NOTE: The following protocol was approved by CDC on 9/28/2021. It is being made available for the public's and researchers' awareness. In summary, the aim of the project described in the protocol is to evaluate the safety of SARS-CoV-2 vaccines in an underserved population from the OCHIN Network, which will complement Vaccine Safety Datalink monitoring activities related to SARS-CoV-2 vaccination.

Monitoring safety of SARS-CoV-2 vaccines in an expanded underserved population in the Vaccine Safety Datalink

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Background and Need

The Food and Drug Administration issued Emergency Use Authorizations (EUAs) for Pfizer-BioNTech and Moderna COVID-19 vaccines in December 2020, followed by an EUA for Janssen in February 2021.[1] Since that time, over 205 million people have received at least one dose of a COVID-19 vaccine in the United States; 174 million have been fully vaccinated (as of August 31, 2021).[2] Along with the recent FDA approval of the Pfizer-BioNtech COVID-19 vaccine ('Comirnaty')[3], recent recommendations have also expanded eligibility for an additional dose to those who are considered immune-compromised[4], and a booster dose recommendation for additional groups.[5]

The Vaccine Safety Datalink (VSD) is conducting safety monitoring of any COVID-19 vaccine that is approved or authorized for use in the United States. However, VSD sites' ability to monitor the safety of the vaccines rapidly and effectively is dependent on sites' access to vaccine and their ability to capture complete data on vaccination across the full population. With the Advisory Committee on Immunization Practices' (ACIP) emphasis on the importance of equity in considering vaccine distribution, and efforts to improve vaccine uptake, there is much attention on understanding the uptake and safety of COVID-19 vaccines among commonly underserved communities (e.g., Medicaid recipients and minority populations).

It is estimated that the VSD includes about 1.21 million Medicaid members, representing 1.7% of the U.S. Medicaid population.[6] A prior report, published by the Institute of Medicine, has called on the VSD to increase the socioeconomic diversity of its population to improve generalizability of vaccine safety assessments and broadening the VSD-included population to include individuals from more diverse backgrounds is of great importance to complement VSD's monitoring activities currently being planned for COVID-19 vaccine safety.

The OCHIN network, comprised of over 600 Community Health Center (CHC) clinics across the United States, serves a population who represent underserved communities. Partnering with OCHIN to evaluate the uptake and subsequent safety of SARS-CoV-2 vaccines among a diverse population would be an opportunity to fill an important gap in both clinical trials and post-licensure monitoring of vaccine safety. The OCHIN network has been a rich resource for public health research and, most recently, has been used to evaluate the impact of COVID-19 on access to preventive care services within the OCHIN network.[7] Building a partnership with OCHIN to incorporate data on individuals vaccinated with a SARS-CoV-2

vaccine within this network would expand our understanding of vaccination uptake to a population that is under-represented in existing vaccine safety research.

Project Objective

To meet the stated objectives, KPNW will subcontract with OCHIN, a multistate Health Center-Controlled Network. OCHIN clinics include a large socioeconomically vulnerable population to complement VSD monitoring activities related to SARS-CoV-2 vaccination and to combine data where appropriate.

Using data from the OCHIN network, KPNW will partner with OCHIN to accomplish aims in a phased approach. Phase 1 will begin in February 2021 and include study objectives related to assessing SARS-CoV-2 vaccination uptake and coverage, overall and in subpopulations. Phase 2 is scheduled to begin in August 2021 and include study objectives related to assessment of safety outcomes following SARS-CoV-2 vaccination and changes in healthcare utilization during the pandemic.

Phase 1

1) Build VSD datasets.
    a. CONSTANT, ENROLL, OUTPT, VACCINE, PROCDRE, PREG EPISODE, FAMID, EDD, LMP (Appendix)

2) Conduct assessments of data quality, completeness, and timeliness across OCHIN-participating clinics.
    a. OCHIN to complete section on how to assess data quality by site and state, and across all sites related to:
        i. Population demographics
        ii. Empanelment
        iii. Vaccine, including identifying IIS data
        iv. COVID-19 risk factors
        v. Pregnancy data (prenatal encounters, pregnancy episodes, pregnancy outcomes, high-risk conditions)
        vi. Ongoing DQ activities (responsive to CDC's DQ process)

3) Estimate SARS-CoV-2 vaccination *uptake*, among individuals accessing OCHIN clinics in prior 18 or 24 months, any time since January 1, 2018.
    a. Assess weekly and cumulative vaccine uptake
    b. Report (weekly) uptake by clinic and state, and stratify states by age group, race/ethnicity, insurance status, income as a percentage of federal poverty level (FPL), SARS-CoV-2 vaccine product and dose number, history of COVID-19 disease, and COVID-19 risk factors

4) Estimate SARS-CoV-2 vaccination *coverage*, among individuals accessing OCHIN clinics in prior 18 or 24 months (any time from January 1, 2018 through December 31, 2023).
    a. Assess weekly and cumulative vaccine uptake
    b. Report (weekly) uptake by clinic and state, and stratify states by age group, race/ethnicity, insurance status, FPL, SARS-CoV-2 vaccine product and dose number, history of COVID-19 diseaseand COVID-19 risk factors
    c. Produce semiannual and annual summary coverage reports

d. Describe concomitant receipt of SARS-CoV-2 and flu and any other combinations of vaccines

5) Estimate SARS-CoV-2 vaccination *uptake during pregnancy* among individuals 12-55 years of age, with pregnancy any time since December 14, 2020 (the first date of vaccine availability).
    a. Assess weekly and cumulative vaccine uptake among pregnant individuals
    b. Report (weekly) uptake by age group, race/ethnicity, insurance status, FPL, SARS-CoV-2 vaccine product and dose number, history of COVID-19 disease, and COVID-19 risk factors
    c. Produce crude weekly uptake reports
    d. Describe concomitant receipt of SARS-CoV-2 and flu and any other combinations of vaccines

6) Estimate SARS-CoV-2 *vaccination coverage among individuals 12-55 years of age before and during pregnancy*, with pregnancy any time from December 14, 2020 until December 31, 2023.
    a. Report (weekly) coverage by OCHIN clinic, age group, race/ethnicity, insurance status, FPL, trimester of vaccination, maternal comorbidities, history of COVID-19 disease, and COVID-19 risk factors
    b. Report one- and two-dose coverage, and describe the time from first to second dose
    c. Report product-specific coverage
    d. Produce semiannual and annual summary coverage reports
    e. Describe concomitant receipt of SARS-CoV-2 and flu and any other combinations of vaccines

Phase 2

7) Conduct assessments of data quality across OCHIN-participating clinics.
    a. OCHIN to complete section on how to assess DQ according to clinic, and state related to:
        i. Adverse event outcomes following SARS-CoV-2 vaccination
            1. Outcomes from DQ process will determine which AE outcomes can be included in Aim 8
        ii. Healthcare utilization during the pandemic period

8) Descriptively summarize SARS-CoV-2 vaccine associated adverse events, as identified in outpatient and specialty care settings.
    a. Generate report with counts and descriptive summaries of pre-specified outcomes following SARS-CoV-2 vaccines according to the VSD Rapid Cycle Analysis (RCA) of SARS-CoV-2 protocol, focusing only on outpatient and specialty care settings

9) Assess changes in health care utilization during the pandemic period.
    a. Outpatient and Telehealth utilization before and after the start of the pandemic for each contributing clinic and state and across all clinics
    b. Combined in-person utilization (OP) and overall utilization (OP, TH) before and after the start of the pandemic for each contributing clinic and across all clinics

Methods

Phase 1

Aim 1- Building VSD Datasets

OCHIN will use VSD data dictionaries to develop datasets for use in Phase 1 objectives (Aims 1-6)

CONSTANT, ENROLL, OUTPT, VACCINE, PROCDRE, PREG EPISODE, FAMID, EDD, LMP (Appendix 1)

Aims 3 and 4 require: CONSTANT, ENROLL, OUTPT, VACCINE, PROCDRE

Aims 5 and 6 require: CONSTANT, ENROLL, OUTPT, VACCINE, PROCDRE, PREG EPISODE, EDD, LMP, FAMID

Aim 2- Data Quality

Population:

The first task related to data quality will involve examining changes in empanelment trends over time, and looking at how different empanelment definitions impact population retention. This will involve looking at population retention using empanelment approaches for an 18-month and 24-month period and determining which definition is optimal for use, going forward. Depending on the outomces of the retention summary, further examination into population retention by select characteristics (such as age, race, ethnicity, FPL, or insurance status) may be warranted.

A similar process, including individuals with a current pregnancy episode, will be developed with the same demographic and risk factor details. Additional DQ processes will be developed as decisions are made around feasibility and use of the dynamic prganncy algorithm vs. OCHIN's pregnancy algorithm.

Vaccination data:

We will identify all SARS-CoV-2 vaccines received by the population from the OCHIN VACCINE file, including vaccine product/manufacturer, date of administration, and lot number. We will detail, where possible, data that was documented through an IIS exchange vs. data from vaccines administered at an OCHIN facility (external vs. internal data). We will look at data by facility, state, and across OCHIN, to identify issues around data capture and variable missingness. To assess for completeness and timeliness of vaccination data, we will look at SARS-CoV-2 vaccination administration patterns over time (weekly from 12/14/2020 to current date) and characterize vaccine reporting, as well as availability of IIS (external) data, by state.

Results from this data quality process will lead to decisions around which facilities to retain for assessments of SARS-CoV-2 vaccination in Aims 3 through 6.

Ongoing data quality checks will be conducted for all datasets, consistent with the data quality reports generated for all VSD sites by the CDC.

Aim 3- "Real-Time" SARS-CoV-2 Vaccine Uptake

Population:

To establish a cohort of individuals for inclusion in each weekly report, OCHIN will use the empanelment process, where any patient who has accessed care in the prior 18 or 24 months (decision pending DQ review) would be considered an active patient. This cohort would be established as the surveillance cohort for each week of assessment.

Vaccination data:

We will identify all SARS-CoV-2 vaccines received by the population from the OCHIN VACCINE file. This file contains data on vaccinations administered at each participating clinic, some of which also incorporate data from their state immunization information systems, which will increase the capture of vaccines received outside of the health plan. We will identify the vaccine product/manufacturer, the date of 1st dose, and the date of 2nd dose (when applicable).

Vaccination uptake:

We will calculate crude SARS-CoV-2 vaccination uptake by dividing the number of individuals vaccinated by the total number of individuals in each weekly surveillance cohort. We will generate weekly reports on Tuesdays, and we will keep a cumulative count of the number who had 1 dose and 2 doses of each specific vaccine product since December 14, 2020. Crude uptake rates will be calculated by age (2-5, 6-11, 12-15 , 16-17, 18-24, 25-34, 35-49, 50-55, 16-55, 18-49, and 18-55 years), race/ethnicity (Hispanic, Non-Hispanic white, Non-Hispanic black, Non-Hispanic other, unknown), insurance status (Medicaid, Medicare, Uninsured, Private), FPL, history of COVID-19 disease, and COVID-19 risk factor status (presence of a high risk condition in prior calendar year, no high risk condition in prior calendar year). We will also calculate clinic- and state- specific rates that will be used to assess data quality and consistency; these clinic-specific rates will only be reviewed by VSD study staff at KPNW and will not be shared outside of the project team.

Aim 4- SARS-CoV-2 Vaccine Coverage Estimates

Population:

We will identify surveillance cohorts for inclusion in a semi-annual report (January 1 through June 30) and January 1 through December 31 for an annual report.

Vaccination data:

We will identify all SARS-CoV-2 vaccines received using data from the OCHIN VACCINE file. This file contains data on vaccinations administered at each participating clinic. Many participating clinics also incorporate data from their state immunization information systems, which will increase the capture of vaccines received outside of the OCHIN facilities.

Vaccination coverage:

We will calculate SARS-CoV-2 vaccination coverage by dividing the number vaccinated by the total number of identified patients during the time period. Weekly, monthly, semiannual, and annual coverage rates will be calculated by age (2-5, 6-11, 12-15, 16-17, 18-24, 25-34, 35-49, 50-55, 16-55, 18-49, and 18-55 years), race/ethnicity (Hispanic, Non-Hispanic white, Non-Hispanic black, Non-Hispanic other, unknown), insurance status (Medicaid, Medicare, Uninsured, Private), FPL, history of COVID-19 disease, and risk factors for severe COVID-19 disease (Table 1). We will assess high risk conditions using several look back period as determined by the study team. We will describe product-specific coverage, completion of the two-dose series (when applicable), and the time between 1st and 2nd doses (when applicable). We will also describe vaccinations received concomitantly with SARS-CoV-2 vaccination.

Aim 5- "Real-Time" SARS-CoV-2 Vaccine Uptake Estimates, during pregnancy

Population:

To generate each weekly report, we will use the VSD DPA and/or OCHIN-specific algorithm to identify individuals 12-55 years of age who had a pregnancy episode at any time from December 14, 2020 through the last day of the prior MMWR surveillance week, with at least two pregnancy indicators during the episode. No further inclusion or exclusion criteria will be applied.

Because the length of the surveillance period spans multiple years, we will periodically reset the reporting period for weekly surveillance to account for individuals who have multiple pregnancy episodes. This will also allow us to adjust our estimates should vaccine recommendations, booster doses, or new SARS-CoV-2 vaccine products be added in the future.

Vaccination data:

We will identify all SARS-CoV-2 vaccines received by the individuals described above from the OCHIN VACCINE file. This file contains data on vaccinations administered at each OCHIN clinic; many participating clinics also incorporate data from their state immunization information systems, which will increase the capture of vaccines received outside of the health plan. We will identify the vaccine product/manufacturer, the date of 1st dose, and the date of 2nd dose (when applicable).

Vaccination uptake:

We will calculate crude SARS-CoV-2 vaccination uptake by dividing the number of pregnant individuals vaccinated by the total number of pregnant individuals identified each week. They may be vaccinated before, during, or after pregnancy. We will generate weekly reports on Tuesdays, and we will keep a cumulative count of the number of individuals who received at least one SARS-CoV-2 vaccination *during* pregnancy since December 14, 2020 as well as the number of individuals who received 1 dose and 2 doses of each specific vaccine product. Crude uptake rates will be calculated by age (2-5, 6-11, 12-15, 16-17, 18-24, 25-34, 35-49, 50-55, 16-55, 18-49, and 18-55 years), race/ethnicity (Hispanic, Non-Hispanic white, Non-Hispanic black, Non-Hispanic other, unknown), insurance status (Medicaid, Medicare, Uninsured, and Private), FPL, history of COVID-19 disease, and COVID-19 risk factor status (presence of a high risk condition in prior calendar year, no high risk condition in prior calendar year). We will also calculate clinic-specific rates that will be used to assess data quality and consistency; these clinic-specific rates will only be reviewed by VSD and OCHIN study staff and will not be shared outside of the project team.

Aim 6 – SARS-CoV-2 Vaccination Coverage Estimates, during pregnancy

Population:

We will use the DPA and/or an OCHIN-specific algorithm to identify individuals 12-55 years of age who had a pregnancy episode overlapping January 1 through June 30 for a semi-annual report, and January 1 through December 31 for an annual report. We will identify and exclude pregnancies that ended in spontaneous abortion (SAB) or therapeutic abortion (TAB), pregnancies that ended prior to 14 weeks' gestation, and pregnancies that had less than 14 weeks between the first and last indicator dates. If multiple pregnancy episodes per individual are identified, we will include the episode during which SARS-CoV-2 vaccination occurred. If the individual was not vaccinated, we will include the last pregnancy episode identified during the period.

Vaccination data:

We will identify all SARS-CoV-2 vaccines received by the individuals described above from the OCHIN VACCINE file. This file contains data on vaccinations administered at each participating clinic; many participating clinics also incorporate data from their state immunization information systems, which will increase the capture of vaccines received outside of the health plan. We will also identify all other vaccines received by the individuals described above so we can describe patterns of concomitant vaccination.

Vaccination coverage:

We will calculate SARS-CoV-2 vaccination coverage prior to or during pregnancy by dividing the number of pregnant individuals vaccinated by the total number of pregnant individuals identified during the time period. We will also describe vaccinations received on the outcome or delivery date, as well as vaccinations received in the post-partum period. Weekly, monthly, semiannual, and annual coverage rates will be calculated by age (2-5, 6-11, 12-15, 16-17, 18-24, 25-34, 35-49, 50-55, 16-55, 18-49, and 18-55 years), race/ethnicity (Hispanic, Non-Hispanic white, Non-Hispanic black, Non-Hispanic other, unknown), FPL, history of COVID-19 disease, maternal comorbidity (see Table 2 for relevant diagnosis codes), and number of face-to-face provider visits (none, 1-5 6-10, >10 visits) during the year. For pregnancies with gestational age data available, we will calculate vaccination coverage by trimester (1^{st}=0 weeks through 13 and 6/7 weeks, 2^{nd}=14 weeks through 27 and 6/7 weeks, 3^{rd}=28 weeks through pregnancy end date). We will also collect data on conditions other than pregnancy that increase the risk of COVID-19 severity (Table 1) and will calculate SARS-CoV-2 vaccination coverage by risk group. We will assess high risk conditions using several look back periods: one year prior to the start of the reporting period through the end of the reporting period, 6 months prior to the start of the reporting period through the end of the reporting period, and during the reporting period. We will describe product-specific coverage, completion of the two-dose series (when applicable), and the time between 1^{st} and 2^{nd} doses (when applicable). We will also describe vaccinations received concomitantly with SARS-CoV-2 vaccination. (Table 4)

Phase 2

Beginning in August 2021, OCHIN will work on study objectives related to assessment of safety outcomes following SARS-CoV-2 vaccination and changes in healthcare utilization during the pandemic.

Aim 7- Data Quality

Population:

We will conduct data quality around identification of pre-specified adverse events (Table 3) to establish background rates of adverse events. We will then look at these events for the empaneled population, following immunization (AEF). We will identify the clinical settings where adverse events are most commonly identified across OCHIN facilities. We will establish processes for conducting chart review, dependent on results from data quality checks.

Aim 8- Summarize vaccine-associated adverse events

Population:

We will provide counts and descriptive summaries of pre-specified outcomes following SARS-CoV-2 vaccines according to the VSD Rapid Cycle Analysis (RCA) of SARS-CoV-2 protocol, focusing only on outpatient and specialty care settings. Specified adverse event outcomes are dynamic and the code list will be updated throughout the study period. (Table 3)

Aim 9 - Assess changes in health care utilization

We will describe outpatient and telehealth utilization before and after the start of the pandemic for each contributing clinic and state and across all facilities. We will generate combined in-person utilization (OP) and overall utilization (OP, TH) before and after the start of the pandemic for each contributing facility, and across facilities.

Strengths and Limitations

In conjunction with the vaccination coverage data from other CDC-sponsored surveys, the findings from this VSD assessment should provide a more complete understanding of SARS-CoV-2 vaccination coverage among a population with broad racial and ethnic diversity and which individuals accessing care in Community Health Center and Federally Qualified Health Care settings; many of whom are on Medicaid or are uninsured. This study will identify vaccinations recorded in medical records, insurance claims, and linked state IIS, which will eliminate recall or social desirability biases inherent in studies relying on self-reported vaccination; however, vaccination status may be misclassified if individuals receive vaccinations outside of the participating delivery systems or state IIS catchment. Seven of the 19 states represented in OCHIN data have bidirectional data exchange with state IIS; the extent to which IIS data may be incorporated into EMR data at other clinics is not yet known. However, with the current reporting mandate for SARS-CoV-2 vaccines, it is expected that reporting for SARS-CoV-2 vaccine will be more routinely documented. Data on some of the co-variates of interest (especially race/ethnicity) may be incomplete in the OCHIN data files. We will rely only on diagnosis codes to identify conditions that increase the risk of complications or severe COVID-19 illness and will not collect data about immunosuppressive medication use, long-term aspirin use, or long-term care facility residence.

Finally, the ability of the DPA to detect pregnancy episodes using OCHIN data is not yet known. OCHIN's ability to produce the pregnancy-related datasets will be evaluated and will directly inform the utility of the DPA for the OCHIN population. If the OCHIN data does provide the needed data elements for the DPA, there is still the possibility of misclassification of pregnancy outcomes and dates, especially in the weekly reports when data from on-going pregnancy episodes may be incomplete.

Data Management

The OCHIN analyst will write the programs to develop the needed datasets, per the VSD data dictionary specifications. OCHIN will extract the needed data for the VSD files from the OCHIN Epic Clarity or the OCHIN Research Data Warehouse. These data sets will be retained at OCHIN and distributed SAS programs will then be shared with OCHIN and run the programs locally against the datasets. Output from these programs would then be shared with KPNW via the described secure data transfer website. KPNW would then use the output to generate reports for submission to the CDC.

The VSD team at KPNW will be primarily responsible for study documentation and archival. The archive will include updated study protocol, SAS programs, IRB documents, SAS output, and manuscripts. It will clearly identify and permanently save these files.

Site responsibilities

OCHIN is responsible for working with KPNW to cede to the KPNW IRB. OCHIN is responsible for creating a data use agreement. The OCHIN data managers will be asked to review the SAS program(s) prior to data extraction and submission to KPNW. OCHIN will participate in development of the study protocol and any related manuscripts.

IRB/DUA

This protocol will require human subjects review at CDC and IRB approval as required by KPNW and OCHIN. KPNW staff will help coordinate ceding to the KPNW IRB and data use agreements with OCHIN.

The study does not involve intervention or interaction with human subjects. We have approval to waive the requirement to obtain informed consent, parental permission, and assent for this study under 45 CFR 46.116(d). As a retrospective analysis of existing data, this activity presents minimal risk to subjects, and use of patient data for this purpose will not adversely affect subjects' rights or welfare. Because of the retrospective nature of this study, along with the volume of patients, it will be impracticable to contact patients to obtain consent.

Vulnerable Populations

Children are included in OCHIN datasets.

Pregnant individuals are included in OCHIN datasets. Given the retrospective nature of most VSD sub-studies, some participants will no longer be pregnant at the time of analysis, though the electronic data may cover a period during pregnancy.

Prisoners and correctional facilities are not included in OCHIN datasets.

Privacy and Confidentiality Provisions

The privacy and confidentiality of all 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 date can only be used for the purpose for which it is obtained, unless such institution or individual has consented to that disclosure. Pursuant to this, all CDC, OCHIN, and KPNW project personnel have signed a nondisclosure statement. Only VSD Study IDs will be used as identification (linkage to personal information is stored at VSD sites and not at the CDC) and all coded information will be stored on secure KPNW computers. This study will utilize a limited data set containing individual level records of protected health information (PHI). The personal identifiers to be included are elements of dates that include date of birth and date of health care visits. Information associated with each health care visit date will include the type of visit (inpatient or outpatient) and the medical diagnoses recorded for the visit. There will be minimal risks to patient privacy and confidentiality. A HIPAA waiver has been granted as this study will only require a limited dataset of protected health information.

References

1. https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/covid-19-vaccines

2. https://covid.cdc.gov/covid-data-tracker/#vaccinations_vacc-total-admin-rate-total

3. https://www.fda.gov/news-events/press-announcements/fda-approves-first-covid-19-vaccine

4. https://www.cdc.gov/coronavirus/2019-ncov/vaccines/recommendations/immuno.html

5. https://www.cdc.gov/coronavirus/2019-ncov/vaccines/booster-shot.html

6. Sukumaran L, McCarthy NL, Li R, et al. Demographic characteristics of members of the Vaccine Safety Datalink (VSD): A comparison with the United States population. *Vaccine.* 2015;33(36):4446-4450.

7. DeVoe JE, Likumahuwa-Ackman SM, Angier HE, et al. A Practice-Based Research Network (PBRN) Roadmap for Evaluating COVID-19 in Community Health Centers: A Report From the OCHIN PBRN. *J Am Board Fam Med.* 2020;33(5):774-778.

Table 1. Populations at Higher Risk for Severe COVID-19 Illness Due to Comorbid Illness (https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/index.html) (current as of 7/22/21)

Asthma (moderate-to-severe)
Cancer
Heart conditions, such as heart failure, coronary artery disease, or cardiomyopathies
Cystic fibrosis
Chronic kidney disease
COPD
Cerebrovascular disease
Neurologic conditions including dementia
Type 1 diabetes mellitus
Type 2 diabetes mellitus
Down syndrome
Pulmonary fibrosis
Hypertension with and w/o chronic complications
Immunocompromised state from blood or bone marrow transplant, immune deficiencies, HIV, use of corticosteroids, or use of other immune weakening medicines**
Immunocompromised state from solid organ transplant
Liver disease
Obesity and severe obesity*
Overweight*
Sickle cell disease
Thalassemia
Substance use/abuse

*assessed with diagnosis codes only
**immunosuppressive medication use will not be assessed

Table 2. Pregnancy complication and comorbidity list, adapted from prior VSD protocols

ICD-9	ICD-10	Label	Timing for events
1A. Complications of pregnancy			
642.xx	O11.x, O11.xx, O11.xxx	Hypertension complicating pregnancy	LMP to delivery
643.xx	O21.x	Excessive vomiting during pregnancy	LMP to delivery
648.0x, 648.8x	O24.4x, O24.xx, O24.xxx	Diabetes during pregnancy	LMP to delivery
648.3x	O99.31, O99.31x, O99.32, O99.32x	Alcohol or Drug dependence during pregnancy	LMP to delivery
649.0x	O99.33, O99.33x	Maternal smoking	LMP to delivery
649.1x, 278.0x	O99.21, O99.21x, E66.0, E66.01, E66.09	Obesity in pregnancy	LMP to delivery
1B. Pre-existing medical conditions			
282.4, 282.6, 284, 286.9	D57.0, D57.0x, D57.1, D57.2, D57.2x, D57.2xx, D57.4, D57.4x, D57.4xx, D57.8, D57.8x, D57.8xx, D60, D60.x, D61.x, D61.xx, D68.6, D68.6x	anemia (excluding iron deficiency) and hypercoagulability (includes antiphospholipid antibody syndrome)	6 months prior to LMP – end of first trimester (12 weeks after LMP)
571.xx	K70-K74	Chronic liver disease and cirrhosis	6 months prior to LMP – end of first trimester (12 weeks after LMP)
250.xx and 251.x, 255.xx, 259.2	O24.0, O24.0x, O24.0xx, O24.1, O24.1x, O24.1xx, O24.2, O24.2x, O24.2xx, O24.3, O24.3x, O24.3xx, E10.x, E10.xx, E10.xxx	Diabetes	6 months prior to LMP – end of first trimester (12 weeks after LMP)
200.xx-208.xx	C81-C96	hematological cancer	6 months prior to LMP – end of first trimester (12 weeks after LMP)
401.x-405.x	O10.x, O10.xx, O10.xxx, I10-I16	Pre-existing hypertension	6 months prior to LMP – end of first trimester (12 weeks after LMP)

V42.x	Z94.0 – Z94.4	Organ transplant	6 months prior to LMP – end of first trimester (12 weeks after LMP)
140.xx-198.xx	O9A.11, O9A.11x, C00-C43, C45-C80	non-hematological cancer	6 months prior to LMP – end of first trimester (12 weeks after LMP)
580.xx-591.xx	N00.1 – N00.7, N01.x, N02.1 – N02.7, N03.1-N03.7, N04.1-N04.7	renal disease	6 months prior to LMP – end of first trimester (12 weeks after LMP)
340, 345.xx	G35, G40.x, G40.xx, G40.xxx	Neurologic (MS and epilepsy)	6 months prior to LMP – end of first trimester (12 weeks after LMP)
446.xx, 710.x, 714.0-714.4, 714.8, 714.89, 714.9	M30.x, M32.x, M32.xx, M05.x, M05.xx, M05.xxx	rheumatologic disease	6 months prior to LMP – end of first trimester (12 weeks after LMP)

Table 3. COVID-19 RCA Outcomes Code List (Draft, Jan 2021)

#	VSD Outcomes	Abbreviation	Risk Window (days)	Chart Review	Monitoring Only	Exclude if COVID-19 in the Prior X Days
1	Acute disseminated encephalomyelitis (settings = E, I)	ADEM	1-21, 1-42	Yes		
2	Acute myocardial infarction (settings = E, I)	AMI	1-21, 1-42			30 days
3	Acute respiratory distress syndrome (settings = E, I)	ARDS	1-21, 1-42		Yes	42 days
4	Anaphylaxis (settings = E, I)	ANAPH	0-1	Yes	Yes	
5	Appendicitis (settings = E, I)	APPND	1-21, 1-42			
6	Bell's Palsy (settings = E, I, O)	BP	1-21, 1-42			30 days
7	Convulsions / seizures (settings = E, I)	SZ	1-21, 1-42 (day 0 included for children)			30 days
8	Disseminated intravascular coagulation (settings = E, I)	DIC	1-21, 1-42			42 days
9	Encephalitis / myelitis / encephalomyelitis / encephalopathy (settings = E, I)	ENCEPH	1-21, 1-42			30 days
10	Guillain-Barré syndrome (settings = E, I)	GBS	1-21, 1-42	Yes		
11	Thrombotic thrombocytopenic purpura (TTP) (settings = E, I)	TTP	1-21, 1-42			30 days
12	Immune thrombocytopenia (settings = E, I, O)	ITP	1-21, 1-42			30 days
13	Kawasaki disease (settings = E, I)	KD	1-21, 1-42			
14	Multisystem Inflammatory Syndrome in Children & Adults (MIS-C, MIS-A) (settings = E, I)	MISC			Yes	
15	Myocarditis / pericarditis (settings = E, I)	MYOC	1-21, 1-42			30 days
16	Narcolepsy and cataplexy (settings = E, I, O)	NARC			Yes	
17	Stroke, hemorrhagic (settings = E, I)	HSTK	1-21, 1-42			30 days
18	Stroke, ischemic (settings = E, I)	ISTK	1-21, 1-42			30 days

19	Transverse myelitis (settings = E, I)	TM	1-21, 1-42	Yes		
20	Venous thromboembolism (settings = E, I, O)	VTE	1-21, 1-42			30 days
21	Pulmonary Embolism (settings = E, I)	PE	1-21, 1-42			30 days
	Notes: specific settings for code search is noted below (E = ED; I = Inpt; O = Outpt)					

Highlighted outcomes for inclusion in OCHIN data

Table 4. Timelines

	2021											2022												2023											
Task	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Jan	Feb	Mar	April	May	June	July	Aug	Sep	Oct	Nov	Dec
Create draft protocol																																			
Project kick-off meeting (CDC, KPNW, OCHIN staff)																																			
Submit IRB application (OCHIN and KPNW)																																			
Monthly reports to CDC (10th of each month)																																			
Team meetings (CDC, KPNW, OCHIN)																																			
Meeting minutes (w/in 7 days of mtg)																																			
Documentation of IRB approval and DUA																																			
Finalize protocol																																			
OCHIN builds datasets																																			
Conduct data quality, Aims 1 through 6																																			
Generate routine (weekly) COVID-19 reports																																			
Generate routine (weekly) COVID-19 reports (including concomitant vaccinations)																																			
Generate routine (weekly) COVID-19 reports (preg)																																			
Conduct data quality, Aims 7 through 8																																			
Develop code to descriptively summarize vaccine-associated AE																																			
Weekly reports of VAE																																			
Conduct chart review (for AE, as needed)																																			
Conduct data quality, Aim 9																																			
Descriptively summarize healthcare utilization																																			
Draft manuscript to CDC																																			
Final manuscript to CDC																																			