COVID-19 Vaccine Pregnancy Registry Protocol

Version 3

Updated October 27, 2022

The pregnancy registry was established under an amendment to the v-safe active surveillance for COVID-19 vaccine safety protocol and was referred to as the v-safe pregnancy surveillance system or v-safe pregnancy registry. As of October 27, 2022, the registry name has been updated as the COVID-19 Vaccine Pregnancy Registry.

Protocol Change History

Version	Date	Change
1	Dec 28, 2020	N/A - Original
2	Mar 18, 2021	1. Background was updated to acknowledge there are now three vaccines with FDA EUA. 2. Methods were updated to describe a new three question follow-up survey that will be administered to v-safe participants who report pregnancy. 3. Methods were updated to indicate the pregnancy registry will now receive full date of birth and race/ethnicity data for participants that may be pregnant from the v-safe survey system 4. Data Collection/Unreachable section (formerly Loss to follow-up) was updated to determine when a participant is considered unreachable.
3	Oct 27, 2022	1. Methods updated to include a post-15-month follow-up, at the time of initiation of calls for the post-15-month follow-up interview, infants will be at least 16 months old. 2. Methods updated to describe eligibility for the COVID-19 Pregnancy Registry based on report of pregnancy into v-safe. 3. Methods updated to indicate that the call center is now staffed by Abt Assoc. 4. Methods updated to reflect that due to resource constraints, over half of participants were interviewed after the pregnancy had ended, rather than through follow-up calls during pregnancy. 5. Information about the process for request and use of medical records for clinical review was added to the methods. 6. Methods updated to reflect a potential additional interview clinical review of the post-15-month follow-up interview. 7. For clarification purposes, going forward “Phase 1” will describe the interview and medical record information collected during pregnancy and, for infants, until they are 4 months of age. “Phase 2” will describe the interview and medical record information collected from or, as a result of, the post-15-month follow-up interview. 8. The registry name is updated to the COVID-19 Vaccine Pregnancy Registry.

COVID-19 Vaccine Pregnancy surveillance

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Protocol amendment summary (December 28, 2020): V-safe is a novel smartphone-based active vaccine safety surveillance program that was implemented at the start of an FDA Emergency Use Authorization (EUA) for COVID-19 vaccine use in the United States. As part of this novel public health surveillance activity established for COVID-19, information about pregnancy status at the time of vaccination and at defined follow-up time points after vaccination will be collected. This protocol amendment will establish the COVID-19 Vaccine Pregnancy Registry and describe the defined time points and protocol for collecting information about pregnant persons exposed to COVID-19 vaccines and their infants. Given the lack of safety data from these pre-EUA clinical trials of COVID-19 vaccines among pregnant persons, the COVID-19 Vaccine Pregnancy Registry will provide critical information to monitor the safety of COVID-19 vaccines administered under EUA and is intended to capture information about pregnant persons who have been vaccinated and their infants. This can inform clinical guidance regarding COVID-19 vaccination during pregnancy and can provide an additional method to detect adverse events that warrant further evaluation using existing safety and database systems.

Protocol Amendment #1 (March 18, 2021)
Summary of updates:

1. Background was updated to acknowledge there are now three COVID-19 vaccines with FDA EUA.
2. Methods were updated to describe a new three question follow-up survey that will be administered to v-safe participants who report pregnancy.
3. Methods were updated to indicate the pregnancy registry will now receive full date of birth and race/ethnicity data for participants that may be pregnant from the v-safe survey system
4. Data Collection/Unreachable section (formerly *Lost to follow-up*) was updated to determine when a participant is considered unreachable.

Protocol Amendment #2 (October 27, 2022)
Summary of updates:

1. Methods were updated to include a post-15-month follow-up interview conducted by phone by the pregnancy registry call center to monitor for birth defects, other infant medical conditions, infant hospitalizations, all-cause infant mortality, SARS-CoV-2 infection in the infant, and maternal thromboembolic, autoimmune, or cardiac diagnoses.
    a. This follow-up will use the cohort of pregnant people enrolled in the COVID-19 Vaccine Pregnancy Registry from January 11, 2021 through August 31, 2022. At the time of initiation of calls for the post-15-month follow-up interview, the infants will be at least 16 months old.
2. Methods were updated to describe eligibility for the COVID-19 Pregnancy Registry based on report of pregnancy into v-safe.
3. Methods were updated to indicate that the call center is now staffed by a contracting company, Abt Associates, and not by CDC staff.
4. Methods were updated to reflect that all pregnancies have been completed and as the pregnancy registry progressed, due to resource constraints, over half of the data were collected through interviews conducted

by phone after the pregnancy had ended, rather than through multiple follow-up calls at specified intervals during pregnancy. Going forward, for the post-1-year follow-up interviews, all data will be collected retrospectively at least 16 months after pregnancies have ended.

5. Information about the process for request and use of medical records for clinical review was added to the methods.
6. Methods were updated to reflect a potential additional interview opportunity that, based on the registry's initial two years, will improve the timeliness of reported data. Specifically, this involves the judicial use of an additional semi-structured phone interview to be conducted by CDC clinicians in cases where it is determined through clinical reviews that some information in addition to that acquired through the post-1-year interview is needed to adjudicate clinical outcomes based on interview data alone. This will allow CDC to provide meaningful outcome analyses and published reports in as timely a way as possible, first, after phone interviews data is collected and analyzed, and subsequently after the time it takes to acquire, abstract, and incorporate the supporting medical record information for the enhanced, medical record-validated reports of outcomes.
7. For clarification purposes, going forward "Phase 1" will be used to describe the interview and medical record information collected during pregnancy and, for infants, until they are 4 months of age. "Phase 2" will be used to describe the interview and medical record information collected from participants of Phase 1 through 15 months following the end of the pregnancy.
8. The registry name is updated throughout to the COVID-19 Vaccine Pregnancy Registry.

Background:

Pregnancy was an exclusion from enrollment in pre-EUA clinical trials for COVID-19 vaccines (www.clinicaltrials.gov). In these pre-EUA clinical trials, pregnancy was screened for and pregnant persons were excluded based on positive urine pregnancy tests; clinical trial participants were recommended to avoid pregnancy during the trial by using reliable and effective contraception. While Pfizer and Moderna vaccine trials did include approximately 36 pregnant persons inadvertently vaccinated during pregnancy, these small numbers are not enough to establish the safety of maternal vaccination (1, 2). Safety data from infants exposed during pregnancy is not available because of the short length of follow up.

On December 1, 2020, the Advisory Committee on Immunization Practices (ACIP) voted that, when a COVID-19 vaccine is authorized by the FDA and recommended by ACIP, healthcare personnel should be offered vaccination in the initial phase of the COVID-19 vaccination program (phase 1a) (3). The healthcare workforce is predominantly female, and women account for 75% of full-time year-round healthcare personnel (4). Females also dominate the largest healthcare occupations, comprising 88% of registered nurses and 86% of healthcare support workers, which includes nursing, psychiatric, and personal and home health aides. Approximately 5% of women of reproductive age are estimated to be pregnant or postpartum at any time, translating to around 330,000 pregnant or newly postpartum women who are healthcare personnel and could be included in phase 1a vaccine allocation. Furthermore, on December 20, 2020, the ACIP voted that phase 1c vaccine allocation includes persons aged 16-64 years with medical conditions that increase the risk for severe COVID-19, of which pregnancy is included (5).

Three COVID-19 vaccines were granted emergency use authorization by the FDA, and ACIP initially stated that pregnant people may choose to receive a COVID-19 vaccine and should discuss risks and benefits with their healthcare providers (6-8). These vaccines include two mRNA vaccines manufactured by Moderna and Pfizer-BioNTech, and one vaccine that uses an adenovirus vector as a platform, the Janssen/Johnson & Johnson vaccine. On May 5, 2022, the FDA limited authorized use of the Janssen COVID-19 vaccine to individuals 18 year of age and older for whom other authorized or approved COVID-19 vaccines are not accessible or clinically

appropriate or to individuals who elect to receive the Janssen COVID-19 vaccine because they would otherwise not receive a COVID-19 vaccine (9). On July 13, 2022, the FDA granted emergency use authorization for a protein adjuvanted COVID-19 vaccine, Novavax, for people 18 years of age and older. Therefore, it is important that post-EUA surveillance systems exist to monitor the safety of all COVID-19 vaccines among known and inadvertently vaccinated pregnant persons.

The CDC's Immunization Safety Office (ISO) implemented several systems to monitor the safety of COVID-19 vaccines (10). The Vaccine Adverse Event Reporting System (VAERS) receives passive reports on adverse events following vaccination from the public, medical providers, and manufacturers, and asks specific questions about pregnancy status at the time of vaccination (10). Pregnancy reports will be abstracted and supplemented with medical records when available. The Vaccine Safety Datalink (VSD) is a collaboration between CDC and nine integrated healthcare systems with demographic, vaccination, and healthcare utilization information on approximately 3% of the US population and 100,000 live births per year (10). The VSD has an electronic pregnancy episode algorithm that monitors COVID-19 vaccine coverage and can be used to perform epidemiologic studies on pregnancy loss, acute adverse events, adverse pregnancy outcomes, and infant development and birth defects following exposure to COVID-19 vaccine in pregnancy (10). The Clinical Immunization Safety Assessment (CISA) project, a collaboration between CDC and seven academic centers, is conducting a clinical trial examining the safety of vaccination during pregnancy (10). However, given the dearth of safety data of COVID-19 vaccines during pregnancy and the novelty of some COVID-19 vaccine candidate platforms (e.g., mRNA), it is essential that vaccine safety data among pregnant persons is comprehensive and captured in near real-time.

Therefore, CDC developed an active smartphone-based surveillance system, or v-safe, to support the work of the Immunization Safety Office (11). v-safe uses text messages with embedded web surveys to collect information on adverse health events and side effects following COVID-19 vaccination (11). Included in the web surveys are questions about pregnancy status at the time of vaccination or shortly after vaccination (11). Participants who indicated receipt of a COVID-19 vaccine during pregnancy or 30 days before the last menstrual period were eligible to be contacted by telephone to enroll in the CDC COVID-19 Vaccine Pregnancy Registry (11). Eligibility for the pregnancy registry was cut-off on June 18, 2021. Individuals who reported pregnancies into v-safe after June 18, 2021 were not included in the potential participant pool due to the volume of participants who reported pregnancies to v-safe. People who chose to participate in the COVID-19 Vaccine Pregnancy Registry were asked questions about pregnancy health conditions, pregnancy outcomes, delivery and postpartum complications, health history, and demographics. Participants who reported live births were asked questions about their infants' health, including any diagnoses of health conditions such as birth defects, hospitalizations, or referrals to specialists, when their infant was at least 3 months old. Information about the participants' and their infants' medical providers was also collected. The COVID-19 Vaccine Pregnancy Registry began enrollment on January 11, 2021 and continued through about August 31, 2022. As of August 31, 2022, a total of 22,952 participants were enrolled into the COVID-19 Vaccine Pregnancy Registry, representing 22,967 pregnancies of which 20,772 had live births. Birth outcome was unknown for 1,179 participants due to participant withdrawal, loss to follow-up (missed 2 sequential scheduled calls), or timed out of last scheduled call (these outcomes may be collected during the 15-month follow up call).

As of September 2022, several publications have described the safety of the COVID-19 vaccines in pregnant people. Data from both the COVID-19 Vaccine Pregnancy Registry and CDC's Vaccine Safety Datalink system (VSD), as well as data from a national registry in Norway, found no increased risk of spontaneous abortion following vaccination (12-14). Additionally, data from VSD and data from birth registries in Norway and Sweden found no increased risk of preterm birth, NICU admission, or small-for-gestational-age outcome among infants

(15,16). Data from cohort studies have also reported no association between COVID-19 vaccination in pregnancy and adverse maternal or birth outcomes (17,18). However, there are few data on the safety profile of infants exposed to COVID-19 vaccination in utero. Therefore, the second phase of surveillance of COVID-19 vaccine safety in pregnancy described in this protocol will evaluate infant outcomes through 15 months of life for infants exposed to a COVID-19 vaccine in utero. It will also evaluate maternal health conditions through 15 months post-partum. The following protocol details the plan to continue follow-up of enrolled COVID-19 Vaccine Pregnancy Registry participants and infants to collect health information through 15 months after the pregnancy outcome.

Objectives:

Objective 1 (Primary): To establish an enhanced active surveillance system for persons exposed to COVID-19 vaccine during pregnancy or in the periconception period to rapidly provide information about the safety of COVID-19 vaccines for pregnant persons and their infants.

Objective 2: Among infants exposed to COVID-19 vaccination in utero:

2a. To evaluate risks for major structural birth defects through 15 months of age, compared to U.S. population-based background rates for major structural birth defects.

2b. To evaluate risks for infant medical conditions, compared to U.S. population-based background rates for selected medical conditions, such as hearing loss.

2c. To describe hospitalizations, surgeries, and medical procedures in the first 15 months of infant life

2d. To describe all-cause infant mortality and compare to U.S. background rates.

Objective 3: Among infants exposed to COVID-19 vaccination in utero:

3a. To report participant-reported prevalence of COVID-19 infection and characterize infants' symptoms based on participant report

3b. To monitor infant COVID-19 vaccination and characterize participant-report of infant adverse effects following COVID-19 vaccination

Objective 4: Among persons who received COVID-19 vaccination during pregnancy, evaluate risks for pregnancy-related medical conditions, including thromboembolic events, as well as new autoimmune conditions, and heart conditions, in the first 15 months postpartum.

Methods:

Surveillance Population and Inclusion Criteria

The population of pregnant persons eligible for surveillance through the pregnancy registry will include those exposed to COVID-19 vaccines during pregnancy or in the periconception period (30 days before LMP through 14 days after LMP) (Figure 1). Additional data will be collected on these pregnant persons; infants born to these persons will be monitored for the first 15 months of life to identify any newborn and infant complications and diagnoses of major birth defects. Persons who are found not to be pregnant at the time of vaccination and are not identified as pregnant within 30 days after vaccination will not be included in the registry. There may be participants who are initially determined to be eligible based on their reported LMP during the first interview

but may later be deemed to be ineligible if gestational age estimation is updated over the course of pregnancy. These participants will be excluded from outcome analyses and the 15-month follow-up survey (n=70).

Identification of exposed pregnancies

The v-safe After Vaccination Health Checker system is an opt-in text messaging and web-based surveillance system that is offered to COVID-19 vaccine recipients. As part of the initial v-safe survey, all non-male participants (i.e., female, prefer not to say, other) will be asked questions about pregnancy status. In addition, screening questions to identify potential pregnancies will be asked at v-safe health check-ins that occur at days 21 and 42 after each vaccine dose (if applicable) and at 3, 6, and 12 months after the last vaccine dose (Figure 2). V-safe data managers at CDC will notify the pregnancy call center team (described below) of potential pregnant vaccine recipients. The pregnancy call center will be staffed by individuals trained to administer the questionnaire and on the handling of PII. To identify as many pregnant persons as possible through v-safe, the follow up plan is:

- If a person answered "yes" to any pregnancy question, on the v-safe text messaging survey, they were sent a follow-up survey by Oracle to respond to three questions. The first question confirmed pregnancy and the other two questions were related to interest in participating in the pregnancy registry. All survey responses were-sent to the pregnancy call center.
- Those who responded “yes” to any pregnancy question, “yes” to being interested in the follow-up survey or who did not respond at all were contacted by the pregnancy call center. During the initial call, the pregnant person was asked if they would like to participate in the pregnancy registry. If they declined, there was no further contact by the pregnancy call center. They remained enrolled in the v-safe text message monitoring system unless they replied with “STOP” to opt out.
- If they no longer participated in the v-safe survey questions (i.e., stopped responding or opted out) after indicating “don’t know” to a pregnancy question, they were contacted by the pregnancy call center within 3 months of their last response to inquire about their pregnancy status.

The CDC COVID-19 Vaccine Pregnancy Registry call center staff were notified of participants who might be pregnant via a dataset that was created from the v-safe After Vaccination Health Checker system. The dataset includes the following variables:

- Unique v-safe ID
- First Name
- Last Name
- Sex
- Full date of birth
- Phone Number
- Zip code
- Time zone
- Preferred language
- Race/ethnicity
- Vaccination dates
- Vaccine type
- Pregnancy response date
- Survey number that identified pregnancy

Data collection:

CDC pregnancy call center and registry

The CDC v- COVID-19 Vaccine Pregnancy Registry call center (referred to in this protocol amendment as call center) has been operated Since August 2021 by a contracting company, Abt Associates, with direction from CDC staff from ISO and other groups at CDC with obstetric and pediatric expertise (including the COVID-19 Epidemiology & Surveillance Task Force Pregnancy and Infant Linked Outcomes Team, which includes clinicians from the Division of Reproductive Health and the Division of Birth Defects and Infant Disorders). The call center staff contacted persons identified as pregnant or potentially pregnant in v-safe by calling or texting them using the mobile phone number provided during v-safe registration. The call center staff is trained to conduct phone interviews with pregnant participants, including: confirmation of the identity of the v-safe participant and whether the person was pregnant at the time of vaccination or within 30 days after vaccination, informing the pregnant person about the pregnancy registry, including risks, benefits, and alternatives, requesting consent for participation in the registry and for release of medical records from healthcare providers, and asking specific survey questions relevant to pregnancy. The call center staff are trained to handle challenging situations, such as pregnancy loss, neonatal or infant death, diagnosis of major birth defects and other severe outcomes and when to defer a call to one of the call center clinicians. During the first phase of the registry, participants were contacted once each trimester after enrollment during pregnancy and up to two time points in the postpartum period: once, 4-8 weeks postpartum, and once after the infant was 3 months old. In this next phase of the registry, addressed in the amendment, an additional phone interview will be attempted at least 15 months after the end of the pregnancy. During this 15-month follow up, where questions about the infants' and participants' health since the end of the pregnancy will be asked, participants will also be asked for permission to be called by a CDC clinician if any additional information is needed to clarify a reported diagnosis or diagnoses. Information collected from the interview and available medical records (if consent for records is provided by the participant) will include demographics, pre-pregnancy and gestational conditions, pregnancy history, COVID-19 vaccine information, pregnancy complications, pregnancy outcome, and infant outcomes.

The initial contact will collect pregnancy history information, including outcomes of prior pregnancies, the gestational dating of the vaccine-exposed pregnancy, and pregnancy and postpartum complications or comorbidities. Previously, call center follow-up interviews occurred once every trimester to identify any pregnancy complications, and a follow-up interview occurred at 4-8 weeks postpartum to obtain information on the delivery, any potential complications in the participant or infant, and to request consent from the participant for release of her and the infant's medical records. By the end of February 2022, all pregnancies reported to v-safe that were included in the pool of potential pregnancy registry participants had ended by the time of initial contact. This was due to resource constraints and the fact that the estimated due date for the pregnancy reported to v-safe was unknown prior to the initial outreach from the pregnancy registry call center. Therefore, for over half of enrolled registry participants, all information about the pregnancy and outcome was collected at the time of the registry's initial outreach. A brief call center follow-up interview occurred when the infant was 3 months old to inquire about any adverse events, including the diagnosis of any birth defects. If the initial call occurred when the infant was older than 3 months old, this information was obtained at the initial call as well. Finally, in the 2nd phase of the registry, focused on the participants' and infants' health in the year following the end of the pregnancy, a single interview will be conducted for the time period through 15 months following the end of the pregnancy. This interview will be administered, when the infant is at least 16 months old to ensure a consistent amount of time has passed since delivery. Participants will be asked about their health status as well as their infant's, including any birth defect diagnoses, infant medical conditions, COVID-19 infections, and hospitalizations, during that 15-month period. Participants who experienced a pregnancy

outcome other than a live birth (e.g., stillbirth, spontaneous abortion, induced abortion, ectopic pregnancy) or have already shared that their infant is deceased will only be asked the set of questions about maternal health. Participants whose pregnancy outcome is not yet known at the time of the 15-month interview will additionally be asked questions about their pregnancy outcome.

For the 15-month follow-up interview, we will use the cohort of pregnant people enrolled in the COVID-19 Vaccine Pregnancy Registry during January 11, 2021—August 31, 2022 (n=22,952 participants; this includes 15 participants who had more than one eligible pregnancy). Of these, we exclude participants who 1) withdrew participation (n=35), 2) indicated that they did not want to be contacted by the registry in the future (responded "no" in the survey for a question asking permission to contact them in the future, n=244), 3) were lost to follow up (missed 2 scheduled calls, n=417), or 4) were deemed ineligible based on vaccination occurring more than 30 days prior to pregnancy onset (n=72). In total, there are approximately 22,203 participants (22,216 pregnancies, 92% with known live birth) eligible for the 15-month follow-up interview. Because participants have already engaged with the pregnancy registry, we expect the number lost to follow-up (LTFU) to be minimal. A 10% LTFU rate would result in a sample size of approximately 19,982 participants, and a 20% LTFU rate would result in a sample size of approximately 17,762 participants.

The COVID-19 Vaccine Pregnancy Registry will coordinate with the v-safe After Vaccination Health Checker system to send a text notification through that platform to eligible pregnancy registry follow-up participants that the registry will be calling to conduct an additional follow-up interview. This message will be sent on a rolling basis to coincide with the calling schedule. Eligible participants will be called at least 15 months after the pregnancy outcome date (when known; otherwise participant's reported estimated due date will be used), with the goal of reaching participants within a 3-month time period (i.e., 16-19 months after the pregnancy outcome). The 15-month follow-up calls will begin in November 2022 and are projected to end by September 2023. At the start of the 15-month follow-up calls, 17% of eligible participants will have had their pregnancy outcome occur over 19 months ago and 83% of eligible participants will be within the call window of 16-19 months. Depending on the time it takes to reach a participant, the proportion of participants reached more than 19 months after their pregnancy outcome may increase. A maximum of 6 phone call attempts per participant will be made before classifying a participant as lost to follow-up. In an effort to minimize the proportion of participants that will be over 19 months post-end of pregnancy at the time of follow-up, there will not be an official piloting stage of this second phase of the registry. Therefore, to monitor script performance and acceptability, up to 20 follow-up calls will be recorded. Participants will be asked if they consent to recording for quality control purposes. If they do not consent, the call will not be recorded but will continue if the participant is willing at that time.

The call center staff will attempt to obtain consent to request and review relevant medical records after the pregnancy conclusion (including medical records from obstetrical visits, ultrasounds, inpatient encounters, emergency room visits, notes from the delivery admission, post-partum visits, and care received for health issues over the 15 months post-end of pregnancy) and through the infants' first 15 months of life (including well visits, genetic testing, specialist and inpatient encounters) in order to verify diagnoses and complement information obtained during the phone interview. For participants who initially agreed to infant medical record release at the 3-month infant follow-up, call center staff will ask permission to contact medical providers again after the infants are 15 months old. Participants were asked during Phase 1 of the registry for consent for CDC to obtain and review maternal medical records after 3 months postpartum if needed; this request will be repeated for the period up to 15 months postpartum during the 15-month interviews. Medical record requests will be limited to those required for development of clinical history and diagnosis verification based on interview responses. The HIPAA Privacy Rule permits covered entities to disclose protected health information without authorization for specified public health purposes, including for FDA-regulated products such as vaccines (see 45

CFR 164.512(b)(1)), so written consent from participants is not required for release of medical records. However, we will attempt to obtain email addresses from participants to send medical record release authorization for clinics who request such authorization for release of medical records.

Unreachable

The pregnancy registry call center might be unable to reach some pregnant persons who received COVID-19 vaccination for a variety of reasons. If there is a lack of response to a telephone call from the call center, the pregnant person receives a voicemail explaining the purpose of the call, in addition to a text message stating that the CDC pregnancy registry attempted to contact them. If the person does not respond to phone calls or text messages despite six separate attempts, performed a week apart at a different time of day, the pregnant person will be considered as unreachable and will no longer be included in the phone survey component of the registry. Any pregnant participant in the call center and registry may opt of out of the phone surveys or medical record release at any time. Opting out of the pregnancy phone surveys and/or medical record release does not preclude continued participation in the v-safe After Vaccination Health Checker system.

Potential for duplication of data

Because the v-safe active surveillance program will also collect information on health impact events among participants that may result in a follow-up call and submission of a VAERS report, there is the potential for duplicative efforts among pregnant persons within v-safe, VAERS, and the pregnancy registry systems. The pregnancy registry, v-safe, and VAERS ISO staff will work closely together to minimize these duplicative efforts and to minimize the potential burden on pregnant persons and their healthcare providers. If a pregnancy is reported at the same time as a clinically important adverse event (defined by v-safe as a symptom or health condition that led to inability to work, led to inability to perform daily activities, or required care from a doctor or other healthcare professional), the event will first be reported to the VAERS call center per the v-safe protocol. After the pregnant person is contacted by the VAERS call center, they will then be contacted by the pregnancy call center team to inquire about their pregnancy and participation in the pregnancy registry. Additionally, if a pregnant person enrolls in v-safe and participates in the pregnancy registry and they or their healthcare provider independently submits a spontaneous VAERS report, the pregnancy registry, to the extent possible, will only collect medical records that are not being collected via the standard VAERS procedures. This will be done, to avoid duplication of efforts to obtain medical records.

Clinical Review:

Obstetric, postpartum, neonatal, and infant outcomes in the pregnancy registry will be reviewed by a panel of CDC clinical subject matter experts in order to accurately and consistently identify and classify potential pregnancy and infant clinical outcomes. The review process will involve examination of all reported clinical data. Subject matter experts on the review panel may include obstetrician/gynecologists, pediatricians, pediatric infectious disease experts, vaccine safety experts, nurses, epidemiologists, analysts, and others with extensive experience in birth defects surveillance. Other pregnancy outcomes may also be reviewed. As needed, experts in specific areas not otherwise covered by the clinical review panel will be consulted (e.g., clinical geneticist, developmental specialist). Data will undergo review by multiple reviewers to ensure consistency in case classification, clinical review quality standards and ensure consensus in the interpretation of reported data and outcomes. If clinical subject matter experts determine that additional information is needed to adjudicate an outcome, CDC clinicians will call participants where this is the case to ask semi-structured questions to obtain necessary information for clinical adjudication based on only interview data. If participants are unable to be

reached or additional information is still needed, medical records will be requested and abstracted by trained medical record abstractors at both the CDC as well as Chickasaw Nation Industries (CNI), a contracting company under the direction of CDC. Medical record abstraction may also be requested to refine outcome definitions or explore unanticipated findings or be requested for additional participants without designated outcomes (i.e., from a "healthy outcome" cohort) to validate the survey data. A minimum of 10% of medical records will be abstracted a second time for quality control assurance. Once re-abstracted, both sets of data will be reviewed by clinicians and subject matter experts for completeness and consistency.

Analysis plan:

Ongoing data quality checks occur to identify errors, including implausible and missing values. Data from the pregnancy registry are analyzed monthly at minimum. Reports include descriptive analyses of any adverse outcomes and rates of follow up among pregnant persons. Specifically, rates are calculated for fetal demise (spontaneous abortion and stillbirth), pregnancy complications (pregnancy induced hypertension, gestational diabetes, pre-eclampsia), adverse birth outcomes (preterm delivery, small for gestational age, low birth weight, neonatal intensive care unit stays), major birth defects, and other outcomes of interest. These proportions may be compared to national averages, published background rates or estimates seen in other data systems with similar demographics. For outcomes that may undergo clinical review and adjudication, sensitivity analyses will be performed that account for any potential recategorization of outcomes following the clinical adjudication processes (clinical review of participant-reported data and/or medical record data by clinical SMEs). Adverse events may be analyzed in aggregate if rare (i.e., any major cardiac defect). Any potential safety signals will be compared to other surveillance systems, such as VAERS, and specifically for birth defects, the CDC's Metropolitan Atlanta Congenital Defects Program or the Texas Birth Defects Registry (19, 20). Persistent signals will be evaluated using more robust surveillance system data (such as the Vaccine Safety Datalink) that have denominator data of pregnant persons who received COVID-19 vaccines and comparison groups of pregnant persons who did not receive COVID-19 vaccines. For rare outcomes, evaluations may also be conducted in other database systems, such as the FDA or the Department of Defense (DOD), for appropriate follow up assessment.

Because we do not have a control group and the pregnancy registry is not nationally-representative, we will compare characteristics of pregnancy registry participants with those of representative samples of pregnant people within the United States to aid in the interpretation of generalizability. For example, we may compare the outcomes with already collected data from other surveillance systems, such as the Pregnancy Risk Assessment Monitoring System or Vaccine Safety Datalink or compare to background rates in the literature.

Outcomes:

Selection of maternal and infant outcomes for this project have been informed by prior evaluations of data from the COVID-19 Vaccine Pregnancy Registry, data in the literature from cohort and case-control studies about COVID-19 and COVID-19 vaccination during pregnancy, and previous studies examining outcomes following maternal vaccination with Tdap and influenza (21, 22). Additionally, outcomes have been selected based on the need to provide information to help guide individuals who are still considering whether to receive vaccination, including booster doses. Birth defects will be adjudicated through clinical review and assigned codes using the Metropolitan Atlanta Congenital Defects Program (19). Other infant medical conditions and maternal medical conditions will be assigned an ICD-10-CM code. Medical record review will help verify appropriate codes assigned at inpatient, outpatient, or emergency department clinical encounters.

Covariates

We will collect participant medical history and demographics at the initial enrollment of participants. These variables include age, race/ethnicity, participant co-morbidities, height, pre-pregnancy weight, and previous obstetrical history. Additionally, we plan to obtain other variables from medical records to further characterize the population and identify potential confounders, including potential risk behaviors and conditions (e.g., smoking status and receipt of prenatal health care). We will ask additional questions to obtain sociodemographic information from the participant at the extended follow-up including marital status, and highest participant education level. We will ask about potential conditions that may be associated with SARS-CoV-2 exposure risk (e.g., daycare attendance). We will confirm zip code of residence at the time of v-safe enrollment and follow-up (entered by participant into v-safe) and use census tract poverty level as a proxy for neighborhood socioeconomic status (SES).

Data quality, and management:

V-safe data is collected, managed, and housed on a secure server by Oracle. Through Health and Human Services (HHS), Oracle has donated IT services to any agency conducting COVID-19 related activities. Oracle is providing IT support for the v-safe After Vaccination Health Checker platform. All data participants report voluntarily into the v-safe After Vaccination Health Checker platform are collected, stored, processed, and transmitted in Federal Risk and Authorization Management Program (FEDRAMP) approved infrastructure environment (23).

CDC ISO data managers will create a dataset for the pregnancy registry call center which includes only those participants who report potential pregnancies. As previously described, the data elements reported directly by participants into the v-safe After Vaccination Health Checker platform that will be shared with the COVID-19 Vaccine Pregnancy Registry are limited to those that allow the pregnancy registry interviewers to reach out to those participants to confirm eligibility through review of dates of pregnancy and receipt of vaccine and to inquire about their willingness to participate in the pregnancy registry. Data acquired through the interviews following this enrollment (including data provided verbally during phone calls and any data obtained through review of select medical records if participants consent) will be stored on an internal CDC server. Data from all components of the pregnancy registry may be combined into a master dataset behind the CDC firewall using unique identification numbers assigned at registration.

Pre-approved CDC investigators and data managers, including CDC contractors, will be the only individuals with access to the full data. All electronic documents, data sets, and files relevant to the project will be stored on network folders with restricted access on CDC computers. The pregnancy registry team at CDC will be primarily responsible for data management activities, including data extraction, documentation and archival of a final data set. The archive will include the protocol, statistical programs, human subjects review documents, statistical output, analytical data sets, and manuscripts. Data sharing plans will be developed at the completion of data collection.

Human subject considerations and confidentiality:

This protocol has received a non-research determination through standard CDC review processes.

CDC is the lead site and surveillance data will include collection of personal identifiable information (PII). This data will be collected for public health surveillance, not for research purposes. PII will not be included in any pregnancy registry analyses, manuscripts, or datasets shared externally. Participation is voluntary and individuals self-enroll at the time of the initial telephone call during which eligibility for the registry is determined. Participants can opt-out of the pregnancy registry at any time and their data will only be used for the time they were considered an active participant. In addition, this activity presents minimal risk to participants, and use of participant data for this purpose will not adversely affect participants' rights or welfare.

308(d) Assurance of Confidentiality Protection was awarded to the COVID-19 Vaccine Pregnancy Registry on April 25, 2022 (references 42 USC 242(k), and 42 USC 242(m)).

Duration:

The anticipated duration of participant's and their infant's inclusion in the pregnancy registry will be up to two years after vaccination, depending on the time point in pregnancy that a person is exposed to vaccine. The decision to discontinue the pregnancy registry program or to modify pregnancy registry procedures to scale back active telephone follow-up will be made in consultation with key stakeholders including the CDC COVID-19 Vaccine Task Force leadership, Immunization Safety Office (ISO) leadership, and FDA.

Limitations and challenges:

Limitations and challenges for the COVID-19 Vaccine Pregnancy Registry include the potential for limited enrollment and retention in the program given its voluntary nature. It might be difficult to contact pregnant and postpartum persons by phone, and to obtain medical records on pregnant persons and infants. Furthermore, vaccinated pregnant persons who choose to participate in both the v-safe After Vaccination Health Checker and the COVID-19 Vaccine Pregnancy Registry might be different from those who do not; therefore, rates of outcomes reported by pregnancy registry participants might not be generalizable to the full population of pregnant COVID-19 vaccine recipients. However, it is possible to compare characteristics of pregnancy registry participants with those of representative samples of pregnant people within the United States. Similarly, pregnant persons who choose to participate in the pregnancy registry might be those who are more likely to have concerns or have experienced adverse events. This potential bias may be minimized by the prospective nature of this surveillance system, by review of medical records and accurate characterization of events. Additionally, a sensitivity analysis examining only outcomes among those who were enrolled and monitored before an adverse pregnancy or birth outcome occurred will be performed. Finally, the information provided by pregnancy registry participants for up to two years after vaccination might be impacted by recall bias, specifically among those for whom we are unable to obtain medical records.

Dissemination of information:

Safety profile information from the pregnancy registry may be presented to the Advisory Committee on Immunization Practices (ACIP) subgroups (such as the Vaccine Safety Technical Subgroup [VaST]), ACIP meetings and other meetings that are requested. Further, at the conclusion of the registry, reports will be written detailing the registry's findings.

Figure 1. Entry into the COVID-19 vaccine pregnancy registry

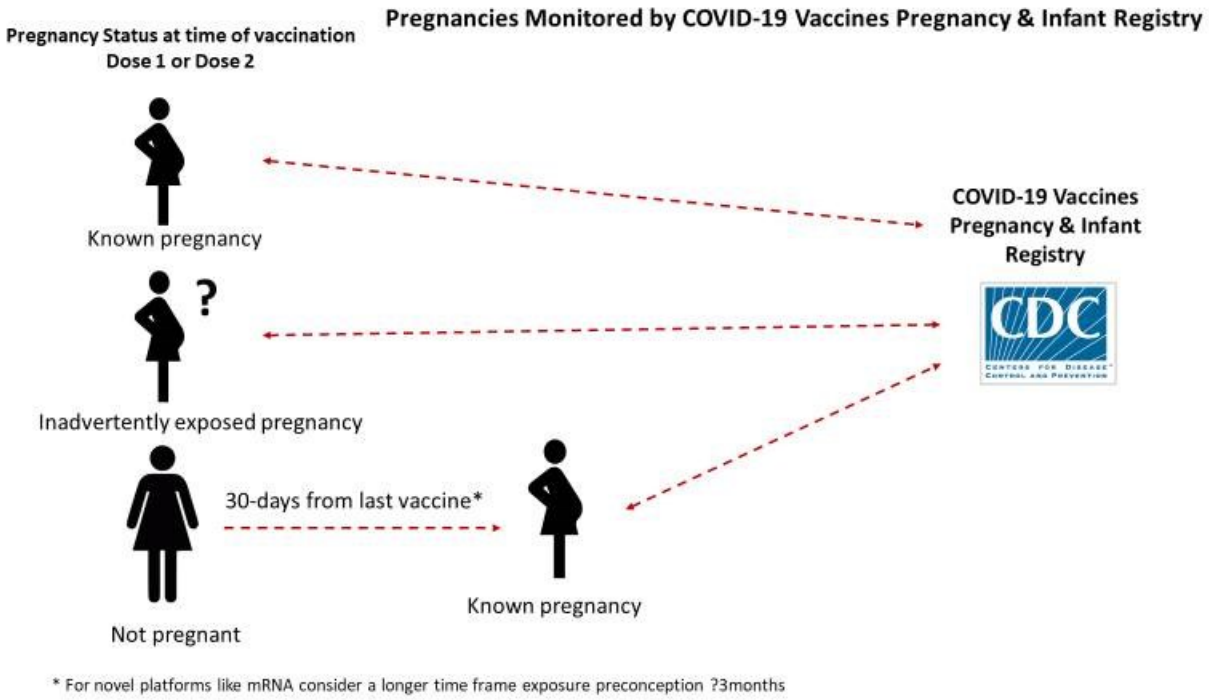

Figure 2. V-safe survey pregnancy ascertainment questions and follow-up from the pregnancy registry call center

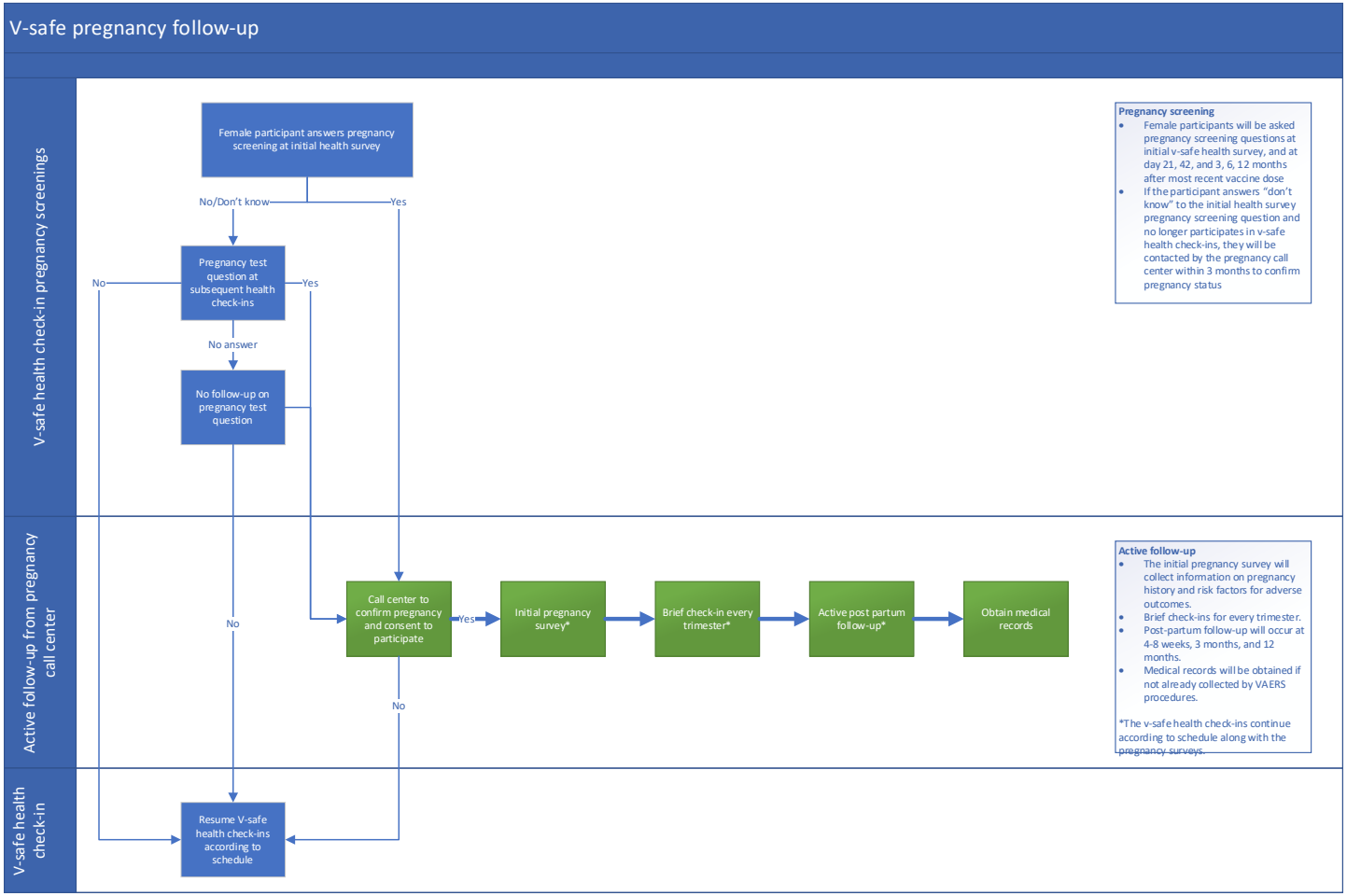

Figure 2 describes the v-safe after vaccination health checker pregnancy ascertainment questions and among participants who report a pregnancy, the follow-up contacts and surveys from the COVID-19 vaccine pregnancy registry call center.

The 1st box on the top right of figure 2 describes the pregnancy screening process for participants in the v-safe after vaccination health checker who identified as female. Female participants are asked pregnancy screening questions at the initial v-safe health survey, and at day 21, 42, and 3, 6, 12 months after most recent vaccine dose. If the participant answers “don’t know” to the initial health survey pregnancy screening question and no longer participates in v-safe health check-ins, she will be contacted by the pregnancy call center within 3 months to confirm pregnancy status. Following the illustration in the diagram, the top-left blue box describes the 1st v-safe health check-in question. Female participants could answer “no/don’t know” or “yes” to the initial pregnancy status screening question. If the reply is “no/don’t know”, they will be screened at each subsequent (at day 21, 42, and 3, 6, 12 months) v-safe health check-in (2nd box). If the response is “no” (3rd box), the remaining v-safe health check-in questions will resume according to schedule.

Active follow-up by the COVID-19 pregnancy registry call center ensues if the participant response to pregnancy status is “yes” at the initial or subsequent screening to confirm pregnancy status (1st green box). A “yes” reply confirming pregnancy status is followed by an initial call center pregnancy survey (2nd ‘green’ box), brief check-in every trimester (3rd “green box), active post-partum follow-up (4th ‘green’ box). The final (5th ‘green box) includes obtaining medical records if permission is provided. A “no” reply will loop back to resuming v-safe health check-ins according to schedule (last ‘blue’ box on the left).

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