SENTINEL PRISM PROGRAM

RAPID SURVEILLANCE CAPABILITY PROTOCOL
2017-18 SEASONAL INFLUENZA VACCINES SURVEILLANCE

Prepared by: Alison Tse Kawai, ScD[1]; Lauren Zichittella, MS[1]; Hector S. Izurieta, MD, MPH[2]; Azadeh Shoaibi, MS, MHS, PhD[2]; Richard A. Forshee, PhD[2]; Cathy Panozzo, PhD[1]; Joyce Obidi, PhD[2]; Kinnera Chada, PhD[2]; Steve Anderson, PhD, MPP[2]; Scott Proestel, MD[2]; Deepa Arya, MD, MPH, MBA[2]; Kevin Haynes, PharmD, MSCE[3]; Lauren Parlett, PhD[3]; Cheryl McMahill-Walraven, PhD, MSW[4]; Smita Bhatia, MCA[4]; Annemarie Kline, MS[4]; Mano Selvan, PhD[5]; Eric Czernizer, MPH[1]; James Williams, MBA[1]; W. Katherine Yih, PhD[1]

Author Affiliations: 1. Department of Population Medicine, Harvard Medical School and Harvard Pilgrim Health Care Institute, Boston, MA; 2. Center for Biologics Evaluation and Research, Food and Drug Administration, Silver Spring, MD; 3. HealthCore, Inc., Alexandria, VA; 4. Aetna Inc., Blue Bell, PA; 5. Humana, Louisville, KY

Version 1 August 4, 2017

Version 2 September 6, 2017

Version 3 November 6, 2017

The Sentinel System is sponsored by the U.S. Food and Drug Administration (FDA) to proactively monitor the safety of FDA-regulated medical products and complements other existing FDA safety surveillance capabilities. The Sentinel System is one piece of FDA's Sentinel Initiative, a long-term, multi-faceted effort to develop a national electronic system. Sentinel Collaborators include Data and Academic Partners that provide access to healthcare data and ongoing scientific, technical, methodological, and organizational expertise. The Sentinel Coordinating Center is funded by the FDA through the Department of Health and Human Services (HHS) Contract number HHSF223201400030I.

Version	Date	Modification	By
V2	09/06/2016	For monitoring of safety outcomes, we will use locally executed SAS code and continuous sequential analysis. We no longer plan to use Sequential Package v. 2.1.1 in R and a "hybrid" analytic approach that is neither strictly continuous sequential analysis nor strictly group sequential analysis.	Sentinel Operations Center Rapid Surveillance Workgroup
V3	11/06/2017	The null hypothesis for sequential analysis of safety outcomes has been modified. The null hypothesis will now be that the risk after influenza vaccination in 2017-18 is no greater than 2.5 times the risk after influenza vaccination in historical seasons.	Sentinel Operations Center Rapid Surveillance Workgroup

Sentinel PRISM Program
Rapid Surveillance Capability Protocol
2017-18 Seasonal Influenza Vaccines Surveillance

Table of Contents

I. INTRODUCTION

The purpose of this project is to conduct influenza vaccine surveillance during the 2017-18 season. Influenza vaccine surveillance is challenging for several reasons. Sentinel data are refreshed on a quarterly basis and contain relatively settled and complete data, the most recent of which are on average 9-12 months old. Near real-time surveillance of influenza vaccines requires more frequent data updates and fresher data if safety problems are to be detected in time to intervene. Influenza vaccines are routinely available in early September, and most vaccines are distributed and administered by late November.

This project will utilize fresher and more frequently updated data from three large Sentinel Data Partners. We will build on efforts from a prior Sentinel activity, "Accessing the Freshest Feasible Data for Conducting Active Influenza Vaccine Safety Surveillance", which conducted influenza vaccine safety surveillance during the 2012-13 and 2013-14 seasons[1]. The main distinction with the present activity is that refreshes, analyses, and reporting will be conducted on a more frequent basis. In the prior activity, Data Partners implemented staggered bi-monthly updates of fresher data, used by the Sentinel Coordinating Center to conduct monthly sequential analysis and reporting. Also, in the present activity, the null hypothesis will be different, in order to guard against false positive results.

In this activity, we will conduct surveillance of influenza vaccines given during the 2017-18 influenza season from August 2017 through April 2018. Each of the Data Partners will be requested to update the fresher data on a once monthly basis from October 2017 through May 2018. The data will be used by the Sentinel Coordinating Center, with the aim of conducting approximately twice-monthly sequential analyses of select safety outcomes and descriptive analyses of post-vaccination occurrence of influenza.

The aims of the project are the following:

Primary aim: To conduct sequential analysis of 4 safety outcomes following influenza vaccination during the 2017-18 season: anaphylaxis, Guillain-Barré syndrome (GBS), Bell's palsy, and febrile seizures

Secondary aim: To conduct descriptive analysis of post-vaccination occurrence of influenza during the 2017-18 season

II. METHODS

A. STUDY PERIODS, POPULATIONS, AND DATA SOURCES

We will conduct surveillance for inactivated influenza vaccines, IIV (among all IIV products combined, and separately among adjuvanted, high-dose, and standard-dose IIV) given from August 1, 2017 through April 30, 2018. Aetna, HealthCore, and Humana ("Data Partners") will provide claims data on vaccine exposures and health outcomes of interest for persons ages six months and older. To minimize processing time and reduce storage requirements for the Data Partners, no enrollment data will be captured.

B. DATA-PROCESSING

The "Rapid Surveillance Source Files" (**RSSFs**) will be health plan member-level files held internally at each Data Partner that include only claims that are adjudicated or, if no reimbursement is expected, recorded (e.g., for capitated health plans where providers are reimbursed for monthly management of the member's health care, not reimbursed for every service provided; or for vaccines obtained using a state-purchasing program and not submitted for reimbursement after administration). The RSSFs are anticipated to be refreshed at the Data Partner sites in the last half of each month. Each new version of the RSSF is anticipated to include data on healthcare events through the end of the most recent prior calendar month.

On an approximately once-monthly basis during the 2017-18 surveillance season, each Data Partner will be asked to translate their RSSFs to the standard-format "Rapid Surveillance Common Data Model" (**RSCDM**). The RSCDM population will include members with a medical claim and/or pharmacy claim on or after 8/1/2017. With each generated version of the RSCDM, previous versions will be overwritten.

Claims and administrative data from the Data Partners (health insurance companies) will be utilized as the data source for this surveillance activity. All medical and pharmacy claims with service and/or fill date(s) on or after 8/1/2016 are to be included. With each generation of the RSCDM, Data Partners will run a distributed SAS program to check data attributes, adherence to the RSCDM, and consistency over time with prior refreshes. Aggregated count output will be sent to the Sentinel Coordinating Center to conduct a limited quality control assessment. Due to rapid timing, any RSCDM that does not pass the quality control assessment and that cannot be fixed within a few days will not be re-run and corrections will be made the following month.

With each generation of the RSCDM, the Data Partners will also run a distributed SAS program to create the "Rapid Surveillance Case Files" (**RSCFs**), a subset of the RSCDM that preserves demographic, medical claims, and dispensing data for cases of the health outcomes being monitored. All generations of the RSCFs will be retained by Data Partners to facilitate the creation of aggregated datasets for analysis, the assessment of data stability over time, and preliminary investigation in the event that a potential increased risk is observed, defined as when the test statistic exceeds a pre-defined threshold.

After creation of the RSCFs, the Data Partners will run a distributed SAS program that aggregates data from the RSCDM and RSCFs to create the "Rapid Surveillance Aggregate (or Analysis) Files" (**RSAFs**). RSAFs are anticipated to include a vaccine file and a diagnosis file, each of which will contain a summary count of the cumulative number of members in each stratum. Variables defining the strata will include week of vaccination, age group, sex, vaccine type, concomitant vaccines (diphtheria tetanus acellular pertussis vaccine (DTaP) and 13-valent pneumococcal conjugate vaccine (PCV13)), dose number, and, in the diagnosis file, health outcome of interest and timing of the outcome relative to the vaccination. The RSAFs will be transferred to analysts at the Sentinel Coordinating Center via secure file transport for quality control assessment and analysis. All generations of the RSAFs will be retained by the Sentinel Coordinating Center.

Each of the 3 Data Partners will be requested to provide cumulative refreshed data at eight points during the 2017-18 season (once-monthly, from October 2017 through May 2018). Using available data meeting the quality checking standard, we will aim to conduct twice-monthly sequential analyses on safety outcomes and descriptive analyses of post-vaccination occurrence of influenza.

C. SAFETY OUTCOMES

The 4 safety outcomes we will monitor in sequential analysis are anaphylaxis, Guillain-Barré Syndrome (GBS), Bell's palsy, and febrile seizures. To increase the positive predictive value and reduce capture of follow-up encounters, we will only count cases from the inpatient and emergency department (ED) settings for anaphylaxis and febrile seizures, and from the inpatient setting for GBS[1-3]. Risk intervals and washout-periods to identify incident events are based on prior work in Sentinel and Vaccine Safety Datalink activities[1,2,4].

The definitions of the 4 outcomes, with their risk intervals, are presented in **Table 1**. Outcomes will be identified using the ICD-9 and ICD-10 codes listed in **Table 2**. ICD-10 codes will be used to assess outcomes occurring during the surveillance period. ICD-9 codes will be used to assess outcomes occurring during the historical seasons, historical vaccinees serving as the comparator.

Table 1. Safety Outcome Definitions

Outcome	Settings	Risk interval	Washout-period to identify incident events*	Vaccine type	Ages
Anaphylaxis	Inpatient or ED	0-1 day	183 days in inpatient or ED	IIV** (pooled), excluding recombinant influenza vaccine	≥ 6 months
				High-dose IIV	≥ 65 years
				Standard dose IIV, excluding adjuvanted IIV	6 months-64 years ≥ 65 years
				Adjuvanted IIV	≥ 65 years
Bell's palsy	Inpatient, ED, or outpatient	1-42 days	365 days in inpatient, ED, or outpatient	IIV (pooled), excluding recombinant influenza vaccine	6 months-17 years 18-64 years ≥65 years
				High-dose IIV	≥ 65 years
				Standard dose IIV, excluding adjuvanted IIV	6 months - 17 years 18-64 years ≥65 years
				Adjuvanted IIV	≥ 65 years
Guillain-Barré Syndrome	Inpatient	1-42 days	365 days in inpatient	Same as Bell's palsy	Same as Bell's palsy
Febrile seizures	Inpatient or ED	0-1 day	183 days in inpatient, ED, or outpatient	IIV without concomitant PCV13	6-23 months

*Since we are not requiring enrollment, it is anticipated that not all cases will have a look-back period of prior data sufficient to establish the specified washout period; the look-back period will be that noted in the table or, if that full period is not available, the maximum period available. Also, for some of the Data Partners, the fresh data sources to be used distinguish among member IDs but not unique individuals. Therefore, the look-back for previous diagnoses of anaphylaxis or seizures will be within member ID, not person ID. This could lead to falsely identifying a follow-up visit as an incident event. For example, if a person had a seizure and then switched health plans/products (leading to a change in member ID) before having a post-vaccination seizure, the earlier one would be overlooked in the electronic look-back.

** Inactivated influenza vaccine; quadrivalent and trivalent inactivated influenza vaccines will be combined in the analyses.

Table 2. ICD-9 and ICD-10 Codes Used to Identify Safety Outcomes

Outcome	Code and Description	
Anaphylaxis	999.42	Anaphylactic reaction due to vaccination
	995.0	Other anaphylactic reaction
	T80.52XA	Anaphylactic reaction due to vaccination, initial encounter
	T78.2XXA	Anaphylactic shock, unspecified, initial encounter
	T88.6XXA	Anaphylactic reaction due to adverse effect of correct drug or medicament properly administered, initial encounter
Bell's palsy	351.0	Bell's palsy
	G51.0	Bell's palsy
Guillain-Barré syndrome	357.0	Acute infective polyneuritis
	G61.0	Guillain-Barré syndrome
Febrile seizures	780.31	Febrile convulsions (simple), unspecified
	780.32	Complex febrile convulsions
	R56.00	Simple febrile convulsions
	R56.01	Complex febrile convulsions

We will monitor for febrile seizures in children 6-23 months of age receiving IIV without concomitant PCV13, since PCV7 was associated with increased risk of febrile seizures in a prior VSD activity[5].

For anaphylaxis, GBS, and Bell's palsy, we plan to do separate sequential analyses for inactivated influenza vaccines (IIV; pooled) and for the following vaccine types: high dose IIV, standard dose IIV, and adjuvanted IIV. Of note, high-dose IIV and adjuvanted IIV are only indicated for adults age 65 years and older. Some of the analyses by vaccine type may be underpowered due to low case numbers. It should be noted that since the Advisory Committee on Immunization Practices (ACIP) did not recommend the use of the live attenuated influenza vaccine (LAIV) for the 2017-2018 season, this vaccine was omitted from this activity.

D. VACCINE EXPOSURES

Influenza vaccination will be ascertained in medical and pharmacy claims by a variety of code types, including the Current Procedural Terminology (CPT) codes, Healthcare Common Procedure Coding System (HCPCS) codes, and National Drug Codes (NDCs). Although some outcomes will be monitored for specific vaccine types (high-dose IIV and adjuvanted IIV), distinction among specific vaccine products will be imperfect except where NDCs are used or a CPT or HCPCS code corresponds to a specific product. Claims of influenza vaccine received by a member within 28 days of a prior influenza vaccination claim will be considered duplicates, such that we would only count the first within this period. A maximum of 2 doses of influenza vaccine per member will be identified during the season.

As noted earlier, we will monitor for febrile seizures among children receiving IIV without concomitant PCV13. Like influenza vaccination, PCV13 vaccination will be ascertained by means of a variety of code types (NDCs, CPT codes, and HCPCS codes).

E. DESIGN FOR MONITORING OF SAFETY OUTCOMES

We will use a vaccinated cohort design with historical comparator to monitor the 4 safety outcomes[1,2]. The design is limited to vaccinated individuals with an administrative record in the health plan data to avoid bias due to immunizations that are not submitted by the patient to their health insurer for reimbursement (e.g., vaccination in the workplace or in a retail pharmacy without health plan member submitting for reimbursement). With this design, the cumulative number of cases in a pre-specified risk interval following vaccination is compared with the number expected based on the rate after a comparable exposure historically. This approach has often been used in sequential analysis for rare outcomes, because it is better powered to detect small elevations in risk and would detect a potential increased risk earlier given the same magnitude, compared to most comparisons with concurrent controls, including the self-controlled risk interval (SCRI) design[6].

The limitation of the vaccinated cohort design with historical controls in influenza vaccine safety surveillance is that historical vaccinees may not be an entirely appropriate comparison group for vaccinees in the season of interest. Confounding may exist due to different population characteristics, secular trends in diagnoses of the health outcomes of interest, different influenza strains from year to year, and/or different influenza vaccines (e.g., trivalent vs quadrivalent IIV; or high-dose vs. standard-dose) available over time. The surveillance season will consist entirely of ICD-10 data, whereas the historical seasons will consist primarily of ICD-9 data. The switch from ICD-9 to ICD-10 could lead to secular trends in diagnoses of the health outcomes of interest. Prior to the start of surveillance, we will assess for such secular trends using the Truven MarketScan Database.

F. ANALYSIS OF SAFETY OUTCOMES

1. Maximized Sequential Probability Ratio Test (maxSPRT)

Two variants of the Maximized Sequential Probability Ratio Test (maxSPRT) will be used to adjust for the repeated looks at the accumulating data entailed in sequential analysis of safety outcomes[7,8]. The test statistic will be the log-likelihood ratio (LLR). These methods adjust for multiple looks of data within the same vaccine-outcome pair. By contrast, they do not adjust for multiple testing of the same outcome across multiple vaccine types.

One-tailed tests will be used, since we will evaluate for elevated risks from vaccination rather than for protective effects. An alpha level of 0.05 will be used for testing of IIV combined and an alpha level of 0.01 for testing of specific vaccine types (i.e., adjuvanted, high-dose, standard-dose IIV) due to multiple hypotheses testing performed in this activity. For the analyses of IIV combined and specific vaccines we will report number of observed and expected events, relative risks, thresholds, and a flag for whether the test statistic exceeds the threshold (yes/no). Since multiple hypothesis testing will be performed in this activity, any discussion of statistical significance will include the caveat that multiple tests are conducted and the overall risk of a Type I error is greater than the nominal p-value threshold.

a. maxSPRT

We will use the Poisson maxSPRT to monitor safety outcomes that are not rare[2,7]. The null hypothesis will be that the risk after influenza vaccination in 2017-18 is no greater than 2.5 times the risk after influenza vaccination in historical seasons. The null hypothesis is to be rejected if, over the course of surveillance, the LLR reaches a pre-specified threshold. The rationale for using a null hypothesis of a relative risk of 2.5 is based on FDA's prior experience with near real-time surveillance using Medicare data, which uses the USPRT statistic, not the MaxSPRT. The results of extensive simulation exercises based on Medicare data showed there is a substantial chance of rejecting a null hypothesis of RR=1 even when there is no increased risk or the increased risk is very small (RR close to 1.0). Ongoing Medicare surveillance studies (using the USPRT statistic) use a null hypothesis that the risk in the surveillance season is no greater than 2.5 times the risk in a historical comparator, because the Medicare simulation exercises demonstrated that this results in high statistical power to detect a risk greater than 3 times the historical comparator, and a low probability of generating a statistically significant signal when the true risk is less than 1.5 times the historical comparator.

The threshold of the LLR will be dictated by the user-specified "upper limit" of expected cases under the null by the end of surveillance and the desired alpha level. The expected counts for each outcome will be determined based on the incidence of outcomes following vaccination in the Sentinel population, as observed in several previous influenza seasons, together with the expected number of vaccines to be administered in the Sentinel population in 2017-18 season, multiplied by 2.5. The null hypothesis will not be rejected if the total number of expected cases surpasses the pre-specified upper limit for surveillance, or if the surveillance ends without reaching this upper limit (and if the LLR has not reached the threshold).

b. CmaxSPRT

We will use the conditional maxSPRT (CmaxSPRT) to monitor rare outcomes[2,8]. Like the Poisson maxSPRT, the CmaxSPRT compares current counts to counts that would be expected based on historical rates, but it does not assume that historical rates are known without error, and instead accounts for uncertainty in these rates. Guided by the results reported in the original CmaxSPRT method paper, we will use the CmaxSPRT instead of the Poisson maxSPRT when the number of cases in the historical data used to obtain the background rates is less than 5 times the upper limit[8]. The null hypothesis and criteria for rejecting and for not rejecting the null will be the same as for the Poisson maxSPRT described above, but the threshold value of the LLR will be dictated by the user-specified upper limit of *observed* (instead of expected) cases and the alpha level. Upper limits will be determined by multiplying the number of cases expected to be observed by 2 so as not to end surveillance too soon to see a potential increased risk in the event that the true relative risk (RR) is around 2. (This differs from the procedure with the Poisson maxSPRT, because CmaxSPRT upper limits are applied to *observed*, not expected, cases.)

2. Continuous vs. Group Sequential

To conduct sequential analysis, Sentinel Coordinating Center analysts will use locally executed SAS code. We will use continuous sequential analysis, as opposed to group sequential analysis. With frequent data updates, continuous sequential methods detect potential increased risks earlier for the same levels of alpha and power.

3. Minimum Number of Cases Needed to Observe Potential Increased Risk

We will require at least 3 events for each of the safety outcomes to occur before a potential increased risk can be observed, comparing the surveillance season cohort to the historical cohort (Poisson maxSPRT or CmaxSPRT). This is proposed to avoid the false detection of a potential increased risk due to a chance early occurrence of 1-2 rare events.

4. Historical Background Rates

Background rates will be needed to calculate expected counts during surveillance, and to establish upper limits for surveillance in sequential analysis. Before the start of surveillance, Data Partners provided these by executing a Sentinel modular program on historical data in the Sentinel Common Data Model (SCDM) (https://www.sentinelinitiative.org/sentinel/routine-querying-tools/level-1-modular-program-queries). Unlike the RSCDM, the SCDM distinguishes individual patient IDs from member IDs for all Data Partners (DPs). Another difference is that no minimum enrollment will be required in the study population included in the surveillance season, whereas the study population included in the historical cohort will be required to be enrolled for a minimum of 183 or 365 days prior to vaccination.

The maximum period for historical background rates will extend from the 2010-11 influenza season through the 2015-16 influenza season. Age group-specific background rates pooled across historical seasons will be used to estimate expected rates during surveillance, using the years and age groups listed in **Table 3**.

Table 3. Historical Influenza Seasons and Age Categories for Adjustments

Outcome	Historical Influenza Seasons	Age Categories for Adjustments
Anaphylaxis	2011-12 through 2015-16	6-23 m, 24-59 m, 5-17 y, 18-64 y, 65-79 y, 80+ y
Bell's palsy	2010-11 through 2015-16	6-23 m, 24-59 m, 5-17 y, 18-24 y, 25-49 y, 50-64 y, 65-79 y, 80+ y
Guillain-Barré syndrome	2010-11 through 2015-16	6-59 m, 5-17 y, 18-24 y, 25-49 y, 50-64 y, 65-79 y, 80+ y
Febrile seizures	2012-13 through 2015-16	6-11 m, 12-23 m

We excluded the 2010-11 influenza season from monitoring of anaphylaxis because the ICD-9 codes did not exist at that time. We excluded the 2010-11 and 2011-12 influenza seasons from monitoring of febrile seizures because IIV formulations from those two years were found to be associated with increased risk of febrile seizures in other surveillance systems. We did not observe any obvious time trends when we plotted the remaining influenza seasons over time and thus will include them all (except for the exclusions described earlier).

5. Adjustment for Incomplete Data

To obtain timely results, we will conduct sequential analyses using fresh and therefore incompletely accrued data. With the vaccinated cohort design with historical comparator, two kinds of adjustment are typically needed for incomplete data, which have been documented by Greene et al[9]. One is for observation intervals that have not yet fully elapsed. For monitoring of anaphylaxis and febrile seizures, this type of adjustment is not needed given that the risk interval is very short (0-1 days post-vaccination)[9]. This adjustment, however, is needed for monitoring of Bell's palsy and GBS, since the risk interval is several weeks (1-42 days post-vaccination).

The other kind of adjustment needed is for lag in the arrival of outcome data relative to health care utilization, which results from delays in submission of a medical claim by a provider and in the processing time of a claim by the health insurer[9]. To characterize lag times, each Data Partner will quantify medical claims data accrual from October 2015 through March 2016 by week after care date for each medical care setting (inpatient, outpatient, and ED). For each week with available data in the post-vaccination risk interval, we will multiply the expected by the fraction of data expected to have arrived, per these Data Partner-specific, medical setting-specific lag characterizations.

Below, we show an example of how the two kinds of adjustment would be implemented for an outcome identified in the inpatient or ED settings, with a 6-week risk interval. Suppose for a stratum of our data defined by date of vaccination, age, and Data Partner, the following is true:

a. 6,000 doses were administered
b. Only the first 3 weeks of the risk interval has elapsed
c. The historical rate in the 6-week risk interval is 3.6/100,000 doses, and therefore the rate expressed per week is 0.6/100,000 doses (calculated as 3.6 cases per 100,000 doses ÷ 6 weeks)
d. 70% of the cases of this outcome usually occur in the ED setting and 30% in the inpatient setting (based on prior analysis of historical data)
e. The *cumulative proportion* of data estimated to accrue in 1 to 3 weeks' time (based on historical data) for the Data Partner is the following
    i. 1 week: 47% of claims in ED setting and 25% of claims in inpatient setting
    ii. 2 weeks: 66% of claims in ED setting and 45% of claims in inpatient setting
    iii. 3 weeks: 75% of claims in ED setting and 60% of claims in inpatient setting

The expected count would be calculated by summing up the number of expected events in each of the 3 weeks that have elapsed since vaccination:

Week 1 of risk interval: [6000 x (0.6/100,000) x 0.70 x 0.75] + [6000 x (0.6/100,000) x 0.30 x 0.60] = 0.02538

Week 2 of risk interval: [6000 x (0.6/100,000) x 0.70 x 0.66] + [6000 x (0.6/100,000) x 0.30 x 0.45] = 0.0215

Week 3 of risk interval: [6000 x (0.6/100,000) x 0.70 x 0.47] + [6000 x (0.6/100,000) x 0.30 x 0.25] = 0.0145

Total expected for stratum (if only the first 3 weeks of the 6-week risk interval has elapsed) = 0.02538 + 0.0215 + 0.0145= 0.0614

6. One-Time Temporal Scan Analysis

One potential limitation of standard vaccine safety designs like the vaccinated cohort design with historical comparator is that the risk interval must be defined *a priori,* based on biological plausibility and/or existing studies[10]. If the risk interval is incorrectly specified with respect to placement and/or length, then any true increased risk could potentially be washed out. At the end of surveillance, we will conduct an exploratory temporal scan analysis of GBS and Bell's palsy for all IIV vaccinees combined, among all age groups combined.

G. DEFINITIONS OF POST-VACCINATION OCCURRENCE OF INFLUENZA

We will identify influenza events in (1) the inpatient setting, and (2) in the inpatient or ED setting, from 14 days post-vaccination through the end of the surveillance season[11]. Influenza events will be excluded if they are preceded by an influenza diagnosis code in any setting during the same influenza season. Age groups to monitor for post-vaccination occurrence of influenza are listed in **Table 4**. ICD-10 codes to identify influenza are listed in **Table 5**.

Table 4. Age Groups for Descriptive Analysis of Post-Vaccination Occurrence of Influenza

Vaccine type	Ages
IIV	6 months-4 years 5-8 years 9-17 years 18-49 years 50-64 years ≥ 65 years
High-dose IIV	≥ 65 years
Adjuvanted IIV	≥ 65 years

Table 5. ICD-9 and ICD-10 Diagnosis Codes to Identify Influenza

Code	Description
J11.00	Influenza due to unidentified influenza virus with unspecified type of pneumonia
J10.00	Influenza due to other identified influenza virus with unspecified type of pneumonia
J10.01	Influenza due to other identified influenza virus with the same other identified influenza virus pneumonia
J10.08	Influenza due to other identified influenza virus with other specified pneumonia
J11.08	Influenza due to unidentified influenza virus with specified pneumonia
J11.1	Influenza due to unidentified influenza virus with other respiratory manifestations
J10.1	Influenza due to other identified influenza virus with other respiratory manifestations
J11.2	Influenza due to unidentified influenza virus with gastrointestinal manifestations
J11.81	Influenza due to unidentified influenza virus with encephalopathy
J11.89	Influenza due to unidentified influenza virus with other manifestations
J10.2	Influenza due to other identified influenza virus with gastrointestinal manifestations
J10.81	Influenza due to other identified influenza virus with encephalopathy
J10.82	Influenza due to other identified influenza virus with myocarditis
J10.83	Influenza due to other identified influenza virus with otitis media
J10.89	Influenza due to other identified influenza virus with other manifestations
J11.82	Influenza due to unidentified influenza virus with myocarditis
J11.83	Influenza due to unidentified influenza virus with otitis media
J09.X1	Influenza due to identified novel influenza A virus with pneumonia
J09.X2	Influenza due to identified novel influenza A virus with other respiratory manifestations
J09.X3	Influenza due to identified novel influenza A virus with gastrointestinal manifestations
J09.X9	Influenza due to identified novel influenza A virus with other manifestations
J10.08	Influenza due to other identified influenza virus with other specified pneumonia
J10.1	Influenza due to other identified influenza virus with other respiratory manifestations
J09.X9	Influenza due to identified novel influenza A virus with other manifestations
J09.X1	Influenza due to identified novel influenza A virus with pneumonia
J09.X2	Influenza due to identified novel influenza A virus with other respiratory manifestations
J09.X3	Influenza due to identified novel influenza A virus with gastrointestinal manifestations
J09.X9	Influenza due to identified novel influenza A virus with other manifestations

H. DESCRIPTIVE ANALYSIS OF POST-VACCINATION OCCURRENCE OF INFLUENZA

Because the analyses of post-vaccination occurrence of influenza are exploratory, they will be purely descriptive and will not include hypothesis testing (i.e., no measures of association, test statistics, or p-values). We will report the number of exposed outcomes following each of the vaccine types monitored and the number of persons exposed to each vaccine type. Exposed person-time will not be reported.

III. REPORTING

After each sequential analysis of safety outcomes and descriptive analysis of post-vaccination occurrence of influenza, a summary report will be generated and sent to workgroup members for review. For safety analyses, the report will show cumulative number of doses of each vaccine type by age group. For each vaccine-outcome-age group, we will report the cumulative number of events in the risk interval, the relative risk, the LLR, and an indicator of whether a potential increased risk has been observed (i.e., whether the LLR has surpassed the threshold).

For analyses of the post-vaccination occurrence of influenza, the report will show the cumulative number of doses of each vaccine type and cumulative number of vaccinated persons receiving each vaccine type, by age group. For each vaccine-outcome-age group, we will report the cumulative number of influenza events during the surveillance season.

IV. REFERENCES

1. Yih WK, Kulldorff M, Sandhu SK, et al. Prospective influenza vaccine safety surveillance using fresh data in the Sentinel System. Pharmacoepidemiol Drug Saf 2016;25:481-92.
2. Lee GM, Greene SK, Weintraub ES, et al. H1N1 and seasonal influenza vaccine safety in the vaccine safety datalink project. Am J Prev Med 2011;41:121-8.
3. Sandhu SK, Hua W, MaCurdy TE, et al. Near real-time surveillance for Guillain-Barré syndrome after influenza vaccination among the Medicare population, 2010/11 to 2013/14. Vaccine 2017;35:2986-92.
4. Kawai AT, Li L, Kulldorff M, et al. Absence of associations between influenza vaccines and increased risks of seizures, Guillain-Barré syndrome, encephalitis, or anaphylaxis in the 2012-2013 season. Pharmacoepidemiol Drug Saf 2014;23:548-53.
5. Duffy J, Weintraub E, Hambidge SJ, et al. Febrile Seizure Risk After Vaccination in Children 6 to 23 Months. Pediatrics 2016;138(1):e20160320.
6. Yih WK, Zichittella L, Sandhu SK, et al. Accessing the Freshest Feasible Data for Conducting Active Influenza Vaccine Safety Surveillance 2015. Available at https://www.sentinelinitiative.org/sites/default/files/Drugs/Assessments/Mini-Sentinel_PRISM_Active-Influenza-Vaccine-Safety-Surveillance-Report_0.pdf.
7. Kulldorff M, Davis RL, Kolczak M, Lewis E, Lieu TA, Platt R. A maximized sequential probability ratio test for drug and vaccine safety surveillance. Sequential Analysis 2011;30:58-78.
8. Li L, Kulldorff M. A conditional maximized sequential probability ratio test for pharmacovigilance. Stat Med 2010;29:284-95.
9. Greene SK, Kulldorff M, Yin R, et al. Near real-time vaccine safety surveillance with partially accrued data. Pharmacoepidemiol Drug Saf 2011;20:583-90.
10. Rowhani-Rahbar A, Klein NP, Dekker CL, et al. Biologically plausible and evidence-based risk intervals in immunization safety research. Vaccine 2012;31:271-7.
11. Shay DK, Chillarige Y, Kelman J, et al. Comparative Effectiveness of High-Dose Versus Standard-Dose Influenza Vaccines Among US Medicare Beneficiaries in Preventing Postinfluenza Deaths During 2012-2013 and 2013-2014. J Infect Dis 2017;215:510-7.