



Protocol:

**Evaluation of Multiple Safety Outcomes following 2023-2024
COVID-19 Vaccination in Persons 6 Months and Older**

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Biologics Effectiveness and Safety (BEST) Initiative

Center for Biologics Evaluation and Research

Office of Biostatistics and Pharmacovigilance

Study Team

FDA	
Joann F. Gruber, PhD, MSPH Carla E. Zelaya, PhD, MSc	Richard Forshee, PhD Steven A. Anderson, PhD, MPP
Acumen, LLC	
Michelle Ondari, MSPH Mao Hu, BS Jessica Hervol, MPH Jingjing An, PhD Chunyi Xia, MHS Yutong Qin, MS Jin Ye, MS Ruobing Lyu, MPP Jing Wang, MS Zhiruo Wan, MS	Bowen Chen, MEng Fengdi Zhang, MPH Nimesh Shah, MPH Xinxin Lin, MPH Purva Shah, MPH Gita Nadimpalli, MD, PhD Gyanada Acharya, MS Laurie Feinberg, MD, MPH, MS Yoganand Chillarige, MPP Thomas MaCurdy, PhD
CVS Health	
Cheryl N McMahon-Walraven, PhD, MSW Djeneba Audrey Djibo, PhD AnneMarie Klein, MS, CHES Vaibhav Sharma, MS Carla Brannan, BA Nancy B. Shaik, BS	Jonathan Deshazo, PhD, MPH Dingwei Dai, MD, PhD Eugenio Abente, PhD Smita Bhatia, MCA Aparna Srikanti, MSc Ana Baquero-Martinez, MA
Optum	
Kandace L. Amend, PhD, MPH Elizabeth J. Bell, PhD, MPH Jennifer Song, MA, MURP Shijie Cai, MS Lauren Peetluk, PhD, MPH	Wafa Tarazi, PhD, MHPA John D. Seeger, DrPH, PharmD Grace Wenya Yang, MPA MA Alexandra Stone, PhD, MS
Carelon Research/IQVIA	
Alex Secora, PhD Christian Reich, MD PhD	Michael Goodman, PhD Lauren Parlett, PhD
Centers for Medicare & Medicaid Services (CMS)	
Jeffrey Kelman, MD, MMSc	

Version Control

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List of Abbreviations

ADEM	Acute disseminated encephalomyelitis
ADI	Area Deprivation Index
AIDS	Autoimmune Deficiency Syndrome
AHRQ	Agency for Healthcare Research and Quality
aIIV4	Adjuvanted quadrivalent inactivated influenza vaccine
AR	Attributable risk
BEST	Biologics Effectiveness and Safety Initiative
CBER	Center for Biologics Evaluation and Research
CBSA	Core-based statistical area
CCI	Charlson Comorbidity Index
ccIIV4	Cell culture-based quadrivalent inactivated influenza vaccine
CDC	Centers for Disease Control and Prevention
CFR	Case Fatality Rate
CMS	Centers for Medicare & Medicaid Services
CPT	Current Procedural Terminology
COVID-19	Coronavirus disease 2019
CVX	Vaccine Administered Codes
DTaP	Diphtheria, tetanus, and acellular pertussis vaccine
EDB	Enrollment Database
EUA	Emergency Use Authorization
FDA	Food and Drug Administration
FFS	Fee-for-Service
GBS	Guillain-Barré Syndrome
HAV	Hepatitis A vaccine

HBV	Hepatitis B vaccine
HCPCS	Healthcare Common Procedure Coding System
Hib	Hemophilus influenzae type b vaccine
HIV	Human Immunodeficiency Virus
HHS	Department of Health and Human Services
HPV	Human papillomavirus vaccine
HS	Hemorrhagic stroke
IIS	Immunization Information System
IIV4	Quadrivalent inactivated influenza vaccine
IIV4-HD	High-dose quadrivalent inactivated influenza vaccine
IP	Inpatient
IPV	Inactivated polio virus vaccine
IRR	Incidence rate ratio
LAIV4	Quadrivalent live attenuated influenza vaccine
MA	Medicare Advantage
MDS	Minimum Data Set
MSP	Medicare Savings Programs
MIS-C	Multisystem inflammatory syndrome in children
MMR	Measles, mumps and rubella vaccine
MRR	Medical Record Review
NDC	National Drug Codes
NHS	Non-hemorrhagic stroke
NPV	Negative Predictive Value
OBPV	Office of Biostatistics and Pharmacovigilance
OP	Outpatient

OP-ED	Outpatient emergency department
OP/PB	Outpatient or Professional
PCV	Pneumococcal conjugate vaccine
PPSV	Pneumococcal polysaccharide conjugate vaccine
PPV	Positive predictive value
QBA	Quantitative bias analysis
QDWI	Qualified Disabled Working Individual
QI	Qualified Individual
QMB	Qualified Medicare Beneficiary
REV	Revenue codes
RMLE	Restricted maximum likelihood estimator
RIV4	Quadrivalent recombinant influenza vaccine
RSV	Respiratory syncytial virus vaccine
RV	Rotavirus vaccine
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SCCS	Self-controlled case series
SE	Standard error
SLMB	Specified Low-Income Medicare Beneficiary
SSD	Shared Systems Data
Tdap	Tetanus, diphtheria, and pertussis vaccination
Td	Tetanus and diphtheria vaccination
TTS	Thrombosis with thrombocytopenia syndrome
TIA	Transient ischemic attack
VAR	Varicella vaccine
WSS	Weighted sum of squares

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1. Background

COVID-19 is an infectious disease caused by the SARS-CoV-2 virus.¹ While COVID-19 presents as mild or moderate respiratory illness in most individuals, it can lead to severe illness particularly among certain groups of people.¹ For instance, older individuals and persons with underlying conditions such as cardiovascular disease, chronic respiratory illness, or cancer have been shown to be more predisposed to developing severe illness.¹ As of September 12, 2023, there have been over 1.14 million reported deaths attributed to COVID-19 in the United States.² In 2022, COVID-19 death rates were shown to be highest among males, persons 85 years and older, and non-Hispanic American Indian or Alaska Native populations.³ Vaccination has been recommended by the Centers for Disease Control and Prevention (CDC) and other expert research institutions as one of the most effective tools to prevent severe COVID-19 and death.⁴

In September 2023, the US Food and Drug Administration (FDA) approved the 2023-2024 Formula COVID-19 mRNA vaccines COMIRNATY and SPIKEVAX for use among individuals 12 years of age and older and authorized the 2023-2024 Formula Pfizer-BioNTech and Moderna COVID-19 mRNA vaccines under Emergency Use Authorization (EUA) for individuals 6 months through 11 years of age.^{5,6} In October 2023, FDA similarly authorized Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula) under EUA for administration among individuals 12 years and older.⁷ For simplicity, vaccines will be referred to as 2023-2024 Pfizer-BioNTech, 2023-2024 Moderna, and 2023-2024 Novavax throughout the remainder of this protocol. With the availability of the updated 2023-2024 COVID-19 vaccines, prior COVID-19 vaccines (e.g., bivalent COVID-19 mRNA vaccines) are no longer authorized for use.^{8,9}

The 2023-2024 COVID-19 vaccines have all been updated to include a monovalent component corresponding to the SARS-CoV-2 Omicron variant XBB.1.5, which is expected to be the most prevalent strain during this period.⁸⁻¹⁰ As of June 2023, the XBB variant accounted for more than 95% of circulating COVID-19 virus strains.¹⁰ To ensure protection against currently circulating variants of the virus, CDC recommended that anyone 6 months and older should get at least one dose of an updated vaccine.

Previous studies have reported a potential association between specific outcomes and COVID-19 vaccines. Near real-time monitoring of pre-specified outcomes in pediatric populations in three administrative claims databases in the United States detected signals for myocarditis/pericarditis following original monovalent BNT162b2 vaccination in persons aged 12-17 years and seizures/convulsions in persons aged 2-4/5 years following original monovalent BNT162b2 and mRNA-1273 COVID-19 mRNA vaccinations.¹¹ A cohort study conducted in four administrative claims databases found that the occurrence of myocarditis/pericarditis after receipt of each COVID-19 mRNA primary series vaccine among those aged 18-64 years was rare but increased compared to pre-COVID-19 background rates.¹² Self-controlled case series studies in the population aged 65 years and older determined that there was no statistically significant increased risk for myocarditis/pericarditis following COVID-19 third/monovalent booster COVID-19 mRNA vaccine doses.¹³ However, there were inconclusive results on the risk of pulmonary embolism following COVID-19 mRNA vaccination.¹³

Monitoring the safety of COVID-19 vaccines available in 2023-2024 is important given their updated formulations and use in vulnerable populations such as elderly persons who typically have multiple comorbidities and declining immune function.¹⁴ This protocol details the study methods that will be used to evaluate the safety of COVID-19 vaccines recommended for 2023-2024.

2. Study Objectives

The objectives of the study are:

- (i) to descriptively monitor the vaccination uptake of the 2023-2024 Pfizer-BioNTech, Moderna, and Novavax COVID-19 vaccines, as well as the observed counts and rates of outcomes for each brand among individuals in three commercial health insurance (aged 6 months–64 years) and the Centers for Medicare & Medicaid Services (CMS) Medicare database (aged 65 years and older).
- (ii) to estimate the incidence rate ratio of several outcomes by comparing the incidence rates of prespecified outcomes in risk compared to control intervals following vaccination using a self-controlled case series design (SCCS).

3. Overview of Study Approach

We will perform safety surveillance in each of three commercial health plans and the Medicare claims databases. The study will include descriptive monitoring to characterize vaccination uptake and inferential analyses assessing the rate of outcomes following COVID-19 vaccination.

Using an observational cohort design, descriptive summaries will be produced monthly to characterize vaccine uptake, outcome counts, and incidence rate estimates for outcomes following COVID-19 vaccination. Further details on the descriptive analyses are discussed in [Section 9.1](#).

For outcomes and vaccine brands with sufficient sample size based on a power analysis described in [Section 9.5](#), inferential analyses will be performed using an SCCS study design to assess the association between COVID-19 vaccines and outcomes among a cohort of persons with the respective outcome. Inferential analyses will consist of two phases: (i) an early SCCS analysis using persons vaccinated relatively early post vaccine authorization/approval to provide rapid detection of potentially elevated outcome incidence rate ratios (IRRs) and (ii) an end-of-surveillance SCCS analysis using additional vaccinated persons to provide a more precise estimation of outcome IRRs. Further details on the SCCS methodology are in [Section 8](#). Analyses will be done separately within each database.

Additional analyses may be considered on an as-needed basis for each outcome based on the appropriateness of design assumptions and method of outcome evaluation.

4. Data Sources

The study will include claims data from three commercial insurance databases – CVS Health, Optum, Carelon Research – and Medicare Fee-For Service (FFS) data from the CMS Medicare Shared Systems Database (SSD). Medicare Advantage (MA) data (also referred to as Medicare Part C) will be used to descriptively monitor COVID-19 vaccination uptake. Additionally, MA data may also be included in the end-of-surveillance SCCS analysis if sufficient vaccinations are observed in Medicare Part C.

The commercial health claims databases provide enrollment, pharmacy or prescription, inpatient (IP), outpatient (OP) and physician health insurance claims for privately insured enrollees. The CVS Health database includes adjudicated claims for enrollees in the Aetna commercial health plan. Optum's pre-adjudicated claims database includes claims that undergo initial processing on a daily basis from providers across the United States who accept patients with health insurance. The Carelon Research Healthcare

Integrated Research Database includes adjudicated claims for Elevance Health commercial health plan enrollees.

Immunization Information System (IIS) vaccination data from participating jurisdictions will be used to supplement commercial health claims data in improving COVID-19 vaccine capture. The FDA BEST Initiative, through its data sharing network, facilitated linkage of claims data with IIS data to enhance capture of vaccinations in insured populations for vaccine surveillance studies. IIS jurisdictions were solicited to share COVID-19 vaccination data that was then linked to member-level claims records by individual commercial health plan data partners, using personally identifiable information and IIS-specific linkage algorithms.

The Medicare claims database includes well-defined longitudinal data that captures healthcare service utilization for millions of enrollees across multiple care settings including IP, outpatient-emergency (OP-ED) and outpatient non-ED, professional services (non-laboratory and laboratory), and pharmacy settings (Medicare Part D). Claims data for the inpatient and outpatient settings will be accessed via the CMS Medicare SSD Shared Systems Data (SSD) for FFS enrollees and the Encounter Data System (EDS) for Medicare Advantage enrollees. Medicare claims data undergo three stages of processing: enumeration, adjudication, and final payment. CMS Medicare SSD will be used which consists of claims sourced after enumeration to reduce data lag. The CMS Medicare Enrollment Database (EDB) will be used to capture patient's demographic characteristics and information on death. Information on nursing home residency status will be captured from the Minimum Data Set (MDS) 3.0, a mandatory clinical assessment administered to all residents in Medicare- and Medicaid-certified nursing homes.¹⁵

Table 1 outlines the administrative claims data sources included in surveillance and summarizes claims data characteristics by data source. IIS data characteristics are not presented, given the variability in data characteristics by IIS jurisdiction and differences in data partner access to IIS registry data.

Table 1. Description of Administrative Claims Data Sources

Data Source	Claims Type	Update Frequency	Data Lag*	Population Enrolled
CVS Health**	Fully Adjudicated	Monthly	Approximately 80% data completeness in 3-4 months for inpatient (IP) claims, 2-3 months for outpatient (OP) claims, and 1-2 months for professional (PB) claims	0-4 years: > 1.1 million 5-11 years: > 1.5 million 12-17 years: > 1.5 million 18-64 years: > 14.5 million
Optum**	Pre-Adjudicated	Bi-Weekly	Approximately 80% data completeness in 1-2 months for IP, OP, and PB claims	0-4 years: > 0.9 million 5-11 years: > 1.3 million 12-17 years: > 1.2 million 18-64 years: > 11.5 million
Carelon Research**	Fully adjudicated	Monthly	Approximately 80% data completeness in 2-3 months for IP claims and 1-2 months for OP and PB claims	0-4 years: > 1.3 million 5-11 years: > 1.8 million 12-17 years: > 1.8 million 18-64 years: > 16.9 million
CMS, Fee-for-Service (FFS) data from Medicare Shared Systems Data (SSD)†	Pre-Adjudicated	Daily	>80% data completeness in 30-70 days for inpatient claims	>29 million beneficiaries annually ¹⁶
CMS, Medicare Advantage (MA) from Encounter Data System (EDS)†	Pre-Adjudicated	Weekly	Approximately 80% data completeness in ~80 days	>30 million beneficiaries annually ¹⁶

* Data lag is based on 2020 claims delay distribution

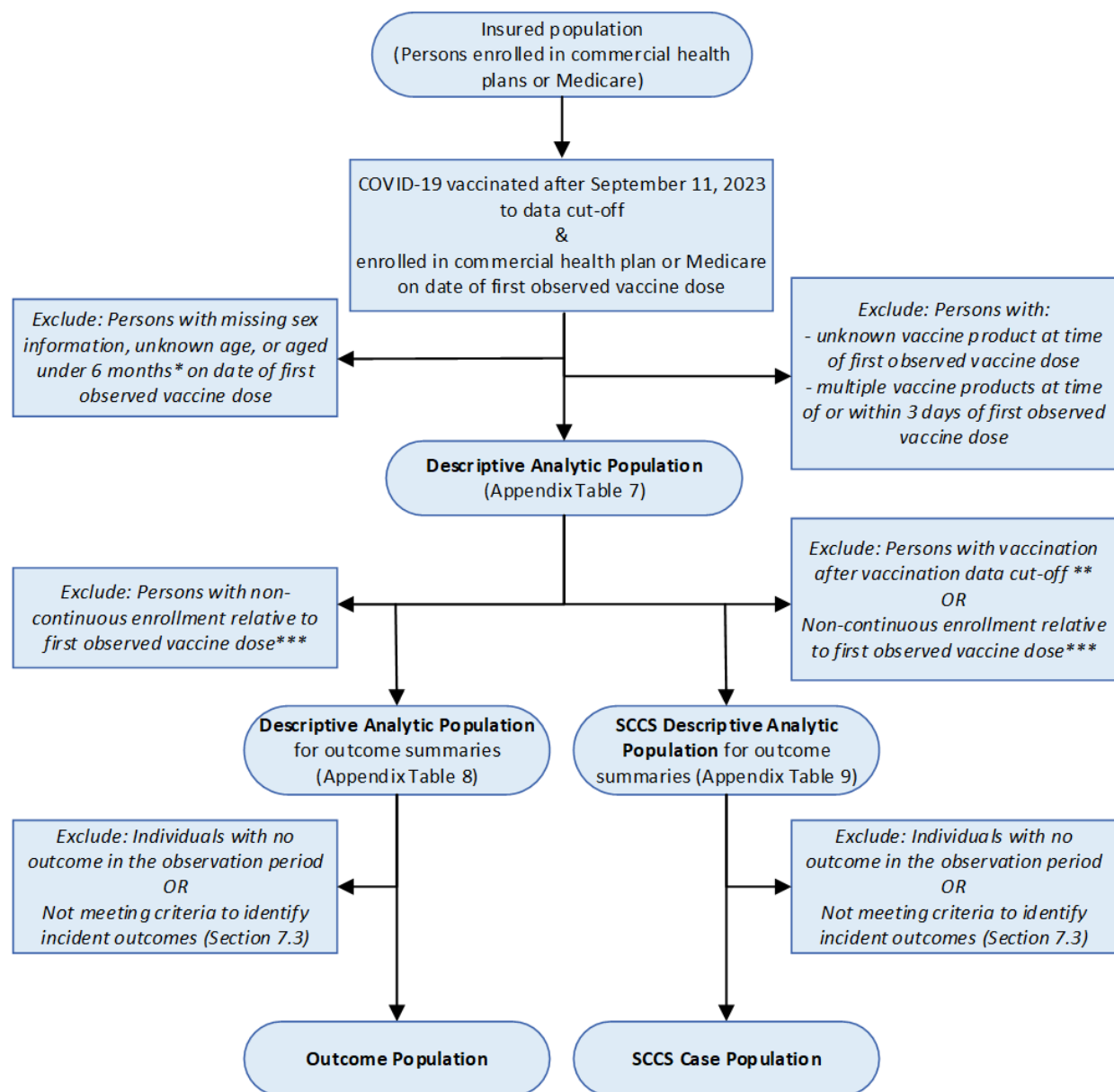
** Average number of annual enrollees in a given age category between 2018-2021

† Number of enrollees in 2023, but only those aged 65 years and older will be included in the study.

5. Study Population

The study population will include individuals aged 6 months and older (commercial health plan population: aged 6 months–64 years, Medicare population: aged 65 years and older) who received a 2023-2024 COVID-19 vaccine dose and met the eligibility criteria for the respective descriptive and inferential analyses (Figure 1).

Figure 1. Population Eligibility Requirements for Descriptive and Inferential Analyses



* Commercial health plan beneficiaries must be aged 6 months-64 years on the date of their first observed vaccine dose for study inclusion, and Medicare beneficiaries must be aged 65 years and older on the date of their first observed vaccine dose for study inclusion.

** Cases eligible for the SCCS analysis will be determined by identifying the number of vaccine exposures whose expected observation period meet a 90% data-completeness threshold. This threshold is met if the last calendar day of the planned

observation period is expected to have 90% or greater data-completeness based on the outcome-specific claims-delay distribution estimated from historical data.

*** Commercial health plan beneficiaries will be required to have continuous enrollment in their respective commercial health plans from 365 days prior to COVID-19 vaccination, except for children aged under 1 year who will require continuous enrollment from 60 days following their birthdate. Medicare FFS beneficiaries will be required to have continuous enrollment in Medicare Parts A and B from 365 days prior to COVID-19 vaccination.

Note: Commercial and Medicare health plan beneficiaries will also require enrollment in a health plan with available prescription or pharmacy health plan data on vaccination date in the secondary analysis only, to ensure comprehensive capture of relevant concomitant immunizations.

6. Study Period

The study start date will be age and vaccine brand-specific, corresponding to the date in which the respective COVID-19 vaccine product was authorized/approved in a given age group.

- 2023-2024 Pfizer-BioNTech COVID-19 Vaccine, 2023-2024 Moderna COVID-19 Vaccine: September 11, 2023 for those 6 months and older^{5,6}
- 2023-2024 Novavax COVID-19 Vaccine: October 3, 2023 for those 12 years and older⁷

COVID-19 vaccines will be captured in the study from the earliest date in which vaccines were authorized/approved for the given age group, through 1 year after the authorization/approval date or until surveillance is deemed no longer necessary by FDA.

7 Study Variables

7.1 Care Setting Definitions

Exposures and outcomes will be identified within relevant care settings of interest based on clinical guidance. These care settings are specific to administrative claims data.

Table 2 defines the inpatient (IP), outpatient and professional (OP/PB), and outpatient emergency department (OP-ED) settings used in this study.

Table 2. Care Setting Definitions

Care Settings	Definition
Inpatient (IP)	Hospital inpatient acute facility claims
Outpatient and Professional (OP/PB)*	Outpatient facility claims or Professional claims that contain at least one non-laboratory place of service**
Outpatient Emergency Department (OP-ED)†	Outpatient facility claims in ED

Note: Admitting diagnoses are excluded in all care settings.

** Including all sources of professional claims (e.g., urgent care)*

*** Independent laboratory place of service code = 81*

† A subset of the OP/PB setting

The IP setting represents hospital inpatient acute facility claims. Hospital inpatient facility claims detail the care and services received by patients during the entire duration of inpatient care. Hospital claims may have more accurate diagnosis coding compared to professional claims, given that provider facilities are reimbursed based on the types of diagnosis coded, which reflect the level of treatment required.

The OP/PB setting represents all outpatient and professional services claims with non-laboratory places of service and captures the broad spectrum of outpatient care regardless of care setting or provider

type. Claims with laboratory places of service are excluded, given that these claims often include “rule-out-diagnoses” that may not reflect existing or underlying conditions present in patients.

The OP-ED setting is a subset of the OP/PB setting and represents outpatient facility claims with services specifically provided in the ED, identified through revenue (REV) codes.

7.2 COVID-19 Vaccine Exposures

The study exposure of interest is receipt of any dose of a 2023-2024 Pfizer-BioNTech, Moderna, or Novavax COVID-19 vaccine. Vaccine doses will be identified in administrative claims data through product-specific codes, defined using Current Procedural Terminology (CPT)/Healthcare Common Procedure Coding System (HCPCS) codes or National Drug Codes (NDCs). CVX codes will be used to identify COVID-19 vaccine exposures in IIS data. The list of valid COVID-19 vaccine codes is specified in Appendix Table 1 and will be continuously reviewed and updated during the course of surveillance.

Based on current vaccine guidance, individuals who have received one or more COVID-19 vaccine doses of any 2023-2024 Formula are included in the study to ensure comprehensive capture of vaccinated individuals (Table 3).¹⁷ The main analysis will evaluate the risk of outcomes for individual vaccine brands separately, across any vaccine dose rather than for individual vaccine doses. The analysis will be restricted to vaccine doses of the same brand (i.e., homologous). If an elevated rate is observed for a specific outcome, exploratory analyses may be performed to assess outcome rates following each individual COVID-19 vaccine dose.

Table 3. Vaccination Schedule for 2023-2024 Updated COVID-19 Vaccines

Population	Age	Number of Recommended 2023-2024 COVID-19 Doses					
		Pfizer-BioNTech		Moderna		Novavax	
		Previously Unvaccinated with COVID-19 Vaccine	Previously Vaccinated with ≥ 1 COVID-19 Vaccine Dose	Previously Unvaccinated with COVID-19 Vaccine	Previously Vaccinated with ≥ 1 COVID-19 Vaccine Dose	Previously Unvaccinated with COVID-19 Vaccine	Previously Vaccinated with ≥ 1 COVID-19 Vaccine Dose
Not Moderately or Severely Immunocompromised	6 mos.-4 yrs.	3	1 or 2*	2	1*	N/A	N/A
	5-11 yrs.	1	1	1	1	N/A	N/A
	12+ yrs.	1	1	1	1	2	1
Moderately/Severely Immunocompromised	6 mos.-4 yrs.	3	1 or 2**	3	1 or 2**	N/A	N/A
	5-11 yrs.	3	1 or 2**	3	1 or 2**	N/A	N/A
	12+ yrs.	3	1 or 2**	3	1 or 2**	2	1

* Individuals with only 1 prior dose of Pfizer-BioNTech are recommended 2 additional homologous COVID-19 vaccine doses, and individuals with 2 or more prior doses of Pfizer-BioNTech are recommended only 1 additional homologous COVID-19 vaccine dose. Individuals who have received 1 or more prior doses of Moderna are recommended 1 additional dose of a homologous COVID-19 vaccine.

** Individuals with only 1 prior dose of Pfizer-BioNTech or Moderna are recommended 2 additional homologous COVID-19 vaccine doses, and individuals with 2 or more prior doses of Pfizer-BioNTech or Moderna are recommended only 1 additional dose of a homologous COVID-19 vaccine.

To deduplicate vaccine exposures i.e., for COVID-19 vaccine exposures identified via multiple sources such as claims and IIS data, we will do the following:

- (i) doses administered within three days of the preceding dose will be consolidated into a single vaccination exposure, regardless of brand;
- (ii) a vaccination exposure of a single vaccine brand will use the date of the first vaccine code observed as the incident vaccination exposure date (day 0);
- (iii) a person with a vaccination exposure of multiple vaccine brands for their first dose will be excluded from the study.
- (iv) a person with a vaccination exposure of multiple vaccine brands for subsequent doses will be included in the study up until the heterologous or unknown brand dose was received.

7.3 Outcomes

Table 4 presents the pre-specified outcomes that will be monitored following COVID-19 vaccination, including specifications for the care settings of interest, clean windows, risk intervals, and control intervals for the statistical analyses ([Section 9](#)). The 2023-2024 COVID-19 Protocol Supplemental File outlines the specific algorithm and codes that will be used to identify outcomes. Outcomes in the observation period are identified in a two-step process: (i) include outcomes that are considered 'incident' after implementing the outcome-specific cleaning window and (ii) retain only the first incident outcome in the observation period.¹⁸

Unless otherwise indicated, each outcome will be monitored in all age groups. If there is a lack of sufficient power to perform the SCCS analysis for a given vaccine brand and outcome, some outcomes may only be descriptively monitored.

The list of outcomes may be updated based on additional evidence including information from other surveillance systems.

Table 4. Outcomes, Care Settings, Clean Windows, Risk Intervals, and Control Intervals for Surveillance

Outcome	Care Setting	Clean Window*	Risk Interval**	Control Interval***
All Populations (ages 6 months and older)				
Acute myocardial infarction	IP	365 days	1-28 days ^{19,20}	29-90 days
Anaphylaxis	IP, OP-ED	30 days	0-1 day ^{21,22}	3-16 days
Appendicitis	IP, OP-ED	365 days	1-42 days ^{23,24}	43-90 days
Deep vein thrombosis	IP, OP/PB	365 days	1-28 days ²⁵⁻²⁷	29-90 days
Disseminated intravascular coagulation	IP, OP-ED	365 days	1-28 days ²⁸	29-90 days
Encephalitis/encephalomyelitis (including acute disseminated encephalomyelitis (ADEM))	IP	183 days	1-42 days ²⁹	43-90 days
Guillain-Barré syndrome (GBS)	IP- primary position only	365 days	1-42 days ^{30,31}	43-90 days
Hemorrhagic stroke (HS) †	IP	365 days	1-21 days ³² 22-42 days ³²	43-90 days
Myocarditis/Pericarditis (Definition 1)	IP, OP-ED	365 days	1-7 days ^{33,34}	8-90 days
Myocarditis/Pericarditis (Definition 2)	IP, OP/PB	365 days	1-7 days ^{33,34}	8-90 days
Non-hemorrhagic stroke (NHS) †	IP	365 days	1-21 days ³² 22-42 days ³²	43-90 days

Outcome	Care Setting	Clean Window*	Risk Interval**	Control Interval***
NHS or Transient ischemic attack (TIA) (NHS/TIA) †	IP (NHS & TIA), OP-ED (TIA)	365 days	1-21 days ³² 22-42 days ³²	43-90 days
Pulmonary embolism	IP	365 days	1-28 days ²⁵⁻²⁷	29-90 days
Transverse myelitis†	IP, OP-ED	365 days	1-42 days ³⁵	43-90 days
Thrombosis with thrombocytopenia syndrome (TTS)	TTS episode‡	365 days	1-28 days ^{36,37}	29-90 days
Pediatric Population (ages 6 months–17 years)				
Multisystem inflammatory syndrome in children (MIS-C)†	IP	180 days	1-42 days ³⁸	43-90 days
Kawasaki disease	IP, OP/PB	365 days	1-28 days ^{39,40}	29-90 days
Ages 6 months–5 years				
Febrile seizure	IP, OP-ED	42 days	0-1 days ⁴¹ 0-7 days ⁴¹	8-63 days

* Clean window is used to define incident outcomes where an individual enters the study cohort only if the outcome of interest did not occur during that interval prior to the observed outcome. For children under 1 year of age, the clean window will be the maximum of either the clean window listed or time since 60-days post-birth. References for the duration of the clean window could not be located in the literature and are instead based on clinician input.

** Risk intervals are determined based on clinical guidance and literature review and are defined as an interval during which excess risk is hypothesized following COVID-19 vaccination.

*** Control interval is defined as all follow-up time during the observation period that is not in the risk interval or in a washout period.

†The algorithm used to identify incident outcomes is complex and is referenced in the Appendix ([Section 14.4](#))

‡TTS is a combined outcome consisting of a thrombotic outcome (e.g., acute myocardial infarction, deep vein thrombosis, etc.) and a thrombocytopenia outcome (defined in the IP, OP/PB setting). The overall setting definition for each thrombotic outcome depends on individual setting definitions for each of these components.

7.4 Covariates

Demographic, medical, and concomitant immunization covariates will be summarized descriptively among all COVID-19 vaccine recipients and among COVID-19 vaccinated persons with an observed outcome. Demographic characteristics will be identified using available data in the commercial health insurance and Medicare enrollment databases. Medical conditions will be identified using ICD-10 diagnosis and procedural codes. Concomitant immunizations will be captured using CPT/HCPCS, NDCs and

CVX codes where applicable ([Section 14.2](#)). Descriptions for all covariates are included in [Section 14.3](#). The following covariates will be summarized:

- (i) Socio-demographic characteristics
 - Sex
 - Age
 - Race/Ethnicity (CMS Medicare only)
 - Urban/Rural Residency Status
 - Health and Human Services (HHS) Region⁴²
 - Facility/Provider type
 - Nursing Home Residency Status⁴³ (CMS Medicare only)
 - Reason for Medicare Eligibility^{44,45} (CMS Medicare only)
 - Medicare-Medicaid Dual Eligibility Status⁴⁶ (CMS Medicare only)
 - Area Deprivation Index (ADI) rank⁴⁷ (CMS Medicare only)
- (ii) Medical conditions or health characteristics (CMS Medicare only and commercial health plan population where feasible)
 - Asthma
 - Blood disorders
 - Chronic lung disease
 - Diabetes
 - Heart disease
 - Kidney disorders
 - Liver disorders
 - Neurological or neurodevelopmental conditions
 - Malignant neoplasms
 - Immunocompromised status⁴⁸ (stratified by the presence or absence of immunocompromised conditions)
 - Charlson Comorbidity Index (CCI)⁴⁹⁻⁵¹
 - Prior hospitalization
 - Prior COVID-19 diagnosis
 - Prior COVID-19 vaccination
- (iii) Concomitant Immunizations
 - For beneficiaries 6 months–49 years:⁵²
 - Hepatitis A vaccine (HAV)
 - Hepatitis B vaccine (HBV)
 - *Hemophilus influenzae* type b (Hib) vaccine (Hib (PRP-T), Hib (PRP-OMP))
 - Measles, mumps and rubella (MMR) vaccine
 - Varicella vaccine (VAR)
 - Rotavirus vaccine (RV1, RV5)
 - Diphtheria, tetanus, and acellular pertussis vaccine (DTaP)
 - Tetanus, diphtheria, and acellular pertussis vaccine (Tdap)
 - Inactivated polio virus vaccine (IPV)
 - Human papillomavirus vaccine (HPV)
 - Meningococcal vaccine (MenACWY-D, MenACWY-CRM, MenACWY-TT, MenB-4C, MenB-FHbp)

- Respiratory Syncytial Virus monoclonal antibodies (RSV-mab [Nirsevimab, Palivizumab] for those aged 6 months – 2 years)
 - Respiratory Syncytial Virus vaccine (RSV)
 - Influenza vaccine (IIV4, ccIV4, RIV4, LAIV4)
 - Pneumococcal vaccine (PCV13, PCV15, PCV20, PPSV23)
 - Zoster vaccine
 - For beneficiaries 50 years and older:⁵²
 - Influenza vaccine (IIV4, ccIV4, RIV4, LAIV4)
 - Pneumococcal vaccine (PCV13, PCV15, PCV20, PPSV23)
 - Respiratory Syncytial Virus (RSV) vaccine
 - Zoster vaccine
- (iv) Dose Number for 2023-2024 COVID-19 vaccines

8. Study Design and Approach

8.1 Self-Controlled Methods

We will use an SCCS design to compare the incidence rate of outcomes during periods of hypothesized excess risk due to the exposure (risk interval) to the incidence rate of outcomes during all other parts of the observation period not in the washout period (control interval). This method assesses outcome incidence within rather than between individuals. The method assumes outcomes will be distributed approximately uniformly over the risk and control intervals if there is no association between the exposure and outcome of interest. If outcomes are concentrated in the risk interval, there is evidence of an association but not necessarily a causal relationship. The SCCS design has a number of assumptions that have to be met in order to ensure unbiased incidence rate estimates, specifically that:

- (i) Occurrence of an outcome does not substantially affect subsequent exposures.
- (ii) Occurrence of an outcome does not affect the length of the observation period.
- (iii) Outcome rates are constant within risk intervals.
 - a) Outcomes must be independently recurrent or rare.
- (iv) Risk and control intervals are correctly specified.

Certain modifications to the SCCS design will be performed to reduce bias from potential violations of these assumptions. Study analyses will be restricted to the post-vaccination control interval to reduce bias from reverse causation, where early occurrences of an outcome affect the likelihood of subsequent exposure (i.e., COVID-19 vaccination). An adjustment developed by Farrington et al. will also be implemented in the CMS Medicare population only to adjust for outcome-dependent observation time.⁵³ This adjustment will be applied to outcomes that meet a pre-specified historical 30-day case fatality rate (CFR) threshold for those aged 65 years and older (Medicare population). The Farrington adjustment will not be applied for the population under 65 years of age (commercial health plan population) given that CFR information will not be available for this group. Outcome-related mortality violates the assumption that outcomes are independent of the observation length; therefore, this adjustment is required to reduce the potential bias from outcome-dependent observation lengths.

8.2. Definition of Observation Period, Risk and Control Intervals

The definitions for the observation periods, risk and control intervals are outcome-specific, and defined below.

8.2.1 Observation Period

The observation period for all outcomes (except anaphylaxis and febrile seizures) will start the day after vaccination (i.e., day 1) and will extend through day 90. The observation period begins on day 1, because outcomes occurring on the day of vaccination may have occurred prior to vaccination (i.e., temporality cannot be established). For anaphylaxis, the observation period will start at day 0, to capture outcomes occurring immediately after vaccination and will extend to day 16. For febrile seizures, the observation period will also start at day 0 and extend to day 63.

Individuals may not be followed through the full length of their observation period if the following censorship criteria occur: death, disenrollment, subsequent heterologous COVID-19 vaccination, subsequent COVID-19 vaccination of unknown brand, or study period end.

8.2.2 Risk Interval

The risk interval is defined as the time during which excess risk is hypothesized following COVID-19 vaccination during the observation period. Risk intervals are outcome-specific and were determined for each outcome based on biological plausibility, literature review, and clinician input (Table 4).

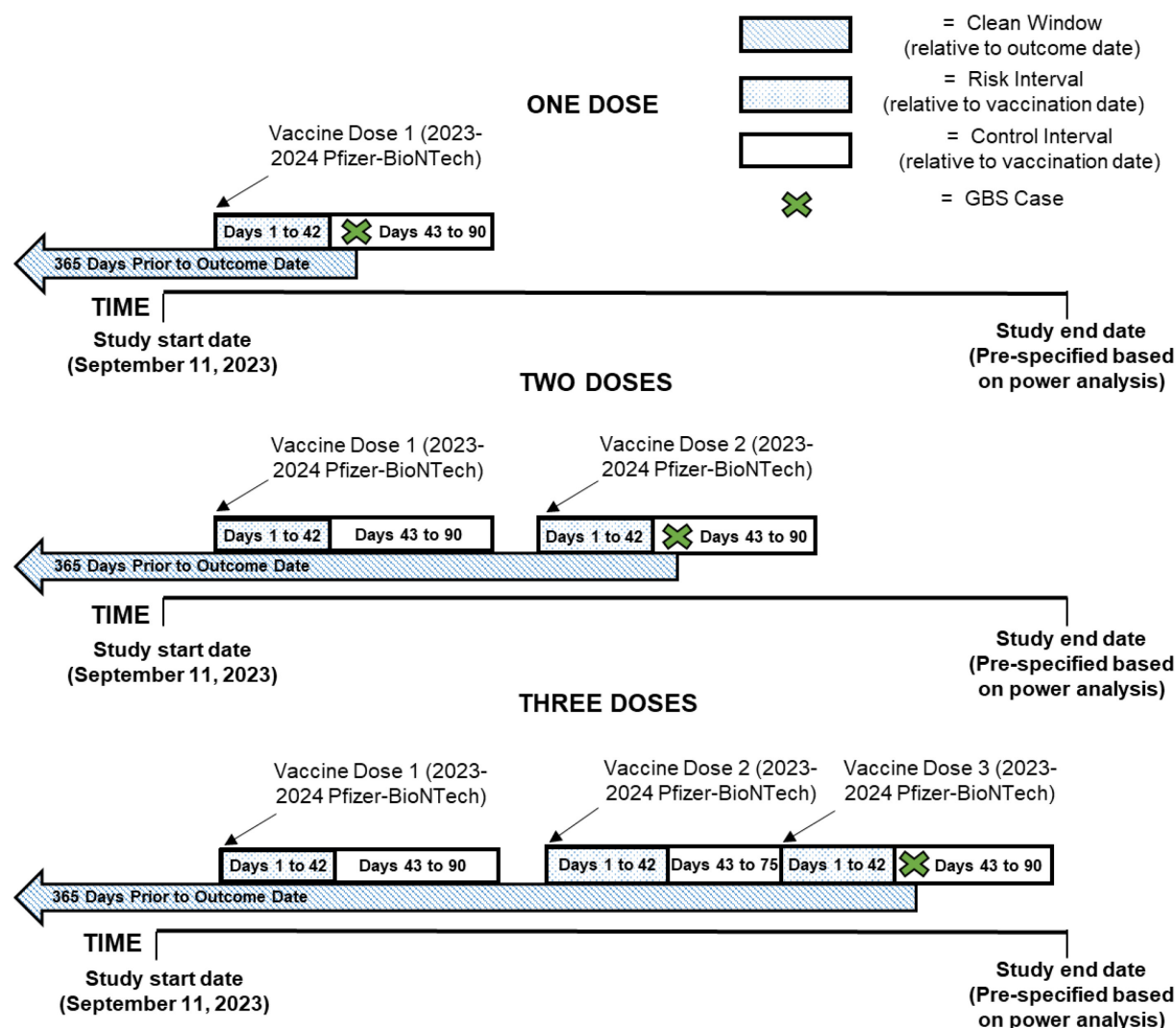
8.2.3 Control Interval

The post-vaccination control interval is defined as all follow-up time during the observation period that is not in the risk interval or washout period.

If an individual receives a subsequent homologous COVID-19 vaccine dose during the risk or control interval of a prior dose, we will censor the prior dose risk or control interval and restart the risk interval for the subsequent dose. For individuals that receive a subsequent heterologous vaccination or vaccination with unknown brand during the risk or control interval of a prior dose, all future follow-up time during their observation period will be censored from the date of the subsequent heterologous vaccination or vaccination with unknown brand.

Figure 2 represents a sample schematic for the risk and control interval definition for individuals with a qualifying GBS event receiving a varying number of COVID-19 vaccine doses. It presents three separate hypothetical scenarios. Within each of these scenarios, the observation period begins the day after vaccination with a 2023-2024 COVID-19 vaccine and extends to day 90 including a risk interval from days 1–42 and a control interval from days 43–90, unless truncated by a subsequent vaccine dose received before the full completion of the 90-day observation period.

Figure 2. Hypothetical Example of Observation Period, Risk, and Control Intervals for an Individual with a Qualifying GBS Outcome Following Vaccination*



* Clean windows, risk intervals, and control intervals will vary by specific outcome.

9. Statistical Analyses

9.1 Descriptive Analyses

Within each of the commercial health insurance and Medicare database populations, we will conduct descriptive analyses to summarize vaccine uptake trends and the characteristics of vaccine recipients and persons that develop an outcome of interest following vaccination. The vaccine uptake summary will be by vaccine brand and dose and assess counts and percentages of demographic characteristics and concomitant immunizations (Appendix Table 7). For commercial health insurance plans, vaccine counts and percentages will be summarized in claims alone (excluding IIS data) and claims and IIS data combined. We will additionally produce a demographic and medical covariate-stratified outcome summary describing the vaccination counts, outcome counts, and outcome rates (per 100,000 person-

years) within individual outcome cohorts, by vaccine brand and dose (Appendix Table 8). A separate demographic and medical covariate-stratified outcome summary will be produced for the SCCS case population providing vaccination counts, outcome counts, and outcome rates (per 100,000 person-years) in outcome-specific cohorts and age groups of interest, by vaccine brand and risk/control interval (Appendix Table 9).

We will also descriptively summarize the frequency of cases with multiple incident outcomes during the observation period and the frequency of cases with death or disenrollment during the observation period, stratified by risk and control interval. All descriptive statistics will be produced on a monthly basis.

9.2 Primary Inferential Analyses

An early SCCS analysis may be conducted in each commercial health plan and the Medicare database to detect potential large associations between any dose of a COVID-19 vaccine brand and pre-specified outcomes during the initial stages of vaccine roll-out. The analysis will be conducted if (i) sufficient sample size is accumulated to detect an incidence rate ratio (IRR) of 3 to 10 with 80% power and a two-sided alpha of 0.01 or (ii) if scientific evidence for regulatory decision-making is needed. Conducting the SCCS analysis shortly after vaccine availability enables the rapid detection of potential safety concerns associated with vaccination that warrant further investigation.

The end-of-surveillance SCCS analysis may be conducted at the end of the surveillance period to detect smaller associations between any dose of a COVID-19 vaccine brand and pre-specified outcomes. This analysis would be conducted following additional accrual of data which would allow for a broader pool of vaccinated persons to be studied. With the increased sample size, the end-of-surveillance analysis would allow for more precise estimation of the association between COVID-19 vaccine exposures and pre-specified outcomes. For vaccine brands and outcomes with sufficient power, the end-of-surveillance analysis date will be determined based on a power analysis that will assess if there are sufficient outcome counts to detect a minimum detectable IRR of 1.2 to 3 following vaccination, at 80% power and a two-sided alpha of 0.01.⁵⁴ However, end-of-surveillance analyses may be performed regardless of power if FDA deems it necessary.

IRR and attributable risk (AR) estimates will be estimated for both early and end-of-surveillance SCCS analyses for vaccine brands and outcomes that are sufficiently powered, as specified in [Section 9.2](#) and [9.3](#). We may produce age-stratified estimates if these analyses are sufficiently powered. Further adjustments to SCCS analyses will be performed to assess the robustness of the IRR and AR estimates ([Section 9.4](#)), with the most adjusted estimates reported as the main analysis estimates because they include the most adjustments for potential confounders that could bias rate estimates. Specifically, we will report the Farrington, seasonality, and PPV-adjusted estimates as the primary estimates in the CMS Medicare population for outcomes with PPV estimates available and that meet a pre-specified historical 30-day CFR threshold. For outcomes with PPV estimates in the CMS Medicare population, however, that do not meet this pre-specified 30-day CFR threshold, we will report the seasonality and PPV-adjusted estimates as the primary estimates. Farrington and seasonality-adjusted estimates will be the primary estimates in the CMS Medicare population for outcomes without PPV estimates available and that meet the pre-specified historical 30-day CFR threshold. For other outcomes without PPV estimates in the CMS Medicare population, however, that do not meet this pre-specified 30-day CFR threshold, we will report the seasonality-adjusted estimates as the primary estimates. CFRs will not be available for the commercial

health plan population, thus we opted to not use the Farrington adjustment for any outcomes in this population. For outcomes with PPV estimates available in the commercial health plan population, the primary estimates will thus be the seasonality and PPV-adjusted estimates. However, for outcomes without PPV estimates in the commercial health plan population, the primary estimates will be the seasonality-adjusted estimates.

9.2.1 IRR Estimation and AR Estimation

If performed, early and end-of-surveillance SCCS analyses will be conducted separately in each of the commercial health plan and Medicare databases. Where sufficiently powered, we will estimate the IRR and AR of outcomes following receipt of updated COVID-19 vaccine doses in risk compared to control intervals for each COVID-19 vaccine brand and outcome. Age-stratified estimates by vaccine brand and outcome may also be produced, if these analyses are sufficiently powered. Age groups for the age stratification will be 6 months–17 years (smaller subgroups if feasible), 18–64 years, and over 65 years. Different age groups may be considered given the background age distribution of some outcomes in the population (e.g., myocarditis/pericarditis).

To estimate the IRR, analyses will compare the outcome rates in risk and control intervals within the same individual using conditional Poisson regression. Additional adjustments (i.e. Farrington, seasonality and/or PPV) will be performed as specified in [Section 9.4](#).

$$\log(E(Y|X)) = \beta_1(\text{risk_interval}) + \log(t) + \text{strata}(\text{patient_id})$$

$Y = \text{Outcome}$

$\text{risk}_{\text{interval}} = \text{binary term indicating outcome occurrence in risk interval}$

$t = \text{number of days in the interval}$

$\text{patient}_{id} = \text{term identifying the patient}$

Under this model, the null and alternative hypotheses are written as, respectively:

$$H_0: e^{\beta_1} = 1 \quad H_a: e^{\beta_1} \neq 1$$

where e^{β_1} will be interpreted as the IRR for the outcome in the risk interval compared to the control interval. Statistical significance will be determined using a two-sided hypothesis test at a significance level of 0.01.⁵⁴ The significance level was selected to reduce the probability of false positive results given the large number of outcomes being studied.⁵⁴ The 95% and 99% confidence intervals for the IRR will be estimated to assess the precision of estimates.

For both early and end-of-surveillance SCCS analyses, the study will also estimate an AR per 100,000 vaccinations and per 100,000 person-years, which will represent the excess number of outcomes associated with vaccination per 100,000 doses and per 100,000 person-years respectively.⁵⁵ The excess number of outcomes within the study population will be calculated by the difference between the expected number of outcomes based on the model and the expected number of outcomes assuming no exposure.

$$\text{Excess Outcomes associated with Vaccination} = E(Y) - E(Y|\text{No exposure}) = \sum_{i=1}^m (E(Y_i|X_i) - E(Y_i|X_i = 0))$$

Y = number of outcomes

m = total number of persons in the study population

Y_i = outcome status of the i th person in the study population

X_i = exposure status of the i th person, where $X_i = 0$ denotes the hypothetical absence of exposure

The AR per 100,000 doses (and per 100,000 person-years) will then be calculated by dividing the excess number of outcomes associated with vaccination by the number of eligible doses (or eligible person-years) and multiplying by 100,000.

The standard error (SE) of the AR is estimated by bootstrap resampling 10,000 times. For each iteration, this study will sample the beneficiaries with outcomes with replacement and calculate the AR. The SE is calculated as the square root of the variance of the 10,000 AR values.

9.3 Secondary Inferential Analyses: Concomitant Immunizations Subgroup Analysis

To evaluate the possibility of outcomes occurring due to administration of COVID-19 vaccines on the same date as other immunizations, a subgroup analysis will be performed based on same-day concomitant immunization status in select circumstances. One subgroup will contain persons with the pre-specified concomitant immunizations observed on the same date as COVID-19 vaccination, and another subgroup will contain persons without any of the pre-specified concomitant immunizations. This analysis will only be performed for outcomes where the primary analysis IRR is elevated and the two-sided p-value is less than or equal to 0.1, a less stringent threshold than the statistical significance threshold of 0.01.⁵⁴ These subgroup analyses will be implemented consistently with the primary analyses specified in [Section 9.2.1](#). Concomitant immunizations of interest for the subgroup analyses will include the immunizations listed in [Section 7.4](#).

9.4 Adjustments to the Primary and Secondary Inferential Analyses

9.4.1 Seasonality Adjustment (Including Farrington Adjustment in CMS Medicare Population for Outcomes Meeting CFR Threshold)

Both the primary and secondary analyses specified in [Section 9.2](#) and [9.3](#) will include a seasonality adjustment for all outcomes. The seasonality adjustment will account for seasonal patterns in outcome incidence rates. Specifically, we will adjust for changes in the baseline rate of outcomes during different calendar months in 2022. The baseline outcome rate will be estimated from a similar population (same age groups in each database) during the same calendar months in 2022, and subsequently included as an offset term in the regression model.

A Farrington adjustment will also be included in the model for the CMS Medicare population only, specifically for outcomes that meet a pre-specified historical 30-day CFR threshold to adjust for outcome-dependent observation time.⁵³ The Farrington and seasonality-adjusted model is defined below.

$$\log(E(Y|X)) = \beta_1 * risk_interval + \log(w(t)) + \log(seasonal_risk) + strata(patient_id)$$

$Y = Outcome$

$risk_interval = binary\ term\ indicating\ AE\ occurrence\ in\ risk\ interval$

$w(t) = Farrington\ adjusted\ weight$

$$seasonal_risk = \frac{1}{IR_r * t} \sum_{m=1}^{12} (IR_m * t_m)$$

$IR_m = daily\ incident\ rate\ for\ month\ 'm'$

$IR_r = daily\ incident\ rate\ for\ reference\ month\ 'r'$

$$t_m = number\ of\ days\ in\ an\ interval\ in\ month\ 'm'\ or\ equivalently\ t = \sum_{m=1}^{12} t_m$$

$patient_id = term\ identifying\ the\ patient$

In this model, the null and alternative hypotheses can be written as, respectively:

$$H_0: e^{\beta_1} = 1 \quad H_a: e^{\beta_1} \neq 1$$

9.4.2 Positive Predictive Value (PPV) Adjustment (Including Farrington Adjustment in CMS Medicare Population for Outcomes Meeting CFR Threshold)

Primary and secondary analyses will also include PPV adjustments for outcomes with PPVs available from previously conducted medical record review (MRR). Particularly for outcomes in the CMS Medicare population with PPV estimates available and that meet a pre-specified historical 30-day CFR threshold, a combined model will be implemented including both PPV and Farrington adjustments to adjust for outcome-dependent observation time.⁵³

To reduce bias from outcome misclassification based on claims-based outcome definitions, PPV-adjusted analyses will be performed through quantitative bias analyses (QBAs) using PPVs available from prior MRR of outcomes following vaccine exposures. The PPV was calculated as the number of chart-confirmed cases over the total number of charts identified using the claims-based outcome definition and returned via the abstraction process. Cases with “insufficient evidence” were not considered chart-confirmed or used in estimating the PPV. Currently, PPVs are only available for a subset of outcomes relevant to the commercial health plan and Medicare populations. Table 5 presents the PPV estimates that will be used for the PPV-adjusted analysis based on prior MRR.

Where PPVs are available, QBA will be conducted by creating multiple datasets where the status of claims-identified cases is imputed by assigning them the status of “chart-confirmed” with the probability equal to the PPV. Analyses conducted on each of the individual imputed datasets will be combined using a rule developed by Schenker and Rubin (1986).⁵⁶ Assuming normality of the coefficient estimates, the z-statistic can be calculated by dividing the coefficient estimate by the model’s standard error. The corresponding p-value can be determined from the z-statistic.

MRR and PPV-adjusted analyses may be performed for additional outcomes, with a statistically significant increase in IRRs identified from primary and secondary analyses. [Section 10](#) provides more detailed information on the planned MRR approach.

Table 5. Outcome Positive Predictive Value (PPV) Estimates from Prior MRR

Outcome (Care Settings*)	PPVs (95% CI)
Medicare Population (65 years and older)	
Acute Myocardial Infarction (IP)	80.00% (70.60%, 87.00%) ¹³
Anaphylaxis (IP, OP-ED)	66.00% (56.00%, 76.00%) ⁵⁷
Guillain-Barré Syndrome (IP–Primary Diagnosis only)	71.00% (63.00%, 79.00%) ⁵⁸
Myocarditis/Pericarditis (IP, OP-ED)	40.00% (16.82%, 68.73%)
Pulmonary Embolism (IP)	83.33% (69.40%, 91.68%) ¹³
Commercial Health Plan Population (6 months–64 years)	
Myocarditis/Pericarditis (IP, OP-ED)	87.80% (74.46%, 94.68%)

Acronym: IP: inpatient, OP-ED: outpatient emergency department

*Care setting definitions are described in [Section 7.1](#).

9.4.3 Seasonality and Positive Predictive Value (PPV) Adjustments (Including Farrington Adjustment in CMS Medicare Population for Outcomes Meeting CFR Threshold)

For outcomes with a PPV available, an additional analysis will be performed including a combined seasonality and PPV adjustment. A Farrington adjustment will additionally be included for the CMS Medicare population only, for a subset of these outcomes that meet the pre-specified historical 30-day CFR threshold to reduce bias from event-dependent observation time.⁵³

9.5 Sensitivity Analyses

9.5.1 Assessment of Washout Period between Risk and Control Intervals

To assess the sensitivity of results to the selection of the post-vaccination risk and control intervals, we will also re-run analyses with a washout period between the intervals.

9.5.2 Exclusion of Persons with COVID-19 in the Past 30 Days

Certain outcomes included in the study have been associated with COVID-19 including pulmonary embolism and myocarditis/pericarditis.^{59,60} To assess the potential influence of recent COVID-19 on results, we will descriptively summarize the frequency of cases with an observed COVID-19 diagnosis in the 30 days prior to the monitored health outcome as specified in [Section 9.1](#). For outcomes with a substantive population with an observed COVID-19 diagnosis in the 30 days prior to their incident outcome diagnosis, we will conduct a sensitivity analysis where we exclude individuals who had a medically-attended COVID-19 diagnosis during this timeframe.

9.5.3 Full Planned Observation Time

To assess the robustness of the Farrington adjustment, a sensitivity analysis will be conducted for outcomes that used a Farrington adjustment in the primary analysis in which the full planned observation time is credited to each individual, regardless of death or disenrollment. No Farrington adjustment will be made as the observation time is not conditional on outcomes.

9.6 Meta-Analyses (Commercial Health Plan Population Analyses Only)

Early and end-of-surveillance SCCS analyses in commercial health plan populations will include a meta-analysis component. A common study protocol and a standard analytical package will be used across all three commercial health claims databases that cover populations with similar demographics, and thus will exclude the Medicare population. A meta-analysis will be performed to pool results from all three commercial health databases to gain higher precision and statistical power using both random-effects and fixed-effect models.

The goal of the meta-analysis is to estimate the pooled result:

$$\hat{\theta} = \frac{\sum_{k=1}^K \hat{\theta}_k \omega_k}{\sum_{k=1}^K \omega_k}$$

Where $\hat{\theta}_k$ is used to represent the estimator (log of IRR) estimated from each data source, where $k = 1, 2, 3$ indicates the data sources—Optum, Carelon Research, CVS Health, respectively; ω is a weight assigned to each estimate.

Random-Effects Meta-Analysis

We will use random-effects meta-analysis to account for the between-study heterogeneity across multiple data sources.

The random-effects model takes the form:

$$\hat{\theta}_k = \mu + \zeta_k + \epsilon_k$$

Where μ is the global true effect of interest, ζ_k is a data source specific random error term and ϵ_k is data source specific sampling error term.

The pooled effect can be estimated by the inverse-variance method

$$\hat{\theta} = \frac{\sum_{k=1}^K \hat{\theta}_k \omega_k^*}{\sum_{k=1}^K \omega_k^*}$$

$$\omega_k^* = \frac{1}{s_k^2 + \tau^2}$$

where s_k^2 represents variance of $\hat{\theta}_k$ estimated for each study, and τ^2 is the variance of the distribution of true effect size.

The Paule-Mandel method will be used to estimate τ^2 as suggested by Veroniki (2016) and Bakbergenuly (2020) who additionally found that the Paule-Mandel estimator is well-suited for when the number of

studies is small. As a sensitivity analysis, we will use the DerSimonian-Laird and restricted maximum likelihood (RMLE) estimators for τ^2 in order to assess the variation in the estimation of τ^2 due to the small number of studies.

Fixed-Effect Meta-Analysis

To address concerns that the random-effects method may not perform well when the number of studies is small, we will additionally run a fixed-effect meta-analysis. The fixed-effects model takes the form:

$$\hat{\theta}_k = \mu + \epsilon_k$$

Where μ is the global true effect of interest, and ϵ_k is data source specific sampling error term. The pooled effect can be estimated by the inverse-variance method

$$\hat{\theta} = \frac{\sum_{k=1}^K \hat{\theta}_k \omega_k}{\sum_{k=1}^K \omega_k}$$

$$\omega_k = \frac{1}{s_k^2}$$

where s_k^2 represents variance of $\hat{\theta}_k$ estimated for each study.

Evaluating Between-Study Heterogeneity

Heterogeneity in a meta-analysis refers to the variation between studies. Evaluating the extent of heterogeneity helps determine the appropriateness of combining different studies. This section describes the methods we will use to evaluate between-study heterogeneity.

Forest Plots

Forest plots will be generated to visualize the variation of IRRs and 95% CIs across data sources.

Cochran's Q

Cochran's Q is defined as a weighted sum of squares (WSS).

$$Q = \sum_{k=1}^K \omega_k (\hat{\theta}_k - \hat{\theta})^2$$

We will use the value of Q to check if there is excess variation in our data. If there is no between-study heterogeneity, Q will approximately follow a chi-square distribution with K-1 degrees of freedom. As Q may be sensitive to the number of studies assessed, an additional complementary statistic will be assessed (further details below).

Higgins & Thompson's I² Statistic

We will also calculate Higgins & Thompson's I² statistic, which is defined as the percentage of variability in the effect sizes that is not caused by sampling error:

$$I^2 = \frac{Q - (K - 1)}{Q}$$

- $I^2 = 25\%$: low heterogeneity
- $I^2 = 50\%$: moderate heterogeneity
- $I^2 = 75\%$: substantial heterogeneity

The 95% CI for I^2 will also be calculated.

9.7 Statistical Power Calculations

Power analyses will be performed to determine when the analyses can be conducted with sufficient sample size to detect the prespecified differences in outcome incidence rate estimates with 80% power and a two-sided alpha of 0.01. For each COVID-19 vaccine brand and outcome, the power for an SCCS analysis will be assessed at various data cut dates. Additional power analyses may be performed for each COVID-19 vaccine brand and outcome within various age groups to determine power for producing age-stratified IRR and AR estimates. The power will be assessed by:

- identifying the number of cases eligible for an SCCS analysis under a 90% data-completeness threshold, and
- calculating the power of an SCCS analysis to detect a minimum IRR of 3 to 10 (early SCCS analysis) or 1.2 to 3 (end-of-surveillance SCCS analysis).

Cases eligible for an SCCS analysis will be determined by first identifying the number of vaccine exposures whose expected observation period meet a 90% data-completeness threshold. This threshold is met if the last calendar day of the planned observation period is expected to have 90% or greater data-completeness based on the outcome-specific claims-delay distribution estimated from historical data. Cases from this vaccinated population will be used in the power analyses.

A 90% threshold for data completeness is required at the specified data cutoff date to reduce differences in data accrual and the likelihood of observing outcomes during risk relative to control intervals. Assuming that outcome observation delays are accurately estimated from historical data, a 90% completeness threshold limits the difference in observation of outcomes in risk intervals (at most 100% complete) versus control intervals (at minimum 90% complete). If the true IRR is 1, the bias due to observation delay is $[(1/0.9)-1]*100 = 11\%$. However, in practice, the data completeness for risk and control intervals will fall between 100% and 90% and we expect the potential bias due to claims delay to be smaller. The 90% data completeness is likely to overestimate the IRR by 10% or less.

10. Medical Record Review

Medical record review may be performed for outcomes with a statistically significant elevation in rates identified from the most adjusted primary analysis results. The purpose of MRR will be to evaluate the accuracy of the claims-based outcome definition(s) used to ensure that true outcome cases have been identified in the analysis. Outcome-specific PPVs and 95% CIs will be estimated based on medical record review to assess the probability of outcome misclassification based on the claims-based definition(s) used. Once PPVs are available from MRR for relevant outcomes, a PPV-adjusted analysis may be performed to adjust for bias from outcome misclassification.

If MRR is required, the first step of the MRR process will be to identify the specific claims-identified cases for which records should be requested. Depending on the number of outcomes, records for either all outcomes or a sample (simple random or representative) of outcomes will be requested. Second, a case review form will be developed in collaboration with clinicians based on the selected case definition. This form outlines the key questions that must be answered using the record to obtain the information necessary to assign case classifications (e.g., confirmed case, probable case, not a case, insufficient evidence).

Once records for the claims-identified cases are received, there are three different abstraction-adjudication workflows that can be followed:

1. *Abstraction followed by algorithmic adjudication:* Trained abstractors will first review the records to extract the information from the medical records (i.e., abstract the records) that is needed to adjudicate (i.e., assign case classifications). If the case definition is clear and uniform, the abstracted information will be evaluated to automatically determine case classifications.
2. *Abstraction followed by expert clinician adjudication (with optional algorithmic adjudication):* Trained abstractors will abstract the records. Abstracted information will be provided to clinicians with expertise on the outcome. The clinician will then review this information, in tandem with the record itself, to assign case classifications. Generally, two clinicians will review each record.
3. *Immediate expert clinician adjudication:* In this option, records will be immediately provided to expert clinicians who will then review the record to review and assign case classifications. Generally, two clinicians will review each record.

If abstraction-adjudication workflow options one or two are selected, an abstraction tool, based on the case review form, will need to be developed. Abstractors will use this tool to extract the information from medical records needed to confirm a diagnosis (as well as limited descriptive information, if desired). As part of this process, we must:

1. test the abstraction tool using a small subset of pilot records to ensure that the tool functions as intended; and
2. develop a user guide for abstractors.

If abstraction-adjudication workflow options two or three are selected, arbitration among the expert clinical reviewers must take place to ensure agreement in case classifications. If the two reviewers for each case agree with the classification, that will be set as the final classification. If the two reviewers disagree, we will facilitate discussions between the two reviewers to determine if a consensus can be reached. If, after the discussions, there is still disagreement, a third clinician will review the case to break that tie.

We will leverage any existing outcome case definitions, case review forms, and analysis infrastructure to complete MRR.

11. Ethical Evaluation

This public health surveillance activity is conducted as part of the FDA CBER's surveillance mandate established in the FDA Amendments Act of 2007. This study uses administrative commercial health plan data from three databases (CVS Health, Optum, and Carelon Research), and Medicare claims data. The

study involves no direct intervention on study participants; data used in this study is de-identified and anonymized before its use; the analysis is conducted in a Federal Information Security Management Act compliant environment; and the results are presented in aggregate.

Using commercial health plan and Medicare administrative data for this public health surveillance activity is permitted under the Health Insurance Portability and Accountability Act Privacy Rule for public health practice without individual authorization. Furthermore, public health surveillance activities, including this study, are not subject to the Common Rule as verified in the Office of Human Research Protections correspondence.⁶¹ Therefore, public health surveillance activities within the Sentinel/BEST Initiative are exempt from Institutional Review Board review and approval. In addition, our study practices are performed in accordance with the Declaration of Helsinki guidelines.⁶²

12. Quality Assurance and Control

The analyses described in this protocol will be conducted using commercial health plan and Medicare databases which are well-characterized databases, in which the Office of Biostatistics and Pharmacovigilance (OBPV) has previously conducted numerous epidemiologic studies. The current study team will perform quality control measures in the databases such as executing verification checks, examining the validity of claims data variables, evaluating stability of enrollment and health outcome trends, and assessing consistency with population selection criteria for the database.

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14. Appendix

14.1 2023-2024 COVID-19 Vaccine Product Code List

Appendix Table 1 presents 2023-2024 COVID-19 vaccine product codes available in CPT, HCPCS, and NDC standardized vocabularies as of September 21, 2023. CVX codes are used in IIS data to identify immunization exposures and will supplement claims data in identifying COVID-19 vaccine administrations in IIS data. This code list will undergo further review and revision during the surveillance process.

Appendix Table 1. COVID-19 Vaccine (2023-2024 Formula) Product Code List

Manufacturer	Name	Code Type	Code	Age Group
Moderna	Moderna COVID-19 Vaccine (2023-2024 Formula)	HCPCS/CPT	91322	12+ years
Moderna	Moderna COVID-19 Vaccine (2023-2024 Formula)	HCPCS/CPT	91321	6 months-11 years
Moderna	Moderna COVID-19 Vaccine (2023-2024 Formula)	CVX (IIS-Specific)	312	12+ years
Moderna	Moderna COVID-19 Vaccine (2023-2024 Formula)	CVX (IIS-Specific)	311	6 months-11 years
Moderna	Moderna COVID-19 Vaccine (2023-2024 Formula)	NDC	80777-0102-96	12+ years
Moderna	Moderna COVID-19 Vaccine (2023-2024 Formula)	NDC	80777-0102-93	12+ years
Moderna	Moderna COVID-19 Vaccine (2023-2024 Formula)	NDC	80777-0102-01	12+ years
Moderna	Moderna COVID-19 Vaccine (2023-2024 Formula)	NDC	80777-0102-95	12+ years
Moderna	Moderna COVID-19 Vaccine (2023-2024 Formula)	NDC	80777-0102-04	12+ years
Moderna	Moderna COVID-19 Vaccine (2023-2024 Formula)	NDC	80777-0287-92	6 months-11 years
Moderna	Moderna COVID-19 Vaccine (2023-2024 Formula)	NDC	80777-0287-07	6 months-11 years
Novavax	Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula)	HCPCS/CPT	91304	12+ years
Novavax	Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula)	CVX (IIS-Specific)	313	12+ years
Novavax	Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula)	NDC	80631-0105-02	12+ years
Novavax	Novavax COVID-19 Vaccine, Adjuvanted (2023-2024 Formula)	NDC	80631-0105-01	12+ years
Pfizer-BioNTech	Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula)	HCPCS/CPT	91320	12+ years
Pfizer-BioNTech	Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula)	HCPCS/CPT	91319	5-11 years
Pfizer-BioNTech	Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula)	HCPCS/CPT	91318	6 months-4 years
Pfizer-BioNTech	Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula)	CVX (IIS-Specific)	309	12+ years
Pfizer-BioNTech	Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula)	CVX (IIS-Specific)	310	5-11 years
Pfizer-BioNTech	Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula)	CVX (IIS-Specific)	308	6 months-4 years

Manufacturer	Name	Code Type	Code	Age Group
Pfizer-BioNTech	Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula)	NDC	00069-2362-10	12+ years
Pfizer-BioNTech	Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula)	NDC	00069-2392-10	12+ years
Pfizer-BioNTech	Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula)	NDC	00069-2362-01	12+ years
Pfizer-BioNTech	Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula)	NDC	00069-2392-01	12+ years
Pfizer-BioNTech	Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula)	NDC	59267-4331-02	5-11 years
Pfizer-BioNTech	Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula)	NDC	59267-4331-01	5-11 years
Pfizer-BioNTech	Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula)	NDC	59267-4315-02	6 months-4 years
Pfizer-BioNTech	Pfizer-BioNTech COVID-19 Vaccine (2023-2024 Formula)	NDC	59267-4315-01	6 months-4 years

Acronyms: HCPCS: Healthcare Common Procedure Coding System; NDC: National Drug Code; CVX: Vaccine Administered Codes.

14.2 Concomitant Immunization Code List

Appendix Table 2. Concomitant Immunization Code List

Vaccine	CVX	CPT / HCPCS	NDC		
Influenza vaccine (IIV4, cclV4, RIV4, LAIV4)	149	90662	19515-0814-41	49281-0423-50	66019-0310-01
	150	90672	19515-0814-52	49281-0423-58	66019-0310-10
	158	90674	33332-0323-03	49281-0423-88	70461-0123-03
	171	90682	33332-0323-04	49281-0639-15	70461-0123-04
	185	90686	33332-0423-10	49281-0639-78	70461-0323-03
	186	90687	33332-0423-11	49281-0723-10	70461-0323-04
	197	90688	49281-0123-65	49281-0723-88	70461-0423-10
	205	90694	49281-0123-88	58160-0909-41	70461-0423-11
		90756	49281-0423-10	58160-0909-52	
Pneumococcal conjugate vaccine (PCV13, PCV15, PCV20), Pneumococcal polysaccharide vaccine (PPSV23)	33	90670	00005-1971-01	00006-4329-02	00006-4943-01
	133	90671	00005-1971-02	00006-4329-03	50090-6026-00
	215	90677	00005-1971-04	00006-4739-00	50090-6026-01
	216	90677	00005-1971-05	00006-4739-01	54868-3339-01
		90732	00005-2000-01	00006-4837-01	54868-3339-09
		G0009	00005-2000-02	00006-4837-02	54868-4320-00
			00005-2000-10	00006-4837-03	54868-4320-09
			00006-4329-01	00006-4943-00	
Hepatitis A*	52	90632	00006-4095-01	50090-1502-00	58160-0815-52
	83	90633	00006-4095-02	50090-1502-09	58160-0825-01
	84	90634	00006-4095-09	55045-3841-01	58160-0825-11
	85	90636	00006-4096-01	58160-0815-01	58160-0825-43
	104	90730	00006-4096-02	58160-0815-05	58160-0825-52
			00006-4096-09	58160-0815-11	58160-0826-01
			00006-4831-01	58160-0815-34	58160-0826-05
			00006-4831-41	58160-0815-41	58160-0826-11
			00006-4841-00	58160-0815-43	58160-0826-34
Hepatitis B*			00006-4841-01	58160-0815-46	58160-0826-43
			00006-4841-41	58160-0815-48	58160-0826-52
Hepatitis B*	8	90371	00006-4093-01	43528-0003-05	58160-0820-01
	30	90636	00006-4093-02	50090-3469-00	58160-0820-11
	42	90697	00006-4093-09	50090-3469-09	58160-0820-43
	43	90723	00006-4094-01	54868-0734-00	58160-0820-52
	44	90731	00006-4094-02	54868-2219-00	58160-0821-01
	45	90739	00006-4094-09	54868-2219-01	58160-0821-05
	51	90740	00006-4898-00	58160-0811-41	58160-0821-11
	104	90743	00006-4898-01	58160-0811-43	58160-0821-34
	110	90744	00006-4980-00	58160-0811-51	58160-0821-43
	146	90745	00006-4981-00	58160-0811-52	58160-0821-52
	189	90746	00006-4981-01	58160-0815-01	63361-0243-10
	220	90747	00006-4992-00	58160-0815-05	63361-0243-15
		90748	00006-4992-01	58160-0815-11	63361-0243-58
		90759	00006-4995-00	58160-0815-34	63361-0243-88
			00006-4995-01	58160-0815-41	63361-0245-10
			00006-4995-41	58160-0815-43	63361-0245-58
			43528-0002-01	58160-0815-46	75052-0001-01
			43528-0002-05	58160-0815-48	75052-0001-10
			43528-0003-01	58160-0815-52	
Human Papillomavirus (HPV)*	62	90649	00006-4045-00	00006-4119-01	50090-4958-01
	118	90650	00006-4045-01	00006-4119-02	58160-0830-05
	165	90651	00006-4045-41	00006-4119-03	58160-0830-34
			00006-4109-01	00006-4121-01	58160-0830-43
			00006-4109-02	00006-4121-02	58160-0830-52
			00006-4109-09	50090-4958-00	

Vaccine	CVX	CPT / HCPCS	NDC		
<i>Hemophilus influenzae</i> type b (Hib)*	22	90644	00006-4897-00	49281-0547-58	
	46	90645	00006-4897-01	49281-0548-58	58160-0816-05
	47	90646	00006-4898-00	49281-0560-05	58160-0818-11
	48	90647	00006-4898-01	49281-0561-01	63361-0243-10
	49	90648	49281-0510-05	58160-0801-11	63361-0243-15
	50	90697	49281-0511-05	58160-0806-01	63361-0243-58
	51	90698	49281-0544-58	58160-0806-05	63361-0243-88
	120	90720	49281-0545-03	58160-0809-01	63361-0245-10
	146	90721	49281-0545-05	58160-0809-05	63361-0245-58
	148	90748	49281-0545-15	58160-0816-01	
Measles, mumps and rubella (MMR)*	3	90707	00006-4171-00	00006-4681-01	54868-0980-00
	94	90710	00006-4171-01	00006-4999-00	58160-0824-15
			00006-4681-00	00006-4999-01	58160-0831-03
Meningococcal*	32		00005-0100-01	49281-0488-78	
	114	90619	00005-0100-02	49281-0489-01	58160-0809-05
	136	90620	00005-0100-05	49281-0489-91	58160-0827-03
	148	90621	00005-0100-10	49281-0589-05	58160-0827-30
	162	90644	46028-0114-01	49281-0589-58	58160-0955-09
	163	90733	46028-0114-02	49281-0590-05	58160-0958-01
	203	90734	46028-0114-11	49281-0590-58	58160-0959-01
			46028-0208-01	50090-6180-00	58160-0976-02
			46028-0218-11	50090-6180-01	58160-0976-06
			46028-0219-11	58160-0801-11	58160-0976-20
Varicella*	21	90396	00006-4171-00	00006-4826-01	
	36	90710	00006-4171-01	00006-4827-00	00006-4999-00
	94	90716	00006-4826-00	00006-4827-01	00006-4999-01
Rotavirus*	116	90680	00006-4047-01	00006-4047-41	58160-0851-01
	119	90681	00006-4047-02	58160-0740-02	58160-0854-52
			00006-4047-20	58160-0740-21	
Tetanus [i.e., Diphtheria, tetanus, and acellular pertussis (DTap); Tetanus, diphtheria, and acellular pertussis (Tdap); Tetanus and diphtheria toxoids (Td)]*	1		00006-4133-01	49281-0400-15	58160-0810-11
	9		00006-4133-41	49281-0400-20	58160-0810-43
	13	90389	13533-0131-00	49281-0400-58	58160-0810-52
	20	90619	13533-0131-01	49281-0400-88	58160-0811-41
	22	90696	14362-0111-03	49281-0400-89	58160-0811-43
	28	90697	14362-0111-04	49281-0510-05	58160-0811-51
	35	90698	17478-0131-00	49281-0511-05	58160-0811-52
	50	90700	17478-0131-01	49281-0544-58	58160-0812-01
	106	90701	21695-0413-01	49281-0545-15	58160-0812-11
	110	90702	49281-0215-10	49281-0548-58	58160-0812-43
	113	90703	49281-0215-15	49281-0560-05	58160-0812-52
	115	90714	49281-0215-58	49281-0561-01	58160-0842-01
	120	90715	49281-0215-88	49281-0562-10	58160-0842-05
	130	90720	49281-0225-10	49281-0562-58	58160-0842-11
	146	90721	49281-0225-58	49281-0564-10	58160-0842-34
	196	90723	49281-0278-10	49281-0564-15	58160-0842-41
	203		49281-0286-01	49281-0564-58	58160-0842-43
			49281-0286-05	49281-0564-88	58160-0842-51
			49281-0286-10	49281-0800-83	58160-0842-52
			49281-0286-58	49281-0820-10	63361-0243-10
			49281-0291-10	50090-2062-00	63361-0243-15
			49281-0291-83	50090-2062-01	63361-0243-58
			49281-0298-10	50090-2883-00	63361-0243-88
			49281-0400-05	50090-2883-09	63361-0245-10
			49281-0400-10	58160-0810-01	63361-0245-58

Vaccine	CVX	CPT / HCPCS	NDC		
Inactivated polio virus (IPV)*			49281-0510-05	49281-0564-58	58160-0811-52
			49281-0511-05	49281-0564-88	58160-0812-01
			49281-0544-58	49281-0860-10	58160-0812-11
	10	90696	49281-0545-15	49281-0860-55	58160-0812-43
	110	90697	49281-0548-58	49281-0860-78	58160-0812-52
	120	90698	49281-0560-05	49281-0860-88	63361-0243-10
	130	90713	49281-0561-01	50090-1693-00	63361-0243-15
	146	90723	49281-0562-10	50090-1693-09	63361-0243-58
			49281-0562-58	58160-0811-41	63361-0243-88
			49281-0564-10	58160-0811-43	63361-0245-10
			49281-0564-15	58160-0811-51	63361-0245-58
Respiratory syncytial virus (RSV)	303	90678	00069-0207-01	00069-0344-05	58160-0744-03
	304	90679	00069-0250-01	00069-0344-10	58160-0848-11
	305		00069-0344-01	58160-0723-03	
Zoster vaccine	36	90396	00006-4963-00	50090-5147-00	58160-0828-01
	121	90736	00006-4963-01	58160-0819-12	58160-0828-03
	187	90750	00006-4963-41	58160-0823-11	

*Vaccine categories include any combination of vaccines that captures the individual vaccine component.

14.3 Covariate Definitions

Appendix Table 3. Description of Covariates

Characteristics	Description
Sex	Sex is determined using the most recent available sex data in the Medicare and commercial enrollment databases, at the time of the individual's first observed COVID-19 vaccine dose. It is a categorical variable that is stratified by male and female.
Age	Age is defined as a person's age at the time of their first observed COVID-19 vaccine dose. Persons will be stratified by the following groups: • Commercial health plans: ages 6 months - 4 years, 5-11, 12-15, 16-17, 18-25, 26-35, 36-45, 46-55, 56-64 years • CMS Medicare FFS: ages 65-69, 70-74, 75-79, 80-84, 85-89, and ≥90 years
Race/Ethnicity (CMS Medicare Only)	Race/Ethnicity using the most recent data in the Medicare database, at the time of the individual's first observed COVID-19 vaccine dose. The variable will be stratified by: • Asian • Black • Hispanic • American Indian/Alaskan Native • White • Other • Missing/Unknown
Urban/Rural	The core-based statistical area (CBSA), which categorizes areas as micropolitan or metropolitan, was assigned based on the beneficiary's most recently available residential address. This is assessed at the time of the individual's first observed COVID-19 vaccine dose. • Metropolitan statistical areas are CBSAs associated with at least one urbanized area that has a population of at least 50,000 or more population, plus adjacent territory that has a high degree of social and economic integration with the core as measured by commuting ties. Persons falling within this category are classified as urban. • Micropolitan statistical areas are a new set of statistical areas that have at least one urban cluster of at least 10,000 but less than 50,000 population, plus adjacent territory that has a high degree of social and economic integration with the core as measured by commuting ties. Persons falling within this category are classified as rural.

Characteristics	Description
Health and Human Services (HHS) Region ⁴²	The Health and Human Services (HHS) region is assigned based on a person's state of residence, and is determined at the time of an individual's first observed COVID-19 vaccine dose. The HHS regions divide up the country into 10 regions, each representing a regional office that directly serves state and local organizations. These regions include: • Region 1 (Connecticut, Maine, Massachusetts, New Hampshire, Rhode Island, and Vermont) • Region 2 (New Jersey, New York, Puerto Rico, and Virgin Islands) • Region 3 (Delaware, District of Columbia, Maryland, Pennsylvania, Virginia, and West Virginia) • Region 4 (Alabama, Florida, Georgia, Kentucky, Mississippi, North Carolina, South Carolina, and Tennessee) • Region 5 (Illinois, Indiana, Michigan, Minnesota, Ohio, Wisconsin) • Region 6 (Arkansas, Louisiana, New Mexico, Oklahoma, and Texas) • Region 7 (Iowa, Kansas, Missouri, and Nebraska) • Region 8 (Colorado, Montana, North Dakota, South Dakota, Utah, Wyoming) • Region 9 (Arizona, California, Hawaii, Nevada, American Samoa, Commonwealth of the Northern Mariana Islands, Federated State of Micronesia, Guam, Marshall Islands, and Republic of Palau) • Region 10 (Alaska, Idaho, Oregon, and Washington)
Facility/Provider Type	Facility or provider type will be assessed at the time of the individual's first observed COVID-19 vaccine dose. This variable will be stratified by: • Hospital • Office Visit • Pharmacy • Skilled Nursing Facility • Home Health Agency • Mass Immunization Center • Other • Missing/Unknown
Nursing Home Residency Status ⁴³ (CMS Medicare Only)	Nursing home residency status will be captured from the Minimum Data Set (MDS) 3.0, a mandatory clinical assessment administered to all residents in Medicare- & Medicaid-certified nursing homes. Nursing home residency status is assessed at the time of an individual's first observed COVID-19 vaccine dose. It is a categorical variable stratified by nursing home residents and non-nursing home residents.

Characteristics	Description
Reason for Medicare Eligibility ^{44,45} (CMS Medicare only)	This represents the original reason for Medicare entitlement determined at the time of an individual's first observed COVID-19 vaccine dose. Persons reason for Medicare eligibility can be classified as: • Aged without ESRD • Aged with ESRD • Disabled without ESRD • Disabled with ESRD • ESRD only The Medicare Status of a beneficiary is identified using the variable 'MDCR_STATUS_CODE_01' commonly found in the CMS Common Medicare Environment (CME) database and is used to distinguish between aged, disabled, and ESRD populations.
Dual-Eligibility Status (CMS Medicare only) ⁶³	Medicare & Medicaid dually eligible beneficiaries are beneficiaries enrolled in both Medicare and Medicaid. The term includes beneficiaries enrolled in Medicare Part A, Part B, or both, and getting full Medicaid benefits or help with Medicare premiums or cost-sharing through one of the Medicare Savings Programs (MSPs) eligibility groups. These MSPs are: Qualified Medicare Beneficiary (QMB) program, Specified Low-Income Medicare Beneficiary (SLMB) program, Qualified Individual (QI) program, and Qualified Disabled Working Individual (QDWI) program. Dual-eligibility status is assessed in the 60 days prior to an individual's first observed COVID-19 vaccine dose.
Area Deprivation Index (ADI) Rank ⁴⁷ (CMS Medicare only)	The Area Deprivation Index (ADI) is an index of seventeen socioeconomic indicators which includes block group measures of education, employment, income, housing, household composition, and household resources. The ADI measure is constructed by ranking the ADI score from low to high for the nation and grouping the blocks into bins corresponding to each 1 percent range of the ADI score. The national ADI ranks block groups from 1 being the least disadvantaged, to 100 being the most disadvantaged in the U.S. It is assessed at the at the time of an individual's first observed COVID-19 vaccine dose.

Characteristics	Description
Medical Conditions (CMS Medicare only, and commercial health plan population where feasible)	The following medical conditions will be monitored for case populations only with a lookback window of 183 days prior to and including the first observed COVID-19 vaccine dose. - Asthma - Blood Disorders - Chronic Lung Disease - Diabetes - Heart Disease - Kidney Disease - Liver Disorders - Neurological / Neurodevelopmental Conditions - Malignant Neoplasms These conditions will be identified using ICD-10-CM codes in IP/OP/PB settings
Immunocompromised Status (CMS Medicare only, and commercial health plan population where feasible)⁴⁸	Immunocompromised status will be determined based on a CBER-adapted algorithm modified from a previously developed and validated algorithm by Greenberg et al. to identify immunocompromised persons. The modified version of the algorithm also includes eight mutually exclusive categories of immunosuppression. Relevant indicators included in the algorithm will be identified in the 183 days prior to the first observed COVID-19 vaccine dose. The conditions will be identified using ICD-10-CM codes and additional codes from AHRQ criteria for identifying individuals at risk of immunosuppression. • HIV / AIDS • Hematological Malignancy and Related Conditions • Immune deficiencies (treatment-dependent and treatment-independent) • Solid Malignancy • Transplant and Related Conditions • Rheumatological / Inflammatory Conditions • Dialysis This variable will be stratified by the presence or absence of immunocompromised status.
Charlson comorbidity index (CMS Medicare only, and commercial health plan population where feasible)^{47,49-51}	The Charlson Comorbidity Index will be used to categorize comorbidities in the case population based on the ICD-10-CM diagnosis codes found in administrative claims data. Each comorbidity category has an associated weight (from 1 to 6) based on the adjusted risk of mortality or resource use and the sum of all the weights. The original index was developed with 19 categories, but has been modified to 17 categories. A score of zero indicates no comorbidities. The higher the score, the higher the predicted mortality rate or the higher the resource use.
Prior Hospitalization (CMS Medicare only, and commercial health plan population where feasible)	The following baseline health characteristic will be monitored for case populations only with a lookback window of 183 days prior to and including the COVID vaccination date. Prior hospitalization will be identified by the presence of an IP stay in the claims data with any diagnoses.

Characteristics	Description
Prior COVID-19 Diagnosis	Prior COVID-19 diagnosis is assessed by identifying outcome cases with a preceding U07.1 code in any care setting in the 30 days prior to and including the incident outcome date.
Prior COVID-19 Vaccination	Prior COVID-19 vaccination is assessed by identifying COVID-19 vaccine CPT and HCPCS codes, or NDCs within 365 days prior to the first observed COVID-19 vaccine dose.
Concomitant Immunizations ⁵²	Concomitant immunizations will be defined as receipt of one of the following vaccinations on the same date as an individual's COVID-19 vaccination: For beneficiaries 6 months–49 years: • Hepatitis A vaccine (HAV) • Hepatitis B vaccine (HBV) • Hemophilus influenzae type b (Hib) vaccine (Hib (PRP-T), Hib (PRP-OMP)) • Measles, mumps and rubella (MMR) vaccine • Varicella vaccine (VAR) • Rotavirus vaccine (RV1, RV5) • Diphtheria, tetanus, and acellular pertussis vaccine (DTaP) • Tetanus, diphtheria, and acellular pertussis vaccine (Tdap) • Inactivated polio virus vaccine (IPV) • Human papillomavirus vaccine (HPV) • Meningococcal vaccine (MenACWY-D, MenACWY-CRM, MenACWY-TT, MenB-4C, MenB-FHbp) • Respiratory Syncytial Virus monoclonal antibodies (RSV-mab [Nirsevimab, Palivizumab, Motavizumab] for those aged 6 months – 2 years) • Influenza vaccine (IIV4, ccIV4, RIV4, LAIV4) • Pneumococcal vaccine (PCV13, PCV15, PCV20, PPSV23) • Respiratory Syncytial Virus vaccine (RSV) • Zoster vaccine For beneficiaries 50 years and older: • Influenza vaccine (IIV4, ccIV4, RIV4, LAIV4) • Pneumococcal vaccine (PCV13, PCV15, PCV20, PPSV23) • Respiratory Syncytial Virus vaccine (RSV) • Zoster vaccine Concomitant immunizations will be captured using HCPCS/CPT and NDCs.
Dose Number for 2023-2024 COVID-19 Vaccines	The dose number for 2023-24 COVID-19 vaccines for individual's will be determined on vaccination date based on chronological order from the first observed COVID-19 vaccine dose.

14.4 Adjustments and Exclusions for Complex Outcomes

Appendix Table 4 summarizes the adjustments and exclusions for identifying eligible incident hemorrhagic stroke (HS), non-hemorrhagic stroke (NHS), and non-hemorrhagic stroke or transient ischemic attack (NHS/TIA) outcomes.

Appendix Table 4. Adjustments and Exclusions for HS, NHS and NHS/TIA

Outcome	Basic Exclusion	Adjust onset date if observed in the day 1 prior to outcome (in all settings)	Exclusions for Prevalence (in all settings)	Exclusions – other known causes (in all settings)
Hemorrhagic Stroke (HS)	<u>If in last 365 days prior to outcome HS in IP setting</u>	I63.9, R51*, R47*, R29.810, R53.1, R42*, R41.82, R40.4, H53.13*, H53.9, G81.9*	<u>If occurs in the 365 window prior to outcome</u> I69*, Z86.73	<u>If in last 30 days prior to outcome</u> U07.1 <u>If in last 1 day prior to outcome</u> S06* <u>In same day as outcome</u> S06*, Physical Trauma Code
Non-Hemorrhagic Stroke (NHS)	<u>If in last 365 days prior to outcome NHS in IP setting</u>	Z92.82, R51*, R47*, R29.810, R53.1, R42*, R41.82, R40.4, G81.9*, H53.9, H53.13*	<u>If occurs in the 365-day window prior to outcome</u> I69*, Z86.73, I48*, D57*, D68.5*	<u>If in last 30 days prior to outcome</u> U07.1 <u>If in last 28 days prior to outcome</u> I21* <u>If in last 1 day prior to outcome</u> S15*, I74* <u>In same day as outcome</u> S15*, I74*, Physical Trauma Code
Non-Hemorrhagic Stroke or Transient Ischemic Attack (NHS/TIA)	<u>If in last 365 days prior to outcome NHS in IP setting or TIA in IP/OP-ED setting</u>	Z92.82, R51*, R47*, R29.810, R53.1, R42*, R41.82, R40.4, G81.9*, H53.9, H53.13*	<u>If occurs in the 365-day window prior to outcome</u> I69*, Z86.73, I48*, D57*, D68.5*	<u>If in last 30 days prior to outcome</u> U07.1 <u>If in last 28 days prior to outcome</u> I21* <u>If in last 1 day prior to outcome</u> S15*, I74* <u>In same day as outcome</u> S15*, I74*, Physical Trauma Code

Appendix Table 5 summarizes the exclusions for identifying eligible incident transverse myelitis outcomes.

Appendix Table 5. Exclusions for Transverse Myelitis

Outcome	Basic Exclusion	Exclusions – other known causes (in all settings)
Transverse Myelitis	<u>If in last 365 days prior to outcome</u> Transverse Myelitis in IP, OP/PB setting	<u>If in last 365 days prior to outcome</u> multiple sclerosis, neuromyelitis optica, other myelitis (infectious causes), spinal trauma, paraplegia and quadriplegia

Appendix Table 6 summarizes the code list that will be used to identify eligible incident MIS-C outcomes. MIS-C outcomes will be identified in the IP setting using the ICD-10-CM M35.81 code. Cleaning will occur in the IP setting for all the codes referenced in Appendix Table 6.

Appendix Table 6. ICD-10 CM Diagnosis Codes for MIS-C

ICD-10-CM	Description	Effective Date
M35.8	Other specified systemic involvement of connective tissue	Prior to January 1, 2021
M35.81	Multisystem Inflammatory Syndrome	January 1, 2021
M35.89	Other specified systemic involvement of connective tissue	January 1, 2022

14.5 Descriptive Analysis Table Shells

Appendix Table 7. Sample Table of Characteristics of Persons Receiving [Vaccine Brand] COVID-19 Vaccines Stratified by Number of Doses Received in the [Data Source] Administrative Claims Database, from September 11, 2023 to [Data Cut]

Vaccine Recipient Characteristics*	≥ 1 Dose		≥ 2 Doses		≥ 3 Doses		≥ 4 Doses	
	Count	Percent	Count	Percent	Count	Percent	Count	Percent
Total	-	-	-	-	-	-	-	-
Age (Years)								
Commercial								
6 mos.-4	-	-	-	-	-	-	-	-
5-11	-	-	-	-	-	-	-	-
12-15	-	-	-	-	-	-	-	-
16-17	-	-	-	-	-	-	-	-
18-25	-	-	-	-	-	-	-	-
26-35	-	-	-	-	-	-	-	-
36-45	-	-	-	-	-	-	-	-
46-55	-	-	-	-	-	-	-	-
56-64	-	-	-	-	-	-	-	-
CMS Medicare								
65-69	-	-	-	-	-	-	-	-
70-74	-	-	-	-	-	-	-	-
75-79	-	-	-	-	-	-	-	-
80-84	-	-	-	-	-	-	-	-
85-89	-	-	-	-	-	-	-	-
≥90	-	-	-	-	-	-	-	-
Sex								
Female	-	-	-	-	-	-	-	-
Male	-	-	-	-	-	-	-	-
Sex and Age (Years)								
Female (Commercial)								

Vaccine Recipient Characteristics*	≥ 1 Dose		≥ 2 Doses		≥ 3 Doses		≥ 4 Doses	
	Count	Percent	Count	Percent	Count	Percent	Count	Percent
6 mos.-4	-	-	-	-	-	-	-	-
5-11	-	-	-	-	-	-	-	-
12-15	-	-	-	-	-	-	-	-
16-17	-	-	-	-	-	-	-	-
18-25	-	-	-	-	-	-	-	-
26-35	-	-	-	-	-	-	-	-
36-45	-	-	-	-	-	-	-	-
46-55	-	-	-	-	-	-	-	-
56-64	-	-	-	-	-	-	-	-
Female (CMS Medicare)								
65-69	-	-	-	-	-	-	-	-
70-74	-	-	-	-	-	-	-	-
75-79	-	-	-	-	-	-	-	-
80-84	-	-	-	-	-	-	-	-
85-89	-	-	-	-	-	-	-	-
≥90	-	-	-	-	-	-	-	-
Male (Commercial)								
6 mos.-4	-	-	-	-	-	-	-	-
5-11	-	-	-	-	-	-	-	-
12-15	-	-	-	-	-	-	-	-
16-17	-	-	-	-	-	-	-	-
18-25	-	-	-	-	-	-	-	-
26-35	-	-	-	-	-	-	-	-
36-45	-	-	-	-	-	-	-	-
46-55	-	-	-	-	-	-	-	-
56-64	-	-	-	-	-	-	-	-
Male (CMS Medicare)								
65-69	-	-	-	-	-	-	-	-

Vaccine Recipient Characteristics*	≥ 1 Dose		≥ 2 Doses		≥ 3 Doses		≥ 4 Doses	
	Count	Percent	Count	Percent	Count	Percent	Count	Percent
70-74	-	-	-	-	-	-	-	-
75-79	-	-	-	-	-	-	-	-
80-84	-	-	-	-	-	-	-	-
85-89	-	-	-	-	-	-	-	-
≥90	-	-	-	-	-	-	-	-
Race/Ethnicity (CMS Medicare Only)								
Asian	-	-	-	-	-	-	-	-
Black	-	-	-	-	-	-	-	-
Hispanic	-	-	-	-	-	-	-	-
American Indian/Alaskan Native	-	-	-	-	-	-	-	-
White	-	-	-	-	-	-	-	-
Other	-	-	-	-	-	-	-	-
Missing/Unknown	-	-	-	-	-	-	-	-
Urban/Rural								
Urban	-	-	-	-	-	-	-	-
Rural	-	-	-	-	-	-	-	-
Missing/Unknown	-	-	-	-	-	-	-	-
HHS Region								
Region 1 (Connecticut, Maine, Massachusetts, New Hampshire, Rhode Island, and Vermont)	-	-	-	-	-	-	-	-
Region 2 (New Jersey, New York, Puerto Rico, and Virgin Islands)	-	-	-	-	-	-	-	-
Region 3 (Delaware, District of Columbia, Maryland, Pennsylvania, Virginia, and West Virginia)	-	-	-	-	-	-	-	-
Region 4 (Alabama, Florida, Georgia, Kentucky, Mississippi, North Carolina, South Carolina, and Tennessee)	-	-	-	-	-	-	-	-

Vaccine Recipient Characteristics*	≥ 1 Dose		≥ 2 Doses		≥ 3 Doses		≥ 4 Doses	
	Count	Percent	Count	Percent	Count	Percent	Count	Percent
Region 5 (Illinois, Indiana, Michigan, Minnesota, Ohio, and Wisconsin)	-	-	-	-	-	-	-	-
Region 6 (Arkansas, Louisiana, New Mexico, Oklahoma, and Texas)	-	-	-	-	-	-	-	-
Region 7 (Iowa, Kansas, Missouri, and Nebraska)	-	-	-	-	-	-	-	-
Region 8 (Colorado, Montana, North Dakota, South Dakota, Utah, and Wyoming)	-	-	-	-	-	-	-	-
Region 9 (Arizona, California, Hawaii, Nevada, American Samoa, Commonwealth of the Northern Mariana Islands, Federated State of Micronesia, Guam, Marshall Islands, and Republic of Palau)	-	-	-	-	-	-	-	-
Region 10 (Alaska, Idaho, Oregon, and Washington)	-	-	-	-	-	-	-	-
Missing/Unknown	-	-	-	-	-	-	-	-
Facility/Provider Type								
Hospital	-	-	-	-	-	-	-	-
Office Visit	-	-	-	-	-	-	-	-
Pharmacy	-	-	-	-	-	-	-	-
Skilled Nursing Facility	-	-	-	-	-	-	-	-
Home Health Agency	-	-	-	-	-	-	-	-
Mass Immunization Center	-	-	-	-	-	-	-	-
Other	-	-	-	-	-	-	-	-
Missing/Unknown	-	-	-	-	-	-	-	-
Nursing Home Residency (CMS Medicare Only)								
Nursing Home	-	-	-	-	-	-	-	-
Non-Nursing Home	-	-	-	-	-	-	-	-
Reason for Medicare Eligibility (CMS Medicare Only)								

Vaccine Recipient Characteristics*	≥ 1 Dose		≥ 2 Doses		≥ 3 Doses		≥ 4 Doses	
	Count	Percent	Count	Percent	Count	Percent	Count	Percent
Aged without ESRD	-	-	-	-	-	-	-	-
Aged with ESRD	-	-	-	-	-	-	-	-
Disabled without ESRD	-	-	-	-	-	-	-	-
Disabled with ESRD	-	-	-	-	-	-	-	-
ESRD Only	-	-	-	-	-	-	-	-
Medicare-Medicaid Dual Eligibility (CMS Medicare Only)								
Dual-Eligibility	-	-	-	-	-	-	-	-
Non-Dual-Eligibility	-	-	-	-	-	-	-	-
Area Deprivation Index (CMS Medicare Only)								
1-10(th)	-	-	-	-	-	-	-	-
11-20	-	-	-	-	-	-	-	-
21-30	-	-	-	-	-	-	-	-
31-40	-	-	-	-	-	-	-	-
41-50	-	-	-	-	-	-	-	-
51-60	-	-	-	-	-	-	-	-
61-70	-	-	-	-	-	-	-	-
71-80	-	-	-	-	-	-	-	-
81-90	-	-	-	-	-	-	-	-
91-100	-	-	-	-	-	-	-	-
Missing/Unknown	-	-	-	-	-	-	-	-
Concomitant Immunization								
Any Concomitant Immunization (Commercial)	-	-	-	-	-	-	-	-
HAV	-	-	-	-	-	-	-	-
HBV	-	-	-	-	-	-	-	-
Hib Vaccine	-	-	-	-	-	-	-	-
MMR Vaccine	-	-	-	-	-	-	-	-
VAR	-	-	-	-	-	-	-	-

Vaccine Recipient Characteristics*	≥ 1 Dose		≥ 2 Doses		≥ 3 Doses		≥ 4 Doses	
	Count	Percent	Count	Percent	Count	Percent	Count	Percent
Rotavirus Vaccine	-	-	-	-	-	-	-	-
DTaP Vaccine	-	-	-	-	-	-	-	-
Tdap Vaccine	-	-	-	-	-	-	-	-
IPV	-	-	-	-	-	-	-	-
HPV	-	-	-	-	-	-	-	-
Meningococcal Vaccine	-	-	-	-	-	-	-	-
RSV-mab	-	-	-	-	-	-	-	-
Influenza Vaccine	-	-	-	-	-	-	-	-
Pneumococcal Vaccine	-	-	-	-	-	-	-	-
RSV Vaccine	-	-	-	-	-	-	-	-
Zoster Vaccine	-	-	-	-	-	-	-	-
Any Concomitant Immunization (CMS Medicare)	-	-	-	-	-	-	-	-
Influenza Vaccine	-	-	-	-	-	-	-	-
Pneumococcal Vaccine	-	-	-	-	-	-	-	-
RSV Vaccine	-	-	-	-	-	-	-	-
Zoster Vaccine	-	-	-	-	-	-	-	-
2023-2024 COVID-19 Vaccine Dose Number								
Dose 1	-	-	-	-	-	-	-	-
Dose 2	-	-	-	-	-	-	-	-
Dose 3	-	-	-	-	-	-	-	-
Dose 4+	-	-	-	-	-	-	-	-

Acronyms: HHS: Health and Human Services; ESRD: End stage renal disease; HAV: Hepatitis A vaccine; HBV: Hepatitis B vaccine; Hib: *Hemophilus influenzae type b*; VAR: Varicella vaccine; DTaP: Diphtheria, tetanus, and acellular pertussis vaccine; Tdap: Tetanus, diphtheria, and acellular pertussis vaccine; IPV: Inactivated polio vaccine; HPV: Human papillomavirus vaccine; RSV-mab: Respiratory syncytial virus monoclonal antibodies; RSV: respiratory syncytial virus.

* Characteristics of the population were assessed during pre-specified time periods relative to vaccination or the incident outcome diagnosis, as specified in Appendix Table 3.

Appendix Table 8. Sample Table of Descriptive Statistics for [Outcome Cohort] Among Persons Receiving a [Vaccine Brand] COVID-19 Vaccine by Number of Doses Received

Patient Characteristic*	≥ # Dose(s)			
	Number of Vaccine Doses	Number of Outcomes	Person-Years	Rate Per 100,000 Person-Years
Total	-	-	-	-
Age (Years)				
Commercial				
6 mos.-4	-	-	-	-
5-11	-	-	-	-
12-15	-	-	-	-
16-17	-	-	-	-
18-25	-	-	-	-
26-35	-	-	-	-
36-45	-	-	-	-
46-55	-	-	-	-
56-64	-	-	-	-
CMS Medicare				
65-69	-	-	-	-
70-74	-	-	-	-
75-79	-	-	-	-
80-84	-	-	-	-
85-89	-	-	-	-
≥90	-	-	-	-
Sex				
Female	-	-	-	-
Male	-	-	-	-
Sex and Age (Years)				

Patient Characteristic*	≥ # Dose(s)			
	Number of Vaccine Doses	Number of Outcomes	Person-Years	Rate Per 100,000 Person-Years
Female (Commercial)				
6 mos.-4	-	-	-	-
5-11	-	-	-	-
12-15	-	-	-	-
16-17	-	-	-	-
18-25	-	-	-	-
26-35	-	-	-	-
36-45	-	-	-	-
46-55	-	-	-	-
56-64	-	-	-	-
Female (CMS Medicare)				
65-69	-	-	-	-
70-74	-	-	-	-
75-79	-	-	-	-
80-84	-	-	-	-
85-89	-	-	-	-
≥90	-	-	-	-
Male (Commercial)				
6 mos.-4	-	-	-	-
5-11	-	-	-	-
12-15	-	-	-	-
16-17	-	-	-	-
18-25	-	-	-	-
26-35	-	-	-	-
36-45	-	-	-	-

Patient Characteristic*	≥ # Dose(s)			
	Number of Vaccine Doses	Number of Outcomes	Person-Years	Rate Per 100,000 Person-Years
46-55	-	-	-	-
56-64	-	-	-	-
Male (CMS Medicare)				
65-69	-	-	-	-
70-74	-	-	-	-
75-79	-	-	-	-
80-84	-	-	-	-
85-89	-	-	-	-
≥90	-	-	-	-
Race/Ethnicity (CMS Medicare Only)				
Asian	-	-	-	-
Black	-	-	-	-
Hispanic	-	-	-	-
American Indian/Alaskan Native	-	-	-	-
White	-	-	-	-
Other	-	-	-	-
Missing/Unknown	-	-	-	-
Urban/Rural				
Urban	-	-	-	-
Rural	-	-	-	-
Missing/Unknown	-	-	-	-
HHS Region				
Region 1 (Connecticut, Maine, Massachusetts, New Hampshire, Rhode Island, and Vermont)	-	-	-	-
Region 2 (New Jersey, New York, Puerto Rico, and Virgin Islands)	-	-	-	-

Patient Characteristic*	≥ # Dose(s)			
	Number of Vaccine Doses	Number of Outcomes	Person-Years	Rate Per 100,000 Person-Years
Region 3 (Delaware, District of Columbia, Maryland, Pennsylvania, Virginia, and West Virginia)	-	-	-	-
Region 4 (Alabama, Florida, Georgia, Kentucky, Mississippi, North Carolina, South Carolina, and Tennessee)	-	-	-	-
Region 5 (Illinois, Indiana, Michigan, Minnesota, Ohio, and Wisconsin)	-	-	-	-
Region 6 (Arkansas, Louisiana, New Mexico, Oklahoma, and Texas)	-	-	-	-
Region 7 (Iowa, Kansas, Missouri, and Nebraska)	-	-	-	-
Region 8 (Colorado, Montana, North Dakota, South Dakota, Utah, and Wyoming)	-	-	-	-
Region 9 (Arizona, California, Hawaii, Nevada, American Samoa, Commonwealth of the Northern Mariana Islands, Federated State of Micronesia, Guam, Marshall Islands, and Republic of Palau)	-	-	-	-
Region 10 (Alaska, Idaho, Oregon, and Washington)	-	-	-	-
Missing/Unknown	-	-	-	-
Facility/Provider Type				
Hospital	-	-	-	-
Office Visit	-	-	-	-
Pharmacy	-	-	-	-
Skilled Nursing Facility	-	-	-	-
Home Health Agency	-	-	-	-
Mass Immunization Center	-	-	-	-
Other	-	-	-	-
Missing/Unknown	-	-	-	-
Nursing Home Residency (CMS Medicare Only)				
Nursing Home	-	-	-	-
Non-Nursing Home	-	-	-	-

Patient Characteristic*	≥ # Dose(s)			
	Number of Vaccine Doses	Number of Outcomes	Person-Years	Rate Per 100,000 Person-Years
Reason for Medicare Eligibility (CMS Medicare Only)				
Aged without ESRD	-	-	-	-
Aged with ESRD	-	-	-	-
Disabled without ESRD	-	-	-	-
Disabled with ESRD	-	-	-	-
ESRD Only	-	-	-	-
Medicare-Medicaid Dual Eligibility (CMS Medicare Only)				
Dual-Eligibility	-	-	-	-
Non-Dual-Eligibility	-	-	-	-
Area Deprivation Index (ADI) (CMS Medicare Only)				
1-10(th)	-	-	-	-
11-20	-	-	-	-
21-30	-	-	-	-
31-40	-	-	-	-
41-50	-	-	-	-
51-60	-	-	-	-
61-70	-	-	-	-
71-80	-	-	-	-
81-90	-	-	-	-
91-100	-	-	-	-
Missing/Unknown	-	-	-	-
Medical Conditions				
Asthma	-	-	-	-
Blood Disorders	-	-	-	-
Chronic Lung Disease	-	-	-	-
Diabetes	-	-	-	-

Patient Characteristic*	≥ # Dose(s)			
	Number of Vaccine Doses	Number of Outcomes	Person-Years	Rate Per 100,000 Person-Years
Heart Disease	-	-	-	-
Kidney Disorders	-	-	-	-
Liver Disorders	-	-	-	-
Neurological or Neurodevelopmental Conditions	-	-	-	-
Malignant Neoplasms	-	-	-	-
Immunocompromised Status				
Yes	-	-	-	-
No	-	-	-	-
Charlson Comorbidity Index				
0	-	-	-	-
1	-	-	-	-
2	-	-	-	-
3	-	-	-	-
4+	-	-	-	-
Prior Hospitalization				
Yes	-	-	-	-
No	-	-	-	-
Prior COVID-19 Diagnosis				
Yes	-	-	-	-
No	-	-	-	-
Prior COVID-19 Vaccination				
Yes	-	-	-	-
No	-	-	-	-
Concomitant Immunization				
Any Concomitant Immunization (Commercial)	-	-	-	-
HAV	-	-	-	-

Patient Characteristic*	≥ # Dose(s)			
	Number of Vaccine Doses	Number of Outcomes	Person-Years	Rate Per 100,000 Person-Years
HBV	-	-	-	-
Hib Vaccine	-	-	-	-
MMR Vaccine	-	-	-	-
VAR	-	-	-	-
Rotavirus Vaccine	-	-	-	-
DTaP Vaccine	-	-	-	-
Tdap Vaccine	-	-	-	-
IPV	-	-	-	-
HPV	-	-	-	-
Meningococcal Vaccine	-	-	-	-
RSV-mab	-	-	-	-
Influenza Vaccine	-	-	-	-
Pneumococcal Vaccine	-	-	-	-
RSV Vaccine	-	-	-	-
Zoster Vaccine	-	-	-	-
Any Concomitant Immunization (CMS Medicare)	-	-	-	-
Influenza Vaccine	-	-	-	-
Pneumococcal Vaccine	-	-	-	-
RSV Vaccine	-	-	-	-
Zoster Vaccine	-	-	-	-
Dose Number for 2023-2024 COVID-19 Vaccines				
Dose 1	-	-	-	-
Dose 2	-	-	-	-
Dose 3	-	-	-	-
Dose 4+	-	-	-	-

Acronyms: HHS: Health and Human Services; ESRD: End stage renal disease; HAV: Hepatitis A vaccine; HBV: Hepatitis B vaccine; Hib: *Hemophilus influenzae type b*; VAR: Varicella vaccine; DTap: Diphtheria, tetanus, and acellular pertussis vaccine; Tdap: Tetanus, diphtheria, and acellular pertussis vaccine; IPV: Inactivated polio vaccine; HPV: Human papillomavirus vaccine; RSV-mab: Respiratory syncytial virus monoclonal antibodies; RSV: respiratory syncytial virus.

* Characteristics of the population were assessed during pre-specified time periods relative to vaccination or the incident outcome diagnosis, as specified in Appendix Table 3.

Appendix Table 9. Sample Table of Descriptive Statistics for [Outcome Cohort] Among Persons Receiving a [Vaccine Brand] COVID-19 Vaccine Brand by Age Category and Risk and Control Intervals

Patient Characteristic*	Age Category**						
	Number of Vaccine Doses	Risk Interval			Control Interval		
		Number of Outcomes	Person-Years	Rate Per 100,000 Person-Years	Number of Outcomes	Person-years	Rate Per 100,000 Person-Years
Total	-	-	-	-	-	-	-
Age (Years)							
Commercial							
6 mos.-4	-	-	-	-	-	-	-
5-11	-	-	-	-	-	-	-
12-15	-	-	-	-	-	-	-
16-17	-	-	-	-	-	-	-
18-25	-	-	-	-	-	-	-
26-35	-	-	-	-	-	-	-
36-45	-	-	-	-	-	-	-
46-55	-	-	-	-	-	-	-
56-64	-	-	-	-	-	-	-
CMS Medicare							
65-69	-	-	-	-	-	-	-
70-74	-	-	-	-	-	-	-
75-79	-	-	-	-	-	-	-
80-84	-	-	-	-	-	-	-
85-89	-	-	-	-	-	-	-
≥90	-	-	-	-	-	-	-
Sex							
Female	-	-	-	-	-	-	-

Patient Characteristic*	Age Category**						
	Number of Vaccine Doses	Risk Interval			Control Interval		
		Number of Outcomes	Person-Years	Rate Per 100,000 Person-Years	Number of Outcomes	Person-years	Rate Per 100,000 Person-Years
Male	-	-	-	-	-	-	-
Sex and Age (Years)							
Female (Commercial)							
6 mos.-4	-	-	-	-	-	-	-
5-11	-	-	-	-	-	-	-
12-15	-	-	-	-	-	-	-
16-17	-	-	-	-	-	-	-
18-25	-	-	-	-	-	-	-
26-35	-	-	-	-	-	-	-
36-45	-	-	-	-	-	-	-
46-55	-	-	-	-	-	-	-
56-64	-	-	-	-	-	-	-
Female (CMS Medicare)							
65-69	-	-	-	-	-	-	-
70-74	-	-	-	-	-	-	-
75-79	-	-	-	-	-	-	-
80-84	-	-	-	-	-	-	-
85-89	-	-	-	-	-	-	-
≥90	-	-	-	-	-	-	-
Male (Commercial)							
6 mos.-4	-	-	-	-	-	-	-
5-11	-	-	-	-	-	-	-
12-15	-	-	-	-	-	-	-

Patient Characteristic*	Age Category**						
	Number of Vaccine Doses	Risk Interval			Control Interval		
		Number of Outcomes	Person-Years	Rate Per 100,000 Person-Years	Number of Outcomes	Person-years	Rate Per 100,000 Person-Years
16-17	-	-	-	-	-	-	-
18-25	-	-	-	-	-	-	-
26-35	-	-	-	-	-	-	-
36-45	-	-	-	-	-	-	-
46-55	-	-	-	-	-	-	-
56-64	-	-	-	-	-	-	-
Male (CMS Medicare)							
65-69	-	-	-	-	-	-	-
70-74	-	-	-	-	-	-	-
75-79	-	-	-	-	-	-	-
80-84	-	-	-	-	-	-	-
85-89	-	-	-	-	-	-	-
≥90	-	-	-	-	-	-	-
Race/Ethnicity (CMS Medicare Only)							
Asian	-	-	-	-	-	-	-
Black	-	-	-	-	-	-	-
Hispanic	-	-	-	-	-	-	-
American Indian/Alaskan Native	-	-	-	-	-	-	-
White	-	-	-	-	-	-	-
Other	-	-	-	-	-	-	-
Missing/Unknown	-	-	-	-	-	-	-
Urban/Rural							
Urban	-	-	-	-	-	-	-

Patient Characteristic*	Age Category**						
	Number of Vaccine Doses	Risk Interval			Control Interval		
		Number of Outcomes	Person-Years	Rate Per 100,000 Person-Years	Number of Outcomes	Person-years	Rate Per 100,000 Person-Years
Rural	-	-	-	-	-	-	-
Missing/Unknown	-	-	-	-	-	-	-
HHS Region							
Region 1 (Connecticut, Maine, Massachusetts, New Hampshire, Rhode Island, and Vermont)	-	-	-	-	-	-	-
Region 2 (New Jersey, New York, Puerto Rico, and Virgin Islands)	-	-	-	-	-	-	-
Region 3 (Delaware, District of Columbia, Maryland, Pennsylvania, Virginia, and West Virginia)	-	-	-	-	-	-	-
Region 4 (Alabama, Florida, Georgia, Kentucky, Mississippi, North Carolina, South Carolina, and Tennessee)	-	-	-	-	-	-	-
Region 5 (Illinois, Indiana, Michigan, Minnesota, Ohio, and Wisconsin)	-	-	-	-	-	-	-
Region 6 (Arkansas, Louisiana, New Mexico, Oklahoma, and Texas)	-	-	-	-	-	-	-
Region 7 (Iowa, Kansas, Missouri, and Nebraska)	-	-	-	-	-	-	-
Region 8 (Colorado, Montana, North Dakota, South Dakota, Utah, and Wyoming)	-	-	-	-	-	-	-
Region 9 (Arizona, California, Hawaii, Nevada, American Samoa, Commonwealth of the Northern Mariana Islands, Federated State of Micronesia, Guam, Marshall Islands, and Republic of Palau)	-	-	-	-	-	-	-
Region 10 (Alaska, Idaho, Oregon, and Washington)	-	-	-	-	-	-	-
Missing/Unknown	-	-	-	-	-	-	-
Facility/Provider Type							
Hospital	-	-	-	-	-	-	-
Office Visit	-	-	-	-	-	-	-

Patient Characteristic*	Age Category**						
	Number of Vaccine Doses	Risk Interval			Control Interval		
		Number of Outcomes	Person-Years	Rate Per 100,000 Person-Years	Number of Outcomes	Person-years	Rate Per 100,000 Person-Years
Pharmacy	-	-	-	-	-	-	-
Skilled Nursing Facility	-	-	-	-	-	-	-
Home Health Agency	-	-	-	-	-	-	-
Mass Immunization Center	-	-	-	-	-	-	-
Other	-	-	-	-	-	-	-
Missing/Unknown	-	-	-	-	-	-	-
Nursing Home Residency (CMS Medicare Only)							
Nursing Home	-	-	-	-	-	-	-
Non-Nursing Home	-	-	-	-	-	-	-
Reason for Medicare Eligibility (CMS Medicare Only)							
Aged without ESRD	-	-	-	-	-	-	-
Aged with ESRD	-	-	-	-	-	-	-
Disabled without ESRD	-	-	-	-	-	-	-
Disabled with ESRD	-	-	-	-	-	-	-
ESRD Only	-	-	-	-	-	-	-
Medicare-Medicaid Dual Eligibility (CMS Medicare Only)							
Dual-Eligibility	-	-	-	-	-	-	-
Non-Dual-Eligibility	-	-	-	-	-	-	-
Area Deprivation Index (ADI) (CMS Medicare Only)							
1-10(th)	-	-	-	-	-	-	-
10-20	-	-	-	-	-	-	-
21-30	-	-	-	-	-	-	-

Patient Characteristic*	Age Category**						
	Number of Vaccine Doses	Risk Interval			Control Interval		
		Number of Outcomes	Person-Years	Rate Per 100,000 Person-Years	Number of Outcomes	Person-years	Rate Per 100,000 Person-Years
31-40	-	-	-	-	-	-	-
41-50	-	-	-	-	-	-	-
51-60	-	-	-	-	-	-	-
61-70	-	-	-	-	-	-	-
71-80	-	-	-	-	-	-	-
81-90	-	-	-	-	-	-	-
91-100	-	-	-	-	-	-	-
Missing/Unknown	-	-	-	-	-	-	-
Medical Conditions							
Asthma	-	-	-	-	-	-	-
Blood Disorders	-	-	-	-	-	-	-
Chronic Lung Disease	-	-	-	-	-	-	-
Diabetes	-	-	-	-	-	-	-
Heart Disease	-	-	-	-	-	-	-
Kidney Disorders	-	-	-	-	-	-	-
Liver Disorders	-	-	-	-	-	-	-
Neurological or Neurodevelopmental Conditions	-	-	-	-	-	-	-
Malignant Neoplasms	-	-	-	-	-	-	-
Immunocompromised Status							
Yes	-	-	-	-	-	-	-
No	-	-	-	-	-	-	-
Charlson Comorbidity Index							
0	-	-	-	-	-	-	-

Patient Characteristic*	Age Category**						
	Number of Vaccine Doses	Risk Interval			Control Interval		
		Number of Outcomes	Person-Years	Rate Per 100,000 Person-Years	Number of Outcomes	Person-years	Rate Per 100,000 Person-Years
1	-	-	-	-	-	-	-
2	-	-	-	-	-	-	-
3	-	-	-	-	-	-	-
4+	-	-	-	-	-	-	-
Prior Hospitalization							
Yes	-	-	-	-	-	-	-
No	-	-	-	-	-	-	-
Prior COVID-19 Diagnosis							
Yes	-	-	-	-	-	-	-
No	-	-	-	-	-	-	-
Prior COVID-19 Vaccination							
Yes	-	-	-	-	-	-	-
No	-	-	-	-	-	-	-
Concomitant Immunizations							
Any Concomitant Immunization (Commercial)	-	-	-	-	-	-	-
HAV	-	-	-	-	-	-	-
HBV	-	-	-	-	-	-	-
Hib Vaccine	-	-	-	-	-	-	-
MMR Vaccine	-	-	-	-	-	-	-
VAR	-	-	-	-	-	-	-
Rotavirus Vaccine	-	-	-	-	-	-	-
DTaP Vaccine	-	-	-	-	-	-	-
Tdap Vaccine	-	-	-	-	-	-	-

Patient Characteristic*	Age Category**						
	Number of Vaccine Doses	Risk Interval			Control Interval		
		Number of Outcomes	Person-Years	Rate Per 100,000 Person-Years	Number of Outcomes	Person-years	Rate Per 100,000 Person-Years
IPV	-	-	-	-	-	-	-
HPV	-	-	-	-	-	-	-
Meningococcal Vaccine	-	-	-	-	-	-	-
RSV-mab	-	-	-	-	-	-	-
Influenza Vaccine	-	-	-	-	-	-	-
Pneumococcal Vaccine	-	-	-	-	-	-	-
RSV Vaccine	-	-	-	-	-	-	-
Zoster Vaccine	-	-	-	-	-	-	-
Any Concomitant Immunization (CMS Medicare)	-	-	-	-	-	-	-
Influenza Vaccine	-	-	-	-	-	-	-
Pneumococcal Vaccine	-	-	-	-	-	-	-
RSV Vaccine	-	-	-	-	-	-	-
Zoster Vaccine	-	-	-	-	-	-	-
2023-2024 COVID-19 Vaccine Dose Number							
Dose 1	-	-	-	-	-	-	-
Dose 2	-	-	-	-	-	-	-
Dose 3	-	-	-	-	-	-	-
Dose 4+	-	-	-	-	-	-	-

Acronyms: HHS: Health and Human Services; ESRD: End stage renal disease; HAV: Hepatitis A vaccine; HBV: Hepatitis B vaccine; Hib: *Hemophilus influenzae type b*; VAR: Varicella vaccine; DTaP: Diphtheria, tetanus, and acellular pertussis vaccine; Tdap: Tetanus, diphtheria, and acellular pertussis vaccine; IPV: Inactivated polio vaccine; HPV: Human papillomavirus vaccine; RSV-mab: Respiratory syncytial virus monoclonal antibodies; RSV: respiratory syncytial virus.

* Characteristics of the population were assessed during pre-specified time periods relative to vaccination or the incident outcome diagnosis, as specified in Appendix Table 3.

** Age stratifications for the commercial health plan population will include age categories for 6 months–4 years, 5–11., 12–17., 6 months–17 years, 18–64 years, and will include for the Medicare population an age category ≥ 65 years.