MINI-SENTINEL CBER/PRISM SURVEILLANCE

ACCESSING THE FRESHEST FEASIBLE DATA FOR CONDUCTING ACTIVE INFLUENZA VACCINE SAFETY SURVEILLANCE

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Mini-Sentinel is a pilot project sponsored by the U.S. Food and Drug Administration (FDA) to inform and facilitate development of a fully operational active surveillance system, the Sentinel System, for monitoring the safety of FDA-regulated medical products. Mini-Sentinel is one piece of the Sentinel Initiative, a multi-faceted effort by the FDA to develop a national electronic system that will complement existing methods of safety surveillance. Mini-Sentinel Collaborators include Data and Academic Partners that provide access to health care data and ongoing scientific, technical, methodological, and organizational expertise. The Mini-Sentinel Coordinating Center is funded by the FDA through the Department of Health and Human Services (HHS) Contract number HHSF223200910006I.

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I. INTRODUCTION

Surveillance for influenza vaccine safety is challenging because the vaccines are given within a short span of time—in the U.S., vaccination is typically concentrated in October-November.(1) Thus, it is imperative to obtain and analyze recent data on a frequent basis if safety problems are to be detected in time to intervene. The CDC-sponsored Vaccine Safety Datalink (VSD) pioneered the development and application of sequential analysis methods to timely data from managed care organizations in order to monitor the safety of influenza and other vaccines in close to real time.(2-5) The Centers for Medicare and Medicaid Services (CMS), in collaboration with FDA, also routinely conducts near-real-time surveillance for influenza vaccine safety,(6-8) typically capturing more than 15 million vaccinees each season. The FDA-sponsored Post-licensure Rapid Immunization Safety Monitoring (PRISM) system was launched as one of several national vaccine safety surveillance systems deployed during the H1N1 pandemic of 2009.(9, 10) The PRISM system used claims data from several large health insurance companies and additional immunization data from several state and city Immunization Information Systems (IISs). The inclusion of IIS data improved PRISM's capture of vaccination data,(10) since much of the H1N1 vaccine was administered outside of traditional health care settings, e.g., at school or at work, and thus was not reliably reflected in claims data. Approaches to data-lag adjustment and analysis were analogous to those used by VSD.(4, 11)

FDA wished to determine the feasibility of conducting sequential analysis for influenza vaccine safety as part of the Mini-Sentinel pilot program. The new system to be created would differ from the original PRISM program for H1N1 vaccine safety surveillance in comprising somewhat different Data Partners, using the data infrastructure developed for Mini-Sentinel, and being constructed in a more systematic, less ad hoc fashion. Currently, Mini-Sentinel data are refreshed on a quarterly basis and contain relatively settled and complete data, the most recent of which are on average 6-9 months old. The time required for data to settle would limit the ability to inform regulatory decisions about the use of influenza vaccine in a timely manner. Thus, the scope of work for this activity was to develop, implement, and evaluate sequential analysis for influenza vaccine safety surveillance in the Mini-Sentinel population in order to develop a potentially sustainable infrastructure to apply to other FDA-regulated medical products that require faster access to safety information, such as drugs used for medical countermeasures. The activity was primarily of an infrastructure-building nature, involving the development of a new data pipeline to access fresher data on a more frequent basis as well as the incorporation of vaccination data from IISs. The four aims of the project were:

a. To identify and evaluate sources of freshest possible data available from PRISM Data Partners
b. To establish a "sequential analysis system" that can use the freshest feasible data from PRISM Data Partners for sequential analysis activities
c. To evaluate the fresh data as compared to the mature data (i.e. the Mini-Sentinel Common Data Model) for the same period
d. To conduct near real-time surveillance for two health outcomes of interest (HOIs) following influenza vaccination (considered active public health surveillance and hypothesis-generating)

Considering the implementation of influenza vaccine safety surveillance in 2013-14 to be the practical test of the system, the protocol stipulated that the final report would focus on Aim 4, incorporating high-level findings from Aims 1-3 as helpful for the interpretation of the Aim 4 results. Nonetheless, Aim 3 is addressed in some depth in Appendix A.

II. METHODS

A. STUDY PERIODS, POPULATIONS, AND DATA SOURCES

We conducted surveillance for influenza vaccine safety for the period September 1, 2013–April 30, 2014. Aetna, HealthCore, and Humana ("Data Partners") provided claims data on vaccine exposures and health outcomes of interest for those aged ≥ 6 months. Additional immunization data for members of the Data Partners were obtained from 8 IISs: Florida, Michigan, Minnesota, New York City, New York State, Pennsylvania, Virginia, and Wisconsin.

The **2012-13 influenza season** was used to pilot the system for the purposes of testing out the new sequential data architecture; identifying and resolving problems; and regularizing data extraction, quality control (QC), and analysis processes ahead of actual surveillance in the **2013-14 influenza season**. Also, data from 2012-13 were used to evaluate the fresh data and to investigate a statistical signal that emerged during 2013-14.

To minimize processing time and reduce storage requirements for the Data Partners, no enrollment data were used in either season.

The evaluation of the fresh data is detailed in Appendix A. An assessment of the experience of working with the IISs and of the IIS data is presented in Appendix B. Appendix C contains a break-down of the study population by sex and age group.

B. DATA-PROCESSING

The "Sequential Source Files" (**SSFs**) were internal, health plan member-level files at each Data Partner that included only claims that were adjudicated or, if no reimbursement was expected, recorded (e.g., for capitated health plans where providers were reimbursed for monthly management of the member's health care, not reimbursed for every service provided; or for vaccines obtained using a state-purchasing program and not submitted for reimbursement after administration; etc.). The SSFs were refreshed at the Data Partner sites in the last half of each month. Each new version of the SSFs normally included data on healthcare events through the end of the prior calendar month.

On approximately a bi-monthly basis during the 2013-14 surveillance season, the Data Partners translated their SSFs to the standard-format "Sequential Data Files" (**SDFs**). (Data were requested on a bi-monthly rather than a monthly basis in order to reduce the burden on the Data Partners.) The SDF population included members with a medical claim on or after 9/1/2012. All medical and pharmacy claims with service and/or fill date(s) on or after 9/1/2012 were included. With each generation of SDFs, Data Partners ran a distributed SAS program to check data attributes and adherence to the PRISM SDF model and to compare the SDFs with the previous set. Output was sent to the coordinating center for evaluation. Prior versions of the SDFs were overwritten.

After QC of the SDFs, the Data Partners ran a distributed SAS program to create the "Sequential Case Files" (**SCFs**), a subset of the SDFs that preserved demographic, medical claim, and dispensing data for cases of interest following vaccination. All generations of SCFs were retained by Data Partners to facilitate the creation of aggregated datasets for analysis, the assessment of data flux over time, and chart review in the event of a statistical signal.

After creation of the SCFs, the Data Partners ran a distributed SAS program that aggregated data from the SDFs and SCFs to create the "Sequential Aggregate (or Analysis) Files" (**SAFs**). SAFs consisted of a vaccine file and a diagnosis file, each with a summary count of the cumulative number of members in each stratum. Variables defining the strata included week of vaccination, age group, sex, vaccine type, certain concomitant vaccines, dose number, and, in the diagnosis file, health outcome of interest and timing of the outcome relative to the vaccination. The SAFs were transferred to coordinating center analysts via secure file transport for QC assessment and analysis. All generations of SAFs were retained.

Immunization data were obtained from IISs once during November 2013-February 2014. Data Partners provided lists of enrolled members as of October 2013 to some or all of the 8 participating IISs, according to the existence of members in the respective state/city and of data-sharing agreements between the parties. Required elements of demographic data and matching algorithms varied by IIS. The IISs returned immunization data for members to the Data Partners, who converted the data into a standard State Vaccine file format, ran a QC program provided by the coordinating center, and returned the results to the coordinating center for evaluation. After data quality was assured, the State Vaccine file was referenced during the aggregation process. IIS data were incorporated into the last generation of each Data Partner's SAFs.

Each of the three Data Partners provided cumulative refreshed data at three points during the 2013-14 season. At the special request of the coordinating center, the Data Partner capable of providing the greatest amount of new data refreshed their data a fourth time, in order to increase statistical power for a signal investigation. Data refreshes by the Data Partners were staggered, and sequential analysis was conducted after each, for a total of 10 sequential analyses over the course of the season.

C. VACCINE EXPOSURES

Vaccination was ascertained by CPT, CVX, HCPCS, and NDC codes. Distinction among specific influenza vaccine products was imperfect except under the following circumstances: NDCs were used; manufacturer information was available in IIS data; or a CPT, CVX, or HCPCS code corresponded to a specific product. For example, Fluzone Quadrivalent (Sanofi Pasteur Inc.) and Fluarix Quadrivalent (GlaxoSmithKline Biologicals) could be distinguished from each other only on the basis of NDC codes; other vaccine code systems did not distinguish between these two brands. Where duplicates existed, defined as more than one influenza vaccine code within 14 days of another, the more specific code was selected, according to a pre-specified prioritization scheme.

We conducted separate sequential analyses for live attenuated influenza vaccine (LAIV) and for (all types pooled) inactivated influenza vaccine (IIV). Any not-otherwise-specified influenza vaccine was combined with pooled inactivated influenza vaccine, considering that inactivated vaccine is more commonly used than live attenuated vaccine. We also tracked dose and outcome counts for the specific intradermal, cell-based, high-dose, recombinant, and quadrivalent inactivated vaccines separately, without statistical analysis.

D. HEALTH OUTCOMES OF INTEREST

We monitored the risk of two health outcomes, anaphylaxis and seizures. For each of these, to increase the positive predictive value (at the expense of sensitivity) and to capture only new cases, we counted cases only from inpatient and emergency department (ED) settings, and we counted only first encounters with an *International Classification of Diseases*, Ninth Revision (ICD-9) code of interest within a 6-month period of time. We monitored seizures in children 6-23 months and 24-59 months of age only. Because the increase in risk of febrile seizures following IIV was greater among children receiving concomitant 13-valent pneumococcal conjugate vaccine (PCV13) in the risk vs. the control period in 2010-11 in the VSD system,(5) seizures in the 6-23 month old age group were stratified by whether or not there was concomitant PCV13 vaccination. The definitions of these outcomes are presented in Table 1. The seizures definition was found to have a positive predictive value of 70% for febrile seizures in another PRISM study of children 6-59 months of age (where incidence was defined as first occurrence in 6 weeks rather than first in 6 months).(12)

Table 1. Outcome definitions

HOI	Codes	Influenza vaccine type	Age group	Setting	First in what period?[a]
1. Anaphylaxis	995.0 999.4	All	IIV: ≥6m LAIV: 2-49 y	Inpatient or ED	6 mo., inpatient or ED setting
2. Seizures in youngest, concomitant PCV13	780.3 (Convulsions) 780.31 (Febrile) 780.32 (Complex) 780.39 (Other)	IIV[b]	6-23 m	Inpatient or ED	6 mo., any setting (including outpatient)
3. Seizures in youngest, no concomitant PCV13	Same as Row 2	IIV[b]	6-23 m	Inpatient or ED	6 mo., any setting (including outpatient)
4. Seizures	Same as Row 2	All	24-59 m	Inpatient or ED	6 mo., any setting (including outpatient)

[a] Since enrollment data were not used, some cases might not have had a full look-back period of prior data, so the look-back period was either 6 months or, if that full period was not available, the maximum period available. Also, the fresh data sources used distinguished among health plan member IDs, not unique individuals. Therefore, the look-back for previous diagnoses of anaphylaxis or seizures was within health plan member ID, not unique patient. For example, if a person had a seizure and then switched health plans/products (leading to a change in member ID) before having a post-vaccination seizure, the earlier one would have been overlooked in the electronic look-back.

[b] Fluzone & Fluzone Quadrivalent (Sanofi Pasteur Inc.) are the only influenza vaccines approved for use in this age group.

E. SEQUENTIAL ANALYSIS DESIGNS AND STATISTICAL METHODS

1. The designs

We used the designs shown in Table 2 in sequential analysis to evaluate whether or not an elevated risk existed:

Table 2. Primary and secondary study designs and risk windows for the two outcomes of interest

	Risk window	Current vs. historical	Self-controlled risk interval
Anaphylaxis	Days 0-1	Primary	N.a.
Seizures	Days 0-1 post-IIV Days 1-3 post-LAIV	Secondary	Primary

We used the current vs. historical comparison for **anaphylaxis** because of its rarity. With this design, the cumulative number of cases in a pre-specified risk interval following vaccination (or other exposure of interest) is compared with the number expected based on the rate after a comparable exposure or visit historically.(4) This approach has often been used in sequential analysis for rare outcomes, because it has better power to detect a small elevation in risk and would detect a signal earlier given the same relative risk (RR) compared to most comparisons with concurrent controls, including the self-controlled risk interval (SCRI) approach described below. The limitation of the current-vs.-historical approach in influenza vaccine safety surveillance is that historical influenza vaccinees may not be an entirely appropriate comparison group for the influenza vaccinees in the season of interest. Confounding may exist due to different population characteristics, secular trends in diagnoses of the health outcomes of interest, and/or the different influenza vaccines available over time.

For **seizures**, we used the self-controlled (SCRI) design(3, 4, 13, 14) as the primary one. With the SCRI design, the cumulative number of cases in a pre-specified risk interval is compared with the cumulative number in a pre-specified control interval, adjusting for unequal interval lengths. This self-controlled design is our preferred approach for influenza vaccine safety monitoring since it controls for fixed potential confounders of interest, such as gender and co-morbidities. One of the limitations of using the SCRI design in near real time surveillance is that time-varying confounders, such as age and seasonality, may bias the findings. However, in our study, confounding due to seasonality was mitigated by the short duration of the risk and control windows, which both occurred within a 21-day period (Table 3). Another limitation is that for rare outcomes, power to detect signals in a timely fashion may be low, particularly if the effect size is modest.

Because of the limitation of greater time-to-signal with the SCRI design, we also used current vs. historical comparison as a secondary method for seizures, in order detect any increased risk earlier than would have been possible with the SCRI method alone. To monitor the safety of LAIV, we conducted two current-vs.-historical comparisons, one using historical rates of seizures after LAIV, the other using historical rates after IIV, thereby addressing two questions: whether the quadrivalent LAIV used in 2013-14 was as safe as trivalent LAIVs historically and whether it was as safe as trivalent IIVs historically.

The details of the various sequential analyses and comparisons are summarized in Table 3, along with the pre-specified end-of-season analyses that were to be conducted in the event of a signal.

2. Maximized sequential probability ratio test (maxSPRT)

Three different variants of the Maximized Sequential Probability Ratio Test (maxSPRT) were used to adjust for the repeated looks at the accumulating data entailed in sequential analysis.(2) The test statistic was the log-likelihood ratio (LLR).

We used the **maxSPRT for Poisson data** for the current vs. historical analysis of anaphylaxis after LAIV and of one seizures outcome (Table 3). The null hypothesis was that the risk after influenza vaccination in 2013-14 was no greater than the risk after influenza vaccination in previous seasons. The null hypothesis of no increased risk was to be rejected if, over the course of surveillance, the LLR reached a pre-specified upper bound, called the "critical value." The critical value 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 of 0.05. The expected counts were determined based on the incidence of anaphylaxis and seizures after IIV in the Mini-Sentinel population, as seen in several previous influenza seasons, together with the expected number of vaccines to be administered in the Mini-Sentinel population in 2013-14. The null hypothesis was not to be rejected if the LLR had not reached the critical value by the time the upper limit was reached or if surveillance ended without reaching this upper limit. Upper limits were chosen such that they were slightly higher than the number of events actually expected, in order to avoid the reduction of power that would have resulted from reaching the upper limit before the end of the season.

We used the **conditional maxSPRT (CmaxSPRT)** for the current vs. historical analysis of anaphylaxis after IIV and of the other three seizures outcomes (Table 3). Similar to the Poisson maxSPRT, the CmaxSPRT allows for a comparison of current counts to counts that would be expected based on historical rates, but it does not assume that historical rates are known without error.(15) In other words, the CmaxSPRT accounts for uncertainty in historical rates. Guided by the results reported in the original CmaxSPRT method paper,(15) we used the CmaxSPRT instead of the Poisson maxSPRT where the number of cases in the historical data used to obtain the background rates was less than 5 times the upper limit; this was the case for the last three seizures outcomes in Table 3. The null hypothesis and criteria for rejecting and for not rejecting the null were as for the Poisson maxSPRT described above, but the critical value of the LLR was dictated by the user-specified upper limit of *observed* (instead of expected) cases and the alpha level (0.05). Upper limits were determined by multiplying the number of cases expected to be observed by 2 so as not to end surveillance too soon to see a signal in the event that the true RR was around 2. (This differs from the procedure with the Poisson maxSPRT, because CmaxSPRT upper limits are applied to *observed*, not expected, cases.)

The **maxSPRT for binomial data** was used for the SCRI analysis of seizures. The null hypothesis was that the risk after influenza vaccination in 2013-14 was no greater than the risk in a control period during the same season for the same individuals. The critical value of the LLR, above which the null hypothesis was to be rejected, was dictated by the user-specified upper limit of observed cases in risk and control intervals combined and the chosen alpha level of 0.05. Upper limits were chosen based on the approximate number of cases that were expected to occur in the risk plus control intervals under the hypothesis of a RR of 2. (As with the CmaxSPRT, which also uses upper limits on *observed* cases, the purpose of using a hypothesis of RR=2 instead of RR=1 was to guard against ending surveillance too soon in the event that the true RR was close to 2.) The null hypothesis was not to be rejected if the upper

limit of observed cases in risk and control intervals was surpassed or if surveillance ended without this upper limit being reached.

One-tailed tests were used, since we were looking only for elevated risks from vaccination rather than for protective effects.

Table 3. Sequential and pre-specified end-of-season analyses

HOI	Influenza vaccine type	Age group	1° sequential analysis method	2° sequential analysis method	Risk interval	Control interval for SCRI	Historical data to be used for current vs. historical comparison	End of season analysis if no signal	End of season analysis if signal, using chart-confirmed cases[a]
Anaphylaxis	IIV	≥6 mo.	Current vs. historical (CmaxSPRT)[b]	n.a.	0-1 days	n.a.	0-1 days post-IIV	Last sequential test	Non-sequential SCRI[a]
Anaphylaxis	LAIV	2-49 years	Current vs. historical (Poisson maxSPRT)[b]	n.a.	0-1 days	n.a.	0-1 days post-**IIV**[c]	Last sequential test	1) Non-sequential SCRI and 2) current LAIV vs. current IIV regression and/or difference-in-difference analysis[a]
Seizures in youngest, concomitant PCV13	IIV	6-23 mo.	SCRI (binomial maxSPRT)	Current vs. historical (Poisson maxSPRT)[b]	0-1 days[d]	14-20 days[e]	0-1 days post-IIV[f]	Last sequential tests: SCRI (1°) and current vs. historical (2°)	None[g]
Seizures in youngest, **no** concomitant PCV13	IIV	6-23 mo.	SCRI (binomial maxSPRT)	Current vs. historical (CmaxSPRT)[b]	0-1 days[d]	14-20 days[e]	0-1 days post-IIV[f]	Last sequential tests: SCRI (1°) and current vs. historical (2°)	None[g]
Seizures	IIV	24-59 mo.	SCRI (binomial maxSPRT)	Current vs. historical (CmaxSPRT)[b]	0-1 days[d]	14-20 days[e]	0-1 days post-IIV[f]	Last sequential tests: SCRI (1°) and current vs. historical (2°)	None[g]
Seizures	LAIV	24-59 mo.	SCRI (binomial maxSPRT)	Current vs. historical (**two**) (CmaxSPRT)[b]	1-3 days[d]	15-20 days[e]	1-3 days post-LAIV **and** 0-1 days post-IIV[f], with rate augmented by 50% to match 3-day post-LAIV risk interval	Last sequential tests: SCRI (1°) and current vs. historical (2°) (**two**)	1) Non-sequential SCRI; but if signal is in current LAIV vs. historical IIV comparison, then 2) current LAIV vs. current IIV regression and/or difference-in-difference analysis[a]

[a] Due to resource constraints, chart review was to be conducted for at most 1 statistical signal (i.e. row in the table). If > 1 signals emerged during sequential analysis, the choice of vaccine-outcome pair for chart review and study design was to be made in consultation with FDA.
[b] See the "Maximized sequential probability ratio test" section above for an explanation of the distinction between the maxSPRT and the CmaxSPRT.
[c] Historical data on anaphylaxis after LAIV are typically very sparse, so post-IIV historical rates were used instead of post-LAIV historical rates.
[d] Seizures risk windows after IIV and LAIV were based on Rowhani-Rahbar et al.(16)
[e] Control window starts a multiple of 7 days after start of risk window to minimize bias from day-of-week effects. Control window starts 2 weeks (instead of 1 week) after vaccination in order to exclude period of increased risk of seizures after MMR or MMRV vaccination. (This is less relevant for the 24-59 month age group, but control windows were kept similar for consistency.)
[f] The historical rates used were from prior to 7/2010, which is also largely prior to any concomitant PCV13 usage. The purpose of this restriction was to exclude influenza seasons in which the risk of post-IIV seizure was elevated and to exclude most concomitant PCV13.
[g] No end-of-season analysis using chart-confirmed cases was planned, because a signal would not have been unexpected, and at least one other national vaccine safety surveillance system was monitoring this outcome.

3. Continuous vs. group sequential analysis

We used *continuous* sequential analysis rather than *group* sequential analysis. Under conditions of frequent data updates, continuous sequential methods detect statistical signals earlier for the same levels of alpha and power.(17)

4. Minimum number of cases to signal

We required at least 3 events to occur before a statistical signal could be generated using the current vs. historical comparison (Poisson maxSPRT or CmaxSPRT); this was to avoid spurious signaling that would otherwise have been possible due to a chance early occurrence of 1-2 rare events. For SCRI (binomial maxSPRT) analyses, we required at least 4 events in risk and control intervals combined for a signal; this was to optimize power and the expected time to signal.

5. Background rates

Background rates were needed in order to calculate expected counts of the outcomes and to help establish upper limits for surveillance for the sequential analyses. Prior to the start of surveillance, Data Partners provided these by executing Mini-Sentinel's Modular Program 3 on historical data in the Mini-Sentinel Common Data Model (M-S CDM), requiring 6 months of pre-vaccination enrollment. The earliest season of available data was 2006-07, 2007-08, or 2008-09, depending on Data Partner. All Data Partners' data went through 2012-13. Post-IIV rates for seizures were restricted to before July 2010 in order to exclude the period during which an increased risk of seizures post-IIV had been observed in other systems.(5) Historical rates were without regard to concomitant vaccination; thus, the same rates were used for seizures in 6-23 month olds with and without concomitant PCV13. Due to the cut-off of data before July 2010, the seizures background rates would not have been appreciably influenced by concomitant PCV13, although PCV7 (as well as other vaccines) would have been in use.

Current-vs.-historical sequential analyses for seizures used age group- and Data Partner-specific background rates. Analyses for anaphylaxis used only age group-specific rates—because of the rarity of anaphylaxis cases, the data from the three Data Partners were combined to produce somewhat more stable age group-specific rates.

Because the background rates required 6 months of pre-vaccination enrollment, while no specific period of prior enrollment was required for patients in the 2013-14 surveillance season, it is possible that the current vs. historical analyses were biased toward signaling. However, as mentioned in the notes for Table 1, only cases that were the first in 6 months or, if 6 months was not available, first in the available prior data for a patient were counted. In other words, although prior enrolled time was not *required*, it was *used* where it existed. Thus, any bias would likely not have been extreme.

6. Adjustment for incomplete data in sequential analysis

We conducted analyses using fresh and therefore incompletely accrued data in order to obtain timely results. There are two kinds of adjustment usually needed for incomplete data, which have been documented by Greene et al.(11) One is for observation intervals that have not yet fully elapsed. For the current vs. historical (Poisson maxSPRT or CmaxSPRT) analysis, this was not needed, as the risk intervals were all at most 3 days long. For the self-controlled (binomial maxSPRT) analysis, we waited for both risk and control intervals to elapse before analyzing cases in the risk and control intervals associated with a particular vaccination week.

The other kind of adjustment needed is for lag in the arrival of outcome data, which results from delays in submission of a medical claim by a provider and in the processing of a claim by the health insurance company. (See Appendix A for more discussion of data lag.) To characterize lag times, each Data Partner quantified medical claims data accrual in 2012 by week after care date for each medical setting. For the current vs. historical (Poisson maxSPRT) analysis, we multiplied the expected by the fraction of data expected to have arrived, according to these Data Partner-specific, medical setting-specific lag characterizations. For example, if for a particular stratum of our data (a) there were 3.3 expected cases of the outcome based on background rates and number of doses administered, (b) 75% of the cases of this outcome usually occur in the ED setting and 25% in the inpatient setting (known from prior analysis of historical data), (c) there were only 2 weeks between the vaccination week and the last possible care date in the batch of data, and (d) in 2 weeks' time 60% of ED data accrue and 5% of inpatient data accrue (known from the data lag characterizations), then the adjusted number of expected cases would have been 3.3 x ((75% x 60%) + (25% x 5%)) =1.5 expected events.

For the self-controlled (binomial maxSPRT) analysis, we did not include events in the risk and control intervals associated with a vaccination week in the analysis until both those intervals had elapsed (as mentioned above) *and* data for both intervals were determined to be $\geq$ 85% complete, according to the data-accrual tables (data lag characterizations). Among the three Data Partners, the number of weeks to get to $\geq$ 85% completeness ranged between 7 and 13 for the ED setting and between 10 and 18 for the inpatient setting.

F. REPORTING

After each sequential analysis, a summary report was generated and sent to colleagues at FDA. The report showed the cumulative number of doses and, for each outcome, the cumulative number of cases in the risk interval, the number expected in the risk interval and (for seizures) observed in the control interval, the relative risk, the LLR, and an indicator of whether a signal had appeared, i.e. whether the LLR had surpassed the critical value.

G. SIGNAL EVALUATION

In our protocol, we stipulated that if a statistical signal appeared, we would check the various inputs, including background rates, and follow other established procedures for investigating sequential analysis signals.(18) In the event of a statistical signal for any of the seizures outcomes in association with IIV, no chart-review was to be conducted, because a signal would not have been unexpected; at least one other national vaccine safety surveillance system was monitoring this outcome; and a prior evaluation of the magnitude of risk, with or without concomitant PCV13, in recent seasons had not been considered great enough to alter vaccination recommendations.

A statistical signal for seizures in 6-23 month old children after IIV and concomitant PCV13 vaccination did initially appear during surveillance using the current vs. historical approach (see Sections III.C. and III.D.). Although this study design was not the preferred one, due to potential differences between historical and current cohorts, it did provide the ability to identify a potential signal in a timely manner. In order to explore potential reasons for this initial signal, we took the following steps: First, we re-examined the historical background rates to ensure the pooled historical population was appropriate as a comparison group (i.e., without secular trends, etc.). Second, we examined the sequential analysis findings for our preferred or primary design (SCRI). Because of limitations in power with this approach, we added an "extra" data refresh and a tenth sequential analysis in order to augment the ability of the SCRI analysis to verify the statistical signal observed with the current vs. historical analysis. In addition, two major explorations were undertaken:

1. We used a cohort design and conducted a logistic regression analysis with concurrent controls, comparing the risk of seizures among children receiving IIV with concomitant PCV13 vs. those receiving IIV without PCV13. (Data on PCV13 without IIV were unavailable.) The question was whether concomitant PCV13 increased the risk of seizures among IIV recipients in the Days 0-1 risk window, adjusting for other covariates described below. We included data from our pilot season, 2012-13, to increase statistical power. To adjust for age, we used an offset term drawn from the febrile seizures background rate curve from the PRISM study on influenza vaccination and febrile seizures.(12) Terms included in the basic model were concomitant PCV13 (yes/no), Data Partner, week of season and week of season-squared (continuous variables), sex, dose, and season. We did not consider the possibility of interaction between IIV and PCV13 vaccines given concomitantly, given the absence of data on PCV13 without IIV.
2. FDA funded an extension of the PRISM study on influenza vaccination and febrile seizures, which used a SCRI design, to include more recent influenza seasons in addition to the 2010-11 season originally addressed in that study.(12) This was considered the more definitive approach, compared with (a) above, in that it was designed to disentangle the independent effects of IIV and PCV13, and it was self-controlled. This approach will also explicitly adjust for age and seasonality. The protocol and the results of the extended febrile seizures study will be presented separately.

III. RESULTS

A. TIMING OF DATA REFRESHES AND ANALYSES

The Data Partners provided cumulative refreshed data three to four times each, on a staggered schedule. One to three sequential analyses were conducted each month between December 2013 and May 2014, each analysis incorporating new data from one Data Partner. Figure 1 shows the sequence of tests conducted; each row represents an influx of new data analyzed, showing the Data Partner whose data were newly added, the months for which vaccinations and cases of outcomes ("health events") were captured (although only incompletely captured, due to data lag), the month in which the data were refreshed by the Data Partner, and the month in which the coordinating center conducted the analysis. There was no urgency to analyze the September 2013 data, as it had been noted that there were too few cases to generate a statistical signal. With the exception of the September 2013 data, analyses were routinely conducted by approximately 6 weeks after the last care date in the respective batch of data (median number of days: 40; range: 30-55; see Appendix A, Table A2, for further details).

Test #, added DP	Sep 2013	Oct 2013	Nov 2013	Dec 2013	Jan 2014	Feb 2014	Mar 2014	Apr 2014	May 2014
1, A	health events	refreshed		**analyzed**					
2, C	health events		refreshed	**analyzed**					
3, B	health events			refreshed **analyzed**					
4, A	health events				refreshed **analyzed**				
5, B	health events				refreshed **analyzed**				
6, C	health events				refreshed	**analyzed**			
7, A	health events						refreshed **analyzed**		
8, B + IIS data	health events						refreshed **analyzed**		
9, C + IIS data	health events							refreshed **analyzed**	
10, A + IIS data	health events								refreshed **analyzed**

Figure 1. History and timing of data refreshes by Data Partners and the 10 sequential analyses of 2013-14, showing, via the shaded "health events" bars, the range of health care dates included in each new influx of data. Tests (analyses) were done on cumulative data; for example, Test 4 included data for September 2013 for Data Partners B and C and data for September-November 2013 for Data Partner A. "Refreshed" appears under the month in which the most recently added data were refreshed by the respective Data Partner. (The conversion of the refreshed source data to PRISM file formats and the QC steps are not shown.) "Analyzed" appears under the month in which the cumulative data, including the respective newest batch, were included in sequential analysis by the coordinating center. There was no urgency to analyze the September 2013 data, as it had been noted that there were too few cases to generate a signal. Data Partner A provided data a fourth time in order to aid in investigating the signal that had emerged. Greater detail is provided in Appendix A, Table A2.

B. VACCINE DOSES

6,682,336 doses of IIV and 782,125 doses of LAIV had been captured by the end of surveillance, reflecting data through April 2014 for one Data Partner and through January and February 2014, respectively, for the other two. The proportion contributed by IISs was 4.3% (see Appendix B for more detail). The cumulative number of doses included in each of the 10 sequential analyses is shown in Figure 2.

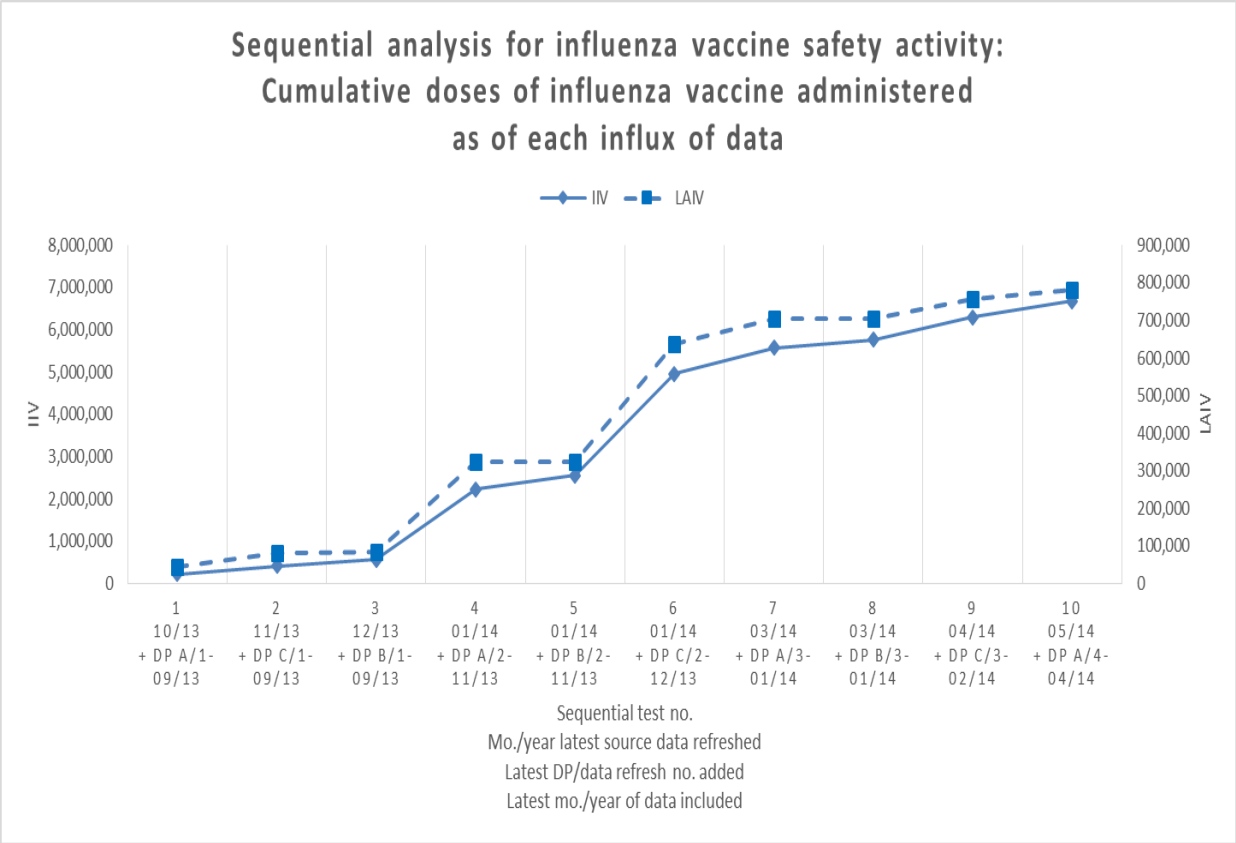

Figure 2. Cumulative doses of influenza vaccine administered as of each influx of data, 2013-14.

Comparatively few doses of the specific intradermal, cell-based, high-dose, recombinant, and quadrivalent inactivated vaccines were distinguished from IIV in general (Table 4). This was due at least in part to the non-specificity of the vaccine codes submitted in health insurance claims. There were zero cases of the outcomes of interest in the risk intervals after these detected doses of specific vaccines.

Table 4. Dose and case counts for selected brands of injectable vaccine[a] as of the end of surveillance

					Non-NDC vaccine codes		
Vaccine[a]	**Outcome**	**Age group**	**Cumulative doses**	**Cumulative events in risk interval (Days 0-1)**	**CPT**	**CVX**	**HCPCS**
Fluzone Quadrivalent[b]	Anaphylaxis	≥6 mo.	1,200	0			
Fluzone Quadrivalent[b]	Seizures	6-59 mo.	4	0			
Fluarix Quadrivalent[b]	Anaphylaxis	≥3 yr.	23,219	0			
Fluarix Quadrivalent[b]	Seizures	3-4 yr.	6	0			
FluBlok (recombinant)	Anaphylaxis	18-49 yr.	123	0	90673	155	Q2033
Fluzone Intradermal	Anaphylaxis	18-64 yr.	133,812	0	90654	144	
Flucelvax (cell-based)	Anaphylaxis	≥18 yr.	35,404	0	90661	153	
Fluzone High Dose	Anaphylaxis	≥65 yr.	336,242	0	90662	135	

[a] Manufacturers are as follows: Fluzone—Sanofi Pasteur, Inc.; Fluarix—GlaxoSmithKline Biologicals; FluBlok—Protein Sciences Corporation; Flucelvax—Novartis Vaccines and Diagnostics, Inc.
[b] Fluzone Quadrivalent and Fluarix Quadrivalent are populated on the basis of NDC codes only; other vaccine code systems do not distinguish adequately between these two IIV4 brands.

C. SEQUENTIAL ANALYSIS

Table 5 shows the results of the 10 sequential analyses.

Current-vs.-historical design: The first three tests included data only for September 2013, during which time there was only 1 case of any outcome, too few to analyze. By Test #4, with data through November 2013 for one of the Data Partners, there were enough cases of post-IIV seizures in 24-59 month olds to analyze. With every new influx of data, the numbers of cases increased, and more of the outcomes could be analyzed. For LAIV vaccine, however, there were too few cases to analyze until Test #9, by which time 3 cases of seizures in 24-59 month olds had accumulated. The number of cases of post-LAIV anaphylaxis, however, remained at 0, with 782,125 doses administered to the 2-49 year old age group as of the end of surveillance.

Using the current vs. historical design, a statistical signal appeared for seizures in 6-23 month olds receiving IIV with concomitant PCV13 in Test #7, conducted in March 2014. There were 9 cases observed among 86,329 concomitant vaccinees, a RR of 3.0, and a LLR of 3.978, surpassing the critical value of 2.874. By Test #10, now with 12 cases observed among 116,133 concomitant vaccinees, the RR had decreased slightly to 2.7. These results are shown in Table 6 (excerpted from Table 5) and Figure 3.

SCRI design: For each Data Partner-vaccination week-setting stratum, data in the control window had to be at least 85% complete before any cases in the stratum (whether in risk or control window) could be analyzed, per our pre-specified data lag adjustment procedures. This, together with the pre-specified minimum of 4 cases in risk plus control windows in order to do an analysis, meant that no SCRI analysis was possible until Test #7, which occurred in March 2014.

No statistical signals emerged in SCRI analysis. Regarding seizures in 6-23 month olds receiving IIV+PCV13, in the last SCRI analysis, there were 4 cases in the risk interval, 10 in the control interval, a RR of 1.4, and a LLR well below the signaling threshold (Table 6 and Figure 3).

Table 5. Sequential analysis results, adjusted for data lag

Table 5. Sequential analysis results			Current vs. Historical							Self-Controlled Risk Interval						
Vaccine	Outcome	Risk interval (days)	Cum. doses	Cum. events observed in risk interval (current)	Cum. events expected in risk interval (historical)	RR (current vs. expected)	Log-likelihood ratio (LLR)[a,b]	Critical value of LLR	Sequential signal?	Control interval (days)	Cum. events in risk interval	Cum. events in control interval	RR (risk interval vs. control interval)	Log-likelihood ratio (LLR)[a,c]	Critical value of LLR	Sequential signal?
Analysis #1, mid-December 2013																
IIV	Anaphylaxis, ≥ 6 mo.	0-1	223,794	0	0.17	0			no							
	Seizures, 6-23 mo., with PCV13	0-1	3,877	0	0.02	0			no	14-20						no
	Seizures, 6-23 mo., without PCV13	0-1	10,271	0	0.06	0			no	14-20						no
	Seizures, 24-59 mo.	0-1	10,375	1	0.06	17.66			no	14-20						no
LAIV	Anaphylaxis, 2-49 yr.	0-1	43,374	0	0.03	0			no							
	Seizures, 24-59 mo.[d]	1-3	10,780	0	0.11	0			no							
	Seizures, 24-59 mo.[e]	1-3	10,780	0	0.14	0			no	15-20						no
Analysis #2, mid-December 2013																
IIV	Anaphylaxis, ≥ 6 mo.	0-1	420,459	0	0.19	0			no							
	Seizures, 6-23 mo., with PCV13	0-1	7,088	0	0.03	0			no	14-20						no
	Seizures, 6-23 mo., without PCV13	0-1	18,965	0	0.08	0			no	14-20						no
	Seizures, 24-59 mo.	0-1	18,890	1	0.06	16.45			no	14-20						no
LAIV	Anaphylaxis, 2-49 yr.	0-1	82,488	0	0.04	0			no							
	Seizures, 24-59 mo.[d]	1-3	20,229	0	0.12	0			no							
	Seizures, 24-59 mo.[e]	1-3	20,229	0	0.16	0			no	15-20						no
Analysis #3, mid-December 2013																
IIV	Anaphylaxis, ≥ 6 mo.	0-1	558,879	0	0.48	0			no							
	Seizures, 6-23 mo., with PCV13	0-1	7,089	0	0.03	0			no	14-20						no
	Seizures, 6-23 mo., without PCV13	0-1	18,968	0	0.08	0			no	14-20						no
	Seizures, 24-59 mo.	0-1	18,897	1	0.06	16.42			no	14-20						no
LAIV	Anaphylaxis, 2-49 yr.	0-1	82,731	0	0.04	0			no							
	Seizures, 24-59 mo.[d]	1-3	20,234	0	0.12	0			no							
	Seizures, 24-59 mo.[e]	1-3	20,234	0	0.16	0			no	15-20						no
Analysis #4, early January 2014																
IIV	Anaphylaxis, ≥ 6 mo.	0-1	2,225,659	2	6.75	0.30			no							
	Seizures, 6-23 mo., with PCV13	0-1	33,064	1	0.90	1.11			no	14-20	0	3	0			no
	Seizures, 6-23 mo., without PCV13	0-1	112,420	1	2.97	0.34			no	14-20	0	1	0			no
	Seizures, 24-59 mo.	0-1	117,299	5	2.46	2.03	0.798	2.829	no	14-20	1	1	3.50			no
LAIV	Anaphylaxis, 2-49 yr.	0-1	323,939	0	0.88	0			no							
	Seizures, 24-59 mo.[d]	1-3	74,106	0	2.32	0			no							
	Seizures, 24-59 mo.[e]	1-3	74,106	0	3.14	0			no	15-20	0	1	0			no
Analysis #5, mid-January 2014																
IIV	Anaphylaxis, ≥ 6 mo.	0-1	2,555,486	4	7.48	0.53	0	3.371	no							
	Seizures, 6-23 mo., with PCV13	0-1	33,072	1	0.90	1.11			no	14-20	0	3	0			no
	Seizures, 6-23 mo., without PCV13	0-1	112,457	1	2.97	0.34			no	14-20	0	1	0			no
	Seizures, 24-59 mo.	0-1	117,356	5	2.46	2.03	0.797	2.829	no	14-20	1	1	3.50			no
LAIV	Anaphylaxis, 2-49 yr.	0-1	324,471	0	0.88	0			no							
	Seizures, 24-59 mo.[d]	1-3	74,142	0	2.32	0			no							
	Seizures, 24-59 mo.[e]	1-3	74,142	0	3.15	0			no	15-20	0	1	0			no

Table 5, continued			Current vs. Historical							Self-Controlled Risk Interval						
Vaccine	Outcome	Risk interval (days)	Cum. doses	Cum. events observed in risk interval (current)	Cum. events expected in risk interval (historical)	RR (current vs. expected)	Log-likelihood ratio (LLR)[a,b]	Critical value of LLR	Sequential signal?	Control interval (days)	Cum. events in risk interval	Cum. events in control interval	RR (risk interval vs. control interval)	Log-likelihood ratio (LLR)[a,c]	Critical value of LLR	Sequential signal?
Analysis #6, mid-February 2014																
IIV	Anaphylaxis, ≥ 6 mo.	0-1	4,952,572	10	14.27	0.70	0	3.371	no							
	Seizures, 6-23 mo., with PCV13	0-1	67,832	6	2.24	2.68	2.158	2.874	no	14-20	0	3	0			no
	Seizures, 6-23 mo., without PCV13	0-1	233,728	4	7.76	0.52	0	3.231	no	14-20	0	2	0			no
	Seizures, 24-59 mo.	0-1	231,934	9	3.71	2.42	1.879	2.829	no	14-20	1	2	1.75			no
LAIV	Anaphylaxis, 2-49 yr.	0-1	635,920	0	1.66	0.00			no							
	Seizures, 24-59 mo.[d]	1-3	139,857	1	3.42	0.29			no							
	Seizures, 24-59 mo.[e]	1-3	139,857	1	5.04	0.20			no	15-20	0	1	0			no
Analysis #7, early March 2014																
IIV	Anaphylaxis, ≥ 6 mo.	0-1	5,573,643	11	17.83	0.62	0	3.371	no							
	Seizures, 6-23 mo., with PCV13	0-1	86,329	9	2.96	3.05	3.978	2.874	yes	14-20	2	5	1.40	0.077	2.850	no
	Seizures, 6-23 mo., without PCV13	0-1	282,686	6	9.95	0.60	0	3.231	no	14-20	2	19	0.37	0	3.247	no
	Seizures, 24-59 mo.	0-1	268,441	9	5.12	1.76	0.789	2.829	no	14-20	5	13	1.35	0.152	2.953	no
LAIV	Anaphylaxis, 2-49 yr.	0-1	704,460	0	2.07	0.00			no							
	Seizures, 24-59 mo.[d]	1-3	153,893	2	4.40	0.45			no							
	Seizures, 24-59 mo.[e]	1-3	153,893	2	6.35	0.32			no	15-20	0	5	0	0	2.904	no
Analysis #8, late March 2014																
IIV	Anaphylaxis, ≥ 6 mo.	0-1	5,757,300	13	18.55	0.70	0	3.371	no							
	Seizures, 6-23 mo., with PCV13	0-1	86,502	9	2.96	3.04	3.964	2.874	yes	14-20	2	5	1.40	0.077	2.850	no
	Seizures, 6-23 mo., without PCV13	0-1	283,514	6	9.99	0.60	0	3.231	no	14-20	2	19	0.37	0	3.247	no
	Seizures, 24-59 mo.	0-1	270,072	9	5.14	1.75	0.775	2.829	no	14-20	5	13	1.35	0.152	2.953	no
LAIV	Anaphylaxis, 2-49 yr.	0-1	705,730	0	2.07	0.00			no							
	Seizures, 24-59 mo.[d]	1-3	154,258	2	4.41	0.45			no							
	Seizures, 24-59 mo.[e]	1-3	154,258	2	6.36	0.31			no	15-20	0	5	0	0	2.904	no
Analysis #9, early April 2014																
IIV	Anaphylaxis, ≥ 6 mo.	0-1	6,296,295	14	21.41	0.65	0	3.371	no							
	Seizures, 6-23 mo., with PCV13	0-1	104,075	12	3.94	3.04	5.301	2.874	yes	14-20	2	8	0.88	0	2.850	no
	Seizures, 6-23 mo., without PCV13	0-1	322,972	7	12.68	0.55	0	3.231	no	14-20	4	35	0.40	0	3.247	no
	Seizures, 24-59 mo.	0-1	299,866	10	5.70	1.75	0.835	2.829	no	14-20	8	25	1.12	0.038	2.953	no
LAIV	Anaphylaxis, 2-49 yr.	0-1	755,894	0	2.37	0.00			no							
	Seizures, 24-59 mo.[d]	1-3	164,263	3	4.79	0.63	0	2.952	no							
	Seizures, 24-59 mo.[e]	1-3	164,263	3	7.02	0.43	0	2.972	no	15-20	2	6	0.67	0	2.904	no
Analysis #10, late May 2014																
IIV	Anaphylaxis, ≥ 6 mo.	0-1	6,682,336	15	23.71	0.63	0	3.371	no							
	Seizures, 6-23 mo., with PCV13	0-1	116,133	12	4.47	2.69	4.326	2.874	yes	14-20	4	10	1.40	0.154	2.850	no
	Seizures, 6-23 mo., without PCV13	0-1	349,628	8	13.91	0.57	0	3.231	no	14-20	5	39	0.45	0	3.247	no
	Seizures, 24-59 mo.	0-1	318,239	10	6.56	1.52	0.474	2.829	no	14-20	8	26	1.08	0.017	2.953	no
LAIV	Anaphylaxis, 2-49 yr.	0-1	782,125	0	2.55	0			no							
	Seizures, 24-59 mo.[d]	1-3	169,089	3	5.22	0.57	0	2.952	no							
	Seizures, 24-59 mo.[e]	1-3	169,089	3	7.59	0.40	0	2.972	no	15-20	3	9	0.67	0	2.904	no

Notes for Table 5:
a Log likelihood ratio set to 0 where RR < 1.
b Number of cumulative events observed must be ≥ 3 for analysis to be conducted.
c Number of cumulative events observed in both intervals must be ≥ 4 for analysis to be conducted.
d Historical rates used are post-IIV.
e Historical rates used are post-LAIV.

Table 6. Sequential analysis results for seizures in 6-23 month olds receiving IIV, adjusted for data lag (excerpted from Table 5)

			Current vs. Historical							Self-Controlled Risk Interval						
Test #	Outcome	Risk interval (days)	Cum. doses	Cum. events observed in risk interval (current)	Cum. events expected in risk interval (histor-ical)	RR (current vs. expected)	Log-likelihood ratio (LLR)[a,b]	Critical value of LLR	Sequen-tial signal?	Control interval (days)	Cum. events in risk interval	Cum. events in control interval	RR (risk interval vs. control interval)	Log-likelihood ratio (LLR)[a,c]	Critical value of LLR	Sequen-tial signal?
6	Seizures, with PCV13	0-1	67,832	6	2.24	2.68	2.158	2.874	no	14-20	0	3	0			no
7	Seizures, with PCV13	0-1	86,329	9	2.96	3.05	3.978	2.874	yes	14-20	2	5	1.40	0.077	2.850	no
8	Seizures, with PCV13	0-1	86,502	9	2.96	3.04	3.964	2.874	yes	14-20	2	5	1.40	0.077	2.850	no
9	Seizures, with PCV13	0-1	104,075	12	3.94	3.04	5.301	2.874	yes	14-20	2	8	0.88	0	2.850	no
10	Seizures, with PCV13	0-1	116,133	12	4.47	2.69	4.326	2.874	yes	14-20	4	10	1.40	0.154	2.850	no
6	Seizures, without PCV13	0-1	233,728	4	7.76	0.52	0	3.231	no	14-20	0	2	0			no
7	Seizures, without PCV13	0-1	282,686	6	9.95	0.60	0	3.231	no	14-20	2	19	0.37	0	3.247	no
8	Seizures, without PCV13	0-1	283,514	6	9.99	0.60	0	3.231	no	14-20	2	19	0.37	0	3.247	no
9	Seizures, without PCV13	0-1	322,972	7	12.68	0.55	0	3.231	no	14-20	4	35	0.40	0	3.247	no
10	Seizures, without PCV13	0-1	349,628	8	13.91	0.57	0	3.231	no	14-20	5	39	0.45	0	3.247	no

a Log likelihood ratio set to 0 where RR < 1.
b Number of cumulative events observed must be ≥ 3 for analysis to be conducted.
c Number of cumulative events observed in both intervals must be ≥ 4 for analysis to be conducted.

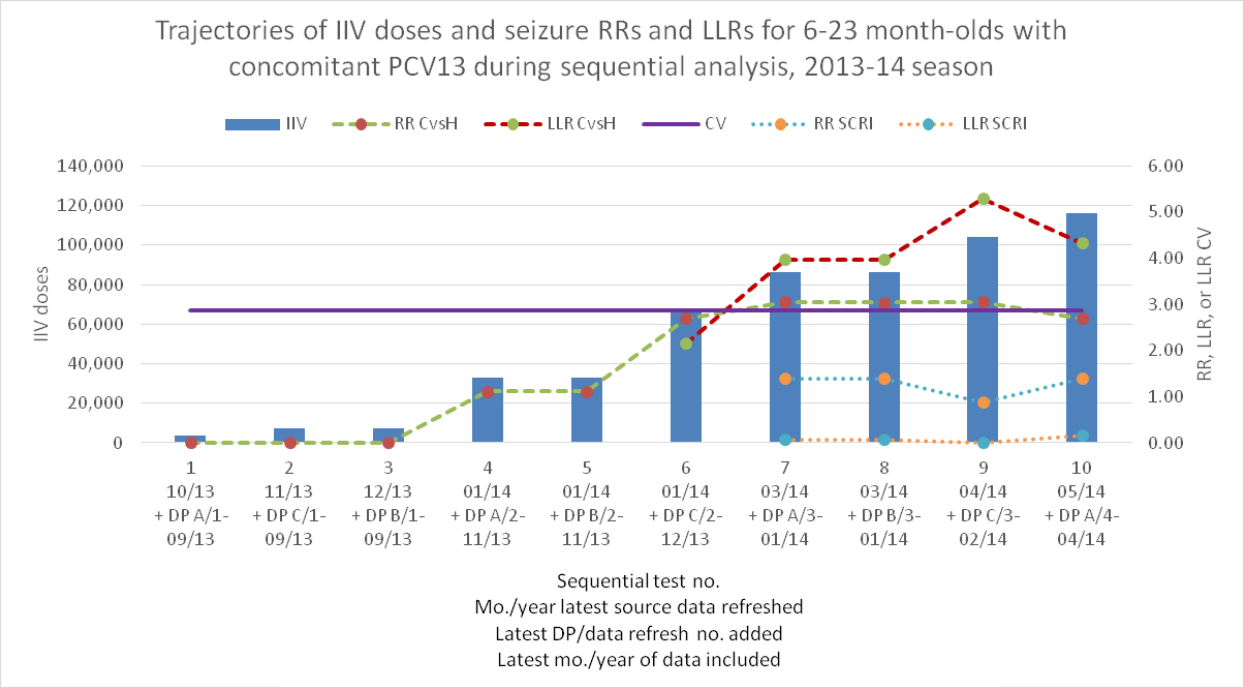

Figure 3. Trajectories of IIV doses and seizure RRs and LLRs for 6-23 month-olds with concomitant PCV13 over the course of sequential analysis. RR CvsH and LLR CvsH are for the current vs. historical analysis. The LLR critical values for the two analysis methods were too close to distinguish from each other; the horizontal purple line represents the LLR critical values (CV) of both. A statistical signal emerged from the current vs. historical analysis in Test #7, and the RR was 2.7 by Test #10. No statistical signal appeared with the SCRI analysis; the RR at Test #10 was 1.4.

D. SIGNAL EVALUATION

1. Background and current rates of seizure

As mentioned in Section II.E.5., the background rates were for influenza vaccination without regard to concomitant vaccination of any kind, and the same Data Partner-specific background rates were used for those with as for those without concomitant PCV13 in current-vs.-historical sequential analysis. The rates were purposely drawn from prior to July 2010 to avoid seasons where an increased risk after IIV (and after IIV+PCV13) had been observed in other studies. Thus, they would have included some concomitant PCV7 but very little PCV13, which was not licensed until February 2010. No obvious secular trend was apparent upon visual inspection of the rates over the period to be used. Point estimates differed somewhat among Data Partners, but confidence intervals overlapped substantially.

Figure 4 shows the background rates in terms of seizures per dose of IIV for each of the three Data Partners separately and for all of them combined. The observed rates for IIV vaccinees with and without concomitant PCV13 in the 2013-14 season are included for comparative purposes, making it easier to understand how a statistical signal emerged for the IIV+PCV13 concomitant vaccinees (and also why the RR was less than 1 for the IIV vaccinees not receiving concomitant PCV13).

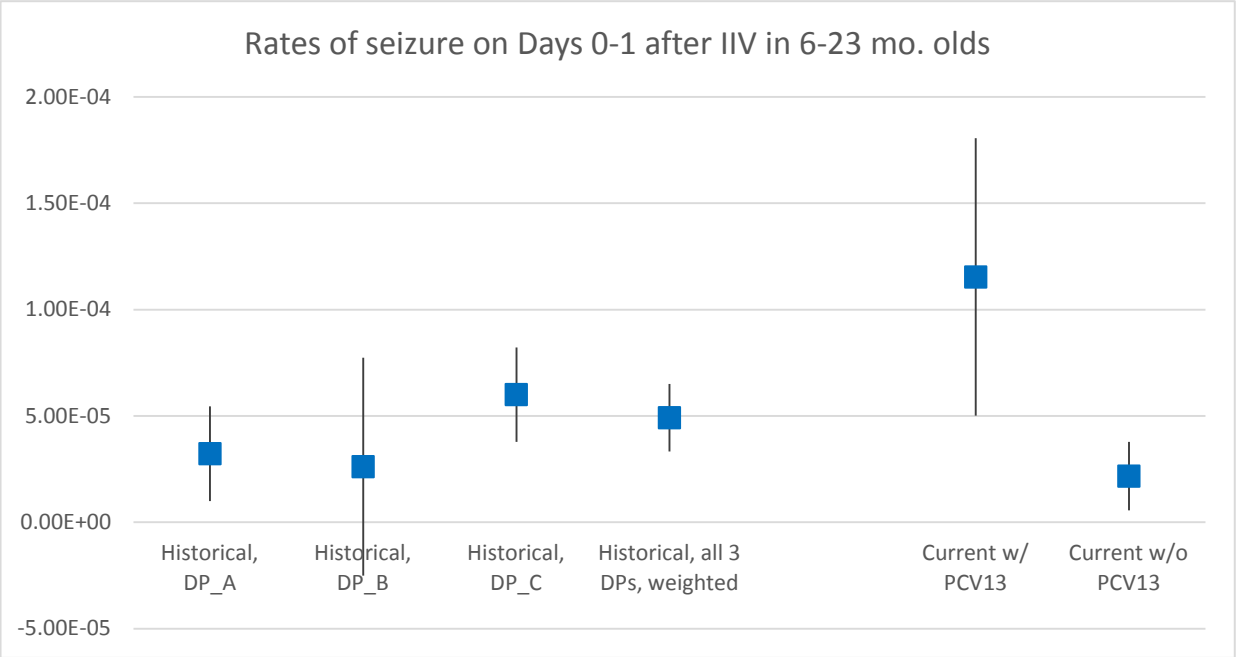

Figure 4. Rates of seizure in 6-23 month olds in terms of number of events in Days 0-1 per dose of IIV. On the left are historical background rates; on the right are observed rates in IIV vaccinees with and without concomitant PCV13 in the 2013-14 season.

The fact that no specific period of prior enrollment was required for patients in the 2013-14 surveillance season, while the background rates required 6 months of pre-vaccination enrollment, theoretically could have biased the current vs. historical analyses toward signaling and may indeed have made the point estimate higher than it would have been had we imposed the same enrollment requirement on both current and historical groups. However, the difference in rates among historical IIV, 2013-14 IIV with PCV13, and 2013-14 IIV without PCV13 vaccinees (Figure 4) suggests that PCV13 was more influential in producing the statistical signal than any differences in enrollment criteria would have been.

The possibility of confounding by age was considered, since an average background rate for the 6-23 month old children was used, and given that (a) PCV13 concomitant vaccinees would tend to be clustered around 6 and 12 months of age, while the IIV vaccinees without regard to concomitant vaccination would be spread more evenly across the full 6-23 month old age range, and (b) seizures incidence varies by age, peaking at around 16 months of age.(19) However, if the number of IIV vaccinations is fairly uniform across the 6-23 month age range, then the average rate for the whole age range would tend to be too high for the younger half of the range (ages 6-14 months), biasing away from signaling, and too low for the older half of the range (ages 15-23 months), biasing toward signaling. Thus, if the concomitant PCV13 vaccinees are in the younger half as expected, then the background rates used would have been too high rather than too low, and the bias would have been away from signaling.

2. Comparison of results from primary and secondary analyses

The primary, SCRI analysis, which compared the risk in exposed vs. unexposed time, did not signal statistically. By Test #10, the RRs of the primary (SCRI) and secondary (current vs. historical) analyses were 1.4 and 2.7, respectively (Table 6 and Figure 3).

3. Regression comparing risk in IIV vaccinees with vs. without concomitant PCV13

The logistic regression analysis of IIV vaccinees in 2012-13 and 2013-14 (adjusting for Data Partner, week of season (linear and squared), sex, dose, and season) found that 6-23-month-old children receiving concomitant IIV and PCV13 had a greater risk of seizures in the 0-1 days following vaccination compared to those receiving IIV without concomitant PCV13, with an OR of 3.1 (95% CI: 1.7, 5.9; p=0.0004). However, this was not a self-controlled analysis, thus it was subject to potential residual confounding. Furthermore, it was not designed to disentangle the effect of concomitant IIV and PCV13 vaccination from the effect of PCV13 vaccination by itself.

E. SYSTEM EVALUATION

The results of the evaluation of the fresh data are presented in Appendix A, and those of the assessment of the IIS experience in Appendix B.

IV. DISCUSSION

This surveillance effort demonstrates the feasibility of obtaining and analyzing Mini-Sentinel data on exposures and health outcomes occurring as recently as 6 weeks in the past. Moreover, Data Partners provided these fresh data on a bi-monthly basis and could potentially do so on a monthly basis, as their source data are updated monthly. The freshness of these data and the frequency with which updated data can be analyzed may hold promise for monitoring the safety of products whose evaluation, for whatever reason, cannot await the minimum 6-9 months it typically takes for Mini-Sentinel data to mature and become available and whose evaluation requires more frequent looks at accumulating data than are possible with the current Mini-Sentinel quarterly updating schedule.

We have also demonstrated the possibility of incorporating vaccination data from IISs into the datasets for analysis. Eighteen DP-IIS matches were conducted, allowing incorporation of IIS data into the last three of the 10 sequential analyses conducted in 2013-14. Only 4.3% of the influenza doses came from IISs alone, but this proportion would be higher (a) under conditions of emergency mass vaccination, as during pandemics, and (b) if the denominator were restricted to Data Partner members living in states with participating IISs. (See Appendix B for a fuller consideration of IIS data.)

As we have found in other vaccine safety research,(4, 10, 20) it was informative to use both the SCRI and the current-vs.-historical designs, which were somewhat complementary. The former, a self-controlled design, controls better for most confounding, but the latter has greater power and can detect risks sooner.(21) We designated the SCRI as the primary design for the seizures outcomes and the current vs. historical comparison as the only design for the anaphylaxis outcome and as the secondary design for the seizures outcomes. An innovation compared to past influenza vaccine safety monitoring efforts(3-5) was the stratification of seizures in 6-23-month-olds into those with and those without concomitant PCV13. This was done in recognition of a possible difference in risk of seizures between the two groups,

as was noted in the VSD in 2010-11, out of a desire not to mask a higher risk in the concomitant vaccinees.(5)

A statistical signal for seizures in 6-23 month-old concomitant IIV+PCV13 vaccinees was seen in the secondary, current-vs.-historical analysis (RR=3.0, decreasing to 2.7 by the last test), where the comparison group was IIV vaccinees (largely without concomitant PCV13) with 6 months prior enrollment in previous seasons. However, no statistical signal was seen in the primary, SCRI analysis (RR=1.4), where the comparison of risk was between exposed and unexposed time from the same concomitant vaccinees. The finding of a potential increased risk in IIV vaccinees receiving concomitant PCV13 compared with IIV vaccinees not receiving PCV13 must be interpreted cautiously since this analysis was not self-controlled and compared the lag-adjusted incidence of seizures using the earliest available clinical data to historical data in the Common Data Model that are more mature and settled. Additionally, lacking data on the risk of seizures in PCV13 vaccinees not receiving IIV, the current study is unable to determine whether the signal, if real, is due to the PCV13 vaccine entirely or to some interaction between 2013-14 IIV and PCV13.

Indications have emerged of a possible increased risk of febrile seizures after IIV vaccination in young children in the U.S. in some prior seasons.(5, 22, 23) However, given the usual annual change in influenza vaccine antigenic composition, the relevance of results from earlier seasons to our finding of 2013-14 is unclear. For example, PRISM did not find a statistically significant elevated risk for febrile seizures in the 2010-11 season. VSD found an increased risk of seizure after IIV in 2010-11(5) and 2011-12(23) (in which seasons the antigenic composition of the vaccine was the same) but not in 2012-13(23) or 2013-14.(24) In 2013-14, like PRISM, VSD stratified the seizures outcome into 6-23- and 24-59-month-old age groups, but, unlike PRISM, they did not stratify the exposure for the 6-23-month-olds into IIV with and IIV without concomitant PCV13. This may explain the apparently different findings between the two systems that season—indeed, if we pool our 6-23-month-old IIV vaccinees (i.e., without regard to concomitant PCV13), the number of observed cases is 20 vs. 18.38 expected, for a relative risk of 1.09 (derived from Table 5, Analysis #10).

The independent risks of IIV and PCV13 with respect to seizures will be examined in a separate study, which will use the SCRI design, incorporate more influenza seasons, and implement adjustments similar to those used in the PRISM study of 2010-11 IIV and febrile seizures.(12) We expect the new study to shed light on the validity of the statistical signal found using the freshest feasible data during surveillance in 2013-14 and the roles of IIV and PCV13. The findings from this signal evaluation study will also help to inform our future surveillance efforts, particularly regarding the interpretation of signals following concomitant vaccination.

Although the signal did not appear until Analysis 7, conducted on 3/10/2014 (exact dates of the 2013-14 sequential analyses are shown in Table A2), it is worth considering if and when the system would have signaled under circumstances of a true increased risk of the magnitude found for Fluvax and Fluvax Junior in Australia in 2010. The ratio of observed to expected in that instance was approximately 9.(25) This is an important example, because the risk identified was sufficiently high to result in changes to ACIP recommendations for the US-equivalent of the Fluvax vaccine (Afluria, CSL Limited) and to lead to a label change to restrict the FDA approved usage of Afluria to children aged 5 years or older, as well as the addition of this information to the Warnings and Precautions section. Simulations found that, if the true RR of seizures among 6-23-month-olds receiving concomitant IIV and PCV13 vaccines had been 9,

as it was for Fluvax, the probability of seeing a signal would have been 90% by Analysis 4 (Table 7), which was conducted on 1/9/2014. The probability of seeing a signal even for true RRs of 8 or 7 was also quite high (85% and 75%, respectively). By Analysis 6, conducted on 2/18/2014, the power to see a signal in the case of a true RR as low as 4 was almost 80%.

Table 7. Probability of signaling for a given relative risk at a given look, using the actual expected counts for the 6-23 month old IIV+PCV13 concomitant vaccinees in 2013-14 and a required minimum-number-of-observed-cases-to-signal of 3. (Simulations and table courtesy of Judith Maro.)

	Expected Counts*→	0.0247	0.0312	0.0313	0.9017	0.9019	2.2362	2.9551	2.9620	3.9419	4.4668
	Looks→	1	2	3	4	5	6	7	8	9	10
RR	2	0.000	0.000	0.000	0.04	0.04	0.17	0.24	0.25	0.27	0.29
	3	0.000	0.000	0.000	0.14	0.14	0.51	0.66	0.66	0.74	0.78
	4	0.000	0.000	0.000	0.29	0.29	0.79	0.90	0.90	0.95	0.97
	5	0.000	0.001	0.001	0.47	0.47	0.93	0.98	0.98	0.99	1.00
	6	0.000	0.001	0.001	0.63	0.63	0.98	1.00	1.00	1.00	1.00
	7	0.001	0.002	0.002	0.75	0.75	1.00	1.00	1.00	1.00	1.00
	8	0.001	0.002	0.002	0.85	0.85	1.00	1.00	1.00	1.00	1.00
	9	0.002	0.003	0.003	0.91	0.91	1.00	1.00	1.00	1.00	1.00
	10	0.002	0.004	0.004	0.95	0.94	1.00	1.00	1.00	1.00	1.00

* The expected count at each look was based on Data Partner-specific background rates and the cumulative number of IIV doses administered concomitantly with PCV13 to 6-23 month olds as of that look, with data lag adjustment applied.

The utility of the active surveillance system appears higher if, instead of restricting ourselves to the relatively small group of 6-23 month olds receiving PCV13 concomitantly with IIV in which our signal occurred, we consider all 6-23 month olds. To do this, we sum the expected counts for the children with IIV with and without concomitant PCV13 and repeat the simulations. As can be seen in Table 8, the probability of detecting a signal for a given true RR is higher at earlier looks compared to in Table 7. For example, by Look 4 (conducted on 1/9/2014) the probability of detecting a signal in the case of a true RR as low as 4 was 90%.

Table 8. Probability of signaling for a given relative risk at a given look, using the expected counts for all 6-23 month old IIV vaccinees in 2013-14 and a required minimum-number-of-observed-cases-to-signal of 3. (Simulations and table courtesy of Judith Maro.)

	Expected Counts*→	0.0881	0.1124	0.1125	3.8738	3.8755	9.9969	12.9072	12.9487	16.6213	18.3813
	Looks→	1	2	3	4	5	6	7	8	9	10
RR	2	0.001	0.002	0.002	0.16	0.16	0.44	0.51	0.52	0.61	0.70
	3	0.002	0.005	0.005	0.61	0.61	0.97	0.99	0.99	1.00	1.00
	4	0.006	0.010	0.011	0.90	0.90	1.00	1.00	1.00	1.00	1.00
	5	0.010	0.020	0.020	0.99	0.99	1.00	1.00	1.00	1.00	1.00
	6	0.017	0.031	0.032	1.00	1.00	1.00	1.00	1.00	1.00	1.00
	7	0.024	0.045	0.046	1.00	1.00	1.00	1.00	1.00	1.00	1.00
	8	0.034	0.064	0.062	1.00	1.00	1.00	1.00	1.00	1.00	1.00
	9	0.046	0.082	0.084	1.00	1.00	1.00	1.00	1.00	1.00	1.00
	10	0.061	0.104	0.104	1.00	1.00	1.00	1.00	1.00	1.00	1.00

* The expected count at each look was based on Data Partner-specific background rates and the cumulative number of IIV doses administered to all 6-23 month old IIV vaccinees as of that look, with data lag adjustment applied.

There are some significant limitations to conducting surveillance using fresh, frequently updated data, particularly for influenza vaccine safety monitoring. (Some of these observations emerged from the in-depth evaluation of the fresh data presented in Appendix A rather than being explicitly treated in the Results section above.)

1. *Cost.* Processing, QC-ing, and analyzing fresh data were resource-intensive for both Data Partners and coordinating center because of the non-routine nature of the work and the frequency of data-processing. To institutionalize such a system would require substantial infrastructure support.

2. *Unpredictability of changes at Data Partners affecting data quality and timeliness.* Although two serious data quality problems were found and resolved during the 2012-13 pilot season (Appendix A, Section C.2.a.), there were a number of system-wide changes or other events at the Data Partners in the 2013-14 surveillance season (Appendix A, Table A2 notes), which, if not noticed and addressed, would have affected data quality and which did lead to delays in data provision. In some cases, these could not have been foreseen or prepared for.

3. *Need for more careful scrutiny of statistical signals when using fresh data compared to mature data.* The comparison of fresh vs. mature data for the 2012-13 season identified some differences in dose counts, case counts, and risk estimates between the two data types (Appendix A, Section C.4.). Risk estimates were more divergent between fresh and mature data for SCRI analyses than for current-vs.-historical analyses. These differences between results from fresh and mature data were likely related to low case counts and consequent instability of risk estimates, possibly combined with inaccuracies in the lag adjustment of analyses using the fresh data. (We conducted the lag characterization in early 2012, and lag patterns might have changed by the 2012-13 and 2013-14 influenza seasons.)

4. *Non-specific influenza vaccine codes.* As mentioned earlier, the lack of brand-specific vaccine codes for many influenza vaccine products in all but the NDC coding system prevented us from identifying all doses of all specific vaccine brands. However, this was not a limitation of the fresh data system per se, but rather of influenza vaccination data in claims in general.

5. *Suboptimal statistical power and time to signal.* Even with the more timely current-vs.-historical analysis, the statistical signal for seizures in 6-23 month old IIV+PCV13 vaccinees was not discovered until March 2014, after the influenza season was essentially over. Statistical power and time to signal would be more favorable if the sample size were larger, which could be achieved by means of a larger surveillance system (more data partners), longer surveillance than is possible for influenza vaccine, a wider age range, or a more common outcome. Longer surveillance seems a particularly feasible option where products other than influenza vaccine are concerned. Alternatively, if we were willing to conduct analyses on less complete data (i.e. <85% of data available in the control interval) or lowered the requirements for number of cases needed to signal, we might be able to identify signals earlier. But these changes would increase the likelihood of false signals.

However, sequential surveillance using fresh data is valuable to FDA not necessarily because the system can identify the smallest risks early (which it may not be able to), but because it can function as a safety net to ensure that the most clinically significant health risks be detected as early as possible within the

same influenza season. The potential for detecting clinically significant risks in a timely fashion, even in a quite small age group, is illustrated by Table 7 and Table 8. The true advantage of fresh data is best viewed by comparing a Mini-Sentinel system that can detect safety concerns at levels that might impact the overall benefit-risk assessment as early as January of the same season, versus a system using mature data that must wait until the following year to assess safety of novel influenza vaccines only retrospectively.

V. CONCLUSIONS

We were able to establish a sequential analysis system that uses fresh data from PRISM Data Partners, demonstrating that it is feasible to obtain and analyze data within 6 weeks of the last care in the dataset. The evaluation of the fresh data did not uncover any alarming concerns, after data quality issues were identified and corrected. We found no statistical signals for anaphylaxis. We did find a statistical signal for seizures, in concomitant IIV+PCV13 vaccinees. This will be studied more fully in a different project, which will be designed to disentangle the independent effects of IIV and PCV13.

The overriding challenge of influenza vaccine safety surveillance is the short period of time during which the vaccine is administered. The statistical signal we detected did not emerge until March 2014, too late for it to have made a difference. In order to improve power and time-to-signal, the possibility of conducting sequential analysis on data from more data partners and/or on data combined from multiple systems could be explored. During the H1N1 pandemic, for example, IISs contributed a large proportion of the influenza vaccine doses ascertained, likely due to the administration of more vaccine than usual in non-traditional settings. In the current project, the IISs contributed few additional doses, in relative terms, and efforts to obtain data from IISs were complicated by non-uniformity and changeability of IIS procedures, requiring a customized approach for each Data Partner-IIS linkage. However, based on the pandemic H1N1 experience, using IISs for vaccine safety monitoring during a pandemic would likely be valuable. Furthermore, the cost in effort of using IIS data could change considerably once national messaging standards are widely adopted by IISs, as such standardization should reduce the amount of custom work needed to obtain these data.

If and when drug or vaccine safety surveillance using frequently updated fresh data is to be implemented in the future, such as possibly during pandemics of treatable or vaccine-preventable disease, extreme vigilance in data quality monitoring will be indispensible. This is true for the M-S CDM data as well, but the task of monitoring the quality of frequently updated unsettled data, to be used for near real-time surveillance, is more pressured and ongoing. Checking data quality must not rely entirely on automated QC systems, as it is difficult to imagine ahead of time all the varieties of mistakes that can lurk in a batch of data—the scrutiny and analytic capabilities of analysts at Data Partner sites and the coordinating center must be employed in examining each new batch. Implementing a pilot run would be useful in order to practice the procedures, identify and resolve problems, and regularize data processes in preparation for prospective surveillance. However, a pilot would not eliminate all surprises, because the data systems of Data Partners will continue to change, sometimes without notice, and the changes can affect data availability and quality.

If circumstances permit, it would be preferable to conduct analyses on the settled, quarterly updated data in the M-S CDM. Sequential analysis of the settled data would provide more timely results than a

one-time analysis, would avoid possible sources of error associated with the incomplete and unsettled nature of fresh data, and would be significantly less challenging than sequential analysis of fresh data.

We conclude that Mini-Sentinel can establish a sequential analysis system that uses fresh data, if needed, for certain situations such as those involving mass medical countermeasures. Barriers to implementation and the relative strengths and weaknesses of using fresh data vs. CDM data should be considered in making decisions about whether and when to use such a system.

VI. APPENDIX A. EVALUATION OF FRESH DATA, 2012-13 AND 2013-14 SEASONS

A. INTRODUCTION

Claims data are dynamic and heterogeneous and differ from electronic medical record data in that their main purpose is reimbursement rather than healthcare. By several months after a healthcare encounter, the claims data associated with it are generally fairly settled in that most claims have been submitted and necessary adjustments made. With respect to data for our analyses, the kinds of differences that can exist between fresh and settled data for the same period of healthcare encounters are the following:

a) More vaccinations and/or cases in the settled data. The main reason for this is delay in the arrival of information to the fresh data sources. Within the claims environment, there are differences in the degree of delay in the arrival of data from healthcare encounters depending on whether patients have fee-for-service (PPO) or capitated (HMO) plans (where providers are reimbursed for monthly management of the member's health care, not reimbursed for every service provided). With fee-for-service plans, coding of procedures tends to be faster than with capitated plans, since claims are being submitted for reimbursement. So in capitated plans, delays in data arrival tend to be longer and more erratic, although there are some individual and collective incentives for entering data, e.g., to meet HEDIS standards or to achieve pay-for-performance goals.

b) More vaccinations and/or cases in the fresh data. Some reasons that fresh data can sometimes have *more* vaccinations or cases than settled data are: 1) after claims are entered and adjudicated, the insurance company might determine that the patient is no longer covered (there are often delays in discovering that patients, or whole employers, discontinue coverage), so the patient is then registered as having disenrolled and the claims are rejected and do not appear in the settled data; 2) the settled data of some Data Partners contain only a fixed number of diagnosis or procedure codes per encounter or per claim, depending on the Data Partner, while the fresh data are not limited in that way; 3) unlike the settled data, fresh data distinguish among "members" but not among unique patients, so more doses and/or cases could potentially appear (see, for example, the note under Table 1 in the main report); and 4) changes in information can cause vaccinations and/or cases originally identified in fresh data to no longer appear in the settled data (see below).

c) Different information about vaccinations or cases in the fresh data compared to the settled data. Information associated with a case can be revised while data are settling. Changes in age (birthdate), medical setting, vaccination or diagnosis date, or vaccination or diagnosis codes can change a vaccination's or case's eligibility to be included in analysis (since outcomes are defined in terms of ICD9 codes, age, setting, time since vaccination, and being the first instance in a certain period of time). Thus, vaccinations and cases can potentially appear, disappear, reappear, and/or change in certain characteristics before the data finally settle.

Our evaluation of the fresh data addressed five aspects: 1) delay in the accrual of data; 2) the data extraction experience, including timeliness; 3) data quality; 4) flux in the data over time; and 5) the degree to which the fresh data agreed with the settled data of the M-S CDM for the same period. The first of these was examined prior to the pilot season. The next three (#2-#4) were examined for both

the 2012-13 pilot season and the 2013-14 surveillance season (except for timeliness, which was only prioritized and tracked in the 2013-14 season). The last (#5) was studied only for 2012-13, due to the wait that would have been required to obtain settled data for 2013-14. All three Data Partners, Aetna, HealthCore, and Humana, participated in both seasons.

B. METHODS

1. Characterization of data lag

We define "data lag" as the delay between a patient visit and the arrival of data on procedures and diagnoses from that visit into the fresh data sources. This delay results from delays in providers submitting medical claims and delays in health insurance companies adjudicating claims, and means the fresh data are incomplete, especially for recent patient visits. Data lag must be adjusted for in order to minimize bias in our analyses of fresh data. For example, our current-vs.-historical comparison uses background rates obtained from settled, complete historical data. If no adjustment were made, we would be comparing *current, incomplete* case counts with expected counts from *historical, complete* data, and the comparison would be biased toward the null. In our self-controlled analysis, we compare the number of cases in the risk window with the number in the comparison window. Because the comparison window is after the risk window, the data in the comparison window tends to be less complete than in the risk window, and without data-lag adjustment the analysis would be biased toward signaling. Thus, it was necessary to characterize the amount of lag in the data in order to adjust for it in the analyses.

Evaluation metrics: To characterize lag times, each Data Partner quantified claims data accrual in terms of the proportion of data ultimately received for a care date that had been received by Week 1, 2, 3, … 52 after the care date. This was done separately for each medical setting—ambulatory, ED, and inpatient. The data lag characterization was conducted in early 2012, prior to the pilot season, and, because of the 52-week follow-up period, was based on care dates prior to 2012. The key metric used in the self-controlled analyses was the number of weeks by which the data from a specific medical setting for a specific Data Partner were determined to be at least 85% complete.

2. Data extraction and assessment of data quality and timeliness

During both the 2012-13 pilot season and the 2013-14 surveillance season, the three Data Partners were each asked to complete three extractions of cumulative data ("refreshes"), using their freshest feasible data. Each refresh involved creating the SDF, SCF, and SAF files, as described in the main report, Section II.B. In 2013-14, as part of a signal investigation, one Data Partner did a fourth refresh, which covered the period 9/1/2013-4/30/2014.

Data Partners completed a questionnaire about data characteristics and quality issues after the initial SDF creation in 2012. The questionnaire collected high-level descriptive statistics for each file type (e.g. Demographic, Diagnosis, Procedure, etc.), such as number of records, number of unique patient IDs, number of records for unique patient IDs, minimum and maximum dates, number and proportion of data missing for certain variables, and minimum and maximum lengths and values for certain variables. In addition, the questionnaire gathered in free text the methods used to translate data to the SDF standard data model. Issues identified in this questionnaire were investigated through e-mail and telephone communication with Data Partners, and the results were documented.

During both the 2012-13 pilot and 2013-14 surveillance seasons, data quality was further assessed by execution of a distributed SAS program after each SDF refresh. The program collected high-level descriptive information on the refreshed data, checked adherence to the rules of the SDF data model, and checked that data fields within and across tables were consistently populated within the refresh and over time. The results were examined, and the status/findings/conclusions documented.

In the 2013-14 surveillance season, a timeliness log was maintained to record date ranges in the refreshes, dates of data refreshment, dates of data provision to the coordinating center, and dates of analysis. Explanations for delays were collected from Data Partners by e-mail and included in the log.

Evaluation metrics: We evaluated data quality in descriptive terms based on assessments of SDFs, SCFs, and/or SAFs and communications with the Data Partners for both the 2012-13 and 2013-14 seasons. Further, in 2013-14, we evaluated timeliness of data provision and analysis in terms of the number of days between the last care date in a batch of data and the dates of data refreshment, provision, and analysis.

3. Assessment of data flux

We define "data flux" as fluctuations in the case data from one refresh to the next in terms of number of cases in the following categories: lost, reappeared without a change in stratification variables, reappeared with a change in stratification variables, and retained but with a change in stratification variables. We expect flux in the freshest feasible data used for influenza vaccine safety surveillance, because the fresh data source is the earliest available version of a Data Partner's adjudicated claims that are typically updated on a monthly basis. Although these claims are adjudicated, it is possible that these fresh data remain subject to change over several months, more so than the more settled data in the M-S CDM. As part of our evaluation of the fresh data, we considered it important to examine the amount and kinds of changes occurring from one set of fresh data to the next for each Data Partner. Thus, we developed a method to describe and quantify flux in the fresh data. The Case Identification Table in the SCF data model created with each data refresh captured the demographic, vaccine, and adverse event detail for each case in a single row. A distributed SAS program compared populations in versions of the Case Identification Table within each season at the patient identifier, vaccine date, vaccine type, and adverse event type level to identify cases that were new, were retained, reappeared, had lost case eligibility, or had been lost completely as of the most recent data. Among retained and reappearing cases, changes in stratification variables were monitored and quantified. Detail on variables related to case eligibility was recorded for cases that lost eligibility.

Data Partners executed the flux assessment program following the capture of any new, fully qualified cases in the SCFs during the 2012-13 and 2013-14 seasons.

Changes that might have affected the analysis results were of special interest. For example, claims from the inpatient setting typically arrive later than those from the emergency department or ambulatory settings. Thus, a case initially recorded with an emergency department setting could ultimately end up with an inpatient setting. Given that lag adjustment is setting-specific and based on mature data, a change in setting could lead to inaccuracies when lag adjustment is applied. Changes in dose number, too, could affect the analysis, if dose-specific analysis is conducted (which it was not in this project), and changes in the timing of an adverse event could be important if the event changes from being in the risk window to being outside of it or vice versa. A loss of cases indicates that changes were made to patient

identifiers, demographics, enrollment, vaccine claims, and/or adverse event claims over time. Such changes affecting case eligibility clearly would have implications for the analysis, as cases that should be included in analysis might not be, and vice versa.

Evaluation metrics: We quantified for each data refresh after the first one the number of cases retained without changing strata, retained with changes in stratification variables, reappeared without changes in stratification variables, reappeared with changes in stratification variables, and lost. We present the results in a more summarized, qualitative way.

4. Comparison of fresh data with mature data

We considered it reasonable, as part of our evaluation of the fresh data, to compare dose counts, case counts, and relative risks from fresh data with those from mature data for the same calendar periods of care dates. When we speak of comparing fresh data with mature data, we are referring to the batches of fresh data (SAFs) incorporated into sequential analysis and to mature data in the same format obtained from the M-S CDM. As specified in the protocol, the comparison of fresh and mature data was conducted for the 2012-13 season but not the 2013-14 season, due to the relatively lengthy period required for data to settle and become available in the CDM. So the fresh data used for the comparison were the 2012-13 SAFs. The settled data for the comparison were obtained by running a PRISM program on Data Partners' M-S CDM data in June 2014 to create files in the same SAF format for the same season. Data Partners' M-S CDMs included claims through 7/31/2013, 9/30/2013, and 10/31/2013, respectively; in view of these dates, the M-S CDM data obtained for all Data Partners for the 2012-13 influenza season were considered complete. In 2012-13, Guillain-Barre syndrome (GBS) was monitored instead of anaphylaxis.

The comparison was purely descriptive, involving no formal hypothesis-testing or adjustment for multiple testing. The sequence of looks at fresh and mature data, along with the data included in each look, are shown in Table A1. Data lag adjustment (see main report, Section II.E.6.) was applied to the fresh data. The mature data were truncated to create datasets covering the same periods as those covered by the corresponding fresh data. The September 2012 data for all three Data Partners were combined in the first look because of the few cases expected in the first month of vaccination, especially with lag adjustment applied. There were data quality issues at one Data Partner during the 2012-13 season (see Section C.2. of this appendix); therefore, we excluded their data from the comparison until the point at which the problems had been corrected.

Table A1. Date ranges of doses included in the comparisons of fresh vs. mature data, by analysis number, study design, and Data Partner, 2012-13

	Dates of doses included for current vs. historical and for SCRI with fresh data[a]			Dates of doses included for SCRI with mature data[b]		
Anal-ysis #	1st Data Partner	2nd Data Partner	3rd Data Partner	1st Data Partner	2nd Data Partner	3rd Data Partner
1	9/1/2012-9/30/2012	9/1/2012-9/30/2012		9/1/2012-9/7/2012	9/1/2012-9/7/2012	
2	9/1/2012 - 11/30/2012	Retain above		9/1/2012 - 11/7/2012	Retain above	
3	Retain above	9/1/2012 - 12/31/2012		Retain above	9/1/2012 - 12/7/2012	
4	9/1/2012 - 1/31/2013	Retain above		9/1/2012 - 1/7/2013	Retain above	
5	Retain above	9/1/2012 - 2/28/2013		Retain above	9/1/2012 - 2/7/2013	
6	Retain above	Retain above	9/1/2012 - 4/30/2013	Retain above	Retain above	9/1/2012 - 4/7/2013

[a] For the SCRI analyses with fresh data, the date ranges shown reflect the original full data to which data lag adjustment was applied. However, this adjustment (see main report, Section II.E.6.) meant that the date ranges of the data actually included were shorter than those shown.

[b] For the SCRI analyses with mature data, in order to ensure inclusion of both the risk and control intervals, we excluded vaccine doses beyond the seventh day of the last month of data, along with their associated outcomes. For example, for the third Data Partner's mature data in Analysis 6, only doses for 9/1/2012-4/7/2013 (and their associated outcomes even if beyond 4/7/2013) were included rather than doses for 9/1/2012-4/30/2013.

The current vs. historical analyses used Data Partner-specific background rates for influenza vaccinees obtained from several years of historical PRISM data in 2012. Six months of pre-vaccination enrolled time was required. Rates for GBS were for all Data Partners combined, due to the rarity of that outcome and resulting instability of Data Partner-specific estimates. Rates for seizures were Data Partner-specific and excluded person-time from 7/2010 on, due to the increased risk of seizures after inactivated influenza vaccination observed in young children in the VSD in 2010-11.

Evaluation metrics: The fresh and the mature data were compared with respect to dose counts, observed and expected case counts (and, for seizure outcomes, observed counts in risk and comparison intervals), and risk estimates for six batches of cumulative data.

C. RESULTS

1. Data lag

Among the three Data Partners, the number of weeks to get to ≥ 85% data completeness ranged between 7 and 13 for the ED setting and between 10 and 18 for the inpatient setting. As an example, the data lag pattern for one Data Partner is shown in Figure A1. (The ambulatory care setting is included in the figure, although it was not used in case identification algorithms (main report, Table 1).)

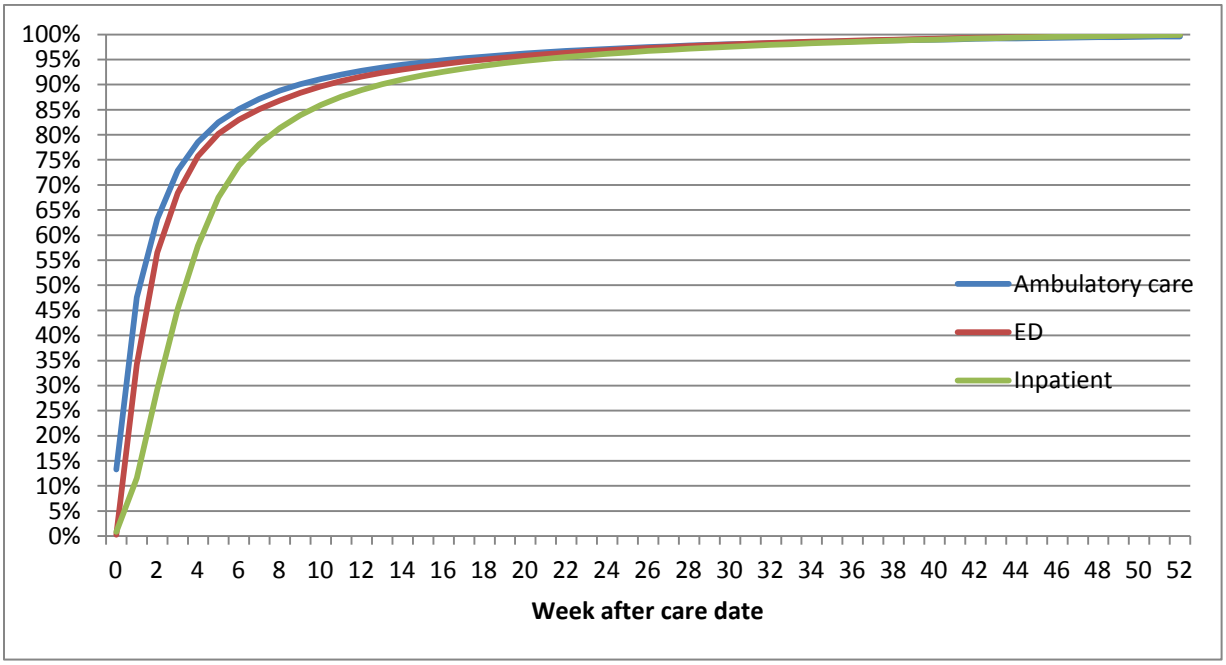

Figure A1. One Data Partner's claims data accrual over time for three medical settings. Data are ~85% complete by 6, 7, and 10 weeks after the care date for ambulatory, ED, and inpatient settings, respectively. The ambulatory care setting was not used in case ascertainment algorithms.

2. Data quality and timeliness

a. 2012-13

Data quality: For two of the Data Partners, no quality problems were identified in any of the three data refreshes. While checking the quality of the other Data Partner's refresh capturing data from 9/1/2012-12/31/2012, we discovered that a significant number of vaccine claims had disappeared from the SDF Dispensing Table relative to its prior version (containing data for 9/1/2012-9/30/2012). The disappearing records were a consequence of a rounding error in the days' supply field that led to the exclusion of valid records from the Dispensing Table. This SDF refresh was considered invalid and was excluded from processing and analysis. A second significant data quality issue was identified while assessing SCF flux in the same Data Partner's final data refresh (containing data for 9/1/2012-4/30/2013). A number of cases in the Case Identification Table had been lost relative to the previous version of this table. This was found to be due to population of the SDF Procedure and Diagnosis Tables with only one procedure/diagnosis code per claim regardless of the actual number of procedure/diagnosis codes on a given claim. Furthermore, the single included procedure/diagnosis

code was chosen at random, resulting in inconsistencies in the procedure/diagnosis code selected for a given medical claim across data refreshes. The Data Partner corrected this problem and recreated the Procedure and Diagnosis Tables for their final refresh, though data from previous refreshes remained unchanged, because the issue was not discovered until the last refresh.

b. 2013-14

Data quality: No data quality problems were identified in the data ultimately provided by Data Partners during 2013-14, although some were encountered during processing at the Data Partners (Table A2).

Data timeliness: Timing and timeliness of data refreshes, provision, and analysis are presented in Table A2. Median time lapses and ranges between various dates are listed below (excluding Refresh #1, where urgency was not high, as we knew there were too few cases to produce a statistical signal):

- last care-date in batch of data to data refresh date: 34 (21-53) days
- data refresh date to date QC'ed data provided to coordinating center: 5 (1-21) days
- date QC'ed data provided to analysis date: 1 (0-7) days
- overall: last care-date in batch of data to analysis date: 40 (30-55) days

Analysis results (after Refresh #1) were generally available about 6 weeks after the end of the most recent calendar month featured in the data (shown with less detail in Figure 1 of the main report). As detailed in the notes in and below Table A2, various obstacles were confronted and overcome. They involved issues at the Data Partners, such as data quality problems, unforeseen system-wide changes, limitations in data processing capacity, and problems in converting IIS data to the required format.

Table A2. Timeliness of sequential data production and analysis, by refresh number and Data Partner, 2013-2014

Refresh #	Data partner	Analysis order planned	Actual analysis order	Intended time-frame of health-event data	Actual time-frame of health-event data	Source data refresh date	Date data intended to be provided	Date QC'd data actually provided	Date of final approved analysis	Notes (long notes are numbered and listed below table)
1	A	1	1	9/1/2012 – 9/30/2013	9/1/2012 – 9/30/2013	10/30/2013	Early Nov.	11/5/2013	12/17/2013	Note 1
1	B	2	3	9/1/2012 – 9/30/2013	9/1/2012 – 9/30/2013	12/3/2013	Early Nov.	12/9/2013	12/17/2013	Note 2
1	C	3	2	9/1/2012 – 10/31/2013	9/1/2012 – 9/30/2013	11/25/2013	Early Dec.	12/2/2013	12/17/2013	Oct. 2013 data excluded due to inaccuracies in pharmacy component of source data
2	A	4	4	9/1/2012 – 11/30/2013	9/1/2012 – 11/30/2013	1/4/2014	Early Jan.	1/9/2014	1/9/2014	Data Partner made changes to program; SDFs then successfully created directly from data warehouse
2	B	5	5	9/1/2012 – 11/30/2013	9/1/2012 – 11/30/2013	1/3/2014	Early Jan.	1/10/2014	1/13/2014	
2	C	6	6	9/1/2012 – 12/31/2013	9/1/2012 – 12/29/2013	1/27/2014	Early Feb.	2/17/2014	2/18/2014	Note 3
3	A	7	7	9/1/2012 – 1/31/2014	9/1/2012 – 1/31/2014	3/4/2014	Early March	3/10/2014	3/10/2014	State Vaccine table mistakenly not incorporated in SAF creation
3	B	8	8	9/1/2012 – 1/31/2014	9/1/2012 – 1/31/2014	3/25/2014	Early March	3/26/2014	3/27/2014	SDFs approved on 3/10 but State Vaccine file not approved until 3/25; Note 4
3	C	9	9	9/1/2012 – 2/28/2014	9/1/2012 – 2/28/2014	4/3/2014	Early April	4/7/2014	4/9/2014	SDFs approved on 4/1 and State Vaccine file approved on 4/3
4	A	10	10	9/1/2012 – 4/30/2014	9/1/2012 – 4/30/2014	5/21/2014	Early June	5/23/2014	5/30/2014	State Vaccine table incorporated in SAFs this time

Notes:

1. Data Partner A, Refresh 1: Delay in obtaining data not pronounced, but worth noting that two tables of the SDFs could not initially be created directly from data warehouse from which all previous SDFs had been generated. The reason was that this first refresh of 2013-14 included many more patients, greatly increasing size of SDFs. Problem temporarily resolved by using local source data for the M-S CDM to create the two SDF tables. After data in hand, no urgency to conduct analysis because only 1 case of any outcome present, not enough to produce a signal.
2. Data Partner B, Refresh 1: Causes of delay: a) IT changes to data structure and variable names, which required subsequent review of documentation and QC; b) temporary inability of SAS server to handle multiple users.
3. Data Partner C, Refresh 2: Refresh completed on 1/27/2014, but SAS files not available until 2/6/2014. Delay due to: a) internal problem in building SDFs; b) delay in moving SDFs from Teradata to SAS environment, due in part to size; c) protracted QC run related to ongoing system capacity issues at Data Partner (well-known to the coordinating center and slated to be addressed by moving to more powerful system sometime in late 2014).
4. Data Partner B, Refresh 3: Delay due to following: a) QC revealed special characters in > 50% of PatIDs. Out of concern that the PatIDs in this refresh would not match those in the previous refresh, Data Partner B agreed to rebuild their source files and refresh their SDFs. b) Observation of unexpected low count of vaccination records from one IIS led to discovery of problem converting that IIS data to required format. c) First State Vaccine QC report revealed error in assigning SIIS variable format; second State Vaccine QC report revealed error in converting CVX codes from one IIS to proper format in State Vaccine table. Subsequently, a previously unknown problem with PatIDs from that IIS was identified.

3. Data flux

The degree of flux (defined as loss or reappearance of cases or changes in the information associated with cases from one batch of a Data Partner's data to the next) detected in the data was generally quite low. In the pilot season, most of the flux was a result of the issues mentioned in Section C.2.a. of this appendix. During the 2013-14 season, there was relatively little flux; most of it was due to the inclusion of IIS data in the last refresh of each Data Partner, which led to a change in the vaccine source value from "claims only" to "claims and IIS" for some cases. The kinds of changes in the data that could potentially affect the analysis results were relatively infrequent during both seasons. (Such potentially influential changes in the freshest feasible source data include changes in healthcare setting, changes in timing of adverse event after vaccination, and loss of cases.)

4. Comparison of fresh data with mature data

The fresh and the mature data were compared with respect to dose counts, observed and expected case counts (and, for seizure outcomes, observed counts in risk and comparison intervals), and risk estimates for six batches of cumulative data. The results of descriptive analyses of fresh and mature data are shown side-by-side in Table A3.

Differences in dose counts: The overall number of IIV doses was always less in the fresh data than in the mature data, with the difference diminishing over the course of the season (Figure A2). The number of LAIV doses in the fresh data likewise started out less than in the mature data, but by Look 4 it had just surpassed the number in the mature data, reaching 1.6% more by Look 6.

Differences in case counts and risk estimates in current-vs.-historical analysis: Regarding the current-vs.-historical comparisons, Figures A3-A5 show numbers of cases of GBS and seizures and RRs in the fresh vs. the mature data. The number of cases was sometimes less, sometimes the same, and sometimes greater in the fresh data than in the mature data. For three vaccine-outcome pairs, RRs were in general fairly close for fresh and mature data over the six sequential looks. However, for IIV-GBS, IIV+PCV13-seizures, and LAIV-seizures, there were differences in case counts and a divergence of RRs between fresh and mature data in some of the looks (Figures A3, A4, and A5, respectively). By Look 6, the RRs were generally similar for fresh and mature data.

Differences in risk estimates in SCRI analysis: Regarding the SCRI analyses, considerably fewer cases were included in the analyses of fresh data than of mature data. This was mainly due to data lag—to minimize bias, adjustment for the lag excluded from analysis cases associated with vaccination weeks and settings for which data in both risk and control windows were estimated to be < 85% complete, and it took 7-13 weeks for ED data to reach 85% completeness and 10-18 weeks for inpatient data to do so (Section C.1. of this appendix). Numbers of cases in the mature data were almost invariably greater than or equal to numbers of cases in the fresh data. RRs were sometimes quite divergent between fresh and mature data, even close to the end of the season (Table A3). For example, the RRs for post-IIV seizures were 0.39 and 1.75 in fresh and mature data, respectively, in Analysis 5. The discrepancy decreased somewhat to RRs of 0.58 and 1.17, respectively, by Analysis 6. RRs for post-LAIV seizures were 2.00 and 1.00 in fresh and mature data, respectively, in both Analyses 5 and 6.

Table A3.					Current vs. Historical								Self-Controlled Risk Interval (SCRI)					
					Using fresh data, with data lag adjustment				Using mature (CDM) data				Using fresh data, with data lag adjustment			Using mature (CDM) data		
Vac-cine	Outcome	Age group	Risk interval (days)	Control interval for SCRI (days)	Cum. doses	Cum. events observed risk interval (current)	Cum. events expected risk interval (historical)	RR (current vs. expected)	Cum. doses	Cum. events observed risk interval (current)	Cum. events expected risk interval (historical)	RR (current vs. expected)	Cum. events risk interval	Cum. events control interval	RR (risk interval vs. control interval)	Cum. events risk interval	Cum. events control interval	RR (risk interval vs. control interval)
Analysis 1																		
IIV	GBS	≥6 mo	1-42		419,205	0	0.2119	0	1,181,333	0	0.3372	0						
	Seizures, w/o PCV13	6-23 mo	0-1	14-20	20,583	0	0.4071	0	38,762	0	0.5283	0	0	0	-	0	1	0
	Seizures, w/ PCV13	6-23 mo	0-1	14-20	7,898	0	0.1589	0	13,738	0	0.1985	0	0	0	-	0	0	-
	Seizures	24-59 mo	0-1	14-20	22,354	0	0.2531	0	44,850	0	0.3342	0	0	0	-	0	0	-
LAIV	GBS	2-49 yr	0-1		54,452	0	0.0191	0	98,407	0	0.0214	0						
	Seizures**	24-59 mo	1-3		14,152	0	0.2428	0	24,767	0	0.2948	0						
	Seizures***	24-59 mo	1-3	15-20	14,152	0	0.7354	0	24,767	0	0.8924	0	0	0	-	0	0	-
Analysis 2																		
IIV	GBS	≥6 mo	1-42		1,775,750	0	3.6449	0	2,394,689	1	4.2000	0.24						
	Seizures, w/o PCV13	6-23 mo	0-1	14-20	99,552	7	2.5166	2.78	112,341	7	2.6514	2.64	1	4	0.88	7	11	2.23
	Seizures, w/ PCV13	6-23 mo	0-1	14-20	31,464	3	0.8021	3.74	35,279	1	0.8374	1.19	0	2	0	1	9	0.39
	Seizures	24-59 mo	0-1	14-20	105,969	1	1.6342	0.61	118,919	1	1.7300	0.58	0	1	0	1	9	0.39
LAIV	GBS	2-49 yr	0-1		232,572	2	0.3315	6.03	247,740	2	0.3316	6.03						
	Seizures**	24-59 mo	1-3		55,705	1	1.3013	0.77	58,532	1	1.3013	0.77						
	Seizures***	24-59 mo	1-3	15-20	55,705	1	3.9540	0.25	58,532	1	3.9529	0.25	0	0	-	1	0	-
Analysis 3																		
IIV	GBS	≥6 mo	1-42		2,505,586	0	6.1012	0	3,054,561	4	6.9185	0.58						
	Seizures, w/o PCV13	6-23 mo	0-1	14-20	104,866	7	2.7761	2.52	119,273	7	2.9922	2.34	1	4	0.88	7	14	1.75
	Seizures, w/ PCV13	6-23 mo	0-1	14-20	33,236	3	0.8904	3.37	37,654	1	0.9555	1.05	0	2	0	1	9	0.39
	Seizures	24-59 mo	0-1	14-20	110,717	1	1.7181	0.58	124,555	1	1.8394	0.54	0	1	0	1	10	0.35
LAIV	GBS	2-49 yr	0-1		246,344	2	0.3659	5.47	263,351	2	0.3711	5.39						
	Seizures**	24-59 mo	1-3		59,065	1	1.3924	0.72	62,066	1	1.4074	0.71						
	Seizures***	24-59 mo	1-3	15-20	59,065	1	4.2153	0.24	62,066	1	4.2569	0.23	0	0	-	1	1	2.00
Analysis 4																		
IIV	GBS	≥6 mo	1-42		3,316,167	2	10.2390	0.20	3,701,134	5	11.0621	0.45						
	Seizures, w/o PCV13	6-23 mo	0-1	14-20	155,273	11	4.6285	2.38	162,199	10	4.8110	2.08	7	12	2.04	10	31	1.13
	Seizures, w/ PCV13	6-23 mo	0-1	14-20	52,951	4	1.5424	2.59	55,179	4	1.5948	2.51	3	9	1.17	4	11	1.27
	Seizures	24-59 mo	0-1	14-20	157,985	5	2.7573	1.81	165,636	6	2.8608	2.10	1	8	0.44	6	11	1.91
LAIV	GBS	2-49 yr	0-1		333,897	2	0.7489	2.67	333,427	2	0.7356	2.72						
	Seizures**	24-59 mo	1-3		77,348	2	2.0599	0.97	76,815	1	2.0269	0.49						
	Seizures***	24-59 mo	1-3	15-20	77,348	2	6.2447	0.32	76,815	1	6.1407	0.16	1	0	-	1	2	1.00
Analysis 5																		
IIV	GBS	≥6 mo	1-42		3,599,878	5	11.4728	0.44	3,812,120	6	12.0633	0.50						
	Seizures, w/o PCV13	6-23 mo	0-1	14-20	158,912	11	4.8100	2.29	163,930	10	4.9298	2.03	7	15	1.63	10	31	1.13
	Seizures, w/ PCV13	6-23 mo	0-1	14-20	54,352	4	1.6113	2.48	56,045	4	1.6467	2.43	3	9	1.17	4	11	1.27
	Seizures	24-59 mo	0-1	14-20	160,853	5	2.8093	1.78	166,963	6	2.8954	2.07	1	9	0.39	6	12	1.75
LAIV	GBS	2-49 yr	0-1		341,061	2	0.7705	2.60	335,956	2	0.7535	2.65						
	Seizures**	24-59 mo	1-3		78,818	2	2.1019	0.95	77,350	1	2.0524	0.49						
	Seizures***	24-59 mo	1-3	15-20	78,818	2	6.3650	0.31	77,350	1	6.2139	0.16	1	1	2.00	1	2	1.00
Analysis 6																		
IIV	GBS	≥6 mo	1-42		6,759,936	10	23.7559	0.42	6,973,265	9	24.4036	0.37						
	Seizures, w/o PCV13	6-23 mo	0-1	14-20	338,461	17	17.2943	0.98	335,449	17	16.8190	1.01	12	39	1.08	17	53	1.12
	Seizures, w/ PCV13	6-23 mo	0-1	14-20	116,586	7	5.8979	1.19	115,746	7	5.7433	1.22	6	16	1.31	7	22	1.11
	Seizures	24-59 mo	0-1	14-20	330,012	7	6.0839	1.15	327,610	8	6.0023	1.33	3	18	0.58	8	24	1.17
LAIV	GBS	2-49 yr	0-1		713,431	2	1.7913	1.12	702,241	2	1.7579	1.14						
	Seizures**	24-59 mo	1-3		163,418	5	4.5773	1.09	160,519	3	4.4853	0.67						
	Seizures***	24-59 mo	1-3	15-20	163,418	5	12.2136	0.41	160,519	3	11.9619	0.25	4	4	2.00	3	6	1.00
	** Historical rates used are post-IIV																	
	*** Historical rates used are post-LAIV																	

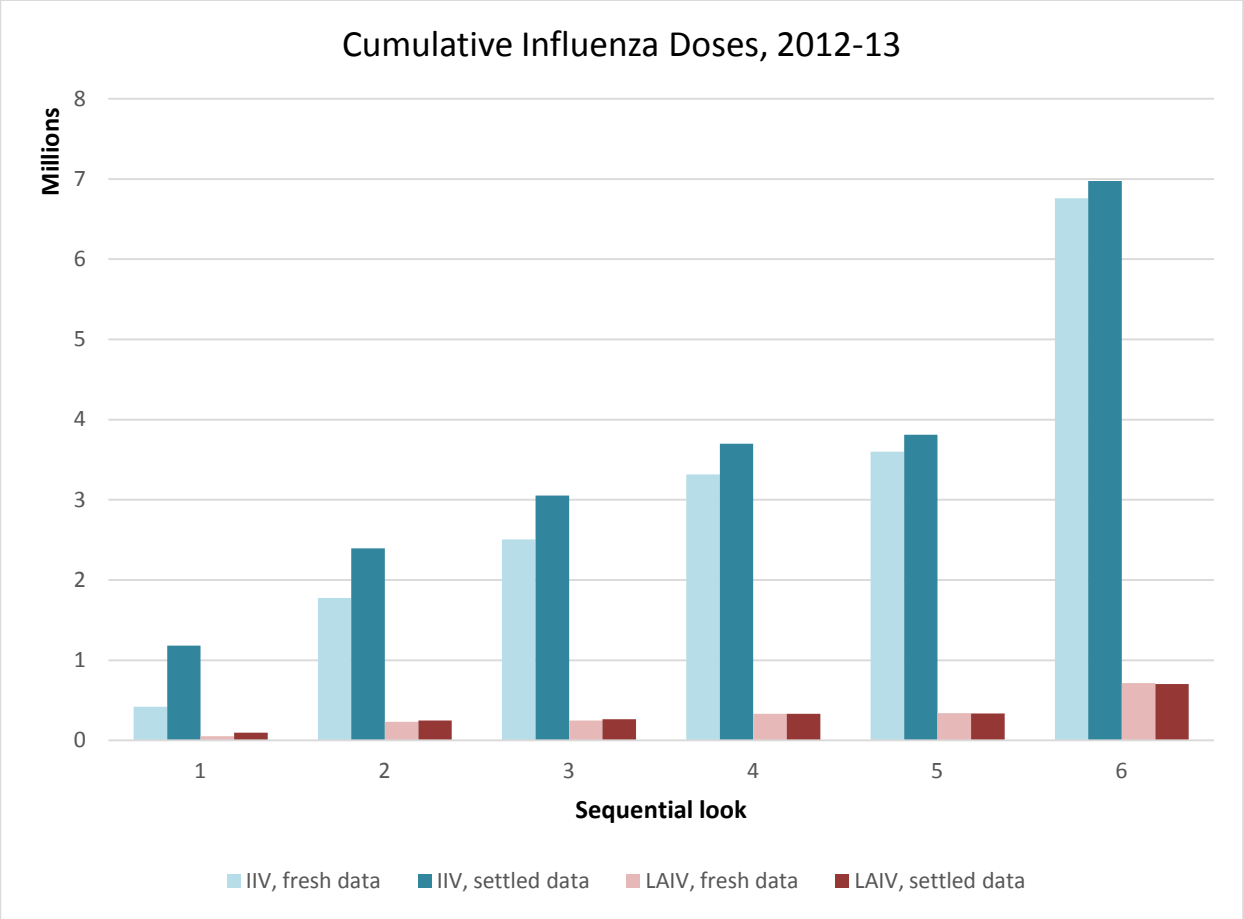

Figure A2. Cumulative influenza doses, 2012-13. The difference in dose counts between fresh and settled data generally decreased over the course of the season. Some differences are expected due to data lag, particularly early in the season. Having fewer doses decreases statistical power.

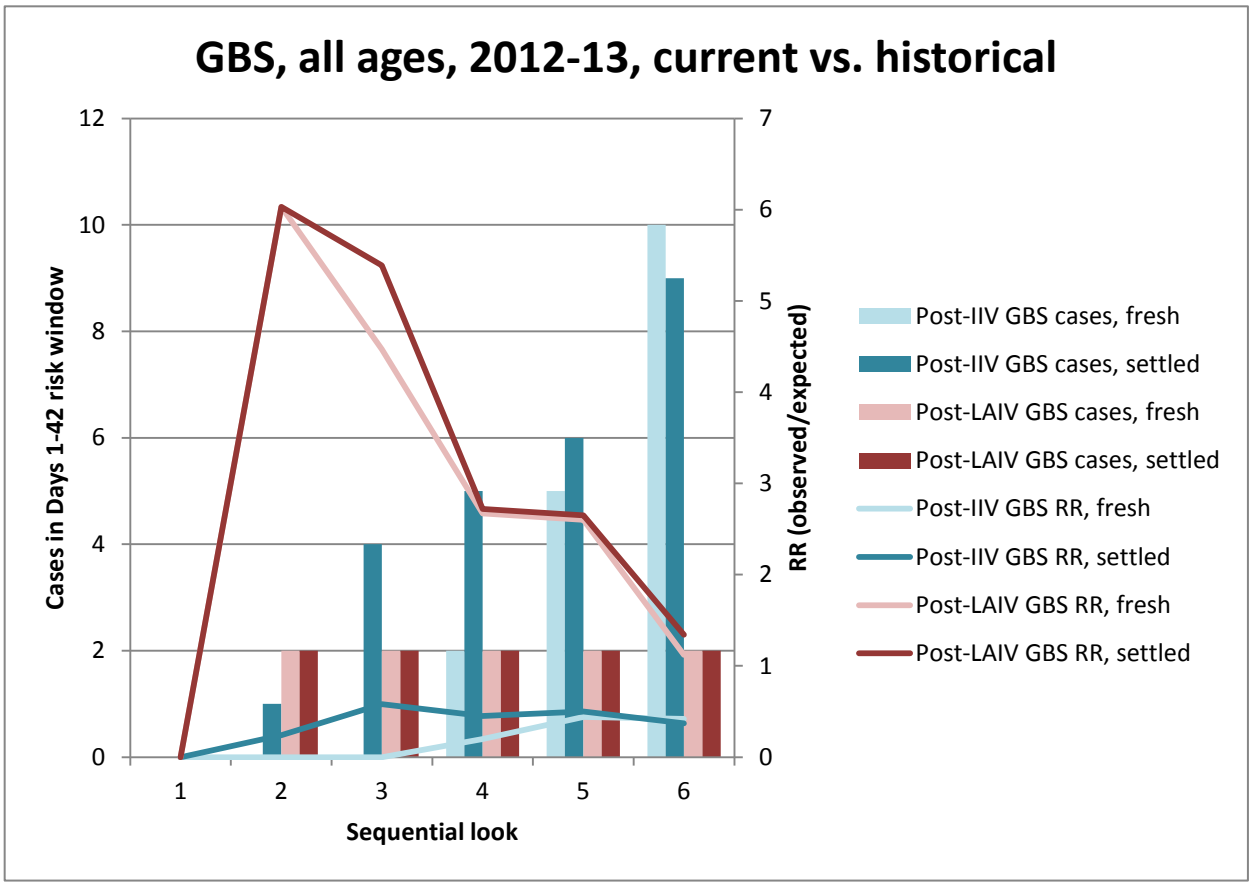

Figure A3. GBS cases and RRs in all ages, 2012-13, current-vs.-historical comparison. Post-LAIV GBS cases and RRs were fairly similar for fresh and settled data over the course of the season. RRs early in surveillance can be high due to chance early occurrences of cases among relatively few vaccinees. This is why the requirement of a minimum number of cases to signal is sometimes applied, as was done for surveillance in 2013-14. If surveillance had been conducted in 2012-13 using the same inputs as in 2013-14, there could have been no signal for LAIV-GBS, at least in part because the minimum number of cases to signal was set at 3. Post-IIV GBS cases and RRs were lower for the fresh data in Looks 2, 3, and 4, due to the delayed accrual of cases in the fresh data, but cases and RRs converged in fresh and settled data in later looks.

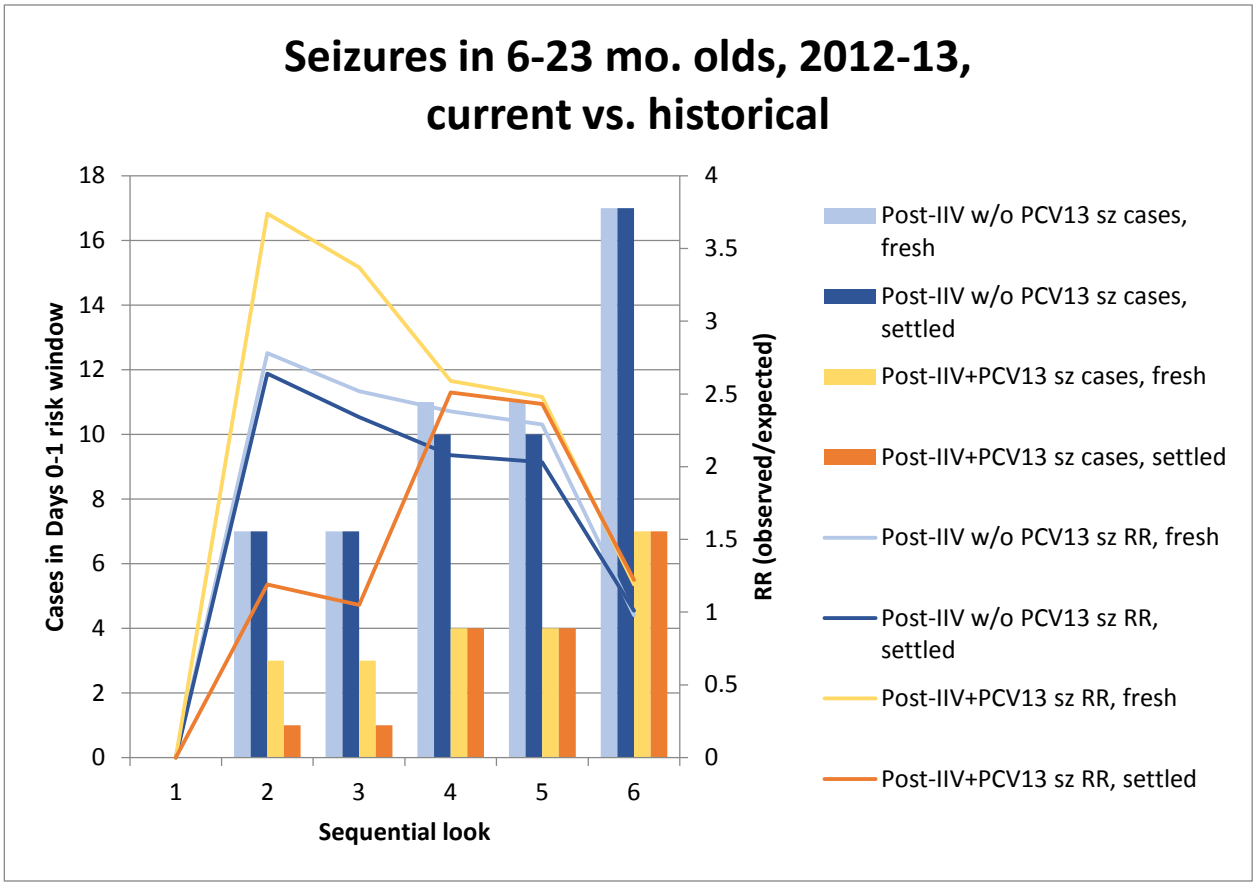

Figure A4. Seizure cases and RRs in 6-23 month olds, 2012-13, current-vs.-historical comparison. Seizure cases and RRs for IIV without concomitant PCV13 were quite similar for fresh and settled data over the course of the season. Seizure cases and RRs for IIV with concomitant PCV13 were divergent for fresh vs. settled data in Looks 2 and 3, with 3 vs. 1 cases in the fresh vs. settled data, but were essentially the same between the two data types in the last three looks. It is possible for fresh data to contain more cases than settled data for the same period, as discussed in Section A of this appendix. Post-hoc maxSPRT analysis showed that there would not have been a signal for seizure in 6-23 month old IIV+PCV13 concomitant vaccinees using the fresh data for 2012-13.

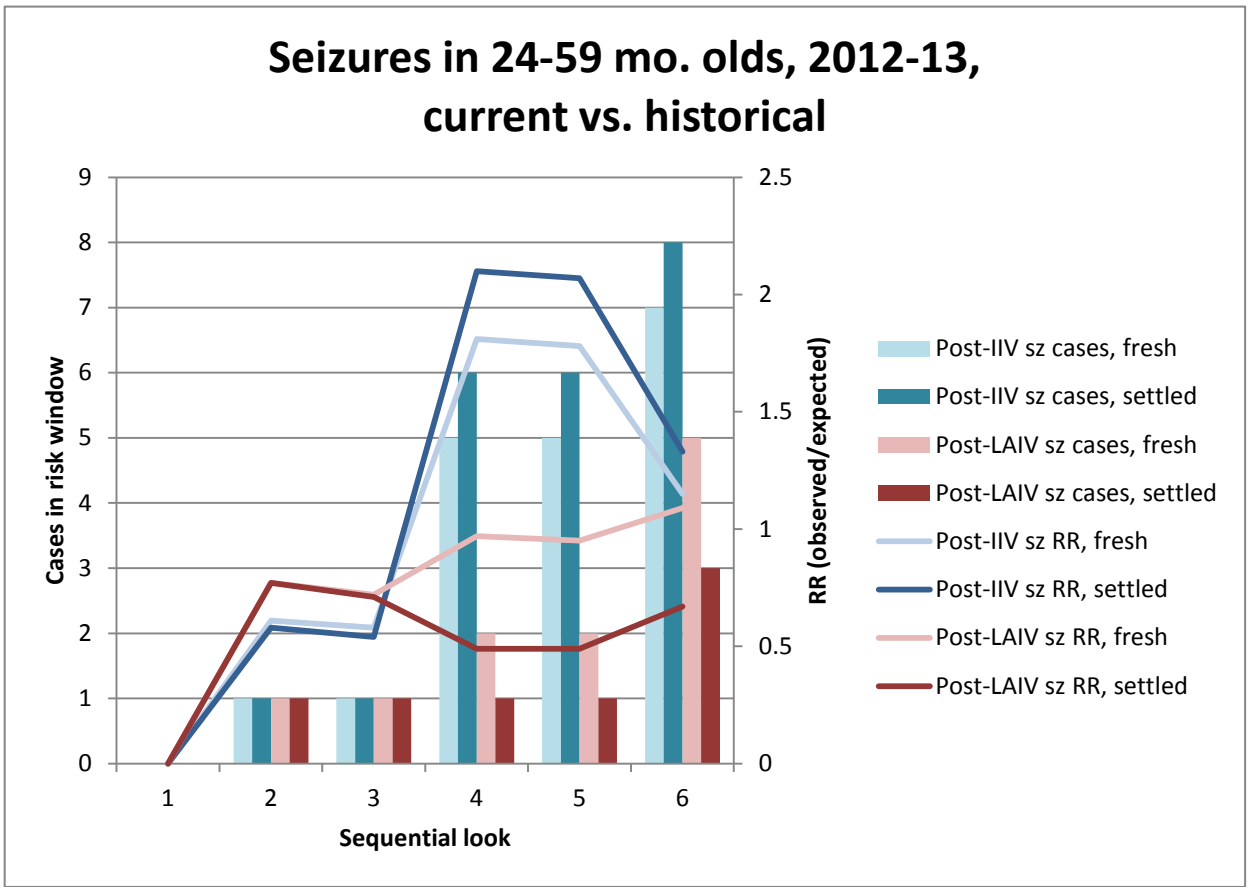

Figure A5. Seizure cases and RRs in 24-59 month olds, 2012-13, current-vs.-historical comparison. Post-IIV seizure cases and RRs were quite similar for fresh and settled data over the course of the season, with 1 more case in the settled than in the fresh data in the last three looks. Post-LAIV seizure cases and RRs differed for fresh vs. settled data in the last three looks, where low case counts meant that a difference of even 1 case could produce a quite different RR. Neither RR (1.1 and 0.7) was alarming, however.

D. DISCUSSION AND CONCLUSIONS

In this evaluation of the fresh data in terms of lag time in accrual, quality, timeliness, flux from one refresh to the next, and differences with mature data, we were reassured that fresh data could be used for sequential analysis for safety monitoring. After the practice of the pilot season, a dataset could be analyzed within 6 weeks of the last care date in it (median number of days: 40; range: 30-55); quality of the datasets provided for analysis was good except with respect to completeness; the kinds of fluctuations in the data that could potentially affect the analysis results were relatively infrequent; and dose and case counts and risk estimates were often similar to those from mature data or tended to converge on those obtained from mature data after several months.

However, we point out a number of cautions and caveats about using fresh data:

1. The delay in the accrual of data at the Data Partners was considerable, with implications for timeliness of any signal detection. According to the 2012 data lag characterization, it took 7-

13 weeks for ED data and 10-18 weeks for inpatient data to reach 85% completeness. This affects particularly the primary, self-controlled analyses, where data must be close to equally complete in both risk and comparison windows in order for analyses not to be biased.

2. There were delays in the provision of analysis datasets, due to system-wide changes or other events at the Data Partners. These included such things as inaccuracies in the pharmacy component of source data, IT changes to data structure and variable names, a temporary inability of a SAS server to handle multiple users, an internal problem in building SDFs, delay in moving SDFs from Teradata to the SAS environment due in part to size, a protracted QC run related to ongoing system capacity issues, and delays related to the incorporation of IIS data. Many of these could not have been foreseen or prepared for. Although some of these issues would have affected the creation of the quarterly refreshes of mature data for Mini-Sentinel general purposes, too, some of them were specific to working with the fresh data.

3. The comparison of fresh and mature data, conducted for the 2012-13 season only, produced mixed results. Risk estimates were more divergent between fresh and mature data for SCRI analyses than for current-vs.-historical analyses. A possible cause of the differences in results between fresh and mature data was the lower case counts in the fresh data (because of data lag and lag adjustment) and resulting instability of the risk estimates. Also, any inaccuracies in the lag characterization would have affected the validity of the results of analyses using the fresh data. (We conducted the lag characterization in early 2012 and do not know the extent to which lag patterns might have changed by the 2012-13 and 2013-14 influenza seasons.)

4. Although the data flux assessment was a creative and manageable way to get a sense of the changeability of data characterizing the cases of interest and, indirectly, of the validity of the fresh data, it included a limited population followed for a limited period of time, and time periods between refreshes were not always the same within or between Data Partners. Thus, the findings of the flux assessment are not necessarily generalizable. Also, cases were defined at the patient identifier, vaccine date, vaccine type, and adverse event type level for comparison, so flux specific to those fields could not be identified.

5. Vigilance about data quality is always required. In the 2012-13 pilot season, one Data Partner had two serious data quality problems: (a) a rounding error in the days' supply field that resulted in the erroneous exclusion of vaccination records, and (b) an incorrect algorithm that led to the selection of only one procedure and one diagnosis code, at random, from each claim instead of all procedure and diagnosis codes. These issues were ultimately found through analysis of data quality and data flux assessments by the coordinating center. In the 2013-14 surveillance season, although no data quality problems were noted in the datasets received by the coordinating center, some data quality problems had been found by Data Partners in the course of creating their patient-level files (Table A2 notes).

VII. APPENDIX B. THE EXPERIENCE WITH IMMUNIZATION INFORMATION SYSTEMS (IISS)

A. INTRODUCTION

The participation of state and city Immunization Information Systems (IISs) in providing immunization data to PRISM was identified as a strength of the system during the H1N1 pandemic of 2009-2010.(9) During that season, the 9 participating IISs contributed 36% and 14%, respectively, of the H1N1 and seasonal influenza vaccine first doses captured by PRISM. (When the denominator was restricted to just those health plan members for whom IIS data were potentially available, i.e. those residing in states whose IIS conducted data exchange with their health plan, IISs contributed 63% of H1N1(10) and 32% of seasonal vaccine first doses.) Subsequently, Baker et al. evaluated the IIS contribution of vaccine doses from 2004-2011 in PRISM using a similar set of Data Partners and IISs, with quite different results.(26) Considering each of the 17 categories of vaccine routinely administered in the U.S., the proportions contributed by the 8 participating IISs ranged between 3% (for rotavirus) and 10% (for hepatitis B), with a median of 7%. The IIS portions of inactivated and live attenuated influenza vaccine doses were 5% and 7%, respectively, compared to the 14% from the earlier PRISM study. (The data were not collected in such a way as to allow recalculation of the contributions when restricting to just the population for which IIS data were potentially available.) (All of the above percentages reflect IIS-only contributions, i.e. doses from IISs that were not also available in the claims data provided by the Data Partners.)

Because the process of data exchange between PRISM Data Partners and IISs has been costly in terms of time, effort, and funds, we undertook an evaluation of the experience with IISs during influenza vaccine safety monitoring. The goal of this simple descriptive evaluation was to provide information and interpretation to guide decisions about whether and under what circumstances to continue seeking immunization data from IISs in future PRISM studies.

B. METHODS

1. Data exchange between Data Partners and IISs

To obtain data from IISs, each Data Partner signed legal and/or user agreements to protect personal health information, specify a secure data transfer mechanism, and define the appropriate use of vaccine histories. After agreements were executed, Data Partners provided IISs demographic information for eligible members as of a recent point in time. IISs used this information to match Data Partner members to existing vaccination records. Data requirements and matching algorithms varied among IISs. The IISs returned immunization data for members to the Data Partners, who converted the data into the M-S CDM standard State Vaccine file format. The Data Partners executed the PRISM State Vaccine QC distributed SAS program, and the output was reviewed by the coordinating center for basic elements of data quality. It was not feasible to assess the completeness or accuracy of vaccination histories received from IISs.

Two sets of Data Partner-IIS matches (or data exchanges) are discussed in this report. One set of 19 Data Partner-IIS exchanges was conducted in 2012, to serve other PRISM vaccine safety studies—those IIS data were not used for influenza vaccine safety monitoring in the 2012-13 pilot season of the current project. The other set of exchanges, totaling 18, was conducted between late 2013 and early 2014, and the resulting IIS data were included in the last three sequential analyses of the 2013-14 surveillance

season of this project. To distinguish more simply between these two sets of exchanges, we will refer to them as the "2012 match" and the "2014 match."

2. Assessment of IIS matching experience without regard to influenza vaccination

In the fall of 2013, the coordinating center asked the Data Partners to provide information in table format about their experience in seeking immunization data from the IISs. The request was made in written form, as a statement of work and a follow-up memo, with table shells, and was discussed on regularly scheduled calls with the Data Partners. The information requested is listed below:

a. The number of the Data Partner's members residing in a state/city with a participating IIS whose records were sent to the respective IIS (A), the number for whom the respective IIS returned *any* immunization data (B), and the ratio B/A, to which we gave the term "yield"
b. For the 2014 match, the date(s) member data were sent to each IIS and date(s) immunization data were received from each IIS, along with notes about any delays or other irregularities in the interactions and processes with the IISs

We used the information from Item a. to compare the yield across matches, Data Partners, and IISs and to check for any patterns. Information from Item b. allowed for analysis of the timeliness and effort required in completing the 2014 match.

3. Assessment of influenza vaccine doses captured by IISs

The Sequential Analysis Files (SAFs) captured influenza vaccine doses from both claims and the 2014 matching activity. Using these files, we determined the number and proportion of influenza doses coming from claims data (with or without duplicate records in the IIS data) and from IIS data only, by season of influenza vaccination (2012-13 or 2013-14), Data Partner, and age group.

C. RESULTS

1. Assessment of IIS matching experience without regard to influenza vaccination

The yields of the Data Partner-IIS matches completed in 2012 and 2014 were variable and showed no clear patterns; for example, no Data Partner or IIS was associated with consistently high or low yields.

In the 2014 data exchange activity, the time between Data Partners' provision of demographic information to IISs and their receipt of immunization data from IISs ranged from 0 (same day) to 65 days, with a median of 5.5 days. Obstacles encountered included the lack of uniformity in IIS systems and requirements; changes in file-format and size-limit requirements; limited file size upload capacity of some IISs, which required Data Partners to split their demographic file into multiple files; errors on the part of Data Partner staff; changes in staff at the IISs; and reconsideration of the legality of data provision to PRISM.

2. Assessment of influenza vaccine doses captured by IISs

Overall, the 2014 Data Partner-IIS data exchange activity contributed 4.3% of the total influenza doses captured in the 2013-14 season (Table B1). (The denominator for this proportion was not restricted to the population for which IIS data were potentially available but rather consisted of the whole study

population, including Data Partner members living in states whose IIS did not exchange data with the Data Partner.) The percentage of doses obtained from IISs only (i.e. without duplicate records in claims data) varied by age group and was highest—8-10%—for people aged ≥ 65. There were slight differences between the two influenza seasons, the IIS-only percentage being slightly higher for most age groups in 2012-13 relative to 2013-14. The contribution of IISs varied considerably by Data Partner, with Data Partner-specific IIS-only percentages for all ages combined of 0.8%, 6%, and 15% for the 2013-14 influenza season, and similar percentages for 2012-13 (data not shown).

Table B1. Contribution of claims and IIS data sources to total influenza doses captured in 2012-13 and 2013-14 influenza seasons for Aetna, HealthCore, and Humana combined. IIS data for both seasons were obtained from the 2014 match.

	2012-13 Season			2013-14 Season		
Age group	**Data Partner***	**SIIS only**	**% SIIS only**	**Data Partner***	**SIIS only**	**% SIIS only**
6-23m	455,563	13,940	2.97%	458,614	8,168	1.75%
24-59m	493,496	17,171	3.36%	474,969	12,630	2.59%
5-17y	1,423,299	59,275	4.00%	1,458,729	47,787	3.17%
18-24y	262,771	12,362	4.49%	274,586	9,863	3.47%
25-49y	1,447,923	63,005	4.17%	1,505,773	55,065	3.53%
50-64y	1,727,284	79,652	4.41%	1,713,526	66,429	3.73%
65-79y	1,262,872	112,697	8.19%	962,603	89,182	8.48%
>=80y	412,409	40,426	8.93%	308,240	34,990	10.19%
All ages	7,485,617	398,528	5.05%	7,157,040	324,114	4.33%

* Data Partner numbers include influenza vaccine doses identified by Data Partners. These vaccines could have been identified by claims only or by both claims and IIS data sources.

D. DISCUSSION AND CONCLUSIONS

Overall, in both the 2012-13 and 2013-14 seasons, between 300,000 and 400,000 influenza doses were provided exclusively by the 8 participating IISs. While the total number of doses contributed by IISs alone was not negligible, in relative terms the 2014 Data Partner-IIS data exchange contributed only **4-5%** of influenza doses (not counting doses captured by both claims *and* IIS data). This is similar to the IIS contributions found by Baker et al. for the same set of Data Partners and IISs over 2004-2011: **5%** for IIV and **7%** for LAIV.(26) However, it contrasts with the experience of PRISM in the 2009-10 H1N1 pandemic season, when **36%** of H1N1 first doses and **14%** of seasonal influenza first doses were contributed by IISs alone. It must be acknowledged that neither the sets of Data Partners nor the sets of participating IISs were identical between the 2009-10 and the 2014 IIS matches; however, there was a fair amount of overlap. It seems likely that the main reason for the difference is that, during the 2009-10 pandemic, a larger proportion of vaccine was administered in non-traditional settings and was not paid for through the traditional health insurance process and was therefore not captured in claims data. If this is the case, then it is possible that in the event of another pandemic, the IIS contribution would be higher than in our current study.

There was some variation in the IIS contribution by age group, influenza season, and Data Partner:

- *Age group:* The percentage of doses from IISs-only was highest (8-10%) for those aged ≥ 65 years. This percentage was most influenced by one Data Partner, which matched with many IISs and has a predominantly elderly population.
- *Influenza season:* The IIS-only percentages were similar between the 2012-13 and 2013-14 influenza seasons. The overall slightly higher IIS-only percentage and total doses in 2012-13 compared with 2013-14 could be due to the fact that all the data were obtained from the 2014 match, which would have allowed for more complete capture of the influenza doses by IISs for the earlier influenza season. Another factor might be the fact that, due to the timing of acquisition of data from the various IISs, claims data often extended through a later date than IIS data. For example, the last refresh of one Data Partner's claims data for the 2013-14 surveillance season occurred in May 2014, a few months after most of their IIS matches had been completed. This timing would have led to an influx of influenza doses from claims for a period in which IISs could not have contributed doses.
- *Data partner:* Not surprisingly, the IIS contribution was highest (15%) for the Data Partner that conducted data exchanges with the most IISs. The IIS contribution was lowest (0.8%) for the Data Partner that excluded the largest proportion of their population from data exchanges with the IISs.

No clear patterns were discernible upon looking at yield (the proportion of eligible members for which any immunization data were returned by the respective IIS) across matches (2012 vs. 2014), Data Partners, or IISs. No single Data Partner or IIS always had the best yield, but rather there was considerable heterogeneity.

It is important to bear in mind that, although basic data quality checking was invariably conducted on the State Vaccine files before they were used for any PRISM analysis, it was not feasible to systematically check the completeness or accuracy of the IIS data. There were surely differences among IISs regarding types of vaccine codes used (some used homegrown codes, for example, which had to be converted to standard codes), rigor of internal QC procedures, matching algorithms, and whether and to what extent any manual review of data to be sent to a Data Partner occurred. As a result, it is likely that data completeness and accuracy varied among IISs. In addition, changes in any of the above elements and/or changes in staff could have led to differences in data quality between the 2012 and 2014 matches *within* IISs.

Obtaining data from IISs has been hampered by cumbersome procedures, non-uniformity of procedures and requirements across IISs, changes in those procedures and requirements over time, staff turnover, and occasionally reemergence of questions about PRISM as a public health activity. The idiosyncrasies of the IISs have required a labor-intensive, customized approach to each.

The PRISM 2011 activity on interoperability for PRISM Data Partners and IISs recognized the problem posed by the lack of standardization and noted that all IISs would soon be making the transition to Health Level 7 (HL7) from flat files. To prepare PRISM to take advantage of this national transition to HL7 messaging, the interoperability workgroup developed an HL7 implementation guide. The final report for the interoperability activity(27) lists the following benefits of PRISM's adopting an HL7 format:

- "Data quality will improve for key data elements of interest to FDA safety surveillance, including improved capture of combination vaccines, vaccine brand names, and vaccine lot numbers

- "There is potential for reduced operating costs, timeliness, and staff effort for both Data Partners and vaccine registries once routine systems are put into place and issues of batch size and automation are resolved
- "It would facilitate the rapid inclusion of new Data Partners or vaccine registries—especially important for pandemic preparedness as vaccine registries are capable of capturing vaccinations outside of traditional health care settings, such as mass vaccination clinics"

The final report(27) predicts that the development of state health information exchanges (HIEs) will facilitate the sharing of data between Data Partners and IISs and lead to gains in efficiency. In addition, the HIEs are working with health insurance companies, including PRISM Data Partners, to create a Master Person Index, which will include member IDs (sometimes multiple IDs per person) and will be updated by means of an automated feed. This is expected to improve the matching rates.

The report(27) recommended reviewing the status of HIE implementation in the summer of 2014 (considering that universal HIE implementation had been planned for 2015) and making decisions then about whether Data Partners should develop HL7 messaging capabilities.

In conclusion, the IISs' contribution of few additional influenza vaccine doses, in relative terms, together with the non-uniformity and changeability of IIS procedures, raises questions about whether IIS data are worth the considerable time and effort currently required to get them. Given PRISM's investment and accumulating experience in IIS data exchanges since the H1N1 pandemic season and the large IIS contribution in that season, it seems reasonable to continue seeking IIS data under the extraordinary circumstances of a pandemic or other emergency vaccination campaign. Under more routine conditions, focusing efforts on exchanging data with IISs in just a few states with a large number of PRISM Data Partner members may be a reasonable approach.

The cost-benefit calculus regarding using IIS data will change considerably once national HL7 messaging standards are widely adopted by IISs, and it would be reasonable to reassess the potential or actual contributions of IISs then.

If IIS data are to be incorporated in future vaccine safety surveillance, whether before or after national HL7 messaging standards are adopted, it would be useful to dedicate staff at the coordinating center and Data Partners to oversee the IIS data exchange, in order to standardize, coordinate, and document the matching procedures; thoroughly check the quality of the resulting data; and communicate with each other and IISs to ensure adherence to procedures and data quality standards.

VIII. APPENDIX C. END-OF-SEASON INFLUENZA DOSE COUNTS BY SEX AND AGE GROUP, 2012-13 PILOT SEASON AND 2013-14 SURVEILLANCE SEASON

Sex	Age Group	2012-13 Pilot Season	2013-14 Surveillance Period
F	6-23 months	221,023	226,791
	24-59 months	241,081	237,792
	5-17 years	697,005	737,510
	18-24 years	155,753	169,978
	25-49 years	865,150	930,887
	50-64 years	952,460	977,573
	65-79 years	688,353	570,316
	>= 80 years	248,514	207,437
	Total	4,069,339	4,058,284
M	6-23 months	234,022	238,947
	24-59 months	252,337	249,520
	5-17 years	725,799	767,131
	18-24 years	106,746	114,202
	25-49 years	580,041	627,389
	50-64 years	767,039	794,316
	65-79 years	574,214	479,312
	>= 80 years	163,768	135,246
	Total	3,403,966	3,406,063
U	6-23 months	2	23
	24-59 months	12	16
	5-17 years	17	32
	18-24 years	5	13
	25-49 years	6	15
	50-64 years	13	14
	65-79 years	6	1
	>= 80 years	1	-
	Total	62	114
All	6-23 months	455,047	465,761
	24-59 months	493,430	487,328
	5-17 years	1,422,821	1,504,673
	18-24 years	262,504	284,193
	25-49 years	1,445,197	1,558,291
	50-64 years	1,719,512	1,771,903
	65-79 years	1,262,573	1,049,629
	>= 80 years	412,283	342,683
	Total	7,473,367	7,464,461

Race/ethnicity data not available.

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