Master Protocol:
Assessment of the Risk of Adverse Events Following Influenza Vaccinations Approved during the 2022-2023 Influenza Season

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Center for Biologics Evaluation and Research
Office of Biostatistics and Pharmacovigilance

CBER Surveillance Program Biologics Effectiveness and Safety (BEST) Initiative

Study Team

FDA/CBER/OBE	
Azadeh Shoaibi, PhD, MHS	
Sylvia Cho, PhD	
Hui Lee Wong, PhD	
Patricia C. Lloyd, PhD, ScM	
Joann F. Gruber, PhD, MSPH	
Tainya C. Clarke, PhD, MPH, MSc	
Richard Forshee, PhD	
Steven A. Anderson, PhD, MPP	
Acumen, LLC	
Michelle Ondari, MSPH	Pablo Freyria Duenas, MA
Chianti Shi, MS	Jingjing An, PhD
Gita Nadimpalli, MD, MPH, PHD	Nimesh Shah, MPH
Shwetha Krishnakumar, BA	Xinxin Lin, MPH
Mao Hu, BS	Zhiruo Wan, MS
Arnstein Lindaas, MA	Meng Chen, MSE
Bradley Lufkin, MPA, MSES	Yoganand Chillarige, MPA

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List of Abbreviations

AE	Adverse event
ADEM	Acute Disseminated Encephalomyelitis
ADI	Area of Deprivation Index
AR	Attributable risk
BEST	Biologics Effectiveness and Safety Initiative
CBER	Center for Biologics Evaluation and Research
CDC	Centers for Disease Control and Prevention
CMS	Centers for Medicare & Medicaid Services
CPT	Current Procedural Terminology
EDB	Enrollment Database
FDA	Food and Drug Administration
FFS	Fee-for-Service
GBS	Guillain Barré -Syndrome (GBS)
HCPCS	Healthcare Common Procedure Coding System
IP	Inpatient
IRR	Incidence rate ratio
MDS	Minimum Data Set
NPV	Negative Predictive Value
OBPV	Office of Biostatics and Pharmacovigilance
OP-ED	Outpatient emergency department
OP/PB	Outpatient or Professional
PCV	Pneumococcal conjugate vaccine
POS	Place of Service
PPV	Positive predictive value
SCCS	Self-controlled case series
SE	Standard error

SSD	Shared Systems Data
Tdap	Tetanus, diphtheria, and pertussis vaccination
Td	Tetanus and diphtheria vaccination

Contents

1. Background/Introduction

There were approximately 290,000-650,000 influenza-related hospitalizations and 19,000-58,000 influenza-related deaths in the United States (U.S.) during the 2022-2023 influenza season (October 1, 2022- April 30, 2023).[1] Evidence from previous influenza seasons, shows that persons aged 65 years and older are at an increased risk for more severe influenza-related symptoms and complications due to age-related comorbidities and decline in immune function.[2] Approximately 50-70% of influenza-related hospitalizations and 70-85% of influenza-related deaths during the 2010-2011 and 2019-2020 influenza seasons were among individuals 65 years of age and older.[2] Vaccination continues to be the primary tool for influenza prevention.[3] Influenza vaccines are recommended for anyone 6 months of age and older and are typically developed with new formulations each influenza season to target the four most prevalent influenza viruses based on available data.[3] Safety monitoring of annual influenza vaccines, particularly among persons 65 and older, is useful because these vaccines are reformulated each year and given this is a particularly vulnerable population.

Historically, adverse events (AEs) following influenza vaccination have been rare. Previous studies conducted in the U.S. and globally over the course of various influenza seasons largely support the safety profile of influenza vaccines showing no elevation in risk associated with several AEs following influenza vaccination.[4-9] However, other studies have found associations between influenza vaccines and certain AEs including anaphylaxis, encephalitis or encephalomyelitis, Guillain Barré -Syndrome (GBS) and transverse myelitis.[10-16] For some AEs, observed elevations in risks have largely been attributed to influenza infection.[4, 17] There is also a potential for the risk of these AEs to be impacted by concomitant vaccination; evidence shows that vaccines such as COVID-19, hepatitis B, pneumococcal, tetanus, diphtheria, pertussis (Tdap), and Shingrix vaccines have displayed an association with some of these AEs when administered independently or concomitantly with other vaccines.[18-21]

For the 2022-23 season, there are multiple influenza vaccines available: Afluria Quadrivalent, Fluarix Quadrivalent, FluLaval Quadrivalent, Fluzone Quadrivalent, Flucelvax Quadrivalent, Flublok Quadrivalent, Fluzone High-Dose Quadrivalent, Fluad Quadrivalent, and FluMist Quadrivalent.[22] Of these vaccines, three are preferentially recommended by the Centers for Disease Control and Prevention (CDC) for use in people aged 65 years or older: Fluzone High-Dose Quadrivalent inactivated vaccine, Flublok Quadrivalent recombinant vaccine, and Fluad Quadrivalent adjuvanted vaccine.[3]

This document details the specifications for a self-controlled case series (SCCS) study in the U.S. to assess the incidence of select AEs (anaphylaxis, encephalitis or encephalomyelitis, GBS, and transverse myelitis) following administration of influenza vaccines approved for use during the 2022-2023 influenza season. These AEs were chosen because they have been studied in other vaccines. This study will be implemented in the Centers for Medicare & Medicaid (CMS) Medicare claims database among persons aged 65 years and older.

2. Objectives

The objective of this public health study is to assess the safety profile of influenza vaccines administered during the 2022-2023 influenza season in the U.S. population aged 65 years and older. The specific objectives are outlined below.

- **Primary Objective**: To estimate the incidence rate of the following AEs: anaphylaxis, encephalitis or encephalomyelitis (including acute disseminated encephalomyelitis (ADEM)), GBS, and transverse myelitis after exposure to influenza vaccines in the risk interval, compared to the incidence rate of the AEs in the control interval. Assessment of AEs incidence rates will be performed for all influenza vaccine types combined together (overall), and for high-dose and adjuvanted vaccine groups separately. Vaccine groupings are presented in Table 3.
    - **Follow-Up Objective (if applicable):** If there is a statistically significant association in the primary analysis indicating a potentially increased rate of an AE in the risk compared to control interval, we will evaluate the potential contribution of concomitant (same-day) vaccination with at least one of five other vaccines to the elevated incidence rate for the given AE. The analysis for the specific outcome(s) with a statistically significant result will be stratified by concomitant vaccination status (influenza vaccination alone, and influenza vaccine *with any* same-day concomitant vaccination). Where sufficiently powered, follow-up analyses by combinations of concomitant vaccines may be performed.
        - Concomitant vaccines of interest are listed below. [1(23, 24)] Table E1 can be referenced for associated vaccine code lists:
            - COVID-19 Bivalent (Pfizer-BioNTech, Moderna)
            - Pneumococcal (PCV15/20, PPSV23)
            - Hepatitis B
            - Tetanus (Tdap, tetanus, diphtheria (Td))
            - Shingrix

3. Data Sources

The study will be performed using the Medicare administrative claims database. The Medicare claims database includes well-defined longitudinal data that captures healthcare service utilization for millions of enrollees across multiple care settings including inpatient, outpatient-emergency department (OP-ED) and outpatient non-ED, professional services non-laboratory and laboratory, and pharmacy settings.

The Medicare Study will include CMS Medicare Shared System Data (SSD) to capture longitudinal healthcare information for persons aged 65 years and older in the study population. Medicare Fee-for-Service (FFS) Part A (inpatient) and Part B (outpatient and physician services) will be used to capture patient's vaccination history, healthcare services, health-related covariates, and diagnoses. Medicare

[1]The selection of concomitant vaccines is based on vaccines recommended for administration in the population aged 65 years and older.

Part D data will also be used as a supplementary source to capture patient's vaccination history. The CMS Medicare Enrollment Database (EDB) will be used to capture patient's demographic characteristics. Medicare claims data undergo three stages of processing: enumeration, adjudication, and final payment. This study will use CMS Medicare SSD which consists of claims sourced after enumeration to reduce data lag. Information on nursing home residency status will be captured from The Minimum Data Set (MDS) 3.0, a mandatory clinical assessment administered to all residents in Medicare and Medicaid certified nursing homes.[25] Table 1 summarizes data characteristics for the Medicare claims data source.

Table 1. Description of Medicare Claims Data Characteristics

Data Source	Claims Type	Update frequency	Data Lag*	Population Enrolled
CMS Medicare Fee-For-Service Shared Systems Fee-for-Service Data (SSD)	Pre-Adjudicated	Daily	>80% data completeness in 30-70 days for inpatient claims	>34 million beneficiaries annually

*Data lag is based on 2020 claims delay distribution

4. Exposure and Adverse Events

4.1 Care Settings

Influenza vaccinations and AEs will be identified in care settings of interest based on clinical guidance, as specified in Section 4.2 and 4.3. Table 2 defines the inpatient (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

* 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 place of service (POS) and revenue (REV) codes, in PB and OP settings, respectively.

4.2 Exposure

The study will focus on influenza vaccinations approved for use during the 2022-2023 influenza season extending from August 1, 2022 to July 31, 2023.[2] Any beneficiary with a relevant vaccine product code between August 1, 2022 and November 12, 2022 (vaccination cutoff date) will be included in the study population. The vaccination cutoff date is the latest date in which influenza vaccines administered will be eligible for inclusion in the study. The rationale for the vaccination cutoff date is further described in Section 5.5.1. For persons eligible for inclusion in the study, only the incident vaccine administration observed during the study period will be included.

Table 3 presents a list of the product-specific administration codes[22] that will be used to identify influenza vaccine exposures by vaccine type and vaccine group. Analyses will be performed across influenza vaccines overall, and by individual vaccine groups (as referenced in Section 5.5). The study will specifically focus on codes recommended for use in persons aged 65 years and older. Current Procedural Terminology (CPT)/Healthcare Common Procedure Coding System (HCPCS) codes will be used to identify influenza vaccines administered. The following list will be expanded to include any additional influenza vaccine codes approved as of the study initiation date.

[2] Based on the effective dates for influenza vaccine codes specific to the 2022-2023 influenza season.

Table 3. 2022-2023 Influenza Vaccine Exposure Code List and Classifications

Code Type	Code	Vaccine Name	Vaccine Type			Vaccine Group
			Vaccine Classification		Abbreviated	
CPT	90662†	Fluzone High-Dose Quadrivalent (2022-2023)	Inactivated	High-dose	IIV4-HD	High-dose
CPT	90674	Flucelvax Quadrivalent (2022-2023)	Inactivated	Cell-cultured	ccIIV4	Other
CPT	90682†	Flublok Quadrivalent (2022-2023)	Recombinant	Recombinant	RIV4	Other
CPT	90686	Fluarix Quadrivalent (2022-2023)	Inactivated	Standard (split virus)	IIV4	Other
		Flulaval Quadrivalent (2022-2023)				Other
		Fluzone Quadrivalent (2022-2023)				Other
		Afluria Quadrivalent (2022-2023)				Other
CPT	90688	Fluzone Quadrivalent (2022-2023)	Inactivated	Standard (split virus)	IIV4	Other
		Afluria Quadrivalent (2022-2023)				Other
CPT	90694†	Fluad Quadrivalent (2022-2023)	Inactivated	Adjuvanted	aIIV4	Adjuvanted
CPT	90756	Flucelvax Quadrivalent (2022-2023)	Inactivated	Cell-cultured	ccIIV4	Other

†CDC preferentially recommended influenza vaccines for use in persons aged 65 years and older[3]
Note: Assessment of AE incidence rates will be performed across approved influenza vaccines overall, and by high-dose and adjuvanted vaccine groups only. No further analyses will be performed restricted to the "other" vaccine grouping as this will likely not be sufficiently powered in this population.

4.3 Adverse Events

AEs of interest in the study are anaphylaxis, encephalitis or encephalomyelitis (including ADEM), GBS, and transverse myelitis. These events were selected due to their potential association with influenza vaccines based on literature review, experience with prior seasons' influenza vaccines, and clinician consultation. AEs will be captured using International Classification of Diseases, 10th Revision, Clinical Modification (ICD-10-CM) diagnosis codes billed in claims.

The study will focus on incident AEs occurring during the observation period, defined as no prior occurrences of the AEs observed during the specified clean period. The clean period is the duration prior to the first AE occurrence during the observation period, during which persons with an observed AE will be excluded from the study population. This ensures that only incident cases of the event are captured. Cleaning occurs relative to the incident AE occurrence date, and within AE-specific care settings.

Table 4 displays the AEs included in the study and summarizes the medical diagnosis codes, care settings, risk and control intervals, and clean periods used in the study.

Table 4. Summary of AE Definitions

AE	AE Definition				
	ICD-10 CM codes	Care Settings*	Risk Interval**	Control Interval***	Clean Period†*
Anaphylaxis	T782XXA, T8052XA	IP,OP-ED	0 - 1 days	3-16 days	30 days
Encephalitis or Encephalomyelitis (including ADEM)	G0400, G0402, G0481, G0490, G053	IP	1 - 42 days	43-90 days	183 days
Guillain-Barré Syndrome	G610	IP (primary diagnosis position)	1 - 42 days	43-90 days	365 days
Transverse Myelitis	G373	IP, OP-ED	1 - 42 days	43-90 days	365 days

* Care setting definitions are specified in Section 4.1.
**Hypothesized period of elevated AE risk relative to vaccination date, during which incident AE occurrences are attributed to the vaccine. Extends from vaccine administration date through AE-specific risk interval.
***Follow-up time during the observation period following the risk interval. Specified relative to vaccination date.
†* Cleaning will occur relative to the incident AE occurrence date, and within AE-specific care settings.

5. Study Design

5.1. Study Population

The study will include eligible vaccinees enrolled in Medicare during the study period who receive an influenza vaccine and meet the inclusion and exclusion criteria below, regardless of AE occurrence. All eligible vaccinees will be used to estimate attributable risks (ARs), whereas a subset population with an observed AE occurrence during the observation period (case population) will be used to estimate IRRs.

Inclusion criteria

(i) Beneficiaries must be enrolled in Medicare Part A (inpatient insurance) and Part B (outpatient and physician services insurance) FFS plans during the observation period, which extends from vaccination date through the earlier of the AE control period end, or any of the censorship criteria (i.e., disenrollment, subsequent influenza vaccination, study period end, or death). Definitions for the risk, control and observation period can be referenced in Section 5.4.
   - If a follow-up concomitant vaccines analysis is applicable, Part D insurance will also be required during the observation period to ensure comprehensive capture of concomitant vaccinations.

(ii) Beneficiaries must have received an influenza vaccine during the study period and prior to the vaccination cutoff date (latest date vaccine administration will be eligible for inclusion in the study). Further information on the rationale for this cutoff is provided in Section 5.5.1.

(iii) Beneficiaries will be required to have continuous enrollment in Medicare Parts A and B FFS from 365 days prior to influenza vaccination through the earlier of the observation period end, or any of the censorship criteria (i.e., disenrollment, subsequent influenza vaccination, or death).

(iv) For the case population only, each case must have a record of an incident AE diagnosis during the observation period.

Exclusion criteria

(i) Medicare beneficiaries less than 65 years of age at the time of influenza vaccination.
(ii) Individuals that do not contribute *any* follow-up time to both risk and control intervals i.e. beneficiaries that meet any of the censorship criteria during the risk interval prior to accumulating time in the control interval will be excluded.
(iii) Individuals vaccinated with multiple influenza vaccine brands on the same day or multiple influenza vaccinations (same/different brand) within 3 days of each other.
(iv) People who received a diagnosis of the AE during the AE-specific clean period.

5.2 Self-Controlled Methods

The SCCS design compares the incidence of AEs during periods of hypothesized excess risk due to the exposure (risk intervals) to the incidence of AEs during all other times (or selected times) during the observation period (control intervals). Only beneficiaries with an incident AE 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 correctly specified.

Certain modifications to the SCCS design will be performed to reduce potential violations to these assumptions. Study analyses will be restricted to the post-vaccination control interval to reduce bias from reverse causation, where early occurrences of an event affect the likelihood of subsequent exposures resulting in accentuated or attenuated effect associations between the exposure and outcome. An adjustment developed by Farrington et al. will also be implemented to adjust for perturbed or curtailed observation time. This will involve conditioning on the age at censoring in cases, and weighting cases by the density of follow-up time from event to censoring.[27] The case fatality rate can range from 10-13% for certain AEs such as GBS, encephalitis or encephalomyelitis, and transverse myelitis.[28-30] As AE-related mortality would violate the assumption that events be independent of the observation length, this adjustment is required to reduce the potential bias from event-dependent observation lengths.

5.3 Study Period

The study period will start on August 1, 2022, the effective date for billing codes for influenza vaccinations approved during the 2022-2023 influenza season,[22] and end on June 2, 2023. The study end date was determined based on the approach detailed in Section 5.5.1 and was established to account for claims delay in the data.

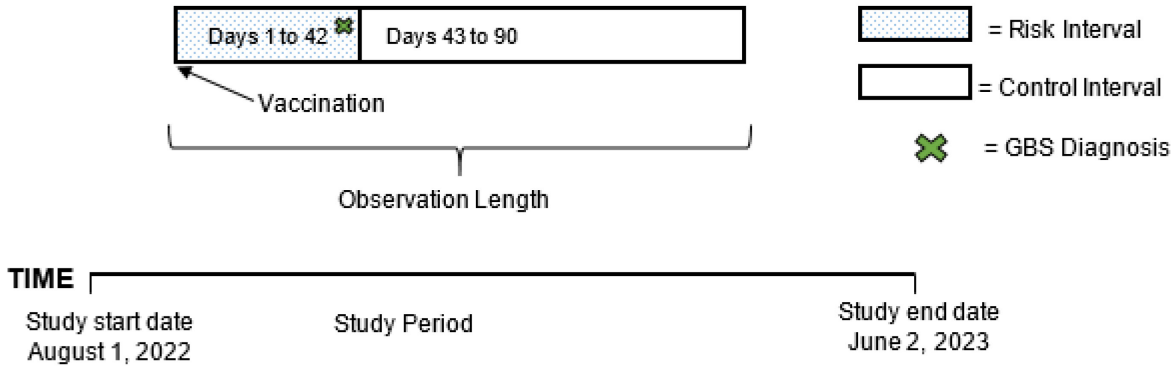
5.4 Risk and Control Interval

5.4.1 Definition of Observation Period, Risk and Control Intervals

Specifications for AE-specific risk and control intervals are presented in Section 4.3.

Figure 1 presents a hypothetical example of the observation period for a person that experiences a qualifying GBS event following 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 AE and based on the presence of any censorship criteria. AE-specific risk and control interval specifications can be referenced in Section 4.3.

Figure 1. Hypothetical Example of Observation Period, Risk and Control Interval for Individual with a Qualifying GBS Event Following Influenza Vaccination



5.4.1.1 Observation Period

The observation period length will be AE-specific. For each individual, the observation period will start from the day following influenza vaccination (except for anaphylaxis which will begin on the day of vaccination) and extend through the earlier of the end of the AE-specific control interval, study period end, or any of the specified censorship criteria (i.e., disenrollment, subsequent influenza vaccination).

5.4.1.2 Risk Interval

The risk interval is similarly AE-specific and is defined as the time during which excess risk is hypothesized following influenza vaccination based on biological plausibility and clinical input. Table 4 in Section 4.3 displays the risk intervals that are used for each AE.

5.4.1.3 Control Interval

The control interval is restricted to the post-vaccination period and is defined as all follow-up time during the observation period following an influenza vaccine that occurs after the risk interval.

5.5 Statistical Analysis

A feasibility analysis will first be conducted as outlined in Section 5.5.1 to determine the study end date. Descriptive and inferential analyses will then be conducted for primary and follow-up analyses (if applicable) as specified in Section 5.5.2-Section 5.5.6.

5.5.1 Feasibility Analysis: Statistical Power and Sample Size

A power analysis will be performed to determine when the analyses can be conducted with sufficient sample size. This will be used to establish the data cut for the analysis, which will inform the study end date. The influenza vaccination uptake distribution in the 2022-2023 influenza season will first be obtained to ensure that the vaccination cutoff date (only vaccines prior to this cutoff will be eligible for inclusion in the study) is selected to capture at least 85% of vaccinations. Then, for each AE, vaccine cutoff date, and influenza vaccine group (reference Table 3), the outcome-specific data cut date will be estimated based on (i) the length of the observation window and (ii) the outcome-specific claims delay distribution with a 90% data completeness requirement. For each AE, vaccination cutoff date and influenza vaccine group, the expected number of events during the observation window will be estimated using the AE-specific historical background rates obtained from 2021. Finally, the minimum detectable IRR will be estimated, defined as the minimum effect size that can be detected in the study based on the expected sample size at 80% power and a two-sided alpha of 0.05. To determine if there is sufficient power to conduct the analysis, for each AE, vaccination cutoff date, and influenza vaccine group, we will identify comparable IRR estimates available in the literature. These will be compared against the minimum detectable IRR estimated in the power analysis, so that the data cut date/study end date used for the analysis can balance the trade-off between being able to detect reasonable differences in incident rates and the timely initiation of analyses.

The 90% completeness threshold was selected to balance the potential bias due to observation of partially accrued post-vaccination control intervals relative to risk intervals and timeliness of the analyses. Assuming that event observation delays are accurately estimated from historical data, a 90% completeness threshold limits the difference in observation of events 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=11%. However, in practice, risk and control interval completeness will fall between 100% and 90% and we expect the potential bias due to claims delay to be smaller. The 90% completeness is likely to overestimate the IRR by 10% or less.

5.5.2 Descriptive Analysis

Descriptive analyses will be performed for the primary and follow-up analyses. For each of the case populations, the descriptive analyses will summarize the cases (counts and percentages) and unadjusted outcome rates following influenza vaccination by risk and control intervals. Descriptive statistics will be summarized for influenza vaccines overall and by high-dose and adjuvanted vaccine groups. Statistics will be summarized overall and by the following characteristics.

(i) Demographics: Age, sex, race/ethnicity, dual eligibility status, region[3], urban/rural, area deprivation index (ADI)[(31)], nursing home residency status
(ii) Health status: Influenza diagnosis (defined by the ICD-10-CM code J10.X) in the 30 days prior to influenza vaccination
(iii) Concomitant vaccines administered on the influenza vaccine administration date (as specified in Section 2)
(iv) Baseline health characteristics (defined by ICD-10 codes) in the 183 days prior to influenza vaccination:
    - Prior hospitalization
    - Asthma
    - Blood disorders
    - Chronic lung disease
    - Diabetes
    - Heart disease
    - Kidney disorders
    - Liver disorders
    - Neurological or neurodevelopmental conditions
    - Malignant neoplasms
    - Immunocompromised status (as binary covariate)[4(32)]
    - Charlson comorbidity index

5.5.3 Primary Inferential Analysis

5.5.3.1 Incidence Rate Ratio (IRR) Estimation

The primary inferential analysis will evaluate the incidence rates of AEs following the influenza vaccines, comparing the rates of AEs in the risk and control intervals using a conditional Poisson regression model, conditioning on the total number of AEs observed for an individual patient in the observation period. This analysis will be restricted to the case population and conducted for each AE for influenza vaccines overall and by high-dose and adjuvanted vaccine groups.

The main primary analysis model will include a Farrington, seasonality and positive predictive value (PPV) adjustment (for AEs 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.[(27)] A separate analysis will be conducted including Farrington and PPV adjustments only, to evaluate the independent effect of the PPV adjustment excluding the seasonality adjustment. Another separate analysis will be performed including Farrington and seasonality adjustments only to evaluate

[3] Covariate will be based on Health and Human Service (HHS) Region as specified on https://www.hhs.gov/about/agencies/iea/regional-offices/region-1/index.html

[4] Beneficiaries' immunocompromised status will be determined based on a CBER-modified algorithm adapted from the Greenberg et al. algorithm, which was developed and validated to identify immunocompromised persons. Details on the algorithm can be found in Appendix 10.21.

the independent effect of the seasonality adjustment. The approach for the seasonality and PPV adjustments are specified in Section 5.5.5.

5.5.4 Follow-Up Inferential Analysis- Concomitant Vaccination Analysis

5.5.4.1 Incidence Rate Ratio (IRR) Estimation

The follow-up inferential analysis will only be performed for AEs for which a statistically significant elevated incidence rate ratio is observed from the primary analysis. This analysis will be implemented consistently with the primary analysis specified in Section 5.5.3.1, except the analysis will be conducted in two separate subgroups. One subgroup will include persons with an observed influenza vaccination *with any* concomitant (same-day) vaccination, and the other subgroup will include persons with influenza vaccination *without any* concomitant (same-day) vaccination. Where sufficiently powered, follow-up analyses may be performed by combinations of concomitant vaccines.

5.5.5 Adjustments to Primary and Follow-Up Analyses

5.5.5.1 Seasonality Adjustment Analysis

Both the primary and follow-up analyses specified in Section 5.5.3 and 5.5.4 will include a seasonality adjustment, given that certain AEs included in the study demonstrate seasonal patterns in incident rates. This seasonality adjustment will adjust for changes in the baseline rate of AEs during different calendar months in the year. The baseline rate of AEs will be estimated from a similar population during the same calendar months in previous years, and subsequently included as an offset term in the regression model. For each AE, 2021 will be the comparator year used to adjust for changes in the baseline rate. Both 2020 and 2021 were considered as historical years for the seasonality adjustment; 2021 was selected as the adjustment period given that 2021 rates are more recent and thus likely more reflective of rates during the study period, and since the 2020 period has the potential to underestimate events due to changes in healthcare utilization during the early pandemic.[33]

The Farrington and seasonality-adjusted model that will be used for the main primary and follow-up analyses is defined below.[27]

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

$Y = AE$
$risk\_interval = binary\ term\ indicating\ AE\ occurrence\ in\ risk\ interval$
$w(t) = Farrington\ adjusted\ weight$

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

$IR_m = daily\ incident\ rate\ for\ month\ m$
$IR_r = daily\ incident\ rate\ for\ reference\ month\ r$
$t_m = number\ of\ days\ in\ an\ interval\ in\ month\ m$

$$t = number\ of\ days\ in\ an\ interval\ or\ equivalently\ t = \sum_{m=1}^{12} t_m$$

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

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

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

Where e^{β_1} is the IRR for the AE in the risk interval compared to control interval adjusting for seasonality and curtailed observation time. A statistically significant coefficient at a pre-specified alpha level of 0.05 will indicate a statistically significant association between influenza vaccination and the AE.

5.5.5.2 Positive Predictive Value (PPV) Adjustment Analysis

For certain AEs with PPVs available from prior medical record review (anaphylaxis and GBS), a PPV-adjustment will be included in the model for both primary and follow-up analyses to ascertain IRR estimates that account for potential outcome misclassification related to the claims-based AE definition. Table 5 presents the PPV estimates that will be used for the adjustment based on medical record review findings from previously published studies using a CMS population. IRRs directly obtained from primary and follow-up analyses without a PPV adjustment may be biased, as a portion of the cases identified during the observation period may not be true cases. PPV-adjusted models will be implemented including the Farrington adjustment only, and in a combined model including both Farrington and seasonality adjustments.

Table 5. AE Positive Predictive Value (PPV) Estimates from Prior Medical Record Review

AE (Setting)	PPV (95% CI)
Anaphylaxis (IP, OP-ED)	66% (95% CI: 56%, 76%)[34]
GBS (IP, primary diagnosis position)	71% (95% CI: 63%, 79%)[35]

5.5.6 Attributable Risk (AR) Estimation

For the primary analyses and when follow-up analyses apply, the study will also estimate an adjusted AR statistic (per 100,000 vaccinations). The AR is the excess number of AE cases divided by the number of eligible beneficiaries (or eligible follow up dose-years). The number of excess AE cases due to the influenza vaccine will be derived directly from the conditional Poisson regression model, defined as the difference between the sum of the model fitted values (i.e., model predicted number of cases), and the sum of the expected cases (i.e., all observed time is treated as control time). 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 AE with replacement and repeat the AR calculation. The SE is calculated as the square root of the variance of the 10,000 AR values. AR estimates will be reported for each of the AEs for influenza vaccines overall, and by high-dose and adjuvanted vaccine groups separately.

6. Medical Record Review

For AEs without PPVs available from previous medical record review, medical record review may be considered if a significant elevation in incidence rates is detected from the study. The purpose of medical record review will be to evaluate the accuracy of the claims-based outcome definition(s) used. AE-specific PPVs and 95% CIs will be estimated to assess the probability of event misclassification based on the claims-based definitions used.

7. 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. The study involves no personal health information; 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 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]

8. Quality Assurance and Control

The analyses described in this protocol will be conducted using Medicare which is a well-characterized administrative claims database, 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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10. Appendix

10.1 Concomitant Vaccination Code List

Concomitant vaccines will be captured using CPT/HCPCS and national drug codes (NDCs). Table E1 outlines the vaccine product and administration codes that will be used to identify persons with concomitant vaccination.

Table E1. Concomitant Vaccine Product and Administration Code List

Concomitant Vaccine	CPT/HCPCS	Vaccine Administration Code	NDC
COVID-19, Bivalent (Pfizer-BioNTech, Moderna)	91312 91315 91313 91314	0124A 0154A 0134A 0144A	N/A
Hepatitis B*	90739 90740 90743 90744 90746 90477 90759 90636 90748	G0010	N/A
Pneumococcal (PCV15/20, PPSV23)	90671 90677 90732	G0009	N/A
Shingrix	90750		58160081912 58160082311 58160082801 58160082803 58160082901 58160082903 50090337200 50090514700

Concomitant Vaccine	CPT/HCPCS	Vaccine Administration Code	NDC		
Tetanus†	90696-90698, 90700,90714, 90715, 90721, 90723		00006413301	49281051005	58160080111
			00006413341	49281051105	58160080605
			00008033903	49281054503,	58160080901,5
			00008034001	549281054515	58160081001
			00026063402	49281054605	58160081011
			13533013100-1	49281054658	58160081041,3,6
			13533063402	49281054758	58160081051,2
			13533063420	49281054858	58160081111
			14362011101,3-4	49281056005	58160081141,3,6
			17478013010	49281056101	58160081151,2
			17478013100-1	49281056210	58160081201
			21695041301	49281056258	58160081211
			21695060801,5	49281056410,5	58160081243,6
			21695060901,5	49281056458	58160081251,2
			23490203301,2	49281056488	58160081601,5
			49281021510,5	49281080083	58160081701,5
			49281021558,88	49281081284	58160081811
			49281022510	49281082010	58160084001
			49281022558	50090288300,9	58160084011
			49281027110	54569145800,900	58160084051
			49281027183	54569146000	58160084111
			49281027510	54569387500	58160084146
			49281027810	54569439800,900	58160084201,5
			49281028601,5	54569496900	58160084211
			49281028610	54569548600	58160084232,4
			49281028658	54569608200	58160084243,6
			49281029110	54569638600	58160084251,2
			49281029183	54569642600	58337130101,2
			49281029810	54868057106	63361024310,5
			49281040010,5	54868319700	63361024358
			49281040020	54868339400,1	63361024388
			49281040058	54868349000	63361024510
			49281040088	54868359700	63361024558
			49281040089	55045394501	68258893901,5

Acronyms: Tdap: tetanus, diphtheria, pertussis; Td: tetanus, diphtheria; DTaP: diphtheria, tetanus, pertussis; IPV: inactivated polio vaccine; Hib: haemophilus influenzae type B.

*Captures vaccine combinations including hepatitis B (hepatitis B and A; hepatitis B and Hib).

†Captures vaccine combinations including tetanus (Tdap, Td, DTaP-HepB-IPV, DTaP-IPV-Hib, DTaP-IPV, DTaP-IPV-Hib-HepB). DTaP combinations used in pediatric populations are included to ensure comprehensive capture of concomitant vaccination in claims.

Note: COVID-19, hepatitis B, and PCV vaccines will be captured using CPT/HCPCS product and administration codes only; these vaccines are billed through the Medicare Part B benefit that uses CPT/HCPCS codes for billing. Shingrix and tetanus vaccines will additionally be captured using NDCs as these vaccines are respectively billed through the Medicare Part D benefit or through both Medicare Part B and D benefits; NDCs are used to bill to Part D.

10.2 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.[32] 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%).[32] 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) HIV/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
(viii) Dialysis