Master Protocol:
Evaluation of Nine Safety Outcomes following 2023-2024 Influenza Vaccination in Persons 6 Months and Older

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Center for Biologics Evaluation and Research
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Biologics Effectiveness and Safety (BEST) Initiative

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List of Abbreviations

ACIP	Advisory Committee on Immunization Practices
ADEM	Acute disseminated encephalomyelitis
ADI	Area Deprivation Index
AHRQ	Agency for Healthcare Research and Quality
AIDS	Autoimmune Deficiency Syndrome
aIIV4	Adjuvanted quadrivalent inactivated influenza vaccine
AR	Attributable risk
BEST	Biologics Effectiveness and Safety Initiative
CBER	Center for Biologics Evaluation and Research
CCI	Charlson Comorbidity Index
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
EDS	Encounter Data System
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
HD-IIV4	High-dose quadrivalent inactivated influenza vaccine
Hib	Hemophilus influenzae type b vaccine
HIV	Human Immunodeficiency Virus
HHS	Department of Health and Human Services
HPV	Human papillomavirus vaccine
HS	Hemorrhagic stroke
ICD-10-CM	International Classification of Diseases, Tenth Revision, Clinical Modification
IIS	Immunization Information System
IIV4	Quadrivalent inactivated influenza vaccine
IP	Inpatient
IPV	Inactivated polio virus vaccine
IRR	Incidence rate ratio
MA	Medicare Advantage
MDS	Minimum Data Set
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-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
REV	Revenue codes
RIV4	Quadrivalent recombinant influenza vaccine
RSV	Respiratory syncytial virus vaccine
SCCS	Self-controlled case series
SE	Standard error
SSD	Shared Systems Data
Tdap	Tetanus, diphtheria, and pertussis vaccination
Td	Tetanus and diphtheria vaccination
TIA	Transient ischemic attack
US	United States
VAR	Varicella vaccine
VRBPAC	Vaccines and Related Biological Products Advisory Committee

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1. Background

Annual influenza vaccines are recommended for individuals 6 months of age and older in the United States (U.S.) to protect against seasonal influenza. For most people, the CDC (Centers for Disease Control and Prevention) recommends one yearly dose of the influenza vaccine.[1] However, children aged 6 months through 8 years who have not previously received ≥2 total doses of quadrivalent influenza vaccine, or whose influenza vaccination history is unknown, need 2 doses of influenza vaccination administered ≥4 weeks apart.[2] Influenza vaccines are reformulated annually to target the expected influenza strains for the upcoming season based on available evidence.[1] The FDA's (Food and Drug Administration) Vaccine and Related Biological Products Advisory Committee (VRBPAC) recommended that the 2023-2024 influenza vaccine composition remain relatively consistent with the 2022-2023 vaccine formulation. The A(H1N1)pdm09 virus formulation was updated from an A/Victoria/2570/2019 (H1N1) pdm09-like virus to an A/Victoria/4897/2022 (H1N1) pdm09-like virus for egg-based vaccines, and from an A/Wisconsin/588/2019 (H1N1) pdm09-like virus formulation to an A/Wisconsin/67/2022 (H1N1) pdm09-like virus for cell- or recombinant-based vaccines.[3, 4] The composition of influenza vaccines for the U.S. 2023-2024 season can be found in Appendix Table 1.

As of March 4, 2023, over half of the total U.S. population (over 173 million people) received the influenza vaccine during the 2022-2023 season. While influenza vaccines are well-established as safe based on evidence from past influenza seasons,[5-8] influenza vaccine safety surveillance is important to monitor safety concerns that may arise from altering the vaccine formulation.[9] This is also important based on the widespread use of influenza vaccines, especially in high-risk populations, such as elderly people and those with preexisting conditions like obesity or diabetes, who may have weaker immune responses to the influenza vaccine compared to people without high-risk conditions.[10]

Multiple inactivated influenza vaccines (IIV4s) and recombinant influenza vaccines (RIV4) are available for the 2023-24 season, with varying age-specific indications. Appendix Table 2 presents a list of the product-specific administration codes(11) that will be used to identify influenza vaccine exposures by vaccine type and group. The Afluria Quadrivalent, Fluarix Quadrivalent, FluLaval Quadrivalent, Fluzone Quadrivalent, and Flucelvax Quadrivalent vaccines are approved for people ages 6 months and older; the Flublok Quadrivalent vaccine is approved for people ages 18 years and older; the Fluzone High-Dose Quadrivalent and Fluad Adjuvanted Quadrivalent vaccines are approved for people ages 65 and older; lastly, the live attenuated FluMist Quadrivalent vaccine is approved for people ages 2 through 49.[12, 13] Of these vaccines, three are preferentially recommended by the Advisory Committee on Immunization Practices (ACIP) for use in people aged 65 years or older: quadrivalent high-dose inactivated influenza vaccine (HD-IIV4), quadrivalent recombinant influenza vaccine (RIV4), and quadrivalent adjuvanted inactivated influenza vaccine (aIIV4).[2]

This protocol details the methods that will be used for monitoring the safety of influenza vaccines available during the 2023-2024 influenza season. Sections 2 and 3 of the protocol present the study objectives and an overview of the study methods that will be used for vaccine safety surveillance, including data sources, study population, study period, and study variables. Section 8.1 describes the Self-Controlled Case Series (SCCS) study design and specifications as an inferential analysis method to evaluate

the risk of various outcomes of interest following exposure to influenza vaccine products. Sections 10-12 describe additional specifications including but not limited to medical record review, and data quality assurance and control measures.

2. Study Objectives

The objectives of the study are:

(i) to descriptively monitor the vaccination uptake of the 2023-2024 influenza vaccines, as well as the observed counts and rates of prespecifed health outcomes 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 each prespecified health outcome by comparing the incidence rates of outcomes in risk compared to control intervals following vaccination using a single self-controlled case series design (SCCS) at the end of the season.

3. Overview of Study Approach

This study will use a retrospective observational cohort design and will conduct safety surveillance using administrative claims data to provide comprehensive characterization of the patterns of influenza vaccine utilization and the rate of these health outcomes following vaccination:

(i) Anaphylaxis

(ii) Encephalitis/Encephalomyelitis/Acute disseminated encephalomyelitis (ADEM)

(iii) Guillain-Barré syndrome

(iv) Transverse myelitis

(v) Febrile Seizure

(vi) Non-hemorrhagic stroke/Transient Ischemic Attack

(vii) Hemorrhagic Stroke

(viii) Non-hemorrhagic stroke

(ix) Transient Ischemic Attack

Descriptive reports will be generated on a monthly basis to summarize the vaccination uptake post-licensure for each influenza vaccine as well as observed outcome counts within pre-defined risk and control intervals (Sections 8.2.2 and 8.2.3).

Upon accrual of sufficient sample size estimated by power analysis described in Section 9.7, inferential analyses will be conducted assessing the association between any influenza vaccine and specified health outcomes using the SCCS study design. The causal inference analysis may include a single end-of-surveillance SCCS analysis to provide the most precise estimate of risk on a larger population of patients. Further details on the SCCS methodology are provided in Section 8.1. Separate SCCS analyses will be

conducted for each outcome of interest for outcomes reaching sufficient sample size. 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 administrative claims data from the Centers for Medicare & Medicaid (CMS) Medicare beneficiaries with Fee-for-Service (FFS) and Medicare advantage (MA) enrollment plans, as well as commercial insurance databases provided by Optum (pre-adjudicated claims), CVS Health and Carelon Research (fully adjudicated claims).

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 influenza 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 influenza 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 inpatient (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 Shared Systems Data (SSD) for FFS enrollees and the Encounter Data System (EDS) for MA 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. Information on nursing home residency status will be captured from the Minimum Data Set (MDS), a mandatory clinical assessment administered to all residents in Medicare and Medicaid certified nursing homes.[14] MA data (also referred to as Medicare Part C) will be utilized to descriptively monitor influenza vaccination uptake. However, MA data may be included in the single end-of-surveillance SCCS analysis if sufficient vaccinations are observed in Medicare Part C. The MA is a federally funded health insurance program that provides Medicare benefits through private insurance company plans. Different plans under MA may have their own health care networks, which include health care providers and care facilities. These plans include Part A, Part B, and usually Part D. The Encounter Data System (EDS) will be used to capture encounter data for Part C beneficiaries.[15]

Table 1 outlines the administrative claims data sources included in this surveillance study, 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 claims, 2-3 months for outpatient claims, and 1-2 months for professional 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 claims†	Pre-Adjudicated	Every two weeks	Approximately 80% data completeness in 1-2 months for inpatient, outpatient, and professional 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 inpatient claims and 1-2 months for outpatient and professional 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 Medicare Shared Systems Fee-for-Service Data (SSD)	Pre-Adjudicated	Daily	>80% data completeness in 30-70 days for inpatient claims	>34 million beneficiaries annually
CMS Medicare Encounter Data System (EDS) Medicare Advantage (MA)	Pre-Adjudicated	Weekly	>80% data completeness in 150-180 days for inpatient claims	>30 million beneficiaries annually

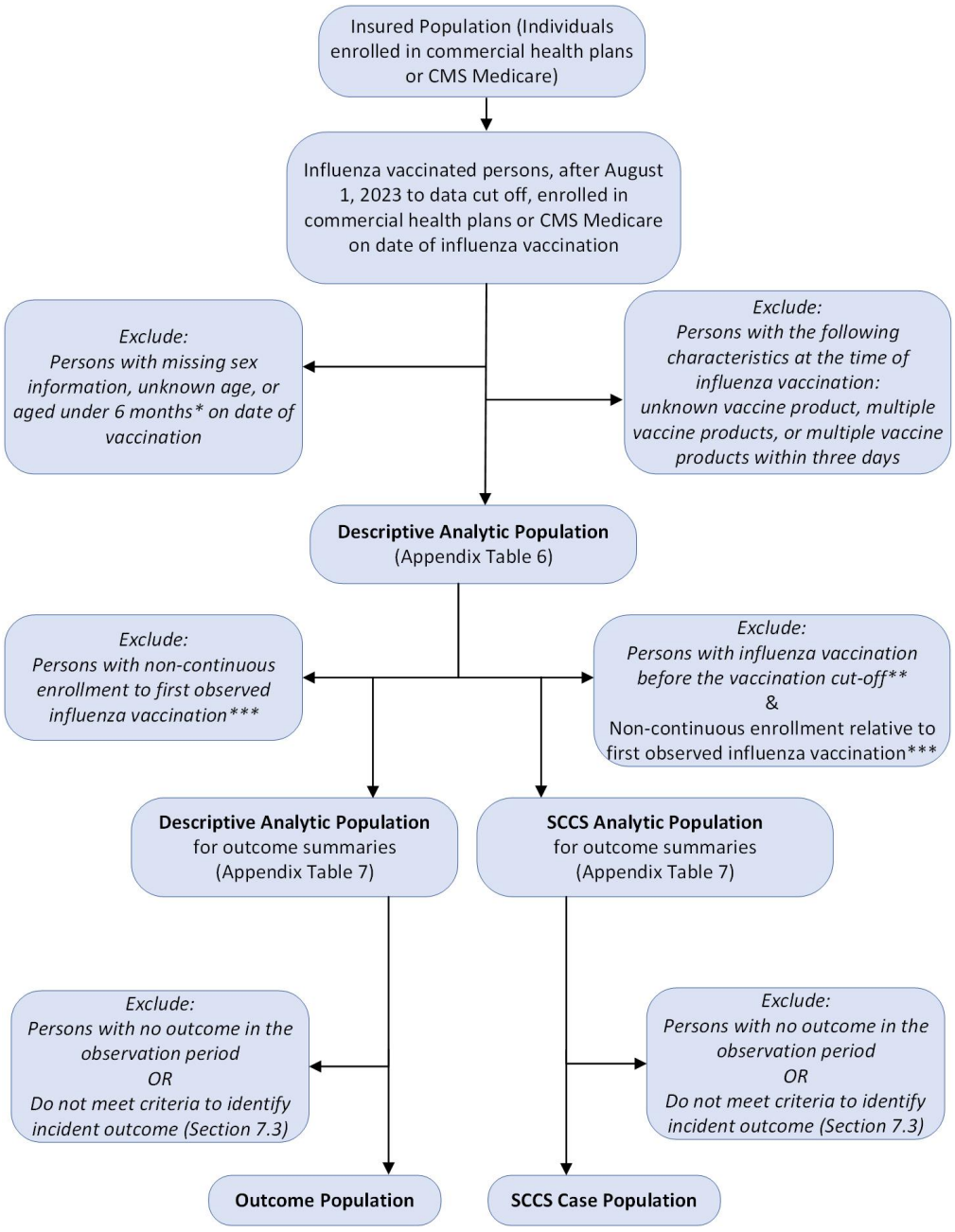
**Data lag is based on 2020 claims delay distribution*

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

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 influenza vaccine and meet 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 vaccine dose for study inclusion, and Medicare beneficiaries must be aged 65 years and older on the date of their first 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 the later of 60 days following their birthdate or 365 days prior to influenza vaccination. Medicare FFS beneficiaries will be required to have continuous enrollment in Medicare Parts A and B from 365 days prior to influenza 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 period will start on August 1, 2023, the effective date for billing codes for influenza vaccinations approved during the 2023-2024 influenza season[11]. The study end date will be determined based on the most recent data available sufficiently accounting for claims delay at the time of analysis and to account for at least 80% vaccine uptake in the 2023-2024 season. The approach used to determine the study end date for the SCCS analysis is specified in Section 8.1.

7. Study Variables

7.1 Care Setting Definitions

Influenza vaccinations and the outcomes of interest will be identified in care settings of interest based on clinical guidance, as specified in Sections 7.2 and 7.3. Table 2 defines the IP, outpatient department and professional (OP/PB), and 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

* Excluding any admitting diagnosis from IP claims

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

** 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 Influenza Vaccination Exposures

The exposure will be defined as the first influenza vaccine administration observed during the study period. Exposures for influenza vaccines will be identified through vaccine-specific codes, including CPT/HCPCS codes and NDCs in the professional, outpatient institutional, inpatient, or pharmacy care settings (Appendix Table 2).

To deduplicate influenza vaccine exposures identified via multiple sources such as claims and IIS data, the following cleaning rules will be applied:

(i) multiple vaccination records containing the same vaccine brand, occurring on the same day or within three days will be deduplicated.
(ii) persons with multiple vaccination records for more than one influenza product, occurring on the same day or within three days will be excluded from the study.

Appendix Table 2 presents a list of the product-specific administration codes[11] that will be used to identify influenza vaccine exposures by vaccine type and group. This list will be continuously reviewed and updated during the course of surveillance. Analyses will be performed for any age-appropriate influenza vaccines (as referenced in Table 3). The main analysis will evaluate the risk of pre-specified health outcomes for any influenza vaccine.

7.3 Outcomes

Table 3 specifies the outcomes of interest that will be monitored following influenza vaccine administration. Outcomes will be identified with *International Classification of Diseases, Tenth Revision, Clinical Modification* (ICD-10-CM) codes in either primary or secondary diagnosis positions (except GBS which will use the primary diagnosis position). For each outcome, the Table 3 outlines the settings of interest, risk interval, control interval, and clean window that will be used to identify incident outcomes, as well as age groups of interest for the SCCS analysis. Unless otherwise indicated, each outcome will be monitored in all age groups and for all influenza vaccines (refer to Appendix Table 2).

This list of outcomes may be further updated based on additional evidence from pre-licensure trials and other surveillance systems indicating additional outcomes with a particular safety concern. Certain outcomes may only be descriptively monitored if there is a lack of sufficient power to perform the SCCS analysis. Additional outcome specific exclusions for stroke outcomes and transverse myelitis can be found in Appendix Table 5.

Table 3. Outcomes, Care Settings, Risk Intervals, Control Intervals, Clean Windows, and Age Groups used in Surveillance

Outcomes	Care Setting	Clean Window*	Risk Interval**	Control Interval***
All Populations (ages 6 months and older)				
Anaphylaxis	IP, OP-ED	30 days	0-1 day[16, 17]	2-16 days
Encephalitis/Encephalomyelitis /ADEM	IP	183 days	1-42 days[18]	43-90 days
Transverse myelitis†	IP, OP-ED	365 days	1-42 days[19]	43-90 days
Non-hemorrhagic stroke/Transient Ischemic Attack†	IP, OP-ED (TIA only)	365 days	1-21 days 22-42 days	43-90 days
Non-hemorrhagic stroke†	IP	365 days	1-21 days 22-42 days [20, 21]	43-90 days
Hemorrhagic Stroke†	IP	365 days	1-21 days 22-42 days	43-90 days
Transient Ischemic Attack†	IP, OP-ED	365 days	22-42 days [20, 21]	43-90 days
Ages 6 months through 5 years				
Febrile Seizure	IP, OP-ED	42 days	0-1 days 0-7 days[22]	8-63 days
CMS Population (ages 65+ years)				
Guillain-Barré syndrome	IP- primary position only	365 days	1-42 days[23, 24]	43-90 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 influenza 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 are complex and are referenced in the Appendix (Section 14.5)

7.4 Covariates

The following covariates will be defined to characterize the population of vaccinees receiving influenza vaccination and outcome cases: demographic, geographic and social economic status characteristics will be identified using information from commercial insurance and Medicare enrollment databases. Immunocompromising and medical conditions, and concomitant vaccinations will be identified using diagnosis or procedure codes identified in medical claims. Medical conditions are assessed in the 365 days prior to vaccination, and concomitant vaccinations are assessed on the same day as influenza vaccination. Descriptive statistics will be summarized as follows:

(i) Demographics:
- Sex
- Age
- Race/Ethnicity (for Medicare population only)
- Rural/Urban residency
- Health and Human Services (HHS) region
- Exposure facility or provider type
- Nursing home status (for Medicare population only)
- Medicare status (for Medicare population only)
- Dual eligibility (for Medicare population only)
- Area Deprivation Index (ADI) rank (for Medicare population only)

(ii) Medical conditions or baseline health characteristics (for case population only):
- Prior hospitalization
- Asthma
- Blood disorders
- Chronic lung disease
- Diabetes
- Heart disease
- Kidney disorders
- Liver disorders
- Neurological or neurodevelopmental conditions
- Malignant neoplasms
- Immunocompromised status (binary variable)
- Charlson Comorbidity Index (CCI)

(iii) Concomitant Vaccination (any of the following, concomitant vaccines not individually evaluated):
- For beneficiaries 6 months – 49 years[25]:
    - COVID-19 vaccine
    - Pneumococcal conjugate vaccine/polysaccharide conjugate vaccine (PCV15, PCV20, PPSV23)
    - Respiratory Syncytial Virus (RSV) vaccine
    - Shingrix vaccine
    - Hepatitis A vaccine
    - Hepatitis B vaccine

- Hemophilus influenzae type b (Hib) vaccine
- Measles, Mumps and Rubella (MMR) vaccine
- Varicella vaccine
- Rotavirus vaccine
- Tetanus (DTaP, Tdap, Td) vaccine
- Inactivated polio virus (IPV) vaccine
- Human papillomavirus (HPV) vaccine
- Meningococcal vaccine

- For beneficiaries 50 years and older[25]:
  - COVID-19 vaccine
  - Pneumococcal conjugate vaccine/polysaccharide conjugate vaccine (PCV15, PCV20, PPSV23)
  - RSV vaccine
  - Shingrix vaccine

8. Study Design and Approach

8.1 Self-Controlled Methods

A single SCCS analysis will be conducted at the end of the season for all health outcomes. The SCCS design compares the incidence of an outcome of interest during periods of hypothesized excess risk due to the exposure (risk intervals) to the incidence of the outcome during all other selected times during the observation period (control intervals). The method assumes that the cases will be distributed roughly uniformly over the risk and control intervals if there is no association between the exposure and outcome of interest. If cases are concentrated in the risk interval(s), there is evidence of an association but not necessarily a causal association. Only beneficiaries with an incident event during the observation period (case population) are sampled in the SCCS design, with estimation of incidence occurring within, rather than between, individuals. The SCCS design has a number of assumptions that have to be met in order to ensure unbiased incidence rate estimates, specifically that[26]:

(i) Occurrence of an event does not substantially affect subsequent exposures.
(ii) Occurrence of an event does not affect the observation length.
(iii) Event rates are constant within risk intervals.
    a) Events must be independently recurrent or rare.
(iv) Risk and control intervals are clearly defined.

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., influenza 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.[27] 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 Period, Risk, and Control Intervals

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 influenza vaccination, or study period end.

8.2.2 Risk Interval

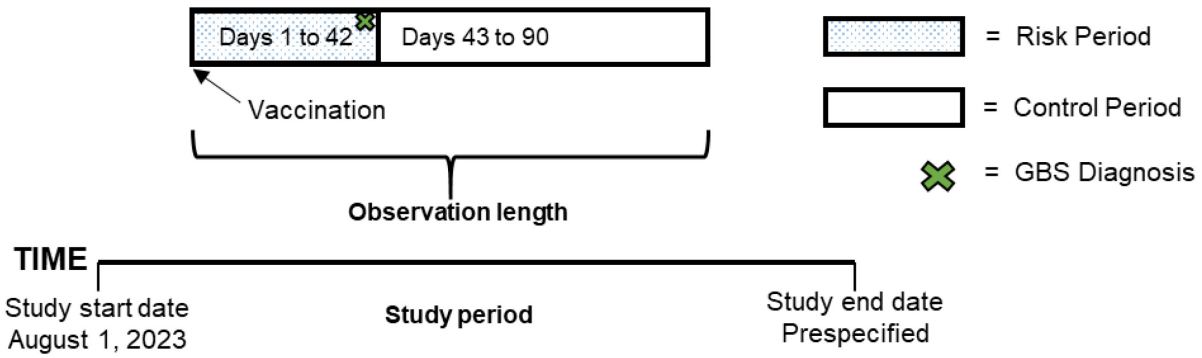
The risk interval is defined as the time during which excess risk is hypothesized following an influenza vaccination during the observation period. Risk intervals are outcome-specific and were determined for each outcome based on biological plausibility, literature review and clinician input (Table 3).

8.2.3 Control Interval

The post-vaccination control interval is defined as all follow-up time during the observation period following the influenza vaccination in the observation window that is outside of the risk interval until the earlier of the end of the observation period, death, disenrollment, subsequent influenza vaccination, or the study period end. Individuals who only accrued data during the risk intervals will be excluded from the analysis. For each outcome, control intervals are specified in Table 3.

Figure 2 represents a sample schematic for the risk and control interval definition for a person that experiences a qualifying GBS event following an influenza vaccination. The observation period for this person will begin on the vaccination date and extend to 90 days following vaccination, including a 42-day risk interval, and a control interval extending from day 43 to day 90 following vaccination. Risk and control intervals for individuals will vary by event and based on the presence of any censorship criteria. Event-specific risk and control interval specifications can be referenced in Table 3.

Figure 2. Hypothetical Example of Observation Period, Risk and Control Interval for Individual with a Qualifying GBS Event Following Influenza Vaccination



9. Statistical Analysis

9.1 Descriptive Analysis

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 Medicare (FFS/MA) enrollment plans to assess counts and percentages of demographic characteristics and concomitant immunizations (Appendix Table 6). 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 age-specific indicators for influenza vaccination (Appendix Table 7). 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, age groups of interest, and risk/control interval (Appendix Table 7).

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 Analysis

A single SCCS analysis may be conducted at the end of the surveillance period to detect associations between any influenza vaccine 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 influenza vaccine exposures and pre-specified outcomes. 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 0.05.[28]

IRR and attributable risk (AR) estimates will be estimated for end-of-surveillance SCCS analyses for vaccine brands and outcomes that are sufficiently powered, as specified in Sections 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

The primary inferential analysis will evaluate the incidence rates of outcomes following any influenza vaccination comparing the rates of events in the risk and control intervals using a conditional Poisson regression model, conditioning on the total number of events observed for an individual patient in the observation period. This analysis will be restricted to the case population and conducted for each outcome for any influenza vaccine overall. For persons aged 65 years and older, additional analyses will also be stratified by high-dose and adjuvanted vaccine groups if adequately powered.

The main model for the primary inferential analysis will include a Farrington, seasonality, and positive predictive value (PPV) adjustment (for events with PPVs available based on medical record review). The Farrington adjustment will be used to account for the reduced observation time that can occur from the occurrence of an event.[29] 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). A separate analysis will be conducted including Farrington and PPV adjustments only, to evaluate the

independent effect of the PPV adjustment on rate estimation. Another separate analysis will be performed including Farrington and seasonality adjustments only to evaluate the independent effect of the seasonality adjustment. The approach for the seasonality and PPV adjustments are specified in Sections 9.4.1 and 9.4.2. An end-of-surveillance SCCS analyses will be conducted separately in each of the commercial health plan and Medicare databases if sufficiently powered.

Where sufficiently powered, we will estimate the IRR and AR of outcomes following receipt of influenza vaccination in risk compared to control intervals for each influenza vaccine 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.

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.

$$\log(E(Y|X) = \beta_1(risk\_interval) + \log(t) + strata(patient\_id)$$

$Y = Outcome$

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

$t = number\ of\ days\ in\ the\ interval$

$patient_{id} = term\ identifying\ the\ patient$

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 $e^{\beta 1}$ 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 0.05.[28] The significance level was selected to reduce the probability of false positive results given the large number of outcomes being studied.[28] The 95% and 99% confidence intervals for the IRR will be estimated to assess the precision of estimates.

For the end-of-surveillance SCCS analyses, the study will also estimate AR per 100,000 vaccinations and per 100,000 person-years, which is the excess number of outcomes due to vaccination per 100,000 doses and per 100,000 person-years.[30] 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.[31]

$$Excess\ Outcomes\ due\ to\ Vaccination = E(Y) - E(Y|No\ exposure)$$
$$= \sum_{i=1}^{m} \left(E(Y_i|X_i) - E(Y_i|X_i = 0) \right)$$

$Y = number\ of\ outcomes$
$m = total\ number\ of\ persons\ in\ the\ study\ population$
$Y_i = outcome\ status\ of\ the\ ith\ person\ in\ the\ study\ population$
$X_i = exposure\ status\ of\ the\ ith\ person, where\ X_i = 0\ denotes\ the\ hypothetical\ absense\ of\ exposure$

The AR per 100,000 doses (and per 100,000 person-years) will then be calculated by dividing the excess number of outcomes due to 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 Analysis: Concomitant Immunizations Subgroup Analysis

The secondary inferential analysis will only be performed for events for which a statistically significant elevated IRR is observed from the primary analysis. This analysis will be implemented consistently with the primary analysis specified in Section 9.2.1, except the analysis will be conducted in two separate subgroups. One subgroup will include persons with an observed influenza vaccination administered on the same day as any of the prespecified concomitant vaccines; the other subgroup will include persons with influenza vaccination without any of the prespecified concomitant (same-day) vaccines. Where sufficiently powered, secondary analyses may be performed by combinations of concomitant vaccines.

9.4 Adjustments to 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 Sections 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 specifically for outcomes with high case fatality rates to adjust for outcome-dependent observation time.[29] The Farrington and seasonality-adjusted model is defined below.

$$\log\big(E(Y|X)\big) = \beta_1 * risk\_interval + \log\big(w(t)\big) + \log\ (seasonal\_risk) + strata\ (patient\_id)$$

$Y = Outcome$

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

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

$$seasonal\_risk = \frac{1}{IR_r * t}\sum_{m=1}^{12}(IR_M * t_m)$$

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

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

$t_m = number\ of\ days\ in\ an\ interval\ in\ month\ 'm'$

$patient\_id = term\ identifying\ the\ patient$

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 with high case fatality rates and PPV estimates available, a combined model will be implemented including both PPV and Farrington adjustments to adjust for outcome-dependent observation time.[27]

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 4 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).[32] 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 4. Outcome Positive Predictive Value (PPV) Estimates from Prior MRR

Outcome (Setting)	PPV (95% CI)
Anaphylaxis (IP, OP-ED)	66% (56%, 76%)[33]
GBS (IP, primary diagnosis position)	71% (63%, 79%)[34]
Non-hemorrhagic stroke (IP)	80% (71%, 87%)[35]

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 a subset of these outcomes identified as having a high case fatality rate to reduce bias from event-dependent observation time.[27]

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 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)

The 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).

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

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 I^2 Statistic

We will also calculate Higgins & Thompson's I^2 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 0.05. For each influenza vaccination and outcome, the power for an SCCS analysis will be assessed at various data cut dates. The power will be assessed by:

(i) identifying the number of cases eligible for an SCCS analysis under a 90% data-completeness threshold, and

(ii) calculating the power of an SCCS analysis to detect a minimum IRR of 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 (MRR) may be performed for outcomes with a statistically significant elevation in risk identified from the primary inferential analysis. 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 event misclassification based on the claims-based definition(s) used. Once PPVs are available from MRR for relevant events, a PPV-adjusted analysis may be performed to adjust for bias from event 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 events, records for either all events or a sample (simple random or representative) of events can 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 (i.e. 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, however the 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 implement the selected case definition and 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 implement the selected case definition and assign case classifications.

If abstraction-adjudication workflow #1 or #2 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 #2 or #3 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 BEST Initiative under the FDA Amendments Act of 2007. This study uses Medicare administrative claims data, and commercial insurer data from three commercial insurer databases (CVS Health, Carelon Research, and Optum). 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 Medicare and commercial insurer 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.[36] 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.[37]

12. Quality Assurance and Control

The analyses described in this protocol will be conducted using Medicare and commercial insurer 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 event trends, and assessing consistency with population selection criteria for the database.

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14. Appendix

14.1 Composition of the Influenza Vaccines for the U.S., 2023-2024

The composition of the influenza vaccine is reviewed annually by the VRBPAC to best match the virus strains found to be most common for the upcoming season. Appendix Table 1 outlines vaccine composition for the 2023-2024 season.[38]

Appendix Table 1. Composition of the Influenza Vaccine for the U.S., 2023-2024

Egg-based influenza vaccines	Cell- or recombinant-based influenza vaccines
• An A/Victoria/4897/2022 (H1N1)pdm09-like virus*	• An A/Wisconsin/67/2022 (H1N1)pdm09-like virus*
• an A/Darwin/9/2021 (H3N2)-like virus	• an A/Darwin/6/2021 (H3N2)-like virus
• a B/Austria/1359417/2021-like virus (B/Victoria lineage)	• a B/Austria/1359417/2021-like virus (B/Victoria lineage)
• a B/Phuket/3073/2013-like virus (B/Yamagata lineage)	• a B/Phuket/3073/2013-like virus (B/Yamagata lineage)

*Updated influenza component differing from the 2022-2023 influenza vaccine composition

14.2 2023-2024 Influenza Vaccine Product Code List

Analyses will be performed for any age-appropriate influenza vaccine for individuals 6 months of age and older, and separately by high-dose or adjuvanted groups for the population 65 years and older. Appendix Table 2 presents a list of the product-specific administration codes[11] that will be used to identify influenza vaccine exposures by vaccine type and group. It will be expanded to include any additional influenza vaccine codes approved as of the study initiation date.

Appendix Table 2. Influenza Vaccine (2023-2024 Formula) Product Code List

Manufacturer	Name	Vaccine Group	Code Type	Code	Age Group
Sanofi Pasteur	Fluzone High-Dose Quadrivalent (2023-2024)	High-Dose	CVX	197	65+ years
Sanofi Pasteur	Fluzone High-Dose Quadrivalent (2023-2024)	High-Dose	CPT	90662†	65+ years
Sanofi Pasteur	Fluzone High-Dose Quadrivalent (2023-2024)	High-Dose	NDC	49281-0123-65	65+ years
Sanofi Pasteur	Fluzone High-Dose Quadrivalent (2023-2024)	High-Dose	NDC	49281-0123-88	65+ years
Seqirus	Flucelvax Quadrivalent (2023-2024)	Other	CVX	171	6+ months
Seqirus	Flucelvax Quadrivalent (2023-2024)	Other	CPT	90674	6+ months

Manufacturer	Name	Vaccine Group	Code Type	Code	Age Group
Seqirus	Flucelvax Quadrivalent (2023-2024)	Other	NDC	70461-0323-03	6+ months
Seqirus	Flucelvax Quadrivalent (2023-2024)	Other	NDC	70461-0323-04	6+ months
Seqirus	Flucelvax Quadrivalent (2023-2024)	Other	NDC	70461-0423-10	6+ months
Seqirus	Flucelvax Quadrivalent (2023-2024)	Other	NDC	70461-0423-11	6+ months
Sanofi Pasteur	Flublok Quadrivalent (2023-2024)	Other	CVX	185	18+ years
Sanofi Pasteur	Flublok Quadrivalent (2023-2024)	Other	CPT	90682	18+ years
Sanofi Pasteur	Flublok Quadrivalent (2023-2024)	Other	NDC	49281-0723-88	18+ years
Sanofi Pasteur	Flublok Quadrivalent (2023-2024)	Other	NDC	49281-0723-10	18+ years
GlaxoSmithKline Biologicals	Fluarix Quadrivalent (2023-2024)	Other	CVX	150	6+ months
GlaxoSmithKline Biologicals	Fluarix Quadrivalent (2023-2024)	Other	CPT	90686	6+ months
GlaxoSmithKline Biologicals	Fluarix Quadrivalent (2023-2024)	Other	NDC	58160-0909-52	6+ months
GlaxoSmithKline Biologicals	Fluarix Quadrivalent (2023-2024)	Other	NDC	58160-0909-41	6+ months
GlaxoSmithKline Biologicals	Flulaval Quadrivalent (2023-2024)	Other	CVX	150	6+ months
GlaxoSmithKline Biologicals	Flulaval Quadrivalent (2023-2024)	Other	CPT	90686	6+ months
GlaxoSmithKline Biologicals	Flulaval Quadrivalent (2023-2024)	Other	NDC	19515-0814-52	6+ months
GlaxoSmithKline Biologicals	Flulaval Quadrivalent (2023-2024)	Other	NDC	19515-0814-41	6+ months
Sanofi Pasteur	Fluzone Quadrivalent (2023-2024)	Other	CVX	150	6+ months

Manufacturer	Name	Vaccine Group	Code Type	Code	Age Group
Sanofi Pasteur	Fluzone Quadrivalent (2023-2024)	Other	CPT	90686	6+ months
Sanofi Pasteur	Fluzone Quadrivalent (2023-2024)	Other	NDC	49281-0423-50	6+ months
Sanofi Pasteur	Fluzone Quadrivalent (2023-2024)	Other	NDC	49281-0423-88	6+ months
Seqirus	Afluria Quadrivalent (2023-2024)	Other	CVX	150	3+ years
Seqirus	Afluria Quadrivalent (2023-2024)	Other	CPT	90686	3+ years
Seqirus	Afluria Quadrivalent (2023-2024)	Other	CPT	90688	3+ years
Seqirus	Afluria Quadrivalent (2023-2024)	Other	NDC	33332-0323-03	3+ years
Seqirus	Afluria Quadrivalent (2023-2024)	Other	NDC	33332-0323-04	3+ years
Seqirus	Afluria Quadrivalent (2023-2024)	Other	CVX	158	6-35 months
Seqirus	Afluria Quadrivalent (2023-2024)	Other	CPT	90687	6-35 months
Seqirus	Afluria Quadrivalent (2023-2024)	Other	NDC	33332-0423-10	6-35 months
Seqirus	Afluria Quadrivalent (2023-2024)	Other	NDC	33332-0423-11	6-35 months
Sanofi Pasteur	Fluzone Quadrivalent (2023-2024)	Other	CVX	158	6+ months
Sanofi Pasteur	Fluzone Quadrivalent (2023-2024)	Other	CPT	90687	6-35 months
Sanofi Pasteur	Fluzone Quadrivalent (2023-2024)	Other	CPT	90688	6+ months
Sanofi Pasteur	Fluzone Quadrivalent (2023-2024)	Other	NDC	49281-0639-78	6+ months
Sanofi Pasteur	Fluzone Quadrivalent (2023-2024)	Other	NDC	49281-0639-15	6+ months

Manufacturer	Name	Vaccine Group	Code Type	Code	Age Group
Seqirus	Fluad Quadrivalent (2023-2024)	Adjuvanted	CVX	205	65+ years
Seqirus	Fluad Quadrivalent (2023-2024)	Adjuvanted	CPT	90688	65+ years
Seqirus	Fluad Quadrivalent (2023-2024)	Adjuvanted	CPT	90694	65+ years
Seqirus	Fluad Quadrivalent (2023-2024)	Adjuvanted	NDC	70461-0123-03	65+ years
Seqirus	Fluad Quadrivalent (2023-2024)	Adjuvanted	CVX	70461-0123-04	65+ years
Seqirus	Flucelvax Quadrivalent (2023-2024)	Other	CVX	186	6+ months
Seqirus	Flucelvax Quadrivalent (2023-2024)	Other	CPT	90756	6+ months
Seqirus	Flucelvax Quadrivalent (2023-2024)	Other	NDC	70461-0323-03	6+ months
Seqirus	Flucelvax Quadrivalent (2023-2024)	Other	NDC	70461-0323-04	6+ months
AstaZeneca	FluMist Quadrivalent (2023-2024)	Other	CVX	149	6+ months
AstaZeneca	FluMist Quadrivalent (2023-2024)	Other	CPT	90672	6+ months
AstaZeneca	FluMist Quadrivalent (2023-2024)	Other	NDC	66019-0310-10	6+ months
AstaZeneca	FluMist Quadrivalent (2023-2024)	Other	NDC	66019-0310-01	6+ months

Acronyms: NDC: National Drug Code; CVX: Vaccine Administered Codes; CPT: Current Procedural Terminology.
†CDC preferentially recommended influenza vaccines for use in persons aged 65 years and older[4]
Note: Incidence rates of outcomes will be estimated for any age-appropriate influenza vaccines overall, and by high-dose and adjuvanted vaccine groups only specifically for the 65+ years population. No analyses will be individually performed for other vaccine types, as these will likely not be sufficiently powered.

14.3 Concomitant Immunization Code List

Concomitant vaccines will be captured using CVX, HCPCS/CPT and NDCs. Appendix Table 3 outlines the vaccine products and administration codes that will be used to identify persons with concomitant vaccinations.

Appendix Table 3. Concomitant Immunization Code List

Vaccine	CVX	CPT / HCPCS	NDC		
COVID-19 (Monovalent Booster – Season 2023-2024)	308 309 310 311 312 313	91304 91310 91318 91319 91320 91321 91322	00069-2362-01 00069-2362-10 00069-2392-01 00069-2392-10 59267-4315-01 59267-4315-02 59267-4331-01	59267-4331-02 80631-0105-01 80631-0105-02 80777-0102-01 80777-0102-04 80777-0102-93 80777-0102-95	80777-0102-96 80777-0287-07 80777-0287-92 80631-0100-01 80631-0100-10 80631-0102-01 80631-0102-10 80777-0102-97
Pneumococcal conjugate vaccine (PCV15, PCV20), Pneumococcal polysaccharide vaccine (PPSV23)	33 215 216	90671 90677 90732 G0009	00005-2000-01 00005-2000-02 00005-2000-10 00006-4329-01	00006-4329-02 00006-4329-03 00006-4739-00 00006-4739-01 00006-4837-01 00006-4837-02 00006-4837-03 00006-4943-00	00006-4943-01 50090-6026-00 50090-6026-01 54868-3339-01 54868-3339-09 54868-4320-00 54868-4320-09
Hepatitis A*	52 83 84 85 104	90632 90633 90634 90636 90730	00006-4095-01 00006-4095-02 00006-4095-09 00006-4096-01 00006-4096-02 00006-4096-09 00006-4831-01 00006-4831-41 00006-4841-00 00006-4841-01 00006-4841-41	50090-1502-00 50090-1502-09 55045-3841-01 58160-0815-01 58160-0815-05 58160-0815-11 58160-0815-34 58160-0815-41 58160-0815-43 58160-0815-46 58160-0815-48	58160-0815-52 58160-0825-01 58160-0825-11 58160-0825-43 58160-0825-52 58160-0826-01 58160-0826-05 58160-0826-11 58160-0826-34 58160-0826-43 58160-0826-52
Hepatitis B*	8 30 42 43 44 45 51 104 110 146 189 220	90371 90636 90697 90723 90731 90739 90740 90743 90744 90745 90746 90747 90748 90759	00006-4093-01 00006-4093-02 00006-4093-09 00006-4094-01 00006-4094-02 00006-4094-09 00006-4898-00 00006-4898-01 00006-4980-00 00006-4981-00 00006-4981-01 00006-4992-00 00006-4992-01 00006-4995-00 00006-4995-01 00006-4995-41 43528-0002-01 43528-0002-05 43528-0003-01	43528-0003-05 50090-3469-00 50090-3469-09 54868-0734-00 54868-2219-00 54868-2219-01 58160-0811-41 58160-0811-43 58160-0811-51 58160-0811-52 58160-0815-01 58160-0815-05 58160-0815-11 58160-0815-34 58160-0815-41 58160-0815-43 58160-0815-46 58160-0815-48 58160-0815-52	58160-0820-01 58160-0820-11 58160-0820-43 58160-0820-52 58160-0821-01 58160-0821-05 58160-0821-11 58160-0821-34 58160-0821-43 58160-0821-52 63361-0243-10 63361-0243-15 63361-0243-58 63361-0243-88 63361-0245-10 63361-0245-58 75052-0001-01 75052-0001-10

Vaccine	CVX	CPT / HCPCS	NDC		
Human Papillomavirus (HPV)*	62 118 165	90649 90650 90651	00006-4045-00 00006-4045-01 00006-4045-41 00006-4109-01 00006-4109-02 00006-4109-09 00006-4119-01 00006-4119-02 00006-4119-03	00006-4121-01 00006-4121-02 50090-4958-00 50090-4958-01 58160-0830-05 58160-0830-34 58160-0830-43 58160-0830-52	
Hemophilus influenzae type b (Hib)*	22 46 47 48 49 50 51 120 146 148	90644 90645 90646 90647 90648 90697 90698 90720 90721 90748	00006-4897-00 00006-4897-01 00006-4898-00 00006-4898-01 49281-0510-05 49281-0511-05 49281-0544-58 49281-0545-03 49281-0545-05 49281-0545-15 49281-0547-58 49281-0548-58 49281-0560-05 49281-0561-01	58160-0801-11 58160-0806-01 58160-0806-05 58160-0809-01 58160-0809-05 58160-0816-01 58160-0816-05 58160-0818-11 63361-0243-10 63361-0243-15 63361-0243-58 63361-0243-88 63361-0245-10 63361-0245-58	
Measles, Mumps and Rubella (MMR)*	3 94	90707 90710	00006-4171-00 00006-4171-01 00006-4681-00 00006-4681-01 00006-4999-00 00006-4999-01 54868-0980-00 58160-0824-15 58160-0831-03		
Meningococcal*	32 114 136 148 162 163 203	90619 90620 90621 90644 90733 90734	00005-0100-01 00005-0100-02 00005-0100-05 00005-0100-10 46028-0114-01 46028-0114-02 46028-0114-11 46028-0208-01 46028-0218-11 46028-0219-11 49281-0487-58	49281-0488-78 49281-0489-01 49281-0489-91 49281-0589-05 49281-0589-58 49281-0590-05 49281-0590-58 50090-6180-00 50090-6180-01 58160-0801-11 58160-0809-01	58160-0809-05 58160-0827-03 58160-0827-30 58160-0955-09 58160-0958-01 58160-0959-01 58160-0976-02 58160-0976-06 58160-0976-20
Varicella*	21 36 94	90396 90710 90716	00006-4171-00 00006-4171-01 00006-4826-00 00006-4826-01 00006-4827-00 00006-4827-01 00006-4999-00 00006-4999-01		

Vaccine	CVX	CPT / HCPCS	NDC		
Rotavirus*	116 119	90680 90681	00006-4047-01 00006-4047-02 00006-4047-20 00006-4047-41 58160-0740-02 58160-0740-21 58160-0851-01 58160-0854-52		
Tetanus [i.e., Diphtheria, tetanus, and acellular pertussis (DTap); Tetanus, diphtheria, and acellular pertussis (Tdap); Tetanus and diphtheria toxoids (Td)]*	1 9 13 20 22 28 35 50 106 110 113 115 120 130 146 196 203	90389 90619 90696 90697 90698 90700 90701 90702 90703 90714 90715 90720 90721 90723	00006-4133-01 00006-4133-41 13533-0131-00 13533-0131-01 14362-0111-03 14362-0111-04 17478-0131-00 17478-0131-01 21695-0413-01 49281-0215-10 49281-0215-15 49281-0215-58 49281-0215-88 49281-0225-10 49281-0225-58 49281-0278-10 49281-0286-01 49281-0286-05 49281-0286-10 49281-0286-58 49281-0291-10 49281-0291-83 49281-0298-10 49281-0400-05 49281-0400-10	49281-0400-15 49281-0400-20 49281-0400-58 49281-0400-88 49281-0400-89 49281-0510-05 49281-0511-05 49281-0544-58 49281-0545-15 49281-0548-58 49281-0560-05 49281-0561-01 49281-0562-10 49281-0562-58 49281-0564-10 49281-0564-15 49281-0564-58 49281-0564-88 49281-0800-83 49281-0820-10 50090-2062-00 50090-2062-01 50090-2883-00 50090-2883-09 58160-0810-01	58160-0810-11 58160-0810-43 58160-0810-52 58160-0811-41 58160-0811-43 58160-0811-51 58160-0811-52 58160-0812-01 58160-0812-11 58160-0812-43 58160-0812-52 58160-0842-01 58160-0842-05 58160-0842-11 58160-0842-34 58160-0842-41 58160-0842-43 58160-0842-51 58160-0842-52 63361-0243-10 63361-0243-15 63361-0243-58 63361-0243-88 63361-0245-10 63361-0245-58
Inactivated polio virus (IPV)*	10 110 120 130 146	90696 90697 90698 90713 90723	49281-0510-05 49281-0511-05 49281-0544-58 49281-0545-15 49281-0548-58 49281-0560-05 49281-0561-01 49281-0562-10 49281-0562-58 49281-0564-10 49281-0564-15	49281-0564-58 49281-0564-88 49281-0860-10 49281-0860-55 49281-0860-78 49281-0860-88 50090-1693-00 50090-1693-09 58160-0811-41 58160-0811-43 58160-0811-51	58160-0811-52 58160-0812-01 58160-0812-11 58160-0812-43 58160-0812-52 63361-0243-10 63361-0243-15 63361-0243-58 63361-0243-88 63361-0245-10 63361-0245-58
Respiratory Syncytial Virus (RSV)	303 304 305	90678 90679	00069-0207-01 00069-0250-01 00069-0344-01 00069-0344-05	00069-0344-10 58160-0723-03 58160-0744-03 58160-0848-11	
Shingles	36 121 187	90396 90736 90750	00006-4963-00 00006-4963-01 00006-4963-41 50090-5147-00 58160-0819-12 58160-0823-11 58160-0828-01 58160-0828-03		

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

14.4 Covariate Definitions

Appendix Table 4. 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 influenza vaccination. It is a categorical variable that is stratified by male and female.
Race/Ethnicity (CMS Medicare Only)	Race/Ethnicity using the most recent data in the Medicare database, at the time of the individual's influenza vaccination. The variable will be stratified by: • Asian • Black • Hispanic • Alaskan Native/American Indian • 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 influenza vaccination. • 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.
Age	Age is defined as a person's age at the time of their first observed influenza vaccination. Persons will be stratified by the following groups: • Commercial health plans: ages 6 months - 4 years, 5-11, 12-15, 16-17, 18-24, 25-29, 30-34, 35-39, 40-44, 45-49, 50-54, 55-59, 60-64 years • CMS Medicare FFS: ages 65-69, 70-74, 75-79, 80-84, 85-89, and 90+ years

Characteristics	Description
Facility/Provider Type	Facility or provider type will be assessed at the time of the influenza vaccination. This variable will be stratified by: • Hospital • Office Visit • Pharmacy • Skilled Nursing Facility • Home Health Agency • Mass Immunization Center • Other • Missing/Unknown
Health and Human Services (HHS) Region[39]	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 influenza vaccination. 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)
Nursing Home Residency Status[40] (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 influenza vaccination. It is a categorical variable stratified by nursing home residents and non-nursing home residents.

Characteristics	Description
Dual-Eligibility Status[41] (CMS Medicare only)	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 1 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 influenza vaccination.
Area Deprivation Index (ADI) Rank[42] (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 influenza vaccination.
Reason for Medicare Eligibility[43, 44] (CMS Medicare only)	This represents the original reason for Medicare entitlement determined at the time of an individual's influenza vaccination. 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.

Characteristics	Description
Concomitant Immunizations	Concomitant immunizations will be defined as receipt of one of the following vaccinations on the same date as an individual's influenza vaccination: For beneficiaries 6 months–49 years: • COVID-19 vaccine • Pneumococcal conjugate vaccine/polysaccharide conjugate vaccine (PCV15, PCV20, PPSV23) • Respiratory Syncytial Virus (RSV) vaccine • Shingrix • Hepatitis A vaccine • Hepatitis B vaccine • Hemophilus influenzae type b (Hib) vaccine • Measles, Mumps and Rubella (MMR) vaccine • Varicella vaccine • Rotavirus vaccine • Tetanus (DTaP, Tdap, Td) vaccine • Inactivated polio virus (IPV) vaccine • Human papillomavirus (HPV) vaccine • Meningococcal vaccine For beneficiaries 50 years and older: • COVID-19 vaccine • Pneumococcal conjugate vaccine/polysaccharide conjugate vaccine (PCV15, PCV20, PPSV23) • Respiratory Syncytial Virus (RSV) vaccine • Shingrix Concomitant immunizations will be captured using HCPCS/CPT and NDCs.
Medical Conditions	The following medical conditions or baseline health characteristics will be monitored for case populations only with a lookback window of 183 days prior to and including influenza vaccination. - 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. These medical conditions will be summarized for Medicare population.

Characteristics	Description
Immunocompromised Status[45]	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 influenza vaccination. The conditions will be identified using ICD-10-CM codes and additional codes from Agency for Healthcare Research and Quality (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. This characteristics will be summarized for Medicare populations.
Charlson comorbidity index[46-48]	The Charlson Comorbidity Index will be used to categorize the prevalence of 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. 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 is the predicted mortality rate or the higher the resource use. This characteristic will be summarized for the Medicare population.
Prior Hospitalization	The following baseline health characteristic will be monitored for case populations only with a lookback window of 183 days prior to and including influenza vaccination date. Prior hospitalization will be identified by the presence of an IP stay in the claims data with any diagnoses. This characteristic will be summarized for the Medicare population.

14.5 Adjustments and Exclusions for Complex Outcomes

Appendix Table 5.1. Adjustments and Exclusions for HS, NHS, NHS/TIA, and TIA

Outcome	Adjust onset date if observed in the 1 day prior to outcome (in all settings)	Exclusions for Prevalence (in all settings)	Exclusions – other known causes (in all settings)
Hemorrhagic Stroke (HS)	I63.9, R51*, R47*, R29.810, R53.1, R42*, R41.82, R40.4, H53.13*, H53.9, G81.9*	If occurs in the 365 window prior to outcome I69*, Z86.73	If in last 30 days prior to outcome U07.1 If in last 1 day prior to outcome S06* If same day as outcome S06*, Physical Trauma Code
Non-Hemorrhagic Stroke (NHS)	Z92.82, R51*, R47*, R29.810, R53.1, R42, R41.82, R40.4, G81.9*, H53.9, H53.13*	If occurs in the 365 window prior to outcome I69*, Z86.73, I48*, D57*, D68.5*	If in last 30 days prior to outcome U07.1 If in last 28 days prior to outcome I21* If in last 1 day prior to outcome S15*, 174* In same day as outcome S15*, I74*, Physical Trauma Code
Non-hemorrhagic stroke or Transient Ischemic Attacks (NHS/TIA)	Z92.82, R51*, R47*, R29.810, R53.1, R42, R41.82, R40.4, G81.9*, H53.9, H53.13*	If occurs in the 365 window prior to outcome I69*, Z86.73, I48*, D57*, D68.5*	If in last 30 days prior to outcome U07.1 If in last 28 days prior to outcome I21* If in last 1 day prior to outcome S15*, 174* In same day as outcome S15*, I74*, Physical Trauma Code

Outcome	Adjust onset date if observed in the 1 day prior to outcome (in all settings)	Exclusions for Prevalence (in all settings)	Exclusions – other known causes (in all settings)
Transient Ischemic Attacks (TIA)	R51*, R47*, R29.810, R53.1, R42, R41.82, R40.4, G81.9*, H53.9, H53.13*	If occurs in the 365 window prior to outcome I69*, Z86.73, I48*, D57*, D68.5*	If in last 30 days prior to outcome U07.1 If in last 28 days prior to outcome I21* If in last 1 day prior to outcome S15* In same day as outcome S15*, Physical Trauma Code

Appendix Table 5.2. Exclusions for Transverse Myelitis

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

14.6 Descriptive Analysis Table Shells

Appendix Table 6. Sample Table of Characteristics of Persons Receiving Influenza Vaccines Stratified by Vaccine Type, from August 1, 2023 to [Data Cut]

Vaccine Recipient Characteristics*	Total Influenza Vaccinations		High-Dose Influenza Vaccinations		Adjuvanted Influenza Vaccinations		Other Influenza Vaccinations	
	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)								

Vaccine Recipient Characteristics*	Total Influenza Vaccinations		High-Dose Influenza Vaccinations		Adjuvanted Influenza Vaccinations		Other Influenza Vaccinations	
	Count	Percent	Count	Percent	Count	Percent	Count	Percent
Total								
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								
46-55								

Vaccine Recipient Characteristics*	Total Influenza Vaccinations		High-Dose Influenza Vaccinations		Adjuvanted Influenza Vaccinations		Other Influenza Vaccinations	
	Count	Percent	Count	Percent	Count	Percent	Count	Percent
Total								
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)								

Vaccine Recipient Characteristics*	Total Influenza Vaccinations		High-Dose Influenza Vaccinations		Adjuvanted Influenza Vaccinations		Other Influenza Vaccinations	
	Count	Percent	Count	Percent	Count	Percent	Count	Percent
Total								
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								
Pharmacy								
Skilled Nursing Facility								
Home Health Agency								
Mass Immunization Center								

Vaccine Recipient Characteristics*	Total Influenza Vaccinations		High-Dose Influenza Vaccinations		Adjuvanted Influenza Vaccinations		Other Influenza Vaccinations	
	Count	Percent	Count	Percent	Count	Percent	Count	Percent
Total								
Other								
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 (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								

Vaccine Recipient Characteristics*	Total Influenza Vaccinations		High-Dose Influenza Vaccinations		Adjuvanted Influenza Vaccinations		Other Influenza Vaccinations	
	Count	Percent	Count	Percent	Count	Percent	Count	Percent
Total								
Concomitant Immunization								
Any Concomitant Immunization (Commercial)								
COVID-19 2023-2024 Vaccine								
Pneumococcal Vaccine								
RSV Vaccine								
Shingrix Vaccine								
Hepatitis A Vaccine								
Hepatitis B Vaccine								
HiB Vaccine								
MMR Vaccine								
Varicella Vaccine								
Rotavirus Vaccine								
Tetanus Vaccine								
IPV Vaccine								
HPV Vaccine								
Meningococcal Vaccine								
Any Concomitant Immunization (Medicare)								
COVID-19 Vaccine								
Pneumococcal Vaccine								
RSV Vaccine								
Shingrix Vaccine								

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 7. Sample Table of Descriptive Statistics – Persons in CMS Medicare and Commercial Data Partners Receiving Influenza Vaccination

Patient characteristic	Influenza Vaccine Type									
	Outcomes of interest									
	Number of vaccines[a]	Total Observed Outcomes			Outcomes Occurring in Risk Interval			Outcomes Occurring in Control Interval		
		Number of outcomes[b]	Person-time (person-years)	Rate per 100,000 person-years	Number of outcomes[b]	Person-time	Rate per 100,000 person-years	Number of outcomes[b]	Person-time	Rate per 100,000 person-years
Total										
Sex										
Male										
Female										
Age										
6 mos. – 4 yrs.										
5 – 11 yrs.										
12- 17 yrs.										
18 – 25 yrs.										
26 – 35 yrs.										
36 – 45 yrs.										
46 – 55 yrs.										
56 – 64 yrs.										
65 – 74 yrs.										
75 – 79 yrs.										
80 – 84 yrs.										
85 – 89 yrs.										
90+ yrs.										
Race/Ethnicity										

Patient characteristic	Influenza Vaccine Type									
	Outcomes of interest									
	Number of vaccines[a]	Total Observed Outcomes			Outcomes Occurring in Risk Interval			Outcomes Occurring in Control Interval		
		Number of outcomes[b]	Person-time (person-years)	Rate per 100,000 person-years	Number of outcomes[b]	Person-time	Rate per 100,000 person-years	Number of outcomes[b]	Person-time	Rate per 100,000 person-years
Total										
White										
Black										
Hispanic										
Asian										
American Indian/Alaskan Native										
Other/Unknown										
Urban/Rural										
Urban										
Rural										
Missing/Unknown										
HHS Region[c]										
Region 1 (Boston)										
Region 2 (New York)										
Region 3 Philadelphia)										
Region 4 (Atlanta)										
Region 5 (Chicago)										
Region 6 (Dallas)										
Region 7 (Kansas City)										
Region 8 (Denver)										
Region 9 (San										

Patient characteristic	Influenza Vaccine Type									
	Outcomes of interest									
	Number of vaccines[a]	Total Observed Outcomes			Outcomes Occurring in Risk Interval			Outcomes Occurring in Control Interval		
		Number of outcomes[b]	Person-time (person-years)	Rate per 100,000 person-years	Number of outcomes[b]	Person-time	Rate per 100,000 person-years	Number of outcomes[b]	Person-time	Rate per 100,000 person-years
Total										
Region 10 (Seattle)										
Missing/Unknown										
Dual-Eligibility Status										
Dual-Eligible										
Non-Dual-Eligible										
Reason for Medicare Eligibility										
Aged-in without ESRD										
Aged-in with ESRD										
Disabled without ESRD										
Disabled with ESRD										
ESRD Only										
Missing/Unknown										
Area Deprivation Index (ADI) Rank										
1-10(th)										
11-20										
21-30										
31-40										
41-50										
51-60										
61-70										

Patient characteristic	Influenza Vaccine Type									
	Outcomes of interest									
	Number of vaccines[a]	Total Observed Outcomes			Outcomes Occurring in Risk Interval			Outcomes Occurring in Control Interval		
		Number of outcomes[b]	Person-time (person-years)	Rate per 100,000 person-years	Number of outcomes[b]	Person-time	Rate per 100,000 person-years	Number of outcomes[b]	Person-time	Rate per 100,000 person-years
Total										
71-80										
81-90										
91-100										
Missing / Unknown										
Nursing Home Residency										
Nursing Home										
Non-Nursing Home										
Medical Conditions										
Prior Hospitalization										
Asthma										
Blood disorders										
Chronic lung disease										
Diabetes										
Heart Disease										
Kidney Disorders										
Liver Disorders										
Neurological or Neurodevelopmental conditions										
Malignant Neoplasms										
Immunocompromised										
Yes										

Patient characteristic	Influenza Vaccine Type									
	Outcomes of interest									
	Number of vaccines[a]	Total Observed Outcomes			Outcomes Occurring in Risk Interval			Outcomes Occurring in Control Interval		
		Number of outcomes[b]	Person-time (person-years)	Rate per 100,000 person-years	Number of outcomes[b]	Person-time	Rate per 100,000 person-years	Number of outcomes[b]	Person-time	Rate per 100,000 person-years
Total										
No										
Charlson Comorbidity										
0										
1										
2										
3										
4+										
Concomitant Vaccination										
COVID-19 2023-24 Vaccine										
RSV Vaccine										
Pneumococcal polysaccharide Vaccine										
Pneumococcal conjugate Vaccine										
Shingrix Vaccine										
Tetanus Vaccine										
Hepatitis A Vaccine										
Hepatitis B Vaccine										
Hib Vaccine										
MMR Vaccine										

Patient characteristic	Influenza Vaccine Type									
	Outcomes of interest									
	Number of vaccines[a]	Total Observed Outcomes			Outcomes Occurring in Risk Interval			Outcomes Occurring in Control Interval		
		Number of outcomes[b]	Person-time (person-years)	Rate per 100,000 person-years	Number of outcomes[b]	Person-time	Rate per 100,000 person-years	Number of outcomes[b]	Person-time	Rate per 100,000 person-years
Total										
Varicella Vaccine										
Rotavirus Vaccine										
DTaP Vaccine										
IPV Vaccine										
Tdap, Td Vaccines										

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.

a The number of observed influenza vaccines that are eligible for the follow up of a specific outcomes

b The rate for outcomes in risk or control intervals, calculated by the number of observed outcomes in the respective interval divided by the total person-time in the interval, displayed per 100,000 person-years.

c Health and Human Service (HHS) regions are administrative regions consisting of multiple U.S. states, established by the Office of Regional Health Operations (OHRO) within the Office of Assistant Secretary Health (OASH) in alignment with its regional offices. Link to map for HHS region https://www.hhs.gov/about/agencies/iea/regional-offices/index.html

d Information for nursing home residence status and race are available in Medicare database only.

14.7 Immunocompromised Algorithm

Individuals' 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.[45] The original algorithm was found to have a high accuracy of identifying immunocompromised persons with a PPV of 94.4% (95% CI 88.8–97.7), negative predictive value (NPV) of 94.3% (95% 91.0-96.6), sensitivity of 87.4% (95% CI 80.6–92.5%) and specificity of 97.6% (95% CI 95.0–99.9%).[45] The CBER-adapted algorithm was developed based on clinical consultation, and was modified to use ICD-10-CM codes and additional codes from the Agency for Healthcare Research and Quality (AHRQ) criteria for identifying individuals at risk of immunosuppression. The modified version of the algorithm also includes eight mutually exclusive (i.e.

implemented one at a time) categories of immunosuppression. Relevant indicators included in the algorithm will be identified in the 183 days prior to influenza vaccination.

i. Human Immunodeficiency Virus (HIV) / Acquired Immunodeficiency Syndrome (AIDS)
ii. Hematological Malignancy and Related Conditions
iii. Immune Deficiencies (treatment-dependent)
iv. Immune Deficiencies (treatment-independent)
v. Solid Malignancy
vi. Transplant and Related Conditions
vii. Rheumatological / Inflammatory Conditions
viii. Dialysis