard deviation.

Propensity score

We will calculate the propensity score to receive a COVID-19 vaccine during pregnancy based on known characteristics using logistic regression, and will include potential confounding variables such as age at pregnancy start date, race/ethnicity, APNCU, and receipt of Tdap or influenza vaccine during pregnancy, and presence of comorbidities increasing risk for adverse birth outcomes and for severe COVID-19 disease, such as diabetes, hypertension, and obesity, as these women may be more likely to be vaccinated during pregnancy. In addition, we will include SARS-CoV-2 virus circulation, calendar week of LMP and site in the propensity score.

In the case we collect additional covariates in a subset of records, we will evaluate whether additional covariates show differences between the vaccinated and unvaccinated groups using the standardized difference method. If we observe that imbalances occur, we will use the sub-classification on the propensity score following Rosenbaum and Rubin,[26] in which the propensity score is defined as the conditional probability to vaccination given the full covariates and the pattern of incomplete covariates. For this, we will estimate the propensity to be vaccinated with the set of the full covariates, and the set of partial covariates, and use these estimated probabilities as propensity scores. Alternative methods can be done using multiple imputation[27,28] or propensity score calibration.[29]

Inverse probability weighting

Stabilized inverse probability weights (SIPW) will be generated by the inverse of the propensity (π_i) as (SIPWi = p/ π_i for vaccinated and SIPWi = (1-p)/(1- π_i) for unvaccinated, where p is the probability of receiving the vaccine without considering the covariates. We will evaluate the performance of the stabilized weights to reduce potential confounding by applying the weights to the study cohort and estimate the standardized difference for each covariate. Standardized differences will be plotted before and after applying stabilized weights for all observed confounders. We will also evaluate whether the distribution of the propensity overlaps between comparator groups (positivity). If positivity assumption does not hold, sensitivity analysis will be performed by truncating the stabilized weights as necessary.[30]

Preliminary Safety Analysis

We plan to conduct an initial data pull in August 2021, limited to live births with pregnancy start date from May 2020 -November 2020, and live births as of June 30, 2021. Aims of this initial data pull are to conduct interim or preliminary analyses of maternal and birth outcomes following COVID-19 vaccination in pregnancy. These analyses will be limited to the primary objectives, comparing women with live births who received one or more COVID-19 vaccines during pregnancy to women who were unvaccinated in pregnancy. Outcomes, inclusion and exclusion criteria (Table 1) and comparisons (Table 3) will be the same as those applied in the full safety analysis.

Table 3. Comparisons by outcome for primary and secondary aims			
Maternal Complications	**Expected timing of first diagnosis in pregnancy**	**Vaccine exposure window**	**Comparator**
Thrombotic events	LMP to postpartum	LMP to 2 days before delivery	Primary: Unexposed during pregnancy or until vaccine exposure Secondary: COVID-19 vaccines received ≥4 weeks before LMP
Myocarditis / pericarditis			
Hypertensive disorders in pregnancy: gestational hypertension / preeclampsia / eclampsia / HELLP	20 weeks gestation or later	LMP to 24 weeks gestation	Primary: Unexposed during pregnancy or until vaccine exposure and before 24 weeks' gestation

Thrombocytopenia: gestational thrombocytopenia / ITP / DIC			Secondary: COVID-19 vaccines received ≥4 weeks before LMP
Gestational diabetes	24 – 28 weeks gestation		
Hemorrhage: intrapartum hemorrhage / postpartum hemorrhage / placental abruption	Peripartum	LMP to 2 days before delivery	Primary: No vaccines during pregnancy Secondary: COVID-19 vaccines received ≥4 weeks before LMP
Birth outcomes			
Preterm birth (<37 weeks' gestation)	Delivery	LMP to 2 days before delivery	Primary: Unexposed during pregnancy or time until vaccine exposure after 22 weeks Secondary: COVID-19 vaccines received ≥4 weeks before LMP
Small-for-gestational age birth (<10th)			

For all outcomes, we will first explore rates and timing of diagnoses in pregnancy and compare to expected background rates. For outcomes with a 0.2 or higher standardized difference in incidence rate, as compared to expected background rates, outcome definitions will be reviewed and possibly modified. In addition, site-based variation in outcome rates will be investigated and, as needed, modifications by site in inclusion and exclusion criteria, may be applied. Chart reviews may also be requested to refine outcome definitions or explore unanticipated findings. If needed, chart abstractions conducted as part of the rapid cycle analyses (for myocarditis or thrombotic events) may be accessed.

For initial or modified outcomes with rates consistent with expected background rates, and consistent across sites, we will report adverse event rates in vaccinated and unvaccinated pregnancies. For thrombotic events and myocarditis / pericarditis, rates will be reported per 10,000 person-weeks, in order to reduce bias due to different observation times for exposed and unexposed. Adverse event rates for thrombocytopenia, postpartum hemorrhage, gestational diabetes, preeclampsia, preterm birth, small-for-gestational age birth and postpartum hemorrhage will be reported per 100 live births.

Association of receipt of COVID-19 vaccine and maternal and birth outcomes with no time dependent exposure (postpartum hemorrhage and small-for-gestational age at birth) will be reported as risk ratios (and risk difference when appropriate) with corresponding 95% confidence intervals for the contrast and after applying inverse probability weights. A Poisson distribution with robust variance using a generalized estimating equation will be used for these invariant time outcomes, robust variance will be used to account for the introduction of inverse probability weights. Time dependent covariate Cox model will be used to analyze preterm birth, thrombotic events, myocarditis/pericarditis, hypertensive disorders, thrombocytopenia, and gestational

diabetes to account for immortal time bias. Covid-19 infection will be incorporated in these models as a time dependent covariate. In addition, we will conduct analyses stratified by vaccine type and by vaccine dose.

Full Cohort Safety Analysis

For the full cohort, including live births with pregnancy start date May 2020 – April 30, 2021, analyses will be as described above for the interim safety analyses. We will also plan secondary analyses, comparing maternal and birth outcomes in women with live births who received one or more COVID-19 vaccines during pregnancy to those who received one or more COVID-19 vaccines 4 weeks prior to pregnancy. This analysis is planned as a sensitivity analysis to address incomplete capture of potential confounders that may also be associated with refusal of vaccination. However, it is possible that early and late adopters, or those seeking vaccination during pregnancy versus prior to pregnancy, may differ in health seeking behaviors. Analysis for this secondary aim will follow the same methods as in primary aims. For the full cohort safety analyses we will use both covariate sets, complete covariate and supplemented covariate set based on cycle file information or ancillary files. In addition, we will explore maternal and birth outcomes by timing of vaccination during pregnancy, grouped as pre-pregnancy, first trimester, second trimester, or third trimester. We will not evaluate whether any of the subgroup factors modify the safety of the vaccine, rather we will compare the safety events within each subgroup. Stabilized weights will be recomputed for each subgroup analysis.

Sensitivity Analysis

For any outcomes that may undergo chart review, we will perform a sensitivity analysis after reassigning the outcome(s) based on the chart review findings. Similarly, if exposure misclassification is a concern, we will conduct probabilistic bias analysis[31] using R episensr package.[32]

Alternative Methods

If any unanticipated research findings are identified, we will review our programs and source data to identify potential errors in outcome classification. We will also discuss internally and work with CDC and our VSD collaborators to discuss potential sources of bias or confounding. If needed, we would also conduct additional validation of outcomes through chart review and/or consider alternate analytic approaches to address bias. Finally, the outcomes selected are informed by GAIA, our prior evaluations of maternal Tdap and IIV vaccine safety, along with ongoing COVID-19 vaccine safety surveillance in non-pregnant populations. If additional potential safety signals are identified through VAERS and other postlicensure surveillance systems, or for COVID-19 vaccines yet to be approved, these outcomes may be added to this evaluation.

Power Analysis

Preliminary data from April data pull for the Maternal acute events following Covid-19 vaccine (VSD #1345), HP VSD internal data, and Coverage of COVID-19 vaccine during pregnancy were used to estimate cohort size and proportion vaccinated during pregnancy for the power analysis.[33]

Coverage of COVID-19 vaccine was set at 15% and 20% to estimate the minimum detectable differences. For birth outcomes, we applied a 30% attrition, because additional data of birth medical records may not be available for all pregnancies. We set the event rate for rare events at 1 per 10,000 for myocarditis, 10 per 10,000 for thrombotic events, 3 per 100 for postpartum hemorrhage, 8 per 100 for preterm birth, SGA, gestational diabetes and hypertensive disorders in pregnancy, and 10 per 100 for gestational thrombocytopenia. Minimum detectable differences are presented in Table 4 for risk ratios assuming alpha of 0.05, power of 80%. Estimates were computed using PASS 2019 software for tests for the ratio of Two Poisson Rates.

Table 4. Minimum detectable risk ratios for maternal and peripartum complication and birth outcomes.

	Sample size Exposed: unexposed	1 per 10,000	10 per 10,000	3 per 100	8 per 100	10 per 100
15% coverage	2500:14000	20.2	4.0	1.38	1.23	1.20
20% coverage	3400:13000	17.3	3.62	1.34	1.20	1.18
15% coverage-30% attrition	2000:10000				1.27	
20% coverage-30% attrition	2400: 9400				1.24	
15% coverage	8000:44800	8.1	2.40	1.21	1.12	1.11
20% coverage	10600:42000	7.2	2.25	1.19	1.11	1.10
15% coverage-30% attrition	7000:30000				1.14	
20% coverage-30% attrition	7500:29500				1.13	

Tests for the ratio of Two Poisson Rates, PASS 2019 Power Analysis and Sample Size Software (2019). NCSS, LLC. Kaysville, Utah, USA, ncss.com/software/pass.

Limitations

Several important limitations to the proposed surveillance should be noted. Because of the urgent need to monitor safety events after COVID-19 vaccination during pregnancy, we will rely on the DPA and will request sites collect gestational age and birth weight from the EHR. The DPA has been shown to be a valid method to identify pregnancies.[33] However, a non-trivial proportion of pregnancies identified through the DPA cannot be assigned to a pregnancy outcome, or lack information to date the pregnancy. To minimize this missing data for pregnancy dating, we will limit inclusion in the analyses to pregnancies among women who entered prenatal care at a VSD site, and with a live birth outcome. To increase the sensitivity of identifying vaccine exposures during pregnancy, we are including vaccine exposures from LMP until 2 days prior to delivery. By excluding vaccine exposures within 2 days of delivery we will not be able to identify immediate risks associated with vaccination – such as preterm births occurring within 1 day of vaccination. Misclassification of exposure status is always a concern but we believe that it will be low in this project. All VSD sites have bidirectional exchange of vaccine data with a regional or state

immunization registry triggered by a visit. Since this surveillance focuses on pregnant women who typically have many prenatal visits, there should be less misclassification of COVID-19 vaccine exposures as compared to non-pregnant populations. Five VSD sites also routinely integrate vaccine data from their state or regional immunization registry, independent of visits to the health system. Furthermore, birthweight will only be available through ancillary files and may not be available for the full cohort of live births during the study period. In addition, some women we classify as exposed during pregnancy may have received their COVID-19 vaccination postpartum. If postpartum COVID-19 vaccination becomes routine we may reconsider how we classify end of pregnancy exposures. Additionally, although we will attempt to evaluate for outcome misclassification, there may be residual confounding related to differences in health care seeking behavior between vaccinated and unvaccinated individuals as well as the timing of COVID-19 vaccine availability, for which we have limited ability to control. Furthermore, for outcomes that can occur at any time during pregnancy, such as myocarditis or thrombotic events, our approach, including all unvaccinated time as compared to time after vaccination, increases the risk of biasing to the null. However, excluding the time unexposed in vaccinated pregnancies may also artificially create a protective effect (vaccinated pregnancies would have shorter risk window than unvaccinated). As such, we will report these outcomes that can occur at any time in pregnancy as person-time and not per live birth. In the first phase of our evaluation of COVID-19 vaccine safety in pregnancy (VSD #1345), we are evaluating myocarditis, thrombotic events and thrombocytopenia, conducting matched analyses with an index date assigned to unvaccinated women and outcomes assessed within 21 or 42 days of vaccination. In contrast, in this protocol, out analytic approach does not include matching and we are identifying all outcomes through delivery and immediately postpartum, offering a complementary method and the opportunity to compare these two analytic approaches. Finally, COVID-19 vaccine guidelines may change during the course of this surveillance. For example, a booster dose may be indicated. Depending on the timing of these changes, modifications to the analytic approach described in this protocol may be needed.

Data Management Plan

The VSD team at HPI will be responsible for data management activities, including data extraction, surveillance evaluation documentation and data archival. Once the initial cohort of eligible pregnancies has been identified, additional exclusions will be applied at HPI. Data will be exchanged using methods that will assure security, primarily through the VSD distributed data model (DDM). The DDM allows all individual level standardized data files to reside at the health plan, and ownership is retained by the VSD site. The DDM maintains confidentiality of the health plan's data by utilizing encrypted and secure methods. HPI will write all relevant SAS code and will share it with CDC and participating sites for approval prior to data extraction.

Pregnancy records included in this surveillance project will be of women 16–49 years of age with a live birth and estimated pregnancy start of LMP from May 1, 2020 – April 30, 2021. In order to capture comorbidities and to identify outcome-specific exclusions present prior to pregnancy, we will pull selected diagnoses (Tables 1 and 2) for the period January 2019 – December 2021. The study period may be modified in accordance to extension in the study timeline. The first data pull will be in August 2021, and will include selected diagnoses for the period January 2019 – July 31, 2021. The final data pull is planned for February 2022.

In order to assess adverse birth outcomes such as small-for-gestation-age birth, we want to obtain gestational age and birth weight for eligible live births. Traditionally gestational age at birth and birth weight can be extracted from the HMOBIRTH table, which is usually updated on an annual basis and has a data lag of 1-2 years. As a result, we are requesting the creation of a new ancillary file that contains gestational age and birth weight from EHR or pregnancy registry for the identified eligible pregnancies end in live birth. This ancillary file will be requested following the initial data pull. We will also pull data from the ancillary platelet file to identify thrombocytopenia.

Archiving will be overseen by the HPI Project Manager and Data Manager and will include the updated surveillance evaluation protocol, work plans, programs, IRB documents, SAS output, manuscripts, surveillance evaluation and analysis documentation, and analysis data sets. The archive process will clearly identify and permanently save those files that were used to produce the interim and final reports and manuscripts.

Data sources: The initial cohort will consist of pregnancies in the PREGEPSD files from the current DDF at date of extraction, and cycle 2020. Data files used will include the following: CONSTANT, ENROLL, VACCINE, INPT, OUTPT, PROCDRE, PREGEPSD for DDF files and cycle files; and, PREG, GCDD, for cycle files. In addition, we will pull data from the following ancillary files: Platelet, Covlrslt, Covltest. (Table 3, below).

Table X. VSD Data Files

VSD File	Purpose
CONSTANT	Basic demographics of population, VSD site
ENROLL	MCO membership start and stop dates to identify pregnant women with constant enrollment 3 months prior to pregnancy start to end of observation period
VACCINE	Determine pregnancy and pre-pregnancy vaccinations
PREG	Additional pregnancy related variables
INPT	Inpatient hospitalizations and diagnostic codes
OUTPT	Outpatient and ED visits and diagnostic codes
PROCDRE	Procedure codes for blood transfusion
PREGEPSD	Pregnancy episode file to identify eligible pregnancies
GCDD	Geocode data when available
ANC.PLATELET	Platelet counts used to identify thrombocytopenia
ANC.COVLRSLT	COVID test result used in RCA
ANC.COVLTEST	COVID laboratory test used in RCA

Site responsibilities: It is our hope that all VSD sites with appropriate data will participate, contributing both electronic and chart review data, if needed.

If needed, we will work with sites to identify populations where birth data (gestational age and birth weight) would be available through EHR data or site-based pregnancy registries.

Confidentiality

This surveillance protocol will be reviewed for a non-research determination in accordance with CDC policy. The protocol will also undergo a determination and IRB review if needed and as required by each participating VSD site. Data use agreements (DUA) will be entered into with participating sites as needed. As the lead site, the HP project manager will help coordinate obtaining IRB approvals and DUAs (where applicable) from each site. The privacy and confidentiality of all subjects will be strictly protected, according to standard VSD procedures. The risks to patient privacy and confidentiality are minimal. Only specific members of the surveillance team will have access to the data. Only VSD Participant IDs will be used; HP and Yale based teams will not have access to names or medical record numbers at other sites.

The surveillance project does not involve intervention or interaction with human subjects. We request to waive the requirement to obtain informed consent, parental permission, and assent for this surveillance project under 45 CFR 46.116(d). As an analysis of existing data collected for non-research purposes, this activity presents minimal risk to subjects, and use of patient data for this purpose will not adversely affect subjects' rights or welfare.

Timeline

Table 4: Timeline for Phase 2: COVID-19 Vaccine Safety Evaluation in Pregnant Women and their Infants

Date	Description
June 4, 2021	Draft proposal to CDC and participating sites
June 17, 2021	Final protocol to CDC and sites
July 12, 2021	Obtain IRB approvals and DUAs
July 15, 2021	SAS code development/testing
August 1, 2021	Finalize SAS code – for initial data pull
August 30, 2021	Interim data extraction and analysis
September 21, 2021	Dissemination of interim findings, as requested
February 1, 2022	Final data extraction
April 15, 2022	Final data analysis
June 15, 2022	Manuscript preparation and submission

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