

PROTOCOL

COVID-19 Vaccine Safety, Spontaneous abortion (SAB) and Stillbirth in the Vaccine Safety
Datalink

VSD #1356

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TWO CASE-CONTROL STUDIES: STILLBIRTH AND COVID-19 VACCINE EXPOSURES SPONTANEOUS ABORTION AND COVID-19 VACCINE EXPOSURES

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LIST OF ABBREVIATIONS

ACIP = Advisory Committee on Immunization Practices

ACOG = American College of Obstetrics and Gynecology

DPA = dynamic pregnancy algorithm

EDD = estimated delivery date

EUA = emergency use authorization

GADx = gestational age specific ICD-10-CM codes

IUFD = intrauterine fetal demise

LMP = last menstrual period

SAB = spontaneous abortion

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

SB = stillbirth

VSD = Vaccine Safety Datalink

ABSTRACT

Pregnant women were excluded from COVID-19 vaccine clinical trials and thus data to date on the safety of COVID-19 vaccines in pregnancy is limited. Three COVID-19 vaccines are now available in the United States and recommended for use in pregnancy. This protocol is the second phase of our work on COVID-19 vaccine safety, spontaneous abortion (SAB) and stillbirth. Previously we implemented SAB and stillbirth surveillance.¹ In this phase we describe our approach for 1) conducting an individually matched case-control study of stillbirths and live births, and 2) conducting an individually matched case-control study of SABs and live births. For the stillbirth case-control study, eligible stillbirth cases occurring from March 1, 2021 to February 28, 2022 will be matched 1:3 by maternal age, pregnancy start, and VSD site to live births, in order to estimate the odds of COVID-19 vaccine exposure during pregnancy and up until the gestational age of the stillbirth. For the SAB case-control study, eligible SAB cases occurring from February 1, 2021 to October 31, 2021 will be matched 1:2 by maternal age, pregnancy start, and VSD site to live births, in order to estimate the odds of COVID-19 vaccine exposure during pregnancy and up until the gestational age of the SAB.

INTRODUCTION

Human infection with SARS-CoV-2, the virus that causes COVID-19, was first described in Wuhan, China in December 2019.² The first reported U.S. COVID-19 case was described in January 2020 in Seattle, WA.³ Given lack of pre-existing immunity to the virus, asymptomatic transmission, along with other challenges, there has been subsequent exponential worldwide spread of infection. In March 2020, the World Health Organization designated COVID-19 as a global pandemic. Worldwide, as of January 12, 2022 over 314 million people have contracted COVID-19 and there have been over 5.5 million deaths due to COVID-19. To date, approximately 1 in 5 cases and 15% COVID-19 deaths have occurred in the U.S.⁴ The COVID-19 pandemic has profoundly impacted our economy, education, and nearly all aspects of day-to-day life.

Vaccination remains the most important and effective tool for preventing hospitalizations and morbidity due to COVID-19 infections. In published data from their Phase III trial, including a median of 2 months of follow-up, the Pfizer-BioNTech COVID-19 (BNT162b2) vaccine had 95% efficacy in preventing symptomatic COVID-19 disease and vaccine-related side effects were consistent with other vaccines.⁵ Similarly, the Moderna vaccine (mRNA-1273) was shown to have 94% efficacy for preventing symptomatic COVID-19 disease.⁶ On December 11, 2020, the FDA issued the Pfizer-BioNTech COVID-19 vaccine an Emergency Use Authorization (EUA) for use in the United States.⁷ On December 12, 2020, the Advisory Committee on Immunization Practices (ACIP) issued recommendations regarding use of this vaccine in individuals 16 years and older.⁸ Subsequently, the FDA also 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, developed by Janssen and using an adenoviral vector, known as Ad26.COV2.S. On August 23, 2021, the FDA fully licensed the Pfizer-BioNTech COVID-19 vaccine for use in individuals 16 years and older. On January 31, 2022, the FDA fully licensed the Moderna COVID-19 vaccine for use in individuals 18 years and older.

Due to waning immunity, along with the emergence of more contagious SARS-CoV-2 variants, starting in September 25, 2021, booster doses of the mRNA vaccines were recommended for selected populations and then on November 29, 2021 these recommendations were expanded to all

adults. ([2021 booster recommendations](#)) The Moderna, Pfizer, and Janssen vaccines were initially recommended by ACIP, without a stated preference. Due to subsequent concerns regarding waning vaccine effectiveness over time, along with risks for rare but severe adverse events following the Janssen vaccine, on December 16, 2021 CDC endorsed the updated ACIP recommendations to preferentially administer the Moderna and Pfizer COVID-19 vaccines. ([mRNA vaccines preferred](#))

Real-world evidence of COVID-19 vaccine effectiveness has come from a range of public health and health system-based data networks. Findings have varied based on timing following vaccination, analytic approach, and predominant circulating variant during the period of study. Nevertheless, real-world effectiveness of 2 mRNA vaccine doses for preventing hospitalization within 5 months of vaccination are 70% or higher in a general adult population⁹⁻¹¹ and booster vaccination is an effective approach for maintaining vaccine effectiveness beyond 5 months.¹²

Initial clinical trials of the COVID-19 vaccines were limited to non-pregnant adults. Pregnancy testing was conducted prior to each vaccine dose and thus vaccine exposures during pregnancy among trial participants were limited to pre-pregnancy or very early in pregnancy, prior to a positive pregnancy test. At the time of 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 LMP (peri-pregnancy), 4 within 30 days after their LMP, and none were vaccinated later in pregnancy. One spontaneous abortion (SAB) was reported in the placebo group. To date, outcomes have not been reported among the remaining 22 pregnancies. Similarly, Moderna reported to the FDA that as of December 2, 2020, there were 13 pregnancies among women in their pivotal Phase 3 trial, 6 in the vaccine group and 7 in the placebo group. There was one SAB and one therapeutic abortion in the placebo group. An additional pregnancy in the placebo group was lost to follow-up. The remaining pregnancies in this trial were ongoing as of December 2020. At the time of EUA submission for Ad26.COV2.S, there were 8 pregnancies reported including 1 SAB in a woman who had received the vaccine.

There is increasing evidence regarding the potential for COVID-19 infections during pregnancy to increase risks for morbidity in pregnant women and to be associated with adverse birth outcomes.¹³⁻¹⁵ Recent analyses of administrative data from over 1.2 million delivery hospitalizations found COVID-19 was associated with higher risks for stillbirth as compared to pregnancies without COVID-19 (aRR 1.90 (95% 1.69-2.15)).¹⁶ Nevertheless, there is a need for further evaluation of this potential association, in studies where the stillbirth outcome and vaccine exposure status can be confirmed. There is also now data on the benefits of COVID-19 vaccination in pregnancy, including the transplacental transfer of antibodies following vaccination.¹⁷ Vaccination during pregnancy is strongly recommended by the U.S. Centers for Disease Control and Prevention (CDC)¹⁸ and an increasing number of healthcare institutions in the U.S. are mandating COVID-19 vaccination, including in pregnant women. As such there is an urgent need for outcome data following use of COVID-19 vaccines in pregnant populations.

Intrauterine fetal demise (IUFD), including SAB (fetal demise before 20 weeks' gestation), and stillbirth (fetal demise at ≥ 20 weeks' gestation), have been identified as important outcomes to be included when evaluating the safety of vaccines in pregnancy.^{19,20} The Vaccine Safety Datalink (VSD), established in 1990, is a collaboration between CDC and nine large health care organizations.²¹ With data on 3% of the U.S. population, automated identification of pregnancies,

the availability of detailed electronic health record (EHR) clinical data, and comprehensive vaccine data, the VSD provides a robust infrastructure for monitoring SAB and stillbirth following COVID-19 vaccination in pregnancy.^{22,23}

The VSD and others have evaluated risks of SAB following COVID-19 vaccination in early pregnancy with no safety signals identified to date.^{1,24,25} Of note, in these previously published studies, SABs were based on self-report,²⁴ automated EHR,¹ or registry data.²⁵ These cases were not clinically reviewed or adjudicated, and thus there was potential for outcome misclassification and for misclassification of the timing of vaccine exposures in relation to fetal demise. The VSD has also conducted monthly surveillance of stillbirths following maternal COVID-19 vaccination in the VSD population. As presented to ACIP on September 22, 2021, from December 2020 – July 2021, we identified 26 stillbirths in women who had received one or more COVID-19 vaccine doses during pregnancy. The mean gestational age at stillbirth was 29.5 weeks (SD 6.6 weeks). Nearly all (96%) had a pregnancy or obstetric complication increasing risk for stillbirth. The timing between vaccination and stillbirth ranged from 8-140 days for dose 1 and 3-112 days for dose 2, with no concerning patterns. During this same time period it was estimated that there were 11,300 live births to women who received one more COVID-19 vaccine doses during pregnancy, given an estimated stillbirth rate following vaccination of approximately 2 per 1,000 live births. ([ACIP VSD slides September 2021](#)) In this protocol we propose to extend the scope of our prior work, evaluating the odds of COVID-19 vaccine exposures in pregnancy and SAB or stillbirth outcomes through a rigorous case-control study, with all eligible pregnancies ending in stillbirth or SAB undergoing chart review and adjudication, and individual matching of cases and controls. In addition, we will explore the odds of COVID-19 infections and stillbirth or SAB in secondary analyses.

OBJECTIVES

1. To conduct case-control study of stillbirths, matched 1:3 by maternal age, pregnancy start, and VSD site to live births, in order to estimate the odds of a COVID-19 vaccine exposure during pregnancy and up until the gestational age of the stillbirth.
 - a. Odds of stillbirth by COVID-19 vaccine dose number (1, 2 or 3), and by mRNA vaccine type (Pfizer or Moderna) will be explored.
 - b. Odds of stillbirth by SARS-CoV-2 infection or COVID-19 diagnoses during pregnancy, categorized by vaccination status (unvaccinated, or received at least one COVID-19 vaccine) will also be explored.
 - c. We will use a time scan to explore whether, among pregnancies ending in stillbirth, there is any clustering by gestational age of vaccination or infection.
 - d. We will use a time scan to explore whether there is any clustering of timing from vaccination or COVID-19 infection to the stillbirth date.
2. To conduct a case-control study of SABs, matched 1:2 by maternal age, pregnancy start, and VSD site to live births or ongoing pregnancies, in order to estimate the odds of a COVID-19 vaccine exposure during pregnancy and up until the gestational age of the SAB.
 - a. Odds of SAB by COVID-19 vaccine dose number (1, 2, or 3), and mRNA vaccine type (Pfizer or Moderna) will be explored by 1-28- and 1-42-day exposure windows.

- b. Odds of SAB by SARS-CoV-2 infection or COVID-19 diagnoses prior to or during pregnancy, categorized by vaccination status (unvaccinated, or received at least one COVID-19 vaccine) will also be explored.
- c. We will use a time scan to explore whether, among pregnancies ending in SAB, there is any clustering by gestational age of vaccinations or COVID-19 infections.
- d. We will use a time scan to explore whether there is any clustering of timing from vaccination or COVID-19 infection to the SAB date.

DATA SOURCES

Data for defining the source population for these case-control studies of stillbirth and COVID-19 vaccination and SAB and COVID-19 vaccination will come from standardized VSD DDF files, created by all participating sites and consistent with the VSD data dictionary. Pregnancies will be selected from the PREGEPSD file, COVID-19 vaccine exposures will be identified using the DDF VACCINE file, with vaccines identified primarily from CVX codes. Sites use EHR, claims and bidirectional communication with state or regional immunization registries to identify vaccines administered within and outside of the health system.²⁶ CONSTANT, ENROLL, INPT, OUTPT and PROCDRE files from the DDFs will also be used. The MORT and ancillary death file will be used to identify any pregnancies lost to follow-up due to maternal mortality. DXID, DXIDHIST, COVLTEST, and COVLRSLT COVID-19 ancillary files will also be used to identify SARS-CoV-2 infections and COVID-19 diagnoses, in order to conduct the proposed secondary analyses.

Pregnancies in the PREGEPS file (ongoing pregnancies) and those ending in live birth, stillbirth or SAB are identified using the dynamic pregnancy algorithm (DPA) on a weekly basis. The DPA applies a hierarchical approach based on available diagnostic and procedure codes to identify pregnancies, and then assigns pregnancy start and end dates, or classifies pregnancies as ongoing. Additional data, including EDD, LMP, gestational age specific ICD-10-CM codes (GADx), and trimester specific care encounters are used to assign gestational age for completed or ongoing pregnancies. For completed pregnancies fixed gestation weeks are assigned if no other information is available. The DPA is an adaptation of the pregnancy episodes algorithm (PEA)²⁷ that has been validated for identifying pregnancies ending in live birth and non-live birth outcomes. Of note, the DPA allows for the accurate identification of ongoing pregnancies with subsequent live birth outcomes 6 or more months prior to birth.²⁸ An additional ancillary file will also include limited maternal and infant variables (see covariate and data management sections).

POPULATION

The population for the two proposed case-control studies, stillbirth and COVID-19 vaccine and SAB and COVID-19 vaccine, will be pregnant women at 8 VSD sites: Kaiser Washington, Kaiser Permanente Northwest, Kaiser Permanente Northern California, Southern California Kaiser Permanente, HealthPartners, Marshfield Clinic, Denver Health, and Kaiser Permanente Colorado. Detailed inclusion and exclusion criteria by objective are described below.

Objective 1 – Case-control study of stillbirths, matched 1:3 by maternal age, pregnancy start date, and VSD site to live births

Source population: In order to capture all stillbirth cases (with gestational ages 20-42 weeks) from March 1, 2021 – February 28, 2022, and eligible live birth controls, the stillbirth case-control

study source population will be singleton pregnancies with EDDs from February 15, 2021 to July 17, 2022 (or estimated pregnancy start May 11, 2020 – October 10, 2021) from participating sites.

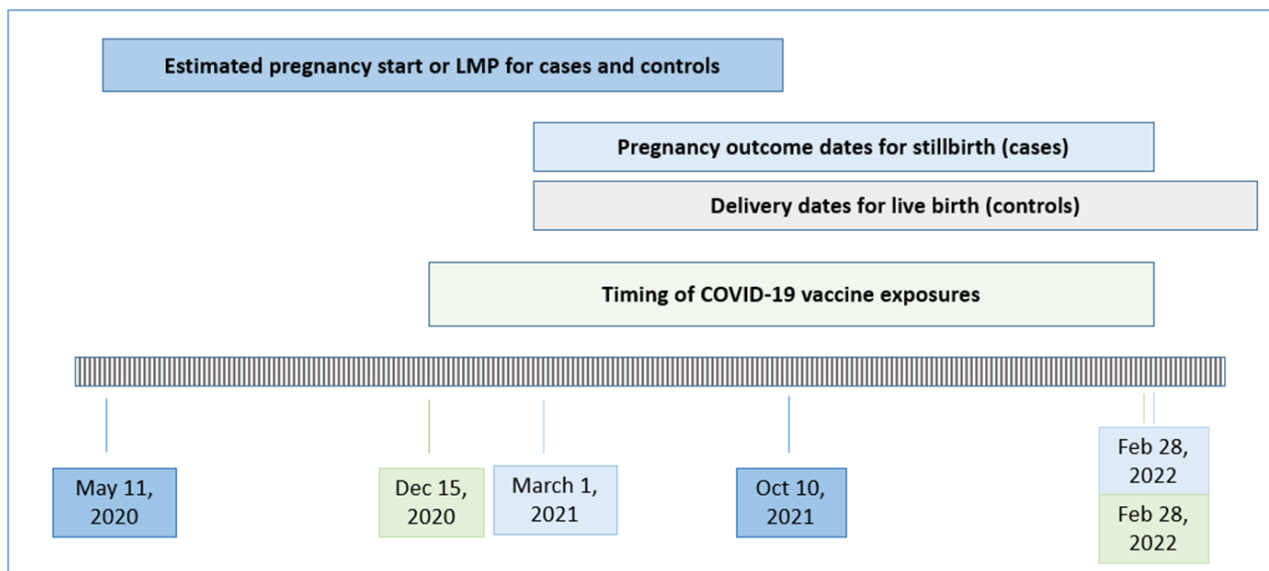
Criteria for inclusion in stillbirth case-control study:

- Stillbirth cases: Stillbirths identified by the DPA as occurring between March 1, 2021 – February 28, 2022. All potentially eligible stillbirths, identified from the DPA, will be confirmed via chart review. Stillbirths occurring between 20- and 42-weeks’ gestation, based on chart review and adjudication will be included.
- Live birth controls: Live births occurring between March 1, 2021 – July 31, 2022, with gestational age 23 – 42 weeks, and birth weight $\geq 500g$
- Both stillbirth cases and live birth controls: at least one prenatal visit, delivery or postpartum care visit in health system, maternal age 16-49 years at pregnancy start and ≤ 60 -day gap during pregnancy in enrollment at a VSD site (or empanelment at Denver Health)

Exclusions:

- Pregnancies with other non-live birth outcomes, including ectopic pregnancy, gestational trophoblastic disease, SAB, or therapeutic abortion, identified by the DPA, diagnosis codes, or chart review
- Pregnancies with no outcome available (missing outcome or an ongoing pregnancy)
- Live births with no gestational age dating available
- Live births with gestational age < 23 weeks, or > 42 weeks, or birth weight $< 500g$
- Multiple gestation pregnancies
- Completed pregnancies in women ≤ 15 years or > 49 years at pregnancy start
- Pregnancies with > 60 -day gap in enrollment at a VSD site (or empanelment at Denver Health)

Figure 1. Eligibility for stillbirth case-control study, based on date of stillbirth and estimated pregnancy start date



Objective 2 – Case-control study of SABs, matched 1:2 by maternal age, pregnancy start, and VSD site to live births

Source population: In order to capture all SABs (with gestational ages 6-19 weeks) occurring from February 1, 2021 – October 31, 2021, and eligible live birth controls, the SAB case control study will include singleton pregnancies with EDDs from June 21, 2021 - June 26, 2022 (or estimated pregnancy starts from September 15, 2020 – September 19, 2021) from participating sites.

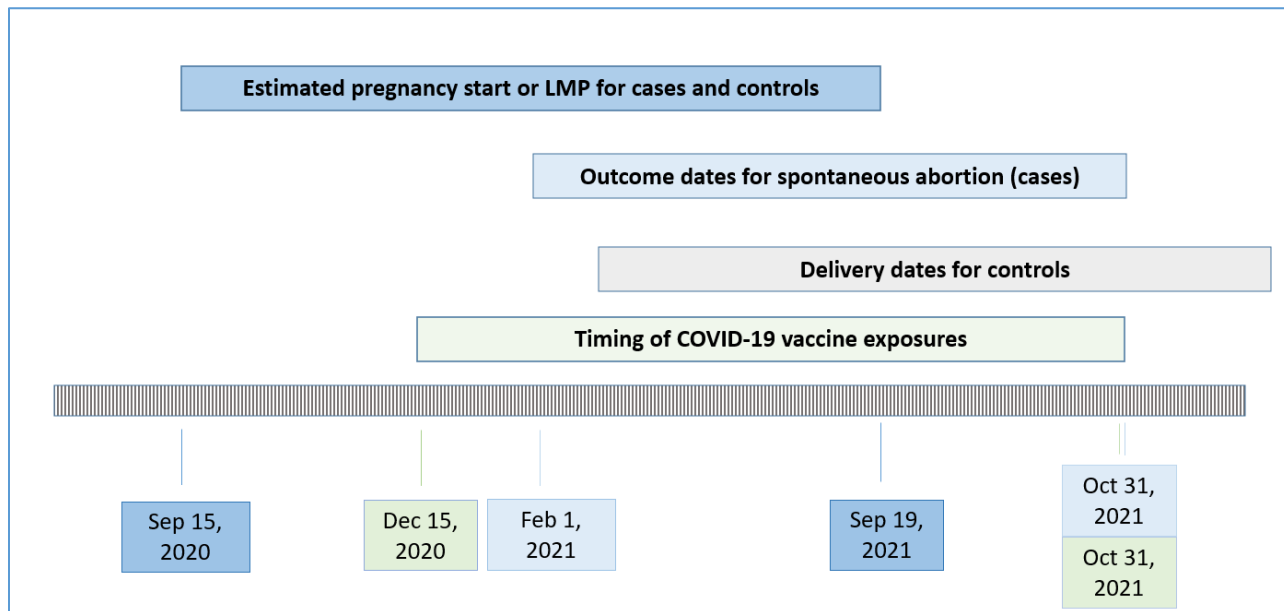
Inclusion criteria:

- SAB cases: Pregnancies identified through the automated pregnancy algorithm as SABs and occurring from February 1, 2021 – October 31, 2021. All potentially eligible SABs, will be confirmed via chart review, as described below. SABs occurring between 6- and 19-weeks' gestation, based on chart review and adjudication will be included.
- Live birth controls: Live births occurring from March 1, 2021 – June 25, 2022, with gestational age 23-42 weeks and birth weight >500g
- Both SAB cases and live birth or ongoing pregnancy controls: 2 or more encounters in health system, including one prior to pregnancy and one during pregnancy or peripartum, maternal age 16-49 years at pregnancy start and ≤60-day gap in enrollment at a VSD site (or empanelment at Denver Health) from 6 months prior to pregnancy start through pregnancy end

Exclusions:

- Pregnancies with other non-live birth outcomes, including stillbirths, ectopic pregnancy, gestational trophoblastic disease, or therapeutic abortion, identified by the automated pregnancy algorithm, diagnoses codes, or chart review.
- Pregnancies with undefined outcomes (missing outcome or an ongoing pregnancy)
- Pregnancies in women ≤15 years or >49 years at pregnancy start date
- Live births <23 weeks, >42 weeks, or <500g
- Live births without gestational age available
- SABs occurring at <6 weeks' gestation or without gestational age available or no records available for chart review
- Multiple gestation pregnancies
- Pregnancies resulting from assisted reproduction, from diagnostic or procedure codes
- Pregnancies with >60-day gap in enrollment at a VSD site (or empanelment at Denver Health), from 6 months prior to pregnancy start, through pregnancy end

Figure 2. Eligibility for spontaneous abortion (SAB) case-control study, based on date of SAB and estimated pregnancy start date



OUTCOMES

STILLBIRTH CASES

Suspected stillbirth cases meeting inclusion/exclusion criteria based on available automated data will be selected for chart review and expert adjudication.

Goals of the chart review and adjudication are:

1. To confirm the pregnancy outcome to be a stillbirth (IUFD at ≥ 20 weeks' gestation consistent with ACOG definitions).²⁹
2. To determine the date and gestational age at fetal demise, utilizing available medical records, ultrasound reports with a focus on first trimester ultrasound, fetal autopsy and pathology reports, and health care encounter notes. As in prior work, pregnancy dating will be confirmed based on a predetermined hierarchy, using 1) the physician-determined gestational age at delivery, 2) estimated delivery date as reported closest to the time of delivery, and 3) last menstrual period date in cases where the first two were not available.²²
3. To identify possible etiologies for the stillbirth, including but not limited to infections, fetal malformations, chromosomal abnormalities, complications of labor and delivery, complications of the umbilical cord or placenta, and maternal comorbidity.

All chart reviews and adjudications will be recorded in REDCap, a web-based system for secure data capture, using standardized forms.³⁰ Data to be collected through chart abstraction will include: EDD, LMP, and maternal characteristics not available from automated data. Redacted results of ultrasounds, pathology testing, and selected prenatal and postpartum visit notes and laboratory tests will also be uploaded into REDCap. In order to facilitate timely completion of chart review, we are

requesting limited data entry at sites. Please see chart abstraction form at end of protocol for more detail. Dr. Lipkind and her team of obstetricians based at Yale University, with prior experience conducting stillbirth case adjudication, will adjudicate all stillbirth cases. We will include in this case-control study eligible stillbirths previously chart reviewed and adjudicated as part of study HP 1346 (COVID-19 vaccine and stillbirth surveillance) and as part of study CDC 1336 (COVID-19 surveillance).

SAB CASES

SAB cases identified meeting inclusion/exclusion criteria based on available automated data will be randomly selected (see below) for chart review and adjudication.

Goals of the chart review and adjudication are:

1. To confirm the pregnancy outcome to be a SAB (IUFD between 6 and 19 weeks' gestation and consistent with ACOG definitions).³¹
2. To estimate the date and gestational age at fetal demise, utilizing available medical records, ultrasound reports with a focus on first trimester ultrasound, fetal autopsy and pathology reports, and health care encounter notes. As in prior work, pregnancy dating will be confirmed based on a predetermined hierarchy, using the physician-determined gestational age at delivery, estimated delivery date as reported closest to the time of the SAB, and last menstrual period date in cases where the first two were not available.

All chart reviews and adjudications will be recorded in REDCap, a web-based system for secure data capture, using standardized forms.³⁰ Data to be collected through chart abstraction will include: EDD, LMP, redacted results of ultrasounds, pathology testing, and selected visit notes and laboratory tests will also be uploaded into REDCap. In order to facilitate timely completion of chart review, we are requesting limited data entry at sites. Please see chart abstraction form at end of protocol for more detail. Drs. Kharbanda and DeSilva, Ms. Seburg, and their team at HealthPartners Institute will conduct the initial round of case review and adjudication. Dr. Lipkind and her team of obstetricians based at Yale University, will adjudicate any complex cases.

LIVE BIRTHS CONTROLS

Data for live birth controls will come from automated data. Ancillary files for gestational age based on delivery or birth records will be used to confirm the birth outcome date and gestational age, or identify exclusions based on birth weight. An initial match of up to 5 controls per case will be performed. When discrepancies in gestational age are observed between the gestational age from the DPA and the gestational age from ancillary files or extreme values (<23 weeks gestation or >42 weeks gestation), sites may be requested to confirm the gestational age or EDD by reviewing the medical record, as a "quick look".

MATCHING

For Objective 1, chart confirmed and adjudicated eligible stillbirth cases will be matched 1:3 to eligible live births using greedy matching. Match variables will include maternal age (+/-3 years), pregnancy start date (+/- 14 days), and VSD site.³² Live birth controls will be censored as of the gestational age of the matched stillbirth case and an index date will be assigned.

For Objective 2, chart confirmed and adjudicated eligible SAB cases will be matched 1:2 to eligible live births or ongoing pregnancy controls using greedy matching. Match variable will include maternal age (+/- 3 years), pregnancy start date (+/- 14 days), and VSD site.³² Ongoing pregnancy and live birth controls will be censored as of the gestational age of the matched SAB case and an index date will be assigned.

VACCINE EXPOSURES

All COVID-19 vaccines approved for use in the U.S. will be identified from standardized VSD DDF VACCINE files. Vaccines will be assigned as occurring during pregnancy and prior to fetal demise based on adjudicated date of fetal demise and adjudicated gestational age at fetal demise, and during pregnancy and prior to the index date based on the matching for live births controls. (Vaccines administered on the adjudicated date of fetal demise or index date for controls will not be included).

For both cases and controls, vaccines will be further classified by dose (first, second, or third) and manufacturer for the mRNA vaccines (Pfizer or Moderna). In addition, for secondary analyses, vaccines will be classified by timing from vaccination to stillbirth or SAB outcome date (or index date for matched control), and with a specific evaluation of vaccines within 28 days and 42 days of the SAB for secondary analyses.

SARS-COV-2 INFECTIONS and COVID-19 DIAGNOSES

We will use all available automated data to identify COVID-19 diagnoses and SARS-COV-2 infections in pregnancies ending live birth, stillbirth or SAB. This will include ICD-10-CM diagnoses from inpatient, outpatient or ED visits, and existing ancillary files with DXID and SARS-COV-2 laboratory data. For stillbirth and SAB cases, COVID-19 diagnosis or laboratory tests SARS-CoV-2 during pregnancy will also be collected via chart review. As part of the case adjudication process, for the SAB and stillbirth cases adjudicators will also review COVID-19 diagnoses and test results to assign any cases with positive results as a confirmed infection (PCR positive) or probable infection (antigen test positive without PCR confirmation of diagnosis without PCR test confirmation) and to classify the timing of infections during pregnancy. For stillbirth and SAB cases with both automated and chart review data on COVID infections we plan a small

validation exercise to compare the results from these two data sources. If >15% of COVID infections from chart review are missed with existing automated files we will consider limited chart reviews of live births or limiting the analysis to clustering exploration of exposures among cases.

Table 1. Maternal Comorbidities
Diabetes
Obesity
Cancer
Sickle cell disease and other hematologic disorders
Lupus and other autoimmune disorders
Cirrhosis, cholestasis and other liver disease
Organ transplant
Renal failure / dialysis / chronic renal disease
Hypertension and other cardiovascular disease – cardiomyopathy, heart failure
Pulmonary disease – persistent asthma, cystic fibrosis
Smoking / nicotine dependence / substance use
SARS-CoV-2 infection during or prior to pregnancy
Prior high-risk pregnancy

COVARIATES

We will pull additional data to characterize the population and to identify potential confounders. These include: maternal age, site, race/ethnicity, number of prenatal encounters up to fetal demise or index date, number of outpatient encounters in

the prior year to pregnancy start, 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 fetal demise (Table 1). We will request an ancillary file to collect poverty level from 5-year ACS census tract as a proxy for neighborhood socioeconomic status (SES), smoking status, and pre-pregnancy weight and height. Additionally, we will collect weekly county SARS-CoV-2 positivity rates from public health records through the HHS protects public data hub [<https://protect-public.hhs.gov>]. Positivity rates during pregnancy will be assessed as a covariate. Presence of comorbidities will be identified in the prior 3 years up to the fetal demise or index date. For the primary analyses of COVID-19 vaccination during pregnancy and SAB or stillbirth outcomes, SARS-CoV-2 infections or COVID diagnoses prior to or during pregnancy will be included as covariates. For secondary analyses, SARS-CoV-2 infections or COVID diagnoses during pregnancy will be the exposures of interest and prior COVID-19 vaccination status will be a categorical variable.

ANALYSIS AND REPORTING

Baseline characteristics will be described by cases and controls, using means and standard deviations, medians and interquartile range, or frequency distribution as appropriate, for each case-control study, stillbirth and spontaneous abortion. Standardized mean differences (SMD) between COVID-19 exposed and unexposed will be used to select covariates for adjustment with an $SMD > 0.10$. Covariates will be selected from a predefined number of potential confounders, i.e. are associated with receipt of COVID-19 vaccine, a risk factor for fetal demise (stillbirth or SAB), and not an instrumental variable based on clinical knowledge.³³

Associations of COVID-19 vaccine for stillbirth and for SAB will be evaluated using a conditional logistic regression with receipt of COVID-19 vaccine during pregnancy as the outcome. Continuous covariates, e.g. maternal age, number of health utilization, BMI, and SARS-CoV-2 positivity rates, will be included in the model as cubic splines. Because maternal age is a matching factor, we will use the deviation of each woman's age to the mean age for the matched set.³⁴ Associations will be reported as odds ratios with 95% confidence intervals with the reference exposure group as unvaccinated women as of the date of fetal demise or index date. Statistical significance is set at a p-value < 0.05 .

Secondary analysis for the stillbirth and SAB case-control studies will include evaluation of the associations of dose of COVID-19 vaccine, receipt of one or two COVID-19 vaccine doses, vaccine manufacturer for mRNA, and 28- and 42- day exposure window prior to fetal demise or index date. Unvaccinated women during pregnancy will be used as a reference exposure group. For SARS-CoV-2 infection and COVID-19 disease, we will create a binary variable for presence of infection or disease during pregnancy and up to the index date. Absence of infection or disease will be used as reference exposure group. A temporal scan statistic will be used to evaluate whether COVID-19 vaccines or SARS-CoV-2 infections/COVID-19 diagnoses are clustered during pregnancy and prior to the fetal demise among women having a stillbirth or SAB.³⁵ Classification of COVID-19 infection status for primary analyses (evaluating vaccination) and classification of COVID-19 vaccine status for secondary analyses (evaluating infection) are shown in Figures 3 and 4.

Figure 3. Classification of COVID-19 vaccines diagnoses / SARS-CoV-2 infections for primary analyses, with COVID-19 vaccination as exposure of interest

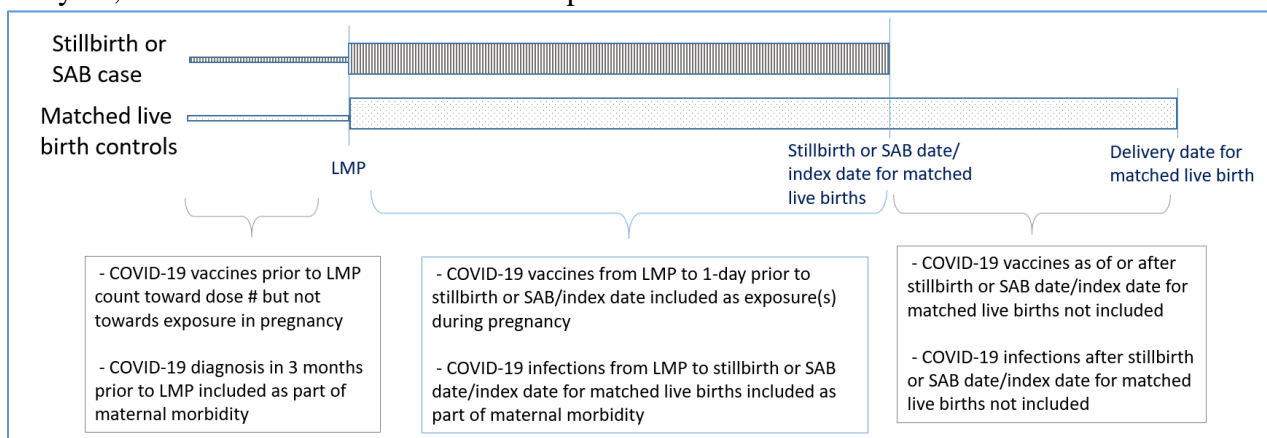
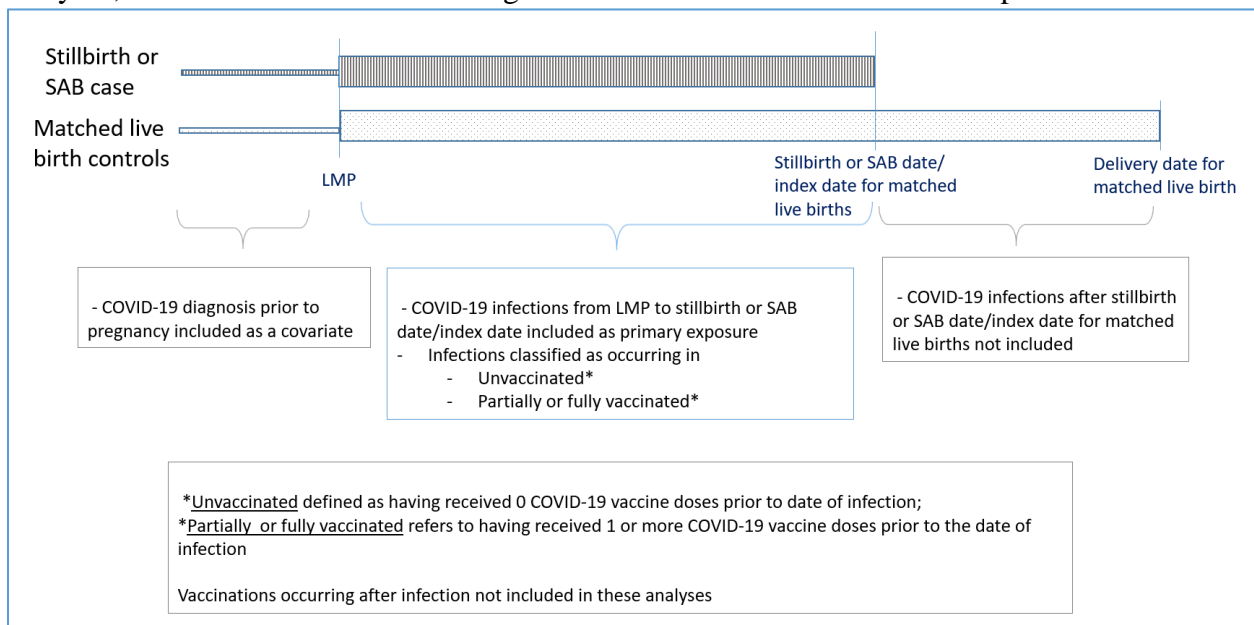


Figure 4. Classification of COVID-19 vaccines diagnoses / SARS-CoV-2 infections for secondary analyses, with COVID-19 vaccines diagnoses / SARS-CoV-2 infections as exposure of interest



POWER

Stillbirth, or IUFD at 20 weeks' gestation or later, is an important yet rare outcome, occurring at a background rate of approximately 5 per 1,000 live births in the VSD.²² In a prior VSD case-control study evaluating stillbirth following maternal vaccination, in order to have sufficient power, the study included stillbirth cases occurring over nearly four years. Based on HP 1346 COVID-19 vaccine stillbirth surveillance study, using the DPA we have identified 736 potential stillbirth cases with a health encounter in the health system during pregnancy, delivery or postpartum from December 15, 2020 to December 31, 2021. For the study period, from March 1, 2021 to February 28, 2022, we expect to identify over 800 potential stillbirths. We expect that at least 50% of these cases are confirmed to be stillbirths after adjudication. The case-control study will have 80% power to detect an odds ratio of 1.5 based on 400 confirmed stillbirth cases and 1:3 match ratio to live

births assuming an exposure of COVID-19 vaccine of 26%, 0.1 correlation of COVID-19 vaccine with other covariates, and alpha value of 0.05. Power estimated using PAS Software, testing for the Odds Ratio in a Matched Case-Control Design.

SAB, or fetal demise before 20 weeks' gestation in a confirmed intrauterine pregnancy occurs in up to 15% of pregnancies and is an important safety outcome following vaccine exposures early in pregnancy.²⁰ Based on HP 1356 COVID-19 vaccine SAB surveillance study, we identified 1128 spontaneous abortions from December 15 to June 28, 2021. In addition, previous studies from our group, HP 1317 9vHPV and SAB and HP 294 4vHPV and SAB, have confirmed 70% of SABs identified by the PEA as SAB cases based on chart review and adjudication. The case-control study will have 80% power to detect an odds ratio of 1.6 based on a site-stratified random sample of 500 confirmed, adjudicated SABs with a 1:2 match ratio to live births assuming an exposure of COVID-19 vaccine of 10%, 0.1 correlation of COVID-19 vaccine with other covariates, and alpha value of 0.05. Power estimated using PAS Software, testing for the Odds Ratio in a Matched Case-Control Design.

LIMITATIONS

Limitations to the proposed case-control studies should be noted. First limitation is in relation to the study power. Due to a limited number of total stillbirth cases, we will only be able to detect an odds ratio of 1.5 or higher for vaccination and stillbirth outcome. Similarly, due to limitations of feasibility and scope, we are only able to conduct enough SAB chart reviews to detect an odds ratio of 1.6 or higher. Second, as a retrospective observational study, we may be limited in the identification of possible confounders. It is not feasible to conduct chart reviews for all live birth controls and thus we can only include covariates identified from automated data files. As in any case-control study, there is potential for bias if the comparison or control population systematically differs from the case population. We will limit this potential bias by applying inclusion and exclusion criteria prior to any matching. In addition, the proposed secondary analyses of COVID infections and stillbirth and SAB outcomes may be biased due to limited testing and missed identification of infections earlier in the pandemic. Furthermore, due to routine screening, infections may be more likely to be identified at a delivery than at other periods in pregnancy.³⁶ Given this potential limitation, alternate matching for adjudicated stillbirths and SABs may be considered for the secondary analyses of COVID infections and IUD outcomes. Finally, booster vaccines are now recommended for all adults who are at least 5 months following their second vaccine dose. Due to the timing of pregnancies and births in this study, we do not anticipate that there will be many who have received their third or booster dose.

DATA MANAGEMENT PLAN

The VSD team at HPI will be responsible for data management activities, including data extraction, surveillance evaluation documentation and archival. Once the initial cohort of stillbirths and SAB cases potentially eligible for chart review has been identified, additional exclusions will be applied at HPM. Similarly, exclusions to the potentially eligible live birth control population will be applied at HPM and all matching will be done at HPM. 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.

For both Objective 1 and Objective 2, we will pull individual level data. We will first pull data for potential SAB and stillbirth cases in order to initiate the chart reviews. This initial pull will include limited pregnancy and outcome indicators based on ICD-10 diagnoses in order to apply automated exclusions. Subsequent data pulls will be done for live births for matching with the adjudicated stillbirth and SAB cases, including limited pregnancy and outcome variables to evaluate the accuracy of the pregnancy outcome, and gestational age. Once individuals are matched, covariates and vaccine data will be pulled in two subsequent data extractions. (see Table 4 for detailed timeline)

Archiving will be overseen by the HPM 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 archival process will clearly identify and permanently save those files that were used to produce the interim and final reports and manuscripts.

Data Sources: Eligible pregnancies ending in stillbirth, SAB, or live births in women 16-49 years will be identified from the DDF PREGPSD files. CONSTANT, ENROLL, OUTPT, INPT, PROCDRE, MORT, and ancillary death files from the DDFs will also be used. COVID-19 vaccine exposures will be identified using the DDF VACCINE file. DXID, DXIDHIST, COVLTEST, and COVLRSLT COVID-19 ancillary files will also be used to identify COVID-19 infections and COVID-19 diagnoses. Ancillary files will include: gestational age at delivery based on delivery and infant records for live births, source of gestational age, infant sex, birth weight, multiple gestation, maternal-infant linkage, ACS 2019 5-year neighborhood data, pre-pregnancy weight and height, and smoking variables.

Table 2. 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 from 3 month prior to pregnancy start
VACCINE	Determine during pregnancy and pre-pregnancy vaccinations
INPT	Inpatient hospitalizations and diagnoses codes
OUTPT	Outpatient and ED visits and diagnoses codes
PROCDRE	Procedure diagnoses codes
PREGPSD	Pregnancy episode file to identify eligible pregnancies
MORT	Mortality data
DEATH	Ancillary mortality data
COVLTEST	Ancillary COVID-19 laboratory test data
COVLRSLT	Ancillary COVID-19 laboratory test result data
DXID	COVID-19 related DXID diagnosis data
DXIDHIST	COVID-19 related DXID diagnosis codes

SITE RESPONSABILITIES

It is our hope that all VSD sites with appropriate data will participate, contributing both electronic and chart review data. Based on the estimated number of eligible stillbirths during the observation period and sample size requirement to achieve desired power for the SAB study we estimate the follow number of charts to be reviewed by sites

Table 3. Chart review estimates by site

Site	Estimated number of new stillbirth charts to be reviewed	Estimated number of stillbirth charts reviewed as or 1/12/2021, as part of ongoing stillbirth surveillance*	Estimated number of SAB charts to be reviewed
SCK	180-200	51	200-250
NCK	180-200	41	200-250
KWA	10-30	19	40-50
NWK	10-30	15	40-50
HPM	10-30	18	40-50
MFC	10-30	14	40-50
KPC	10-30	9	40-50
DH	10-30	30	40-50
Total	420-580	135	640-800

*No additional chart review for these cases will be needed

HUMAN SUBJECTS AND 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

Date	Description
January 19, 2021	Draft proposal to CDC and participating sites
January 26, 2021	Presentation on VSD Pregnancy call
February 4, 2022	Final protocol to CDC and sites
February 15, 2022	IRB approvals and DUAs completed, as needed
March 1, 2022	SAS code development/testing
March 19, 2022	Submit final data abstraction code to CDC and sites
April 19, 2022	Start stillbirth chart reviews and adjudications
July 1, 2022	Start SAB chart reviews and adjudications
September 1, 2022	Pull live births for matching with adjudicated stillbirth cases
October 15, 2022	Pull vaccine and covariate data for live births matched with stillbirth cases
December 1, 2022	Pull live births for matching with adjudicated SAB cases
February 1, 2022	Pull covariate and vaccine data for live births matched with SAB cases
March 19, 2023	Interim analyses for SAB and stillbirth case-control surveillance
June 19, 2023	Submit draft manuscript to CDC
August 19, 2023	Submit final manuscript to CDC
September 19, 2023	Archive of final datasets

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STILLBIRTH ABSTRACTION FORM**GENERAL INSTRUCTIONS**

- DATA TO BE ENTERED DIRECTLY INTO REDCAP DATABASE
- ALL WOMEN SELECTED HAVE A SUSPECTED OR POSSIBLE STILLBIRTH BASED ON AUTOMATED DATA (DIAGNOSTIC OR PROCEDURE CODES)

PART A: DEMOGRAPHICS AND CHART SCREENING

A1. Abtractor ID: _____

A2. Abstraction date: __ / __ / __ - - - -

Questions A3 through A6 will be pre-populated in REDCap, from VSD automated files

A3. VSD study ID: _____

A4. Site:

- 1 SCK (Kaiser Southern California)
 2 NCK (Kaiser Northern California)
 3 KWA (Kaiser Washington)
 4 NWK (Kaiser Permanente Northwest)
 5 HPM (HealthPartners)
 6 MFC (Marshfield Clinic)
 7 KPC (Kaiser Permanente Colorado)
 8 DH (Denver Health)

A5. Date of pregnancy outcome: __ / __ / __ - - - -

A6. Mother's age at delivery: __ __ years

A7. Please enter the mother's month and year of birth __ / ____ (to confirm in correct chart)

A8. Are there encounters with documented pregnancy information between the [ref diagnosis date - 90 days] and the [ref diagnosis date + 30 days] in the electronic medical record?

- 1 Yes
 2 No (**STOP abstraction**)

A9. Is a fetal demise (stillbirth or spontaneous abortion) documented in the medical record between [ref diagnosis date-30 days] and [ref diagnosis date + 30 days]? *Note for multiple gestation pregnancies, please mark as yes if there has been a demise of at least one fetus*

- 1 Yes (Continue with question A10)
 2 No (Continue with question A9.1)

A9.1 Please indicate the outcome of this pregnancy.

- 1 Ectopic pregnancy (**STOP abstraction**)
 2 Elective / therapeutic abortion (**STOP abstraction**)
 3 Live birth (Continue with A9.2)
 4 Ongoing pregnancy (**STOP abstraction**)
 5 Pregnancy outcome not known (**STOP abstraction**)

6 Other _____

A9.2 For a live birth, please indicate status of the newborn

- 1 Live birth, discharged from hospital (**STOP abstraction**)
 2 Live birth, neonatal demise (**STOP abstraction**)
 3 Live birth, neonatal status not known (**STOP abstraction**)

A10. Was this a multiple gestation pregnancy? (e.g. twin, triplet, ...)

- 1 Yes (**STOP abstraction**)
 2 No (Continue with A11)

A11. Please indicate the earliest date that a fetal demise was diagnosed (no fetal heartbeat) based on pregnancy dating at that visit

__ / __ / ____ or date unknown

A12. Please indicate the estimated gestational age at fetal demise (date from A11)

__ weeks __ days or gestational age unknown

A13. Please indicate EDD (estimated delivery date) for this pregnancy

__ / __ / ____ or date unknown

A13.1 Please indicate date of last menstrual period (LMP)

__ / __ / ____ or date unknown

PART B: CLINICAL FINDINGS

B1. Please indicate delivery or pregnancy end date __ / __ / ____

B1.2 Was there spontaneous or induced labor, or was a D&C (dilation and curettage) or D&E (dilation and evacuation) or other surgical procedure performed?

- 1 Spontaneous
 2 Induced
 3 D&E
 4 D&C
 5 Other surgical procedure

B1.3 Was a heartbeat noted in the fetus after delivery?

- 1 Yes
 2 No / not documented

B1.4 Was a resuscitation attempted after delivery? (Includes positive pressure ventilation, administration of oxygen, chest compressions or administration of epinephrine)

- 1 Yes
 2 No / not documented

B1.5 Was fetal demise confirmed at delivery (Apgars = 0, 0; No spontaneous respirations)

- 1 Yes
2 No / not documented

PART C: MATERNAL LABORATORY TESTING

PLEASE INDICATE IF ANY OF THE FOLLOWING TESTS WERE PERFORMED DURING PREGNANCY OR IMMEDIATELY POSTPARTUM

C1. COVID-19 PCR at time of delivery

- 1 **COVID-19 PCR positive, redacted results uploaded**
2 **COVID-19 PCR negative, redacted results uploaded**
3 COVID-19 PCR performed, results not available
4 COVID-19 not performed

C2. COVID-19 PCR during pregnancy, before delivery

- 1 **COVID-19 PCR positive, redacted results uploaded**
2 **COVID-19 PCR negative, redacted results uploaded**
3 COVID-19 PCR performed, results not available
4 COVID-19 not performed

C2.1 COVID-19 antigen testing, at time of delivery

- 1 **COVID-19 PCR positive, redacted results uploaded**
2 **COVID-19 PCR negative, redacted results uploaded**
3 COVID-19 antigen testing performed, results not available
4 COVID-19 antigen testing not performed

C2.2 COVID-19 antigen testing, during pregnancy, before delivery

- 1 **COVID-19 PCR positive, redacted results uploaded**
2 **COVID-19 PCR negative, redacted results uploaded**
3 COVID-19 antigen testing performed, results not available
4 COVID-19 antigen testing not performed

C3. Antiphospholipid antibody

- 1 **Antiphospholipid antibody abnormal, redacted results uploaded**
2 Antiphospholipid antibody performed, results within normal limits
3 Antiphospholipid antibody performed but records not available
4 Antiphospholipid antibody not performed

C4. Group B Strep Culture (GBS)

- 1 **GBS culture positive, redacted results uploaded**
2 GBS culture negative
3 GBS culture performed but records not available
4 GBS culture not performed

C5. Toxoplasmosis (serum antibody, IgG and IgM)

- 1 **Toxoplasmosis serum antibody abnormal, redacted results uploaded**
- 2 Toxoplasmosis serum antibody performed, results normal / negative
- 3 Toxoplasmosis serum antibody performed but records not available
- 4 Toxoplasmosis serum antibody not performed

C6. Cytomegalovirus or CMV (serum antibody, IgG and IgM)

- 1 **CMV serum antibody abnormal, redacted results uploaded**
- 2 CMV serum antibody performed, results normal / negative
- 3 CMV serum antibody performed but records not available
- 4 CMV serum antibody not performed

C7. Herpes Simplex (serum antibody, blood, skin culture or PCR)

- 1 **Herpes Simplex (serum antibody, blood, skin culture or PCR) abnormal, redacted results uploaded**
- 2 Herpes Simplex testing performed, results normal / negative
- 3 Herpes Simplex testing performed but records not available
- 4 Herpes Simplex testing not performed

C8. Syphilis (RPR, treponemal antibody testing (FTA-ABS))

- 1 **Syphilis (RPR or FTA-ABS) abnormal, redacted results for both tests uploaded**
- 2 Syphilis (RPR or FTA-ABS) performed, results normal / negative
- 3 Syphilis (RPR or FTA-ABS) performed but records not available
- 4 Syphilis (RPR or FTA-ABS) not performed

C9. Drug screening (urine or blood)

- 1 **Drug screening (urine or blood) abnormal for drug other than THC, redacted results uploaded**
- 2 Drug screening (urine or blood) performed, results normal / negative
- 3 Drug screening (urine or blood) performed but records not available
- 4 Drug screening (urine or blood) not performed

C10. Please indicate if cell-free DNA testing (NIPT) was performed with records available during this pregnancy (upload any available results)

- 1 **Yes and records available for uploading**
- 2 Yes, but records not available for uploading
- 3 No, cell-free DNA testing was not performed for this pregnancy

C11. Please indicate if first trimester screening (nuchal translucency ultrasound and blood tests) performed with records available during this pregnancy (upload any available results)

- 1 **Yes and records available for uploading**
- 2 Yes, but records not available for uploading
- 3 No, first trimester screening not performed for this pregnancy

C12. Please indicate if second trimester screening (quad screening or maternal serum alpha-fetoprotein (MSAFP) alone) performed with records available during this pregnancy (upload any available results)

- 1 **Yes and records available for uploading**
- 2 Yes, but records not available for uploading
- 3 No, second trimester screening not performed for this pregnancy

C13. Please provide any additional notes regarding abnormal laboratory testing during pregnancy or immediately postpartum, particularly if redacted results not available. Please be sure to add test type, units, date of test and result.

PART D: PATHOLOGY FETAL KARYOTYPE SCREENING

D1. Please indicate if placental pathology performed with records available during this pregnancy

- 1 **Yes and records available for uploading**
- 2 Yes, but records not available for uploading
- 3 No, placental pathology not performed for this pregnancy

D2. Please indicate if fetal autopsy performed with records available during this pregnancy

- 1 **Yes and records available for uploading**
- 2 Yes, but records not available for uploading
- 3 No, fetal autopsy not performed for this pregnancy

D3. Please indicate if fetal karyotype performed with records available during this pregnancy

- 1 **Yes and records available for uploading**
- 2 Yes, but records not available for uploading
- 3 No, fetal karyotype not performed for this pregnancy

Note fetal karyotype may follow amniocentesis, chorionic villus sampling

Please uploaded redacted copies of all pathology and karyotype screening reports for this pregnancy

D4. Please provide any additional notes regarding pathology results, particularly if redacted results not available

PART E: ULTRASOUND

E1. Please indicate total number of ultrasounds with records available during this pregnancy

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E2. Please provide any additional notes regarding ultrasounds, particularly if redacted results not available

PART F: CLINICAL ENCOUNTERS

F1. Please indicate total number of health care encounters (include prenatal and postnatal obstetric care visits, emergency department (ED) visits) with records available for the period [ref diagnosis date – 30 days through ref diagnosis date + 60 days]

--

F2. Please provide any additional notes regarding prenatal, 6-week postpartum, ED and delivery records, particularly if redacted results not available

Data from medical record to be redacted and uploaded (based on data entered in chart review)

1. Any abnormal laboratory tests noted and any available nuchal, quad, AFP, or cell free DNA screening (from Part C)
2. All pathology results for this pregnancy: fetal autopsy, fetal karyotype, and placental pathology report (from Part D)
3. Ultrasound reports: All available for this pregnancy if possible; If all ultrasounds are not available, priority is to include at least one official ultrasound between 8-14 weeks to establish dating, at least one official ultrasound between 18-22 weeks to evaluate for fetal anomalies, and all ultrasounds within 30 days of delivery (from Part E)
4. Clinical encounters: include notes from all prenatal or ED encounters from 30 days prior to delivery and include postpartum obstetric encounter and physician / obstetric note from delivery (from Part F)

SPONTANEOUS ABORTION (SAB) ABSTRACTION FORM**GENERAL INSTRUCTIONS**

- DATA TO BE ENTERED DIRECTLY INTO REDCAP DATABASE
- ALL WOMEN SELECTED HAVE A SUSPECTED OR POSSIBLE SAB BASED ON AUTOMATED DATA (DIAGNOSTIC OR PROCEDURE CODES)

PART A: DEMOGRAPHICS AND CHART SCREENING

A1. Abtractor ID: _____

A2. Abstraction date: __ __ / __ __ / __ __ __ __

Questions A3 through A6 will be pre-populated in REDCap, from VSD automated files

A3. VSD study ID: _____

A4. Site:

- 1 SCK (Kaiser Southern California)
 2 NCK (Kaiser Northern California)
 3 KWA (Kaiser Washington)
 4 NWK (Kaiser Permanente Northwest)
 5 HPM (HealthPartners)
 6 MFC (Marshfield Clinic)
 7 KPC (Kaiser Permanente Colorado)
 8 DH (Denver Health)

A5. Date of pregnancy outcome: __ __ / __ __ / __ __ __ __

A6. Mother's age at pregnancy outcome date: __ __ years

A7. Please enter the mother's month and year of birth __ __ / __ __ __ __ (to confirm in correct chart)

A8. Are there any records [outpatient, ER, inpatient, phone, telemedicine] confirming a pregnancy between the [ref diagnosis date – 90 days] and the [ref diagnosis date + 30 days] in the electronic medical record?

- 1 Yes
 2 No (**STOP abstraction**)

A9. Was this a multiple gestation pregnancy? (e.g. twin, triplet, ...)

- 1 Yes (**STOP abstraction**)
 2 No (Continue with A11)

A10. Is a spontaneous abortion documented in the medical record between [ref diagnosis date-60 days] and [ref diagnosis date + 30 days]?

- 1 Yes (Continue with question A11)
 2 No (Continue with question A10.1)

A10.1 Please indicate the outcome of this pregnancy. (**STOP abstraction after completing A10.1**)

- 1 Ectopic pregnancy
- 2 Elective / therapeutic abortion
- 3 Live birth
- 4 Ongoing pregnancy
- 5 Pregnancy outcome not known
- 6 Stillbirth
- 7 Other _____

A11. Please indicate EDD (estimated delivery date) for this pregnancy

__/__/____ or date unknown

A12. Please indicate date of last menstrual period (LMP) for this pregnancy

__/__/____ or date unknown

PART B: CLINICAL FINDINGS AND PATHOLOGY
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B1. Please indicate delivery or pregnancy end date __/__/____

B2. Did the patient have one or more prenatal care visits (in-person or telemedicine) prior to the delivery or pregnancy end date?

- 1 Yes
- 2 No

B2. Symptoms of a spontaneous abortion include abdominal pain, abdominal cramping and vaginal bleeding or spotting. Did the patient have any of these symptoms prior to the delivery or pregnancy end date (from B1)

- 1 Yes (Continue with Question B2.1)
- 2 No (Continue with B3)

B2.1 Please indicate date of onset of SAB symptoms __/__/____

B3. Was spontaneous passage of fetal tissue documented in health record?

- 1 Yes (Continue with Question B3.1)
- 2 No or not documented (Continue with Question B4)

B3.1 Please indicate date of the spontaneous passage of fetal tissue __/__/____

B4. Did the patient have a dilation and curettage (D&C)?

- 1 Yes (Continue with B4.1)
 2 No or not documented (Continue with Question B5)

B4.1 Please indicate date of the D&C ___/___/_____

B5. Were fetal tissue/products of conception sent for pathology?

- 1 Yes (Continue with Question B5.1)
 2 No or not documented (Continue with Question C1)

B5.1 Please indicate if fetal tissue/products of conception pathology results are:

- 1 **Redacted and uploaded**
 2 **Copied and pasted below**
 3 **Unavailable**

B6. For fetal pathology/products of conception results pasted below, please include date of test and impression, when available _____

PART C: MATERNAL LABORATORY TESTING

PLEASE INDICATE IF ANY OF THE FOLLOWING TESTS WERE PERFORMED DURING PREGNANCY

C1. COVID-19 PCR at time of delivery

- 1 **COVID-19 PCR performed redacted results uploaded**
 2 **COVID-19 PCR performed, results copied and pasted below**
 3 COVID-19 PCR performed, results not available
 4 COVID-19 PCR not performed

C2. COVID-19 PCR during pregnancy, before delivery

- 1 **COVID-19 PCR performed redacted results uploaded**
 2 **COVID-19 PCR negative, results copied and pasted below**
 3 COVID-19 PCR performed, results not available
 4 COVID-19 PCR not performed

C3. COVID-19 antigen testing, during pregnancy or at time of delivery

- 1 **COVID-19 antigen testing performed redacted results uploaded**
 2 **COVID-19 antigen testing, results copied and pasted below**
 3 COVID-19 antigen testing performed, results not available
 4 COVID-19 antigen testing not performed

C4. Quantitative HCG (blood testing)

- 1 Quantitative HCG (blood testing) performed, **redacted results uploaded**
 2 Quantitative HCG (blood testing) performed, **results copied and pasted below**

3 Quantitative HCG (blood testing) not performed

C5. For any COVID-19 PCR or antigen testing results entered here, please include date of test, test type and result. For any Quantitative HCG results entered here, please include date of test, result and unit (mIU/mL). Quantitative HCG results after a fetal demise is confirmed are not needed.

PART D: ULTRASOUND

D1. Were there any ultrasounds with records available during this pregnancy

- 1 Yes (Continue with Question D1.1)
 2 No (Continue with C1)

D1.1 Please indicate number of ultrasounds with records available during this pregnancy

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D1.2 Please indicate if ultrasound results are

- 1 **Redacted and uploaded**
 2 **Copied and pasted below**

<p>D2. For ultrasound results pasted below, please include date of ultrasound, measurements (in mm) for crown-rump length, yolks sac, gestational sac, and fetal heart rate (bpm) and impressions, when available _____</p> <p>_____</p> <p>_____</p> <p>_____</p>

PART E: CLINICAL ENCOUNTERS

E1. Please indicate total number of health care encounters (include prenatal and postnatal obstetric care visits, emergency department (ED) visits) with records available for the period [ref diagnosis date – 30 days through ref diagnosis date + 60 days]

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<p>E2. Please provide any additional notes regarding prenatal, 6-week postpartum, ED and delivery records, particularly if redacted results not available</p> <p>_____</p> <p>_____</p> <p>_____</p>

Data from medical record to be redacted and uploaded (based on data entered in chart review)

1. Pathology results for this pregnancy: fetal pathology report (from Part B)
2. Any quantitative HCG testing (from Part C)
3. Ultrasound reports: All available for this pregnancy if possible; (from Part D)
4. Clinical encounters: include notes from all prenatal or ED encounters from 30 days prior to delivery and include postpartum obstetric encounter and physician / obstetric note from delivery (from Part E)