SENTINEL PRISM PROGRAM

RAPID SURVEILLANCE OF THE 2017-18 U.S. SEASONAL INFLUENZA VACCINES

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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.

Sentinel PRISM Program
Rapid Surveillance of the
2017-18 U.S. Seasonal Influenza Vaccines

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I. INTRODUCTION

Influenza vaccine surveillance is challenging because the vaccine formulation often changes every year. Since influenza vaccines are routinely available in early September and most vaccines are distributed and administered by late November, safety monitoring during the fall months is critical for consumer safety. The Sentinel System contains administrative claims data, the most recent of which are about 9-12 months old. Near real-time surveillance of influenza vaccines requires more recent data and more frequent data updates, resulting in fresher (e.g., claims may be less than one-month-old) but potentially less stable data.

It is important to characterize the potential risks of influenza vaccination in the context of its benefits. A recent white paper found that Sentinel's Post-Licensure Rapid Immunization Safety Monitoring (PRISM) can be useful in answering certain vaccine effectiveness questions.[1] Since the effectiveness of influenza vaccines can vary by type, population characteristics, and season, applying near real-time surveillance techniques to monitor effectiveness could be helpful in assessing the full impact of regulatory actions taken in the event of a vaccine safety concern.

In this project, we expanded the work conducted in a prior Sentinel activity that conducted influenza vaccine safety surveillance during the 2012-13 and 2013-14 seasons.[2] We similarly incorporated data from three large Sentinel Data Partners, but we analyzed data that were updated monthly rather than every other month. Further, the present study revised the null hypothesis to more carefully guard against false positive results and added an exploratory analysis of vaccine effectiveness outcomes. Specifically, our aims were to: 1) conduct sequential analysis for four safety outcomes, including anaphylaxis, Guillain-Barré syndrome (GBS), Bell's palsy, and febrile seizures, following influenza vaccination during the 2017-18 season, and 2) conduct descriptive analysis of post-vaccination occurrence of influenza during the 2017-18 season.

II. METHODS

A. SURVEILLANCE AND COHORT DATA SOURCES

We conducted safety surveillance for inactivated influenza vaccines (IIV) administered from August 1, 2017 through April 30, 2018. Three large national insurers, Aetna, Anthem/HealthCore, and Humana (Sentinel "Data Partners") participated, providing claims data on vaccine exposures and health outcomes of interest for persons ages 6 months and older who had a medical or pharmacy claim on or after August 1, 2016.

The source files were health plan member level files held internally at each Data Partner that included only claims that were adjudicated, or if no reimbursement was expected, recorded. Unlike the regular Sentinel files typically refreshed on a yearly to quarterly basis, these files were refreshed at the Data Partners monthly, contained smaller populations, and had fewer data tables. To minimize processing time and reduce storage requirements for the Data Partners, no enrollment data were captured. For example, no information from the enrollment files such as health plan start and end dates were assessed per protocol, any data not passing quality assurance within several days of detection were not included in the current data analysis, but were eligible to be included in subsequent analyses once the issue(s) were addressed.

Each of the 3 Data Partners was requested to provide cumulative refreshed data at 8 timepoints during the 2017-18 season (once-monthly, from October 2017 through May 2018). We aimed to conduct sequential analyses on safety outcomes and descriptive analyses of post-vaccination occurrence of influenza whenever one or more Data Partners provided refreshed data, up to two times per month.

Variables defining the strata in our analytic files included week of influenza vaccination, age group, sex, vaccine type, dose number, and health outcome of interest, including the timing of the outcome relative to the influenza vaccination. The Data Partners ran a distributed SAS program that aggregated the data and subsequently transferred the files to the Sentinel Operations Center via a secure file sharing system for the quality assurance assessment and analysis.

Demographic, medical claim, and dispensing data were preserved for observed cases of the specified health outcomes of interest. This facilitated the creation of aggregated datasets for analysis, the assessment of data stability over time, and preliminary investigation if an increased risk of a safety outcome was observed.

B. VACCINE EXPOSURES

The following vaccine groups were monitored: IIV pooled, standard-dose IIV, high-dose IIV, and adjuvanted IIV (**Table 1**). The IIV pooled and standard-dose IIV groups included both trivalent and quadrivalent formulations. The IIV pooled group also included both the high-dose and adjuvanted IIV groups, while the standard-dose IIV group excluded these vaccine types. The live-attenuated influenza vaccine was not recommended for use by the Advisory Committee on Immunization Practices (ACIP) for the 2017-18 influenza season resulting in low distribution and usage in the U.S., so we did not monitor it.[3] In addition, due to anticipated low uptake, we did not monitor trivalent and quadrivalent formulations of recombinant influenza vaccines. We monitored for febrile seizures among children receiving IIV without concomitant PCV13, so we captured PCV13 vaccination in the collected data as well.[4,5] IIV administration with concomitant PCV13 was excluded from the analysis due to the increased risk of febrile seizures after PCV13 observed in a previous PRISM study.[6]

Influenza and PCV13 vaccinations were 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). Since the CDC recommends that children under 9 years of age who receive their first influenza vaccine obtain 2 influenza vaccine doses at least 28 days apart, but otherwise recommends only 1 influenza vaccine dose per season, health plan members could contribute up to 2 influenza vaccine claims if they were administered at least 28 days apart. Any additional doses or doses administered less than 28 days apart were excluded.

C. SAFETY OUTCOMES

The four safety outcomes monitored in sequential analyses included anaphylaxis, Guillain-Barré Syndrome (GBS), Bell's palsy, and febrile seizures. These outcomes were identified using ICD-9-CM and ICD-10-CM codes (anaphylaxis: 999.42, 995.0, T80.52XA, T78.2XXA, T88.6XXA; Bell's palsy: 351.0, G51.0; GBS: 357.0, G61.0; febrile seizures: 780.31, 780.32, R56.00, R56.01). ICD-10-CM codes were used to assess outcomes occurring during the surveillance period, while ICD-9-CM codes were used to assess outcomes occurring during the historical comparator seasons.

To increase the positive predictive value and reduce capture of follow-up encounters, we counted cases from only inpatient and emergency department (ED) settings for anaphylaxis and febrile seizures,[2,4,7] and from only the inpatient setting for GBS[8]. Risk intervals and washout-periods to identify incident events were based on prior work in Sentinel and Vaccine Safety Datalink activities,[2,4,7] and are presented in

Table 1. Of note, since we did not capture enrollment data, we could not require members to have continuous enrollment. Therefore, the look-back period to define incident events used either the washout period in the table, or if that value was greater than a member's enrolled time, the maximum period available.

Table 1. Vaccine Types Monitored and 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

*IIV= inactivated influenza vaccine. This group included all trivalent and quadrivalent inactivated influenza vaccine formulations, including high-dose and adjuvanted influenza vaccines.

D. DESIGN FOR MONITORING OF SAFETY OUTCOMES

We used a vaccinated cohort design with historical comparator to monitor the four safety outcomes[2,7]. With this design, the cumulative number of cases in a prespecified risk interval following vaccination is compared with the number expected based on the rate after a comparable exposure historically. The design is limited to vaccinated individuals and has often been used in sequential analyses 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.[9]

E. ANALYSIS OF SAFETY OUTCOMES

1. Maximized Sequential Probability Ratio Test (maxSPRT)

Two variants of the Maximized Sequential Probability Ratio Test (maxSPRT) were used to adjust for the repeated looks at the accumulating data entailed in sequential analyses of safety outcomes.[10-11] The test statistic is the log-likelihood ratio (LLR). One-tailed tests with an alpha level of 0.05 were used for testing of IIV combined, while alpha levels of 0.01 were used for testing of specific vaccine types (i.e., adjuvanted, high-dose, standard-dose IIV). One-tailed tests rather than two-tailed tests were used because the focus was on detecting elevated risks from vaccination as opposed to protective effects. For all analyses, we reported the number of observed and expected events, relative risks, thresholds, and whether the test statistic exceeded the threshold.

a. maxSPRT

We used the Poisson maxSPRT to monitor safety outcomes whenever the number of historical cases used to estimate the background rate was greater than or equal to five times the upper limit (i.e., when outcomes were not rare).[7,10] Based on this criterion, we applied the Poisson maxSPRT to the following vaccine outcome pairs: the adjuvanted IIV and standard-dose IIV groups among those ≥ 65 years for anaphylaxis, Bell's palsy, and GBS; and the high-dose IIV group for Bell's palsy and GBS.

The null hypothesis was that the risk after influenza vaccination in 2017-18 was no greater than 2.5 times the risk after influenza vaccination in historical seasons. The rationale for using a null hypothesis with a relative risk of 2.5 was based on FDA's prior experience with near real-time surveillance using Medicare data, which uses the Updating Sequential Probability Ratio Test statistic, not the maxSPRT. The null hypothesis was to be rejected if, over the course of surveillance, the LLR reached a prespecified threshold. The threshold of the LLR was dictated by the user-specified "upper limit" of expected cases under the null by the end of surveillance and the desired alpha level. The upper limit for each outcome was determined by multiplying the incidence (number of cases in risk window per influenza vaccine dose), as observed in several previous influenza seasons, by the expected number of doses to be administered in the Sentinel population in 2017-18 season, and multiplying that product by 2.5. The null hypothesis was not rejected if the total number of expected cases surpassed the pre-specified upper limit, or if the surveillance ended without this upper limit being reached (if the LLR had not reached the threshold).

b. CmaxSPRT

We used the conditional maxSPRT (CmaxSPRT) to monitor outcomes whenever the number of historical cases used to estimate the background rate was less than five times the upper limit (i.e., when the outcomes were rare).[7,11] Based on this criterion, we applied the CmaxSPRT to the following vaccine-outcome pairs: the IIV without PCV13 group for febrile seizures; the IIV pooled group for anaphylaxis, Bell's palsy, and GBS (all age groups); the high-dose IIV group for anaphylaxis; and the standard-dose IIV group for anaphylaxis, Bell's palsy, and GBS (all age groups, except ≥65 year-olds).[11] 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. The null hypothesis and criteria for rejecting and for not rejecting the null were the same as for the Poisson maxSPRT described above, but in the CmaxSPRT, the threshold value of the LLR was dictated by the user-specified upper limit of *observed* (instead of expected) cases and the alpha level.

2. Continuous versus Group Sequential

To conduct sequential analysis, we executed SAS code locally which allowed us to aggregate the data across sites. We used continuous sequential analysis, as opposed to group sequential analysis because 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 required at least three events to accumulate for each safety outcome before hypothesis testing was conducted to minimize spurious detection of increased risk due to the early occurrence of 1-2 rare events by chance. Statistical alerts due to random cases occurring early in surveillance were occasionally seen in vaccine safety surveillance conducted by CDC's Vaccine Safety Datalink in the early years.[12] Use of a required minimum of cases has become somewhat standard. A minimum of three for current-vs.-historical comparison was also used in the prior PRISM influenza vaccine safety study.[13]

4. Historical Background Rates

Background rates of safety outcomes were required to estimate expected counts during surveillance, and to establish upper limits for surveillance in sequential analysis. Before the start of surveillance, Data Partners provided such estimates by executing a Sentinel modular program on historical data in the Sentinel Common Data Model (SCDM).[14] Age group-specific background rates pooled across historical seasons were used to estimate expected rates during surveillance, using the years and age groups listed in **Table 2**.

Table 2. 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-CM 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 2 years were found to be associated with increased risk of febrile seizures in other surveillance systems.[5]

5. Adjustment for Incomplete Data

To obtain timely results, we conducted sequential analyses using fresh and therefore incompletely accrued data. With the vaccinated cohort design with historical comparator, two kinds of adjustment are needed for incomplete data.[15] One is for observation intervals that have not yet fully elapsed. For monitoring of anaphylaxis and febrile seizures, this type of adjustment was not needed given that the risk interval was short (0-1 days post-vaccination).[15] This adjustment, however, was needed for monitoring of Bell's palsy and GBS, since the risk interval was 6 weeks long (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.[15] To characterize lag times, each Data Partner quantified medical claims data accrual from October 2015 through March 2016 by week after care date for each medical care setting (inpatient, outpatient, and emergency department [ED]). For each week with available data in the post-vaccination risk interval, we multiplied the expected by the fraction of data expected to have arrived, per these Data Partner-specific, medical setting-specific lag characterizations.

6. 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.* The putative risk interval is based on biological plausibility and/or existing studies;[16] however, if it is incorrectly specified, then any true increased risk could potentially be missed. Therefore, at the end of surveillance, we conducted an exploratory temporal scan analysis of GBS and Bell's palsy after pooled IIV, among all age groups combined. The purpose was to check whether there might be a shorter period of increased risk within the pre-specified Days 1-42 follow-up period.

F. DEFINITIONS AND ANALYSIS OF POST-VACCINATION OCCURRENCE OF INFLUENZA

We identified influenza events from 14 days post-vaccination through the end of the surveillance season in (1) the inpatient setting, and (2) in the inpatient or ED setting.[17] We identified influenza events using ICD-10-CM codes (J09*-J11*). To avoid including follow-up visits for an earlier episode of illness, influenza events were excluded if they were preceded by an influenza diagnosis code in any setting during the same influenza season. Post-vaccination occurrence of influenza was reported by age group and vaccine type. Since the analyses of post-vaccination occurrence of influenza were purely exploratory, they did not include hypothesis testing (i.e., no measures of association, test statistics, or p-values were estimated).

III. RESULTS

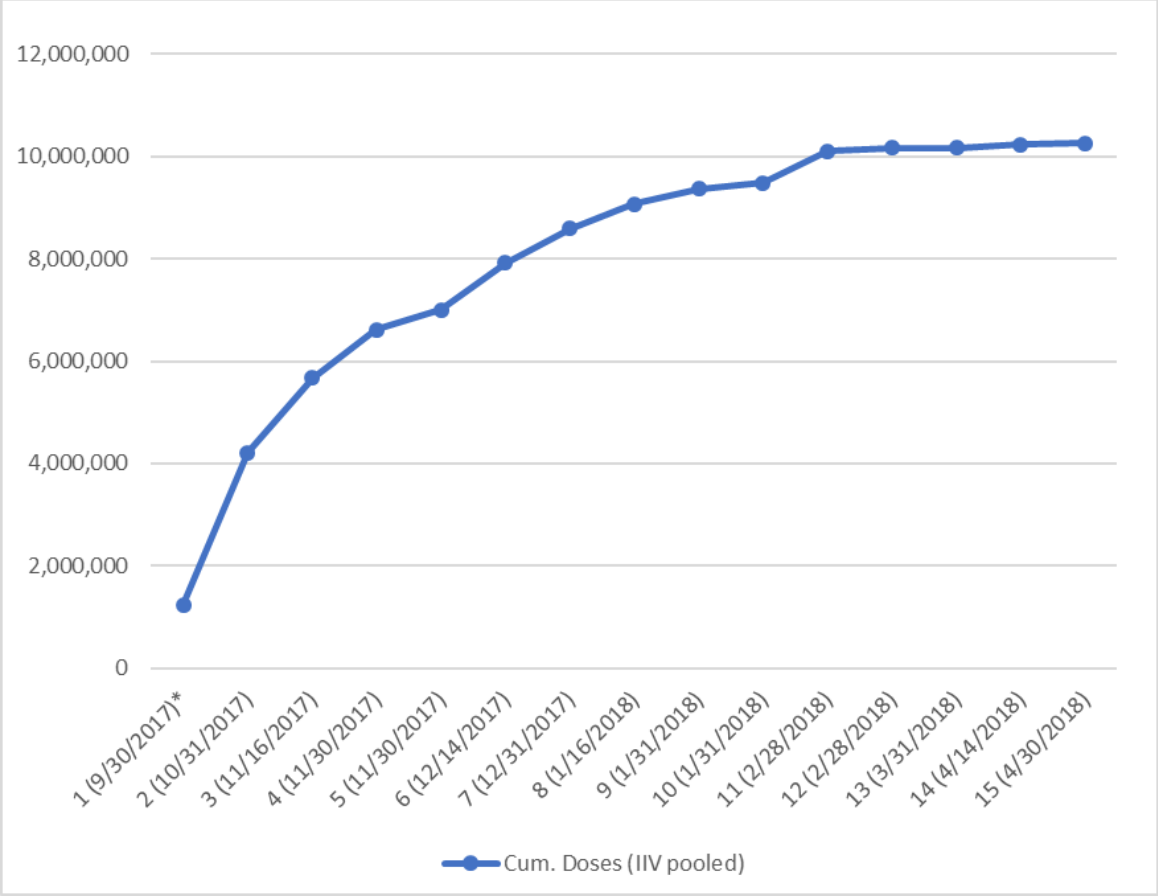
A. REPORTING

A total of 15 sequential analyses monitoring safety outcomes and 15 descriptive analyses monitoring vaccine effectiveness outcomes were completed covering the surveillance period, August 1, 2017–April 30, 2018. Each analysis included new data from one to three Data Partners. Monthly data refreshes were available at different times from each Data Partner, and we tried to run analyses as soon as new data were made available. Thus, some analyses (i.e., Analyses 4 and 5, and Analyses 11 and 12) report the same date because the second and/or third Data Partner contributed data with the same week-ending at a later time. The most recent data included in reports were generally 3-4 weeks old. Based on claims accrual from October 2015–March 2016, data from the outpatient and emergency department settings were estimated to be at least 80% complete by 5-7 weeks after the date of service or claim, depending on Data Partner. The time to 80% completion was longer for data from the inpatient setting at approximately 10-13 weeks.

B. TOTAL DOSES ADMINISTERED

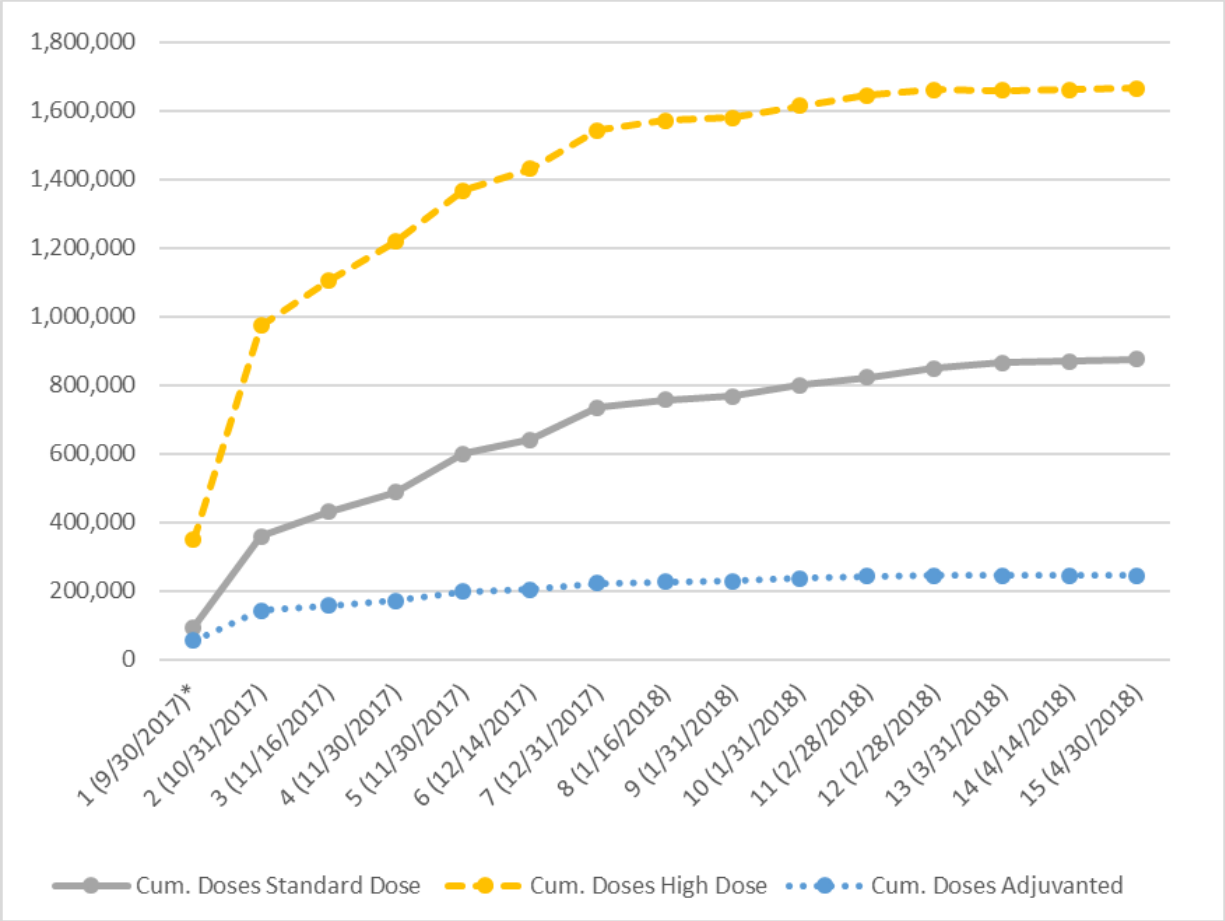
A total of 10,264,443 influenza vaccine doses were administered to health plan members ≥6 months of age (**Figure 1**). Among members ≥65 years-old, 1,664,205 received high-dose IIV, 874,517 received standard dose IIV, and 243,718 received adjuvanted IIV (**Figure 2**). Among children 6-23 months of age, 385,848 cumulative doses of IIV without concomitant PCV13 were administered (**Figure 3**).

Figure 1. Number of inactivated influenza vaccine (IIV) (pooled) doses administered to health plan members ≥6 months old, by analysis number, August 1, 2017–April 30, 2018



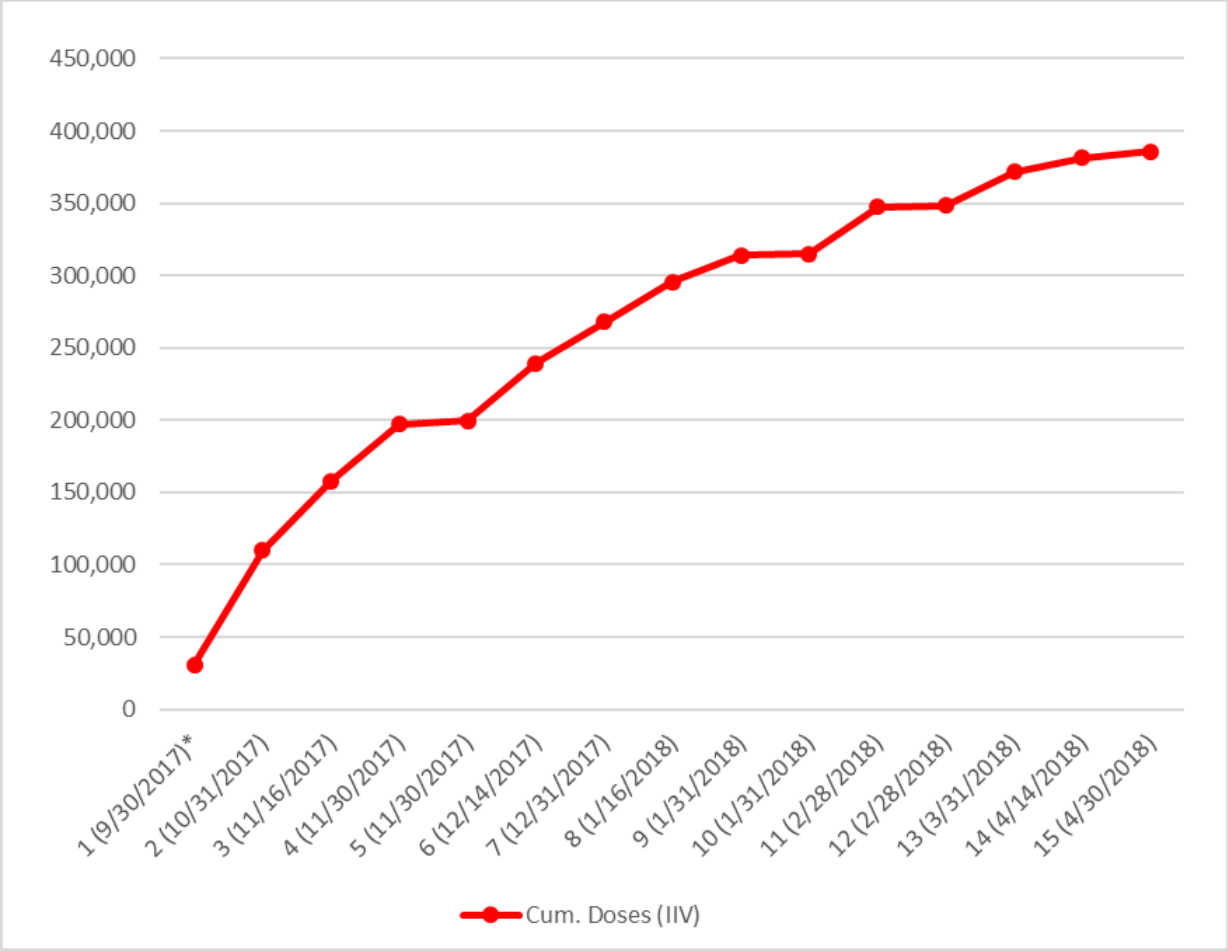
*Dates designate the most recent available data included in the analysis.

Figure 2. Number of high-dose, standard-dose, and adjuvanted inactivated influenza vaccine doses administered to health plan members ≥65 years old, by analysis number, August 1, 2017–April 30, 2018



*Dates designate the most recent available data included in the analysis.

Figure 3. Number of inactivated influenza vaccine (IIV) doses administered without concomitant pneumococcal conjugate vaccine (PCV13) to health plan members 6-23 months old, by analysis number, August 1, 2017–April 30, 2018



*Dates designate the most recent available data included in the analysis.

C. SAFETY ANALYSES

We did not reject the null hypothesis that the risk after influenza vaccination in 2017-2018 was ≤ 2.5 times the risk after influenza vaccination in historical seasons for any of the four outcomes. Because no statistically significant results emerged and because the analyses were cumulative, we present here only the safety results from the last analysis (Analysis 15), which included data from all three Data Partners over the entire surveillance period (**Table 3**). Complete results from Analyses 1-14 can be found in the **Appendix**.

Relative risks at the end of surveillance were all ≤1.2 except in the case of GBS after adjuvanted IIV, where it was 1.8 (5 observed events/2.8 expected events) in adults ≥65 years-old (**Table 3**). In the safety analysis assessing Bell's palsy in adults ≥65 years-old who received adjuvanted influenza vaccine, the upper limit was reached in Analysis 12, so per protocol, we ended sequential analysis for this group, but continued to update event counts as well as the observed-to-expected ratio, as mentioned in the footnote of **Table 3**. For 4 vaccine-outcome pairs (anaphylaxis in both the high-dose and adjuvanted IIV groups, and GBS in both the standard and pooled IIV group 6 months–17 years), the cumulative number of observed events never reached 3, so we did not conduct formal hypothesis testing.

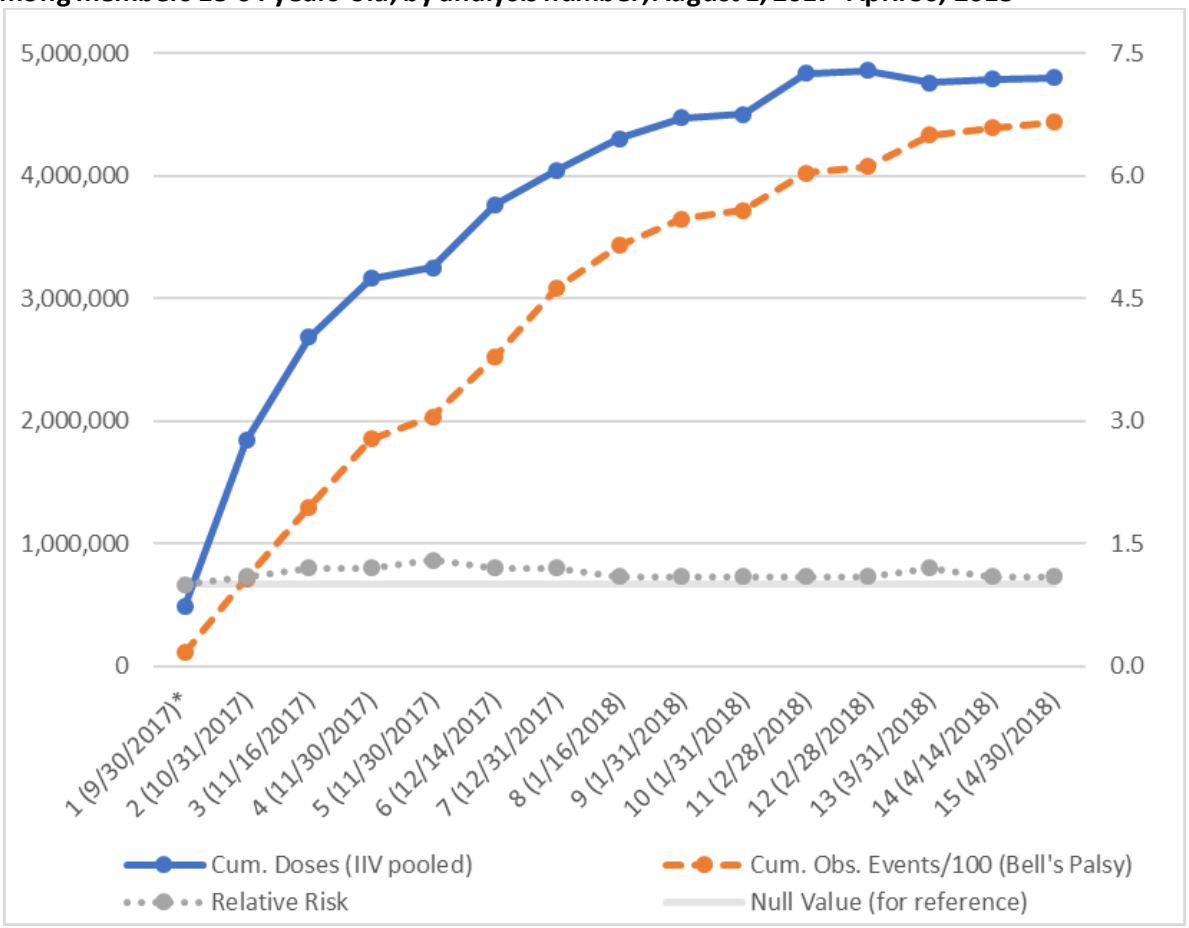
Table 3. Sequential analysis of safety outcomes, adjusted for partially accrued risk intervals and lag in data accrual, Analysis 15 (final analysis), August 1, 2017–April 30, 2018

	Vaccine type	Risk interval (days post-vaccination)	Ages	Cum. Doses	Cum. Observed Events	Cum. Expected Events	RR (Observed/ Expected)	Log-likelihood ratio (LLR)[b]	Critical value of LLR	Null hypothesis rejected?[c]
Febrile seizures	IIV, without concomitant PCV13	0-1	6-23 m	385,848	6	12.8	0.5	0.0	3.1	No
Anaphylaxis	IIV (pooled)	0-1	≥6 m	10,264,443	22	42.8	0.5	0.0	3.5	No
	High dose IIV	0-1	≥65 y	1,664,205	2	6.2	0.3	.	4.7	N/A
	Standard dose IIV	0-1	6 m-64 y	7,482,003	17	32.6	0.5	0.0	5.2	No
		0-1	≥65 y	874,517	3	3.2	0.9	0.0	4.6	No
	Adjuvanted IIV	0-1	≥65 y	243,718	0	0.9	0.0	.	3.8	N/A
Bell's palsy	IIV (pooled)	1-42	6 m-17 y	2,683,752	50	52.5	1.0	0.0	3.5	No
		1-42	18-64 y	4,798,251	666	585.9	1.1	0.0	3.7	No
		1-42	≥65 y	2,782,440	514	462.2	1.1	0.0	3.7	No
	High dose IIV	1-42	≥65 y	1,664,205	304	276.8	1.1	0.0	5.7	No
	Standard dose IIV	1-42	6 m-17 y	2,683,752	50	52.5	1.0	0.0	5.3	No
		1-42	18-64 y	4,798,251	666	585.9	1.1	0.0	5.4	No
		1-42	≥65 y	874,517	169	144.9	1.2	0.0	5.7	No
	Adjuvanted IIV	1-42	≥65 y	243,718	41	40.5	1.0	N/A[d]	N/A[d]	UL Reached[d]
GBS	IIV (pooled)	1-42	6 m-17 y	2,683,752	1	4.3	0.2	.	2.5	N/A
		1-42	18-64 y	4,798,251	26	25.8	1.0	0.0	3.4	No
		1-42	≥65 y	2,782,440	23	32.2	0.7	0.0	3.5	No
	High dose IIV	1-42	≥65 y	1,664,205	14	19.3	0.7	0.0	5.1	No
	Standard dose IIV	1-42	6 m-17 y	2,683,752	1	4.3	0.2	.	4.2	N/A
		1-42	18-64 y	4,798,251	26	25.8	1.0	0.0	5.2	No
		1-42	≥65 y	874,517	4	10.1	0.4	0.0	5.1	No
	Adjuvanted IIV	1-42	≥65 y	243,718	5	2.8	1.8	0.0	4.1	No

[a] Null hypothesis is that the risk after influenza vaccination in 2017-18 is no greater than 2.5 times the risk after influenza vaccination in historical seasons.
[b] LLR is set to zero if RR < 2.5.
[c] Per protocol, number of cumulative observed events must be ≥3 for a signal of possible increased risk to be generated; "N/A" means number of cumulative observed events is <3.
[d] Upper limit was reached in Analysis #12, and sequential analysis stopped. However, dose and event counts and RR continue to be updated.

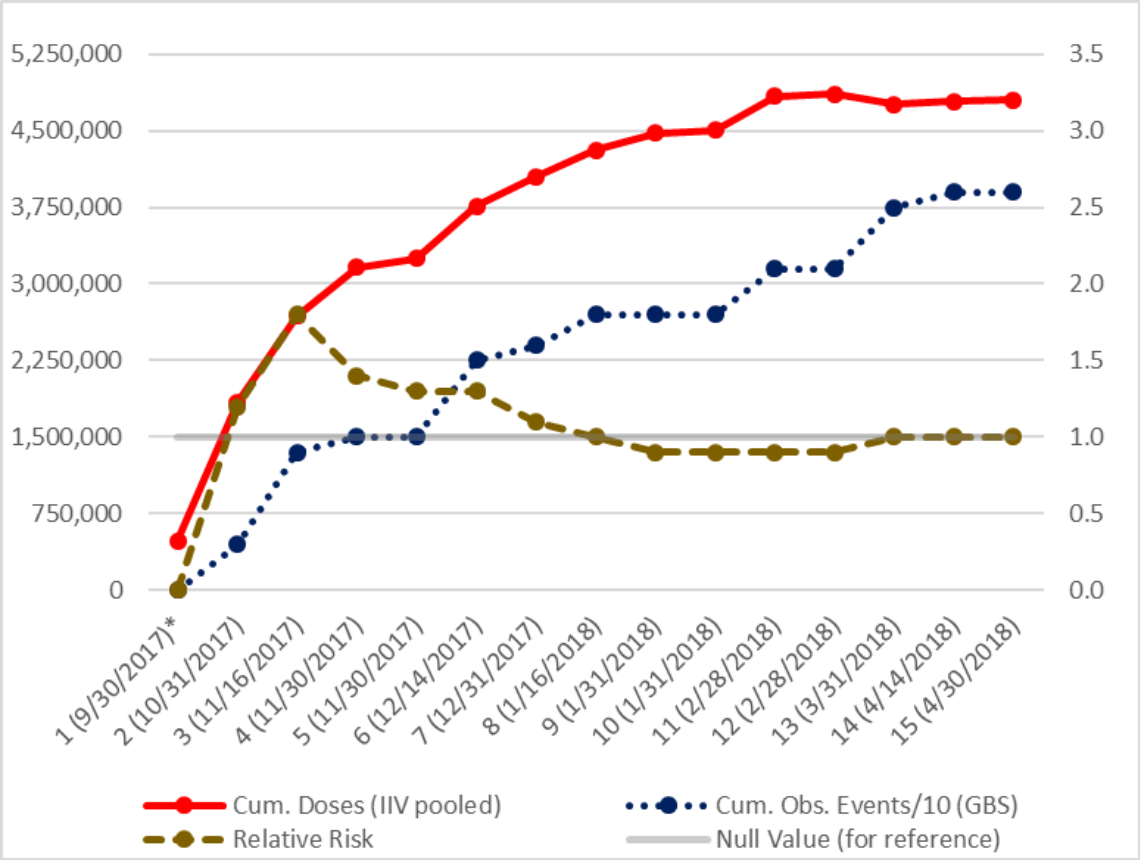
To illustrate how the cumulative influenza vaccine doses, cumulative observed events, and relative risk varied over the course of the 15 sequential analyses, we graphed a common outcome (Bell's palsy) and a rare outcome (GBS) among influenza vaccinees 18-64 years-old (**Figure 4, Figure 5)**.

Figure 4. Number of inactivated influenza vaccine (pooled) doses (primary y-axis), and number of observed Bell's palsy events (secondary y-axis) and corresponding relative risk (secondary y-axis) among members 18-64 years-old, by analysis number, August 1, 2017–April 30, 2018



*Dates designate the most recent available data included in the analysis.

Figure 5. Number of inactivated influenza vaccine (pooled) doses (primary y-axis), and number of observed GBS events (secondary y-axis), and corresponding relative risk (secondary y-axis) among members 18-64 years-old, by analysis number, August 1, 2017–April 30, 2018



*Dates designate the most recent available data included in the analysis.

D. TEMPORAL SCAN ANLAYSES FOR SELECTED SAFETEY OUTCOMES

The end-of-season temporal scan analyses of cases of Bell's palsy and GBS after pooled IIV found no clusters within Days 1-42 post-vaccination that were statistically significant or close to statistically significant (lowest p-values of any clusters were 0.68 and 0.81 for Bell's palsy and GBS, respectively). No observed clustering of cases in the days following influenza vaccination provides further evidence of no association between influenza vaccines and Bell's palsy or GBS in the 2017-18 season. **Figure 6** and **Figure 7** show the temporal distributions of the cases.

Figure 6. Number of Bell's palsy cases by day after inactivated influenza vaccination, August 1, 2017–April 30, 2018

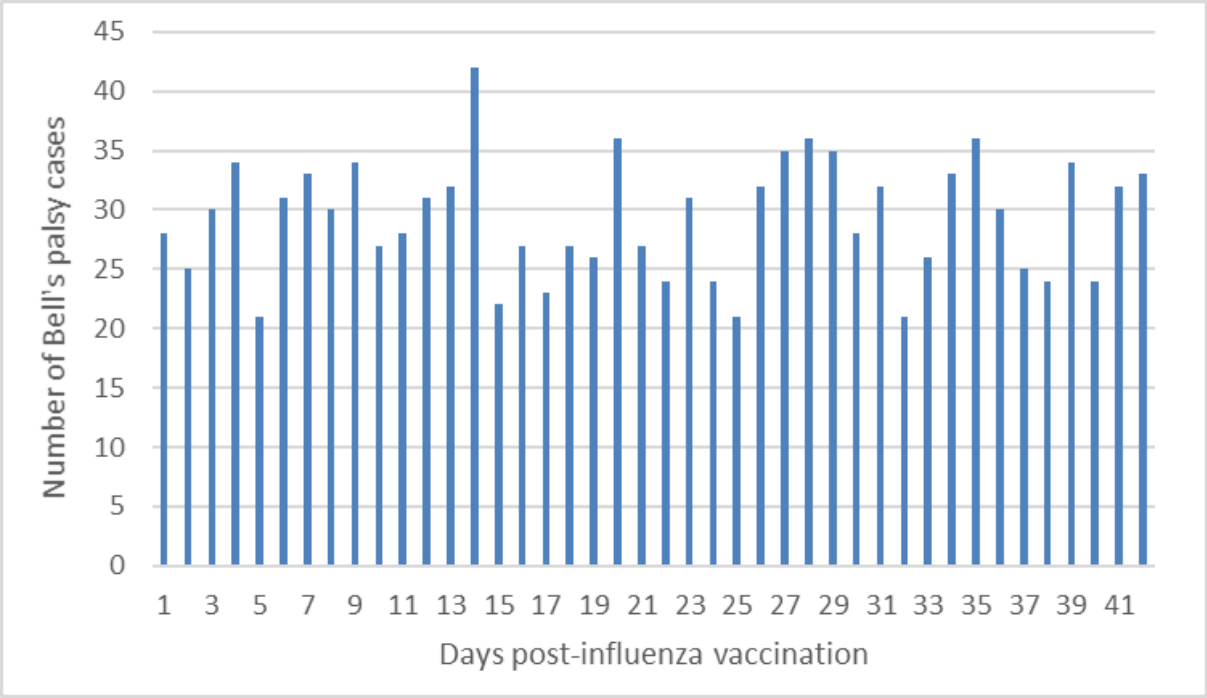
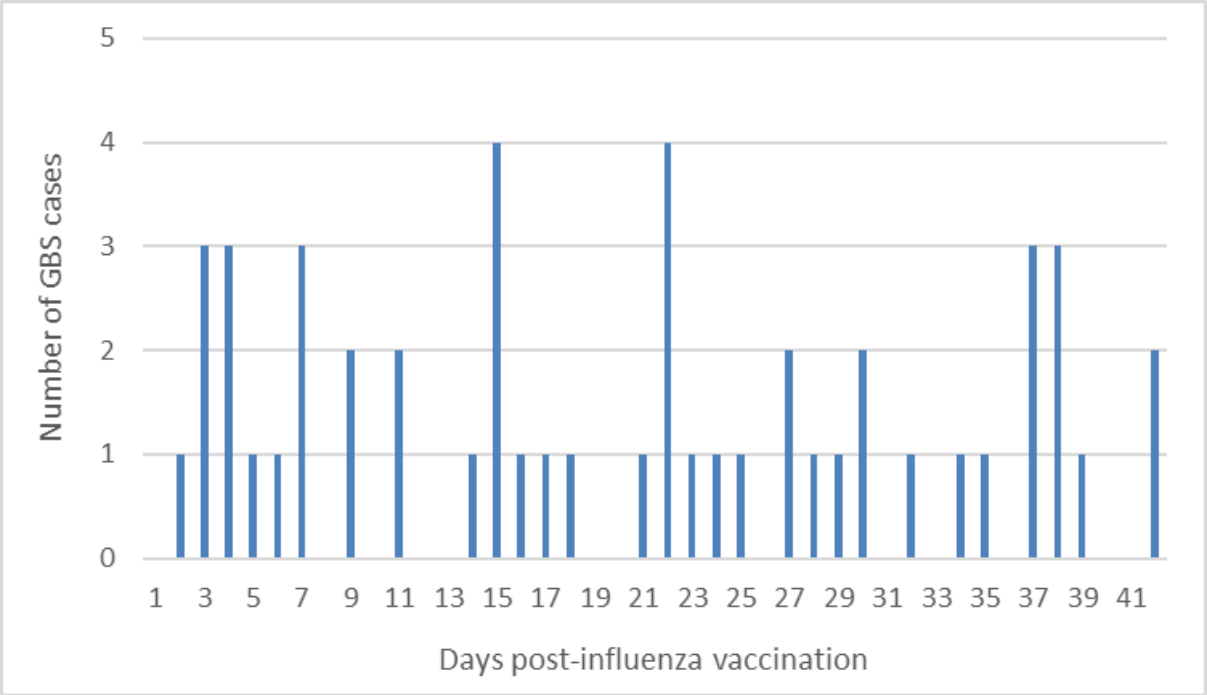


Figure 7. Number of GBS cases by day after inactivated influenza vaccination, August 1, 2017–April 30, 2018



E. DESCRIPTIVE ANALYSES OF INFLUENZA AFTER VACCINATION

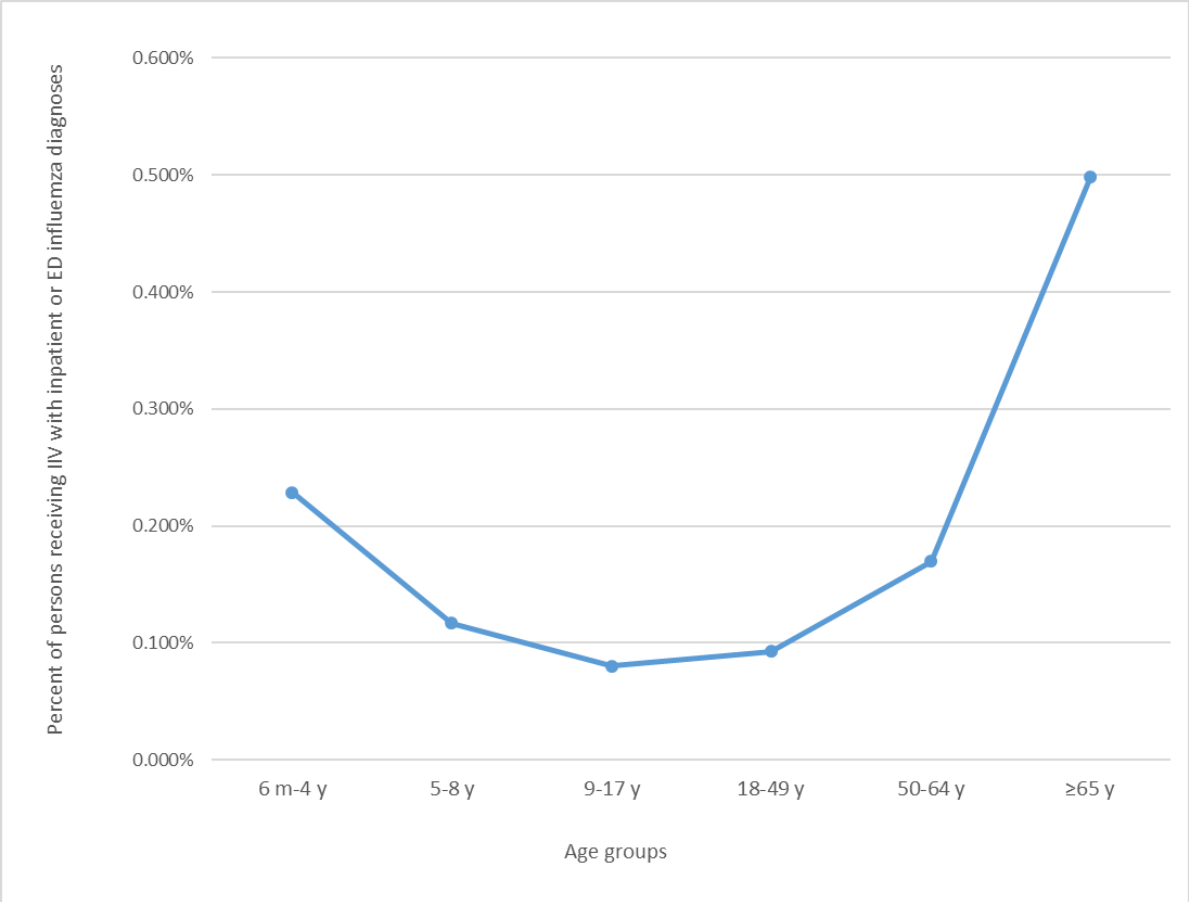
The cumulative numbers of doses, exposed persons, and persons with influenza diagnoses as of the last sequential analysis are shown in **Table 4**.

Table 4. Descriptive analysis of post-vaccination occurrence of influenza, Analysis 15 (final analysis), August 1, 2017–April 30, 2018

	Vaccine type	Ages	Cum. Doses	No. of Exposed Persons	Cum. Observed Events
Influenza in inpatient or ED setting	IIV (pooled)	6 m-4 y	994,602	822,021	1,879
		5-8 y	592,521	589,804	689
		9-17 y	1,096,629	1,094,679	876
		18-49 y	2,486,931	2,482,196	2,302
		50-64 y	2,311,320	2,305,736	3,916
		≥65 y	2,782,440	2,770,613	13,807
	High-dose IIV	≥65 y	1,664,205	1,659,333	8,174
	Adjuvanted IIV	≥65 y	243,718	242,729	1,182
Influenza in inpatient setting	IIV (pooled)	6 m-17 y	2,683,752	2,506,504	360
		18-64 y	4,798,251	4,787,932	1,773
		≥65 y	2,782,440	2,770,613	6,919
	High-dose IIV	≥65 y	1,664,205	1,659,333	4,028
	Adjuvanted IIV	≥65 y	243,718	242,729	600

In view of the incomplete data as well as the fact that we did not collect data on potential confounders such as comorbidities, we do not believe that the crude comparative vaccine effectiveness estimates obtainable from this table would be accurate. However, we note that the *relative* values of the age-specific quotient of number of influenza diagnoses in the inpatient or ED settings (for which the age groups are more specific) and number of vaccinated persons as of this last analysis form a J-shaped curve from the youngest age group (0.23%) to the 9-17 year age group (0.08%) to the ≥ 65 year age group (0.50%) (**Figure 8**). This shape conforms to known age-specific differences in severity of influenza disease.[18]

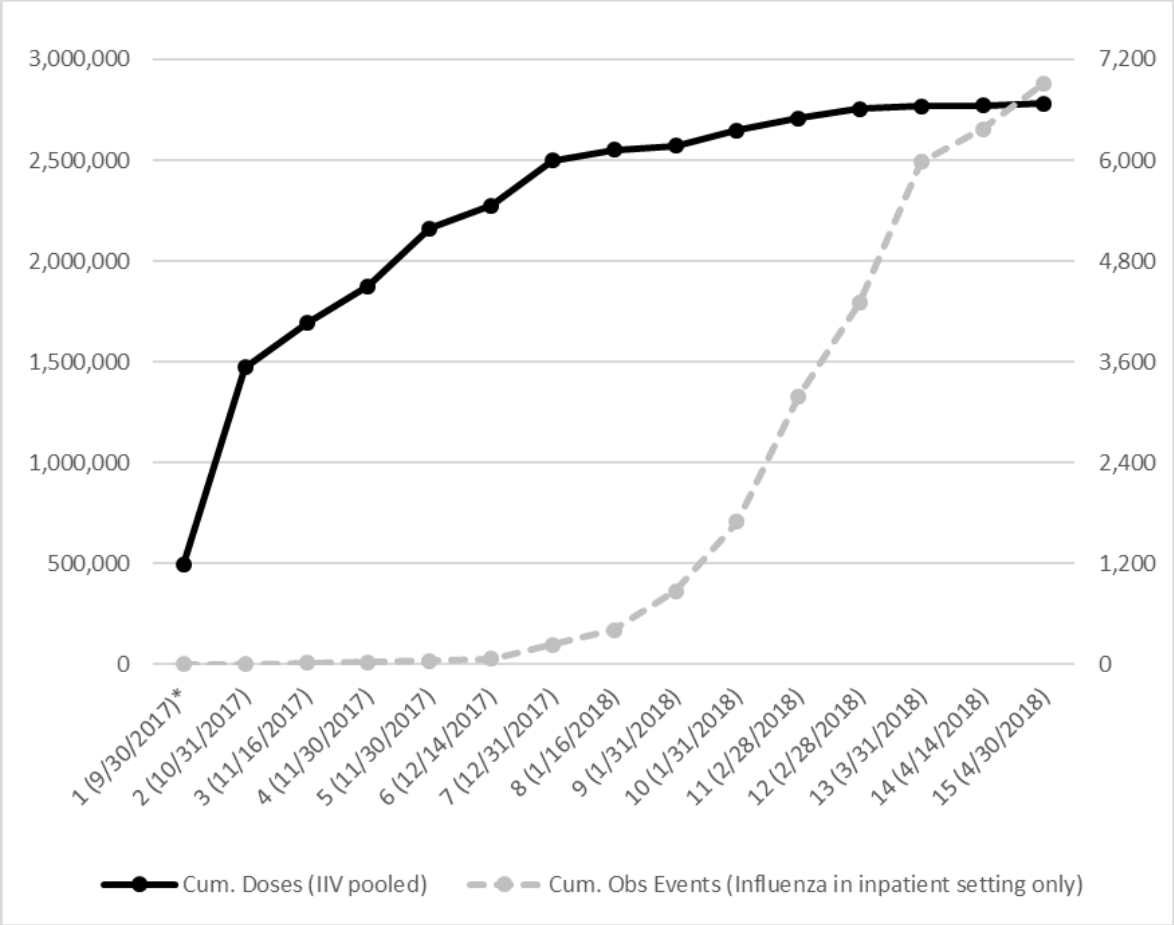
Figure 8. Percentage of persons receiving inactivated influenza vaccine (IIV) with an inpatient or emergency department diagnosis of influenza, Analysis 15 (final analysis), August 1, 2017–April 30, 2018



In contrast to the uptake of influenza vaccine which accumulates rapidly in the early months and then more slowly in the later months, the accumulation of influenza diagnoses shows the opposite pattern (**Figure 9, Figure 10**), consistent with the fact that influenza does not normally circulate widely in the fall months.

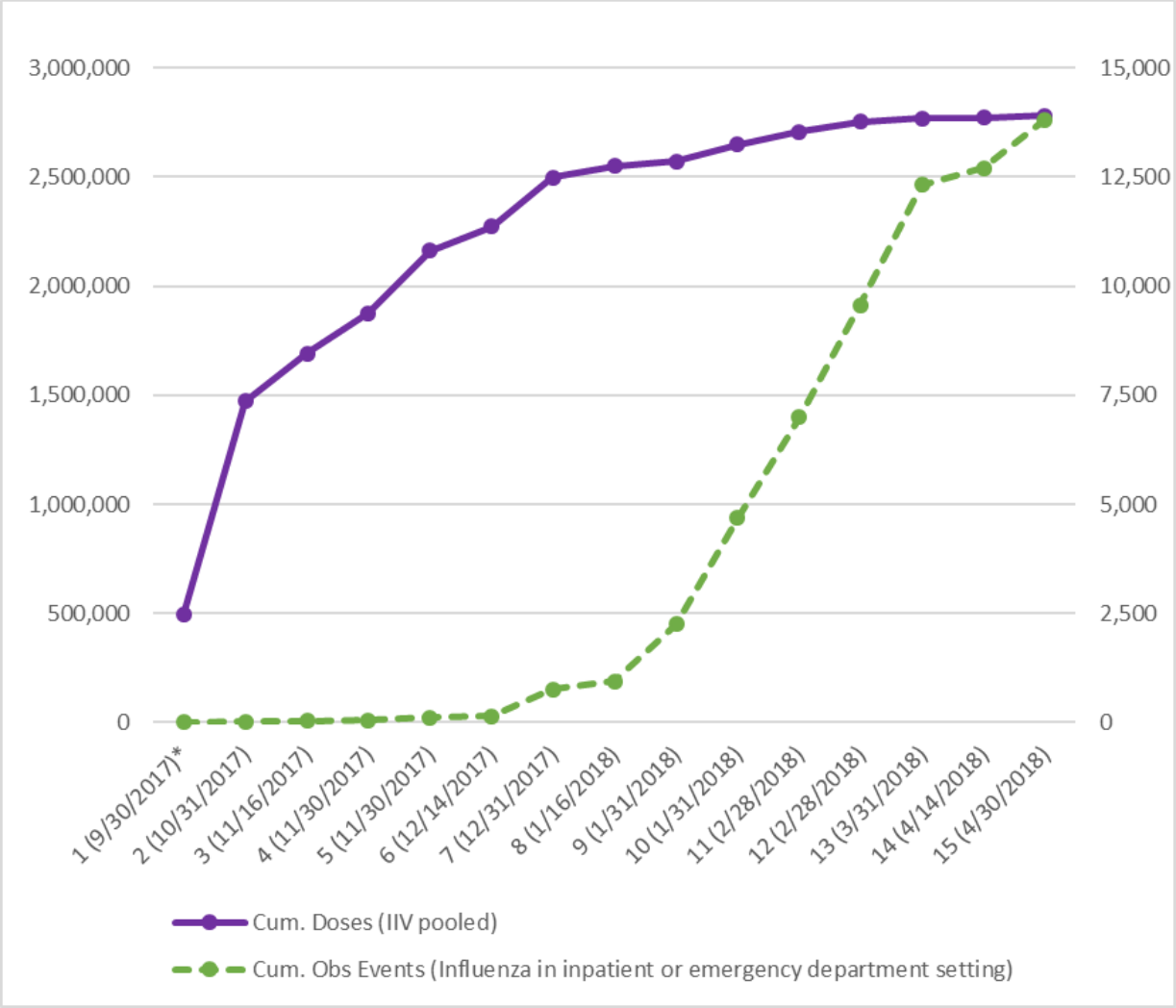
Of note, while CDC influenza-like-illness (ILI) surveillance found that ILI activity in 2017-18 first increased in November, peaked in January and February, and remained elevated through the end of March,[19] our observed periods of initial increase and peak in influenza hospitalization and ED diagnoses are shifted towards later timepoints, and also show continuing accumulation at the end of surveillance due to the data lag.

Figure 9. Number of inactivated influenza vaccine (pooled) doses (primary y-axis) and observed influenza events in the inpatient setting (secondary y-axis) among members ≥65 years-old, by analysis number, August 1, 2017–April 30, 2018



*Dates designate the most recent available data included in the analysis.

Figure 10. Number of inactivated influenza vaccine (pooled) doses (primary y-axis) and observed influenza events in the inpatient or emergency department settings (secondary y-axis) among members ≥65 years-old, by analysis number, August 1, 2017–April 30, 2018



*Dates designate the most recent available data included in the analysis.

IV. DISCUSSION

A. SUMMARY

During the 2017-18 influenza season, we observed no safety signals for febrile seizures, anaphylaxis, Bell's palsy, or GBS among the various vaccine and age groups monitored. We further assessed the number of influenza diagnoses in the inpatient setting (only) and the inpatient or ED settings among vaccinated health plan members and found that we could readily use our programs to obtain these raw counts.

B. LIMITATIONS

This study is subject to some limitations. First, in our data quality assurance procedures we preserved all cases from one analysis to the next, but we did not preserve the cumulative doses, as we did not expect to see declines from one analysis to the next. However, due to cleaning of pharmacy data at one Data Partner, we saw a decline in the overall cumulative doses between Analysis 12 and 13 (from 10,173,881 to 10,165,841, respectively). Since the overall decline in cumulative doses from Analysis 12 to 13 was very small and the number of cases were preserved, we do not suspect that this issue impacted our overall conclusions for Analysis 13 (i.e., no safety signals). Second, since we did not require health plan member enrollment, not all cases had enough data to meet the look-back period designated to establish incidence. Therefore, some prevalent cases could have been included, which would have increased the chances of signaling. Third, the vaccinated cohort design with historical comparator may generate an imperfect comparison group for vaccinees in the present influenza season. Confounding may exist due to different population characteristics, secular trends in diagnoses of health outcomes of interest, different influenza strains from year-to-year, and the availability and usage patterns of different influenza vaccines over time. For example, differences in the proportion of members receiving influenza vaccines in the workplace or at clinics that do not bill for influenza vaccine may vary by season, and their exclusion from the cohort may shift population characteristics. In addition, historical seasons consisted of primarily ICD-9-CM data, whereas the current season consisted of entirely ICD-10-CM data, and we did not assess consistency in the background rates of GBS, febrile seizures, Bell's palsy, and anaphylaxis across the coding eras. Regarding the third limitation, however, the vaccinated cohort design with historical comparator is better powered to detect small elevations in risk and thus identify potential increased risks earlier compared to designs that use concurrent controls, such as the self-controlled risk interval design.[9] Finally, we may have imperfectly characterized the Data Partner lag during the 2017-18 season because it was estimated from claims data accrual from October 2015–March 2016. However, they represented the most recent complete data available at the time of the characterization, and as far as we know, no major changes that would have dramatically affected the average lag time at each Data Partner site occurred prior to or during our 2017-18 surveillance period.

C. LESSONS LEARNED AND RECOMMENDATIONS

These analyses generated several important lessons about the use of fresh data for vaccine safety and effectiveness surveillance. Below, we list lessons learned followed by an associated recommendation that should be considered in future Sentinel System analyses that use fresh data.

First, utilizing existing data and programming infrastructure as well as involving experienced scientific staff is highly desirable, given the labor-intensive demands of near-real time sequential analysis. We built on a previous Sentinel System activity that updated data bi-monthly (rather than monthly) during the 2012-13 and 2013-14 influenza seasons. The previous experience greatly facilitated programming

efforts and preparation of study inputs. We recommend that existing infrastructure be used whenever possible, and that study planning begin as early as possible. Our preparation for 2017-18 influenza vaccine surveillance began in early 2017, but we would have needed to start preparations much earlier if it had been necessary to create new analytic programs. If sequential analysis using fresh data were to become a routine activity, we would suggest automating as many processes as possible.

Second, sequential analysis using fresh data involves many persons with specialized skills, including programmer-analysts, epidemiologists, biostatisticians, and program managers at both the Sentinel Operations Center and Data Partner sites. In particular, the special knowledge that investigators at the participating Data Partner sites contribute concerning their unique data processes and interpretations of QA findings and other results is critical to the success of this type of surveillance, where fresh data are updated frequently. We had standing calls with Data Partners throughout the surveillance season and interacted with them on multiple occasions during the study preparation phase (e.g., discussed data lag characterizations). The relationships we established before surveillance began facilitated the investigation of data issues when they arose during the surveillance period. Likewise, understanding the needs of FDA before surveillance began was critical in implementing the appropriate study hypothesis and determining the desired outputs of the descriptive analyses of vaccine effectiveness outcomes. These pre-surveillance efforts facilitated communication of study results once surveillance began. The entire surveillance team (i.e., FDA, Sentinel Operations Center, Data Partners) considered it worthwhile to come together for twice-monthly calls to discuss results. We recommend that future activities utilizing fresh data engage all involved stakeholders regularly and, when possible, persons are cross-trained to maintain the proper, specialized subject matter expertise at each site.

Finally, although we did not observe any safety signals during our surveillance period, it should be recognized that if one had been observed, a very large, additional amount of effort among FDA, the Sentinel Operations Center, and the Data Partners would have been required to conduct proper follow-up. Follow-up may include activities such as medical chart review to confirm cases and sensitivity analyses that vary inputs to quantify the robustness of the findings. We recommend that safety signal follow-up plans be finalized before the start of surveillance and each site be assured of having the additional resources necessary to conduct such investigations.

D. CONCLUSIONS

During the 2017-18 influenza vaccine season, we monitored safety outcomes following receipt of influenza vaccines and did not observe any safety signals for febrile seizures, anaphylaxis, Bell's palsy, or GBS after IIV pooled, standard-dose IIV, high-dose IIV, or adjuvanted IIV for the age groups that we assessed. Influenza vaccine effectiveness outcomes were monitored descriptively and showed a continuing increasing trend as of the end of surveillance on April 30, 2018. Near real-time sequential analysis of influenza vaccine safety requires dedicated planning and potentially extensive resources in the event of a safety signal. Maximizing automation and developing fruitful partnerships can help overcome the challenges.

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VII. APPENDIX

Appendix A1. Sequential analysis of safety outcomes, adjusted for partially accrued risk intervals and lag in data accrual, Analysis 1, August 1, 2017–September 30, 2017

	Vaccine type	Risk interval (days post-vaccination)	Ages	Cum. Doses	Cum. Observed Events	Cum. Expected Events	RR (Observed/ Expected)	Log-likelihood ratio (LLR)[b]	Critical value of LLR	Null hypothesis rejected?[c]
Febrile seizures	IIV, without concomitant PCV13	0-1	6-23 m	30,818	0	0.6	0.0	.	3.1	N/A
Anaphylaxis	IIV (pooled)	0-1	≥6 m	1,231,413	1	2.2	0.5	.	3.5	N/A
	High dose IIV	0-1	≥65 y	349,067	0	0.5	0.0	.	4.7	N/A
	Standard dose IIV	0-1	6 m-64 y	736,478	1	1.5	0.7	.	5.2	N/A
		0-1	≥65 y	92,394	0	0.1	0.0	.	4.6	N/A
	Adjuvanted IIV	0-1	≥65 y	53,474	0	0.1	0.0	.	3.8	N/A
Bell's palsy	IIV (pooled)	1-42	6 m-17 y	251,993	0	1.4	0.0	.	3.5	N/A
		1-42	18-64 y	484,485	17	16.3	1.0	0.0	3.7	No
		1-42	≥65 y	494,935	15	19.0	0.8	0.0	3.7	No
	High dose IIV	1-42	≥65 y	349,067	14	13.2	1.1	0.0	5.7	No
	Standard dose IIV	1-42	6 m-17 y	251,993	0	1.4	0.0	.	5.3	N/A
		1-42	18-64 y	484,485	17	16.3	1.0	0.0	5.4	No
		1-42	≥65 y	92,394	0	3.5	0.0	.	5.7	N/A
	Adjuvanted IIV	1-42	≥65 y	53,474	1	2.2	0.4	.	5.0	N/A
GBS	IIV (pooled)	1-42	6 m-17 y	251,993	0	0.1	0.0	.	2.5	N/A
		1-42	18-64 y	484,485	0	0.4	0.0	.	3.4	N/A
		1-42	≥65 y	494,935	0	0.7	0.0	.	3.5	N/A
	High dose IIV	1-42	≥65 y	349,067	0	0.5	0.0	.	5.1	N/A
	Standard dose IIV	1-42	6 m-17 y	251,993	0	0.1	0.0	.	4.2	N/A
		1-42	18-64 y	484,485	0	0.4	0.0	.	5.2	N/A
		1-42	≥65 y	92,394	0	0.1	0.0	.	5.1	N/A
	Adjuvanted IIV	1-42	≥65 y	53,474	0	0.1	0.0	.	4.1	N/A

[a] Null hypothesis is that the risk after influenza vaccination in 2017-18 is no greater than 2.5 times the risk after influenza vaccination in historical seasons.

[b] LLR is set to zero if RR < 2.5.
[c] Per protocol, number of cumulative observed events must be ≥ 3 for a signal of possible increased risk to be generated; "N/A" mea ns number of cumulative observed events is < 3.

Appendix A2. Descriptive analysis of post-vaccination occurrence of influenza, Analysis 1, August 1, 2017–September 30, 2017

	Vaccine type	Ages	Cum. Doses	No. of exposed persons	Cum. Observed Events
Influenza in inpatient or ED setting	IIV (pooled)	6 m-4 y	91,655	91,223	0
		5-8 y	55,171	55,161	0
		9-17 y	105,167	105,158	0
		18-49 y	233,192	233,159	0
		50-64 y	251,293	251,248	0
		≥65 y	494,935	494,823	0
	High dose IIV	≥65 y	349,067	348,996	0
	Adjuvanted IIV	≥65 y	53,474	53,459	0
Influenza in inpatient setting	IIV (pooled)	6 m-17 y	251,993	251,542	0
		18-64 y	484,485	484,407	0
		≥65 y	494,935	494,823	0
	High dose IIV	≥65 y	349,067	348,996	0
	Adjuvanted IIV	≥65 y	53,474	53,459	0

Appendix B1. Sequential analysis of safety outcomes, adjusted for partially accrued risk intervals and lag in data accrual, Analysis 2, August 1, 2017–October 31, 2017

	Vaccine type	Risk interval (days post-vaccination)	Ages	Cum. Doses	Cum. Observed Events	Cum. Expected Events	RR (Observed/ Expected)	Log-likelihood ratio (LLR)[b]	Critical value of LLR	Null hypothesis rejected?[c]
Febrile seizures	IIV, without concomitant PCV13	0-1	6-23 m	109,895	0	2.6	0.0	.	3.1	N/A
Anaphylaxis	IIV (pooled)	0-1	≥6 m	4,214,984	2	10.5	0.2	.	3.5	N/A
	High dose IIV	0-1	≥65 y	972,683	1	2.3	0.4	.	4.7	N/A
	Standard dose IIV	0-1	6 m-64 y	2,741,746	1	7.0	0.1	.	5.2	N/A
		0-1	≥65 y	358,891	0	0.8	0.0	.	4.6	N/A
	Adjuvanted IIV	0-1	≥65 y	141,664	0	0.3	0.0	.	3.8	N/A
Bell's palsy	IIV (pooled)	1-42	6 m-17 y	898,890	4	7.4	0.5	0.0	3.5	No
		1-42	18-64 y	1,842,856	107	94.1	1.1	0.0	3.7	No
		1-42	≥65 y	1,473,238	113	116.9	1.0	0.0	3.7	No
	High dose IIV	1-42	≥65 y	972,683	80	77.9	1.0	0.0	5.7	No
	Standard dose IIV	1-42	6 m-17 y	898,890	4	7.4	0.5	0.0	5.3	No
		1-42	18-64 y	1,842,856	107	94.1	1.1	0.0	5.4	No
		1-42	≥65 y	358,891	24	28.1	0.9	0.0	5.7	No
	Adjuvanted IIV	1-42	≥65 y	141,664	9	10.8	0.8	0.0	5.0	No
GBS	IIV (pooled)	1-42	6 m-17 y	898,890	0	0.4	0.0	.	2.5	N/A
		1-42	18-64 y	1,842,856	3	2.6	1.2	0.0	3.4	No
		1-42	≥65 y	1,473,238	1	5.4	0.2	.	3.5	N/A
	High dose IIV	1-42	≥65 y	972,683	0	3.6	0.0	.	5.1	N/A
	Standard dose IIV	1-42	6 m-17 y	898,890	0	0.4	0.0	.	4.2	N/A
		1-42	18-64 y	1,842,856	3	2.6	1.2	0.0	5.2	No
		1-42	≥65 y	358,891	0	1.3	0.0	.	5.1	N/A
	Adjuvanted IIV	1-42	≥65 y	141,664	1	0.5	1.9	.	4.1	N/A

[a] Null hypothesis is that the risk after influenza vaccination in 2017-18 is no greater than 2.5 times the risk after influenza vaccination in historical seasons.

[b] LLR is set to zero if RR < 2.5.

[c] Per protocol, number of cumulative observed events must be ≥ 3 for a signal of possible increased risk to be generated; "N/A" means number of cumulative observed events is < 3.

Appendix B2. Descriptive analysis of post-vaccination occurrence of influenza, Analysis 2, August 1, 2017–October 31, 2017

	Vaccine type	Ages	Cum. Doses	No. of exposed persons	Cum. Observed Events
Influenza in inpatient or ED setting	IIV (pooled)	6 m-4 y	323,271	312,178	3
		5-8 y	206,816	206,669	0
		9-17 y	368,803	368,696	1
		18-49 y	899,816	899,526	8
		50-64 y	943,040	942,654	12
		≥65 y	1,473,238	1,472,265	21
	High dose IIV	≥65 y	972,683	972,143	13
	Adjuvanted IIV	≥65 y	141,664	141,566	5
Influenza in inpatient setting	IIV (pooled)	6 m-17 y	898,890	887,543	0
		18-64 y	1,842,856	1,842,180	4
		≥65 y	1,473,238	1,472,265	5
	High dose IIV	≥65 y	972,683	972,143	4
	Adjuvanted IIV	≥65 y	141,664	141,566	0

Appendix C1. Sequential analysis of safety outcomes, adjusted for partially accrued risk intervals and lag in data accrual, Analysis 3, August 1, 2017–November 16, 2017

	Vaccine type	Risk interval (days post-vaccination)	Ages	Cum. Doses	Cum. Observed Events	Cum. Expected Events	RR (Observed/ Expected)	Log-likelihood ratio (LLR)[b]	Critical value of LLR	Null hypothesis rejected?[c]
Febrile seizures	IIV, without concomitant PCV13	0-1	6-23 m	157,723	0	3.9	0.0	.	3.1	N/A
Anaphylaxis	IIV (pooled)	0-1	≥6 m	5,675,298	3	15.5	0.2	0.0	3.5	No
	High dose IIV	0-1	≥65 y	1,104,035	1	2.7	0.4	.	4.7	N/A
	Standard dose IIV	0-1	6 m-64 y	3,983,687	2	11.4	0.2	.	5.2	N/A
		0-1	≥65 y	430,657	0	1.0	0.0	.	4.6	N/A
	Adjuvanted IIV	0-1	≥65 y	156,919	0	0.4	0.0	.	3.8	N/A
Bell's palsy	IIV (pooled)	1-42	6 m-17 y	1,299,458	12	12.3	1.0	0.0	3.5	No
		1-42	18-64 y	2,684,229	195	163.2	1.2	0.0	3.7	No
		1-42	≥65 y	1,691,611	153	142.3	1.1	0.0	3.7	No
	High dose IIV	1-42	≥65 y	1,104,035	105	93.9	1.1	0.0	5.7	No
	Standard dose IIV	1-42	6 m-17 y	1,299,458	12	12.3	1.0	0.0	5.3	No
		1-42	18-64 y	2,684,229	195	163.2	1.2	0.0	5.4	No
		1-42	≥65 y	430,657	37	35.6	1.0	0.0	5.7	No
	Adjuvanted IIV	1-42	≥65 y	156,919	11	12.7	0.9	0.0	5.0	No
GBS	IIV (pooled)	1-42	6 m-17 y	1,299,458	0	0.7	0.0	.	2.5	N/A
		1-42	18-64 y	2,684,229	9	4.9	1.8	0.0	3.4	No
		1-42	≥65 y	1,691,611	1	6.8	0.1	.	3.5	N/A
	High dose IIV	1-42	≥65 y	1,104,035	0	4.5	0.0	.	5.1	N/A
	Standard dose IIV	1-42	6 m-17 y	1,299,458	0	0.7	0.0	.	4.2	N/A
		1-42	18-64 y	2,684,229	9	4.9	1.8	0.0	5.2	No
		1-42	≥65 y	430,657	0	1.7	0.0	.	5.1	N/A
	Adjuvanted IIV	1-42	≥65 y	156,919	1	0.6	1.6	.	4.1	N/A

[a] Null hypothesis is that the risk after influenza vaccination in 2017-18 is no greater than 2.5 times the risk after influenza vaccination in historical seasons.
[b] LLR is set to zero if RR < 2.5.
[c] Per protocol, number of cumulative observed events must be ≥ 3 for a signal of possible increased risk to be generated; "N/A" means number of cumulative observed events is < 3.

Appendix C2. Descriptive analysis of post-vaccination occurrence of influenza, Analysis 3, August 1, 2017–November 16, 2017

	Vaccine type	Ages	Cum. Doses	No. of exposed persons	Cum. Observed Events
Influenza in inpatient or ED setting	IIV (pooled)	6 m-4 y	450,684	427,367	3
		5-8 y	303,592	303,252	0
		9-17 y	545,182	544,966	1
		18-49 y	1,326,455	1,325,895	9
		50-64 y	1,357,774	1,357,088	14
		≥65 y	1,691,611	1,690,408	34
	High dose IIV	≥65 y	1,104,035	1,103,386	20
	Adjuvanted IIV	≥65 y	156,919	156,795	5
Influenza in inpatient setting	IIV (pooled)	6 m-17 y	1,299,458	1,275,585	0
		18-64 y	2,684,229	2,682,983	6
		≥65 y	1,691,611	1,690,408	17
	High dose IIV	≥65 y	1,104,035	1,103,386	10
	Adjuvanted IIV	≥65 y	156,919	156,795	0

Appendix D1. Sequential analysis of safety outcomes, adjusted for partially accrued risk intervals and lag in data accrual, Analysis 4, August 1, 2017–November 30, 2017

	Vaccine type	Risk interval (days post-vaccination)	Ages	Cum. Doses	Cum. Observed Events	Cum. Expected Events	RR (Observed/ Expected)	Log-likelihood ratio (LLR)[b]	Critical value of LLR	Null hypothesis rejected?[c]
Febrile seizures	IIV, without concomitant PCV13	0-1	6-23 m	196,984	4	5.2	0.8	0.0	3.1	No
Anaphylaxis	IIV (pooled)	0-1	≥6 m	6,615,459	8	19.4	0.4	0.0	3.5	No
	High dose IIV	0-1	≥65 y	1,217,357	1	3.2	0.3	.	4.7	N/A
	Standard dose IIV	0-1	6 m-64 y	4,740,599	6	14.6	0.4	0.0	5.2	No
		0-1	≥65 y	486,732	1	1.3	0.8	.	4.6	N/A
	Adjuvanted IIV	0-1	≥65 y	170,771	0	0.4	0.0	.	3.8	N/A
Bell's palsy	IIV (pooled)	1-42	6 m-17 y	1,579,077	16	17.8	0.9	0.0	3.5	No
		1-42	18-64 y	3,161,522	278	224.5	1.2	0.0	3.7	No
		1-42	≥65 y	1,874,860	201	181.0	1.1	0.0	3.7	No
	High dose IIV	1-42	≥65 y	1,217,357	141	119.8	1.2	0.0	5.7	No
	Standard dose IIV	1-42	6 m-17 y	1,579,077	16	17.8	0.9	0.0	5.3	No
		1-42	18-64 y	3,161,522	278	224.5	1.2	0.0	5.4	No
		1-42	≥65 y	486,732	47	46.0	1.0	0.0	5.7	No
	Adjuvanted IIV	1-42	≥65 y	170,771	13	15.2	0.9	0.0	5.0	No
GBS	IIV (pooled)	1-42	6 m-17 y	1,579,077	0	1.1	0.0	.	2.5	N/A
		1-42	18-64 y	3,161,522	10	7.2	1.4	0.0	3.4	No
		1-42	≥65 y	1,874,860	3	9.2	0.3	0.0	3.5	No
	High dose IIV	1-42	≥65 y	1,217,357	2	6.2	0.3	.	5.1	N/A
	Standard dose IIV	1-42	6 m-17 y	1,579,077	0	1.1	0.0	.	4.2	N/A
		1-42	18-64 y	3,161,522	10	7.2	1.4	0.0	5.2	No
		1-42	≥65 y	486,732	0	2.3	0.0	.	5.1	N/A
	Adjuvanted IIV	1-42	≥65 y	170,771	1	0.8	1.3	.	4.1	N/A

[a] Null hypothesis is that the risk after influenza vaccination in 2017-18 is no greater than 2.5 times the risk after influenza vaccination in historical seasons.

[b] LLR is set to zero if RR < 2.5.

[c] Per protocol, number of cumulative observed events must be ≥ 3 for a signal of possible increased risk to be generated; "N/A" means number of cumulative observed events is < 3.

Appendix D2. Descriptive analysis of post-vaccination occurrence of influenza, Analysis 4, August 1, 2017–November 30, 2017

	Vaccine type	Ages	Cum. Doses	No. of exposed persons	Cum. Observed Events
Influenza in inpatient or ED setting	IIV (pooled)	6 m-4 y	549,223	508,578	22
		5-8 y	367,635	367,068	3
		9-17 y	662,219	661,820	6
		18-49 y	1,586,772	1,585,805	27
		50-64 y	1,574,750	1,573,711	38
		≥65 y	1,874,860	1,873,026	59
	High dose IIV	≥65 y	1,217,357	1,216,422	41
	Adjuvanted IIV	≥65 y	170,771	170,596	7
Influenza in inpatient setting	IIV (pooled)	6 m-17 y	1,579,077	1,537,466	0
		18-64 y	3,161,522	3,159,516	10
		≥65 y	1,874,860	1,873,026	23
	High dose IIV	≥65 y	1,217,357	1,216,422	15
	Adjuvanted IIV	≥65 y	170,771	170,596	1

Appendix E1. Sequential analysis of safety outcomes, adjusted for partially accrued risk intervals and lag in data accrual, Analysis 5, August 1, 2017–November 30, 2017

	Vaccine type	Risk interval (days post-vaccination)	Ages	Cum. Doses	Cum. Observed Events	Cum. Expected Events	RR (Observed/ Expected)	Log-likelihood ratio (LLR)[b]	Critical value of LLR	Null hypothesis rejected?[c]
Febrile seizures	IIV, without concomitant PCV13	0-1	6-23 m	199,370	4	5.3	0.8	0.0	3.1	No
Anaphylaxis	IIV (pooled)	0-1	≥6 m	7,007,823	9	21.3	0.4	0.0	3.5	No
	High dose IIV	0-1	≥65 y	1,366,101	1	3.9	0.3	.	4.7	N/A
	Standard dose IIV	0-1	6 m-64 y	4,846,716	7	15.1	0.5	0.0	5.2	No
		0-1	≥65 y	598,523	1	1.7	0.6	.	4.6	N/A
	Adjuvanted IIV	0-1	≥65 y	196,483	0	0.6	0.0	.	3.8	N/A
Bell's palsy	IIV (pooled)	1-42	6 m-17 y	1,596,944	17	18.2	0.9	0.0	3.5	No
		1-42	18-64 y	3,249,772	305	238.2	1.3	0.0	3.7	No
		1-42	≥65 y	2,161,107	279	246.2	1.1	0.0	3.7	No
	High dose IIV	1-42	≥65 y	1,366,101	175	157.2	1.1	0.0	5.7	No
	Standard dose IIV	1-42	6 m-17 y	1,596,944	17	18.2	0.9	0.0	5.3	No
		1-42	18-64 y	3,249,772	305	238.2	1.3	0.0	5.4	No
		1-42	≥65 y	598,523	81	67.0	1.2	0.0	5.7	No
	Adjuvanted IIV	1-42	≥65 y	196,483	23	22.0	1.0	0.0	5.0	No
GBS	IIV (pooled)	1-42	6 m-17 y	1,596,944	0	1.1	0.0	.	2.5	N/A
		1-42	18-64 y	3,249,772	10	7.8	1.3	0.0	3.4	No
		1-42	≥65 y	2,161,107	8	13.6	0.6	0.0	3.5	No
	High dose IIV	1-42	≥65 y	1,366,101	5	8.7	0.6	0.0	5.1	No
	Standard dose IIV	1-42	6 m-17 y	1,596,944	0	1.1	0.0	.	4.2	N/A
		1-42	18-64 y	3,249,772	10	7.8	1.3	0.0	5.2	No
		1-42	≥65 y	598,523	2	3.6	0.5	.	5.1	N/A
	Adjuvanted IIV	1-42	≥65 y	196,483	1	1.2	0.8	.	4.1	N/A

[a] Null hypothesis is that the risk after influenza vaccination in 2017-18 is no greater than 2.5 times the risk after influenza vaccination in historical seasons.
[b] LLR is set to zero if RR < 2.5.
[c] Per protocol, number of cumulative observed events must be ≥ 3 for a signal of possible increased risk to be generated; "N/A" means number of cumulative observed events is < 3.

Appendix E2. Descriptive analysis of post-vaccination occurrence of influenza, Analysis 5, August 1, 2017–November 30, 2017

	Vaccine type	Ages	Cum. Doses	No. of exposed persons	Cum. Observed Events
Influenza in inpatient or ED setting	IIV (pooled)	6 m-4 y	555,742	514,196	23
		5-8 y	371,630	371,056	3
		9-17 y	669,572	669,163	7
		18-49 y	1,615,154	1,614,126	29
		50-64 y	1,634,618	1,633,396	48
		≥65 y	2,161,107	2,158,270	119
	High dose IIV	≥65 y	1,366,101	1,364,725	80
	Adjuvanted IIV	≥65 y	196,483	196,235	9
Influenza in inpatient setting	IIV (pooled)	6 m-17 y	1,596,944	1,554,415	0
		18-64 y	3,249,772	3,247,522	12
		≥65 y	2,161,107	2,158,270	45
	High dose IIV	≥65 y	1,366,101	1,364,725	29
	Adjuvanted IIV	≥65 y	196,483	196,235	1

Appendix F1. Sequential analysis of safety outcomes, adjusted for partially accrued risk intervals and lag in data accrual, Analysis 6, August 1, 2017–December 14, 2017

	Vaccine type	Risk interval (days post-vaccination)	Ages	Cum. Doses	Cum. Observed Events	Cum. Expected Events	RR (Observed/ Expected)	Log-likelihood ratio (LLR)[b]	Critical value of LLR	Null hypothesis rejected?[c]
Febrile seizures	IIV, without concomitant PCV13	0-1	6-23 m	239,142	5	6.7	0.7	0.0	3.1	No
Anaphylaxis	IIV (pooled)	0-1	≥6 m	7,914,537	11	26.1	0.4	0.0	3.5	No
	High dose IIV	0-1	≥65 y	1,429,040	1	4.2	0.2	.	4.7	N/A
	Standard dose IIV	0-1	6 m-64 y	5,640,682	9	19.4	0.5	0.0	5.2	No
		0-1	≥65 y	640,666	1	1.9	0.5	.	4.6	N/A
	Adjuvanted IIV	0-1	≥65 y	204,149	0	0.6	0.0	.	3.8	N/A
Bell's palsy	IIV (pooled)	1-42	6 m-17 y	1,876,202	24	24.9	1.0	0.0	3.5	No
		1-42	18-64 y	3,764,480	379	324.6	1.2	0.0	3.7	No
		1-42	≥65 y	2,273,855	311	273.6	1.1	0.0	3.7	No
	High dose IIV	1-42	≥65 y	1,429,040	195	173.6	1.1	0.0	5.7	No
	Standard dose IIV	1-42	6 m-17 y	1,876,202	24	24.9	1.0	0.0	5.3	No
		1-42	18-64 y	3,764,480	379	324.6	1.2	0.0	5.4	No
		1-42	≥65 y	640,666	90	76.0	1.2	0.0	5.7	No
	Adjuvanted IIV	1-42	≥65 y	204,149	26	24.0	1.1	0.0	5.0	No
GBS	IIV (pooled)	1-42	6 m-17 y	1,876,202	0	1.6	0.0	.	2.5	N/A
		1-42	18-64 y	3,764,480	15	11.5	1.3	0.0	3.4	No
		1-42	≥65 y	2,273,855	10	15.5	0.6	0.0	3.5	No
	High dose IIV	1-42	≥65 y	1,429,040	7	9.9	0.7	0.0	5.1	No
	Standard dose IIV	1-42	6 m-17 y	1,876,202	0	1.6	0.0	.	4.2	N/A
		1-42	18-64 y	3,764,480	15	11.5	1.3	0.0	5.2	No
		1-42	≥65 y	640,666	2	4.3	0.5	.	5.1	N/A
	Adjuvanted IIV	1-42	≥65 y	204,149	1	1.4	0.7	.	4.1	N/A

[a] Null hypothesis is that the risk after influenza vaccination in 2017-18 is no greater than 2.5 times the risk after influenza vaccination in historical seasons.

[b] LLR is set to zero if RR < 2.5.

[c] Per protocol, number of cumulative observed events must be ≥ 3 for a signal of possible increased risk to be generated; "N/A" means number of cumulative observed events is < 3.

Appendix F2. Descriptive analysis of post-vaccination occurrence of influenza, Analysis 6, August 1, 2017–December 14, 2017

	Vaccine type	Ages	Cum. Doses	No. of exposed persons	Cum. Observed Events
Influenza in inpatient or ED setting	IIV (pooled)	6 m-4 y	652,641	591,471	34
		5-8 y	433,359	432,496	4
		9-17 y	790,202	789,598	8
		18-49 y	1,886,195	1,884,774	32
		50-64 y	1,878,285	1,876,635	61
		≥65 y	2,273,855	2,270,688	140
	High dose IIV	≥65 y	1,429,040	1,427,505	95
	Adjuvanted IIV	≥65 y	204,149	203,886	10
Influenza in inpatient setting	IIV (pooled)	6 m-17 y	1,876,202	1,813,565	8
		18-64 y	3,764,480	3,761,409	28
		≥65 y	2,273,855	2,270,688	66
	High dose IIV	≥65 y	1,429,040	1,427,505	44
	Adjuvanted IIV	≥65 y	204,149	203,886	2

Appendix G1. Sequential analysis of safety outcomes, adjusted for partially accrued risk intervals and lag in data accrual, Analysis 7, August 1, 2017–December 31, 2017

	Vaccine type	Risk interval (days post-vaccination)	Ages	Cum. Doses	Cum. Observed Events	Cum. Expected Events	RR (Observed/ Expected)	Log-likelihood ratio (LLR)[b]	Critical value of LLR	Null hypothesis rejected?[c]
Febrile seizures	IIV, without concomitant PCV13	0-1	6-23 m	267,796	5	7.9	0.6	0.0	3.1	No
Anaphylaxis	IIV (pooled)	0-1	≥6 m	8,585,362	11	30.3	0.4	0.0	3.5	No
	High dose IIV	0-1	≥65 y	1,541,197	1	5.0	0.2	.	4.7	N/A
	Standard dose IIV	0-1	6 m-64 y	6,088,162	9	22.2	0.4	0.0	5.2	No
		0-1	≥65 y	733,770	1	2.3	0.4	.	4.6	N/A
	Adjuvanted IIV	0-1	≥65 y	222,233	0	0.7	0.0	.	3.8	N/A
Bell's palsy	IIV (pooled)	1-42	6 m-17 y	2,041,211	31	30.6	1.0	0.0	3.5	No
		1-42	18-64 y	4,046,951	463	387.0	1.2	0.0	3.7	No
		1-42	≥65 y	2,497,200	392	352.7	1.1	0.0	3.7	No
	High dose IIV	1-42	≥65 y	1,541,197	244	219.2	1.1	0.0	5.7	No
	Standard dose IIV	1-42	6 m-17 y	2,041,211	31	30.6	1.0	0.0	5.3	No
		1-42	18-64 y	4,046,951	463	387.0	1.2	0.0	5.4	No
		1-42	≥65 y	733,770	115	102.3	1.1	0.0	5.7	No
	Adjuvanted IIV	1-42	≥65 y	222,233	33	31.2	1.1	0.0	5.0	No
GBS	IIV (pooled)	1-42	6 m-17 y	2,041,211	1	2.1	0.5	.	2.5	N/A
		1-42	18-64 y	4,046,951	16	14.6	1.1	0.0	3.4	No
		1-42	≥65 y	2,497,200	14	22.0	0.6	0.0	3.5	No
	High dose IIV	1-42	≥65 y	1,541,197	9	13.7	0.7	0.0	5.1	No
	Standard dose IIV	1-42	6 m-17 y	2,041,211	1	2.1	0.5	.	4.2	N/A
		1-42	18-64 y	4,046,951	16	14.6	1.1	0.0	5.2	No
		1-42	≥65 y	733,770	3	6.3	0.5	0.0	5.1	No
	Adjuvanted IIV	1-42	≥65 y	222,233	2	2.0	1.0	.	4.1	N/A

a Null hypothesis is that the risk after influenza vaccination in 2017-18 is no greater than 2.5 times the risk after influenza vaccination in historical seasons.
b LLR is set to zero if RR < 2.5.
c Per protocol, number of cumulative observed events must be ≥ 3 for a signal of possible increased risk to be generated; "N/A" means number of cumulative observed events is < 3.

Appendix G2. Descriptive analysis of post-vaccination occurrence of influenza, Analysis 7, August 1, 2017–December 31, 2017

	Vaccine type	Ages	Cum. Doses	No. of exposed persons	Cum. Observed Events
Influenza in inpatient or ED setting	IIV (pooled)	6 m-4 y	719,784	638,493	151
		5-8 y	466,960	465,809	42
		9-17 y	854,467	853,683	65
		18-49 y	2,034,274	2,032,381	190
		50-64 y	2,012,677	2,010,354	252
		≥65 y	2,497,200	2,491,982	764
	High dose IIV	≥65 y	1,541,197	1,538,820	476
	Adjuvanted IIV	≥65 y	222,233	221,808	60
Influenza in inpatient setting	IIV (pooled)	6 m-17 y	2,041,211	1,957,985	20
		18-64 y	4,046,951	4,042,735	53
		≥65 y	2,497,200	2,491,982	233
	High dose IIV	≥65 y	1,541,197	1,538,820	142
	Adjuvanted IIV	≥65 y	222,233	221,808	15

Appendix H1. Sequential analysis of safety outcomes, adjusted for partially accrued risk intervals and lag in data accrual, Analysis 8, August 1, 2017–January 16, 2018

	Vaccine type	Risk interval (days post-vaccination)	Ages	Cum. Doses	Cum. Observed Events	Cum. Expected Events	RR (Observed/ Expected)	Log-likelihood ratio (LLR)[b]	Critical value of LLR	Null hypothesis rejected?[c]
Febrile seizures	IIV, without concomitant PCV13	0-1	6-23 m	295,695	6	9.3	0.6	0.0	3.1	No
Anaphylaxis	IIV (pooled)	0-1	≥6 m	9,064,579	12	33.9	0.4	0.0	3.5	No
	High dose IIV	0-1	≥65 y	1,570,107	1	5.2	0.2	.	4.7	N/A
	Standard dose IIV	0-1	6 m-64 y	6,512,749	10	25.5	0.4	0.0	5.2	No
		0-1	≥65 y	756,398	1	2.5	0.4	.	4.6	N/A
	Adjuvanted IIV	0-1	≥65 y	225,325	0	0.7	0.0	.	3.8	N/A
Bell's palsy	IIV (pooled)	1-42	6 m-17 y	2,206,630	35	37.0	0.9	0.0	3.5	No
		1-42	18-64 y	4,306,119	515	457.8	1.1	0.0	3.7	No
		1-42	≥65 y	2,551,830	416	373.1	1.1	0.0	3.7	No
	High dose IIV	1-42	≥65 y	1,570,107	259	230.9	1.1	0.0	5.7	No
	Standard dose IIV	1-42	6 m-17 y	2,206,630	35	37.0	0.9	0.0	5.3	No
		1-42	18-64 y	4,306,119	515	457.8	1.1	0.0	5.4	No
		1-42	≥65 y	756,398	123	109.5	1.1	0.0	5.7	No
	Adjuvanted IIV	1-42	≥65 y	225,325	34	32.6	1.0	0.0	5.0	No
GBS	IIV (pooled)	1-42	6 m-17 y	2,206,630	1	2.7	0.4	.	2.5	N/A
		1-42	18-64 y	4,306,119	18	18.4	1.0	0.0	3.4	No
		1-42	≥65 y	2,551,830	14	23.8	0.6	0.0	3.5	No
	High dose IIV	1-42	≥65 y	1,570,107	9	14.8	0.6	0.0	5.1	No
	Standard dose IIV	1-42	6 m-17 y	2,206,630	1	2.7	0.4	.	4.2	N/A
		1-42	18-64 y	4,306,119	18	18.4	1.0	0.0	5.2	No
		1-42	≥65 y	756,398	3	6.9	0.4	0.0	5.1	No
	Adjuvanted IIV	1-42	≥65 y	225,325	2	2.1	1.0	.	4.1	N/A

[a] Null hypothesis is that the risk after influenza vaccination in 2017-18 is no greater than 2.5 times the risk after influenza vaccination in historical seasons.
[b] LLR is set to zero if RR < 2.5.
[c] Per protocol, number of cumulative observed events must be ≥ 3 for a signal of possible increased risk to be generated; "N/A" means number of cumulative observed events is < 3.

Appendix H2. Descriptive analysis of post-vaccination occurrence of influenza, Analysis 8, August 1, 2017–January 16, 2018

	Vaccine type	Ages	Cum. Doses	No. of exposed persons	Cum. Observed Events
Influenza in inpatient or ED setting	IIV (pooled)	6 m-4 y	784,513	684,076	185
		5-8 y	500,439	498,986	45
		9-17 y	921,678	920,717	71
		18-49 y	2,177,419	2,175,105	242
		50-64 y	2,128,700	2,125,937	333
		≥65 y	2,551,830	2,546,246	944
	High dose IIV	≥65 y	1,570,107	1,567,592	595
	Adjuvanted IIV	≥65 y	225,325	224,878	67
Influenza in inpatient setting	IIV (pooled)	6 m-17 y	2,206,630	2,103,779	49
		18-64 y	4,306,119	4,301,042	172
		≥65 y	2,551,830	2,546,246	412
	High dose IIV	≥65 y	1,570,107	1,567,592	260
	Adjuvanted IIV	≥65 y	225,325	224,878	22

Appendix I1. Sequential analysis of safety outcomes, adjusted for partially accrued risk intervals and lag in data accrual, Analysis 9, August 1, 2017–January 31, 2018

	Vaccine type	Risk interval (days post-vaccination)	Ages	Cum. Doses	Cum. Observed Events	Cum. Expected Events	RR (Observed/ Expected)	Log-likelihood ratio (LLR)[b]	Critical value of LLR	Null hypothesis rejected?[c]
Febrile seizures	IIV, without concomitant PCV13	0-1	6-23 m	313,700	6	9.9	0.6	0.0	3.1	No
Anaphylaxis	IIV (pooled)	0-1	≥6 m	9,371,809	12	35.5	0.3	0.0	3.5	No
	High dose IIV	0-1	≥65 y	1,579,394	1	5.3	0.2	.	4.7	N/A
	Standard dose IIV	0-1	6 m-64 y	6,799,219	10	26.9	0.4	0.0	5.2	No
		0-1	≥65 y	765,537	1	2.5	0.4	.	4.6	N/A
	Adjuvanted IIV	0-1	≥65 y	227,659	0	0.8	0.0	.	3.8	N/A
Bell's palsy	IIV (pooled)	1-42	6 m-17 y	2,327,172	37	39.9	0.9	0.0	3.5	No
		1-42	18-64 y	4,472,047	547	483.1	1.1	0.0	3.7	No
		1-42	≥65 y	2,572,590	430	381.4	1.1	0.0	3.7	No
	High dose IIV	1-42	≥65 y	1,579,394	267	235.8	1.1	0.0	5.7	No
	Standard dose IIV	1-42	6 m-17 y	2,327,172	37	39.9	0.9	0.0	5.3	No
		1-42	18-64 y	4,472,047	547	483.1	1.1	0.0	5.4	No
		1-42	≥65 y	765,537	127	112.3	1.1	0.0	5.7	No
	Adjuvanted IIV	1-42	≥65 y	227,659	36	33.2	1.1	0.0	5.0	No
GBS	IIV (pooled)	1-42	6 m-17 y	2,327,172	1	3.0	0.3	.	2.5	N/A
		1-42	18-64 y	4,472,047	18	19.7	0.9	0.0	3.4	No
		1-42	≥65 y	2,572,590	14	24.7	0.6	0.0	3.5	No
	High dose IIV	1-42	≥65 y	1,579,394	9	15.3	0.6	0.0	5.1	No
	Standard dose IIV	1-42	6 m-17 y	2,327,172	1	3.0	0.3	.	4.2	N/A
		1-42	18-64 y	4,472,047	18	19.7	0.9	0.0	5.2	No
		1-42	≥65 y	765,537	3	7.2	0.4	0.0	5.1	No
	Adjuvanted IIV	1-42	≥65 y	227,659	2	2.1	0.9	.	4.1	N/A

[a] Null hypothesis is that the risk after influenza vaccination in 2017-18 is no greater than 2.5 times the risk after influenza vaccination in historical seasons.
[b] LLR is set to zero if RR < 2.5.
[c] Per protocol, number of cumulative observed events must be ≥ 3 for a signal of possible increased risk to be generated; "N/A" means number of cumulative observed events is < 3.

Appendix I2. Descriptive analysis of post-vaccination occurrence of influenza, Analysis 9, August 1, 2017–January 31, 2018

	Vaccine type	Ages	Cum. Doses	No. of exposed persons	Cum. Observed Events
Influenza in inpatient or ED setting	IIV (pooled)	6 m-4 y	830,481	716,019	631
		5-8 y	525,314	523,654	177
		9-17 y	971,377	970,180	244
		18-49 y	2,282,111	2,279,302	765
		50-64 y	2,189,936	2,186,730	929
		≥65 y	2,572,590	2,566,358	2,254
	High dose IIV	≥65 y	1,579,394	1,576,554	1,441
	Adjuvanted IIV	≥65 y	227,659	227,170	154
Influenza in inpatient setting	IIV (pooled)	6 m-17 y	2,327,172	2,209,853	81
		18-64 y	4,472,047	4,466,032	278
		≥65 y	2,572,590	2,566,358	877
	High dose IIV	≥65 y	1,579,394	1,576,554	539
	Adjuvanted IIV	≥65 y	227,659	227,170	60

Appendix J1. Sequential analysis of safety outcomes, adjusted for partially accrued risk intervals and lag in data accrual, Analysis 10, August 1, 2017–January 31, 2018

	Vaccine type	Risk interval (days post-vaccination)	Ages	Cum. Doses	Cum. Observed Events	Cum. Expected Events	RR (Observed/ Expected)	Log-likelihood ratio (LLR)[b]	Critical value of LLR	Null hypothesis rejected?[c]
Febrile seizures	IIV, without concomitant PCV13	0-1	6-23 m	314,773	6	9.9	0.6	0.0	3.1	No
Anaphylaxis	IIV (pooled)	0-1	≥6 m	9,486,965	13	36.1	0.4	0.0	3.5	No
	High dose IIV	0-1	≥65 y	1,613,478	1	5.5	0.2	.	4.7	N/A
	Standard dose IIV	0-1	6 m-64 y	6,838,453	10	27.1	0.4	0.0	5.2	No
		0-1	≥65 y	798,985	2	2.7	0.7	.	4.6	N/A
	Adjuvanted IIV	0-1	≥65 y	236,049	0	0.8	0.0	.	3.8	N/A
Bell's palsy	IIV (pooled)	1-42	6 m-17 y	2,334,860	37	40.0	0.9	0.0	3.5	No
		1-42	18-64 y	4,503,593	558	488.6	1.1	0.0	3.7	No
		1-42	≥65 y	2,648,512	453	402.8	1.1	0.0	3.7	No
	High dose IIV	1-42	≥65 y	1,613,478	276	246.7	1.1	0.0	5.7	No
	Standard dose IIV	1-42	6 m-17 y	2,334,860	37	40.0	0.9	0.0	5.3	No
		1-42	18-64 y	4,503,593	558	488.6	1.1	0.0	5.4	No
		1-42	≥65 y	798,985	140	120.7	1.2	0.0	5.7	No
	Adjuvanted IIV	1-42	≥65 y	236,049	37	35.4	1.0	0.0	5.0	No
GBS	IIV (pooled)	1-42	6 m-17 y	2,334,860	1	3.0	0.3	.	2.5	N/A
		1-42	18-64 y	4,503,593	18	20.0	0.9	0.0	3.4	No
		1-42	≥65 y	2,648,512	18	26.5	0.7	0.0	3.5	No
	High dose IIV	1-42	≥65 y	1,613,478	11	16.2	0.7	0.0	5.1	No
	Standard dose IIV	1-42	6 m-17 y	2,334,860	1	3.0	0.3	.	4.2	N/A
		1-42	18-64 y	4,503,593	18	20.0	0.9	0.0	5.2	No
		1-42	≥65 y	798,985	3	7.9	0.4	0.0	5.1	No
	Adjuvanted IIV	1-42	≥65 y	236,049	4	2.3	1.7	0.0	4.1	No

[a] Null hypothesis is that the risk after influenza vaccination in 2017-18 is no greater than 2.5 times the risk after influenza vaccination in historical seasons.
[b] LLR is set to zero if RR < 2.5.
[c] Per protocol, number of cumulative observed events must be ≥ 3 for a signal of possible increased risk to be generated; "N/A" means number of cumulative observed events is < 3.

Appendix J2. Descriptive analysis of post-vaccination occurrence of influenza, Analysis 10, August 1, 2017–January 31, 2018

	Vaccine type	Ages	Cum. Doses	No. of exposed persons	Cum. Observed Events
Influenza in inpatient or ED setting	IIV (pooled)	6 m-4 y	833,397	718,069	647
		5-8 y	526,804	525,128	185
		9-17 y	974,659	973,454	251
		18-49 y	2,293,673	2,290,781	867
		50-64 y	2,209,920	2,206,364	1,387
		≥65 y	2,648,512	2,640,678	4,692
	High dose IIV	≥65 y	1,613,478	1,609,986	2,804
	Adjuvanted IIV	≥65 y	236,049	235,330	389
Influenza in inpatient setting	IIV (pooled)	6 m-17 y	2,334,860	2,216,651	82
		18-64 y	4,503,593	4,497,145	402
		≥65 y	2,648,512	2,640,678	1,697
	High dose IIV	≥65 y	1,613,478	1,609,986	984
	Adjuvanted IIV	≥65 y	236,049	235,330	147

Appendix K1. Sequential analysis of safety outcomes, adjusted for partially accrued risk intervals and lag in data accrual, Analysis 11, August 1, 2017–February 28, 2018

	Vaccine type	Risk interval (days post-vaccination)	Ages	Cum. Doses	Cum. Observed Events	Cum. Expected Events	RR (Observed/ Expected)	Log-likelihood ratio (LLR)[b]	Critical value of LLR	Null hypothesis rejected?[c]
Febrile seizures	IIV, without concomitant PCV13	0-1	6-23 m	347,428	6	11.2	0.5	0.0	3.1	No
Anaphylaxis	IIV (pooled)	0-1	≥6 m	10,102,332	15	39.4	0.4	0.0	3.5	No
	High dose IIV	0-1	≥65 y	1,644,648	1	5.7	0.2	.	4.7	N/A
	Standard dose IIV	0-1	6 m-64 y	7,393,911	12	30.1	0.4	0.0	5.2	No
		0-1	≥65 y	822,616	2	2.8	0.7	.	4.6	N/A
	Adjuvanted IIV	0-1	≥65 y	241,157	0	0.8	0.0	.	3.8	N/A
Bell's palsy	IIV (pooled)	1-42	6 m-17 y	2,557,044	44	45.6	1.0	0.0	3.5	No
		1-42	18-64 y	4,836,867	603	542.1	1.1	0.0	3.7	No
		1-42	≥65 y	2,708,421	472	419.9	1.1	0.0	3.7	No
	High dose IIV	1-42	≥65 y	1,644,648	286	256.4	1.1	0.0	5.7	No
	Standard dose IIV	1-42	6 m-17 y	2,557,044	44	45.6	1.0	0.0	5.3	No
		1-42	18-64 y	4,836,867	603	542.1	1.1	0.0	5.4	No
		1-42	≥65 y	822,616	147	126.7	1.2	0.0	5.7	No
	Adjuvanted IIV	1-42	≥65 y	241,157	39	36.8	1.1	0.0	5.0	No
GBS	IIV (pooled)	1-42	6 m-17 y	2,557,044	1	3.5	0.3	.	2.5	N/A
		1-42	18-64 y	4,836,867	21	22.8	0.9	0.0	3.4	No
		1-42	≥65 y	2,708,421	19	28.0	0.7	0.0	3.5	No
	High dose IIV	1-42	≥65 y	1,644,648	12	17.2	0.7	0.0	5.1	No
	Standard dose IIV	1-42	6 m-17 y	2,557,044	1	3.5	0.3	.	4.2	N/A
		1-42	18-64 y	4,836,867	21	22.8	0.9	0.0	5.2	No
		1-42	≥65 y	822,616	3	8.4	0.4	0.0	5.1	No
	Adjuvanted IIV	1-42	≥65 y	241,157	4	2.4	1.6	0.0	4.1	No

[a] Null hypothesis is that the risk after influenza vaccination in 2017-18 is no greater than 2.5 times the risk after influenza vaccination in historical seasons.
[b] LLR is set to zero if RR < 2.5.
[c] Per protocol, number of cumulative observed events must be ≥ 3 for a signal of possible increased risk to be generated; "N/A" means number of cumulative observed events is < 3.

Appendix K2. Descriptive analysis of post-vaccination occurrence of influenza, Analysis 11, August 1, 2017–February 28, 2018

	Vaccine type	Ages	Cum. Doses	No. of exposed persons	Cum. Observed Events
Influenza in inpatient or ED setting	IIV (pooled)	6 m-4 y	916,151	776,493	1,314
		5-8 y	572,252	570,115	460
		9-17 y	1,068,641	1,066,962	617
		18-49 y	2,494,497	2,490,530	1,565
		50-64 y	2,342,370	2,337,870	2,277
		≥65 y	2,708,421	2,699,590	6,997
	High dose IIV	≥65 y	1,644,648	1,640,714	4,250
	Adjuvanted IIV	≥65 y	241,157	240,357	532
Influenza in inpatient setting	IIV (pooled)	6 m-17 y	2,557,044	2,413,570	194
		18-64 y	4,836,867	4,828,400	891
		≥65 y	2,708,421	2,699,590	3,193
	High dose IIV	≥65 y	1,644,648	1,640,714	1,891
	Adjuvanted IIV	≥65 y	241,157	240,357	247

Appendix L1. Sequential analysis of safety outcomes, adjusted for partially accrued risk intervals and lag in data accrual, Analysis 12, August 1, 2017–February 28, 2018

	Vaccine type	Risk interval (days post-vaccination)	Ages	Cum. Doses	Cum. Observed Events	Cum. Expected Events	RR (Observed/ Expected)	Log-likelihood ratio (LLR)[b]	Critical value of LLR	Null hypothesis rejected?[c]
Febrile seizures	IIV, without concomitant PCV13	0-1	6-23 m	348,169	6	11.2	0.5	0.0	3.1	No
Anaphylaxis	IIV (pooled)	0-1	≥6 m	10,173,881	17	39.9	0.4	0.0	3.5	No
	High dose IIV	0-1	≥65 y	1,661,367	1	5.9	0.2	.	4.7	N/A
	Standard dose IIV	0-1	6 m-64 y	7,418,925	14	30.2	0.5	0.0	5.2	No
		0-1	≥65 y	848,990	2	3.0	0.7	.	4.6	N/A
	Adjuvanted IIV	0-1	≥65 y	244,599	0	0.9	0.0	.	3.8	N/A
Bell's palsy	IIV (pooled)	1-42	6 m-17 y	2,562,370	44	45.8	1.0	0.0	3.5	No
		1-42	18-64 y	4,856,555	611	546.3	1.1	0.0	3.7	No
		1-42	≥65 y	2,754,956	491	434.6	1.1	0.0	3.7	No
	High dose IIV	1-42	≥65 y	1,661,367	296	263.2	1.1	0.0	5.7	No
	Standard dose IIV	1-42	6 m-17 y	2,562,370	44	45.8	1.0	0.0	5.3	No
		1-42	18-64 y	4,856,555	611	546.3	1.1	0.0	5.4	No
		1-42	≥65 y	848,990	155	133.1	1.2	0.0	5.7	No
	Adjuvanted IIV	1-42	≥65 y	244,599	40	38.3	1.0	0.0	5.0	UL Reached
GBS	IIV (pooled)	1-42	6 m-17 y	2,562,370	1	3.6	0.3	.	2.5	N/A
		1-42	18-64 y	4,856,555	21	23.0	0.9	0.0	3.4	No
		1-42	≥65 y	2,754,956	21	29.2	0.7	0.0	3.5	No
	High dose IIV	1-42	≥65 y	1,661,367	13	17.7	0.7	0.0	5.1	No
	Standard dose IIV	1-42	6 m-17 y	2,562,370	1	3.6	0.3	.	4.2	N/A
		1-42	18-64 y	4,856,555	21	23.0	0.9	0.0	5.2	No
		1-42	≥65 y	848,990	4	8.9	0.4	0.0	5.1	No
	Adjuvanted IIV	1-42	≥65 y	244,599	4	2.6	1.6	0.0	4.1	No

[a] Null hypothesis is that the risk after influenza vaccination in 2017-18 is no greater than 2.5 times the risk after influenza vaccination in historical seasons.
[b] LLR is set to zero if RR < 2.5.
[c] Per protocol, number of cumulative observed events must be ≥ 3 for a signal of possible increased risk to be generated; "N/A" means number of cumulative observed events is < 3.

Appendix L2. Descriptive analysis of post-vaccination occurrence of influenza, Analysis 12, August 1, 2017–February 28, 2018

	Vaccine type	Ages	Cum. Doses	No. of exposed persons	Cum. Observed Events
Influenza in inpatient or ED setting	IIV (pooled)	6 m-4 y	918,217	777,966	1,346
		5-8 y	573,349	571,199	474
		9-17 y	1,070,804	1,069,113	636
		18-49 y	2,501,386	2,497,303	1,716
		50-64 y	2,355,169	2,350,318	2,797
		≥65 y	2,754,956	2,744,837	9,559
	High dose IIV	≥65 y	1,661,367	1,656,959	5,709
	Adjuvanted IIV	≥65 y	244,599	243,682	794
Influenza in inpatient setting	IIV (pooled)	6 m-17 y	2,562,370	2,418,278	197
		18-64 y	4,856,555	4,847,621	1,062
		≥65 y	2,754,956	2,744,837	4,299
	High dose IIV	≥65 y	1,661,367	1,656,959	2,511
	Adjuvanted IIV	≥65 y	244,599	243,682	370

Appendix M1. Sequential analysis of safety outcomes, adjusted for partially accrued risk intervals and lag in data accrual, Analysis 13, August 1, 2017–March 31, 2018

	Vaccine type	Risk interval (days post-vaccination)	Ages	Cum. Doses	Cum. Observed Events	Cum. Expected Events	RR (Observed/ Expected)	Log-likelihood ratio (LLR)[b]	Critical value of LLR	Null hypothesis rejected?[c]
Febrile seizures	IIV, without concomitant PCV13	0-1	6-23 m	371,751	6	12.1	0.5	0.0	3.1	No
Anaphylaxis	IIV (pooled)	0-1	≥6 m	10,165,841	22	41.3	0.5	0.0	3.5	No
	High dose IIV	0-1	≥65 y	1,659,061	2	6.0	0.3	.	4.7	N/A
	Standard dose IIV	0-1	6 m-64 y	7,398,338	17	31.3	0.5	0.0	5.2	No
		0-1	≥65 y	865,305	3	3.1	1.0	0.0	4.6	No
	Adjuvanted IIV	0-1	≥65 y	243,137	0	0.9	0.0	.	3.8	N/A
Bell's palsy	IIV (pooled)	1-42	6 m-17 y	2,641,248	47	49.7	0.9	0.0	3.5	No
		1-42	18-64 y	4,757,090	650	562.5	1.2	0.0	3.7	No
		1-42	≥65 y	2,767,503	504	450.3	1.1	0.0	3.7	No
	High dose IIV	1-42	≥65 y	1,659,061	299	270.7	1.1	0.0	5.7	No
	Standard dose IIV	1-42	6 m-17 y	2,641,248	47	49.7	0.9	0.0	5.3	No
		1-42	18-64 y	4,757,090	650	562.5	1.2	0.0	5.4	No
		1-42	≥65 y	865,305	164	140.1	1.2	0.0	5.7	No
	Adjuvanted IIV	1-42	≥65 y	243,137	41	39.5	1.0	N/A[d]	N/A[d]	UL Reached
GBS	IIV (pooled)	1-42	6 m-17 y	2,641,248	1	3.9	0.3	.	2.5	N/A
		1-42	18-64 y	4,757,090	25	24.2	1.0	0.0	3.4	No
		1-42	≥65 y	2,767,503	23	30.8	0.7	0.0	3.5	No
	High dose IIV	1-42	≥65 y	1,659,061	14	18.6	0.8	0.0	5.1	No
	Standard dose IIV	1-42	6 m-17 y	2,641,248	1	3.9	0.3	.	4.2	N/A
		1-42	18-64 y	4,757,090	25	24.2	1.0	0.0	5.2	No
		1-42	≥65 y	865,305	4	9.6	0.4	0.0	5.1	No
	Adjuvanted IIV	1-42	≥65 y	243,137	5	2.7	1.9	0.0	4.1	No

a Null hypothesis is that the risk after influenza vaccination in 2017-18 is no greater than 2.5 times the risk after influenza vaccination in historical seasons.
b LLR is set to zero if RR < 2.5.
c Per protocol, number of cumulative observed events must be ≥ 3 for a signal of possible increased risk to be generated; "N/A" means number of cumulative observed events is < 3.
d Upper limit was reached in Analysis #12, and sequential analysis stopped. However, dose and event counts and RR continue to be updated.

Appendix M2. Descriptive analysis of post-vaccination occurrence of influenza, Analysis 13, August 1, 2017–March 31, 2018

	Vaccine type	Ages	Cum. Doses	No. of exposed persons	Cum. Observed Events
Influenza in inpatient or ED setting	IIV (pooled)	6 m-4 y	968,580	808,448	1,701
		5-8 y	587,019	584,520	620
		9-17 y	1,085,649	1,083,787	799
		18-49 y	2,461,335	2,456,923	2,116
		50-64 y	2,295,755	2,290,514	3,513
		≥65 y	2,767,503	2,756,287	12,314
	High dose IIV	≥65 y	1,659,061	1,654,342	7,290
	Adjuvanted IIV	≥65 y	243,137	242,159	1,052
Influenza in inpatient setting	IIV (pooled)	6 m-17 y	2,641,248	2,476,755	307
		18-64 y	4,757,090	4,747,437	1,516
		≥65 y	2,767,503	2,756,287	5,981
	High dose IIV	≥65 y	1,659,061	1,654,342	3,484
	Adjuvanted IIV	≥65 y	243,137	242,159	520

Appendix N1. Sequential analysis of safety outcomes, adjusted for partially accrued risk intervals and lag in data accrual, Analysis 14, August 1, 2017–April 14, 2018

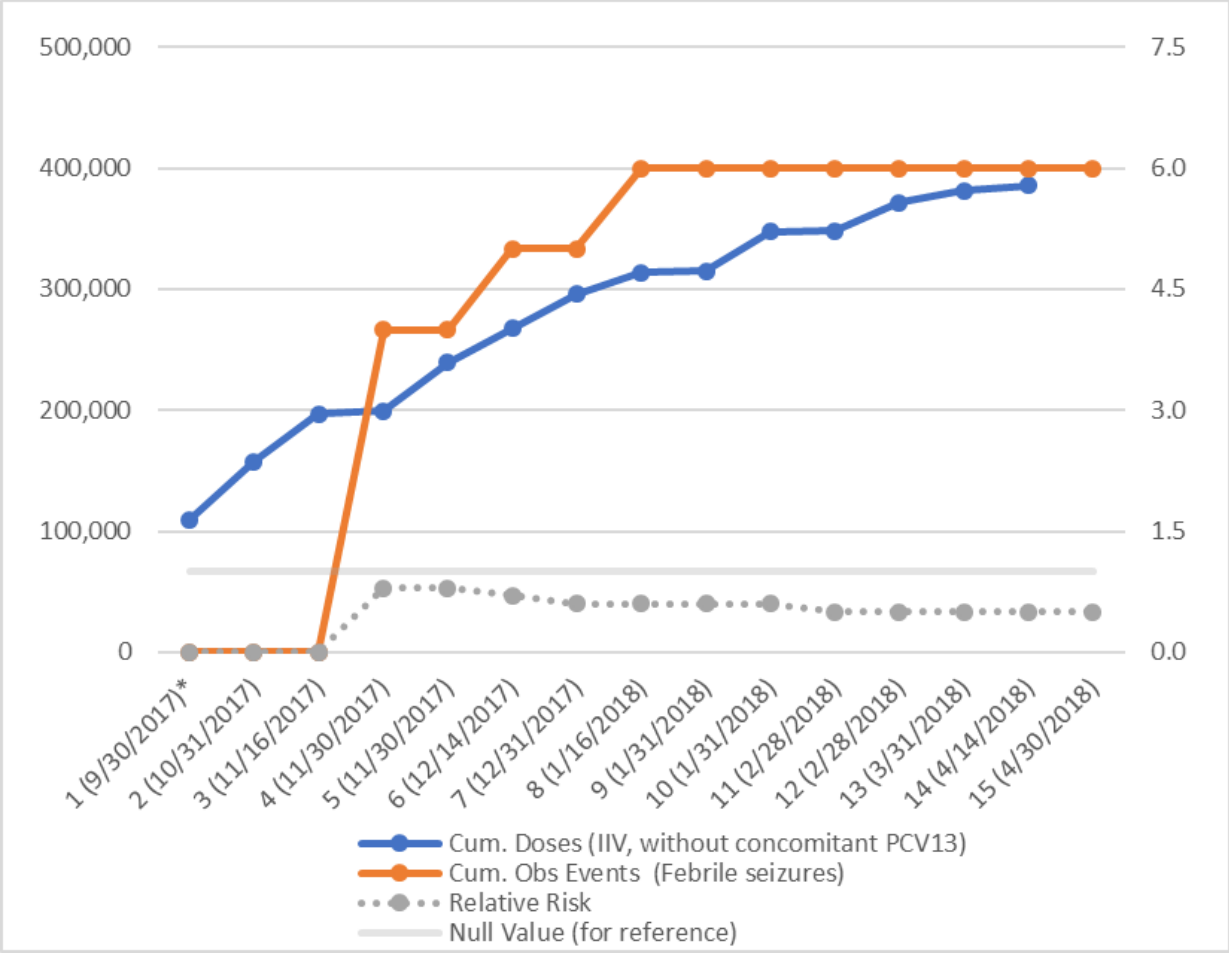
	Vaccine type	Risk interval (days post-vaccination)	Ages	Cum. Doses	Cum. Observed Events	Cum. Expected Events	RR (Observed/ Expected)	Log-likelihood ratio (LLR)[b]	Critical value of LLR	Null hypothesis rejected?[c]
Febrile seizures	IIV, without concomitant PCV13	0-1	6-23 m	381,208	6	12.5	0.5	0.0	3.1	No
Anaphylaxis	IIV (pooled)	0-1	≥6 m	10,230,617	22	42.1	0.5	0.0	3.5	No
	High dose IIV	0-1	≥65 y	1,661,411	2	6.0	0.3	.	4.7	N/A
	Standard dose IIV	0-1	6 m-64 y	7,457,668	17	32.0	0.5	0.0	5.2	No
		0-1	≥65 y	868,197	3	3.1	1.0	0.0	4.6	No
	Adjuvanted IIV	0-1	≥65 y	243,341	0	0.9	0.0	.	3.8	N/A
Bell's palsy	IIV (pooled)	1-42	6 m-17 y	2,671,577	49	51.4	1.0	0.0	3.5	No
		1-42	18-64 y	4,786,091	659	576.9	1.1	0.0	3.7	No
		1-42	≥65 y	2,772,949	508	453.6	1.1	0.0	3.7	No
	High dose IIV	1-42	≥65 y	1,661,411	302	272.4	1.1	0.0	5.7	No
	Standard dose IIV	1-42	6 m-17 y	2,671,577	49	51.4	1.0	0.0	5.3	No
		1-42	18-64 y	4,786,091	659	576.9	1.1	0.0	5.4	No
		1-42	≥65 y	868,197	165	141.5	1.2	0.0	5.7	No
	Adjuvanted IIV	1-42	≥65 y	243,341	41	39.7	1.0	N/A[d]	N/A[d]	UL Reached
GBS	IIV (pooled)	1-42	6 m-17 y	2,671,577	1	4.1	0.2	.	2.5	N/A
		1-42	18-64 y	4,786,091	26	25.1	1.0	0.0	3.4	No
		1-42	≥65 y	2,772,949	23	31.1	0.7	0.0	3.5	No
	High dose IIV	1-42	≥65 y	1,661,411	14	18.7	0.7	0.0	5.1	No
	Standard dose IIV	1-42	6 m-17 y	2,671,577	1	4.1	0.2	.	4.2	N/A
		1-42	18-64 y	4,786,091	26	25.1	1.0	0.0	5.2	No
		1-42	≥65 y	868,197	4	9.7	0.4	0.0	5.1	No
	Adjuvanted IIV	1-42	≥65 y	243,341	5	2.7	1.8	0.0	4.1	No

[a] Null hypothesis is that the risk after influenza vaccination in 2017-18 is no greater than 2.5 times the risk after influenza vaccination in historical seasons.
[b] LLR is set to zero if RR < 2.5.
[c] Per protocol, number of cumulative observed events must be ≥ 3 for a signal of possible increased risk to be generated; "N/A" means number of cumulative observed events is < 3.
[d] Upper limit was reached in Analysis #12, and sequential analysis stopped. However, dose and event counts and RR continue to be updated.

Appendix N2. Descriptive analysis of post-vaccination occurrence of influenza, Analysis 14, August 1, 2017–April 14, 2018

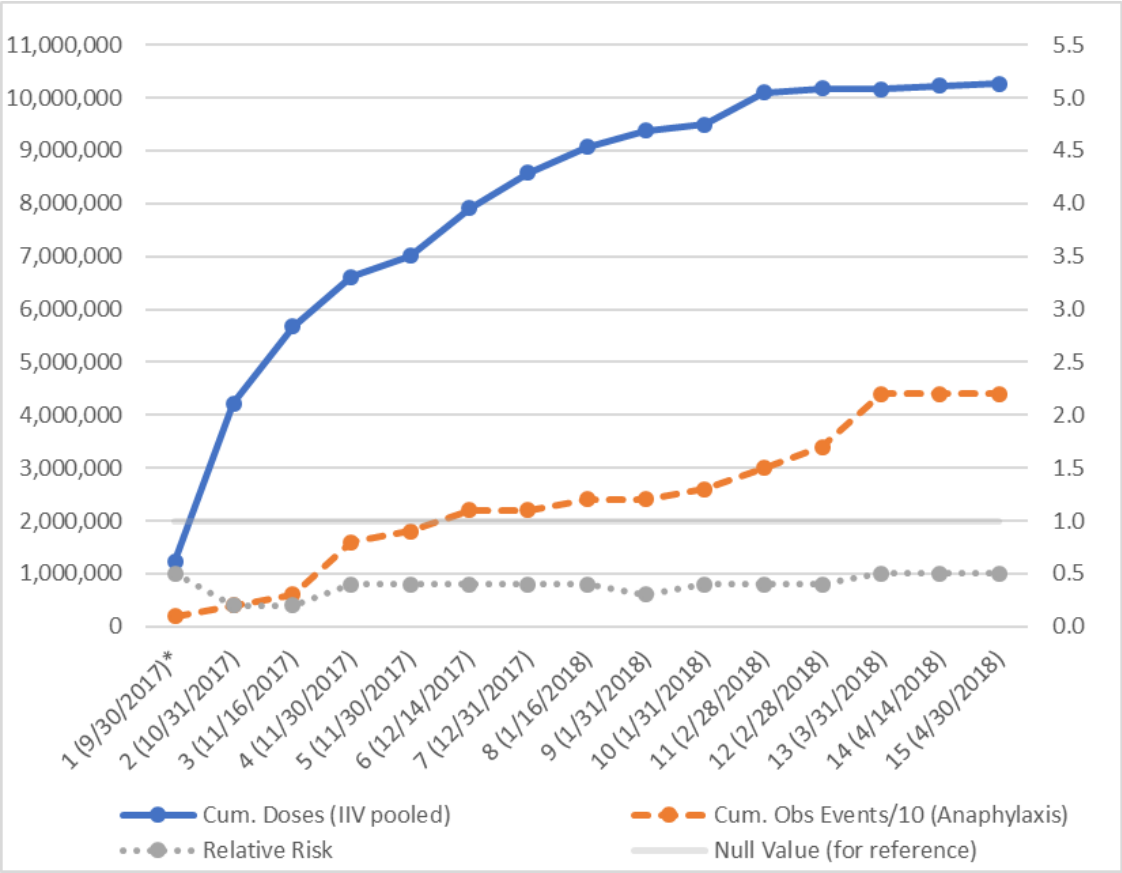
	Vaccine type	Ages	Cum. Doses	No. of exposed persons	Cum. Observed Events
Influenza in inpatient or ED setting	IIV (pooled)	6 m-4 y	986,458	818,288	1,736
		5-8 y	591,155	588,505	631
		9-17 y	1,093,964	1,092,045	815
		18-49 y	2,479,978	2,475,371	2,173
		50-64 y	2,306,113	2,300,701	3,622
		≥65 y	2,772,949	2,761,598	12,706
	High dose IIV	≥65 y	1,661,411	1,656,653	7,510
	Adjuvanted IIV	≥65 y	243,341	242,363	1,088
Influenza in inpatient setting	IIV (pooled)	6 m-17 y	2,671,577	2,498,838	342
		18-64 y	4,786,091	4,776,072	1,656
		≥65 y	2,772,949	2,761,598	6,368
	High dose IIV	≥65 y	1,661,411	1,656,653	3,701
	Adjuvanted IIV	≥65 y	243,341	242,363	555

Appendix O. Number of inactivated influenza vaccine (without concomitant PCV13) doses (primary y-axis), and number of observed febrile seizure events (secondary y-axis), and corresponding relative risk (secondary y-axis) among members 6-23 months-old, by analysis number, August 1, 2017–April 30, 2018



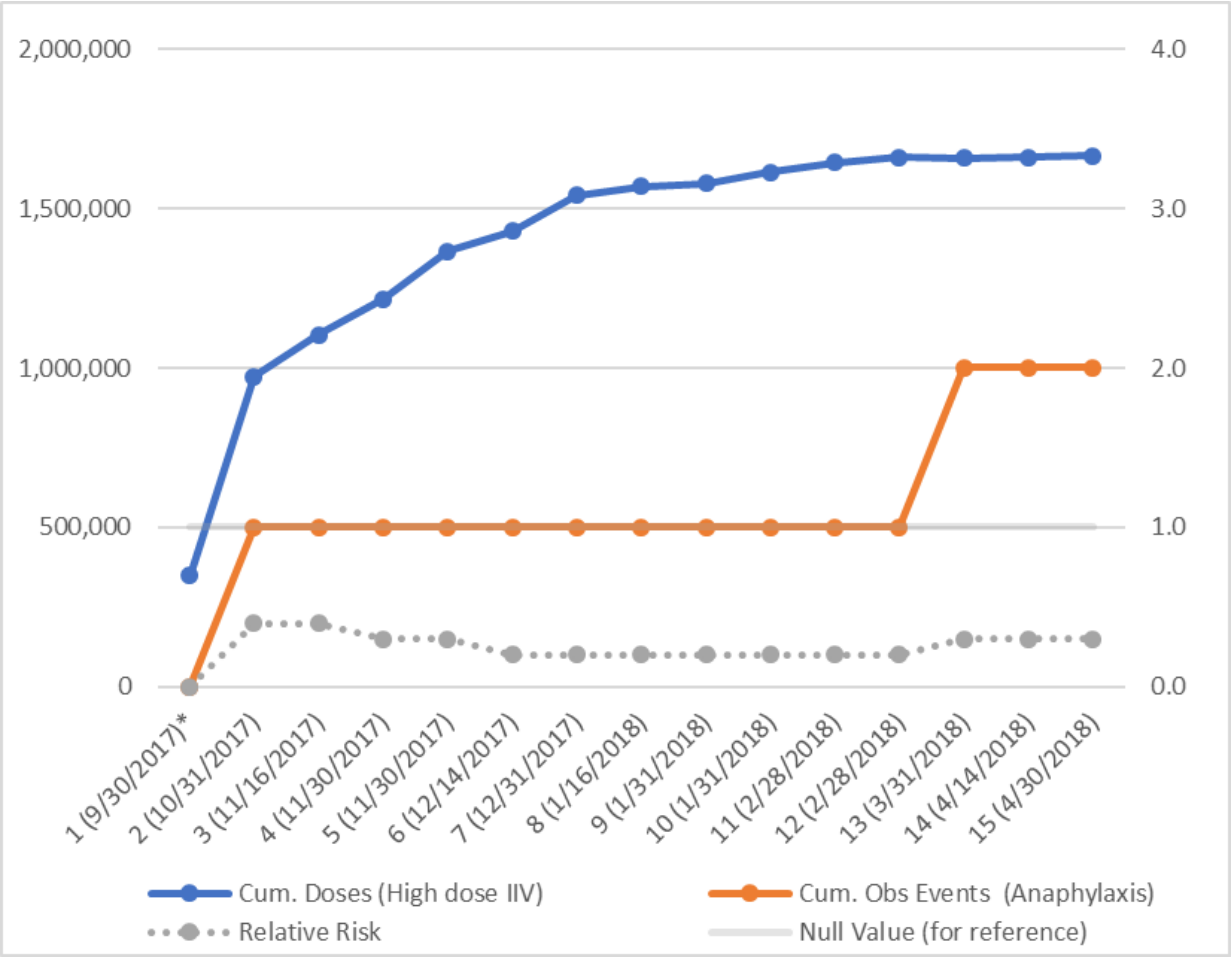
*Dates designate the most recent available data included in the analysis.

Appendix P. Number of inactivated influenza vaccine (pooled) doses (primary y-axis), and number of observed anaphylaxis events (secondary y-axis), and corresponding relative risk (secondary y-axis) among members ≥6 months-old, by analysis number, August 1, 2017–April 30, 2018



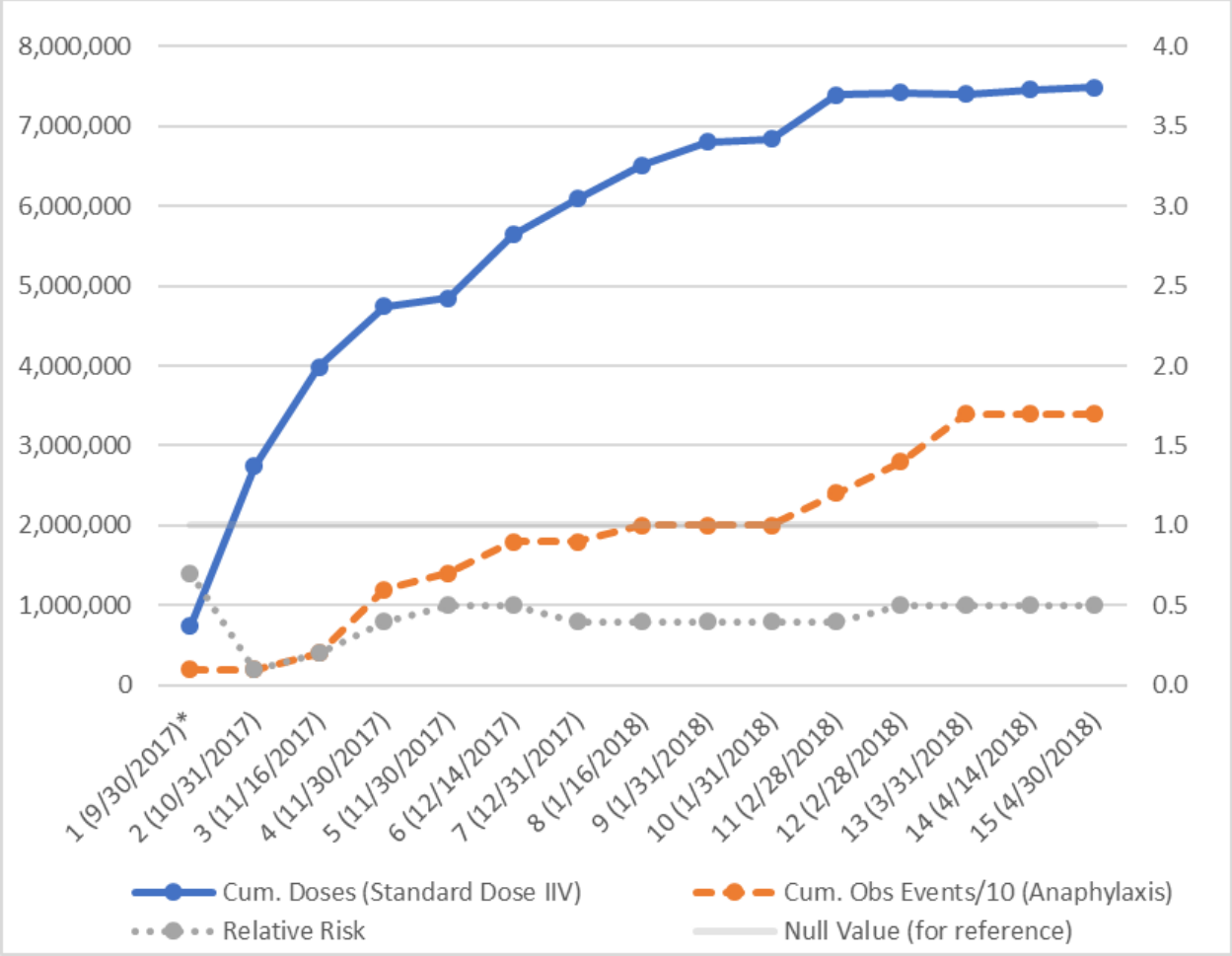
*Dates designate the most recent available data included in the analysis.

Appendix Q. Number of inactivated influenza vaccine (high dose) doses (primary y-axis), and number of observed anaphylaxis events (secondary y-axis), and corresponding relative risk (secondary y-axis) among members ≥65 years-old, by analysis number, August 1, 2017–April 30, 2018



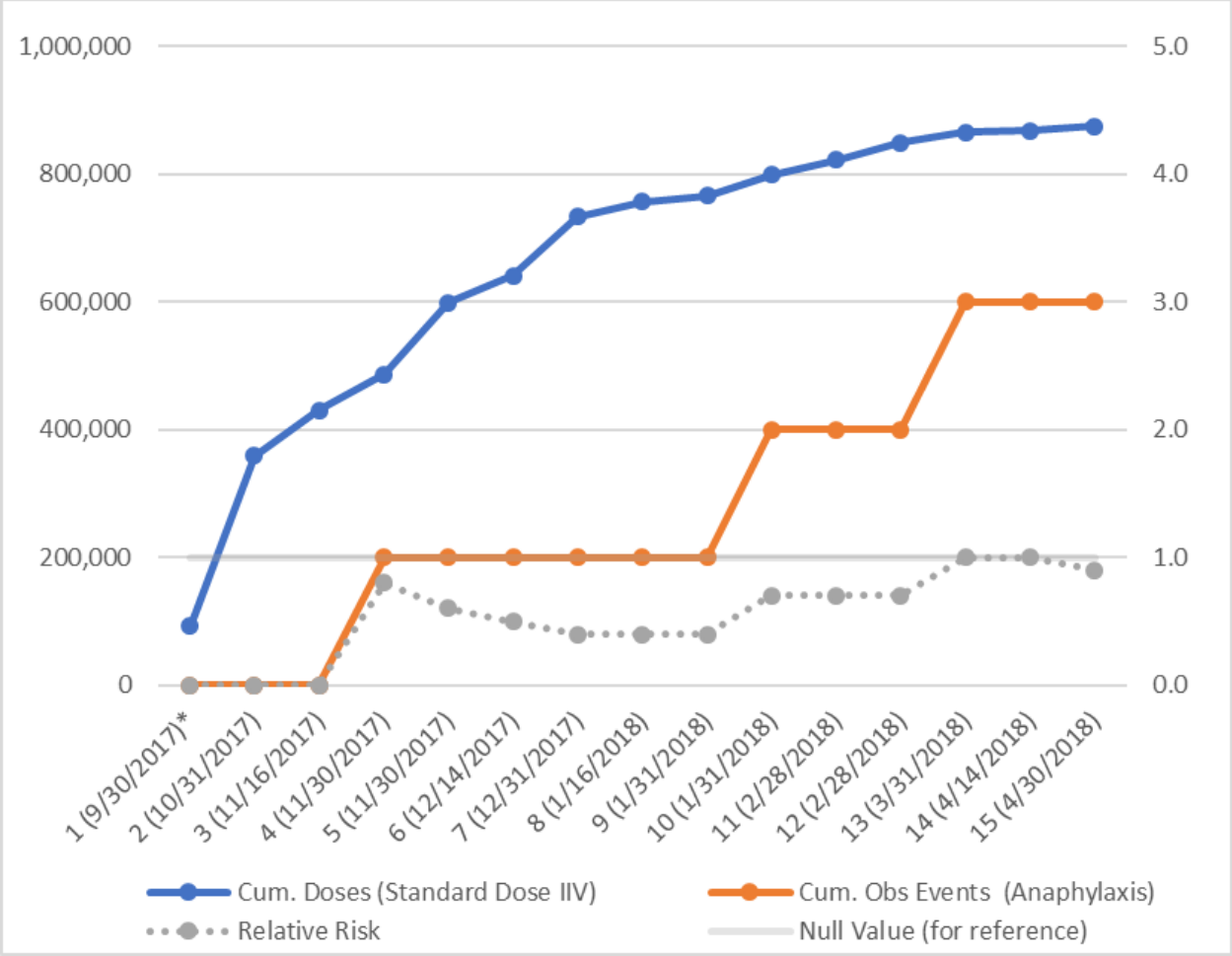
*Dates designate the most recent available data included in the analysis.

Appendix R. Number of inactivated influenza vaccine (standard dose) doses (primary y-axis), and number of observed anaphylaxis events (secondary y-axis), and corresponding relative risk (secondary y-axis) among members 6 months-64 years-old, by analysis number, August 1, 2017–April 30, 2018



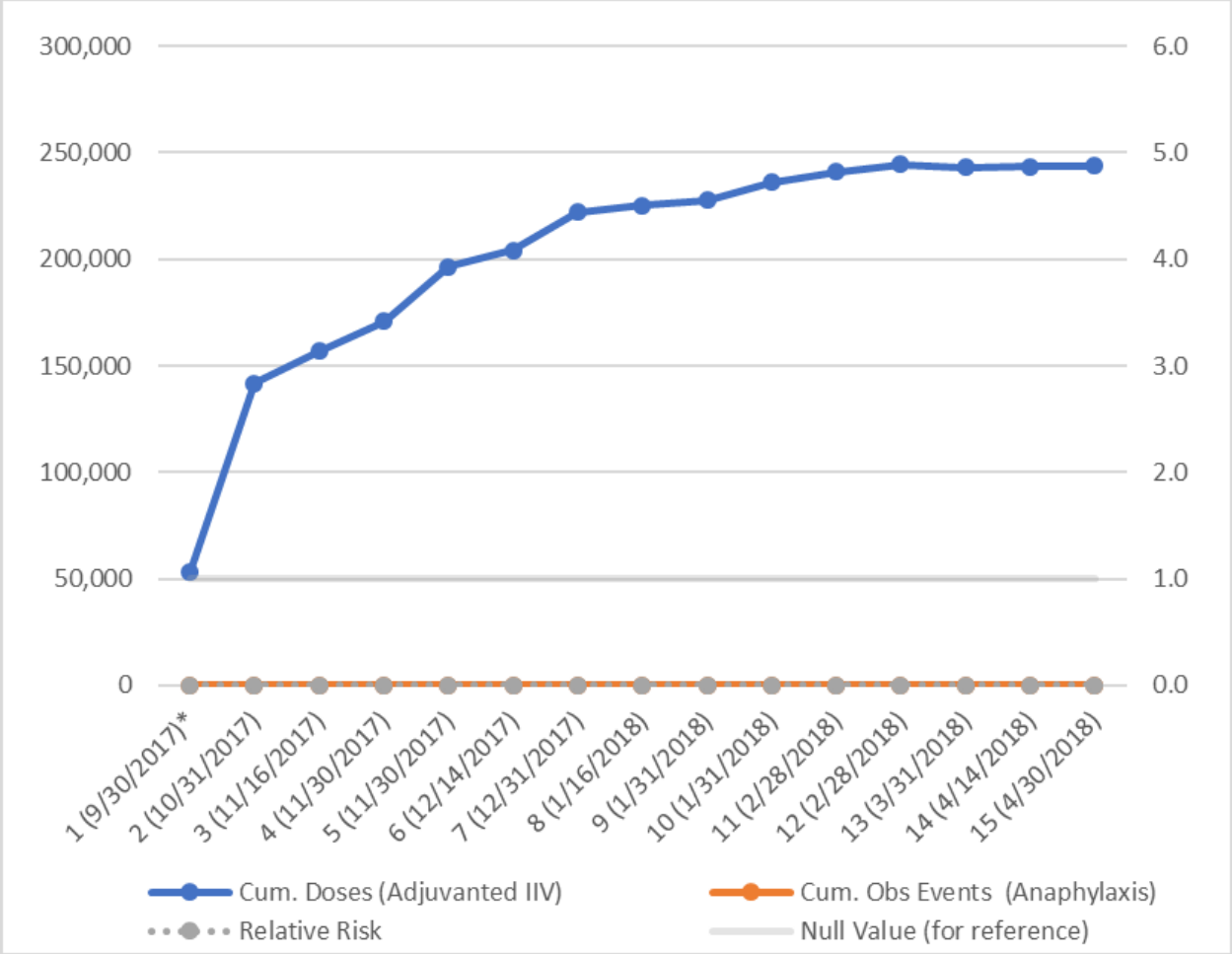
*Dates designate the most recent available data included in the analysis.

Appendix S. Number of inactivated influenza vaccine (standard dose) doses (primary y-axis), and number of observed anaphylaxis events (secondary y-axis), and corresponding relative risk (secondary y-axis) among members ≥65 years-old, by analysis number, August 1, 2017–April 30, 2018



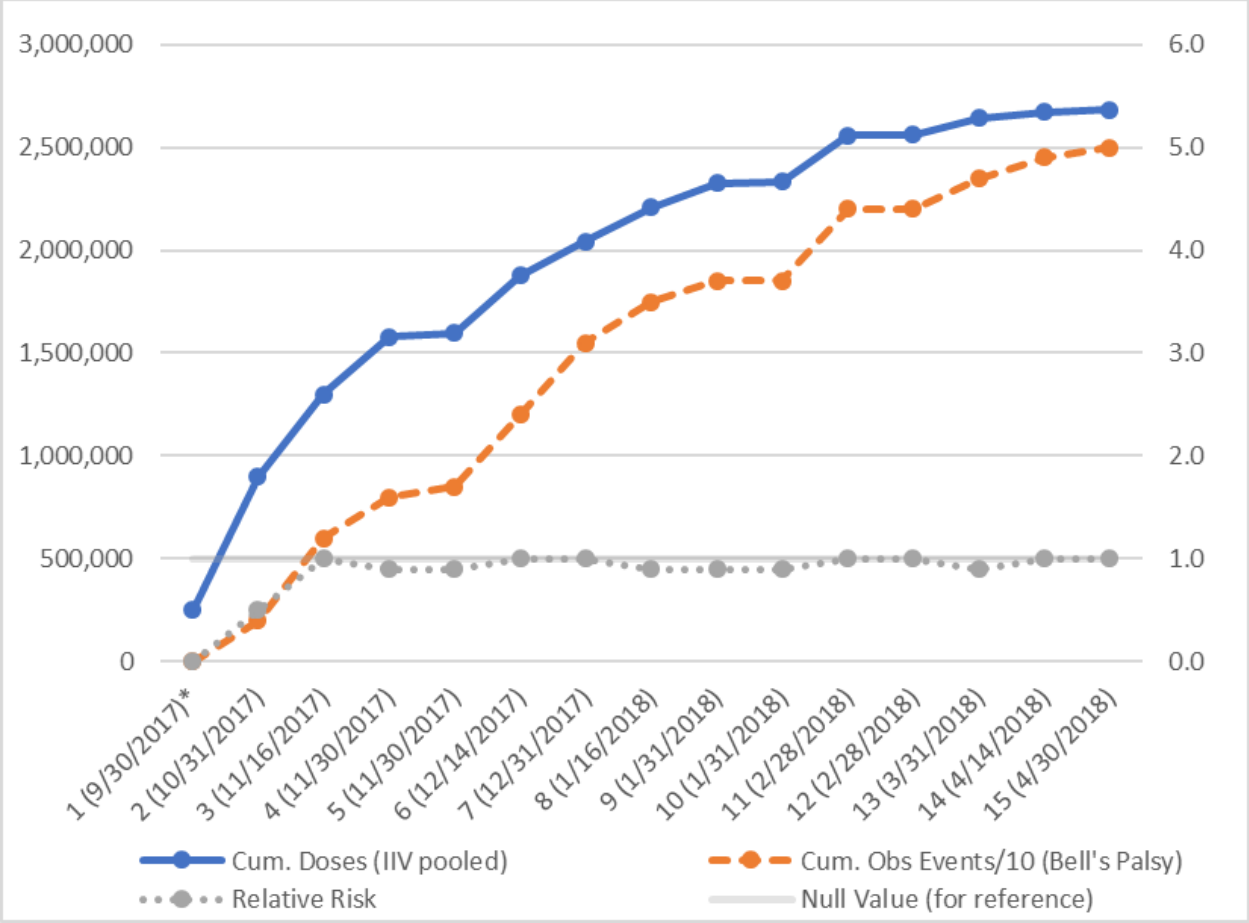
*Dates designate the most recent available data included in the analysis.

Appendix T. Number of inactivated influenza vaccine (adjuvanted) doses (primary y-axis), and number of observed anaphylaxis events (secondary y-axis), and corresponding relative risk (secondary y-axis) among members ≥65 years-old, by analysis number, August 1, 2017–April 30, 2018



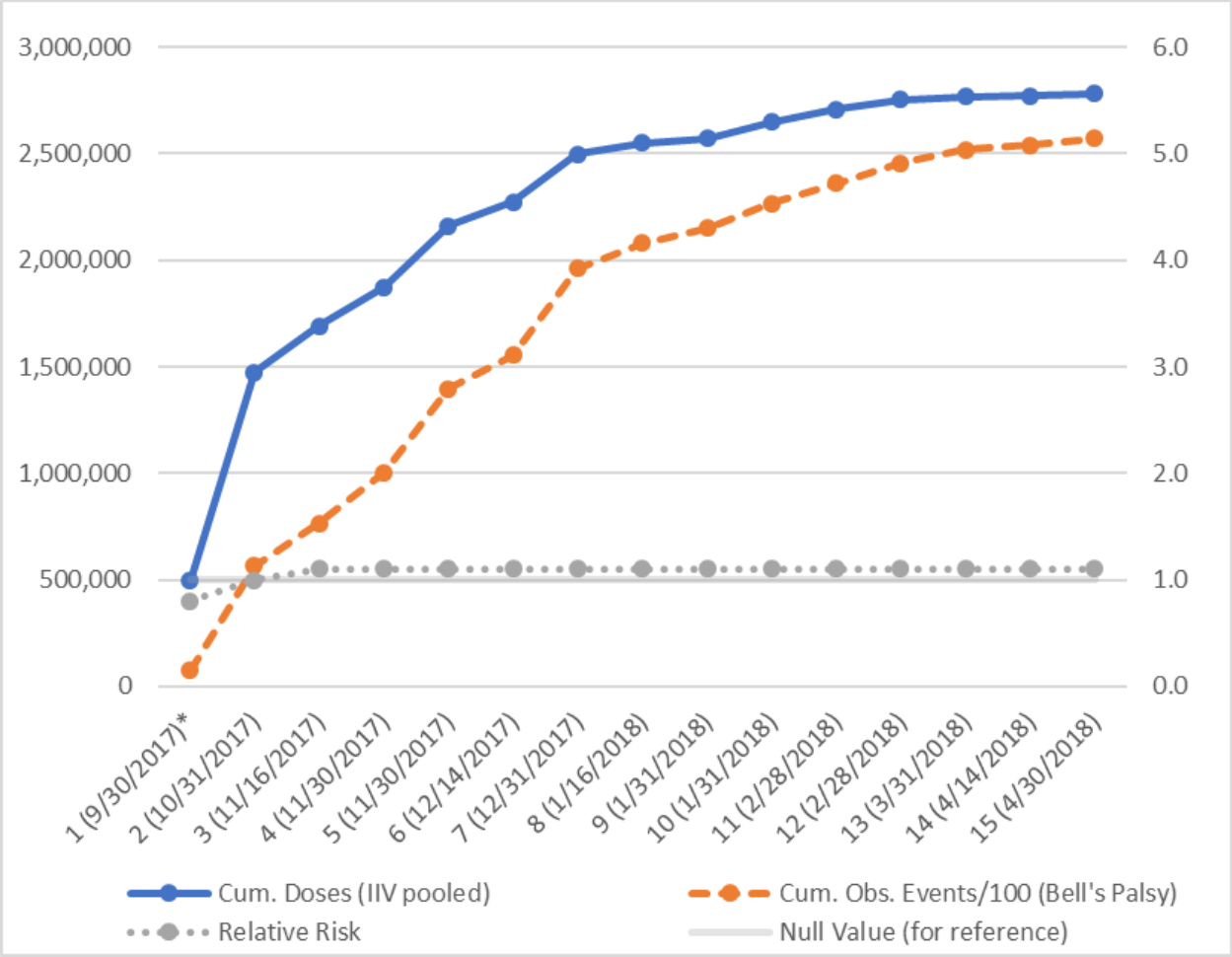
*Dates designate the most recent available data included in the analysis.

Appendix U. Number of inactivated influenza vaccine (pooled) doses (primary y-axis), and number of observed Bell's palsy events (secondary y-axis), and corresponding relative risk (secondary y-axis) among members 6 months-17 years-old, by analysis number, August 1, 2017–April 30, 2018



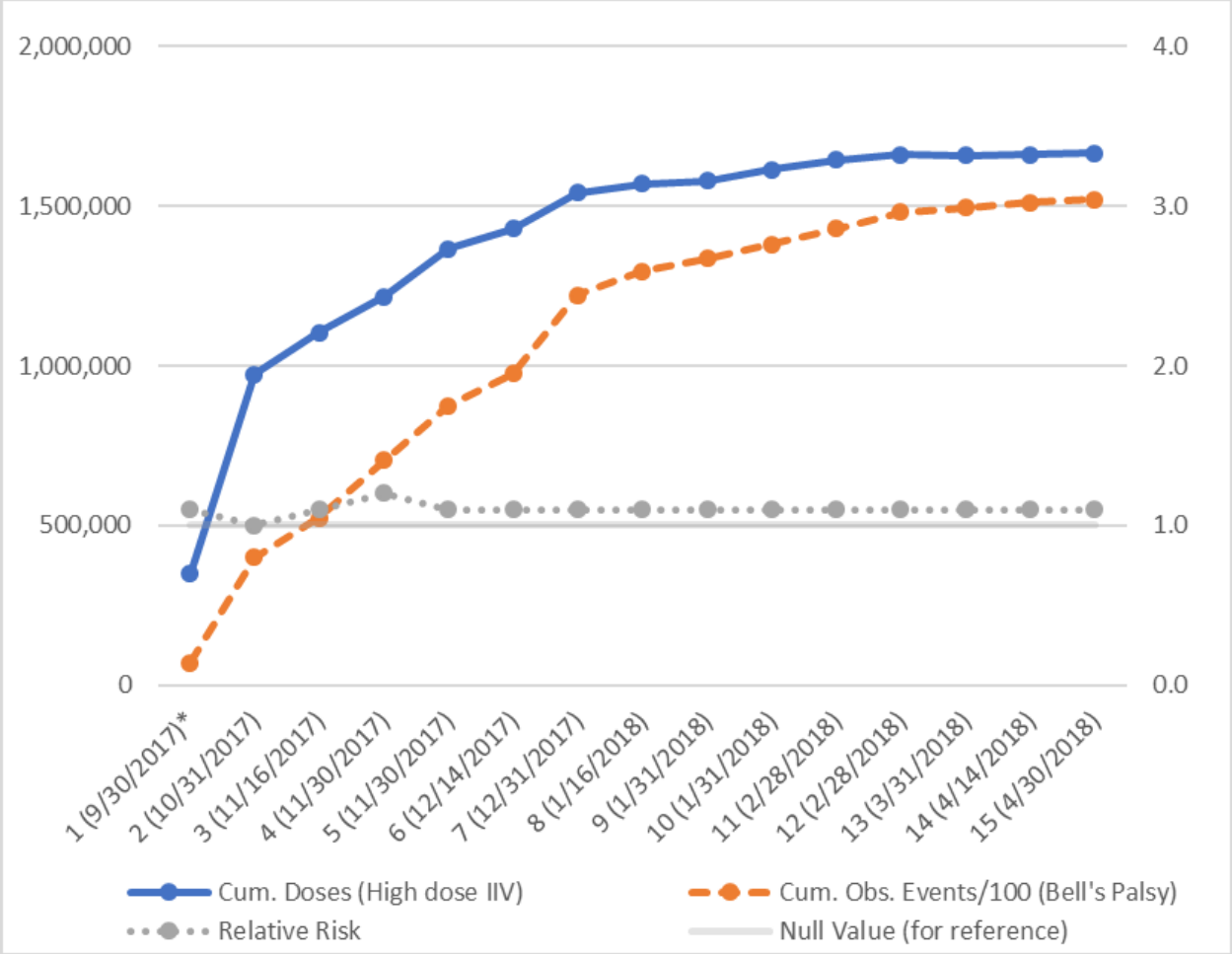
*Dates designate the most recent available data included in the analysis.

Appendix V. Number of inactivated influenza vaccine (pooled) doses (primary y-axis), and number of observed Bell's palsy events (secondary y-axis), and corresponding relative risk (secondary y-axis) among members ≥65 years-old, by analysis number, August 1, 2017–April 30, 2018



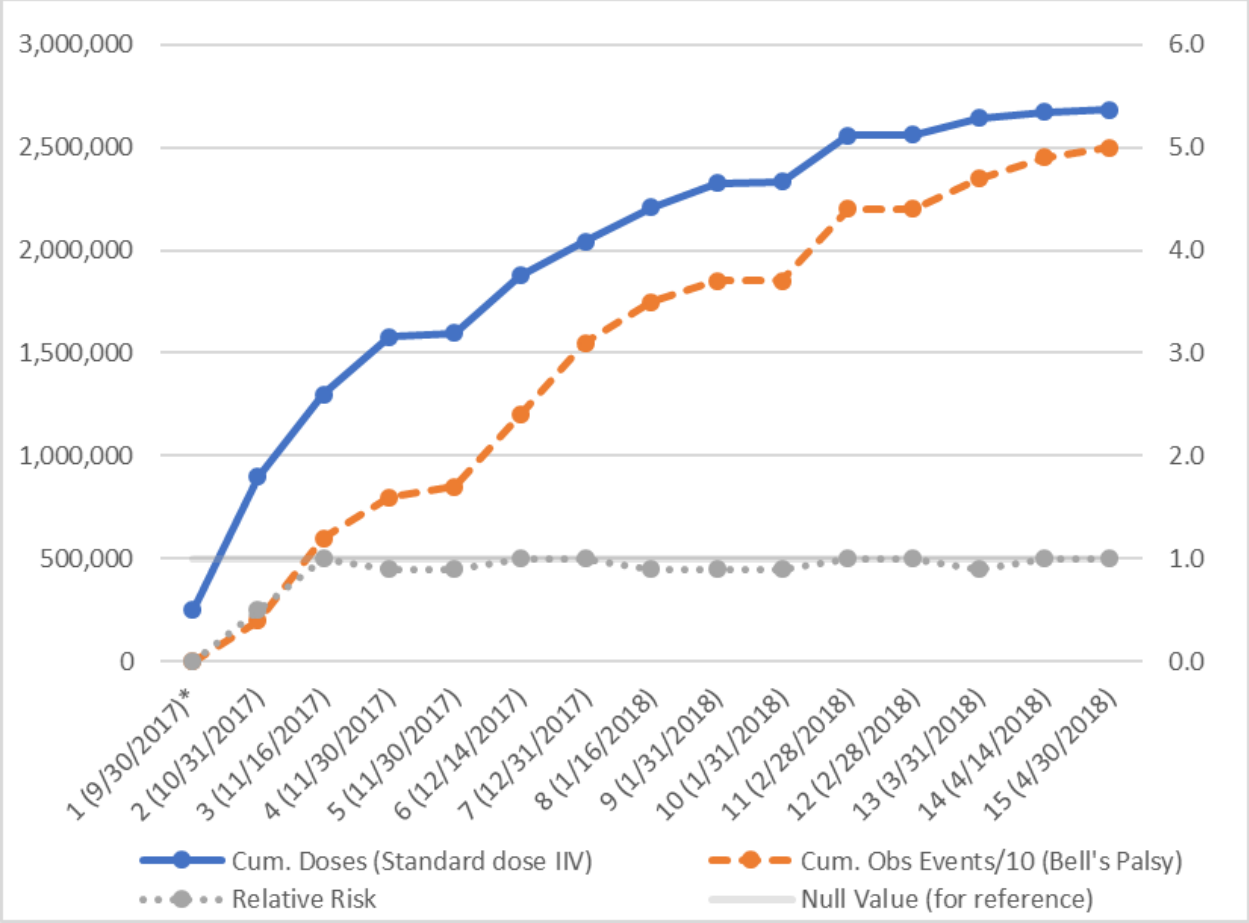
*Dates designate the most recent available data included in the analysis.

Appendix W. Number of inactivated influenza vaccine (high dose) doses (primary y-axis), and number of observed Bell's palsy events (secondary y-axis), and corresponding relative risk (secondary y-axis) among members ≥65 years-old, by analysis number, August 1, 2017–April 30, 2018



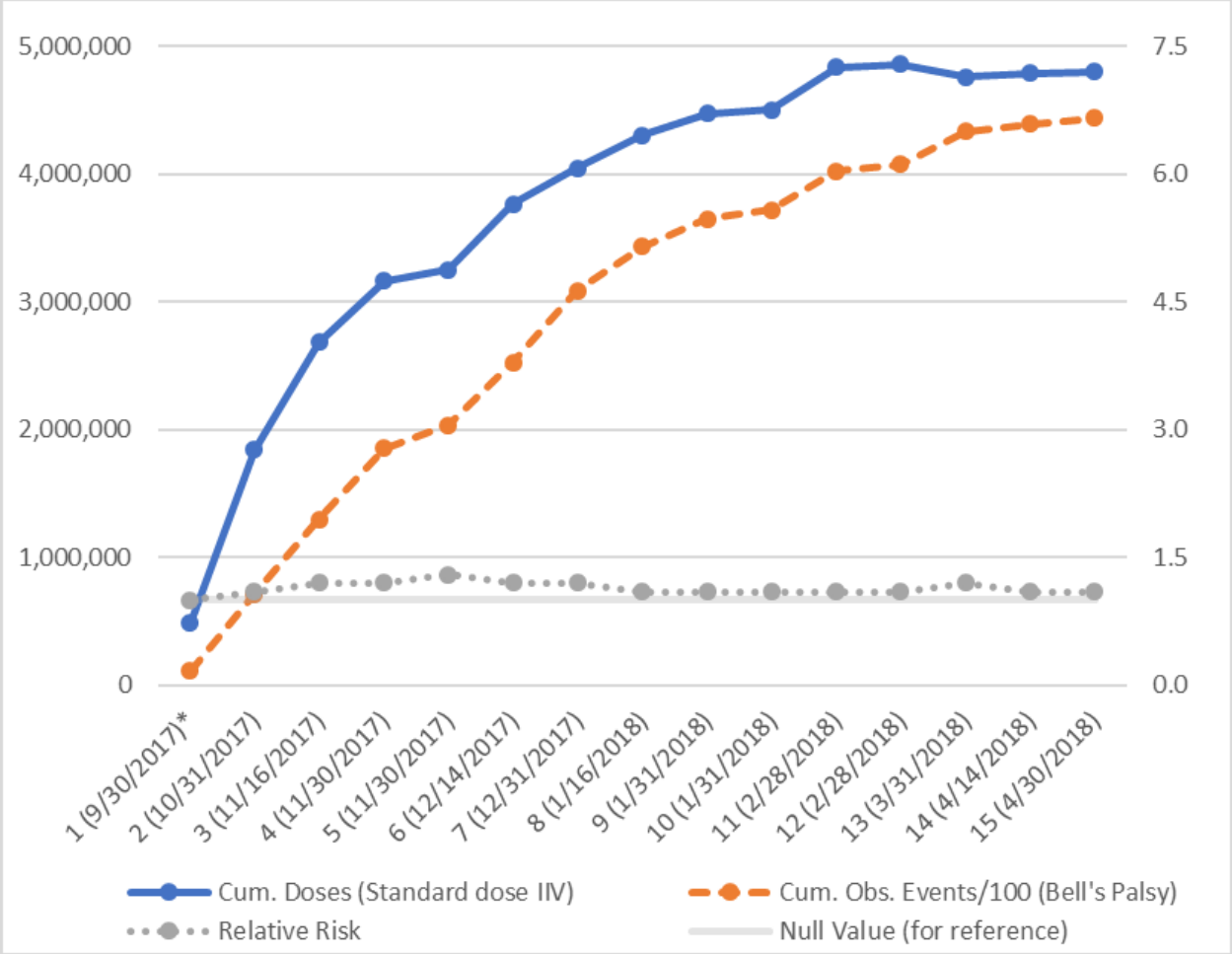
*Dates designate the most recent available data included in the analysis.

Appendix X. Number of inactivated influenza vaccine (standard dose) doses (primary y-axis), and number of observed Bell's palsy events (secondary y-axis), and corresponding relative risk (secondary y-axis) among members 6 months-17 years-old, by analysis number, August 1, 2017–April 30, 2018



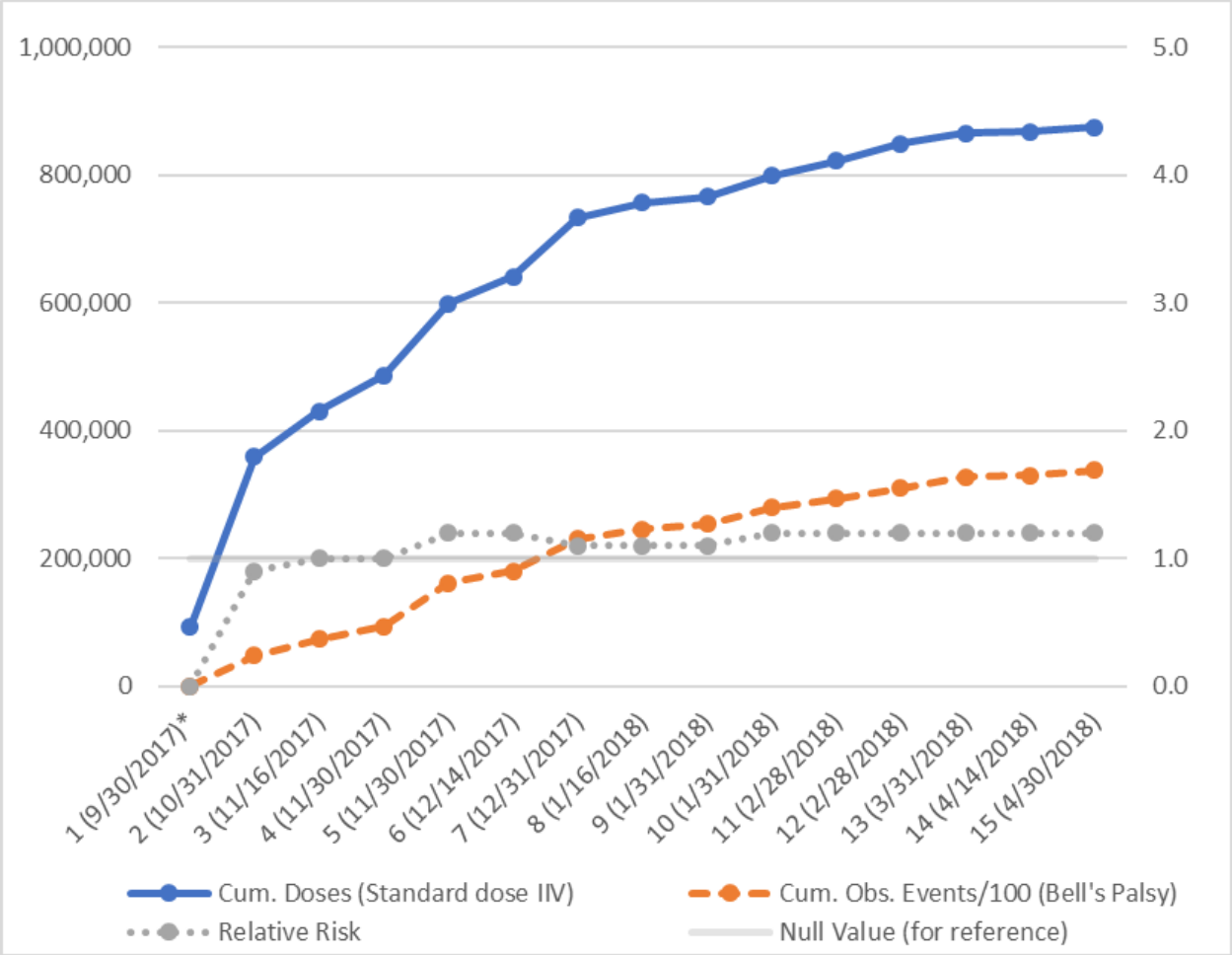
*Dates designate the most recent available data included in the analysis.

Appendix Y. Number of inactivated influenza vaccine (standard dose) doses (primary y-axis), and number of observed Bell's palsy events (secondary y-axis), and corresponding relative risk (secondary y-axis) among members 18-64 years-old, by analysis number, August 1, 2017–April 30, 2018



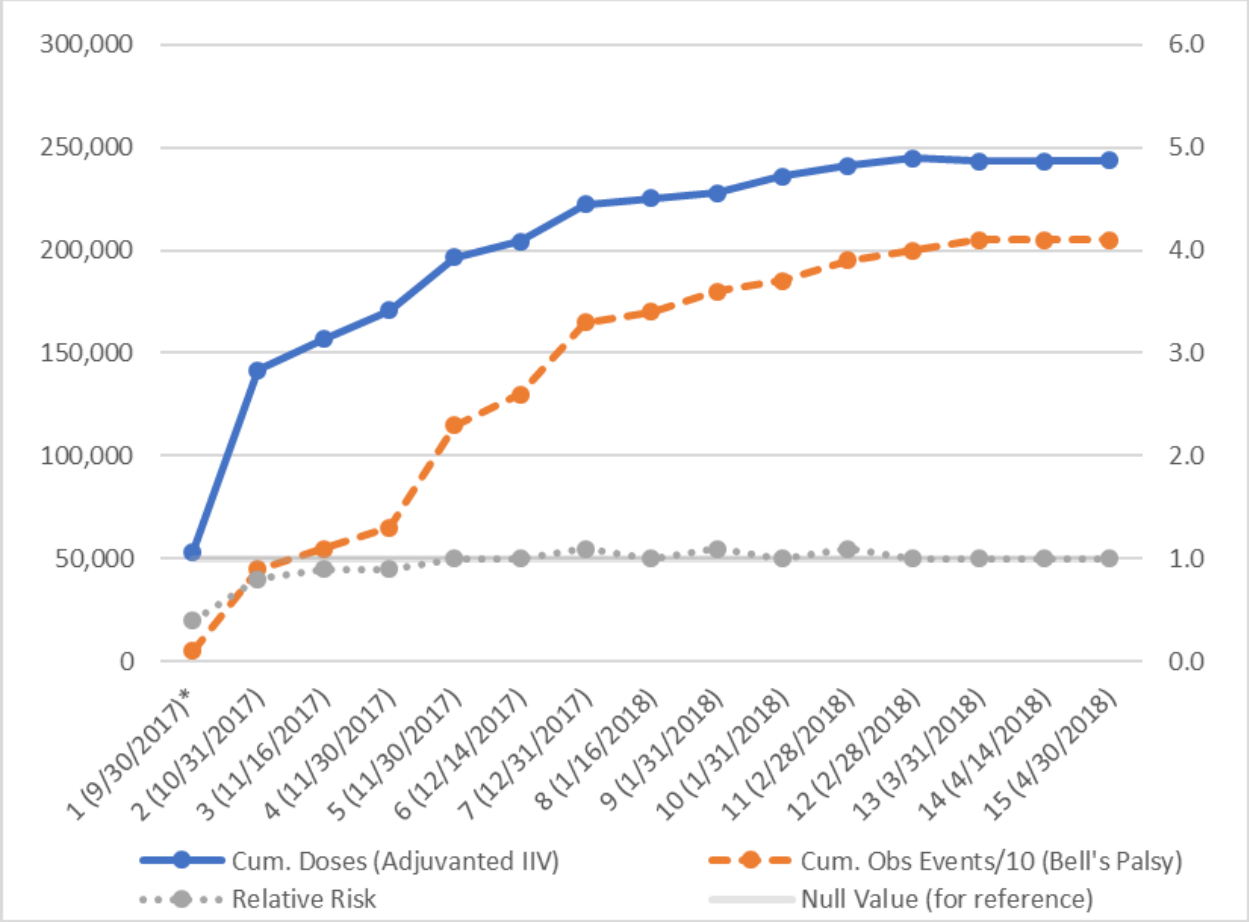
*Dates designate the most recent available data included in the analysis.

Appendix Z. Number of inactivated influenza vaccine (standard dose) doses (primary y-axis), and number of observed Bell's palsy events (secondary y-axis), and corresponding relative risk (secondary y-axis) among members ≥65 years-old, by analysis number, August 1, 2017–April 30, 2018



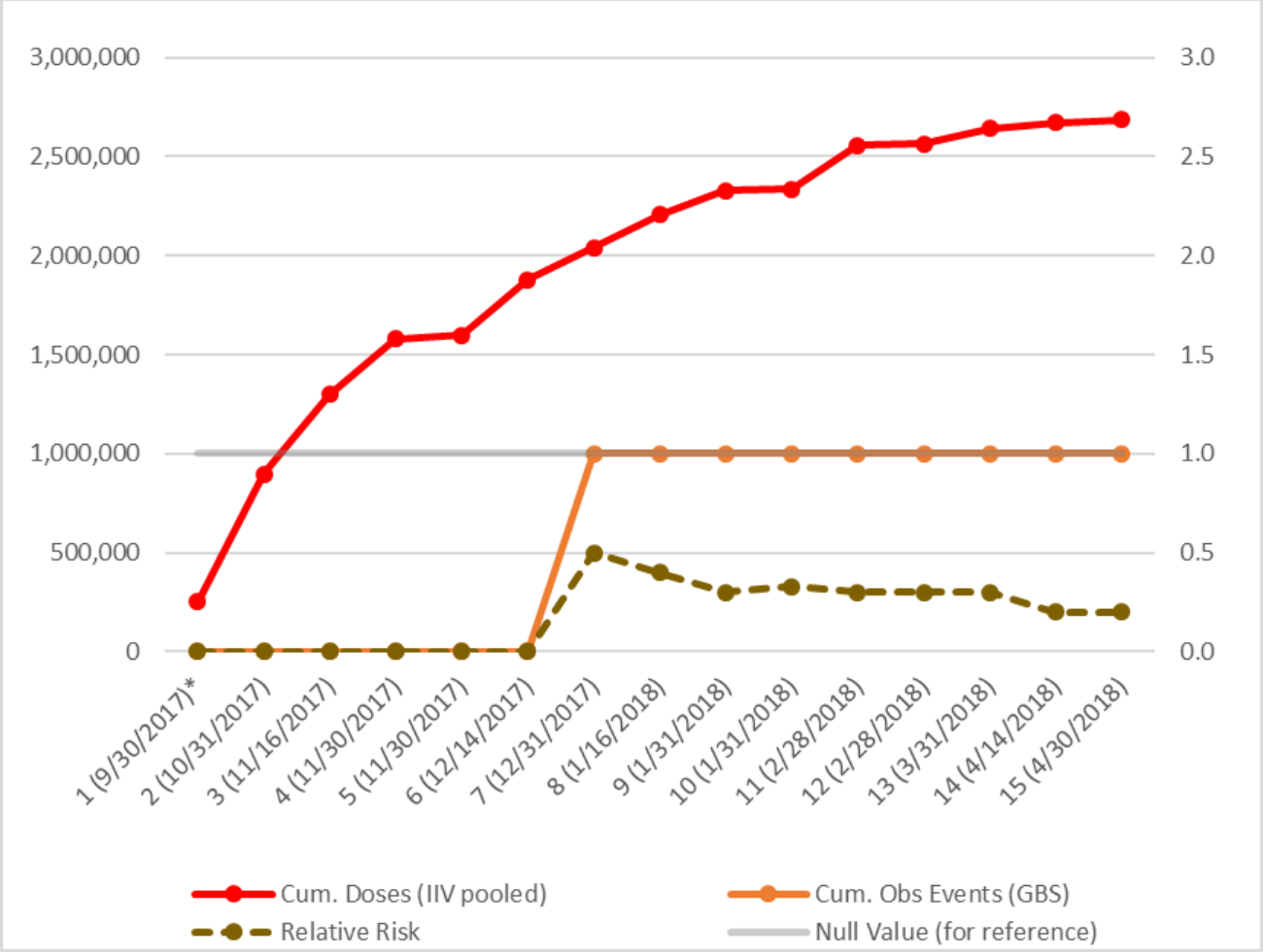
*Dates designate the most recent available data included in the analysis.

Appendix AA. Number of inactivated influenza vaccine (adjuvanted) doses (primary y-axis), and number of observed Bell's palsy events (secondary y-axis), and corresponding relative risk (secondary y-axis) among members ≥65 years-old, by analysis number, August 1, 2017–April 30, 2018



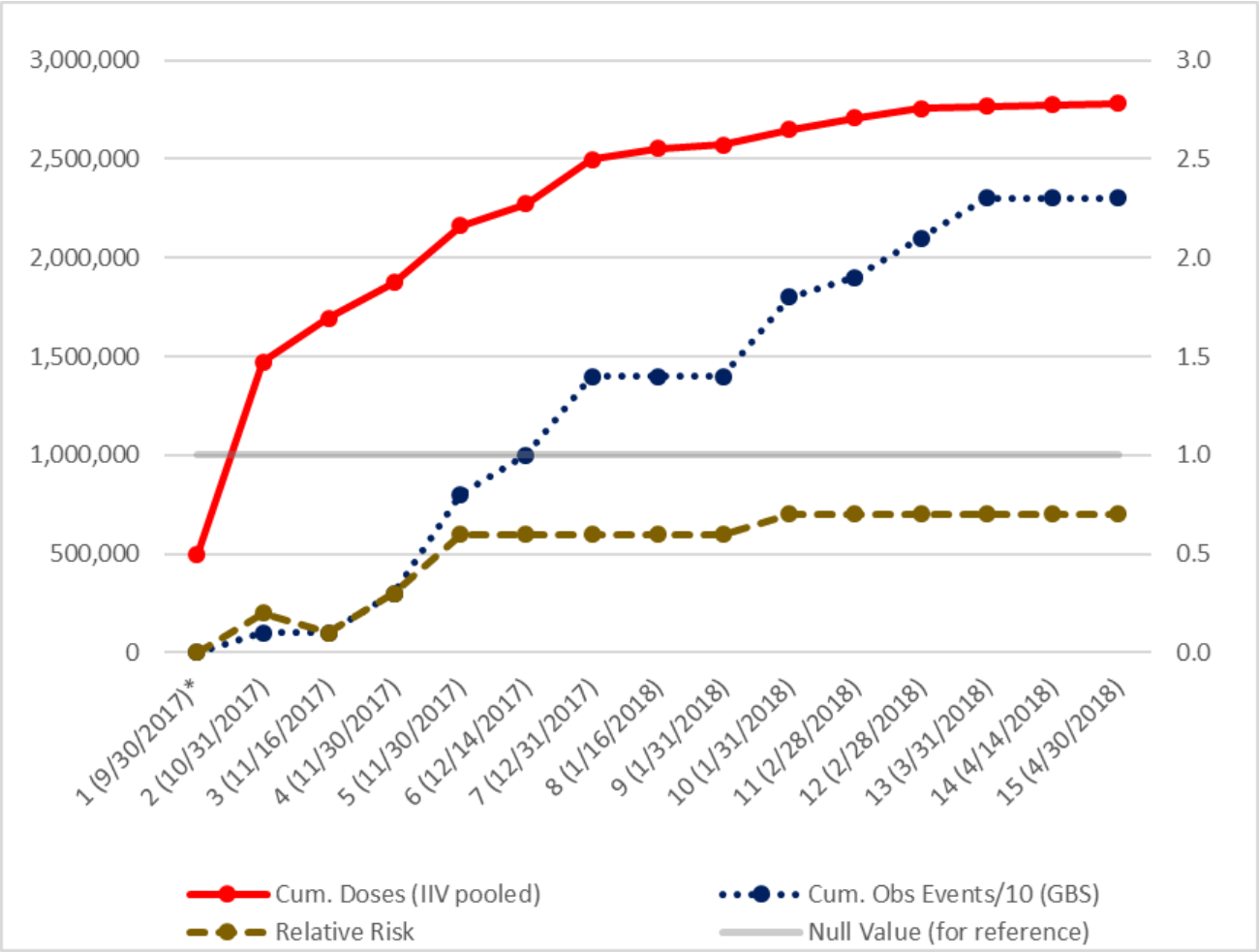
*Dates designate the most recent available data included in the analysis.

Appendix BB. Number of inactivated influenza vaccine (pooled) doses (primary y-axis), and number of observed GBS events (secondary y-axis), and corresponding relative risk (secondary y-axis) among members 6 months-17 years-old, by analysis number, August 1, 2017–April 30, 2018



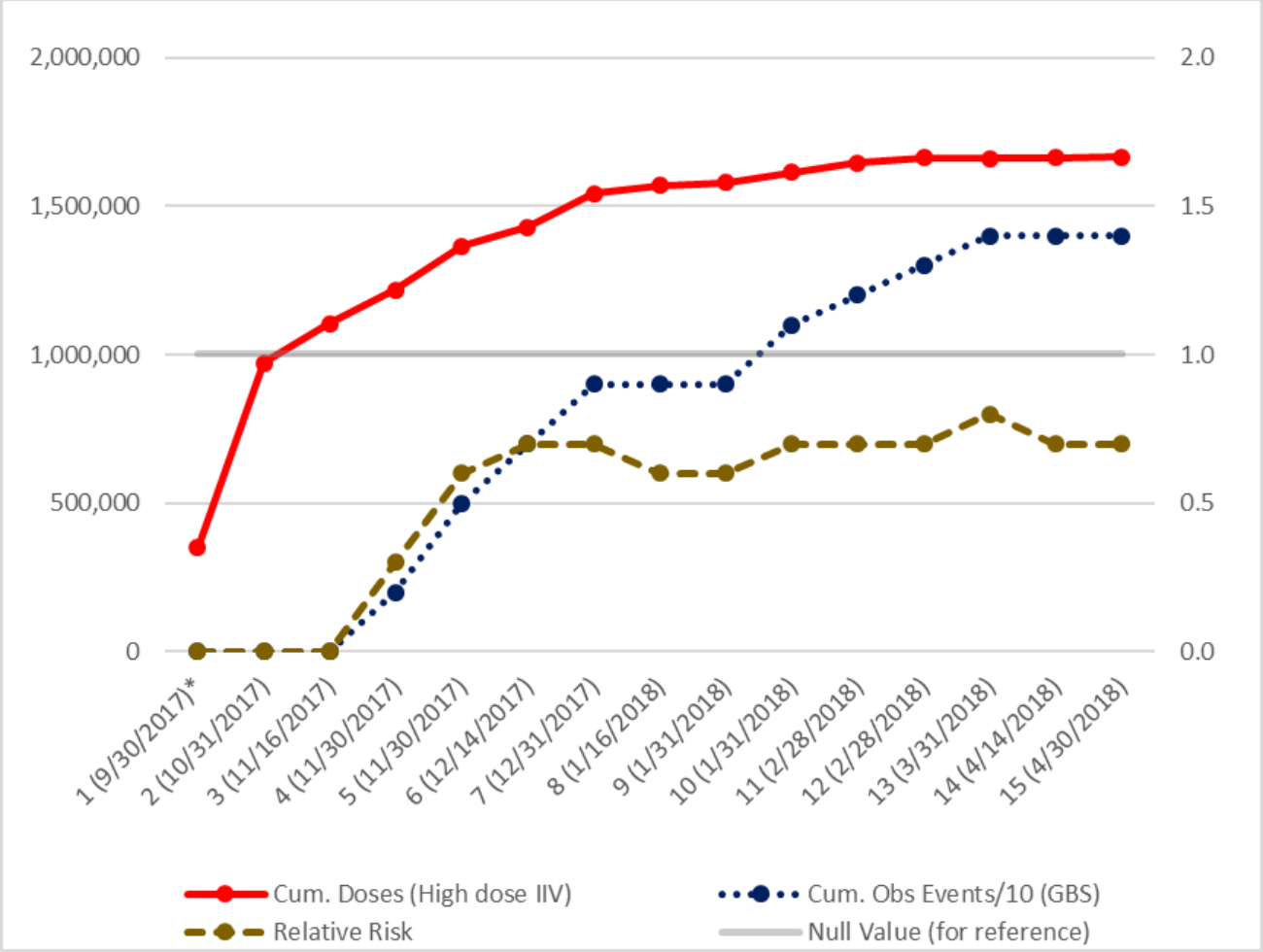
*Dates designate the most recent available data included in the analysis.

Appendix CC. Number of inactivated influenza vaccine (pooled) doses (primary y-axis), and number of observed GBS events (secondary y-axis), and corresponding relative risk (secondary y-axis) among members ≥65 years-old, by analysis number, August 1, 2017–April 30, 2018



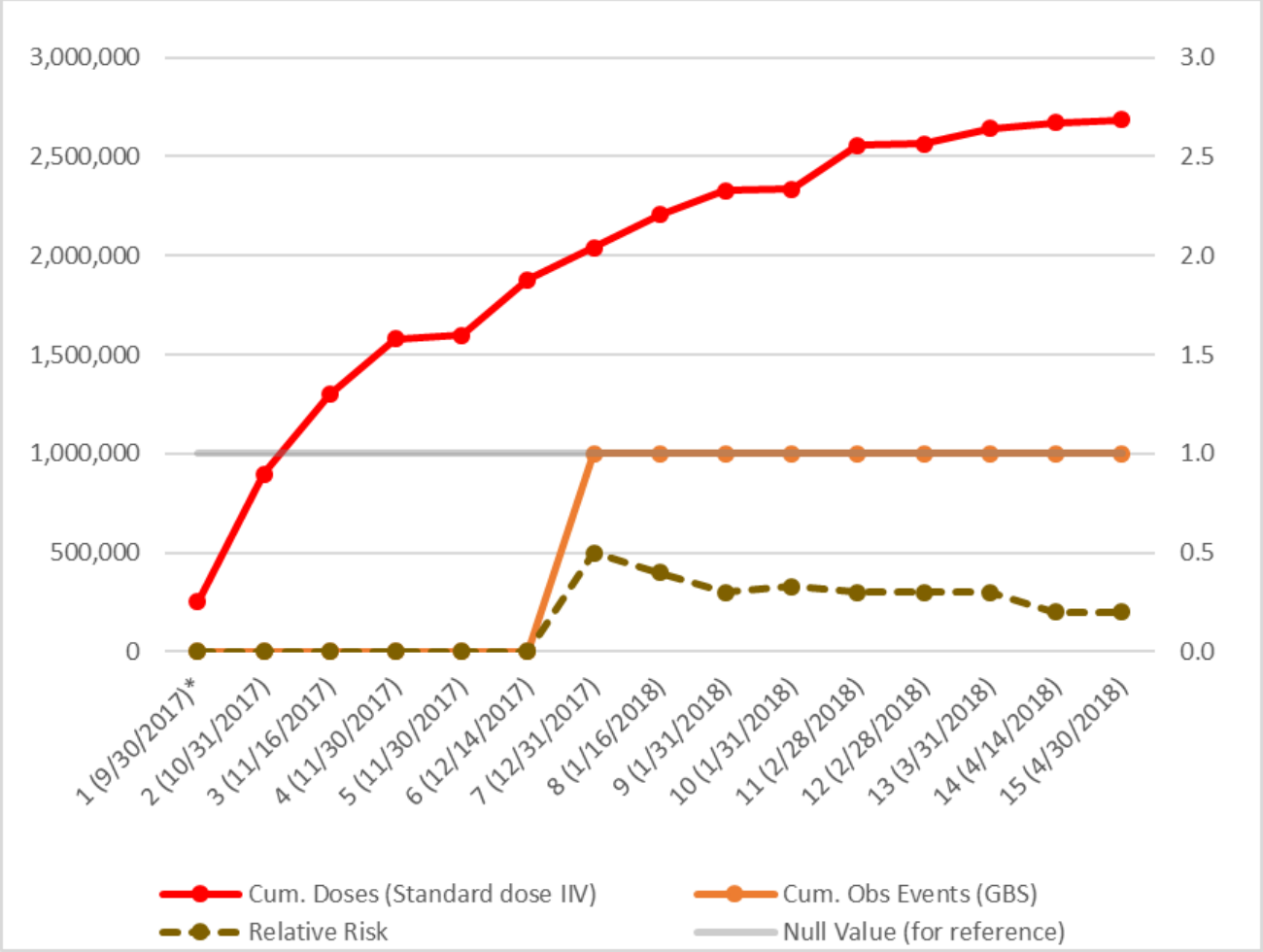
*Dates designate the most recent available data included in the analysis.

Appendix DD. Number of inactivated influenza vaccine (high dose) doses (primary y-axis), and number of observed GBS events (secondary y-axis), and corresponding relative risk (secondary y-axis) among members ≥65 years-old, by analysis number, August 1, 2017–April 30, 2018



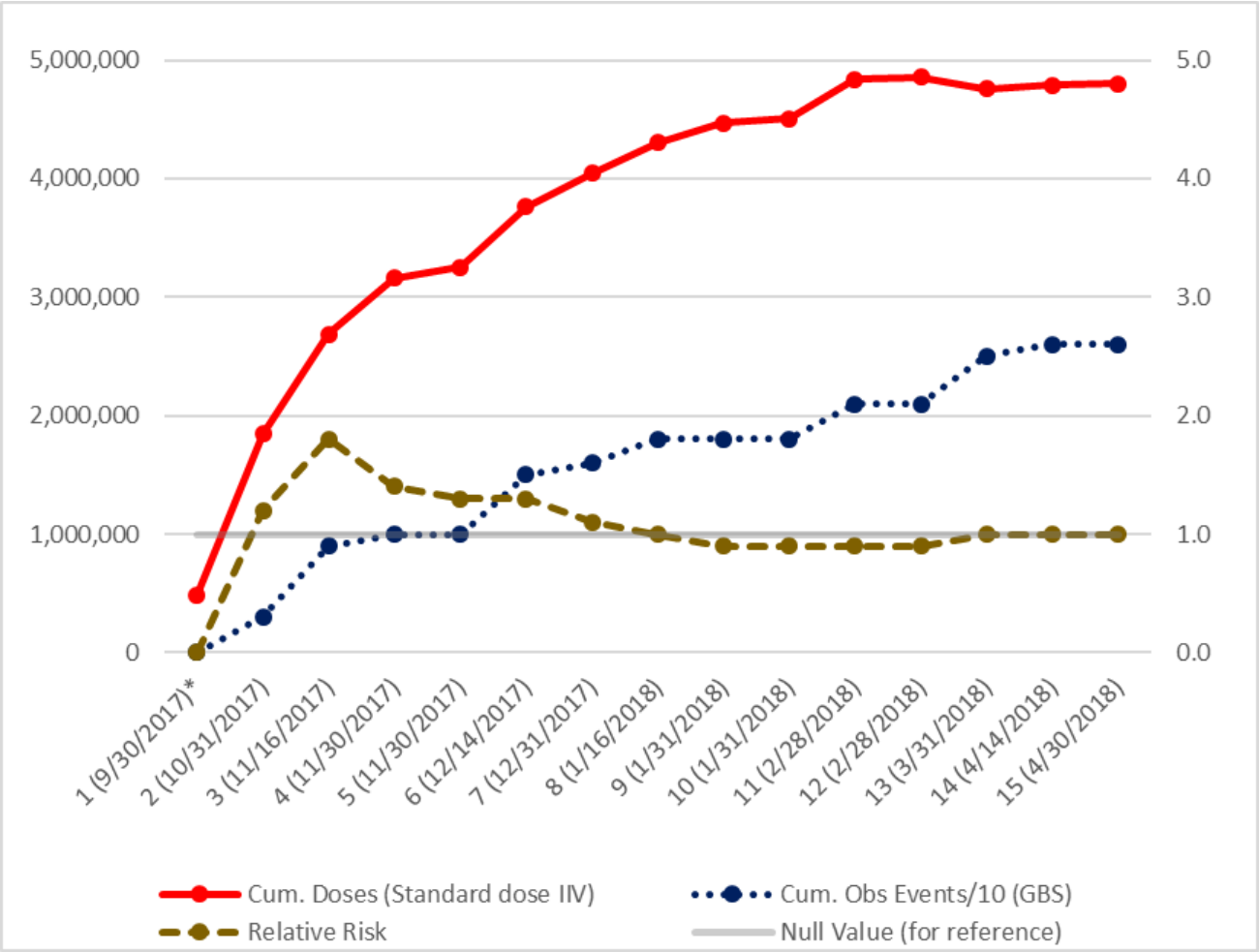
*Dates designate the most recent available data included in the analysis.

Appendix EE. Number of inactivated influenza vaccine (standard dose) doses (primary y-axis), and number of observed GBS events (secondary y-axis), and corresponding relative risk (secondary y-axis) among members 6 months-17 years-old, by analysis number, August 1, 2017–April 30, 2018



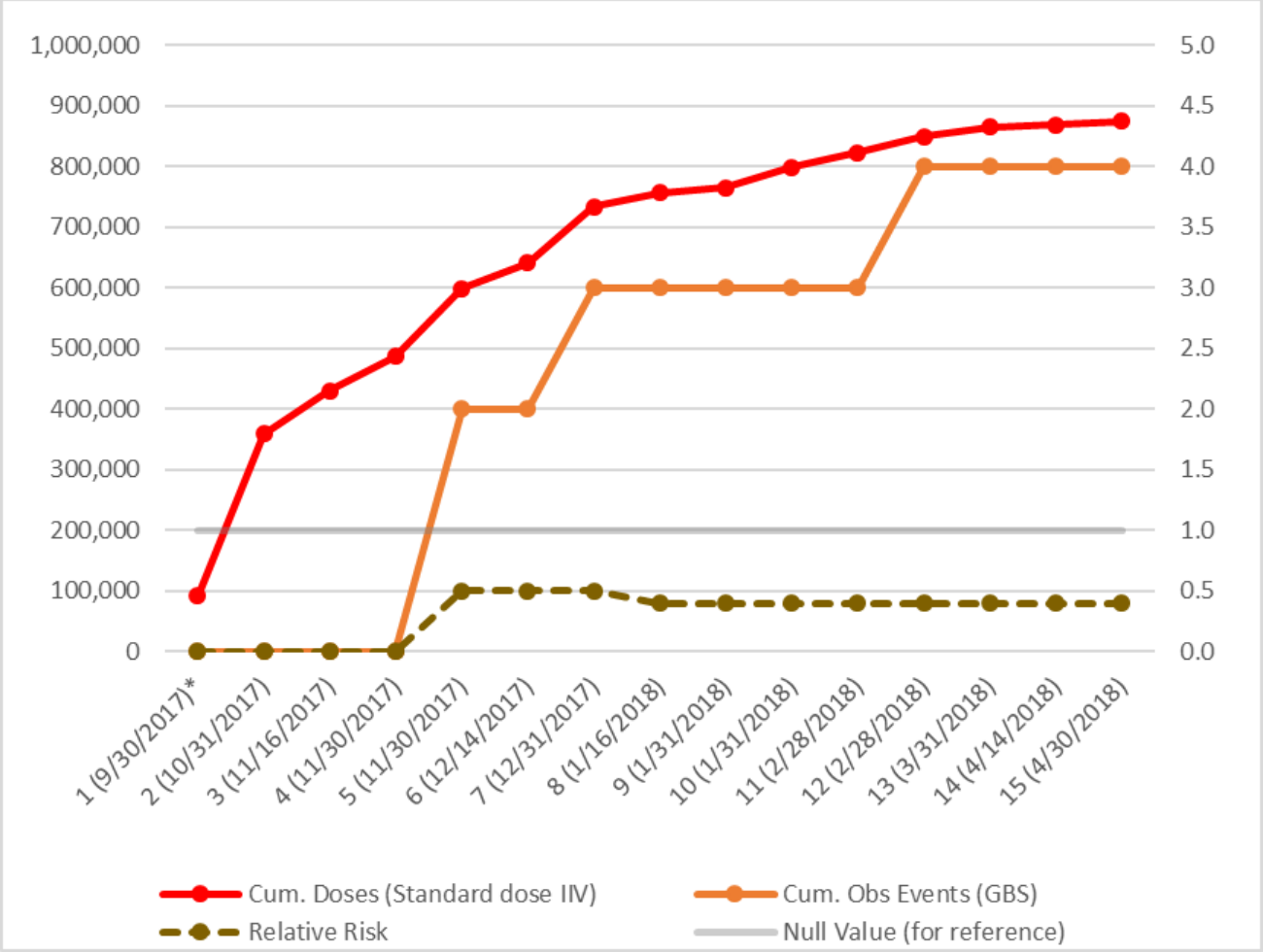
*Dates designate the most recent available data included in the analysis.

Appendix FF. Number of inactivated influenza vaccine (standard dose) doses (primary y-axis), and number of observed GBS events (secondary y-axis), and corresponding relative risk (secondary y-axis) among members 18-64 years-old, by analysis number, August 1, 2017–April 30, 2018



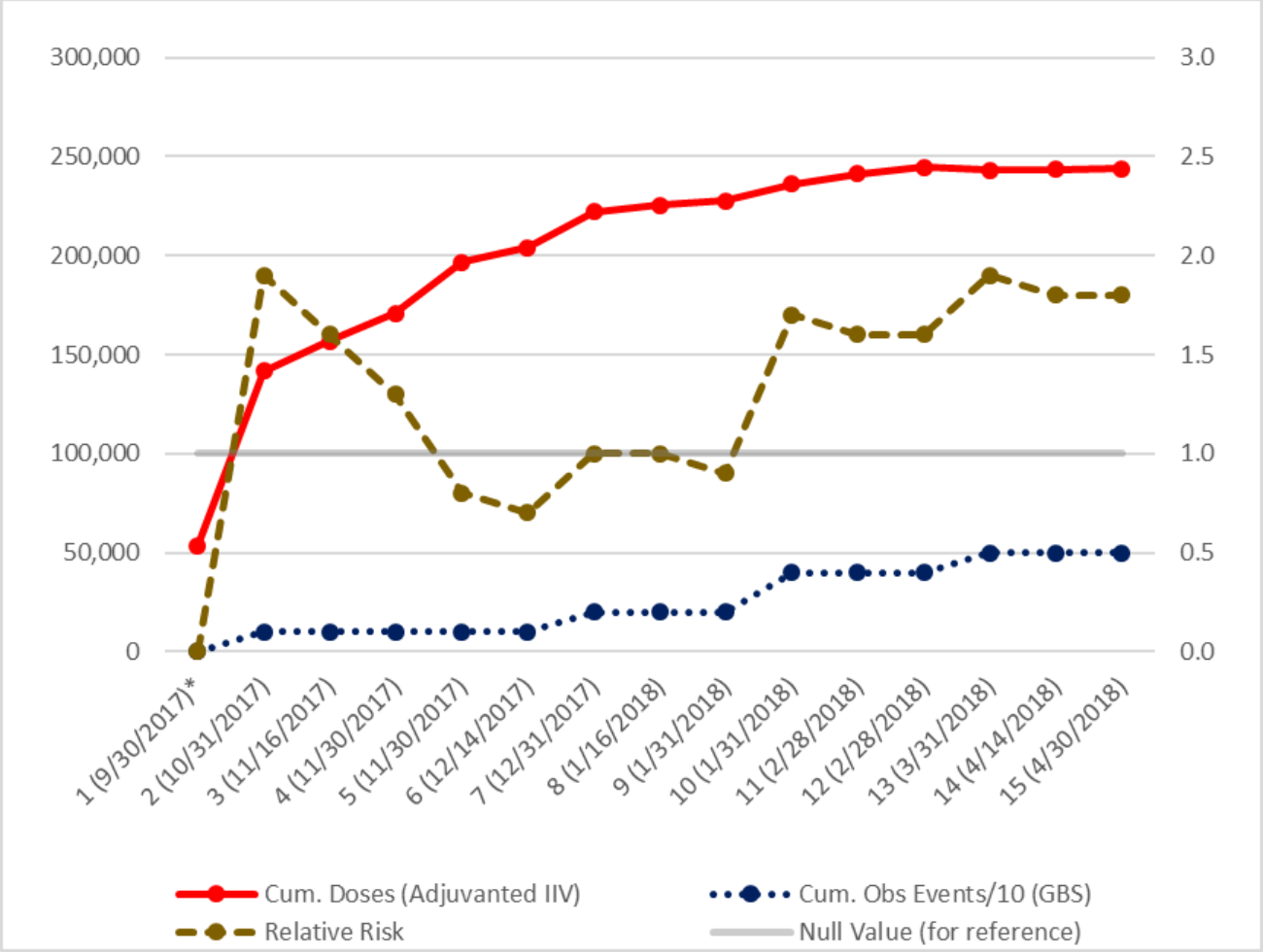
*Dates designate the most recent available data included in the analysis.

Appendix GG. Number of inactivated influenza vaccine (standard dose) doses (primary y-axis), and number of observed GBS events (secondary y-axis), and corresponding relative risk (secondary y-axis) among members ≥65 years-old, by analysis number, August 1, 2017–April 30, 2018



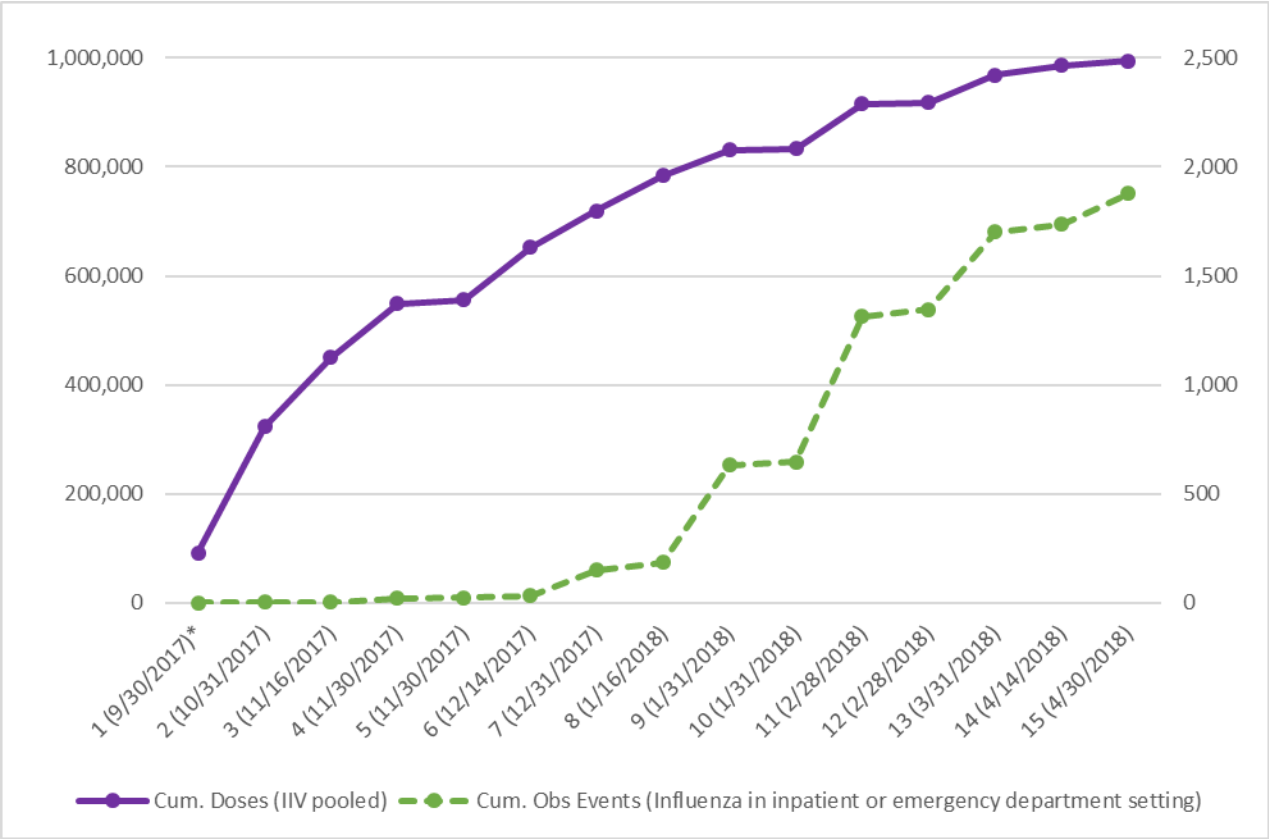
*Dates designate the most recent available data included in the analysis.

Appendix HH. Number of inactivated influenza vaccine (adjuvanted) doses (primary y-axis), and number of observed GBS events (secondary y-axis), and corresponding relative risk (secondary y-axis) among members ≥65 years-old, by analysis number, August 1, 2017–April 30, 2018



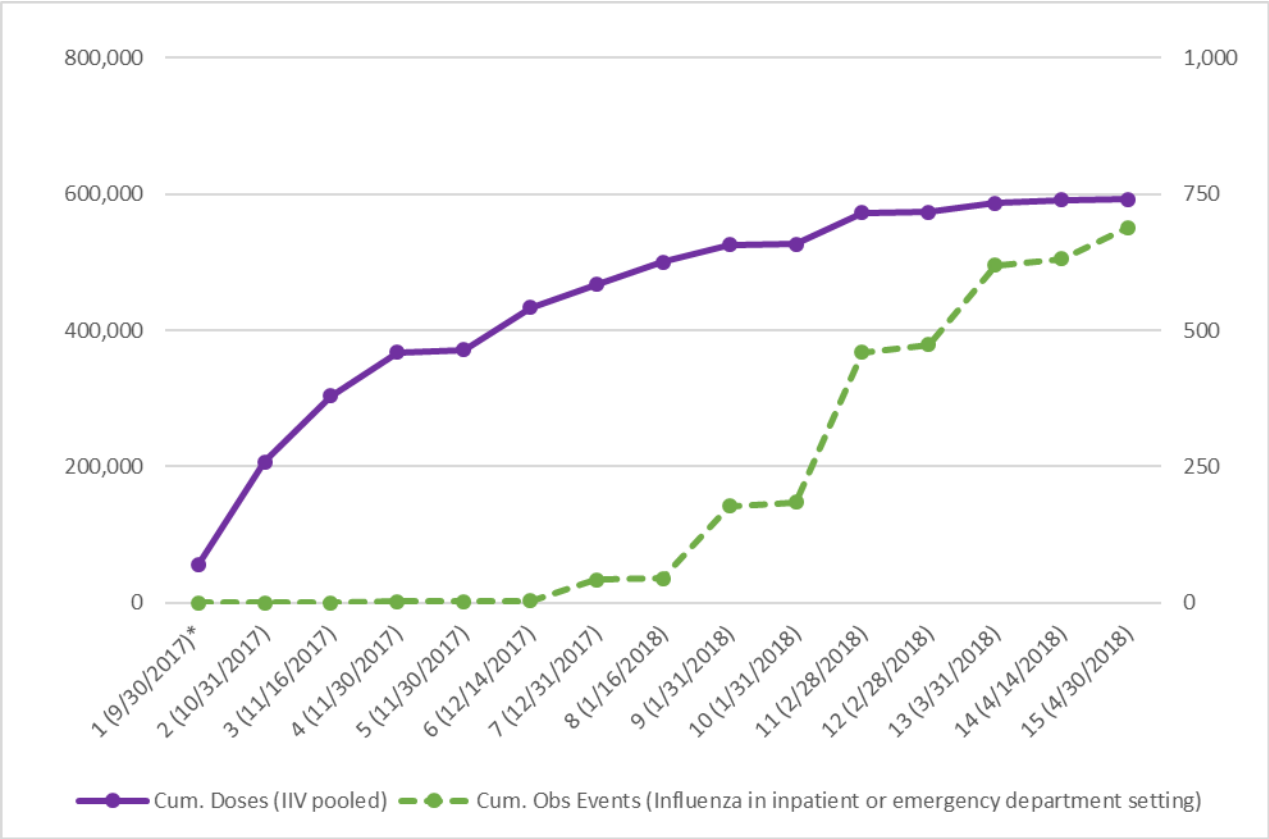
*Dates designate the most recent available data included in the analysis.

Appendix II. Number of inactivated influenza vaccine (pooled) doses (primary y-axis), and number of observed influenza events in the inpatient or emergency department settings (secondary y-axis), among members 6 months-4 years-old, by analysis number, August 1, 2017–April 30, 2018



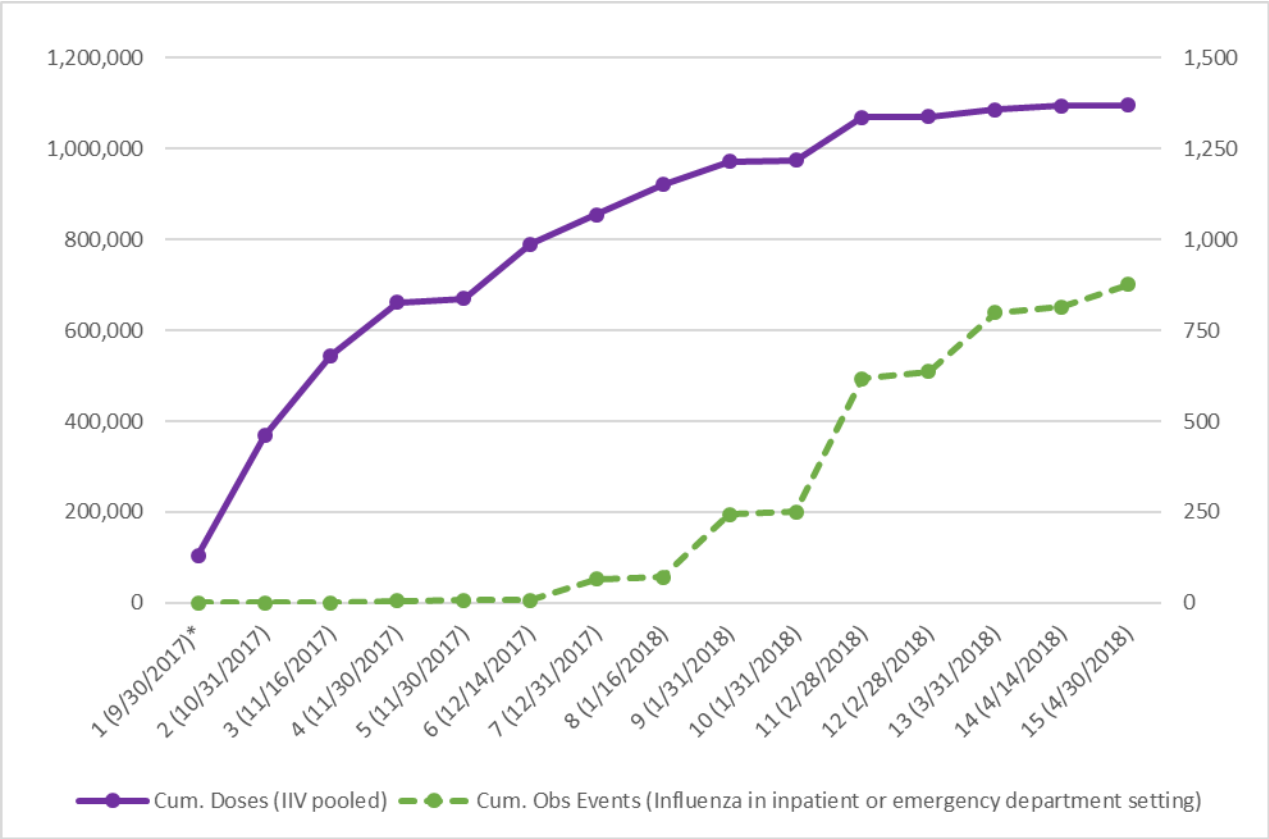
*Dates designate the most recent available data included in the analysis.

Appendix JJ. Number of inactivated influenza vaccine (pooled) doses (primary y-axis), and number of observed influenza events in the inpatient or emergency department settings (secondary y-axis), among members 5-8 years-old, by analysis number, August 1, 2017–April 30, 2018



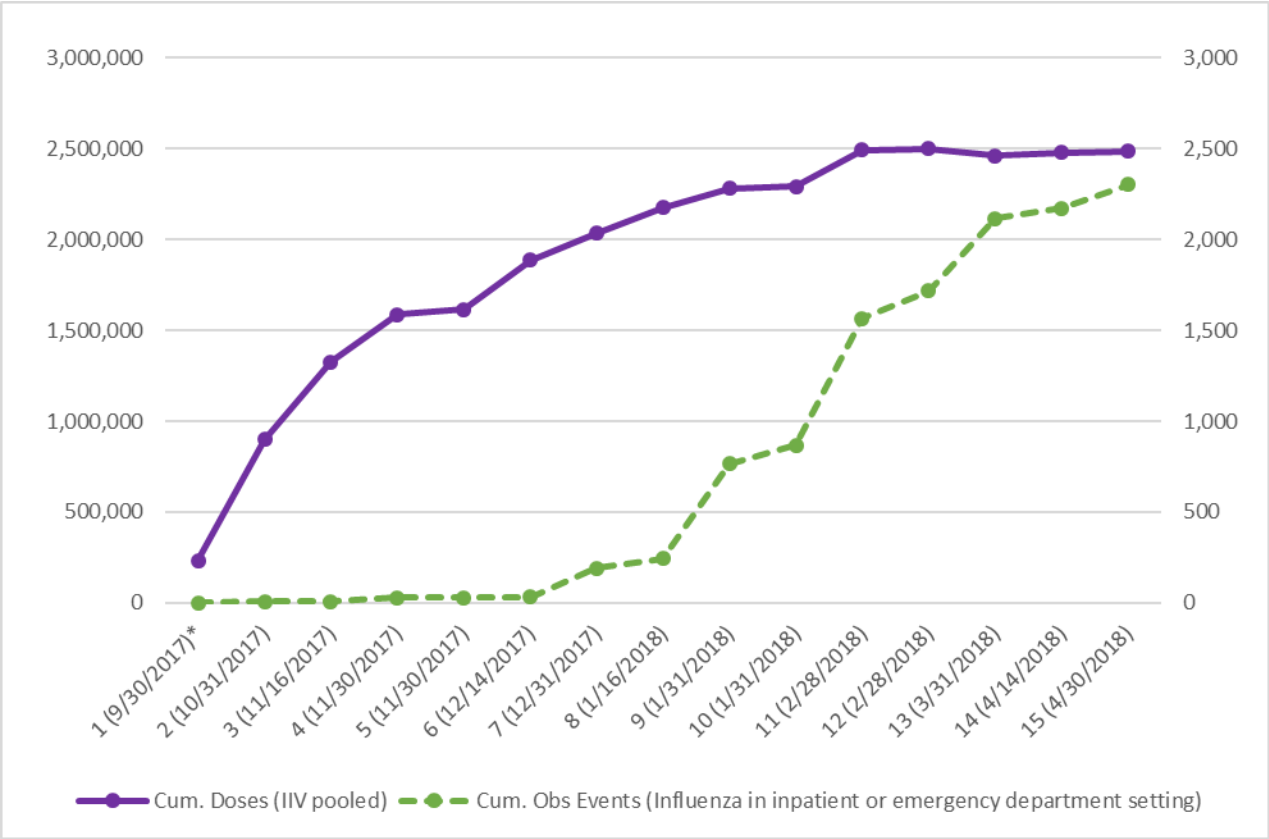
*Dates designate the most recent available data included in the analysis.

Appendix KK. Number of inactivated influenza vaccine (pooled) doses (primary y-axis), and number of observed influenza events in the inpatient or emergency department settings (secondary y-axis), among members 9-17 years-old, by analysis number, August 1, 2017–April 30, 2018



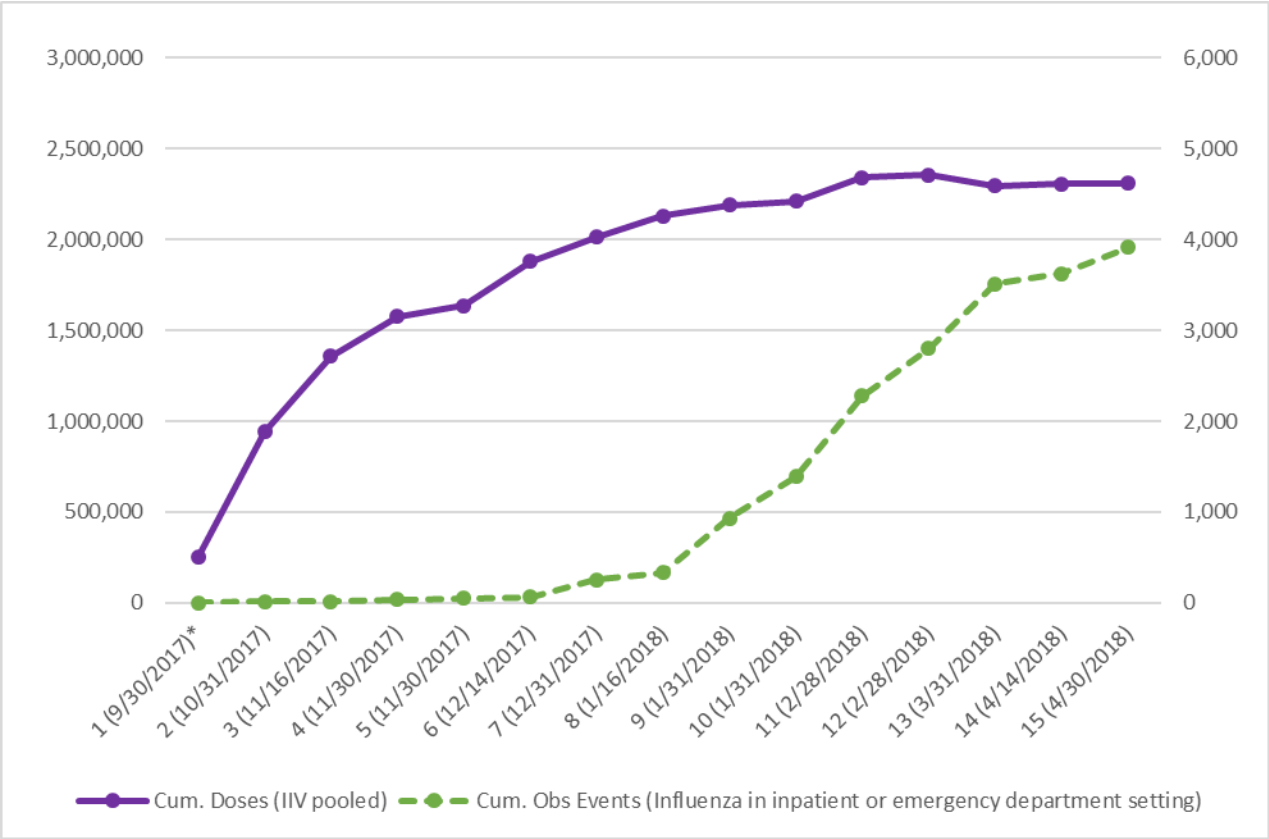
*Dates designate the most recent available data included in the analysis.

Appendix LL. Number of inactivated influenza vaccine (pooled) doses (primary y-axis), and number of observed influenza events in the inpatient or emergency department settings (secondary y-axis), among members 18-49 years-old, by analysis number, August 1, 2017–April 30, 2018



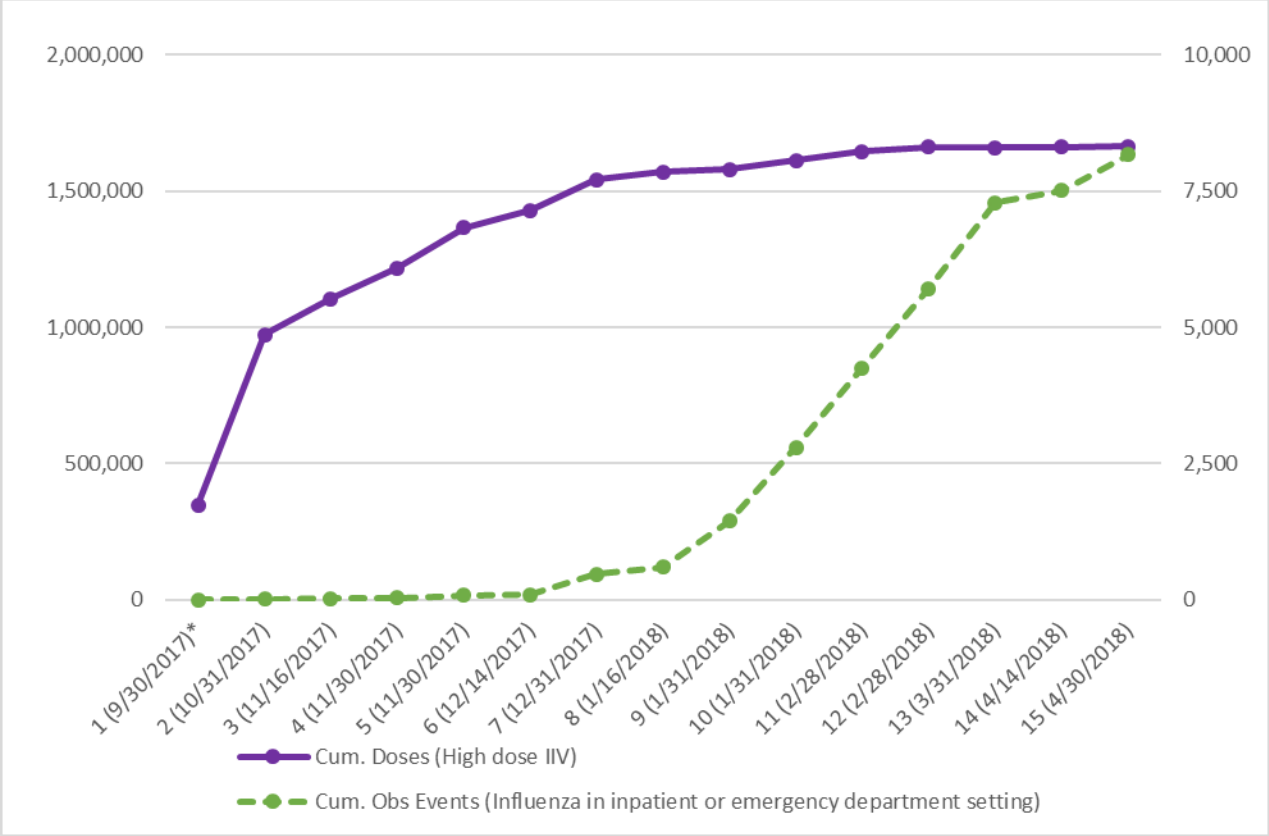
*Dates designate the most recent available data included in the analysis.

Appendix MM. Number of inactivated influenza vaccine (pooled) doses (primary y-axis), and number of observed influenza events in the inpatient or emergency department settings (secondary y-axis), among members 50-64 years-old, by analysis number, August 1, 2017–April 30, 2018



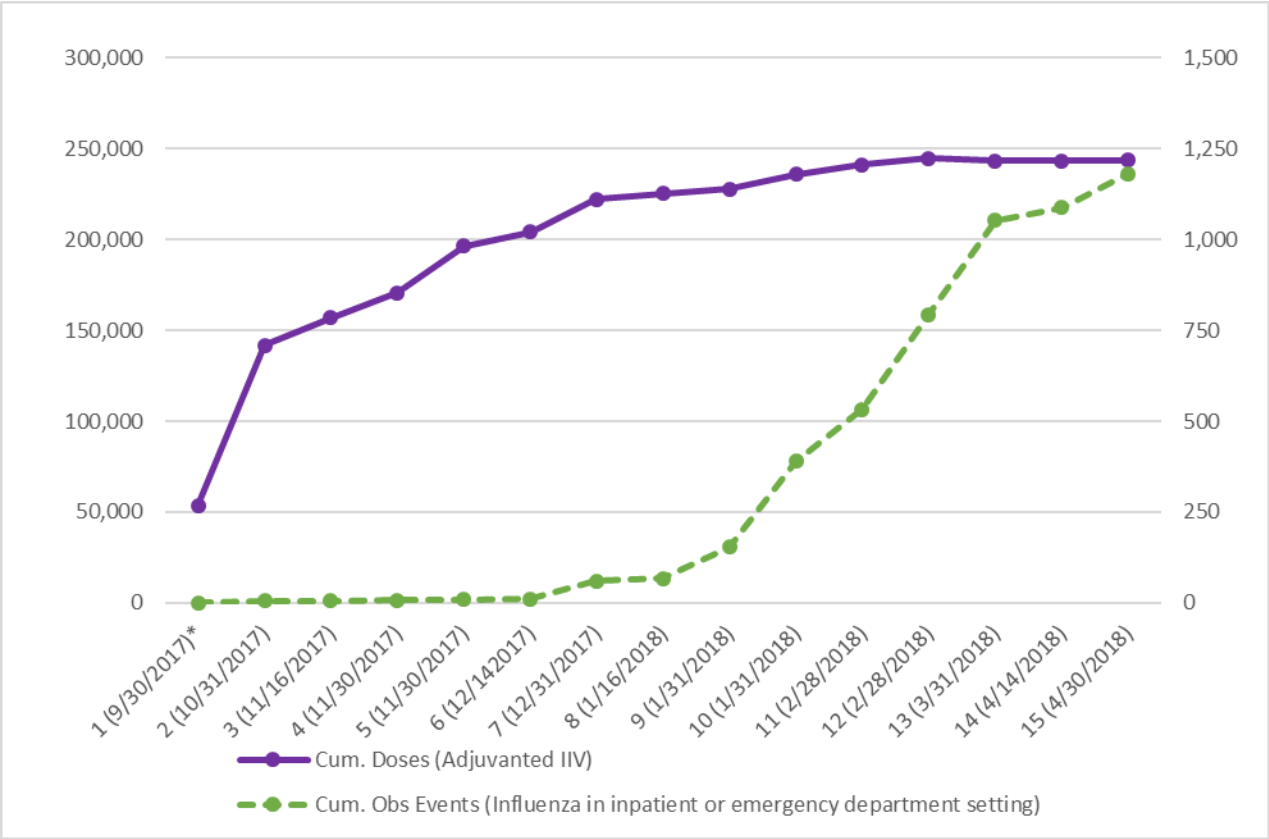
*Dates designate the most recent available data included in the analysis.

Appendix NN. Number of inactivated influenza vaccine (high dose) doses (primary y-axis), and number of observed influenza events in the inpatient or emergency department settings (secondary y-axis), among members ≥65 years-old, by analysis number, August 1, 2017–April 30, 2018



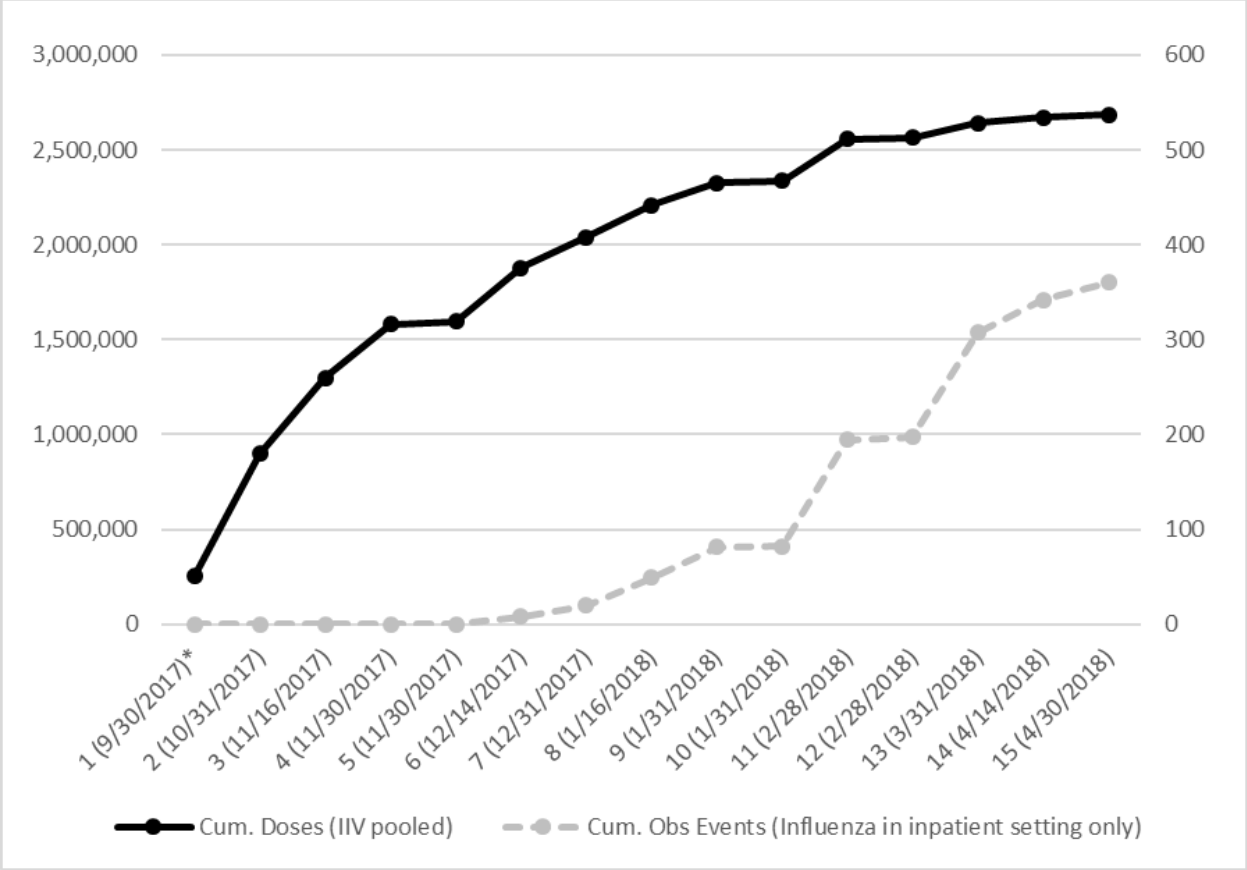
*Dates designate the most recent available data included in the analysis.

Appendix OO. Number of inactivated influenza vaccine (adjuvanted) doses (primary y-axis), and number of observed influenza events in the inpatient or emergency department settings (secondary y-axis), among members ≥65 years-old, by analysis number, August 1, 2017–April 30, 2018



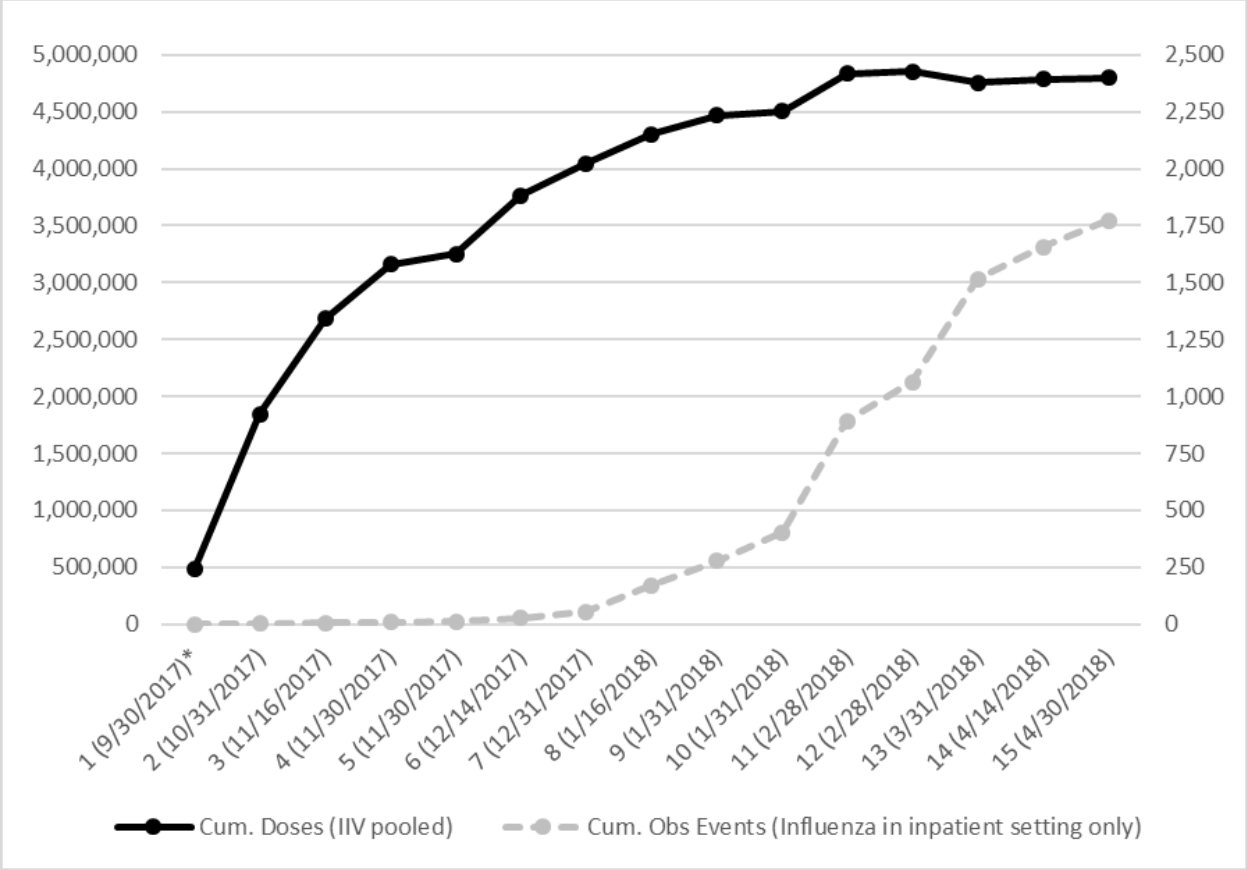
*Dates designate the most recent available data included in the analysis.

Appendix PP. Number of inactivated influenza vaccine (pooled) doses (primary y-axis), and number of observed influenza events in the inpatient setting (secondary y-axis), among members 6 months-17 years-old, by analysis number, August 1, 2017–April 30, 2018



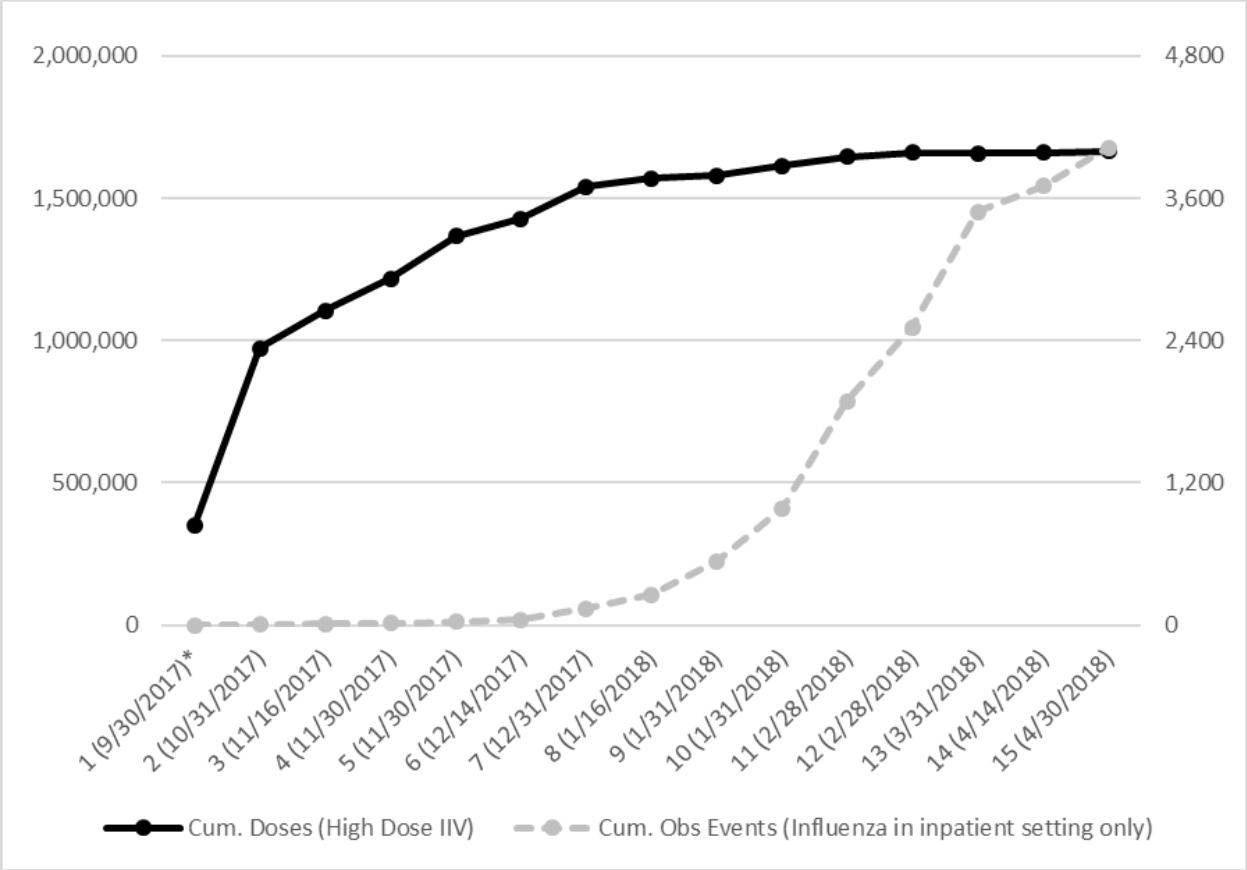
*Dates designate the most recent available data included in the analysis.

Appendix QQ. Number of inactivated influenza vaccine (pooled) doses (primary y-axis), and number of observed influenza events in the inpatient setting (secondary y-axis), among members 18-64 years-old, by analysis number, August 1, 2017–April 30, 2018



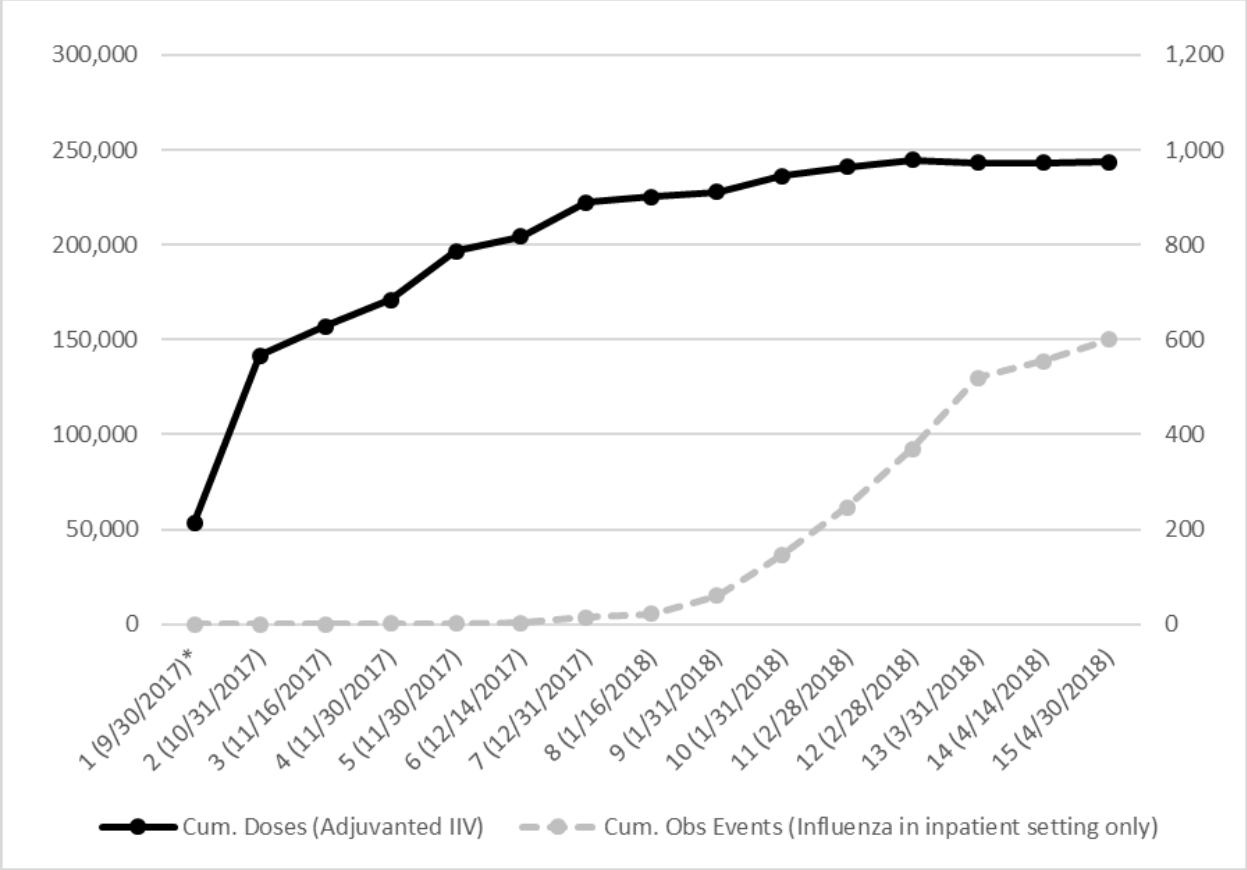
*Dates designate the most recent available data included in the analysis.

Appendix RR. Number of inactivated influenza vaccine (high dose) doses (primary y-axis), and number of observed influenza events in the inpatient setting (secondary y-axis), among members ≥65 years-old, by analysis number, August 1, 2017–April 30, 2018



*Dates designate the most recent available data included in the analysis.

Appendix SS. Number of inactivated influenza vaccine (adjuvanted) doses (primary y-axis), and number of observed influenza events in the inpatient setting (secondary y-axis), among members ≥65 years-old, by analysis number, August 1, 2017–April 30, 2018



*Dates designate the most recent available data included in the analysis.