PROTOCOL

Infections through 6 months of age among infants born to women who received COVID-19 vaccination while pregnant or breastfeeding

VSD # TBD

Version 1.2

14 December 2021

Lead site: Immunization Safety Office (ISO) Centers for Disease Control and Prevention (CDC)

Investigators:
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Role of CDC and collaborating sites: CDC will be leading the analysis and taking primary responsibility for protocol development, data analysis, and interpretation of results. CDC will have access to coded, private information. VSD sites will provide feedback on the study design, develop ancillary laboratory files, conduct chart reviews, and assist with the preparation of reports for publication.

Study title: Infections through 6 months of age among infants born to women who received COVID-19 vaccination while pregnant or breastfeeding

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Protocol summary: This study will use the Vaccine Safety Datalink (VSD) to investigate the safety of maternal COVID-19 vaccination administered in pregnancy and in the postpartum period up to 6 weeks after delivery while breastfeeding on infant infectious outcomes through 6 months of life.

Background:

It is estimated that >150,000 pregnant women in the United States (US)[1] have contracted coronavirus disease 2019 (COVID-19), caused by the respiratory pathogen, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Approximately 5% of women in the US of reproductive age are expected to be pregnant or postpartum at any given time. Therefore, the burden of COVID-19 in pregnant and postpartum women is anticipated to increase in the setting of the ongoing pandemic. Pregnant women are at increased risk for severe illness due to COVID-19 and may be at increased risk for adverse birth outcomes including preterm birth and stillbirth.[2-4]

Pregnant and lactating women have historically been excluded from clinical vaccine trials, and similarly, initial trials for COVID-19 vaccine did not include pregnant women.[5] While there are now clinical trials enrolling pregnant women,[6,7] safety data are not yet available to guide critical policy decisions. Initial developmental and reproductive toxicity (DART) studies on Pfizer-BioNTech BNT162b2 and Moderna mRNA-1273 vaccines in animals have not shown adverse effects with respect to pregnancy, fetal development, parturition or postnatal development.[8,9] Additionally, preliminary surveillance data have shown no safety signals regarding birth outcomes in women who received mRNA COVID-19 vaccines in pregnancy.[10-12] Given data from currently licensed maternal vaccines,[13] infant protection from maternal COVID-19 vaccination through transplacental antibody transfer or mucosal immunity through breastfeeding may be hypothesized; however, it is paramount to ensure no adverse effects to the developing infant as a result. Known risks of COVID-19 infection for pregnant and lactating women and their infants make the evaluation of the safety profile of maternal COVID-19 vaccinations critical to inform evidence-based assessment of the risks and benefits of COVID-19 vaccination during pregnancy and lactation.

Vaccine safety data in pregnant populations is often limited due to lack of pre-licensure clinical vaccine trials. Reactogenicity and safety profiles are often evaluated in the post-licensure period using passive methods, which may be limited by small sample sizes and inadequate study design.[14] Population-based data systems, such as the Vaccine Safety Datalink (VSD), a collaborative effort between the Centers for Disease Control and Prevention (CDC) and nine partner healthcare organizations, provides useful information about the safety of maternal vaccination that can be used to inform regulatory and policy decisions surrounding maternal immunization.[15,16] The VSD can successfully identify pregnancy episodes using a Pregnancy Episode Algorithm (PEA)[16] and has evaluated the safety of maternal influenza and tetanus toxoid, reduced diphtheria toxoid and acellular pertussis (Tdap) vaccines, given during pregnancy on infant outcomes.[17] The PEA has recently been adapted to a Dynamic Pregnancy Algorithm (DPA) which can identify pregnancy episodes in real time, a tool necessary given the need for real time data in the ongoing COVID-19 pandemic.[18] To that end, the VSD provides an opportunity to plan systematic data collection of indicators of safety among infants born to women who received COVID-19 vaccination during pregnancy.

Initial recommendations from CDC for phased allocation of COVID-19 vaccine rollout included health care personnel, with estimates that approximately 330,000 could be pregnant or recently postpartum at the time of vaccination, as well as those with high risk medical conditions including pregnancy. [19] [20] Currently CDC recommends pregnant women receive COVID-19 vaccination due to the increased risk of severe illness due to COVID-19 and while it is not known exactly how many pregnant or postpartum women in the US have received COVID-19 vaccination, recent VSD data from 14 December 2020 through 8 May 2021 identified 135,968 pregnant women with 22,197 (16.3%) of these who had received ≥1 dose of a COVID-19 vaccine during

pregnancy.[21] Further, recent estimates show that >178,000 participants in v-safe, a novel, active, web-based surveillance system implemented by CDC have indicated they were pregnant at the time of vaccination.[22]

CDC is currently evaluating maternal and neonatal safety outcomes in pregnant women who received COVID-19 vaccination, including, in regard to fetal and neonatal outcomes, spontaneous abortion, stillbirth, prematurity, low birth weight, and neonatal death. The Global Alignment of Immunization Safety Assessment in Pregnancy (GAIA), an initiative of the Brighton Collaboration, has identified priority outcomes to assess the safety of maternal vaccinations.[23] In addition to those outcomes already being evaluated by CDC, the GAIA initiative calls out neonatal infections as an area of priority.[24] These outcomes, including neonatal infections, have also been highlighted as critical for safety evaluation in maternal COVID-19 vaccination.[25] While it has been shown that maternal antibodies interfere with the infant immune response to vaccination in early life,[26] another mechanism of biologic plausibility which may lead to an increase in infections after COVID-19 vaccination in pregnancy or while lactating has not been postulated.

Looking at similar data from maternal influenza vaccination, Hviid et al. found a statistically significant increased risk for sepsis and "other infections" in a cohort of Danish children exposed to pandemic influenza A (H1N1) vaccination in pregnancy during a 5-year follow up period; multiple testing was hypothesized as an explanation for the increased risk, and when using the Bonferroni correction, the increased risk for sepsis and "other infections" was not observed.[27] Additionally, a significant decrease in upper respiratory and gastrointestinal infections was found in this cohort.[27] Further data that exist to evaluate infections in infants exposed to maternal influenza vaccination beyond the neonatal period do not suggest an increase in infectious infant adverse outcomes.[28,29] Nevertheless, it is necessary to ensure there are no safety concerns regarding infant infections following maternal COVID-19 vaccination, given the complex interaction of maternal antibodies with infant immune response, novel mRNA vaccination platforms, and the historic inclusion of pregnant women early in vaccine rollout.

The unprecedented inclusion of pregnant and postpartum women in early COVID-19 vaccine rollout will yield a rich dataset to evaluate infectious safety outcomes of infants born to women who received COVID-19 vaccination while pregnant or postpartum and to impact health policy decisions.

Specific aims:

Aim 1: Evaluate the association of maternal COVID-19 vaccine exposure during pregnancy with medically attended adverse infant infectious outcomes through 1 month and 6 months of life.
Approach: Identify inpatient, emergency department (ED), and outpatient encounters for respiratory infections (e.g., COVID-19 infection, pneumonia, bronchiolitis, other upper or lower respiratory illness), bacteremia and sepsis, and meningitis in the infant to evaluate association with maternal COVID-19 vaccination in pregnancy.

Aim 2: Evaluate the association of maternal COVID-19 vaccine administration in the postpartum period up to 6 weeks after delivery in women who are breastfeeding with medically attended adverse infant infectious outcomes through 1 month and 6 months of life (exploratory).
Approach: Identify inpatient, ED, and outpatient encounters for respiratory infections (e.g., COVID-19 infection, pneumonia, bronchiolitis, other upper or lower respiratory illness), bacteremia and sepsis, and meningitis to evaluate association with maternal COVID-19 vaccination given in the 6 weeks after delivery while breastfeeding.

Methods and analysis plan:

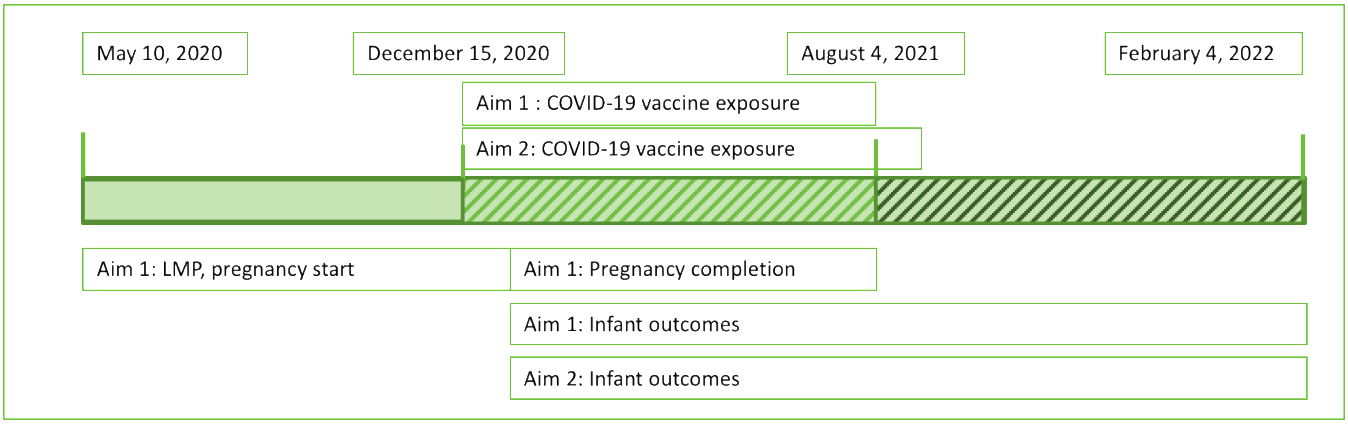

Figure 1: Characteristics of the study cohort including pregnancy start dates, pregnancy completion dates, COVID-19 vaccine exposure dates and infant outcome dates for each aim.

Aim 1: Evaluate the association of maternal COVID-19 vaccine exposure during pregnancy with medically attended adverse infant infectious outcomes through 1 month and 6 months of life.

Study design, population, and period: A retrospective observational cohort study utilizing automated data obtained through the VSD of pregnant women 16-49 years of age with pregnancy start dates within the study period, May 10, 2020 to October 25, 2020 will be completed. Rates of adverse infectious outcomes of infants born to women exposed to one or more COVID-19 vaccine doses during pregnancy from December 15, 2020 to August 4, 2021 will be compared to rates for these outcomes in women with pregnancies during the same time period who did not receive a COVID-19 vaccine during pregnancy or postpartum (Figure 1).

Inclusion criteria:

- Women aged 16-49 years who were pregnant within the study period and continuously enrolled from 6 months prior to pregnancy and through 2 months after pregnancy end or 2 months prior to the end of the study period
- Women with a completed singleton live birth pregnancy, linked to an infant record
- Women with at least one antenatal, delivery or postpartum care visit
- Infants enrolled in the first 3 months of life and at least 3 months of enrollment in the first 6 months of life who have at least one well child visit.

Exclusion criteria:

- Pregnancies with the following outcomes: ectopic pregnancy, therapeutic abortion, spontaneous abortion, stillbirth, gestational trophoblastic disease or unknown pregnancy outcome
- Multiple gestation pregnancies
- Pregnancies that are ongoing at the time of the data pull
- Pregnancies in which the mother received a COVID-19 vaccine postpartum
- Infants without any well child encounters during the study period, suggesting they may be receiving care outside of the health system.

Exposure definition: The primary exposure of interest is receipt of one or more doses of COVID-19 vaccination during pregnancy. COVID-19 vaccination status will be identified using vaccine administered codes (Table 1). COVID-19 vaccine exposed will be defined as receiving one or more COVID-19 vaccines during any trimester of pregnancy and before the date of delivery. COVID-19 vaccine unexposed will be defined as receiving no COVID-

19 vaccine during pregnancy, through date of delivery and in the postpartum period. COVID-19 vaccine exposed and COVID-19 vaccine unexposed will be compared for analysis.

CVX Code	Full Vaccine Name	Note
207	SARS-COV-2 (COVID-19) vaccine, mRNA, spike protein, LNP, preservative free, 100 mcg/0.5mL dose	EUA 12/18/2020, 2-dose vaccine. Used to record Moderna vaccines administered in the US and in non-US locations (includes tradename Spikevax)
208	SARS-COV-2 (COVID-19) vaccine, mRNA, spike protein, LNP, preservative free, 30 mcg/0.3mL dose	EUA 12/11/2020, 2-dose vaccine. Used to record Pfizer vaccines administered in the US and in non-US locations (includes tradename Comirnaty)
212	SARS-COV-2 (COVID-19) vaccine, vector non-replicating, recombinant spike protein-Ad26, preservative free, 0.5 mL	EUA 02/27/2021, 1-dose vaccine. Used to record Janssen/J&J vaccines administered in the US and in non-US locations

Table 1: Vaccine-administered CVX codes for VACCINE FILE youth and adult cohorts from Vaccine Safety Datalink Data Dictionary 2020.

Identification of pregnant women and infants: We will use the VSD dynamic pregnancy algorithm (DPA) to identify pregnant women with pregnancy start dates (or last menstrual period (LMP)) between May 10, 2020 and October 25, 2020. Mother-infant dyads will be identified, and only live births will be included. Infant records will be identified through internal linkages to maternal pregnancy records.

Outcome measures: The International Classification of Disease, Tenth (ICD-10) Revision, Clinical Modification codes as well as laboratory records will be used to identify outcome parameters (Table 2). Infant infectious health outcomes will be assessed for each pregnancy identified, linked to an infant record. Outcomes of interest include infant first and total encounters for infections including inpatient, ED and outpatient respiratory infections (COVID-19 infection, influenza, respiratory syncytial virus (RSV), bacterial or viral pneumonia, bronchiolitis, other upper or lower respiratory illness), bloodstream infections (bacteremia, bacterial sepsis, or culture-negative sepsis), and meningitis (bacterial meningitis, viral meningitis, and culture-negative meningitis). We will plan to assess the number of independent events as well as the total number of encounters to assess health care utilization in the same child. Additionally, outcomes in the first month of life will be limited to inpatient and ED encounters to distinguish true infections. Outpatient respiratory outcomes will be treated as a secondary analysis, and data will be examined for those from 30 days to 6 months of life to determine feasibility of this analysis. Outcomes will be analyzed separately and as a composite to assess for association.

Infant Outcomes		ICD-10-CM codes in infant record	Setting
Respiratory infections	COVID-19	U07.1, J12.82, positive SARS-CoV-2 PCR or Ag test	Inpatient, Outpatient or ED (use first diagnosis in any setting for onset date) Inpatient or ED in first month of life
	Influenza	J09.*, J10.*, J11.*, positive influenza A or B PCR or Ag test	
	RSV	J12.11, J20.5, J21.0, B97.4, positive RSV PCR or Ag test	
	Bacterial pneumonia	J15.*	
	Viral pneumonia	J12.*	
	Bronchiolitis	J21.*	
	Other upper respiratory illness	J06.*	
	Other lower respiratory illness	J22.*	
Bloodstream infections	Bacteremia	R78.81, or positive blood culture	Inpatient, Outpatient or ED (use first diagnosis in any setting for onset date) Inpatient or ED in first month of life
	Sepsis	A40.*, A41.* (excluding A41.9), A32.7 P36.*, R65* or positive blood culture	
	Culture-negative sepsis	A41.9	
Meningitis	Bacterial meningitis	G00.*, G01.*, A01.01, A02.21, A17.0, A20.3, A32.1, A39.0, A42.81, A50.41, A54.81, positive cerebral spinal fluid (CSF) culture or CSF PCR panel for bacterial etiology	Inpatient, Outpatient or ED (use first diagnosis in any setting for onset date) Inpatient or ED in first month of life
	Viral meningitis	A87.*, B00.3, B01.0, B02.1, B05.1, B26.1, B27.02, B27.12, B27.82, B27.92, positive CSF PCR test for viral etiology	
	Culture-negative meningitis	G03.9	

Table 2: Infant infectious outcomes to be identified using ICD-10-CM codes in infant records from inpatient, outpatient, or ED encounters or laboratory data.

Analysis: Descriptive statistics will be used to describe variables of interest including demographics of pregnant women, information surrounding maternal COVID-19 vaccination during pregnancy, levels of circulating COVID-19, during second trimester of pregnancy to align with time of vaccination for this cohort, which will be calculated using state-level or county-level percentage of positive COVID-19 test results,[30] maternal pre-existing medical conditions, prenatal complications, and delivery data (gestational age and birthweight) (Table 3). Descriptive statistics will be reported in univariate analyses using means and standard deviations or medians and interquartile ranges for continuous data and counts and percentage for categorical data. Rates of infant infectious outcomes will be computed (Table 4). Association of receipt of COVID-19 vaccine and events in the intervals, 0-30 days of life and 1-6 months of life for each of the infectious outcomes will be reported as incidence rate ratios with corresponding 95% confidence intervals after applying inverse probability weights. (Table 4). An offset will be used to account for differences in follow up time. Statistical significance will be set at a p-value of 0.05.

Characteristic	Maternal COVID-19 vaccine exposed		Maternal COVID-19 vaccine unexposed	
	n	% (95%CI)	n	% (95% CI)
Demographics				
Age (years), median (SD)				
Race				
White				
Black				
Asian				
Hawaiian or other Pacific Islander				
Native American or Aleutian				
Maternal COVID-19 vaccination				
COVID-19 vaccination in pregnancy			N/A	N/A
Partial vaccination (1/2 doses)			N/A	N/A
Complete vaccination (1/1 or 2/2 doses)			N/A	N/A
Pfizer-BioNTech vaccine			N/A	N/A
Moderna mRNA-1273 vaccine			N/A	N/A
Janssen/Johnson & Johnson vaccine			N/A	N/A
High level of influenza circulation				
High level of RSV circulation				
Pre-existing health conditions				
Asthma				
Lung disease				
Heart disease				
Immunodeficiency				
Smoker				
Other condition				
Delivery data				
Gestational age				
Birth weight				

Table 3: Characteristics of COVID-19 vaccination exposure in women exposed and unexposed to COVID-19 vaccination in pregnancy across Vaccine Safety Datalink sites

Exposure or Outcome of Interest	Maternal COVID-19 vaccine exposed				Maternal COVID-19 vaccine unexposed				Incidence rate ratio	
	n (%)	n (%)	30-day rate	6-month rate	n (%)	n (%)	30-day rate	6-month rate	30-day IRR (95% CI)	6-month IRR (95% CI)
Respiratory infections										
COVID-19										
Influenza										
RSV										
Bacterial pneumonia										
Viral pneumonia										
Bronchiolitis										
Other upper respiratory illness										
Other lower respiratory illness										
Bloodstream infections										
Bacteremia										
Sepsis										
Culture-negative sepsis										
Meningitis										
Bacterial meningitis										
Viral meningitis										
Culture-negative meningitis										
Composite infectious outcomes										

Table 4: Infant outcome rates and incidence rate ratios among mother-infant dyads exposed or unexposed to maternal COVID-19 vaccination in pregnancy or while breastfeeding across Vaccine Safety Datalink sites (table will be duplicated for each, Aim 1 and Aim 2)

Confounding adjustment: To identify potential confounders, characteristics of women who are exposed and unexposed to COVID-19 vaccine during pregnancy will be tabulated, and the standardized differences will be compared. The standardized differences for each covariate will be calculated by dividing the mean difference between the two groups by the estimate of the common standard deviation. The propensity score to receive a COVID-19 vaccine during pregnancy will be calculated based on known characteristics using logistic regression and potential confounding variables including pregnancy start date, maternal age, maternal race/ethnicity, other maternal vaccines received during pregnancy, maternal comorbidities, state- or county-level of positive COVID-19 test results[30] and VSD site.

Inverse probability weighting: Stabilized inverse probability weighting will be generated. The ability of the stabilized weights to reduce potential confounding will be determined by applying the weights to the cohort and estimating the standardized difference for each covariate. Standardized differences will be evaluated before and after applying stabilized weights for observed confounders. Assuming positivity for the study, it will be ensured that propensity scores are between zero and one, there is no clustering around zero or one and distribution of the propensity on the comparator group will be evaluated.If the positivity assumption does not hold, sensitivity analysis will be performed. Additional assumptions will need to be made using this approach, including exchangability and consistency. The unvaccinated cohort will represent the unexposed status of the fully vaccinated cohort, assuming no unmeasured confounders. We will count the exposure as having received one or more vaccines during the study period. Therefore, partial and full vaccination status will both be considered exposure.

Power analysis: Preliminary data indicate that there are approximately 50,000 participants in the VSD cohort of pregnant women in our study period with approximately 20% vaccine coverage during pregnancy. A 30% attrition rate was applied as a modest estimate of availability of infant data. The event rate for events in the first 6 months of life was set at 25 per 100 for respiratory infections, 10 per 10,000 for bloodstream infections and 1 per 10,000 for meningitis. Minimum detectable differences are presented below for risk ratios assuming alpha of 0.05 and power of 80% (Table 5). Estimates were computed using Power Analysis and Sample Size (PASS) 2019 software.

	Sample size Exposed: unexposed	1 per 10,000	10 per 10,000	25 per 100
20% coverage	10000:40000	7.5	2.3	1.06
20% coverage 30% attrition	7000:28000	9.7	2.6	1.07

Table 5: Minimum detectable risk ratios for infant outcomes among infants born to women exposed versus unexposed to COVID-19 vaccination during pregnancy. PASS 2019. NCSS, LLC. Kaysville, Utah, USA, ncss.com/software/pass.

Aim 2: Evaluate the association of maternal COVID-19 vaccine administration in the postpartum period up to 6 weeks after delivery in women who are breastfeeding with medically attended adverse infant infectious outcomes through 1 month and 6 months of life (exploratory)*.*

Study design, population and period: A retrospective observational matched cohort study utilizing automated data obtained through the VSD will be performed. Mother-infant dyads of pregnant women 16-49 years of age and their infants will be identified from the source cohort with infant dates of birth from December 15, 2020 to August 4, 2021 who breastfed. Rates of adverse infectious outcomes of infants born to women exposed to one or more COVID-19 vaccine doses while breastfeeding will be compared to rates for these outcomes in women with pregnancies during the same time period who did not receive a COVID-19 vaccine during pregnancy or while breastfeeding (Figure 1).

Inclusion criteria:

- Mother-infant dyads including women aged 16-49 years who had a completed singleton live birth pregnancy during the study period, linked to an infant record
- Women with at least one postnatal care visit or infants with at least one well child visit
- Mother-infant dyads who were identified to be breastfeeding during the study period (breastfeeding status will be assessed by postnatal care or infant well child encounter using ICD-10, DXID codes or other internal codes for breastfeeding)
- Infants enrolled in the first 3 months of life and at least 3 months of enrollment in the first 6 months of life who have at least one well child visit.

Exclusion criteria:

- Pregnancies with the following oucomes: non-live birth and multiple gestation
- Pregnancies in which the mother received a COVID-19 vaccine during pregnancy
- Infants without any well child encounters during the study period, suggesting they may be receiving care outside of the health system.

Matching: In order to form matched pairs, mother-infant dyads will be matched (1:2) on maternal age, VSD site, and infant date of birth (+/- 7 days) using an optimal matching algorithm. An index date will be assigned in order to match vaccinated and unvaccinated dyads. The index date will be the vaccination date for the exposed dyad.

Exposure definition: The primary exposure of interest is receipt of one or more doses of COVID-19 vaccination given during the postpartum period to breastfeeding women. COVID-19 vaccination will be identified using vaccine administered codes (Table 1). COVID-19 vaccine exposed will be defined as receiving one or more COVID-19 vaccines during the postpartum period while breastfeeding. COVID-19 vaccine unexposed will be defined as lack of receipt of COVID-19 vaccination in the postpartum period while breastfeeding and lack of COVID-19 vaccination given during pregnancy. COVID-19 vaccine exposed and COVID-19 vaccine unexposed will be compared for analysis.

Chart review: A sample manual chart review of DXID, ICD-10 codes, such as Z39.1, and other internal codes for breastfeeding status to ensure that automated data codes represent true incident diagnosis will be completed. Charts for infants who are and are not receiving breastmilk according to automated codes will be reviewed to ensure a representative sample and accuracy of these codes. Approximately 100 chart reviews will be completed divided between participating VSD sites with available breastfeeding data, for approximately 20 chart reviews per site (Form 1).

Identification of pregnant women: We will use the VSD DPA to identify women who were pregnant and had a live birth pregnancy outcome infant date of birth between December 15, 2020 to August 4, 2021. Mother-infant dyads will be identified, and only live births will be included. Of the women with live birth singleton pregnancies and infants born within the study period, data on breastfeeding status will be extracted.

Outcome measures: ICD-10 codes as well as laboratory records will be used to identify outcome parameters (Table 2). Outcomes of interest include first and total infant encounters for infections including inpatient, emergency department and outpatient respiratory infections (COVID-19 infection, influenza, respiratory syncytial virus (RSV), bacterial or viral pneumonia, bronchiolitis, other upper or lower respiratory illness), bloodstream infections (bacteremia, bacterial sepsis, or culture-negative sepsis), and meningitis (bacterial meningitis, viral meningitis, and culture-negative meningitis). We will plan to assess the number of independent events as well as the total number of encounters to examine health care utilization in the same child. Additionally, any outcomes in the first month of life will be limited to inpatient and ED encounters to distinguish true infections. Outpatient respiratory outcomes will be treated as a secondary analysis, and data will be examined for those from 30 days to 6 months of life to determine feasibility of analysis. Outcomes will be analyzed separately and as a composite to assess for association. COVID-19 vaccination must precede the infectious outcome.

Analysis: Descriptive statistics will be used to describe variables of interest including demographics of pregnant women, information surrounding maternal COVID-19 vaccination while breastfeeding, levels of circulating COVID-19, influenza, and RSV using state- or county- level percentages of positive test results[30], maternal pre-existing medical conditions, prenatal complications, gestational age, birthweight, and infant medical conditions and routine childhood vaccines received (Table 6). Descriptive statistics will be reported in univariate analyses using means and standard deviations or medians and interquartile ranges for continuous data and counts and percentage for categorical data. Rates of infant infectious outcomes will be computed (Table 4). Finally, association of receipt of COVID-19 vaccine and events in the intervals, 0-30 days of life and 1-6 months of life for each of the infectious outcomes will be reported as incidence rate ratios 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 and the introduction of inverse probability weights. We will use the number of follow up days to account for follow up truncation due to receipt

of COVID-19 vaccine during the first month of life. The first follow up period will be truncated at 30 days of life and the second at 6 months of life or end of study period (Table 4). An offset will be used to account for differences in follow up time.

Characteristic	Maternal COVID-19 vaccine exposed		Maternal COVID-19 vaccine unexposed	
	n	% (95%CI)	n	% (95% CI)
Demographics				
Age (years), median (SD)				
Race				
White Black Asian Hawaiian or other Pacific Islander Native American or Aleutian				
High level of COVID-19 circulation				
High level of influenza circulation				
High level of RSV circulation				
Pre-existing health conditions				
Asthma Lung disease Heart disease Immunodeficiency Smoker Other condition				
Delivery data				
Gestational age Birth weight				
Infant medical conditions				
Lung disease Heart disease Immunodeficiency Birth defect Other condition				
Infant vaccinations				
Hepatitis B				
Rotavirus				
Diptheria, tetanus, & acellular pertussis				
Haemophilus influenzae type b				
Pneumococcal conjugate				
Inactivated poliovirus				
Maternal COVID-19 vaccination				
COVID-19 vaccination while breastfeeding			N/A	N/A
Partial vaccination (1/2 doses)			N/A	N/A
Complete vaccination (1/1 or 2/2 doses)			N/A	N/A
Pfizer-BioNTech vaccine			N/A	N/A
Moderna mRNA-1273 vaccine			N/A	N/A
Janssen/Johnson & Johnson vaccine			N/A	N/A

Table 6: Characteristics of COVID-19 vaccination exposure in postpartum women exposed and unexposed to COVID-19 vaccination while breastfeeding across Vaccine Safety Datalink sites

Confounding adjustment: To identify potential confounders, characteristics of women who are exposed and unexposed to COVID-19 vaccine while breastfeeding will be tabulated, and the standardized differences will be compared. The standardized differences for each covariate will be calculated by dividing the mean difference between the two groups by the estimate of the common standard deviation. The propensity score to receive a

COVID-19 vaccine while breastfeeding will be calculated based on known characteristics using logistic regression and potential confounding variables including pregnancy start date, maternal age, maternal race/ethnicity, other maternal vaccines received during pregnancy or postpartum, maternal comorbidities, SARS-CoV-2 circulation and VSD site.

Inverse probability weighting: Stabilized inverse probability weighting will be generated. The ability of the stabilized weights to reduce potential confounding will be determined by applying the weights to the cohort and estimating the standardized difference for each covariate. Standardized differences will be evaluated before and after applying stabilized weights for observed confounders. Assuming positivity for the study, it will be ensured that propensity scores are between zero and one, there is no clustering around zero or one and distribution of the propensity on the comparator group will be evaluated. If the positivity assumption does not hold, sensitivity analysis will be performed. Additional assumptions will need to be made using this approach, including exchangability and consistency. The unvaccinated cohort will represent the unexposed status of the fully vaccinated cohort, assuming no unmeasured confounders. We will count the exposure as having received one or more vaccines during the study period. Therefore, partial and full vaccination status will both be considered exposure.

Power analysis: Data from the VSD indicate approximately 50,000 participants in the VSD cohort of pregnant women in our study period with a modest estimate that at least 6,000 likely received one or more doses of COVID-19 vaccination in the postpartum period while breastfeeding. A 30% attrition rate was applied as a modest estimate of availability of infant data. The rate for events in the first 6 months of life was set at 25 per 100 for respiratory infections, 10 per 10,000 for bloodstream infections and 1 per 10,000 for meningitis. Minimum detectable differences are presented below for risk ratios assuming alpha of 0.05 and power of 80% (Table 7). Estimates were computed using Power Analysis and Sample Size (PASS) 2019 software.

	Sample size Exposed: unexposed	1 per 10,000	10 per 10,000	25 per 100
20% coverage	6000:12000	13.5	3.1	1.09
20% coverage 30% attrition	4200:8400	20.2	3.9	1.11

Table 7: Minimum detectable risk ratios for infant outcomes among infants born to women exposed versus unexposed to COVID-19 vaccination while breastfeeding. PASS 2019. NCSS, LLC. Kaysville, Utah, USA, ncss.com/software/pass.

Limitations: As a retrospective cohort study, data will be limited to that attainable through the VSD. Given the complexity of COVID-19 vaccination rollout, it is possible that some vaccines may be missed, however all VSD sites routinely obtain vaccination data from state and regional immunization information systems. Further, while we plan to confirm our approach to gathering breastfeeding data using chart confirmation of a subset of cases to ensure DXID and ICD-10 codes as well as other internal breastfeeding codes are representative of breastfeeding status, it would not be feasible to confirm every case. Inherent differences in women who chose to receive vaccination while pregnant or breastfeeding may exist which we may not be able to account for in our study. This study will also will have limited power to assess rare events. Certain factors such as number of children in the home and daycare status of the child, which is not routinely available in VSD data, may also impact our outcomes of interest. We are only capturing medically attended events, although our outcomes are generally ones that involve outpatient or inpatient encounters. Our study period does not include booster dose administration, so we will be unable to study association of booster doses and our outcomes.

Data management plan:

Data files: When possible, we will use the same cohort and data VSD study #1351 to reduce the burden of gather additional overlapping data on sites. This initial cohort consists of pregnancies in the PREGEPSD files from the current DDF at date of extraction, and cycle 2020. Data files included are: CONSTANT, ENROLL, VACCINE, INPT, OUTPT, PROCDRE, PREGEPSD for DDF files and cycle files; and PREG, GCDD for cycle files (Table 8). In addition, data will be pulled from VSD data to create ancillary files to obtain breastfeeding data and relevant laboratory data for infant outcomes. The cohorts used in this study may be used for future methodology development studies.

VSD file	Content
CONSTANT	Basic demographics of population, VSD site
ENROLL	MCO membership start and stop dates to identify pregnant women with constant enrollment 3 months prior to pregnancy start to end of observation period
VACCINE	Determine pregnancy, postpartum 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 relevant to infant hospitalizations, outpatient and ED visits
PREGEPSD	Pregnancy episode file to identify eligible pregnancies
GCDD	Geocode data when available
LABORATROY.X	Laboratory results related to infant infection outcomes (SARS-CoV-2 PCR or Ag, influenza A or B PCR or Ag, RSV PCR or Ag, positive blood culture, positive CSF culture and CSF PCR panel)
ANCILLARY.X	Breastfeeding data

Table 8: Data management and information to obtained for each VSD data file

Data management: The CDC VSD team will be primarily responsible for data management activities including data extraction, study documentation and archival. All electronic documents, data sets, and files relevant to the project will be stored on network folders or CDC computers with restricted access. Collaborators at VSD sites will abstract data from medical records and 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. CDC will write all relevant SAS code and will share it with participating sites for approval prior to data extraction.

Plan for human subjects:

Risks and benefits: The privacy and confidentiality of study subjects will be strictly protected according to VSD standard procedures. The VSD project is covered by an Assurance of Confidentiality. CDC has obtained an Assurance of Confidentiality under Section 308(d) of the Public Health Service Act (42 U.S.C. 242 m(d)), which provides that this data can only be used for the purpose for which is obtained, unless such institution or individual has consented to that disclosure. Pursuant to this, all CDC and VSD site project personnel have signed a nondisclosure statement. There will be minimal risks to patient privacy and confidentiality. Only VSD Study IDs will be used as identification (linkage to personal information is stored at VSD sites and not at CDC), and all coded information will be stored on secure CDC computers. The research described will be beneficial as new knowledge regarding the safety of maternal COVID-19 vaccines is a priority area for the Immunization Safety Office and for vaccine policy. There are minimal risks to privacy based on the lack of identifiable information that will be available to CDC investigators, which are reasonable in relation to the importance of the knowledge to be gained.

Equitable selection of subjects: Subject selection is based on clinical parameters and the availability of data to assess the research objectives. No segment of the population is unfairly excluded from the benefits of this research, and no segment of the population bears an undue burden of research risks.

Informed consent: The surveillance project does not involve intervention or interaction with human subjects. A waiver of consent is being requested under 45 CFR 46.116(d) as the research is no more than a minimal risk as described above, the waiver will not adversely affect subjects' rights of welfare, and the research could not be practicably be conducted without the waiver.

Impact and future direction: This preliminary data will help fill gaps in safety data on infectious outcomes in infants of pregnant and breastfeeding women who receive COVID-19 vaccination and may help inform policy and regulatory decisions surrounding COVID-19 vaccination in pregnancy and the postpartum period. The proposed infant safety data is paramount, given the historic speed, rollout, and uptake of COVID-19 vaccination in pregnant and lactating women. Further, this example may set the stage in allowing for earlier inclusion of pregnant and breastfeeding women in vaccine trials to evaluate efficacy and safety of maternal immunizations. Improving outcomes for pregnant women and their infants from COVID-19 is a priority with global reach, which can hopefully be done safely though maternal immunization. The impact of the proposed research goes even further in informing future research on the safety of forthcoming maternal immunizations.

Projected timeline:

Task	Action	Timeline
1	Review concept on VSD pregnancy call	September 2021
2	Review protocol on project call	November 2021
3	Submit revised protocol to CDC	December 2021
4	Final protocol approved	February 2022
5	Obtain IRB and DUA approval, as needed by sites	March 2022
6	Create analytic datasets	April 2022
7	Conduct analyses and chart reviews	May-July 2022
8	Manuscript preparation and submission	September 2022

Table 9: Anticpated timeline for completion of this study to evaluate infant infections following maternal COVID-19 vaccination in pregnancy or while lactating

Resources:

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Appendix:

Form 1: Chart review abstraction form to be used to confirm automated breastfeeding data are consistent with chart confirmed breastfeeding data

VSD #TBD – INFANT INFECTIONS AND MATERNAL COVID-19 VACCINATION
BREASTFEEDING QUICK REVIEW 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)

Breastfeeding Status: 1☐ Currently breastfeeding 2☐ Currently not breastfeeding

Breastfeeding Information Source: 1☐ DXID code 2☐ ICD-10 code 9☐ Other breastfeeding code

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

ABSTRACTOR INFORMATION

Abstractor Initials: _____

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

BREASTFEEDING DIAGNOSIS

1. Did the mother or infant have an encounter within ±1 day of breastfeeding diagnosis date?
   1☐ Yes
   0☐ No → STOP abstraction
   9☐ Unknown → STOP abstraction

2. Was the mother described to be breastfeeding (if a postpartum visit) or infant described to be receiving breastmilk (if a well child visit) during the encounter?
   1☐ Yes
   0☐ No → STOP abstraction
   9☐ Unknown → STOP abstraction

3. Is the amount of breastmilk versus formula being fed to the infant described?
   1☐ Yes → move to question 4
   0☐ No → skip question 4
   9☐ Unknown → skip question 4

4. What amount of breastmilk is the infant receiving?
   1☐ Full breastmilk/No formula
   2☐ Partial breastmilk/Partial formula
   9☐ Unknown

ABSTRACTION COMMENTS

Comments:

ADJUDICATION

Adjudicator Initials: _____

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

Breastfeeding from chart review consistent with breastfeeding from automated data?

1☐ Yes
0☐ No
9☐ Unknown

Comments: