PROTOCOL

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

VSD #1345

Version 1.5

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SURVEILLANCE FOR ACUTE ADVERSE EVENTS FOLLOWING
COVID-19 VACCINE EXPOSURES DURING PREGNANCY

Lead Investigators: Malini DeSilva, MD, MPH, Elyse Kharbanda, MD, MPH, Gabriela Vazquez-Benitez, PhD, Heather Lipkind, MD, MS, Kimberly Vesco, MD, MPH

Lead site: HealthPartners Institute

Collaborating Investigators: Matt Daley, MD, Darios Getahun, MD, PhD, MPH, Ousseny Zerbo, PhD, Allison Naleway, PhD, Mike Jackson, PhD, Joshua Williams, MD, Simon Hambidge, MD, PhD, Tom Boyce, MD, MPH, Candace Fuller, PhD, MPH, Michael M. McNeil, MD, MPH, Christine K. Olson, MD, MPH

Protocol Change History

Version	Date	Change
1.0	1/19/2021	N/A – Original protocol
1.1	1/28/2021	Minor edits to outcomes, response to CDC comments, version approved by CDC
1.2	1/29/2021	Replaced anaphylaxis quick review chart review form with updated anaphylaxis abstraction form, version, provided by Marshfield (Kayla Hanson)
1.3	2/26/2021	Minor edits to outcomes; Added preliminary data pull for analysis of pregnant women who had received a COVID vaccine, for vaccines administered 12/15/20 – 02/15/2021 and testing procedures for June data pull Added ancillary files used in the RCA, added background on Ad26.COV2.S (Janssen COVID-19 vaccine)
1.4	4/13/2021	Minor edits to outcomes
1.5	6/03/2021	1. Added gestational thrombocytopenia code to Appendix A 2. Aligned Appendix A with RCA codes as follows: a. Removed "Embolism/thrombosis superficial LE veins, I82.81* b. Removed I82.6* from VTE codes and replaced with more specific codes I82.60 and I82.62 c. Added TTS diagnostic codes d. Modified exclusion lists for AMI, convulsions/seizure, encephalitis/myelitis, VTE, TTP, hemorrhagic stroke, TTS, and CVST e. Modified included codes for appendicitis, VTE, and platelet disorders f. Modified look back period for January 1, 2018 for convulsions/seizure and DIC g. Added codes to adjust onset date for VTE, ischemic stroke, hemorrhagic stroke, and CVST 3. Added the following risk categories to Table 1: Asthma, cerebral vascular disease, chronic liver disease, and smoking 4. Appendix C, high risk conditions table is a separate Excel file 5. Minor modifications to wording of introduction and outcomes sections

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LIST OF ABBREVIATIONS

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

CPT® = Common Procedural Terminology

DDM = distributed data model

DPA = dynamic pregnancy algorithm

EDD = estimated delivery date

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

LMP = last menstrual period

RCA = rapid cycle analysis

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 COVID-19 vaccine clinical trials and thus data to date on safety of COVID-19 vaccines in pregnancy is limited. Two COVID-19 mRNA vaccines are now available in the United States and the first adenovirus vector vaccine was just approved under emergency use authorization (EUA) and pregnancy is *not* a contraindication to vaccination. As such there is an urgent need for outcome data following use of COVID-19 vaccines in pregnant populations. This protocol is the first phase of the COVID-19 vaccine safety surveillance in pregnant women and their infants. In this phase of surveillance, using an observational age, site, and pregnancy start date matched cohort design, we will evaluate pre-specified acute (0–42 day) vaccine safety outcomes following COVID-19 vaccine exposures during pregnancy or in the 4 weeks prior to pregnancy start, as compared to unvaccinated pregnancies. Surveillance will be conducted from December 2020 through December 2022, with an initial exploration of acute safety outcomes starting 6 months after introduction of COVID-19 vaccines.

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, along with other challenges in containment, there has been an exponential worldwide spread of infection. In March 2020, the World Health Organization designated COVID-19 as a global pandemic. Worldwide, as of June 29, 2021 over 182 million people have contracted COVID-19 and there have been nearly 4 million deaths due to COVID-19. To date, approximately one-fifth of cases and one-sixth COVID-19 deaths have occurred in the U.S.[2]

The COVID-19 pandemic has profoundly impacted the global 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 through vaccination will facilitate re-opening of society without continued widespread outbreaks. Phase II results from several vaccine candidates have demonstrated promising results, including robust antibody responses and no serious vaccine-related adverse events.[4,5] 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.[6] 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. The most commonly reported adverse events were local reactions, predominantly pain at injection site. The most common systemic events were fatigue and headache; lymphadenopathy was reported by 64 vaccine recipients (0.3%) and 6 placebo recipients (<0.1%). These reactions were more common following the second vaccine dose.[6] Similarly, the Moderna mRNA COVID-19 vaccine was reported to have 94% efficacy for preventing COVID-19 disease with an overall favorable safety profile.[7] 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.[8] 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.[9] 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. Additional COVID-19 vaccines are currently in Phase III trials in the United States and may be authorized and recommended for use in the coming months.

To date, clinical trials of COVID-19 vaccines have been limited to non-pregnant adults. Pregnancy testing was conducted prior to each vaccine dose and thus vaccine exposures during pregnancy were limited to 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 at the time of EUA submission. 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 are ongoing. For both COVID-19 mRNA vaccines now in use under EUA, pregnancy is *not* a contraindication to vaccination.[10,11] At the time of EUA submission for Ad26.COV2.S, there were 8 pregnancies reported during the phase III safety clinical trial.

There is increasing evidence regarding 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] Despite the lack of comprehensive data on COVID-19 vaccine safety in pregnancy, the known risks of SARS-CoV-2infection may potentially 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.[15,16]

Now that COVID-19 vaccines are in use in the U.S., and pregnancy is not a contraindication, there is an urgent need to monitor the safety of these vaccines when administered during or around the time of pregnancy. As vaccination during pregnancy may occur early in pregnancy, there could be a lag of 7 months or greater before birth outcomes following these exposures can be assessed. As such, for this first stage of our planned surveillance of COVID-19 vaccine safety in pregnancy we will focus on acute safety outcomes, i.e., those occurring within 42 days of vaccination. In the first month of COVID-19 vaccine distribution, one acute vaccine-related adverse event, anaphylaxis, has received significant attention. In a January 6, 2021, MMWR report, 21 cases of post-vaccination anaphylaxis events were described. Based on vaccines administered as of publication, the estimated rate of anaphylaxis following COVID-19 vaccination was estimated to be 11.1 per 1 million doses administered.[17] In more recent data, presented to ACIP on January 27, 2021, rates for anaphylaxis following COVID-19 vaccination

were in the range of 3 to 5 per 1 million doses. Although still a rare adverse event, the reported rate of anaphylaxis following COVID-19 vaccination was higher than that reported following other routine vaccines.[18] 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. In the first phase of this surveillance evaluation, "COVID-19 Vaccine Safety Evaluation in Pregnant Women and their Infants," we propose using a retrospective observational matched cohort comparing those receiving COVID-19 vaccine during pregnancy or in the 4 weeks prior to their last menstrual period (LMP) ("exposed"), and pregnant women not receiving COVID-19 vaccine ("unexposed"), similar to prior VSD evaluations of acute outcomes following maternal vaccination with Tdap, monovalent H1N1, and IIV.[20-22]

Objectives

1. Objective 1: Every 6 months, starting in June 2021, to perform surveillance of acute safety outcomes following maternal COVID-19 vaccination, comparing women exposed to COVID-19 vaccine during pregnancy or in the 4 weeks prior to LMP (pre-pregnancy), and unexposed pregnant women.
    a. Analyses of acute safety outcomes will be grouped by the risk window after vaccination: 0–6 days, 1–21 days, and 1–42 days.
    b. Analyses of acute safety outcomes will be grouped by 22 major outcome categories.

2. Objective 2: In December 2022, after 2 years of COVID-19 vaccine distribution, to evaluate acute safety outcomes following maternal COVID-19 vaccination, comparing women exposed to COVID-19 vaccine during pregnancy or in the 4 weeks prior to LMP (pre-pregnancy), and unexposed women , stratified by vaccine type and vaccine dose.
    a. Analyses of acute safety outcome will be grouped by the risk window after vaccination: 0–6 days, 1–21 days, and 1–42 days.
    b. Analyses of acute safety outcomes will be grouped by 22 major outcome categories.

Design

We will use a retrospective observational matched cohort of pregnant women identified within the VSD population from December 2020–December 2022. Women exposed to a COVID-19 vaccine during pregnancy or in the 4 weeks prior to LMP, will be matched on age, VSD site, and pregnancy start date, to women unexposed to COVID-19 vaccine.

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, Southern California Kaiser Permanente, HealthPartners, Marshfield Clinic, Denver Health, and Kaiser Permanente Colorado.

Inclusion criteria

- At least one prenatal care indicator in first or second trimester, including an International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) code for supervision of a normal or high-risk pregnancy, care for pregnancy complications with indication of trimester, or a gestational week diagnosis, or a Common Procedural Terminology (CPT®) code for a trimester-specific procedure (e.g. first trimester ultrasound).

Exclusion criteria

- Ectopic pregnancy, therapeutic abortion, or gestational trophoblastic disease

Exposure and comparator

Exposure: The primary exposure is receipt of a COVID-19 vaccine during pregnancy or in the 4 weeks prior to LMP, for vaccines administered from December 2020 – December 2022. Vaccines will be identified from standardized DDF Vaccine files, with vaccines identified primarily from CVX Codes. We will also include vaccines identified by sites through CPT® or GPI codes, if available in the DDF Vaccine files. We include women vaccinated in the 4 weeks prior to LMP as exposed to account for uncertainty related to pregnancy dating in early pregnancy. We will classify timing of vaccine administration as pre-pregnancy (i.e., 4 weeks prior to LMP through LMP) or during pregnancy using the dynamic pregnancy algorithm (DPA) and possibly supplemented with additional data available through trimester specific ICD-10-CM diagnostic codes or selected CPT® codes. Receipt of COVID-19 vaccine at any gestational age during pregnancy or in the 4 weeks prior to LMP will be included in the Objective 1, 6-month surveillance. In the Objective 2 evaluation, with data following 24-months of COVID-19 vaccination, we will classify exposures as pre-pregnancy (4 weeks prior to LMP to LMP), first trimester, second trimester, or third trimester. In the Objective 2 analyses, we will also stratify analyses by type of vaccine, (mRNA, viral vector, or recombinant protein), and by vaccine dose (first or second).

Comparator: The comparator is no history of a COVID-19 vaccine administered in the 4 weeks prior to LMP through the end of pregnancy or date of data pull for ongoing pregnancies. Pregnant women with no COVID-19 vaccine exposures during pregnancy or within 4 weeks of LMP who are matched will be assigned an index date equivalent to the gestational day of vaccination or days prior to pregnancy start date for their vaccinated match.

Outcomes

Pre-specified acute safety outcomes (0–6 days following vaccination and 1–21 or 1–42 days following vaccination) are shown in Appendix A. Specific outcomes and windows have been informed based on biologic plausibility, data from the COVID-19 vaccine clinical trials, reporting to the Vaccine Adverse Event Reporting System (VAERS),[6,17,23-25] and concurrent VSD studies related to COVID-19 vaccine safety. In addition, outcome selection has been informed by the need to provide evidence to help guide pregnant women, who were excluded

from the vaccine clinical trials and are considering whether to be vaccinated. Adverse events will be identified using ICD-10-CM codes assigned at inpatient, outpatient, or emergency department clinical encounters. Relevant diagnostic settings (e.g., inpatient, outpatient, or emergency department), risk windows, exclusion windows, and diagnosis exclusions are also listed in Appendix A. Additional exclusions may be added for consistency with data from other VSD COVID-19 vaccine safety studies, specifically the ongoing rapid cycle analysis (RCA) surveillance.

Given the expected timing of event onset, the only outcome we plan to evaluate on day 0 (the day of vaccination) will be anaphylaxis diagnosed in the outpatient, emergency department or inpatient settings. Given the increased concerns regarding this outcome, we plan to confirm through chart review and adjudication all potential cases identified through ICD-10-CM codes. As our surveillance population of women vaccinated in pregnancy will overlap with that in the rapid cycle analysis (RCA), we will use the results of the VSD COVID-19 RCA chart review and adjudication to evaluate potential anaphylaxis cases, whether they meet Brighton case definitions and timing of the onset of symptoms in relation to COVID-19 vaccination.[26] As in this study we are including outpatient anaphylaxis codes, while outpatient anaphylaxis cases are not included in the RCA, we may identify additional cases requiring chart review. The anaphylaxis rapid chart review form will be used and is included as Appendix B.

No other chart reviews are planned *a priori*. However, we may request additional 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.

Table 1. Maternal Comorbidities
Asthma
Diabetes
Obesity
Cancer
Other hematologic disorders
Autoimmune disorders
Organ transplant
Renal failure / dialysis
Hypertension and other cardiovascular disease
Chronic obstructive pulmonary disease
Cerebral vascular disease
Chronic liver disease
Smoking
Pregnancy complications Gestational hypertension / preeclampsia Gestational diabetes

Risk intervals will be censored at 7 days after the end of pregnancy or at the time of administration of a second vaccine dose, if either of these occur before the end of the 21-day or 42-day risk windows. Acute outcomes after a second vaccine dose will be evaluated with the risk interval starting at the date of administration of the second dose.

Covariates

We will pull additional data to characterize the surveillance population and to identify potential confounders. Variables included in both the Objective 1 ongoing, every 6-month surveillance and the Objective 2, end of two year surveillance include age, site, race/ethnicity, healthcare utilization prior to pregnancy, and presence of comorbidities associated with increased risk for severe COVID-19 (Table 1). Additional conditions and specific diagnoses will be added based on a modified list of high risk conditions used in the RCA and other VSD studies (Appendix C). In addition to the high risk conditions included in other VSD studies, we have also included pregnancy specific high risk codes.

For the Objective 2, end of two year surveillance, for women with pregnancies ending in 2021, we will also be able to 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 (e.g., smoking status, pre-pregnancy weight and height) available in the PREG file.

Matching and other methods for confounding adjustment

To account for confounding we will use a two-step approach: 1) we will match pregnancies exposed to COVID-19 vaccine to unexposed pregnancies to assign an index date for the unexposed pregnancies; 2) we will estimate the inverse weights using propensity scores and apply weights in the regression model.

Dating of pregnancy start date

Pregnancy start date is assigned in the DPA based on a hierarchical algorithm using EDD, ICD-10-CM gestational week diagnostic codes, and LMP. However for ongoing pregnancies, dating may be missing in 30% of pregnancy episodes (internal DDF data from HealthPartners for November 2020). To increase the availability of dating for ongoing pregnancies, for a sample of pregnancies from all VSD sites, we will first pull pregnancy indicators with first, second, or third trimester identifiers from the look up tables used by the VSD's dynamic pregnancy algorithm (DPA) including supervision of normal or high-risk pregnancy, care for pregnancy complications with indication of trimester, specific ICD-10-CM code indicating gestational age, or a CPT® code for first trimester obstetric ultrasound. We will select the first pregnancy indicator and date for this indicator for each identified pregnancy. For pregnancy indicators without a specified gestational age, we will assign an 8-week gestational age for the first diagnosis with a first trimester indicator, an 18-week gestational age for the first diagnosis with a second trimester indicator and a 29 week gestational age for the first diagnosis with a third trimester indicator. These gestational age assignments by trimester are informed by data exploration at HealthPartners and may be adjusted following exploration of data for all VSD sites. For HealthPartners data, applying this additional gestational age imputation, we were able to date 50% of pregnancies with no pregnancy start date in the DPA. In addition, by restricting the sample to pregnancies with at least two pregnancy indicators, 95% of ongoing HealthPartners pregnancies in the DPA for November 2020 would have a pregnancy start date. We will repeat this analysis for a sample of pregnancies from all sites (see data management section for specification of the sample). We will then apply this additional gestational age dating to calculate an estimated pregnancy start. We may reevaluate our pregnancy dating, inclusion criteria, and matching procedures after exploring the first data pull for all sites.

Matching method to select unexposed pregnancies and index date assignment

Pregnancies exposed to COVID-19 vaccine administered during pregnancy or in the 4 weeks prior to LMP will be matched to unexposed pregnancies with a 1:2 matching ratio on VSD site, maternal age (+/- 3 years), date of pregnancy start date (+/- 2 weeks), and pregnancy status at the gestational age of vaccination. Matching will be done without replacement using optimal matching as applied in our previous studies.[21,22,27,28] Unvaccinated women will be assigned an index date at the same gestational age of vaccination for their exposed matched counterpart.

Identification of potential confounders in the matched cohort
We will tabulate characteristics of matched women who are exposed and unexposed to COVID-19 vaccine pre-pregnancy or 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, health utilization and receipt of other vaccines during pregnancy prior to COVID-19 vaccine or index date, and presence of comorbidities increasing risk for severe COVID-19 disease, such as diabetes, hypertension, obesity, as these women may be more likely to be vaccinated during pregnancy.

We will evaluate whether additional information based on the subset with data collected through the VSD cycle files will reduce potential bias. In this subset, 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,[29] 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[30,31] or propensity score calibration.[32]

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 matched 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 above 20 (or as necessary).

Objective 1: 6-month Safety Analysis

At the request of CDC, we have added a preliminary data pull to evaluate pregnant women with COVID-19 vaccine exposures between 12/15/20 – 2/15/21. Aims of this initial data pull are to provide count data on acute adverse events following vaccination in pregnancy. There will not be a comparison group for this initial data exploration. Outcomes, inclusion and exclusion criteria will be the same as those applied in the 6-month safety analysis.

We will report adverse event rates for separate risk intervals (days 0–6, 1–21 and 1–42) and for each of the 22 adverse event outcomes per 10,000 pregnancies for COVID-19 vaccine exposed and unexposed in the matched cohort.

Association of receipt of COVID-19 vaccine and acute events in the intervals, 0–6, 1–21 and 1–42 days post-vaccination, and for each of the 22 adverse events outcomes will be reported as risk ratios (and risk difference when appropriate) with corresponding 95% confidence intervals for the matched contrast and after applying inverse probability weights. A Poisson distribution with robust variance using a generalized estimating equation will be used to account for the correlation introduced by the matching of the groups exposed and unexposed to COVID-19 vaccine during pregnancy and the introduction of inverse probability weights. For both the 1–21 and 1–42 day intervals, we will use the number of follow-up days to account for follow up truncation due to receipt of a second COVID-19 vaccine or end of pregnancy + 7 days, standardized to the length of the follow-up window. The analysis will be repeated at each of the 6-month cumulative surveillance time points.

Objective 2: Full Cohort Safety Analysis

For the Objective 2 full matched cohort, analyses will be as described above, but stratified by vaccine type and by vaccine dose. For these end of 2-year analyses we will use both covariate sets, complete covariate and supplemented covariate set based on cycle file information. In addition, we will explore acute safety 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 anaphylaxis and other 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[33] using R episensr package.[34]

Alternative Methods

We will review our inclusion criteria to select pregnancies for which we could improve the pregnancy dating. Based on a preliminary review of internal data, those women with only one pregnancy indicator may have a historical pregnancy diagnosis, or an error in diagnostic coding. We will also explore whether inclusion of all vaccine exposures up until end of pregnancy leads to misclassification of postpartum vaccination as during pregnancy. If this is a problem, we may add an exclusion of vaccines administered within 7 days of end of pregnancy. 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 based on

ongoing vaccine safety surveillance and data from the COVID-19 vaccine clinical trials. If additional potential safety signals are identified through VAERS and other postlicensure surveillance systems, or for vaccines yet to be approved, these outcomes may be added to this evaluation.

Power Analysis

This evaluation is underpowered for the 6-month cumulative surveillance analyses and has limited power to analyze the full cohort. As shown in the power estimates (Table 2, below), depending on the use of COVID-19 vaccine in pregnancy, we could detect risk ratios of at least 2.5 for events with a rate of 30 per 10,000, if at least 3,200 women are vaccinated during pregnancy. Because of the limited power, we are not pre-specifying thresholds indicating a signal for the 6-month surveillance analyses. We will monitor COVID-19 vaccine coverage in pregnancy and consider updating power estimates based on exposures in the first 6 months of vaccine distribution.

Table 2. Minimum detectable risk ratios for acute events.

Sample size	5 per 10,000	10 per 10,000	30 per 10,000
800:1,600	18.8	10.7	5.0
1600:3200	10.7	6.5	3.4
2400:4800	7.9	5.0	2.8
3200:6400	6.5	4.2	2.5

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. The primary limitation is uncertainty regarding pregnancy start date and pregnancy outcome. Because of the urgent need to monitor safety events after COVID-19 vaccination during pregnancy, we will rely on the DPA for the evaluation of acute outcomes. The DPA has been shown to be a valid method to identify pregnancies. 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 of acute outcomes to pregnancies among women who entered prenatal care, and we will also require continuous insurance coverage from 3 months prior to pregnancy start through end of pregnancy or end of the observation period, or empanelment at Denver Health. This will increase our ability to estimate the start date of pregnancy based on ICD-10-CM codes, and to identify the end of pregnancy. To increase the sensitivity of identifying vaccine exposures during pregnancy, and accounting for potential missing data on pregnancy dating, we are including vaccine exposures within 4 weeks of LMP and all those occurring until the end of pregnancy. By not excluding women with vaccinations in the 7-days prior to end of pregnancy, 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 adjust for outcome misclassification, there may be residual confounding related to health care seeking behavior between vaccinated and unvaccinated individuals as well as availability of COVID-19 vaccinations, for which we have limited ability to control.

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 continuous insurance coverage from 3 months prior to pregnancy start through the end of pregnancy or end of observation period, or empanelment at Denver Health (pregnancy cohort) for pregnancies with an outcome date or ongoing after December 1, 2020 to December 2022, excluding ectopic pregnancies, therapeutic abortion, or gestational trophoblastic disease. The study period may be modified in accordance to extension in the study timeline. The first data pull will be done after 3 months of the vaccine program, followed by 6-month data pulls. Inclusion of records in the 3-month data pull will follow the same approach to the every 6-month data pulls. Result of 3-month data pull will facilitate reporting data on adverse events after vaccination, and review procedures for matching exposed pregnancies to unexposed. For the first data pull, diagnoses will be limited to adverse events and exclusions, and supervision of care diagnoses.

In order to explore the use of trimester-specific pregnancy indicators (ICD-10-CM or CPT® codes) across VSD sites, to inform our approach to optimize dating for ongoing pregnancies and review the inclusion criteria, we are planning a single data extraction for pregnancies ending after December 1, 2020, or ongoing at the time of data extraction, excluding ectopic pregnancy, therapeutic abortion, or gestational trophoblastic disease. For these women, we will pull data from the following DDF files, CONSTANT, ENROLL, INPT, OUTPT, PROCDRE, PREGEPSD, EDD and LMP. We will extract all pregnancy-related ICD-10-CM codes from the pregdiag201808 lookup table, and a subset of pregnancy-related CPT® codes from the PREGCPT201808 lookup table. Data will include records with dates after January 1, 2020.

We will collect diagnoses to identify pre-existing and maternal conditions for the 6-month data pulls (Table 1). Acute outcomes and exclusions listed in Appendix A will be collected using a 3-digit code from October 2015 through December 2022. We will use a sensitive approach to collect diagnoses using 3-digit codes from inpatient and outpatient sources. This method was selected because we expect that adverse events and exclusions will be updated periodically based on changes in RCA program. We expect that the size of this file will be small because it is a young population. Additional diagnoses for supervision of care based on the pregdiag201808 lookup table (or current table) will be pull for dating purposes. Exclusion criteria and cohort matching will be applied locally by HPI programming team. If MORT and ancillary death file is available, we will use the data to censor or exclude the pregnancy record.

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 2021. If the study timeline is extended, and the cycle 2022 is available, we will pull additional data from this cycle file. Data files used will include the following: CONSTANT, ENROLL, VACCINE, INPT, OUTPT, PROCDRE, PREGEPSD, MORT, ancillary death if available for DDF files and cycle files; and, PREG, GCDD, MORT for cycle files. In addition, we will pull data from the following ancillary files: PLATELET, Covlrslt, Covltest, and dxid that are used in the RCA event program. (Table 3, below).

Table 3. VSD Data Files

VSD File	Purpose
CONSTANT	Basic demographics of population, VSD site
ENROLL	MCO membership start and stop dates to monitor insurance enrollment as needed.
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
PREGEPSD	Pregnancy episode file to identify eligible pregnancies
GCDD	Geocode data
MORT	Mortality data
ANC.PLATELET	Platelet data used in the RCA
ANC.COVLRSLT	COVID test result used in RCA
ANC.COVLTEST	COVID laboratory test used in RCA
ANC.DXID	COVID DXID 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.

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 (DUAs) 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

Date	Description
December 19, 2020	Draft proposal to CDC and participating sites
January 19, 2021	Final protocol to CDC and sites
February 1, 2021	Submit data abstraction code for exploratory data pull to sites*
February 19, 2021	Obtain IRB approvals and DUAs
March 1, 2021	SAS code development/testing
March 19, 2021	Finalize SAS code – for initial data pull
July 19, 2021	Interim Data extraction and analysis – for 6-month safety analysis
January 19, 2022	Interim Data extraction and analysis – for 12-month safety analysis
July 19, 2022	Interim Data extraction and analysis – for 18-month safety analysis
January 19, 2023	Final data extraction
March 19, 2023	Final data analysis
May 19, 2023	Manuscript preparation and submission

*Program to be run as soon as approved by sites, as results needed to inform final program due on 3/19/21; Will await IRB approval as needed, based on site-based requirements

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Appendix A: Selected acute safety outcomes for COVID-19 Vaccine Safety Evaluation in Pregnant Women and their Infants

Category	Outcome	ICD-10-CM	Settings	Exposure Windows	First in what period? (First ever back to Oct 2015 unless noted)	Exclusions
Anaphylaxis	Anaphylactic shock, unspecified	T78.2*	E, I, O	0-1	First in 7 days	
	Anaphylaxis due to drug	T88.6*				
	Anaphylaxis due to vaccine	T80.52*				
Local and other allergic reactions	Angioneurotic edema	T78.3*	E, I, O, T	1-6 days	First in 60 days	
	Allergy, unspecified	T78.40*				
	Other serum reaction to vaccine	T80.62*				
	Allergic urticaria	L50.0				
	Idiopathic urticaria	L50.1				
	Other urticaria	L50.8				
	Urticaria, unspecified	L50.9				
	Unspecified viral infection characterized by skin and mucous membrane lesions	B09				
	Other specified viral infections characterized by skin and mucous membrane lesions	B08.8				
	Erythema multiforme	L51.0, .8, .9				
	Erythematous condition, NOS	L53.9				
	Rash and other non-specific eruptions	R21				
	Arthus phenomenon, initial encounter	T78.41*				
	Cellulitis upper limb	L03.113, .114				
	Cellulitis unspecified location	L03.119				
Fever	Post vaccination Fever	R50.83	E, I, O, T	1 - 6 days	First in 7 days	
	Fever, unspecified	R50.9				

Non-specific symptoms	Weakness (subset of malaise and fatigue)	R53.1	E, I, O, T	1 - 6 days	First in 30 days	
	Other malaise	R53.81				
	Other fatigue	R53.83				
	Pregnancy related exhaustion and fatigue, first trimester	O26.811				
	Pregnancy related exhaustion and fatigue, second trimester	O26.812				
	Pregnancy related exhaustion and fatigue, third trimester	O26.813				
	Pregnancy related exhaustion and fatigue, unspecified trimester	O26.819				
	Other complications following vaccination, not elsewhere classified, initial encounter	T88.1*				
ADEM	ADEM unspecified	G04.00	E, I	1 - 21, 1 - 42	First ever	
	ADEM after immunization	G04.02				
AMI	Acute myocardial infarction	I21.*	E,I	1 - 21, 1 - 42	First ever	COVID+ lab test or COVID-19 ICD-10 code in the last 30 days; trauma in prior 7 days (V00-Y99); If occurs EVER prior to case: I22.*, I23.*, I25.1, I25.2
Appendicitis	Acute appendicitis	K35*	E,I	1 - 21, 1 - 42	First ever	
	Other appendicitis	K36				
	Unspecified appendicitis	K37				
Bell's Palsy	Bell's palsy	G51.0	E, I, O	1 - 21, 1 - 42	First ever	COVID+ lab test or COVID-19 ICD-10 code in the last 30 days; A69.2*, A92.5, B00.*, B02.* in last 14 days; If occurs EVER prior to case: D86.*

Convulsions/ seizure	Unspecified convulsions	R56.9	E, I	1 - 21, 1 - 42	First ever back to Jan 1 2018	COVID+ lab test or COVID-19 ICD-10 code in the last 30 days; If in past year prior to case: G03.1, Z86.61, S06.3*, S06.9*; If same day as case:, S06.0X9A If in last 3 days prior to case: I60.*, I61.*, I62.*, I63.* If in last 7 days prior to case: A17.0, A17.82, A27.81, A32.1*, A39.0, A39.81, A41.9, A69.21, A85.*, A86, A87.* A88.0, A88.8, A89, A92.31, A92.5, B00.*, B01.0, B01.11, B02.*, B05.*, B06.*, B10.81, B26.*, B45.1, B58.2, B96.0, G00.*, G01, G02, G03.0, G03.8, G04.3*, G04.81, G04.90, G05.3, G92, G93.41, G95.1*, G95.89, J09.*, J10.*, J11.*, R65.20, R65.21; If occurs EVER prior to case: F44.5, G40, I69.*, Z86.73
DIC	DIC	D65	E, I	1 - 21, 1 - 42	First ever back to Jan 1 2018	COVID+ lab test or COVID-19 ICD-10 code in the last 30 days; If in last 42 days prior to case: First COVID-19 diagnosis code or COVID-19 positive lab test ; If in last 14 days prior to case: Physical trauma code C92.4*, K85.*, S06.*, T30-T32
Encephalitis / myelitis	Subacute necrotizing myelitis of central nervous system	G37.4	E, I	1-21, 1-42	First ever	COVID+ lab test or COVID-19 ICD-10 code in the last 30 days; If occurs EVER prior to case: G03.1, Z86.61; If in last 7 days prior to case: A17.0, A17.82, A32.1*, A39.0, A39.81, A41.9, A69.21, A85.*, A86, A87.*, A88.0, A88.8, A89, A92.31, A92.5, B00.*, B01.0, B01.1*, B02.*, B05.*, B06.*, B10.81, B26.*, B45.1, B58.2, B96.0, G00.*, G01, G02, G03.0, G03.8, G04.31, G95.1*, G95.89, J09.*, J10.*, J11.*, R65.20, R65.21
	Acute necrotizing hemorrhagic encephalopathy, unspecified	G04.30				
	Postimmunization acute necrotizing hemorrhagic encephalopathy	G04.32				
	Other acute necrotizing hemorrhagic encephalopathy	G04.39				
	Other myelitis, encephalitis, encephalomyelitis	G04.8*				
	Encephalitis, myelitis, and encephalomyelitis, unspecified	G04.9*				

	Encephalitis, myelitis and encephalomyelitis in diseases classified elsewhere	G05.*				
GBS	Guillain-Barré Syndrome	G61.0	E, I	1 - 21, 1 - 42	First ever	If occurs EVER prior to case: G65.0
Other Nerve disorders	Trigeminal neuralgia	G50.0	E, I, O	1 - 21, 1 - 42	First ever	COVID+ lab test or COVID-19 ICD-10 code in the last 30 days; A69.2*, A92.5, B00.*, B02.* in last 14 days; If occurs EVER prior to case: D86.*
	Atypical facial pain	G50.1				
	Other disorders of trigeminal nerve	G50.8				
PE	Pulmonary embolism	I26.*	E, I, O	1 - 21, 1 - 42	First ever	COVID+ lab test or COVID-19 ICD-10 code in the last 30 days; If occurs EVER prior to case: I27.82, Z86.71*; If in last 14 days prior to case: Physical trauma code (V00-Y99), T79.1*
Venous thromboembolism (VTE) Will use M7965, M7966, M79604, M79605, M79606, and R224 as onset date if appears in 14 days prior to incident VTE	Acute embolism/thrombosis of SVC	I82.210	E, I, O	1 - 21, 1 - 42	First ever	COVID+ lab test or COVID-19 ICD-10 code in the last 30 days; If occurs EVER prior to case: I27.82, I82.211, I82.221, I82.291, I82.5*, I82.7*, I82.A2, I82.B2*, I82.C2*, I82.891, I82.91, Z86.71*; Physical trauma code in the past 60 days: (V00-Y99, M67.9*, M80.*, M84.3*, M99.*, Z08, Z51.89, C, S, T Z30.011, Z79.890 If in last 14 days prior to case: Pneumonia code (A22.1, B25.0, A37.01, A37.11, A37.81, A37.91, A48.1, B44.0, B77.81, J12.*, J13, J14, J15.*, J16.*, J17, J18.*), I50.*, T79.1*
	Acute embolism/thrombosis of IVC	I82.220				
	Acute embolism/thrombosis other thoracic veins	I82.290				
	Embolism/thrombosis renal vein	I82.3				
	Embolism/thrombosis lower extremity	I82.4*				
	Acute embolism and thrombosis of unspecified veins of upper extremity	I82.60				
	Acute embolism and thrombosis of deep veins of upper extremity	I82.62				
	Embolism/thrombosis axillary vein	I82.A1*				
	Embolism/thrombosis subclavian vein	I82.B1*				
	Embolism/thrombosis internal jugular vein	I82.C1*				
	Acute embolism and thrombosis of other veins	I82.890				
	Acute embolism and thrombosis of unspecified vein	I82.90				
	Pulmonary embolism	I26.*				

	Deep phlebothrombosis pregnancy	O22.3*				
	Other venous complications in pregnancy	O22.8*				
	Venous complication in pregnancy, unspecified	O22.9*				
TTP	TTP	M31.1	E, I, O	1 - 21, 1 - 42	First ever	COVID+ lab test or COVID-19 ICD-10 code in the last 30 days; If in the previous year: B20, C00-C96, Z51.11, Z94.81, Z94.84; If platelet <100k in prior year
Platelet disorders	ITP	D69.3 O99.11*	E, I, O	1 - 21, 1 - 42	First ever	COVID+ lab test or COVID-19 ICD-10 code in the last 30 days; 1st ever: Known illnesses causing thrombocytopenia: B20, C00 – C96, D18.0*, D80 – D89, D59.0 – D59.2, D59.3, D61.*, D65, K70 – K77, D69.0, M32.*, Z51.11; If platelet <100k in prior year
Myocarditis / pericarditis	Viral myocarditis	B33.22	E, I	1 - 21, 1 - 42	First in 60 days	COVID+ lab test or COVID-19 ICD-10 code in the last 30 days
	Viral pericarditis	B33.23				
	Acute pericarditis	I30.*				
	Acute myocarditis	I40.*				
Lymphadenopathy /Lymphadenitis	Localized swelling, mass and lump, upper limb	R22.30	E, I, O, T	1 - 21, not 1 - 42	First in 60 days	
	Localized swelling, mass and lump, right upper limb	R22.31				
	Localized swelling, mass and lump, left upper limb	R22.32				
	Enlarged lymph nodes	R59.*				
	Pain in upper arm	M79.62*				
	Acute lymphadenitis upper limb	L04.2				
	Acute lymphadenitis unspecified location	L04.9				
Skin/mucosal disorders	Stevens-Johnson syndrome	L51.1	E, I, O	1 - 21, 1 - 42	First ever	
	Toxic epidermal necrolysis [Lyell] L51.2	L51.2, L51.3				

Stroke, ischemic Will use Z9282, R51, R47, R29810, R531, R42, R4182, R404, G819, H539, H5313* as onset if seen one day before case	Other transient cerebral ischemic attacks and related syndromes	G45.8	E, I	1 - 21, 1 - 42	First ever	COVID+ lab test or COVID-19 ICD-10 code in the last 30 days; If occurs EVER prior to case: I69.*, Z86.73; If in last 1 day prior to case: S15.*, I74.* If in last 28 days prior to case: I21.*; If EVER prior to case: I48.*, D57.*, D68.5*; If same day as case: S15.*, I74.*, Physical trauma codes (V00-Y99)
	Transient cerebral ischemic attack, unspecified	G45.9				
	Cerebral infarction, unspecified	I63.*				
Stroke, hemorrhagic Will use I639, R51, R47, R29810, R531, R42, R4182, R404, H5313, H539, G819 as onset if seen one day before case	Nontraumatic subarachnoid hemorrhage	I60.*	E, I	1 - 21, 1 - 42	First ever	COVID+ lab test or COVID-19 ICD-10 code in the last 30 days; If occurs EVER prior to case: I69.*, Z86.73; If in last 1 day prior to case: S06; Same day exclusions: Physical trauma codes (V00-Y99)
	Nontraumatic intracerebral hemorrhage	I61.*				
	Other and unspecified nontraumatic intracranial hemorrhage	I62.*				
Transverse myelitis	Transverse myelitis	G37.3	E, I	1 - 21, 1 - 42	First ever	
Thrombosis with Thrombocytopenia Syndrome (TTS), includes the listed diagnostic codes along with platelets <150,000	Nonpyogenic thrombosis of intracranial venous system*	I67.6	E, I	1 - 21, 1 - 42	First ever	COVID+ lab test or COVID-19 ICD-10 code in the last 30 days
	Intracranial and intraspinal phlebitis and thrombophlebitis	G08				
	Cerebral infarction due to cerebral venous thrombosis, nonpyogenic**	I63.6				
	CVST in pregnancy	O22.5*				
	CVST in puerperium	O87.3				
	Portal vein thrombosis	I81				
	Acute vascular disorders of intestine (captures mesenteric vein thromboses)	K55.0*				
	Budd-Chiari syndrome (aka hepatic vein embolism/thrombosis)	I82.0				
	Acute embolism and thrombosis of other specified veins** (captures splenic vein thrombosis)	I82.890				

	Ischemia and infarction of kidney (captures renal artery embolism/thrombosis	N28.0				
	Embolism and thrombosis of abdominal aorta	I74.0*				
	Embolism and thrombosis of other and unspecified parts of aorta	I74.1*				
	Embolism and thrombosis of arteries of the lower extremities	I74.3				
	Embolism and thrombosis of iliac artery	I74.5				
	Embolism and thrombosis of other arteries	I74.8				
	Embolism and thrombosis of unspecified artery	I74.9				
Cerebral venous sinus thrombosis (CVST) Will use R51, R531, R42, R4182, R410, H539, H532, G932, H4710, I82C1, I609, I619, I629, I639, or G43909 as onset if seen within 7 days before case	CVST	I67.6, G08, I63.6	E, I	1 - 21, 1 - 42	First ever	COVID+ lab test or COVID-19 ICD-10 code in the last 30 days; If on the same day: S02*, S06.*, S09*, S15*, and Physical trauma codes (V00-Y99)
	CVST in pregnancy	O22.5*				
	CVST in puerperium	O87.3				

*Settings: E = Emergency department; I = Inpatient; O = Outpatient; T=Telemedicine

Appendix B: FROM VSD #1342 – COVID-19 RCA ANAPHYLAXIS ABSTRACTION FORM V1.0

AUTOMATED DATA

VSD Study ID: _____

VSD Site: 1☐ KPW 2☐ HP 3☐ KPC 4☐ MFC 5☐ NCK 6☐ NWK 7☐ SCK 8☐ DH

Date of Birth: __ __/__ __ /__ __ __ __ (mm/dd/yyyy)

Sex: 1☐ Male 2☐ Female

Number of COVID-19 Vaccine Doses Received: 1☐ 1 2☐ 2

COVID-19 Dose 1 Vaccination Date: __ __ /__ __ /__ __ __ __ (mm/dd/yyyy)

COVID-19 Dose 1 Vaccine Manufacturer: 1☐ Pfizer 2☐ Moderna 9☐ Unknown

COVID-19 Dose 2 Vaccination Date: __ __ /__ __ /__ __ __ __ (mm/dd/yyyy)

COVID-19 Dose 2 Vaccine Manufacturer: 1☐ Pfizer 2☐ Moderna 9☐ Unknown

Anaphylaxis Diagnosis Date: __ __ /__ __ /__ __ __ __ (mm/dd/yyyy)

ABSTRACTOR INFORMATION

Abstractor Initials: _____

Abstraction Date: __ __ /__ __ /__ __ __ __ (mm/dd/yyyy)

DIAGNOSIS VERIFICATION

1. Are there notes available from a healthcare encounter within ±1 day of (anaphylaxis diagnosis date)?
   1☐ Yes
   0☐ No → answer Q1a

   1a. Are there any notes from a later date describing what happened on (anaphylaxis diagnosis date)?
   1☐ Yes
   0☐ No → skip to Q27

2. Did the patient seek care for incident (new onset) anaphylaxis or other allergic reaction within ±1 day of (anaphylaxis diagnosis date)?
   1☐ Yes → answer Q2a
   0☐ No → answer Q2b then STOP abstraction
   9☐ Unknown → STOP abstraction

2a. What was the date of the healthcare encounter? __ __ /__ __ /__ __ __ __ (mm/dd/yyyy)

2b. What was the reason for the patient's encounter within ±1 day of (anaphylaxis diagnosis date)

1☐ Follow-up for previous encounter related to anaphylaxis → answer Q2c then STOP abstraction
2☐ EpiPen refill for a known anaphylaxis diagnosis
3☐ To receive allergy shots
4☐ No evidence of current or prior anaphylaxis (miscode)
5☐ Other, specify: _____
6☐ Unknown

2c. What was the date of the previous encounter for anaphylaxis?
__ __ /__ __ /__ __ __ __ (mm/dd/yyyy) ☐ Unknown

3. Where did the patient seek care for incident anaphylaxis or allergic reaction on (reference date)? (Select all that apply)

1☐ Hospital inpatient → answer Q3a-b
2☐ Emergency department
3☐ Urgent care
4☐ Outpatient clinic
5☐ Telehealth
6☐ Other, specify: _____
7☐ Unknown

3a. Was the patient admitted to an intensive care unit (ICU)?

1☐ Yes
0☐ No
9☐ Unknown

3b. What date was the patient discharged from the hospital?
__ __ /__ __ /__ __ __ __ (mm/dd/yyyy) ☐ Unknown

4. What was the clinical diagnosis on (reference date)?

1☐ Anaphylaxis → answer Q4a-b
2☐ Possible anaphylaxis (clinician could not rule out) → answer Q4a-b
3☐ Allergic reaction other than anaphylaxis → answer Q4a-b
4☐ Unknown

4a. Copy the diagnosis text from the medical record: _____

4b. Which healthcare provider(s) made the diagnosis on (reference date)? (Select all that apply)

1☐ ER
2☐ Family practice
3☐ Pediatrician
4☐ Internist
5☐ Allergist
6☐ Other, specify: _____
7☐ Unknown

VACCINATION

5. Was a COVID-19 vaccine given on (reference date) or the day before (reference date)?
   1☐ Yes → answer Q5a-c
   0☐ No
   9☐ Unknown

   5a. When was the COVID-19 vaccine administered?
   Date: __ __ /__ __ /__ __ __ __ (mm/dd/yyyy)
   Time: __ __ : __ __ (hh:mm) ☐ Unknown
   Was the vaccination time exact or estimated? ☐ Exact ☐ Estimated

   5b. Which COVID-19 vaccine did the patient receive on (vaccination date)?
   1☐ Moderna
   2☐ Pfizer
   9☐ Unknown

   5c. Did onset of anaphylaxis symptoms begin before or after COVID-19 vaccination on (vaccination date)?
   1☐ Symptoms started before vaccination
   2☐ Symptoms started after vaccination
   9☐ Unknown

6. Has the patient received any prior doses of COVID-19 vaccine?
   1☐ Yes → answer Q6a-b
   0☐ No
   9☐ Unknown

   6a. When was the previous dose of COVID-19 vaccine administered?
   Date: __ __ /__ __ /__ __ __ __ (mm/dd/yyyy)

   6b. Which COVID-19 vaccine did the patient receive previously?
   1☐ Moderna
   2☐ Pfizer
   9☐ Unknown

7. Were any other vaccines administered on (reference date) or the day before (reference date)?
   1☐ Yes → Specify: _____
   0☐ No
   9☐ Unknown

EXPOSURES

8. Did the patient receive any other treatments on (vaccination date) prior to vaccination?
   1☐ Yes → Specify: _____
   0☐ No
   9☐ Unknown

9. Did the healthcare providers(s) that made the diagnosis attribute the episode to a specific exposure?

1☐ Yes → answer Q9a
0☐ No
9☐ Unknown

9a. What was the exposure? (Select all that apply)
1☐ Vaccine(s)
2☐ Drug(s)
3☐ Food
4☐ Latex
5☐ Insect bite/sting
6☐ Other, specify: _____
7☐ Unknown

VITAL SIGNS

10. Record the vital signs taken on (reference date), closest to but after onset of anaphylactic symptoms:
10a. Temperature __ __ __ ☐ Unknown
Units: 1☐ °F 2☐ °C
10b. Respiratory rate __ __ __ breaths/minute ☐ Unknown
10c. Heart rate __ __ __ beats/minute ☐ Unknown
10d. Blood pressure __ __ __ / __ __ __ mmHg ☐ Unknown

SIGNS & SYMPTOMS

11. When did the first symptoms of anaphylaxis begin?
Date: __ __ /__ __ /__ __ __ __ (mm/dd/yyyy) ☐ Unknown
Time: __ __ : __ __ (hh:mm) ☐ Unknown
Was the time of symptom onset exact or estimated? ☐ Exact ☐ Estimated

12. Copy the text from the medical record describing the patient's symptoms:
_____

13. Did the patient have any of the following dermatologic or mucocutaneous symptoms?

a. Urticaria (hives)	1☐ Yes 0☐ No 9☐ Unknown
b. Localized urticaria (hives) at the vaccination site	1☐ Yes 0☐ No 9☐ Unknown
c. Angioedema (well demarcated and not hereditary)	1☐ Yes 0☐ No 9☐ Unknown
d. Flushing (erythema or redness of the skin)	1☐ Yes 0☐ No 9☐ Unknown
e. Itching (pruritus)	1☐ Yes 0☐ No 9☐ Unknown

f. Skin rash	1☐ Yes 0☐ No 9☐ Unknown
g. Prickle sensation	1☐ Yes 0☐ No 9☐ Unknown
h. Red or itchy eyes (conjunctivitis, inflammation of the mucous membranes of the eye)	1☐ Yes 0☐ No 9☐ Unknown
i. Rhinorrhea (nasal discharge)	1☐ Yes 0☐ No 9☐ Unknown
j. Nasal congestion	1☐ Yes 0☐ No 9☐ Unknown
k. Other dermatologic or mucocutaneous symptom(s)	1☐ Yes, specify: _____ 0☐ No 9☐ Unknown

14. Did the patient have any of the following respiratory symptoms?

a. Wheezing (bronchospasm)	1☐ Yes 0☐ No 9☐ Unknown
b. Dyspnea (shortness of breath)	1☐ Yes 0☐ No 9☐ Unknown
c. Difficulty or distress in breathing	1☐ Yes 0☐ No 9☐ Unknown
d. Cyanosis (bluish discoloration of skin and mucous membranes)	1☐ Yes 0☐ No 9☐ Unknown
e. Rapid breathing (tachypnea) Adolescent (12-17 years): >16 breaths per minute Adult (≥18 years): >25 breaths per minute	1☐ Yes 0☐ No 9☐ Unknown
f. Stridor (high pitched sound on inspiration from throat or larynx)	1☐ Yes 0☐ No 9☐ Unknown
g. Increased use of accessory respiratory muscles (e.g., sternocleidomastoid, intercostals, etc.)	1☐ Yes 0☐ No 9☐ Unknown
h. Sensation of “tingling” in upper airway (in lips, tongue, mouth, throat, or other parts of upper airway)	1☐ Yes 0☐ No 9☐ Unknown
i. Unusual sensation in the throat (a closing, burning, or lump in throat sensation)	1☐ Yes 0☐ No 9☐ Unknown

j. Upper airway swelling or edema (of lips, tongue, mouth, throat, or other parts of upper airway)	1☐ Yes 0☐ No 9☐ Unknown
k. Drooling or excess salivation	1☐ Yes 0☐ No 9☐ Unknown
l. Laryngospasm	1☐ Yes 0☐ No 9☐ Unknown
m. Sensation of chest tightness (or chest pressure or chest pain)	1☐ Yes 0☐ No 9☐ Unknown
n. Respiratory arrest	1☐ Yes 0☐ No 9☐ Unknown
o. Retractions (intercostal/subcostal/sternal in-drawing or recession)	1☐ Yes 0☐ No 9☐ Unknown
p. Grunting	1☐ Yes 0☐ No 9☐ Unknown
q. Persistent dry cough	1☐ Yes 0☐ No 9☐ Unknown
r. Hoarse voice or change in voice	1☐ Yes 0☐ No 9☐ Unknown
s. Sneezing	1☐ Yes 0☐ No 9☐ Unknown
t. Other respiratory symptom(s)	1☐ Yes, specify: _____ 0☐ No 9☐ Unknown

15. Did the patient have any of the following cardiovascular symptoms?

a. Hypotension Systolic BP <90 mmHg (or >30% decrease from the patient's baseline)	1☐ Yes 0☐ No 9☐ Unknown
b. Clinical diagnosis of uncompensated shock	1☐ Yes 0☐ No 9☐ Unknown
c. Abnormal heart rhythm (arrhythmia/dysrhythmia)	1☐ Yes 0☐ No 9☐ Unknown
d. Cardiovascular collapse	1☐ Yes 0☐ No 9☐ Unknown

e. Prolonged capillary refill time (>3 seconds)	1☐ Yes 0☐ No 9☐ Unknown
f. Persistent tachycardia Adolescent (12-17 years): >100 bpm Adult (≥18 years): >120 bpm	1☐ Yes 0☐ No 9☐ Unknown
g. Reduced central pulse volume Evident on non-invasive plethysmography	1☐ Yes 0☐ No 9☐ Unknown
h. Syncope or loss of consciousness	1☐ Yes 0☐ No 9☐ Unknown
i. Decreased level of consciousness	1☐ Yes 0☐ No 9☐ Unknown
j. Other cardiovascular symptom(s)	1☐ Yes, specify: _____ 0☐ No 9☐ Unknown

16. Did the patient have any of the following gastrointestinal symptoms?

a. Nausea	1☐ Yes 0☐ No 9☐ Unknown
b. Vomiting	1☐ Yes 0☐ No 9☐ Unknown
c. Diarrhea	1☐ Yes 0☐ No 9☐ Unknown
d. Abdominal pain/cramps	1☐ Yes 0☐ No 9☐ Unknown
e. Other gastrointestinal symptom(s)	1☐ Yes, specify: _____ 0☐ No 9☐ Unknown

17. Did the patient have any of the following neurologic symptoms?

a. Irritability	1☐ Yes 0☐ No 9☐ Unknown
b. Lethargy	1☐ Yes 0☐ No 9☐ Unknown
c. Disorientation	1☐ Yes 0☐ No 9☐ Unknown

d. Dizziness	1☐ Yes 0☐ No 9☐ Unknown
e. Lightheadedness	1☐ Yes 0☐ No 9☐ Unknown
f. Tremor	1☐ Yes 0☐ No 9☐ Unknown
g. Seizure	1☐ Yes 0☐ No 9☐ Unknown
h. Other neurologic symptom(s)	1☐ Yes, specify: _____ 0☐ No 9☐ Unknown

LABORATORY & DIAGNOSTIC TESTING

18. Was serum mast cell tryptase testing done?
    1☐ Yes → answer Q18a
    0☐ No
    9☐ Unknown

    18a. What was the result?
        1☐ Normal
        2☐ Abnormal
        9☐ Unknown

19. Did the patient have any other laboratory testing done specifically to evaluate anaphylaxis?
    1☐ Yes → answer Q19a

    0☐ No
    9☐ Unknown

    19a. List the test name(s) and result(s): _____

20. Did the patient have any diagnostic imaging done?
    1☐ Yes → answer Q20a
    0☐ No
    9☐ Unknown

    20a. List the type(s) of imaging and copy the radiology report(s):
    _____

TREATMENTS

21. Were any of the following treatments used during the anaphylaxis episode? (Select all that apply)
    1☐ Epinephrine
    2☐ Antihistamines

3☐ H2 blockers
4☐ Corticosteroids
5☐ Volume replacement (intravenous fluid therapy)
6☐ Supplemental oxygen
7☐ Bronchodilators
8☐ Vasopressors
9☐ Inotropic drugs
10☐ Other, specify: _____
11☐ None of the above
12☐ Unknown

PATIENT OUTCOME

22. What was the patient's outcome?
1☐ Recovered
2☐ Died due to anaphylaxis or complications of anaphylaxis
3☐ Other, specify: _____
9☐ Unknown → SKIP to Q25

23. What was the duration of the anaphylaxis episode?
__ __ __ minutes ☐ Unknown
☐ Exact ☐ Estimated

24. Was the patient given a diagnosis of a biphasic reaction (defined as symptoms that recur 8-12 hours after onset of the first episode)?
1☐ Yes
0☐ No
9☐ Unknown

25. Did the patient have a follow-up encounter with an allergist?
1☐ Yes → answer Q25a-e
0☐ No
9☐ Unknown

25a. When was the patient's follow-up encounter?
Date: __ __ /__ __ /__ __ __ __ (mm/dd/yyyy) ☐ Unknown

25b. Did the allergist confirm the diagnosis as anaphylaxis?
1☐ Yes, confirmed anaphylaxis
2☐ Unsure, possibly anaphylaxis/could not rule out
3☐ No → What diagnosis was given? _____
9☐ Unknown

25c. Did the allergist agree that a COVID-19 vaccine was the trigger?
1☐ Yes, COVID-19 vaccine was the only trigger
2☐ Yes, COVID-19 vaccine and something else were triggers → What was the other trigger? _____
3☐ No, COVID-19 vaccine was not the trigger → What was the trigger? _____
9☐ Unknown

25d. Did the allergist prescribe any treatment?

1☐ Yes → Specify: _____
0☐ No
9☐ Unknown

25e. Did the allergist give any recommendations about future COVID-19 vaccination?

1☐ Yes, avoid COVID-19 vaccine
2☐ Yes, receive COVID-19 vaccine with precautions (e.g., extra monitoring)
3☐ Yes, receive COVID-19 vaccine without precautions
4☐ No, was not discussed
9☐ Unknown

PATIENT HISTORY

26. Did the patient have a history of any of the following conditions? (Select all that apply)

1☐ Anaphylaxis → answer Q26a
2☐ Anaphylactoid reaction → answer Q26a
3☐ Asthma
4☐ Hay fever
5☐ Atopic dermatitis
6☐ Contact dermatitis
7☐ Chronic urticaria
8☐ Allergic conjunctivitis
9☐ Allergic bronchitis
10☐ Allergic rhinitis (chronic rhinitis, rhinitis)
11☐ Reactive airway disease or bronchiolitis
12☐ Other allergies → answer Q26b
13☐ None of the above
14☐ Unknown

26a. Specify the trigger of previous anaphylaxis or anaphylactoid reaction:

_____

26b. What type of allergy does the patient have?

1☐ Food, specify: _____
2☐ Drug, specify: _____
3☐ Other, specify: _____
4☐ Unknown

27. Did the patient have a history of any the following medications? (Select all that apply)

1☐ EpiPen
2☐ Allergy shots/desensitization/immunotherapy
3☐ Albuterol inhaled oral
4☐ Ipratropium inhaled oral
5☐ Cromolyn inhaled oral
6☐ Leukotriene modifier inhaled oral
7☐ Steroid-containing → answer Q27a

8☐ None of the above
9☐ Unknown

27a. Specify the type of steroid-containing medication:
1☐ Fluticasone oral
2☐ Budesonide oral
3☐ Mometasone oral
4☐ Beclomethasone oral
5☐ Ciclesonide nasal
6☐ Unknown

ABSTRACTION COMMENTS

Comments:

ADJUDICATION

Adjudicator Initials: _____

Adjudication Date: __ __ /__ __ /__ __ __ __ (mm/dd/yyyy)

Brighton Level of Diagnostic Certainty
1☐ Level 1
2☐ Level 2
3☐ Level 3
4☐ Level 4
5☐ Not a case

Comments: