Rapid Cycle Analysis (RCA) to monitor the safety of COVID-19 vaccines in near real-time within the Vaccine Safety Datalink

VSD Project #1342

Version 1.4
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Principal Investigators: Nicola Klein, MD, PhD[1], James Donahue, DVM, PhD[2], Eric Weintraub, MPH[3]

Project Team: Laurie Aukes[1], Joan Bartlett[1], Ed Belongia[2], Berwick Chan[1], Frank DeStefano[3], Bruce Fireman[1], Kristin Goddard[1], Kayla Hanson[2], Burney Kieke[2], Catherine Lee[1], Ned Lewis[1], Dave McClure[2], Mike McNeil[3], Karen Nunley[1], Pat Ross[1], Erica Scotty[2], Tom Shimabukuro[3], Arnold Yee[1], Ousseny Zerbo[1]

VSD Co-Investigators: Jason Glanz[4], Simon Hambidge[5], Elyse Kharbanda[7], Bruno Lewin[6] Allison Naleway[8], Jen Nelson[9], Josh Williams[5], Stan Xu[6], Katherine Yih[10]

1. Kaiser Permanente Northern California, Vaccine Study Center, Oakland, CA
2. Marshfield Clinic Research Institute, Marshfield, WI
3. U.S. Centers for Disease Control and Prevention, Immunization Safety Office, Atlanta, GA
4. Kaiser Permanente Colorado, Denver, CO
5. Denver Health, Denver, CO
6. Kaiser Permanente Southern California, Los Angeles, CA
7. HealthPartners, Bloomington, MN
8. Kaiser Permanente Northwest, Portland, OR
9. Kaiser Permanente Washington, Seattle, WA
10. Harvard Pilgrim Health Care Institute, Boston, MA

Protocol Change History

Version	Date	Change
1.0	2.5.2021	N/A – Original protocol
1.1	3.3.2021	Minor edits to the anaphylaxis definition and addition of the Janssen COVID-19 vaccine.
1.2	5.10.2021	Methods updates to detail rationale for 42 day analyses. Outcome updates to reflect new outcomes of CVST and TTS.
1.3	11.12.2021	Updated investigator list, exposure definitions, outcomes and chart review specifications, and methods for historical comparator analysis.
1.4	2.1.2022	Updated myocarditis/pericarditis ICD codes, vaccine CVX codes, statistical signaling criteria for 5-11 year old primary series analyses and booster dose analyses, and chart review specifications.

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Glossary of Abbreviations

Abbreviation	Definition
ACIP	Advisory Committee on Immunization Practices
ADEM	Acute disseminated encephalomyelitis
AMI	Acute myocardial infarction
ARDS	Acute respiratory distress syndrome
BLA	Biologics License Application
CDC	Centers for Disease Control and Prevention
CMaxSPRT	Conditional maximized sequential probability ratio test
COVID-19	Coronavirus disease 2019
CVX	Vaccine administered code
DDF	Dynamic data files
DIC	Disseminated intravascular coagulation
DoD	Department of Defense
DUA	Data use agreement
ED	Emergency department
EUA	Emergency use authorization
FDA	Food and Drug Administration
GBS	Guillain-Barré syndrome
H0	Null hypothesis
HIPAA	Health Insurance Portability and Accountability Act
ICD-10	International Classification of Disease, 10th Revision
IIS	Immunization information systems
IRB	Institutional review board
ITP	Immune thrombocytopenia
KPNC	Kaiser Permanente Northern California
KD	Kawasaki disease
MaxSPRT	Maximized sequential probability ratio test
MCRI	Marshfield Clinic Research Institute
MIS-A	Multisystem inflammatory syndrome in adults
MIS-C	Multisystem inflammatory syndrome in children
mRNA	Messenger ribonucleic acid
PE	Pulmonary embolism
PHI	Protected Health Information
RCA	Rapid Cycle Analysis
RR	Relative risk
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
TM	Transverse myelitis
TTP	Thrombotic thrombocytopenic purpura
VA	Veterans Affairs
VAERS	Vaccine Adverse Event Reporting System
VSD	Vaccine Safety Datalink
VTE	Venous thromboembolism

PROTOCOL SYNOPSIS

Title: Rapid Cycle Analysis (RCA) activities in order to monitor the safety of COVID-19 vaccines in near real-time within the Vaccine Safety Datalink (VSD)	
Short Title: COVID-19 RCA	
Project Rationale	The cause of the COVID-19 pandemic, severe acute respiratory syndrome coronavirus 2, has infected millions of people in the U.S. and resulted in over 400,000 deaths. Vaccines to combat the disease have been developed at an unprecedented pace, but rapid and accurate assessment of the safety of these vaccines is essential.
Project Objectives	The primary objective is to conduct near-real time safety surveillance for COVID-19 vaccines in the VSD using both concurrent and historical comparator groups.
Project Design	The design is prospective with data updated and aggregated weekly.
Population Characteristics	The VSD is a collaboration between CDC and 9 healthcare organizations; the VSD population is approximately 12 million people, of which about 20% are children and 16% are 65 years or older.
Project Duration	Surveillance will begin in late 2020 and continue for a minimum of two years.
Outcomes	Pre-specified outcomes for surveillance have been identified and delineated following a collaborative effort between VSD and CDC investigators and other federal agencies.
Analysis	The cumulative incidence of pre-specified outcomes observed during post-vaccination risk intervals will be calculated and compared to an expected count. The effect measures are rate ratios or relative risks. The methods used to derive expected counts are specific to the comparator group used in the analysis.

Background and Need

In December 2019, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged in Wuhan, China. SARS-CoV-2 has led to the most devastating pandemic of the past century, with high morbidity and mortality (https://epidemicstats.com/coronavirus/), along with severe disruptions to economic and social life globally[1,2].

The clinical manifestations of coronavirus disease 2019 (COVID-19) range from asymptomatic to severe respiratory distress syndrome necessitating mechanical ventilation and support in an intensive care unit [3-9]. Although severe COVID-19 in young children is relatively uncommon, individuals who are young and apparently healthy have experienced serious disease [10]. In addition to respiratory system complications, there is increasing recognition that SARS-CoV-2 affects other organ systems, including the central nervous, cardiovascular, renal and endocrine systems[7,8,11-21]. In severe cases, COVID-19 triggers systemic inflammation which can lead to multi-organ failure and death[3,8,9,22-24].

The virus that causes COVID-19 is highly contagious and is transmitted by respiratory droplets, and possibly also by aerosol and contact with infected objects (fomites)[25,26]. Although quarantine, isolation, masking, disinfecting, and social distancing have, to some extent, mitigated the spread of SARS-CoV-2, the virus appears to reemerge when these measures are relaxed. On October 20, 2020 the FDA approved the antiviral drug remdesivir to treat COVID-19 and in November 2020 they issued emergency use authorization (EUA) for two antibody treatments.[27,28]. It is clear the optimal way to protect the population is with safe and effective vaccines.

Recently, two vaccines manufacturers (Moderna and Pfizer/BioNTech) submitted data to the U.S. Food and Drug Administration (FDA) as part of an application for EUA of their messenger ribonucleic acid (mRNA) vaccines; both vaccines showed more than 90% efficacy in phase III clinical trials[29,30]. On December 11, 2020, the FDA issued an EUA for the Pfizer/BioNTech mRNA vaccine in ages 16 years of age and above[31]. On December 18, 2020 the FDA issued an EUA for the Moderna mRNA vaccine in ages 18 years of age and above[32]. The Advisory Committee of Immunization Practices (ACIP) voted to recommend both vaccines for use, and also outlined a prioritization scheme for vaccine allocation[33]. Vaccination of priority groups, including healthcare workers, began in late December. Several additional vaccine candidates against SARS-CoV-2 are in phase III or other phases of development.

While phase III clinical trials are important for identifying potential outcomes associated with new vaccines, some outcomes may not be identified in pre-authorization trials due to limited statistical power, strict inclusion criteria, limited duration of participant follow-up, and participants who may not be similar to the population ultimately receiving the vaccine. Additionally, the currently authorized COVID-19 vaccines utilize mRNA, a novel platform that has not been used for other licensed vaccines[34]. Another two COVID-19 vaccines in late-stage clinical development utilize replication-deficient adenovirus vectors, another novel platform. Further, the unprecedented speed with which these vaccines are being developed also risks increasing vaccine hesitancy, especially if substantial segments of the public perceive that vaccine safety has not been rigorously evaluated. Thus, a rapid and accurate assessment of vaccine safety is needed to maintain public trust and to inform policy recommendations.

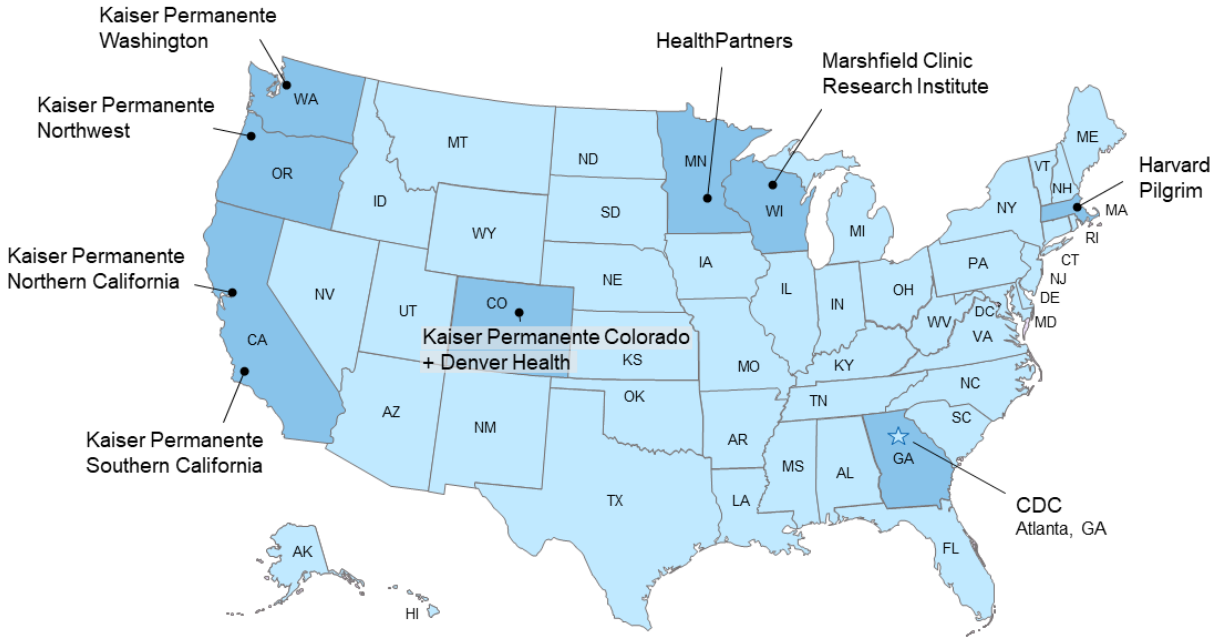
A priority of the Vaccine Safety Datalink (VSD) is to assess the safety of new vaccines and vaccines with new indications for use. The Rapid Cycle Analysis (RCA) methods in VSD were developed to allow population-based monitoring of potential outcomes associated with a vaccine in near real-time by examining outcome rates in recent vaccinees during risk intervals in relation to rates during comparison intervals. The associations produced by this approach are considered statistical signals that indicate the need for additional analytic investigation. RCA has been previously conducted in the VSD for various vaccines including MMRV[35], rotavirus[36], influenza[37], and HPV[38].

Project Objectives

Kaiser Permanente Northern California (KPNC) and Marshfield Clinic Research Institute (MCRI) research teams will work collaboratively with all Vaccine Safety Datalink sites and the Centers for Disease Control and Prevention (CDC) to complete the following project objectives:

1. To conduct near-real time safety surveillance for COVID-19 vaccines in the VSD:
    a. Using concurrent comparators (KPNC)
    b. Using historical comparators (MCRI)
2. To describe the uptake of COVID-19 vaccines over time in the VSD (KPNC)
3. To conduct long-term safety surveillance for COVID-19 vaccines in the VSD (MCRI)

Overall Surveillance Population



The VSD is a collaboration between the Immunization Safety Office at the CDC and nine integrated healthcare systems across the U.S. Healthcare systems contribute data on their members and patients, creating a large population of individuals for whom near complete immunization and healthcare records are available. The VSD population is approximately 12 million people, or 3.6% of the U.S. population. The VSD population includes individuals across the age spectrum; about 20% are children and 16% are 65 years or older.

The VSD RCA surveillance population will include all current VSD members. One of the COVID-19 vaccines has initially been authorized for persons 16 years of age and above[31]. Therefore, the initial surveillance population will consist of individuals who are ≥16 years old. As needed, this age range will be modified to stay consistent with the age groups receiving vaccination.

Exposure Classification

Exposure to COVID-19 vaccines will be identified by CVX codes in VSD vaccine data files. Multiple vaccine products for COVID-19 are available in the U.S. and currently available products require a primary vaccination series of either 1 or 2 doses (Table 1). We will ascertain vaccination date, product, manufacturer, and dose number for each exposure. Currently, some VSD sites have mechanisms in place to capture vaccinations that occur outside of their healthcare system while other sites are working to establish such procedures. Vaccinations identified from outside sources (e.g., retail pharmacies) may be initially coded at some VSD sites using other systems such as CPT but are then translated into CVX codes for use in VSD.

Table 1: Current CVX Codes for COVID-19 Vaccines[1]

Vaccine Product	CVX Code	CVX Code Description	Vaccination Schedule[2]
Moderna COVID-19 Vaccine (SPIKEVAX)	207	SARS-CoV-2 (COVID-19) vaccine, mRNA, spike protein, LNP, preservative free, 100 mcg or 50 mcg dose	2 doses separated by 28 days
Pfizer/BioNTech COVID-19 Vaccine (COMIRNATY)	208	SARS-CoV-2 (COVID-19) vaccine, mRNA, spike protein, LNP, preservative free, 30 mcg/0.3mL dose	2 doses separated by 21 days
Janssen COVID-19 Vaccine	212	SARS-COV-2 (COVID-19) vaccine, vector non-replicating, recombinant spike protein-Ad26, preservative free, 0.5 mL	1 dose
N/A	213	SARS-CoV-2 (COVID-19) vaccine, unspecified	N/A
Pfizer/BioNTech COVID-19 Vaccine	217	SARS-COV-2 (COVID-19) vaccine, mRNA, spike protein, LNP, preservative free, 30 mcg/0.3 mL dose, tris-sucrose formulation	2 doses separated by at least 21 days
Pfizer/BioNTech COVID-19 Vaccine	218	SARS-COV-2 (COVID-19) vaccine, mRNA, spike protein, LNP, preservative free, 10 mcg/0.2 mL dose, tris-sucrose formulation	2 doses separated by at least 21 days

[1]Additional vaccines will be included as they have CVX codes assigned.
[2] Current minimum interval for Dose 2 is 14 days post Dose 1. This may be shifted as appropriate for new vaccines.

All doses of COVID-19 vaccines will be extracted from the VSD vaccine data files to facilitate monitoring of doses beyond the primary series as appropriate. Planned gaps of 2 months following an initial dose of Janssen and 5 months following a primary series of Pfizer/BioNTech or Moderna vaccine will be implemented for all doses subsequent to the primary series.

Objective #1: Near Real-Time Safety Surveillance of COVID-19 Vaccines

Near real-time safety surveillance of COVID-19 vaccines will be conducted in the VSD using RCA methods. Surveillance will be conducted for pre-specified outcomes of interest, and several types of analyses will be conducted using different comparators. KPNC will lead analyses using concurrent comparators and MCRI will lead analyses using historical comparators.

Duration of Surveillance

Near real-time surveillance will begin in late December 2020 following availability of COVID-19 vaccines at VSD sites. When surveillance will end is uncertain at this time, but we currently plan to conduct surveillance for approximately 2 years.

Pre-Specified Outcomes

We identified a priority list of 21 outcomes, developed case ascertainment algorithms, and defined post-vaccination risk and comparison intervals (Table 2). This list was developed and refined in consultation with CDC, the VSD RCA working group, and in coordination with other federal agency stakeholders (i.e., Department of Defense [DoD], FDA, and Veterans Affairs [VA]). Case ascertainment criteria for all outcomes were reviewed for accuracy and completeness by relevant subject matter expert clinicians. As further results of phase III clinical trials become available or we become aware of additional potential vaccine safety concerns (e.g., from the Vaccine Adverse Event Reporting System [VAERS]), the outcome list will be updated as appropriate in consultation with investigators at CDC, FDA, and other federal partners. The sequential analytic approach is designed to be as flexible as possible to allow for the inclusion of new outcomes during the surveillance period. For example, cerebral venous sinus thrombosis (CVST) and thrombosis with thrombocytopenia syndrome (TTS) were added in May 2021 after postauthorization monitoring identified these as potential adverse events after Janssen vaccine.

Medically attended outcomes will be identified from International Classification of Disease, 10th Revision (ICD-10), diagnosis codes in VSD data files. For most outcomes, we will evaluate a primary risk interval of 1-21 days and a longer risk interval of 1-42 days. We will also monitor day 0 (day of vaccination) outcome events, but these will not be included in any planned comparative analyses. Diagnosis codes for most outcomes will be restricted to those assigned in the emergency department (ED) and inpatient settings only; outpatient codes will be included for some outcomes including immune thrombocytopenia (ITP), Bell's palsy, narcolepsy, and venous thromboembolism (VTE). To avoid double-counting events in the same risk interval, we will include only the first event that occurred during the risk interval. However, if different events occurred on the same date, all such events will be counted. Four outcomes will only be monitored – there will be no comparisons of observed-versus-expected events in the risk interval (with or without sequential testing) for acute respiratory distress syndrome (ARDS), anaphylaxis, narcolepsy, and multisystem inflammatory syndrome in adults and children (MIS-A and MIS-C). For MIS-A/MIS-C, ARDS, and narcolepsy we will extract all events up to 84 days post-

vaccination for monitoring purposes. Anaphylaxis will be monitored in the 0-1 days post vaccination. Where available, we will also use the internal diagnostic code, "anaphylaxis due to COVID-19 vaccine" (all settings, including outpatient), to supplement identification of potential cases of anaphylaxis.

Table 2: Outcomes of Interest

Outcomes for comparative analyses [1] [2] [3]	**ICD-10 code(s)**	**Setting[4]**	**Planned chart review[5]**	**Codes for lookback to adjust onset date (all settings)[6]**
Acute disseminated encephalomyelitis (ADEM)	G04.00, G04.02	E, I	Y	n/a
Acute myocardial infarction (AMI)	I21.*	E, I	N	n/a
Appendicitis	K35.*, K36, K37, K38.8	E, I	N	n/a
Bell's palsy	G51.0	E, I, O	N	n/a
Cerebral venous sinus thrombosis (CVST)	G08, I63.6, I67.6	E, I	Y	If in 7 days prior to case: R51.*, R53.1, R42.*, R41.82, R41.0, H53.9, H53.2, G93.2, H47.10, I82.C1, I60.9, I61.9, I62.9, I63.9
Convulsions / seizures	R56.0*, R56.9	E, I	N	n/a
Disseminated intravascular coagulation (DIC)	D65	E, I	N	n/a
Encephalitis / myelitis / encephalomyelitis / (not ADEM or TM)	G04.30, G04.32, G04.39, G04.8*, G04.9*, G05.*, G37.4	E, I	N	n/a
Guillain-Barré syndrome (GBS)	G61.0	E, I	Y	n/a
Immune thrombocytopenia (ITP)	D69.3	E, I, O	N	If in 1 year prior to case: low platelet count <100 K/µL
Kawasaki disease (KD)	M30.3	E, I	N	n/a
Myocarditis / pericarditis	B33.22, B33.23, I30.*, I31.9, I40.*, I51.4	E, I	Y (<40 years)	n/a
Pulmonary embolism (PE)	I26.*	E, I	N	n/a
Stroke, hemorrhagic	I60.*, I61.*, I62.*	E, I	N	If in 1 day prior to case: I63.9, R51.*, R47.*, R29.810, R53.1, R42.*, R41.82, R40.4, H53.13*, H53.9, G81.9*

Stroke, ischemic	G45.8, G45.9, I63.*	E, I	N	If in 1 day prior to case: Z92.82, R51.*, R47.*, R29.810, R53.1, R42.*, R41.82, R40.4, G81.9*, H53.9, H53.13*
Thrombosis with thrombocytopenia syndrome (TTS)	Requires platelet count of <150,000 and one of the following ICD-10 codes: G08, I63.6, I67.6, I74.0*, I74.1*, I74.3, I74.5, I74.8, I74.9, I81, I82.0, I82.890, K55.0*, N28.0	E, I	Y	n/a
Thrombotic thrombocytopenic purpura (TTP)	M31.1	E, I	N	n/a
Transverse myelitis (TM)	G37.3	E, I	Y	n/a
Venous thromboembolism (VTE)	I26.*, I82.210, I82.220, I82.290, I82.3, I82.4*, I82.60*, I82.62*, I82.A1*, I82.B1*, I82.C1*, I82.890, I82.90	E, I, O	N	If in 14 days prior to case: M79.65*, M79.66*, R22.4*
Outcomes for monitoring [1] [2] [3]	**ICD-10 code(s)**	**Setting[4]**	**Planned chart review**	**Monitoring period**
Acute respiratory distress syndrome (ARDS)	J80	E, I	N	0-84 days
Anaphylaxis	T78.2*, T80.52*, T88.6*	E, I	Y	0-1 days
Anaphylaxis secondary	Internal diagnostic code: "anaphylaxis due to COVID-19 vaccine"	E, I, O	Y	0-84 days
Multisystem inflammatory syndrome in children (MIS-C) / Multisystem inflammatory syndrome in adults (MIS-A)	M35.8 + U07.1 (new code effective 1-Jan-2021 is M35.81)	E, I	Y	0-84 days

Narcolepsy / cataplexy	G47.41*	E, I, O	N	0-84 days

[1] Primary risk interval of 1-21 days and a longer risk interval of 1-42 days.
[2] First in what period?" is first since October 1, 2015 (the start of ICD-10 coding) for all outcomes except for myocarditis/pericarditis which is first in 60 days, and anaphylaxis which is first in 7 days.
[3] A complete listing of exclusions can be found in Appendix 1.
[4] E=Emergency Department, I=Inpatient, O=Outpatient.
[5] Y=Yes, N=No
[6] n/a=not applicable

Methods and Analyses using Concurrent Comparators

Analytical Strategies

KPNC will tabulate the cumulative incidence of the targeted outcomes during pre-specified post-vaccination risk intervals. For each outcome, the cumulative number of events observed in the risk interval will be compared to the number expected. The number expected will be derived from the three types of comparators described below, the first of which will be primary when available:

(a) vaccinated concurrent comparators in a comparison interval after COVID-19 vaccination.
- On each day, outcome incidence in the vaccinees who are in their risk interval will be compared to outcome incidence in vaccinees who are concurrently—on the same calendar date—in their comparison interval.
- Analyses will be stratified in risk sets anchored to the calendar dates of outcome events.
- Analyses will be stratified by age group, sex, race/ethnicity, and VSD site, as well as by calendar date.

(b) unvaccinated concurrent comparators
- On each day, outcome incidence in vaccinees who are in their risk interval will be compared to outcome incidence in unvaccinated individuals who are concurrently—on the same calendar date—at risk.
- Analyses will be stratified in risk sets anchored to the calendar dates of outcome events.
- Analyses will be stratified by age group, sex, race/ethnicity, and VSD site, as well as by calendar date.

(c) self-controls in a comparison interval after COVID-19 vaccination.
- Among the vaccinees who had an outcome event in either the risk interval or the comparison interval, we compare outcome incidence in the risk interval with outcome incidence in the comparison interval.

During the initial days of safety surveillance when vaccinations have only just begun, no vaccinees will yet be in a comparison interval, and so comparator types (a) and (c) will not be available yet. Before (a) becomes available, we plan to use (b) for our primary comparators. When (a) is available, (b) and (c) will be used for supplementary analyses as discussed further in *Statistical Analyses* below.

An important advantage of (a) and (c) is that analyses are not confounded by time-stable co-morbidities, propensities to use health services, or demographics because the same vaccinees contribute person time to both the risk and the comparison intervals (detailed in Table 3 below).

An important advantage of (a) and (b) is that the follow-up time in the comparison interval occurs on the same calendar dates as the follow-up time in the risk interval. Careful control for each day-at-risk avoids bias that can arise from marked day-to-day variation—such as variation between weekdays and weekends—in vaccine delivery and admissions to emergency rooms and hospitals. Self-controls (c) are less well-adjusted for calendar time because in every stratum (or risk set) the outcome events in the comparison interval occur on later calendar dates than the outcome events in the risk interval. Unvaccinated concurrent comparators (b) are well-adjusted for calendar time but have the disadvantage that they can be biased by comorbidities and propensities that are associated with both the outcome and vaccination status.

Table 3. Advantages and Limitation of the Different Analytic Designs

Analytic Design	Advantages	Limitations
Primary		
(a) Vaccinated concurrent	- Not confounded by time-stable co-morbidities, propensities to use health services, or demographics - Follow-up in the comparison interval is on the same calendar dates as follow-up time in the risk interval - Avoids bias that can arise from day-to-day variation in health services - Reduces bias that can arise from data lags	- Transient difficulty finding appropriate comparators soon after a new risk group becomes eligible for vaccine
(b) Unvaccinated concurrent	- Well-adjusted for calendar time	- Bias from comorbidities, demographics and propensities that may be associated with both the outcome and vaccination status
Supplemental		
(c) Self-Control	- Not confounded by time-stable co-morbidities, propensities to use health services, or demographics as the same vaccinees are contributing person time to both the risk and the comparison intervals	- Bias from differences between risk and comparison intervals in calendar time - Analyses are less timely and can only include vaccinees for whom the comparison interval is complete, and the data have settled

Statistical Analysis

Poisson regression will be used to compare outcome incidence during risk intervals with incidence during comparison intervals. The log of the expected count of events in a risk or comparison interval in a stratum on a calendar day will be modelled as a function of whether the stratum's vaccinees are in a risk versus a comparison interval on that day. The analysis will be

conditioned on age-group sex, race-ethnicity, and VSD site, (which define the strata), as well as calendar day. The log person-days in each risk or comparison interval will be included in the regression model as the offset. This "offset" sets the expectation that if, for example, on Jan 20, 10% more vaccinees (in an age-sex-race-site stratum) are in their risk interval than in their comparison interval, then we expect—under the null—10% more outcome events in risk interval than in the comparison interval.

Rate ratios – estimating the ratio of outcome incidence in the risk interval divided by outcome incidence in the comparison interval – will be reported with 95% confidence intervals.

Separate analyses will be conducted for each type of COVID-19 vaccine used in the VSD population. There will also be combined analyses which include follow-up after either mRNA vaccine. For each 2-dose vaccine used in the VSD population, we will conduct separate analyses for each of three types of 21-day risk interval: the 21 days following Dose 1, the 21 days following Dose 2, and the days that are in the 21 days after either dose. For each of these risk intervals, the comparators will be vaccinees on days when they are more than 21 days from their most recent dose but less than 42 days from their most recent dose. Note that the days eligible for a Dose 1 comparison interval may be interrupted by a Dose 2 risk interval so as to include days before and after Dose 2. The Dose 2 comparison interval will only include days that are more than 21 days after Dose 2. Similarly, we will conduct separate analyses for each of these types of the longer 42-day risk interval.

Sequential analyses will be conducted as data are updated and analyzed weekly. For each outcome, the primary analysis each week will include a sequential test of the one-sided null hypothesis that the vaccine does not increase risk during the risk interval. The threshold for a signal – rejecting the null hypothesis – will be pre-specified by an alpha-spending plan designed to keep the overall chance of a Type I error below 0.05. Initially, the 2-sided the p-value required for a signal at a weekly analysis will be approximately 0.0096 (amounting to a one-sided p-value of 0.0048). If our alpha-spending plan keeps the threshold for a signal at this level for up to 2 years (104 weekly analyses) we keep the overall chance of a Type 1 error below 0.05.

For any outcome, weekly analyses will not begin sequential testing until at least two outcome events have been observed in the risk interval (due to concerns about the credibility of a signal that would be based on only one event in the risk interval). Thus, a weekly analysis with only a single outcome in the risk interval will be reported but will not be considered a "signal" regardless of its nominal level of statistical significance.

We also note that sequential testing will be done only in analyses with vaccinated concurrent comparators; consequently, sequential tests will have little power (or no power) until a non-trivial number of vaccinees have been observed in comparison intervals. For analyses of the longer 42-day risk interval, vaccinated concurrent comparators ordinarily do not start contributing follow-up until 63 days after a Pfizer Dose 1 or 70 days after a Moderna Dose 1. We will not begin sequential testing of hypotheses regarding the 42-day risk interval until June 1, 2021, by which time we expect sufficient follow-up in the 42-day comparison interval.

For a 2-dose vaccine, sequential tests of the 42-day risk interval will only pertain to the 42 days after Dose 2. Separate analyses of risk during the 42 days following Dose 1 of a 2-dose series would be problematic because 2-3 weeks of the 42-days after Dose 1 are also after Dose 2.

We will adjust the initial threshold required for a signal for an outcome added later in surveillance (e.g., CVST) so as to gradually align the "alpha spent" on the new outcome with the alpha spent on outcomes monitored since December 2020. For example, for CVST this will yield a threshold of approximately $p<0.01$ for a signal in the 1st three weekly analyses, and thereafter we will use the same 0.0048 threshold used for outcomes monitored since December 2020.

Sequential analyses of the safety of the primary series in children ages 5-11 years use a signaling threshold of 0.0061 to account for 1 year of weekly monitoring (rather than two years planned for the primary series administered to individuals aged 12 years and older).

We also plan to evaluate the safety of booster doses weekly for one year. The threshold for a signal in the surveillance of booster doses is 0.01, somewhat less stringent than the 0.0061 threshold for surveillance of ages 5-11, because we expect about 20% of all post-booster follow-up will be available at the first weekly analysis. The more stringent threshold for surveillance of the primary series for ages 5-11 years assumes that equal amounts of follow-up would be added at each weekly analysis.

Signaling criteria will not be considered "stopping rules". Surveillance will continue to be updated weekly after the threshold for a signal has been met, and supplementary analyses will be added to help interpret the apparent vaccine-outcome association (as described below). However, continued formal sequential testing would no longer be appropriate or relevant for the hypothesis.

The multiplicity of different hypotheses tested will be taken into consideration informally. Formal sequential tests of an outcome accounts for the multiplicity of times a hypothesis about that outcome is tested, but not for the multiplicity of different hypotheses that we test about different outcomes.

Trends in outcome incidence over calendar time, and heterogeneity across age-sex-race-site subgroups will be tracked. We will also look for possible variation in outcome incidence within a risk interval or comparison interval – i.e., whether incidence is higher or lower during a period of consecutive days defined by time-since-vaccination (for example, whether incidence of the outcome is high on days 1-3 after vaccination, or whether incidence varies over time-since-vaccination during the comparison interval).

Rate ratio estimates will be reported with nominal 95% confidence intervals, rather than confidence intervals that are widened to correspond with the threshold of the sequential tests. Use of such widened ("repeated") confidence intervals would be less consistent with the current thinking among many epidemiologists and statisticians to deemphasize the p value[39,40].

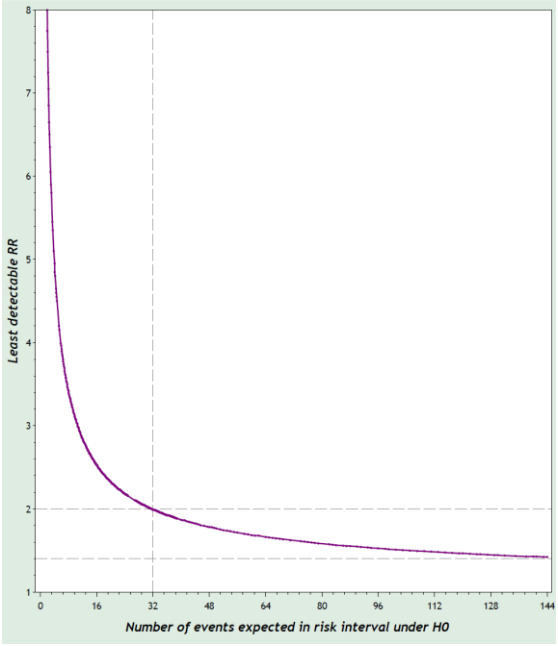
As noted above in the section headed "Analytic Strategies", if vaccinated concurrent comparators are unavailable, then our primary analyses will use unvaccinated concurrent

comparators. To address concerns about potential biases in such analyses, we may conduct "difference-in-differences" analyses whereby we account for any pre-existing differences in risk – between vaccinees and the unvaccinated – that may be observed before the pandemic. Such a similar "difference-in-differences" analysis can also be used to address possible concerns about bias in our primary analyses using vaccinated concurrent comparators, bias that could arise from differences between individuals who are earlier versus later "in the line" for receiving vaccination. However, we note that this difference-in-differences approach would be problematic if the propensity/priority for COVID-19 vaccination is affected by a history of an outcome event in 2019. For example, if Bell's palsy in 2019 becomes a contraindication to vaccination against COVID-19, this approach would yield a biased estimate of the vaccine's effect on risk of Bell's palsy.

Statistical Power

Figure 1 shows the power of the proposed risk interval analysis comparing the incidence of outcome events in vaccinees during the risk interval with incidence in vaccinees during a comparison interval of equal length. The magnitude of the rate ratio that we can detect with 80% power will decrease as the expected number of events increases. If our alpha-spending plan sets the threshold for a signal at each weekly look to be a two-sided p-value of 0.0096, amounting to a one-sided p-value of 0.0048 then a rate ratio of 4 will be detectable with at least 80% power when we can expect 5 outcome events. A rate ratio of 2 will be detectable when we can expect 32 events; a rate ratio of 1.5 will be detectable when we can expect 105 events.

Figure 1. Rate Ratios Detectable with >80% Power, by the Number of Events Expected in the Risk Interval under H0



Whereas Figure 1 above shows the rate ratios detectable by a single risk interval analysis, Table 4 below reports on the distribution of time-to-signal—the number of weekly analyses until we expect to have a 0.50, 0.80, or 0.95 probability of detecting a rate ratio of 1.5, 2.0, or 3.0. For example, the top row of Table 4 indicates that the chance of detecting RR=1.5 exceeds 50% by

the 55th week and exceeds 80% by the 101st week. For this rare outcome the chance of detecting RR=1.5 will never exceed 95%. The chance of detecting RR=3.0 for this outcome exceeds 50% by week 7, exceeds 80% by week 11, and exceeds 95% by week 17. These time-to-signal estimates are based on simulations with 5 million iterations of each scenario in the table. For simplicity, the expected incidence of outcome events (under H_0) was constant over time in each scenario, and the amount of follow-up in the risk and comparison intervals was always equal.

Table 4. Time-to-Signal by the Rate Ratio and the N of Outcome Events Expected Weekly under H_0

		Week when chance of signal passes		
		50%	80%	95%
Rate Ratio	**Outcomes/week expected in the risk interval**			
1.5	**1 (TTP)**	**55**	**101**	
	20 (seizure)	**4**	**6**	**9**
	100 (AMI)	**1**	**2**	**2**
2.0	**1 (TTP)**	**19**	**32**	**49**
	20 (seizure)	**2**	**2**	**3**
	100 (AMI)	**1**	**1**	**1**
3.0	**1 (TTP)**	**7**	**11**	**17**
	20 (seizure)	**1**	**1**	**1**
	100 (AMI)	**1**	**1**	**1**

Methods and Analyses using Historical Comparators

Pre-specified Outcomes

A primary advantage of the historical analyses lies in the ability to provide stable comparator estimates for rare outcomes, but if the outcomes are relatively common during the surveillance period, the concurrent analysis estimates would be strongly preferred because they would likely be less affected by various biases. Therefore, the formal historical comparator analysis reporting (i.e., weekly sequential analysis) may be restricted to a subset of outcomes in **Table 2.** Historical data would, however, still be captured for all outcomes to provide background and context for the concurrent analyses.

Historical Comparator Groups

Historical comparator groups are well-suited for outcomes that are relatively rare because they can utilize multiple years of data to produce stable estimates of expected outcome rates. In addition, these expected outcome rates can be modeled prior to the start of vaccine safety surveillance (e.g., smoothed age-specific rates can be generated and stored in a static file for use in computation of expected outcome counts during the surveillance period). For the COVID-19 RCA, we will use two historical comparator groups to estimate the association between COVID-19 vaccination and pre-specified outcomes. One historical comparator group is the general VSD population with age and sex distributions that mirror those of COVID-19 vaccine recipients at the time of the analysis; this comparator group is used to estimate general background person-time rates. Expected counts are produced by multiplying the observed number of COVID-19 vaccine doses by the rates prorated to the length of the post-vaccination risk interval. In general, we expect these background rates to be relatively stable. As a result, they may be preferred for

evaluating rare events such as Guillain-Barré syndrome (GBS) or transverse myelitis (TM). We will examine the patterns of background rates across the historical period to determine if the incidence of specific outcomes has changed over time and if it is appropriate to use aggregate rates for the entire period versus a shorter time period, or if we need to project trends into the surveillance period.

The composition of the second historical comparator group will differ for adults (≥18 years old) and children (≤17 years old). For adults, the group will include persons having both 1) a well visit in the historical period, and 2) an influenza vaccine in the 18 months prior to the well visit. This group is modeled after a comparator group evaluated and used for the recent Shingrix RCA. We will identify persons in the adult comparator group using two well visit ICD-10 diagnosis codes:

Z00.00 'Encounter for general adult medical examination without abnormal findings', and
Z00.01 'Encounter for general adult medical examination with abnormal findings'.

Because people may have multiple well visits during the historical period, we will randomly select up to two visits per person and no more than one per year. The comparator group will be age and sex comparable with the vaccinated group; other variables (e.g., race) will also be included as feasible. The date of the well visit will serve as the anchor for the post-visit risk intervals within which outcome events are tabulated.

For children, the second historical comparator group will include persons who had a visit for routine or catch-up vaccination. Comparator vaccines for adolescents (aged 12-17 years) include Tdap, Td, meningococcal, HPV, varicella, HepA, HepB, MMR and IPV and for children aged 5-11 years include DTaP, IPV, MMR, varicella, Tdap, Td, MenACWY, HPV, HepA, HepB, DTaP-HepB-IPV and DTaP-IPV. The date of the comparator vaccination visit will serve as the anchor for the post-visit risk intervals within which outcome events are tabulated.

These second comparator groups address the concern that vaccinated and unvaccinated people may have systematic differences that could bias or confound the association between the outcomes and the vaccine. We hypothesize that these comparator groups will have greater similarity to recipients of COVID-19 vaccines than the general VSD population. Additionally, this comparator was used in the 9vHPV RCA.

Based on its use in the Shingrix RCA, we anticipate that the well visit-based comparator group will be appropriate for older adults (≥50 years) in the COVID-19 RCA. However, it is not known if this approach will work for younger adults. Therefore, we will explore other comparator groups by comparing their baseline characteristics with the vaccinated group after the vaccine has been more widely distributed within the VSD. Other possible comparator groups include individuals with various combinations of well visits and/or administration of age-appropriate non-influenza comparator vaccines, such as Td/Tdap, pneumococcal, meningococcal, and varicella. We will similarly evaluate the comparability of children in the two comparator groups with those vaccinated with COVID-19 vaccines.

Our comparator group definitions may also reflect the fact that vaccine authorization and allocation may target individuals with high-risk conditions that increase the risk for severe

COVID-19. The method by which individuals will be identified as high risk will be determined by CDC and harmonized with other ongoing COVID-19 vaccine safety research efforts. In addition, we acknowledge that the current protocol is oriented to adult vaccine recipients because there is limited clinical trial data for children to date. Prior to authorization or approval of a vaccine for children, the protocol will be modified as needed (e.g., the list of outcomes and characteristics of the historical comparator groups).

Data for the historical comparator groups will be derived from the VSD population during the period October 1, 2016 (one year after the start of ICD-10 coding) through December 31, 2019 (preceding the start of the COVID-19 pandemic). The 12 months preceding the start of the historical comparator period (October 1, 2015 – September 30, 2016) will be used as a 'run-in' period to identify prevalent conditions among persons in VSD. However, we recognize that early in the pandemic healthcare facilities were advised to reduce in-person care where possible to preserve resources, such as personal protective equipment and hospital beds, and to care for COVID-19 patients[41]. Evidence for this change in utilization can be found in reports demonstrating decreases in cardiac catheterizations and hospitalization for acute myocardial infarction (AMI) in the first few months of 2020[42,43]. We think it is plausible that some pandemic-induced changes in utilization levels relevant to this RCA will return to approximate pre-pandemic levels at some point in the surveillance period (e.g., mid-2021) because most of our pre-specified outcomes are serious conditions that require emergent or inpatient care. However, a prolonged impact of the pandemic on health care is also plausible. To address this concern, we will extract historical data for the pre-specified outcomes starting on January 1, 2020 and going forward at least through the end of 2020 to separately examine and describe the background rates and trends over this period. It is unclear whether any secular trends observed in the pre-pandemic or pre-vaccination phase of the pandemic will carry forward into the surveillance period (i.e., the vaccination phase of the pandemic and beyond). We will collect and evaluate data for these periods and consult with our co-investigators when deciding how to characterize the background data in the sequential analyses. In addition, the RCA will be informed by results from a separate task order led by investigators at KPSC, the objective of which is to describe in detail the effects of the pandemic on resource utilization within VSD. It is likely that the historical analyses will be affected by changes in resource utilization to a greater extent than the concurrent analysis because it derives expected counts from the pre-pandemic period.

Surveillance using historical comparator groups will begin after consultation with RCA and CDC investigators, after all requisite preparatory computations have been made (e.g., critical values and upper limits), and will be informed by vaccine utilization characteristics within the VSD population, which will be monitored weekly.

Historical Comparator Analytic Methods

We will estimate relative risks (RR) for pre-specified outcomes analyzed sequentially using the Poisson-based maximized sequential probability ratio test (MaxSPRT) [44] and the Conditional MaxSPRT (CMaxSPRT) [45]. We plan to use CMaxSPRT, which accounts for uncertainty in the historical data, whenever the count in the comparison group used to obtain the background rate is less than 5 times the upper limit (i.e., the pre-specified number of cases of a particular outcome expected in the surveillance period under the null hypothesis). Analyses will incorporate

adjustments for partially completed risk intervals, censoring of dose 1 follow-up time by dose 2, and seasonality (adjustment at the level of month). The analysis will also account for delayed data accrual. Preliminary analyses of historical data, which included separate evaluations of lags in outpatient, inpatient, and vaccination data, indicated that a 12-week lag before each weekly analysis would allow adequate time for administrative corrections to most of the relevant electronic data, improve data completeness, and be the simplest to implement.

Subgroup-specific RRs (e.g., by age and sex) will be computed every week based on the observed rate of a specific outcome in the risk interval following a COVID-19 vaccination and the expected rate for that subgroup derived from the comparator group. Expected values will be calculated in cells defined by site, age, sex, and race and aggregated to the level of the analytic subgroup (e.g., females, 18-64 years). The test statistic to assess the one-sided statistical significance of the relative risk is the log-likelihood ratio. If the test statistic exceeds a predefined critical value, the null hypothesis of no elevated risk is rejected and is considered a 'statistical signal'. The maximum length of surveillance ('upper limit') is expressed in terms of the expected number of events under the null and is derived from background rates and estimated COVID-19 doses during the surveillance period. Formal analysis continues until (1) the test statistic exceeds the critical value and a statistical signal is produced, (2) the total number of observed outcomes in the risk interval reaches the upper limit, or (3) the surveillance period ends. Although reporting of formal analyses (i.e., sequential testing) will cease after a statistical signal or the upper limit is reached, weekly surveillance will continue for the duration of the RCA to provide additional information regarding specific vaccine-outcome associations. However, continued formal analyses would not be appropriate. Previous historical RCA investigations required a minimum number of outcomes (e.g., 2 or 3) before declaring that an analysis has 'signaled'. However, these minimums are arbitrary and because we expect that most of the pre-selected outcomes will be rare in children less than 12 years old, our analyses will not impose such restrictions. Instead, we will conduct sequential analyses whenever possible and evaluate the results in the context of observed counts, historical background rates, and calculated upper limits. We will perform analyses in subgroups defined by characteristics such as age group and sex.

CMaxSPRT was developed as an extension of MaxSPRT[45]. In addition to accounting for the uncertainty in the surveillance population and preserving the type I error rate, it further accounts for uncertainty in estimating the historical comparator rates instead of treating them as known. CMaxSPRT will likely be coupled with the historical well visit-based or vaccination visit-based comparator group(s) and will compare the outcomes in the risk interval following COVID-19 vaccination with outcomes in the risk interval following the well (or vaccination) visit during the historical period. As noted above, we intend to use CMaxSPRT when the outcome count in the risk window for the comparison group is less than 5 times the upper limit[45]. Note that CMaxSPRT analyses are precluded in subgroups in which there are no events in the risk interval in the historical period.

The sequential methods used in this analysis will permit us to maintain an overall one-sided type I error rate of 0.05 across the multiple tests performed for each outcome, subgroup, and statistical method combination. We recognize that while the sequential methods will account for the repeated weekly analyses for each outcome/subgroup combination, it does not account for the numerous statistical tests across the different combinations that will be performed during this

RCA. While this may increase the probability of a false positive result, all signals will be evaluated by VSD vaccine safety experts following an established protocol (described in a separate section below).

Statistical Power

The number of persons who will be administered the COVID-19 vaccine in VSD is difficult to predict due to issues related to availability, priority group distribution, and acceptance. The number of doses of COVID-19 vaccine needed to detect a range of relative risks (RR) ranges widely from a low of 10,000 to detect a RR of 5.0 for a comparatively common outcome (AMI) to many millions of doses to detect a RR of 1.5 for a rare outcome (GBS) (Table 5).

Table 5. Number of Doses Required to Detect Relative Risks for Infrequent and Rare Outcomes among Adults

	Expected (background)		**Upper limit of number of doses for:**			
Outcome	**Incident rate per 10^6 p-y**	**Counts per 10^6 doses in 1-21 day interval**	**RR=1.5**	**RR=2**	**RR=3**	**RR=5**
Acute myocardial infarction	2,000	100	300,000	90,000	30,000	10,000
Bell's palsy	300	20	2.5×10^6	750,000	250,000	100,000
Guillain-Barré syndrome	20	1	50×10^6	15×10^6	5×10^6	2×10^6

Notes

1. Expected (background) incidence rates are median estimates from subgroups in published studies (AMI: Reynolds K, et al. Am J Med 2017;130:317-327; Bell's palsy: Rowhani-Rahbar A, et al. Neuroepidemiology 2012;38:252-8; GBS: Sejvar JJ, et al. Neuroepidemiology 2011;36:123-33).
2. Assuming 1 to 21 day risk interval, Poisson MAXSPRT with 80% power, 0.05 overall alpha and general adult VSD comparison groups. (Conditional Poisson CMAXSPRT for GBS). Minimum number of 3 events to signal. Calculations from Sequential R Package (3.2), Silva and Kulldorff, with number of doses to signal from Eric Weintraub Excel file (Oct 14, 2020).

Assessment of the Lag in Automated Data Accrual

Data lags are a recognized characteristic of electronic medical record systems in which there is a delay between the time an encounter actually occurred and when information from the encounter is available in the automated data. One approach used by VSD investigators to account for data lags in RCA investigations is to delay the analysis for a period of time (e.g., 12 weeks) to allow for more complete capture of data and to ensure that sufficient time has passed to cover post-vaccination risk intervals. While imposing a lag in the analysis negatively impacts the timeliness of signal detection, it allows the data to stabilize and enhances the validity of the results. For most RCA investigations this timeliness-validity trade-off is acceptable, but in a pandemic situation there will be demands for more immediate results and a desire to analyze data as they become available. Therefore, we will explore the feasibility of data accrual lag adjustments in the MaxSPRT and CMaxSPRT analyses that will preclude the need to delay initiation of the analyses and permit timelier signal identification. We will use separate data lag adjustment factors by site, setting, age group and week, where the latter corresponds to the number of weeks since the AE occurred (i.e., smaller values for week correspond to lower proportions of the AE

appearing in the source data). This general approach to data lag adjustment is used in the ongoing influenza vaccine RCA surveillance.

Site-specific estimates related to the completeness of data captured over time in VSD have not been updated recently. As part of this RCA project, aggregate encounter data from the inpatient, emergency department, and outpatient settings will be extracted prospectively to estimate the lag in accrual in each setting. Assessments will be conducted for all encounters combined, as well as encounters with diagnosis codes for the pre-specified outcomes selected for this RCA. Because the data will be collected prospectively, updated estimates of data lag may not be available at the time historical sequential analyses commence. In this situation, we will use the estimates currently being employed in the influenza RCA until the updated estimates become available. In addition, the need to distribute the COVID-19 vaccine as rapidly and widely as possible presents unique problems that adversely impact the capture of vaccine information by the VSD sites. For example, if people are administered vaccine in non-standard settings, such as community centers or mobile vaccination clinics, this data may not be available for clinical or research use in a timely fashion. Therefore, we also explore the extent to which accrual of vaccination data was delayed.

Preliminary analyses of various data lag adjustments described above indicated that a 12-week lag implemented before each weekly analysis provided the optimum correction for delayed data accrual.

Covariates

Separate analyses will be conducted within strata defined by age group, sex, vaccine product, and dose. Covariates (i.e., additional factors incorporated into the observed vs. comparator group comparisons) include VSD site and race/ethnicity. Comorbid conditions, presence of a high-risk condition, and healthcare utilization measures may be considered with input from CDC and the VSD RCA working group.

Potential Signal Assessment

If the criteria for a signal are met, we will already have the supplemental comparator analyses available for context and interpretation of results. It is assumed that any association that is detected with RCA may require additional evaluation to determine whether the signals are real or spurious.

This additional evaluation may include the following:

- Data quality assessment for errors, anomalies, or unusual patterns.
- Temporal scan statistics to determine if occurrences of the outcome are clustered within segments of the relevant risk interval following vaccination.
    - This will include examination of clusters of outcomes if they appear during brief sub-intervals within the risk interval, or if they appear to cluster in subgroups defined by age, sex, race/ethnicity, site, and known prior COVID-19 disease.
- Site-specific estimates may be computed (if possible) to determine if the association is consistent across the sites. If the association is driven by a particularly strong association at one site, additional analyses will be focused on that site (e.g., quality assessment of the data, chart review, etc.).

- Chart review of outcomes to confirm possible cases and collect additional data. Some particularly serious outcomes will be subject to chart review as they occur rather than following a signal (e.g., GBS, anaphylaxis).
- Evaluation of the weekly routine supplementary analyses.

Associations that persist after evaluation will be communicated to the relevant stakeholders (e.g., reported to ACIP) and may be investigated by more standard epidemiological methods such as case-centered, case-control or cohort studies.

Objective #2: Uptake Monitoring Over Time of COVID-19 Vaccines
After a COVID-19 vaccine becomes routinely available in the VSD (i.e., not as part of clinical trials), we will monitor vaccine coverage overall, and in strata defined by age group, sex, race/ethnicity, and VSD site. Surveillance of vaccine coverage will be updated weekly. For each week during the surveillance period, we will tabulate the number of doses delivered, the cumulative number of doses, and vaccine coverage. For a 2-dose vaccine we will monitor each dose and use methods for censored time-to-event data to monitor time to second dose among first dose vaccinees. We will also plot curves showing the percentage who have received the second dose by days since the first dose. If different vaccines are in use in the VSD population, we will monitor vaccine coverage separately for each type of vaccine, and for all COVID-19 vaccines combined.

Objective #3: Long-Term Safety Surveillance of COVID-19 Vaccines
Following completion of near real-time surveillance, long-term surveillance will be conducted to continue monitoring the risk of pre-specified outcomes following COVID-19 vaccination. Aggregate data will continue to be collected on a weekly basis and formal, non-sequential analyses for select outcomes (to be determined) will be conducted with periodicity to be determined. In the event of a signal, individual-level data may be requested for a formal epidemiological analysis. Our approach to long-term analyses for COVID-19 vaccines may be patterned after the long-term analyses currently being conducted for the 9-valent human papillomavirus (9vHPV) vaccine. In the coming months, we will work with CDC and VSD co-investigators to determine the outcomes to be studied and specifics of the analytic methods.

Data Collection, Quality and Management
Automated data will be extracted from standardized VSD files at each participating site. Sites that participate in VSD produce weekly dynamic data files (DDF) that capture information on demographics, immunizations, and ICD-10-coded diagnoses assigned by health care providers in outpatient, emergency, or hospital encounters. The DDF will be used as the primary data source for both Aims 1 and 2, including identifying and following vaccine recipients for outcomes of interest. Cycle files updated on an annual basis may also be used to extract historical data. As co-lead sites, KPNC and MCRI will develop SAS programs to extract data needed for this RCA. Standard VSD files that will be accessed are: constant, enroll, vaccine, inpt, outpt; ancillary files include: platelet, dxidhist, dxid, covltest, covlrslt; and weekly generated datasets covid19vachr and pregpsd_ddf. Additional standard data files including procdre and mort and mdcdYYYY may be accessed if necessary.

The unique VSD identification number (VSD ID) will be used to link information between data files. A series of core programs that aggregates data will be run by CDC on the DDFs at each participating site on a weekly basis. As with all VSD studies, the DDFs produced by each site remain on that site's server. Apart from data needed for the self-control comparator analyses, only aggregated summary data will be transferred to MCRI and KPNC servers for analyses. Additional SAS programs will be developed to extract data for computation of background rates and for signal investigation. Individual-level automated data will be extracted on a weekly basis to facilitate the self-control analyses and may also be requested as part of signal investigation. All SAS programs will be distributed to data managers at participating sites for review and approval prior to being run. We will assess data quality in an ongoing manner to verify case and vaccination status for each outcome.

Chart Review

We will conduct routine chart review for selected rare outcomes after the primary series - acute disseminated encephalomyelitis (ADEM), anaphylaxis, cerebral venous sinus thrombosis (CVST), Guillain-Barré syndrome (GBS), multisystem inflammatory syndrome in children/adults (MIS-C/A), thrombosis with thrombocytopenia syndrome (TTS) and transverse myelitis (TM) - shortly after a case is detected and prior to analysis. For booster doses, we will conduct routine chart review for anaphylaxis. Additionally, chart review may be conducted for other outcomes after the primary series or booster doses in response to a signal within our surveillance or safety concerns that arise elsewhere. VSD initiated chart review for myocarditis/pericarditis among individuals <40 years of age after mRNA vaccines in June 2021. If the criteria for a signal are met, further analyses of the vaccine-outcome association may be undertaken through chart review for any outcome, especially of the outcomes that occur in vaccinees during the risk interval. The goal of the chart reviews will be to verify the automated diagnosis, confirm the outcome as incident, and abstract additional information from the medical record not readily available via automated data such as symptom onset date and results of diagnostic testing.

As co-leading sites, in collaboration with CDC and with feedback from participating sites, KPNC and MCRI will design, test, and validate chart review forms and manage all chart reviews across the participating sites. Both MCRI and KPNC have prior experience creating and using chart abstraction forms and will collaborate with CDC and participating sites to design the chart abstraction tool elements. Outcome case criteria will be based on criteria in the literature and in consultation with CDC, VSD investigators, and subject matter experts. Additionally, before chart abstraction is rolled out to all sites, KPNC or MCRI will pilot the tool at their site (and potentially one participating site) to further refine the abstraction tool.

A detailed instruction manual will be developed and distributed to ensure consistent data collection across sites; training sessions for abstractors may also be conducted. Each site will be provided with a line list of cases to review that will contain at a minimum the VSD ID number, outcome, and date of diagnosis. As is standard in VSD to ensure confidentiality, unique subject identification numbers are included on all abstraction forms so that the data is linkable to the electronic medical record data if further information and/or corrections are needed later. Data managers at each site will be responsible for linking VSD ID to the medical record number. Chart reviews will be performed by trained abstractors at each participating site via manual

review of paper and/or electronic medical records. Chart review data will be directly entered into a secure, online REDCap database hosted by MCRI. Each individual user will receive a unique username and password. Data access groups will be configured to ensure that users only have access to data on individuals from their site, with the exception of KPNC and MCRI, which will have access to all data captured in the database. Completed abstractions will be reviewed and adjudicated as needed by subject matter experts at KPNC, MCRI, and/or CDC.

We will confirm that all data being collected in the abstraction form only contains information that is allowable as outlined in the Limited Data Set described in the Data Use Agreement (DUA).

Challenges and Limitations

The overarching challenge to a vaccine safety study of COVID-19 vaccines is the inherent uncertainty of confronting a pandemic caused by an emerging infection; the epidemiology, immunology, natural history, and clinical spectrum of COVID-19 are still being elucidated. In addition, the severity and extent of the pandemic has necessitated the development of vaccines at an astonishing pace. In normal circumstances, there is a wealth of data that accrues over years and accompanies vaccines that are approved for use under the FDA's Biologics License Application (BLA). However, such data will not soon be available for COVID-19 vaccines, and they are being reviewed and authorized under EUA[46]. We will work to adapt the RCA to the available data as it accrues.

Because COVID-19 vaccine distribution includes nontraditional settings and methods (e.g., retail pharmacies), some vaccines may not be recorded in VSD files or data entry may be delayed. Our primary concurrent analyses, which use vaccinated concurrent comparators, would not be biased by such under-ascertainment of vaccination (though they would lose some power and generalizability). Also, different COVID-19 vaccines may be used by different VSD sites at different times. Each vaccine type will require a separate analysis since their safety profiles may be distinct. It is also quite possible that new vaccines will be approved and introduced to the VSD population over the course of the proposed surveillance period. The RCA infrastructure proposed is flexible and can readily accommodate new vaccines. Power will be limited for some outcomes, especially in subgroups.

There is evidence that a substantial proportion of the population are hesitant about vaccination[47]. Biases could arise in our supplementary analysis when using unvaccinated comparators.

The pre-specified outcomes selected for this project will be based on data from clinical trials of the COVID-19 vaccines and from clinical data related to COVID-19. However, because in general clinical trials are limited in size and follow-up time, some of the pre-specified events we select may be based on existing general knowledge of vaccine-related outcomes, clinical manifestations of COVID-19, and biologic plausibility. In addition, as clinical data accrues, we will work with CDC and VSD investigators to identify and incorporate new outcomes of concern into the surveillance plan.

Project Timeline and Dissemination of Results

This project will commence in fall 2020 and is expected to continue for approximately 3 years. Surveillance will begin as soon as there is COVID-19 vaccine uptake within the VSD, which is anticipated in late 2020. Formal sequential analyses will commence when the COVID-19 vaccine is distributed in sufficient volume throughout the VSD population. Data extraction and chart review will occur throughout the surveillance period. Surveillance reports will be shared routinely with CDC and participating sites. Interim results may be presented to the ACIP, other federal partners, and/or in MMWR publications. Following completion of surveillance, final results will be presented to the ACIP and a manuscript will be prepared for submission to a peer-reviewed journal. Long-term surveillance is expected to continue for selected rare or high priority outcomes.

Human Subjects Considerations and Confidentiality

Institutional Review Board (IRB) approval may be required at some participating VSD sites, although it is anticipated that this protocol will fall under the category of surveillance, not research, at CDC. KPNC and MCRI project managers will work with participating sites at the beginning of the project to determine which, if any, sites need to submit project-specific documents, including the protocol and chart review forms, to their IRB for review.

The privacy and confidentiality of all subjects under surveillance will be strictly protected according to standard VSD 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 it 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.

Whenever possible, only aggregate data will be transferred to KPNC and MCRI for analysis. When individual-level data is needed, variables will be restricted to those needed for the analysis and will not contain any direct identifiers, although the data will include indirect identifiers such as date of birth, date of vaccination, and date of diagnosis, which are considered protected health information (PHI) under the Health Insurance Portability and Accountability Act (HIPAA). Transfer of data will occur via the secure VSD Hub; pre-existing agreements between VSD sites permit the transfer of limited datasets using this method.

Individual medical records will only be accessed if and when chart review is necessary, such as to confirm cases of serious outcomes. Chart reviews will be conducted at individual sites by designated personnel and direct identifiers required to link the automated data with a medical record will not be transferred to KPNC or MCRI. Chart review data will be directly entered into an online REDCap database hosted by MCRI. If portions of the medical record are requested, non-essential patient identifiers will be redacted prior to upload into REDCap. REDCap databases are secure and HIPAA compliant and REDCap has previously been used for chart abstraction studies in the VSD. If needed, technical information will be provided to participating sites so that a security review or risk assessment can be conducted.

The surveillance project does not involve intervention or interaction with human subjects and is an analysis of existing data collected for non-research purposes. Sites have been granted a waiver

for the requirement to obtain informed consent and HIPAA authorization from subjects in this surveillance project. Risks are minimal and are limited to the inadvertent disclosure of PHI.

Site Responsibilities

This surveillance project will be co-led by investigators at KPNC and MCRI, in collaboration with the Immunization Safety Office at CDC. Investigators at participating sites and the CDC will be invited to contribute to protocol development, chart review form development, as well as interpretation and reporting of results. Participating VSD sites will be responsible for the following tasks:

- Obtaining and providing documentation of IRB and data transfer approval, when applicable.
- Reviewing and approving SAS programs; and
- Conducting chart reviews.

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Appendix 1. Exclusion Codes for Outcomes of Interest

Table 1: Exclusions for Outcomes of Interest

Outcome	**Exclusions for Prevalence -** with lookback period for exclusion	**Exclusions – other known causes (in all settings) -** with lookback period for exclusion (not including same day unless noted in column to the right)	**Exclusions – same day, other known causes (in all settings)**
EXCLUSIONS FOR OUTCOMES OF INTEREST FOR COMPARATIVE ANALYSES			
Acute disseminated encephalomyelitis (ADEM)	n/a	n/a	n/a
Acute myocardial infarction (AMI)	If occurs EVER prior to case: I22.*, I23.*, I25.2	If in last 30 days prior to case: First COVID-19 diagnosis code or COVID-19 positive lab test If in last 7 days prior to case: Physical trauma code[2] If EVER prior to case: I25.1*	Same exclusions as column to the left
Appendicitis	n/a	n/a	n/a
Bell's palsy	n/a	If in last 30 days prior to case: First COVID-19 diagnosis code or COVID-19 positive lab test If in last 14 days prior to case: A69.2*, A92.5, B00.*, B02.* If EVER prior to case: D86.*	Same exclusions as column to the left
Cerebral venous sinus thrombosis (CVST)	n/a	If in last 30 days prior to case: First COVID-19 diagnosis code or COVID-19 positive lab test Exclude if incident case occurs any time during pregnancy or within 6 weeks after pregnancy ends: O22.5*, O87.3	If same day as incident case: S02.*, S06.*, S09.*, S15.*, Physical trauma code[2]
Convulsions / seizures	If occurs EVER prior to case: F44.5, G40.A*, G40.B*, G40.0*, G40.1*, G40.2*, G40.3*, G40.4*, G40.5*, G40.8*, G40.9*	If in last 30 days prior to case: First COVID-19 diagnosis code or COVID-19 positive lab test If in last 1 year prior to case: S06.3*, S06.9*, G03.1, Z86.61 If EVER prior to case: I69.*, Z86.73, If in last 3 days prior to case: I60.*, I61.*, I62.*, I63.* If in last 7 days prior to case: A17.0, A17.82, A27.81, A32.1*, A39.0, A39.81, A41.9, A69.21, A85.*, A86, A87.* A88.0, A88.8, A89, A92.31, A92.5, B00.*, B01.0, B01.11, B02.*, B05.*, B06.*, B10.81, B26.*, B45.1, B58.2, B96.0, G00.*, G01, G02, G03.0, G03.8, G04.3*, G04.81, G04.90, G05.3, G92, G93.41, G95.1*, G95.89, J09.*, J10.*, J11.*, R65.20, R65.21	If same day as case: S06.3*, S06.9*, S06.0X9A
Disseminated intravascular coagulation (DIC)	n/a	If in last 42 days prior to case: First COVID-19 diagnosis code or COVID-19 positive lab test If in last 14 days prior to case: Physical trauma code[2] C92.4*, K85.*, O45.02*, O46.02*, O67.0, S06.*, T30-T32	Same exclusions as column to the left

Outcome	**Exclusions for Prevalence -** with lookback period for exclusion	**Exclusions – other known causes (in all settings) -** with lookback period for exclusion (not including same day unless noted in column to the right)	**Exclusions – same day, other known causes (in all settings)**
Encephalitis / myelitis / encephalomyelitis / encephalopathy (not ADEM or TM)	If occurs EVER prior to case: G03.1, Z86.61	If in last 30 days prior to case: First COVID-19 diagnosis code or COVID-19 positive lab test If in last 7 days prior to case: A17.0, A17.82, A27.81, A32.1*, A39.0, A39.81, A41.9, A69.21, A85.*, A86, A87.*, A88.0, A88.8, A89, A92.31, A92.5, B00.*, B01.0, B01.1*, B02.*, B05.*, B06.*, B10.81, B26.*, B45.1, B58.2, B96.0, G00.*, G01, G02, G03.0, G03.8, G04.31, G95.1*, G95.89, J09.*, J10.*, J11.*, R65.20, R65.21	Same exclusions as column to the left
Guillain-Barré syndrome (GBS)	If occurs EVER prior to case: G65.0	n/a	n/a
Immune thrombocytopenia (ITP)	n/a	If in last 30 days prior to case: First COVID-19 diagnosis code or COVID-19 positive lab test If EVER prior to case: B20, C00-C96, D18.0*, D59.0-D59.2, D59.3, D61.*, D65, D69.0, D80-D89, K70-K77, M32.*, Z51.11	n/a
Kawasaki disease (KD)	n/a	n/a	n/a
Myocarditis / pericarditis	n/a	If in last 30 days prior to case: First COVID-19 diagnosis code or COVID-19 positive lab test	Same exclusions as column to the left
Stroke, hemorrhagic	If occurs EVER prior to case: I69.*, Z86.73	If in last 30 days prior to case: First COVID-19 diagnosis code or COVID-19 positive lab test If in last 1 day prior to case: S06.*	If same day as case: S06.*, Physical trauma code[2]
Stroke, ischemic	If occurs EVER prior to case: I69.*, Z86.73	If in last 30 days prior to case: First COVID-19 diagnosis code or COVID-19 positive lab test If in last 1 day prior to case: S15.*, I74.* If in last 28 days prior to case: I21.* If EVER prior to case: I48.*, D57.*, D68.5*	If same day as case: S15.*, I74.*, Physical trauma code[2]
Thrombotic thrombocytopenia purpura (TTP)	n/a	If in last 30 days prior to case: First COVID-19 diagnosis code or COVID-19 positive lab test If in last 1 year prior to case: B20, C00-C96, Z51.11, Z94.84 If anytime during pregnancy or within 6 weeks after pregnancy ends: Search pregnancy database OR O99.1*	n/a
Thrombosis with thrombocytopenia syndrome (TTS)	n/a	n/a	n/a
Transverse myelitis (TM)	n/a	n/a	n/a
Venous Thromboembolism (VTE)	If occurs EVER prior to case: I27.82, I82.211, I82.221, I82.291,	If in last 30 days prior to case: First COVID-19 diagnosis code or COVID-19 positive lab test	Same exclusions as column to the

Outcome	**Exclusions for Prevalence -** with lookback period for exclusion	**Exclusions – other known causes (in all settings) -** with lookback period for exclusion (not including same day unless noted in column to the right)	**Exclusions – same day, other known causes (in all settings)**
	I82.5*, I82.7*, I82.A2, I82.B2*, I82.C2*, I82.891, I82.91, Z86.71*	If in last 60 days prior to case: Pregnancy outcome OR O08.2, O22.3*, O22.5*, O87.1, O88.2*, Physical trauma code[2], M67.9*, M80.*, M84.3*, M99.*, S00-T88, Z08, Z09, Z51.5, Z51.89, C00-C96, Z30.011, Z79.890 If in last 14 days prior to case: Pneumonia code[3], I50.*, O88.0*, O88.1*, T79.1* If EVER prior to case: D68.5*, D68.6*	left minus COVID-19
Pulmonary embolism	If occurs EVER prior to case: I27.82, Z86.71*	If in last 30 days prior to case: First COVID-19 diagnosis code or COVID-19 positive lab test If in last 14 days prior to case: Physical trauma code[2], O88.0*, O88.1*, T79.1*	Same exclusions as column to the left minus COVID-19
EXCLUSIONS FOR OUTCOMES OF INTEREST FOR MONITORING			
Acute respiratory distress syndrome (ARDS)	n/a	If in last 42 days prior to case: First COVID-19 diagnosis code or COVID-19 positive lab test If in last 14 days prior to case: Sepsis code[1] Physical trauma code[2] J09.*, J10.*, J11.*, J68.*, J69.0, J70.5, J70.8, J70.9, K85.*, T75.1*	Same exclusions as column to the left
Anaphylaxis	n/a	n/a	n/a
Multisystem Inflammatory Syndrome in Children (MIS-C) & Multisystem Inflammatory Syndrome in Adults (MIS-A)	n/a	n/a	n/a
Narcolepsy and cataplexy	n/a	n/a	n/a

[1] Sepsis codes: A02.1, A20.7, A22.7, A26.7, A32.7, A39.1, A39.2, A39.3, A39.4, A39.89, A39.9, A40.*, A41.*, A42.7, A54.86, B00.7, B37.7, O85, O86.04, R65.2*, R78.81, T81.44*

[2] Physical trauma codes: V00-Y99

[3] Pneumonia codes: A22.1, B25.0, A37.01, A37.11, A37.81, A37.91, A48.1, B44.0, B77.81, J12.*, J13, J14, J15.*, J16.*, J17, J18.*