MINI-SENTINEL CBER/PRISM SURVEILLANCE PROTOCOL

INFLUENZA VACCINES AND FEBRILE SEIZURES

Version 2

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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.

History of Modifications

Version	Date	Modification	By
V2	04/26/2013	A footnote was added on page 6 to describe the rationale behind the choice a 0-1 day risk interval for examining risk of febrile seizure following trivalent influenza vaccine.	Influenza Vaccines and Febrile Seizures Workgroup
V2	04/26/2013	A footnote was added on page 8 to clarify data sources and methods for capturing manufacturer of TIV products. The footnote also clarifies that we will report the number of cases by source of manufacturer information.	Influenza Vaccines and Febrile Seizures Workgroup
V2	04/26/2013	A footnote was added on page 10 to reference other vaccine safety evaluations that identified potential febrile seizure cases via ICD9 codes and considered a clinical diagnosis of seizure in the medical record as confirmation of a seizure.	Influenza Vaccines and Febrile Seizures Workgroup
V2	04/26/2013	The criteria for determining presence of a fever has been modified to either (1) a parent report of fever or (2) temperature measurement of ≥38 C within 24 hours of the seizure. In version 1 of the protocol, at least one of these criteria was required to occur within 24 hours *before* the seizure.	Influenza Vaccines and Febrile Seizures Workgroup
V2	04/26/2013	A footnote was added on page 12 to specify that we will report data on the number of additional vaccines received on separate days from the index vaccines.	Influenza Vaccines and Febrile Seizures Workgroup
V2	04/26/2013	A footnote was added on page 12 to clarify the rationale behind the focus on Prevnar 13, DTaP-containing vaccines, and TIV as potential effect modifiers and confounders. We also clarified in this footnote that we will report data on the frequency of cases receiving other vaccines administered concomitantly.	Influenza Vaccines and Febrile Seizures Workgroup

V2	04/26/2013	Two footnotes were added on page 14 to clarify the methods and data sources for determining dose numbers of TIV, Prevnar 13, and DTaP-containing vaccines. We also clarified in this footnote that we will report data on the source of data used to determine dose number.	Influenza Vaccines and Febrile Seizures Workgroup
V2	04/26/2013	• The analysis plan for aim 1 was modified so that the primary analysis will incorporate adjustments for time-varying confounding by age and calendar time, whereas the secondary analysis will not. In version 1 of the protocol, the order of the primary vs. secondary analysis was reversed with respect to whether these adjustments would be made. • We also clarified that the model for the background rate of febrile seizures would be finalized prior to using it for age and seasonality adjustments. • We modified the analysis plan such that we will incorporate the uncertainty in the background rates used for age and seasonality adjustments if a method is available. In version 1 of the protocol, we stated that we would treat the background rates as known with certainty.	Influenza Vaccines and Febrile Seizures Workgroup

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Influenza Vaccines And Febrile Seizures

Table of Contents

I. BACKGROUND 1
A. PUBLIC HEALTH SIGNIFICANCE AND STUDY MOTIVATION 1
II. PRIMARY OBJECTIVES 4
III. SECONDARY OBJECTIVES 4
IV. EXPLORATORY OBJECTIVES 4
V. METHODS 5
OBJECTIVE 1: 5
1a. Study population 5
1b. Study design 5
1c. Exposure 7
1d. Case definition 8
1e. Potential confounders and effect modifiers 12
1f. Analysis plan 15
OBJECTIVE 2: 16
2a. Study population 16
2b. Study design 16
2c. Statistical analyses 18
OBJECTIVE 3: 19
3a. Study population and study design 19
3b. Statistical analysis 19
OBJECTIVE 4 19
4a. Study population 21
4b. Study design 21
4c. Exposure 21
4d. Outcome 21
4e. Statistical analysis 21
OBJECTIVE 5: 22
5a. Study population 22
5b. Exposure 22
5c. Outcome 23
5d. Statistical analysis 23
VI. POWER CALCULATIONS 23
VII. DATA SET CREATION AND REGISTRY MAPPING 23
VIII. INSTITUTIONAL REVIEW BOARD APPROVAL AND OTHER AUTHORIZATIONS 24
IX. ACKNOWLEDGEMENTS 25
X. REFERENCES 25

I. BACKGROUND

A. PUBLIC HEALTH SIGNIFICANCE AND STUDY MOTIVATION

During the 2010 Southern Hemisphere influenza season in Australia, an increased risk of febrile seizures was found in children 6 months to 4 years of age in the 24 hours following a trivalent inactivated influenza vaccine (TIV) manufactured by CSL Biotherapies (Fluvax ®, Fluvax Junior ®)[1]. This increased risk was not observed for other TIVs administered in the 2010 Southern Hemisphere influenza season As a result, in the summer preceding the 2010-11 Northern Hemisphere influenza season, the U.S. Advisory Committee on Immunization Practices (ACIP) recommended avoiding use of Afluria®, an antigenically equivalent vaccine manufactured by CSL Biotherapies, in children ages 6 months to 8 years when feasible, and FDA updated the Warnings and Precautions sections of the Prescribing Information for Afluria to inform healthcare professionals that administration of a 2010 Southern Hemisphere TIV manufactured by CSL Biotherapies had been associated with an increased risk of fever and febrile seizure among young children, predominantly less than 5 years of age, in Australia[2,3].

In the United States, seven FDA approved TIVs were available for use during the 2010-2011 influenza season in adults and children: Afluria® (CSL Biotherapies), Fluarix® (GlaxoSmithKline), Flulaval® (GlaxoSmithKline), Agriflu® (Novartis),Fluvirin® (Novartis), Fluzone® (Sanofi Pasteur), and Fluzone High-Dose® (Sanofi Pasteur)[4]. Flumist® (MedImmune), a live attenuated influenza vaccine (LAIV) was also available for use in persons 2-49 years of age during the 2010-11 influenza season. Of the TIVs available for use for the 2010-2011 influenza season (*Table 1*), Fluvirin, Fluvirin, and Fluzone, were FDA approved for a portion of or the full age range of 6 months through 4 years, with Fluzone being the only FDA approved TIV for children ages 6 months through 2 years. The FDA approved use of Afluria was changed from 6 months and older to 5 years and older on July 15, 2011[5].

Table 1: TIVs approved for use in children during the 2010-2011 season

Manufacturer	Product	FDA Approved Use[a]	ACIP Recommended Use
CSL Biotherapies	Afluria	≥5 years	≥9 years
Novartis Vaccines	Fluvirin	≥4 years	≥4 years
GlaxoSmithKline	Fluarix	≥3 years	≥3 years
Sanofi Pasteur	Fluzone	≥6 months	≥6 months

[a]The FDA approved use of Afluria was changed from ≥6 months to ≥5 years in July 2011.

For the 2010-2011 influenza season, the ACIP recommended that all children 6 months through 8 years of age receiving a seasonal influenza vaccine for the first time receive 2 doses of seasonal influenza vaccine[4]. Children 6 months through 8 years of age who had received seasonal influenza vaccine for the first time during the prior 2009-2010 season but had received only 1 dose were also recommended to receive 2 doses of 2010-11 seasonal influenza vaccine. Furthermore, children 6 months through 8 years

of age who had not received at least 1 dose of influenza A (H1N1) 2009 monovalent vaccine were recommended to receive 2 doses of 2010-2011 seasonal influenza vaccine[4].

Several studies of influenza vaccines conducted in the U.S. in seasons prior to 2010-2011 did not suggest an elevated risk of seizures in the 0-7, 0-2, or 1-3 days following influenza vaccination (0 being the day of vaccination)[6-9]. For the first time in the United States, during the 2010-2011 Northern Hemisphere influenza season, signals were identified for elevated risk of seizures following TIV in young children in two complementary systems, the Vaccine Adverse Event Reporting System (VAERS) and the Vaccine Safety Datalink (VSD)[10]. Beginning in October 2010, investigators from VAERS, a spontaneous reporting system co-managed by the CDC and FDA, conducted bimonthly disproportionate reporting analysis to identify adverse events reported more frequently than expected following TIV[11]. By November 23, 2011, disproportional reporting for febrile seizures was detected for Fluzone but not other 2010-2011 TIV products. In subsequent analysis conducted on December 10, 2010 the signal persisted. The majority of cases were chart confirmed and occurred in children less than 2 years of age (83%). On January 20, 2011, a communication was posted on the FDA website to notify the public about the VAERS findings for Fluzone, provide information regarding febrile seizures and influenza vaccination, and inform the public that further analyses and studies were underway[10,12].

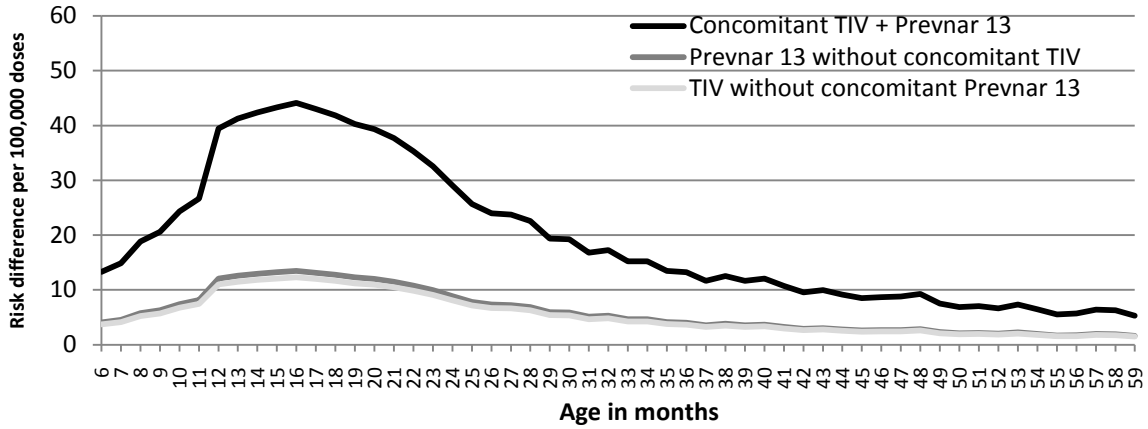
During the 2010-2011 season in approximately 200,000 children ages 6 months through 4 years, the Vaccine Safety Datalink (VSD), a collaboration between CDC and 8 medical care organizations, conducted surveillance for seizures using a 0-1 day risk interval, which was shorter than in prior seasons due to the finding in Australia [13]. Based on automated data, statistically increased risks of seizures following receipt of a TIV were identified the week of November 14, 2010 using a current vs. historical design and in the week of December 26, 2010 using a self-controlled risk interval design, when the log likelihood ratios exceeded the predetermined critical values of statistical significance during weekly sequential analysis. After the potential cases following TIV were chart confirmed, a combined analysis of all TIV products using the self-controlled risk interval design revealed that receipt of a TIV was associated with an elevated risk of febrile seizures after adjusting for concomitant Prevnar 13® (Pfizer) (*Table 2*). In exploratory analyses, the estimated IRR (incidence rate ratio) for febrile seizures in children 24-59 months appeared to be lower than the IRR in children ages 6-23 months. However, the confidence intervals for the age group specific IRRs were wide (*Table 2*), and the p-value for statistical test of difference in IRRs between age groups was not significant (p 0.41).

Table 2: Incidence rate ratio (IRR) estimates for febrile seizures for 1st dose of TIV in the 2010-11 influenza season adjusted for concomitant 13-valent pneumococcal conjugate vaccine (Prevnar 13) in children age 6-59 months and stratified by age group (6-23 and 24-59 months), self-controlled risk interval design, Vaccine Safety Datalink, August 1, 2010 to February 5, 2011

Age in months	IRR comparing the risk vs. control interval following receipt of a TIV, adjusted for concomitant Prevnar 13 (95% CI)	Number of cases in risk and control intervals
6-59	2.4 (1.2, 4.7)	47
6-23	3.0 (1.2, 7.4)	32
24-59	1.6 (0.5, 5.2)	15

In the VSD study, the magnitude of the risk difference comparing risk of seizures in the 0-1 days versus 14-20 days following TIV differed by whether a child had received concomitant 13-valent pneumococcal conjugate vaccine (Prevnar 13). The risk difference also varied by age, due to the varying baseline risk of febrile seizures[14]. Overall, the highest risk difference was seen in children 12-23 months of age receiving a TIV concomitantly with Prevnar 13 as shown below:

Figure 1: Risk difference estimates for febrile seizures following 1st dose TIV stratified by receipt of concomitant 13-valent pneumococcal conjugate vaccine (Prevnar 13) and following any dose of Prevnar 13 without a concomitant TIV by age in months, self-controlled risk interval design in the Vaccine Safety Datalink, August 1, 2010 to February 5, 2011



Based on the VSD's findings, the Vaccine Information Statement for the TIVs were updated for the 2011-2012 and 2012-13 seasons to include information about the potential for an increased risk of febrile seizures following co-administration of a TIV and Prevnar 13 in young children[10,15]. However, several questions remain. First, information on the confounding or synergistic role of vaccines other than Prevnar 13 that were commonly co-administered with a TIV, such as diphtheria tetanus pertussis (DTaP) containing vaccines, was not available in the VSD study. Additionally, the VSD study did not formally test for effect modification on the attributable risk scale of TIV by Prevnar 13 and/or DTaP co-administration, which would suggest that co-administration is associated with an overall higher risk of febrile seizures

when compared to separate day vaccination. The primary purpose of the present study is to examine the risk of febrile seizures following a 2010-2011 TIV in children ages 6-59 months and to compare the risk of febrile seizures following same day vs. separate day administration of a TIV and Prevnar 13 and/or DTaP.

II. PRIMARY OBJECTIVES

1. Among children ages 6 months through 59 months with the use of a self-controlled risk interval design, to estimate the relative risk of febrile seizures comparing the risk vs. control intervals following any TIV dose in the 2010-2011 season, adjusted for confounding by concomitant vaccines.

   Furthermore, we will *explore* whether the relative risk is modified by

   a. DTaP containing vaccines and/or Prevnar 13 co-administration
   b. Age (categorically, 6-23 vs. 24–59 months)
   c. Prior history of seizures and family history of seizures
   d. Vaccine product type (i.e. manufacturer)
   e. Dose number in the 2010-2011 season

2. Among TIV vaccinees, examine whether receipt of concomitant vaccines of interest is associated with an overall greater risk of febrile seizures when compared to vaccination on separate days by examining for effect modification by concomitant vaccines on the attributable risk scale.

III. SECONDARY OBJECTIVES

1. To evaluate the positive predictive value of three alternative febrile seizures definitions that use ICD9 data:
   a. ICD9 diagnosis code for seizure (780.3, 780.31, 780.32, or 780.39) in the inpatient or ED setting
   b. ICD9 diagnosis code for febrile seizure (780.31) in the inpatient or ED setting
   c. ICD9 diagnosis code for seizure (780.3, 780.31, 780.32, or 780.39) + ICD9 code for medically attended fever (780.6, 780.60, 780.61, 780.62, or 780.63) on the same day in the inpatient or ED setting

IV. EXPLORATORY OBJECTIVES

1. Using a self-controlled risk interval design, to explore whether the risk of medically attended fever identified in claims data is elevated following any 2010-11 TIV dose in the risk vs. control intervals, without medical record confirmation.

2. Using a self-controlled risk interval design, explore whether the risk of seizures identified in claims data is elevated following any 2010-11 live attenuated influenza vaccine dose in the risk vs. control intervals, without medical record confirmation.

V. METHODS

OBJECTIVE 1: Among children ages 6 months through 59 months with the use of a self-controlled risk interval design, to estimate the relative risk of febrile seizures comparing the risk vs. control intervals following any TIV dose in the 2010-2011 season, adjusted for confounding by concomitant vaccines.

1a. Study population

The proposed data partners for participation in Activity 1 of PRISM 2011 include Aetna, HealthCore, and Humana. The population will consist of children 6-59 months of age who were members of any of the participating data partners for all of or a portion of the period of interest, July 1, 2010 to June 30, 2011. Within this population, children will be included in the study if they received a TIV, DTaP containing vaccine, or Prevnar 13 during the study period and at a minimum, were enrolled in the health plan from 180 days prior to vaccination through 20 days after vaccination. We have elected to use the enrollment criterion of 180 days prior to vaccination to optimize the ability to identify history of seizure and patient comorbidities, while balancing the possibility of a large loss of case numbers with a stricter pre-vaccination enrollment criterion.

1b. Study design

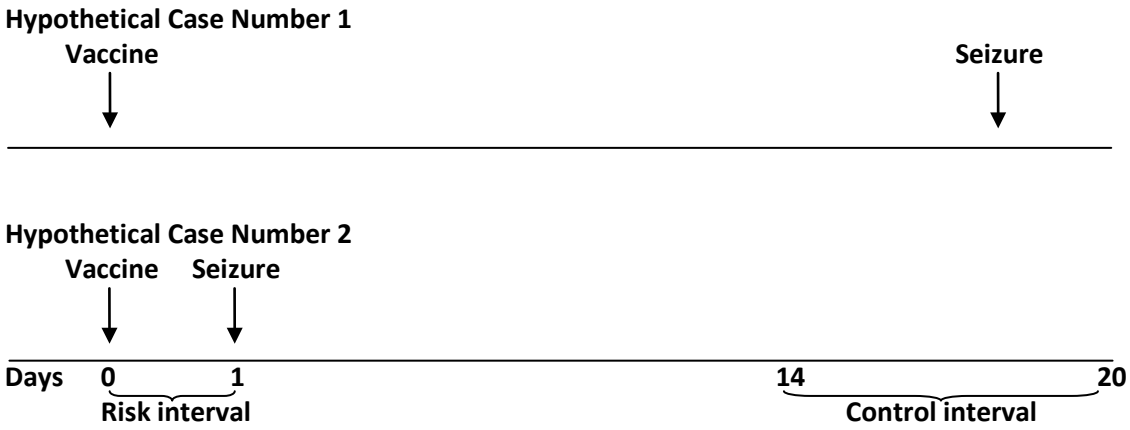
For Objective 1, we propose to use the self-controlled risk interval design, a form of a self-matched cohort design, to examine the null hypothesis that there is no association between TIV and seizure in a defined risk interval after vaccination. This design is well suited to study well-defined clinical events that follow exposures that have acute and transient effects. Because the self-controlled risk interval design compares risk in a risk vs. control interval within vaccinated individuals, it implicitly controls for bias due to time invariant confounders, such as race and socioeconomic status. Additionally, by only including vaccinated individuals, it avoids exposure misclassification resulting from individuals receiving influenza vaccines in non-traditional settings, which may not be captured in the current study's data sources (i.e. claims and registry data). The potential disadvantage of this study design is that it does not implicitly adjust for time varying confounders such as age or calendar time (i.e. seasonality), though the bias can be minimized by selecting risk and control intervals relatively close in time. An additional limitation is that the self-controlled risk interval design assumes that there is no excess risk due to vaccination in the control interval and that there is no carry over effect of vaccination between the risk and control interval. This will be mitigated by allowing a sufficient period of time (i.e., 12 days) to elapse between the risk and control intervals to allow for a wash out period. Because only vaccinated cases are informative in this study design, we will be unable to examine or identify overall risk factors for febrile seizures.

As *Figure 2* illustrates, exposed person time will be in the defined risk interval of 0-1 days post-vaccination[i] and unexposed person time will consist of person time in a control interval beyond the risk

[i] A literature review performed by the Risk Interval Working Group of the Clinical Immunization Safety Assessment Network, an external collaboration between the CDC and six medical research centers [Rowhani-Rahbar et al., Vaccine 31 (2012):271-277], informed the choice of the 0-1 day risk interval for this protocol. The working group found a total of seven clinical trials that were informative with regard to the timing of fever onset following

interval (days 14-20). In order to adjust for confounding by co-administration with diphtheria tetanus and pertussis (DTaP) containing vaccines and 13-valent pneumococcal conjugate vaccine (Prevnar 13), we will collect information on seizures in the similarly defined risk interval of 0-1 days post-vaccination and control interval of 14-20 days post-vaccination for these other vaccines, *regardless of co-administration with TIV.* We have elected to use this control interval for two main reasons: (a) a longer control interval produces more stable estimates of the background rate of febrile seizures, compared to a one or two day comparison interval, (b) this interval is identical to prior VSD study and enables PRISM to directly add to the existing safety information, and (c) avoids overlap with the known increased risk of febrile seizures in the 7-10 days following measles containing vaccines which may have been given on the same day [16,17]. Moreover, as discussed in the analysis section below, the unequal lengths of time for the risk and control intervals will be accounted for through analysis of rates as opposed to risks (i.e. proportions).

Figure 2: Self-controlled risk interval design to evaluate incidence rate ratios comparing rates in risk vs. control intervals. Two potential cases are shown below in relation to TIV administration. Only vaccinated cases are included in the study design.



influenza vaccine in children 2 years of age and younger, with the studies generally suggesting onset of fever within a short interval of time (i.e., generally within 48 hours post-vaccination). Furthermore, the working group cited data from the Vaccine Adverse Event Reporting System, a passive reporting system, suggesting a uni-modal distribution of febrile convulsion onset, with the majority of post-TIV cases occurring on day 0 or 1 in children 2 years of age and younger. Additionally, the study that identified an increased risk of febrile seizure following TIV in children 6 months to 4 years of age during the 2010 Southern Hemisphere influenza season in Australia informs our risk interval choice [Armstrong et al., BMJ Open 2011 1:e000016]. In that study, the median time from TIV to febrile convulsion onset was 7 hours, with over 90% of cases having onset within 12 hours. We selected the 0-1 day risk interval based on the available data as described above in this footnote. Longer risk intervals may inadvertently include periods of lower risk, and may underestimate the magnitude of or miss a true increased risk [Rowhani-Rahbar et al., Vaccine 31 (2012):271-277]. Shorter risk intervals may limit power to detect an increased risk, particularly if true cases are excluded.

1c. Exposure

TIV will be identified using claims data from the data partners and immunization registry data from any of eight participating registries (i.e. immunization information systems, IISs): Florida, Michigan, Minnesota, New York City, New York State, Pennsylvania, Virginia, and Wisconsin. CPT (Current Procedural Terminology), Healthcare Common Procedure Coding System (HCPCS), National Drug Code (NDC), and International Classification of Diseases, 9th Edition (ICD9) codes (Table 3) will be used to identify TIV in claims data and CDC Vaccine Administered (CVX) codes will be used to identify TIV in IIS data. NDC codes are not listed due to the large number of codes (>190), but can be obtained directly from protocol authors via email (Alison_Kawai@HPHC.org). ICD9 diagnosis codes will only be used to identify TIV exposure if and only if the ICD9 diagnosis code for vaccination not carried out (V64.0*) is *not* present on the same day. Though whole virus vaccines are no longer available for use in the U.S. and Agriflu and Fluzone High-Dose are not approved for use in children, we will include these codes for the purposes of identifying potential receipt of other TIVs because they may represent miscoding of other influenza vaccines. Alternatively, codes for Agriflu and Fluzone High-Dose in this study population may be due to inappropriate administration outside of the approved age ranges. Vaccine product types and brand names will be confirmed through chart review for vaccinations identified in claims data.[ii]

Table 3: Vaccine codes to identify potential administration of TIVs. NDC codes will also be used to identify potential administration of TIV products.

Description	Code	Code Type
Influenza virus vaccine, split virus, preservative free, for children 6-35 months of age, for intramuscular use	90655	CPT
Influenza virus vaccine, split virus, preservative free, for use in individuals 3 years of age and above, for intramuscular use	90656	CPT
Influenza virus vaccine, split virus, for children 6-35 months of age, for intramuscular use	90657	CPT
Influenza virus vaccine, split virus, for use in individuals 3 years of age and above, for intramuscular use	90658	CPT
Influenza virus vaccine, whole virus, for intramuscular or jet injection use	90659	CPT
Influenza virus vaccine	90724	CPT
Influenza virus vaccine, split virus, preservative free, enhanced immunogenicity via increased antigen content, for intramuscular use	90662	CPT
Influenza, seasonal, injectable, preservative free	140	CVX
Influenza, seasonal, injectable	141	CVX
Influenza virus vaccine, split virus (incl. purified surface antigen)	15	CVX

[ii] The primary analysis will be focused on risk of febrile seizure after TIV in all products combined. We will conduct secondary analyses by manufacturer. Manufacturer data will be captured by medical record review, product-specific HCPCS codes, product-specific NDC codes, and manufacturer information recorded in immunization registry data. We will also use vaccine codes that correspond to a single FDA-approved product (i.e. when no other FDA-approved products exist). We will report the source of manufacturer information (medical record vs. HCPCS vs. NDC codes vs. registry vs. vaccine code corresponding to only one FDA-approved product).

Description	Code	Code Type
Influenza virus vaccine, whole virus	16	CVX
Influenza virus vaccine, unspecified formulation	88	CVX
Influenza, high dose seasonal, preservative-free	135	CVX
Administration of influenza virus vaccine	G0008	HCPCS
Influenza virus vaccine, split virus, for intramuscular use (Agriflu)	Q2034	HCPCS
Influenza virus vaccine, split virus, when administered to individuals 3 years of age and older, for intramuscular use (Afluria)	Q2035	HCPCS
Influenza virus vaccine, split virus, when administered to individuals 3 years of age and older, for intramuscular use (Flulaval)	Q2036	HCPCS
Influenza virus vaccine, split virus, when administered to individuals 3 years of age and older, for intramuscular use (Fluvirin)	Q2037	HCPCS
Influenza virus vaccine, split virus, when administered to individuals 3 years of age and older, for intramuscular use (Fluzone)	Q2038	HCPCS
Influenza virus vaccine, split virus, when administered to individuals 3 years of age and older, for intramuscular use (Not Otherwise Specified)	Q2039	HCPCS
Need for prophylactic vaccination and inoculation against influenza	V04.81	ICD9 Diagnosis
Need for prophylactic vaccination and inoculation against streptococcus pneumoniae [pneumococcus] and influenza	V06.6	ICD9 Diagnosis
Prophylactic vaccination against influenza	99.52	ICD9 Procedure

1d. Case definition

Identifying potential febrile seizure cases (ICD9 data)

Potential cases of febrile seizure will be identified in the electronic data by any of the following ICD9 diagnosis codes occurring in the inpatient or emergency department (ED) setting: 780.3 (seizures), 780.31 (febrile seizures), 780.32 (complex febrile seizures), or 780.39 (other seizures). These codes were used in the VSD and shown to have positive predictive values between 71% and 83% for chart confirmed febrile seizures following receipt of a TIV among children 6 through 59 months of age [18]. Of note, starting in 2011, the ICD9 included a new diagnosis code for posttraumatic seizures (780.33), which will not be considered in any of the case definitions because this code is to be used for acute symptomatic seizures following a head injury. Only codes that are the first in a 42-day period (occurring in any setting) will be included to avoid including follow-up visits for seizure episodes. The first in 42-day criterion was selected to allow for comparability with the VSD study.

Medical record reviews

All cases identified in claims that occur in the 0-1 or 14-20 days following TIV will undergo medical review. We will also review charts of potential seizure cases identified in claims following DTaP containing vaccines or PCV13. Medical record reviews will be conducted to confirm that potential cases are febrile seizures. Information on family history of seizures, prior history of seizures, coinfections, and comorbidities will also be collected from the medical record for the seizure visit. The maximum total number of cases to be reviewed is 200 among all data partners combined. If the total available number of cases exceeds 200, a sampling scheme of potential cases will be created.

A primary case definition will require a clinician diagnosis of seizure and presence of a fever (further specified below), while a secondary case definition will only require a clinician diagnosis of seizure without confirmation of a fever (Figure 3). First, potential cases will be identified by ICD9 codes. Potential cases will then undergo a chart review process, which will first entail obtaining copies of the medical record for seizures visits and for vaccine visits with redaction of patient identifiers. Redacted medical records will be sent to Harvard Pilgrim Health Care Institute, where chart review and data extraction will take place using structured case report forms. Finally, all potential seizure cases will be adjudicated by a pediatrician. A clinician diagnosis of seizure in the medical record will be considered confirmation of a seizure occurrence, and these patients will be further examined to determine the presence of a fever, as described in Figure 3.[13] [iii] In addition to confirming the seizure, the clinician adjudicator will determine whether patients with chart- confirmed seizures also meet Brighton Levels 1-3 (*Table 4*), based on generalized motor manifestations and state of consciousness documented in the medical record.[19] We will report the number of chart-confirmed seizures and whether they meet criteria for Brighton Levels 1-3.

Specifically, our primary case definition will include potential cases that have a clinician diagnosis of seizure and have documentation in the medical record of the presence of a fever, defined as parent report of fever or temperature measurement of ≥38 °C within 24 hours of the seizure, or a clinician diagnosis of febrile seizure. Potential cases that have a diagnosis of afebrile seizure in the medical record will be excluded. To improve sensitivity, a secondary case definition will also include potential cases that meet adjudication criteria for generalized seizure, but with no documentation of the presence of fever.

[iii] Consistent with other vaccine safety evaluations [Tse et al., Vaccine 2012 30 (2012): 2024-31; Klein et al., Pediatrics 126(1): e1-e8] that used ICD9-coded data to identify potential cases of febrile seizure, we consider a clinical diagnosis of seizure in the medical record as confirmation of a seizure.

Figure 3: General schematic for cases under primary and secondary definitions. An "X" indicates that potential cases do not meet primary or secondary case definitions.

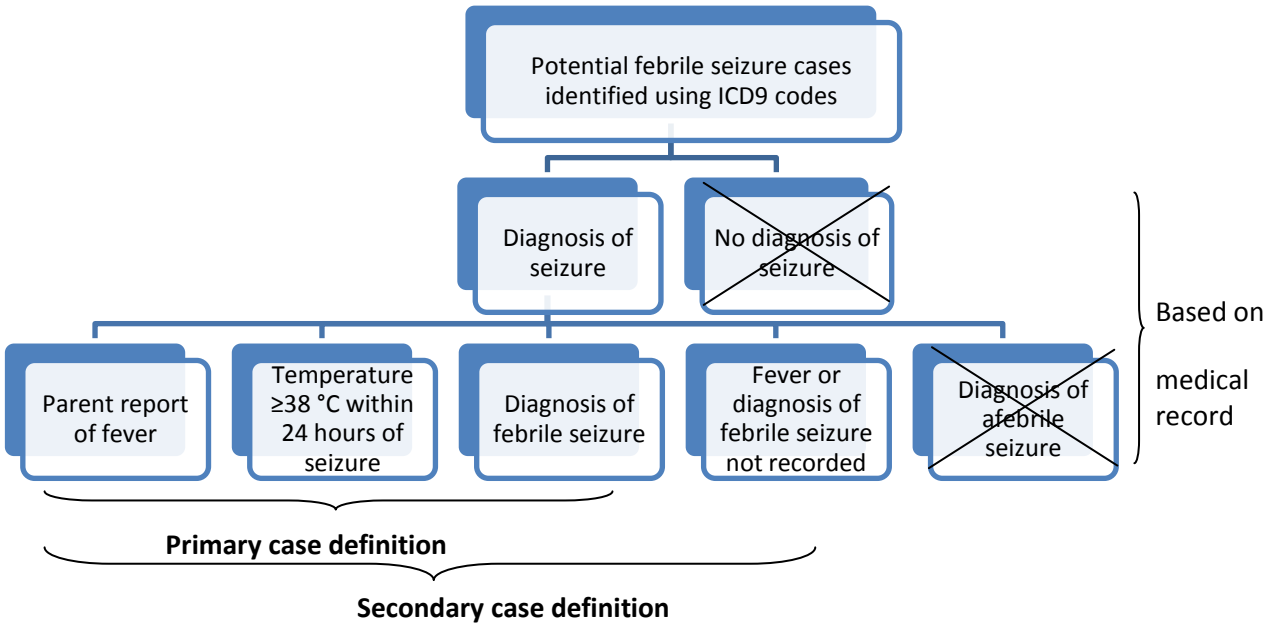


Table 4: Criteria for diagnostic certainty of generalized seizures [13,19]

Level of diagnostic certainty[a]	**Required data**
Diagnosis of seizure	Clinician diagnosis of seizure
Brighton Level 1	Clinician diagnosis of seizure AND witnessed sudden loss of consciousness[b] AND generalized[c] tonic[d], clonic[e], tonic-clonic[f], or atonic[g,h] motor manifestations
Brighton Level 2	Clinician diagnosis of seizure AND history of unconsciousness[b,i] AND generalized[c] tonic[d], clonic[e], tonic-clonic[f], or atonic[g,h] motor manifestations
Brighton Level 3	Clinician diagnosis of seizure AND history of unconsciousness[b,i] AND other generalized motor manifestations[j]

[a]All potential cases identified with ICD9 codes are to be adjudicated by a pediatrician. Potential cases that have a clinician diagnosis of seizure will be considered to have met criteria for generalized seizures and will be further examined for consideration as a febrile seizure case unless they have a diagnosis of afebrile seizure in the medical record. We will identify whether chart-confirmed seizures also meet criteria for Brighton Levels 1-3.
[b]Unconsciousness includes unreactive to verbal and painful stimuli
[c]Synonymous: bilateral, more than minimal muscle involvement
[d]A sustained increase in muscle contraction lasting a few seconds to a few minutes
[e]Sudden, brief (<100 ms) involuntary contractions of the same muscle groups, regularly repetitive at a frequency of about two to three contraction(s)
[f]A sequence consisting of a tonic followed by a clonic phase
[g]A sudden loss of tone in postural muscles, often preceded by a myoclonic jerk and precipitated by hyperventilation
[h]In the absence of hypotonic hyporesponsive episode (as defined by Brighton Collaboration), syncope, and myoclonic jerks
[i] History of unconsciousness (i.e. the sudden loss of consciousness was not observed, but the patient was found unconscious)
[j]Other generalized motor manifestations include less specific descriptions such as shaking, trembling, shivering, quivering.

1e. Potential confounders and effect modifiers

Because the study design is self-controlled, the analysis will be inherently adjusted for measured and unmeasured confounders that do not vary over relatively short periods of time, such as gender, race/ethnicity and chronic disorders. However, because concomitant vaccinations may act as confounders and/or effect modifiers, we will collect information on these factors and adjust for them in multivariate regression.

In the primary analysis, we will adjust for time varying age in weeks and calendar time in weeks using background rates from the PRISM cohort of children (both vaccinated and unvaccinated) during the 2010-2011 influenza season. A secondary analysis will be conducted without adjustments for time-varying age and calendar time.

Information on seizures following vaccines commonly administered concomitantly with TIV will be collected using the same outcome definition described previously and will be examined as potential confounders or effect modifiers. Though analyses on concomitant vaccines will focus on concomitant Prevnar 13 and DTaP containing vaccines because they were the most commonly co-administered vaccines in the VSD, we will also collect information on the types and number of vaccines co-administered with TIV in potential seizure cases identified with ICD9 data.[iv,v] We will also examine effect modification by number of vaccines received concomitantly with TIV. However, this analysis will be considered to be exploratory in nature due to anticipated low case numbers in each stratum.

Prevnar 13 will be identified in claims data using CPT, HCPCS, NDC, and ICD9 diagnosis codes. ICD9 diagnosis codes will only be used to identify Prevnar 13 exposure if and only if the ICD9 diagnosis code for vaccination not carried out (V64.0*) is not present on the same day. Prevnar 13 will be identified in IIS data using CVX codes (*Table 5*).

[iv] Additional TIV, DTaP, or Prevnar 13 vaccines in the control interval of the index vaccine(s) could elevate the rate of febrile seizures in the control interval of the index vaccine and bias the relative risk for the index vaccine(s) downwards. MMR or MMRV received in the 5-12 days prior to the index vaccine(s) could elevate the rate of febrile seizures in the risk interval of the index vaccine and bias the relative risk for the index vaccine(s) upwards. We will report data regarding the number of additional vaccine(s) received on separate days from the index vaccine(s), where the risk interval of the additional vaccine(s) overlaps with the risk or control intervals of the index vaccine(s).

[v] For this protocol, adjustment for confounding and examination for effect modification by concomitant vaccines are focused on vaccines that have been associated with febrile seizures in the scientific literature, including 2010-11 TIV, Prevnar 13 and DTaP-containing vaccines [Tse et al., Vaccine 2012 30:2024-31; Sun et al., JAMA 307(8):823-831]. Because MMRV and MMR vaccines have been previously associated with febrile seizures in the 5-12 days post-vaccination [Klein et al, Pediatrics 2010 126(1): e1-e8; Jacobsen et al., Vaccine 2009 27(34) 4656–4661], we chose a control interval of 14-20 days to avoid overlap with the period of increased risk following measles-containing vaccines when administered concomitantly with TIV, Prevnar 13, or DTaP-containing vaccines. We will report data on the frequency of cases receiving other vaccines administered concomitantly with the main exposures of interest (TIV, Prevnar 13, and DTaP-containing vaccines).

Table 5: CPT and CVX codes used to identify potential administration of Prevnar 13. NDC codes corresponding to the vaccines in this table will also be used to identify potential administration of Prevnar 13.

Description	Code	Code Type
Pneumococcal conjugate vaccine, 13 valent, for intramuscular use	90670	CPT
Pneumococcal conjugate vaccine, polyvalent, for children under five years, for intramuscular use	90669	CPT
Pneumococcal conjugate vaccine, 13 valent	133	CVX
Pneumococcal conjugate vaccine, 7 valent	100	CVX
Pneumococcal, unspecified formulation	109	CVX
Administration of pneumococcal vaccine	G0009	HCPCS
Pneumococcal conjugate vaccine, polyvalent, intramuscular, for children from five years to nine years of age who have not previously received the vaccine	S0195	HCPCS
Need for prophylactic vaccination and inoculation against streptococcus pneumonia	V03.82	ID9 Diagnosis
Need for prophylactic vaccination and inoculation against streptococcus pneumoniae [pneumococcus] and influenza	V06.6	ICD9 Diagnosis

DTaP will be defined as DTaP alone or administered in any combination vaccine and will be identified in claims data using CPT and ICD9 diagnosis codes and in IIS data using CVX codes (*Table 6*). ICD9 diagnosis codes will be used to identify DTaP exposure if and only if the ICD9 diagnosis code for vaccination not carried out (V64.0*) is not present on the same day.

Table 6: Vaccine codes to identify potential administration of DTaP containing vaccines. NDC codes corresponding to the vaccines in this table will also be used to identify potential administration of DTaP containing vaccines.

Description	Code	Code Type
Diphtheria, tetanus toxoids, acellular pertussis vaccine and poliovirus vaccine, inactivated (DTaP-IPV), when administered to children 4 years through 6 years of age, for intramuscular use	90696	CPT
Diphtheria, tetanus toxoids, and acellular pertussis vaccine, haemophilus influenza Type B, and poliovirus vaccine, inactivated (DTaP - Hib - IPV), for intramuscular use	90698	CPT
Diphtheria, tetanus toxoids, and acellular pertussis vaccine (DTaP), for use in individuals younger than seven years, for intramuscular use	90700	CPT
Diphtheria, tetanus toxoids, and acellular pertussis vaccine and Hemophilus influenza B vaccine (DTaP-Hib), for intramuscular use	90721	CPT
Diphtheria, tetanus toxoids, acellular pertussis vaccine, Hepatitis B, and poliovirus vaccine, inactivated (DTaP-HepB-IPV), for intramuscular use	90723	CPT

Description	Code	Code Type
Diphtheria, tetanus toxoids and acellular pertussis vaccine, and poliovirus vaccine, inactivated	130	CVX
Diphtheria, tetanus toxoids and acellular pertussis vaccine, Haemophilus influenzae type b conjugate, and poliovirus vaccine, inactivated (DTaP-Hib-IPV)	120	CVX
Diphtheria, tetanus toxoids and acellular pertussis vaccine	20	CVX
Diphtheria, tetanus toxoids and acellular pertussis vaccine, 5 pertussis antigens	106	CVX
DTaP-Haemophilus influenzae type b conjugate vaccine	50	CVX
DTaP-hepatitis B and poliovirus vaccine	110	CVX
DTaP, unspecified formulation	107	CVX
Need for prophylactic vaccination and inoculation against combinations of diseases, diphtheria-tetanus-pertussis, combined	V06.1	ICD9 Diagnosis

Data on coinfections (e.g., otitis media, UTI, pneumonia) will be collected from the medical record for the seizure visit and will be used only for descriptive purposes. Age at vaccination (6-23 vs. 24-59 months), prior history of seizures, and family history of seizures will be examined as potential effect modifiers of incidence rate ratios for TIV. Information on family history of seizures and comorbidities such as prior history of seizures will be obtained from the medical record for the seizure visit. Product specific analysis for TIV will be conducted by stratifying models by manufacturer, which will be obtained from the medical record, where available. If manufacturer data are not available in the medical record, we will obtain manufacturer information from product specific claims codes (i.e., NDC or product-specific HCPCS codes) or as recorded in IIS data. If none of the above data sources are available for obtaining manufacturer information, we will infer manufacturer based on claims codes in instances where only one FDA approved vaccine corresponds to the code's description.[vi]

In addition, since 2 doses of influenza vaccine are recommended in children 6 months through 8 years of age receiving seasonal influenza vaccine for the first time, we will also consider effect modification by dose number in the 2010-2011 season by stratifying by dose number. For the purposes of this TIV dose specific analysis, to ensure that dose number can be accurately assessed, only doses for which children that have been enrolled continuously since the beginning of the influenza season (defined as July 1, 2010) will be included.[vii]

Finally, we will consider conducting dose number specific analyses for DTaP and Prevnar 13 to explore potential effect modification. Prevnar 13 was approved in February 2010, succeeding Prevnar, which

[vi] See footnote on page 8 for more information regarding reporting analyses by manufacturer.

[vii] We will determine TIV dose number based on information available from the medical record. We will also use claims data to determine TIV dose number in children who have continuous health plan enrollment from the beginning of the influenza season. We will report the source of dose number information (medical record vs. claims data).

was approved in 2000[20]. In March 2010, the ACIP published recommendations for routine vaccination with Prevnar 13 at ages 2, 4, 6, and 12-15 months in children who had no prior pneumococcal vaccinations. Children who had begun the 4-dose pneumococcal series with Prevnar were recommended to complete the series with Prevnar 13. In addition, children ages 14-59 months who had received 4 doses of Prevnar were recommended to receive a single supplemental dose of Prevnar 13. For the dose-specific Prevnar 13 analysis, we will consider stratifying jointly by dose number of the index Prevnar 13 vaccine *and* prior number of Prevnar doses. For the purposes of DTaP and Prevnar 13 dose specific analyses, to maximize the ability to accurately assess dose number, only doses for which children have been enrolled continuously since birth will be included. Because power will be diminished due to this enrollment requirement and stratification, dose specific analyses for Prevnar 13 and/or DTaP containing vaccines will be considered to be exploratory.[viii]

1f. Analysis plan

Descriptive analysis

Univariate and bivariate descriptive analyses in tables, histograms, and other graphs will be produced prior to hypothesis testing to characterize the TIV, DTaP, Prevnar 13, and seizure data. This will include information on the age at vaccination, sex, data partner, and manufacturer. Using computerized data, we will describe the types and timing of other vaccines in relation to seizure cases. For descriptive purposes in three separate univariate conditional Poisson models, we will also estimate the unadjusted relative risk for febrile seizures following TIV, DTaP, and Prevnar 13. The background rate of febrile seizures in all children, regardless of vaccination, will be estimated using ICD9 data from historical PRISM data.

Main analysis

To estimate incidence rate ratios, we will use conditional Poisson regression, where the outcome is the occurrence of febrile seizure and the main exposure of interest is interval type with respect to receipt of a TIV (i.e., risk or control interval). To adjust for confounding by co-administration of DTaP containing vaccines and Prevnar 13, we will include main effect terms in the model.

The primary analysis will be adjusted for confounding by time-varying age and seasonality, while an alternative analysis will be unadjusted for time-varying age and seasonality. Specifically, in the primary analysis, we will adjust for age and seasonality using ICD9-coded data on the background rate of seizures in the PRISM cohort (vaccinated and unvaccinated) during the 2010-2011 influenza season. These rates will be incorporated into the conditional Poisson model described above via the offset term to incorporate a child's different baseline risk of seizures by age and calendar time across any given child's

[viii] We will determine DTaP and Prevnar13 dose number based on information available from the medical record. We will also use claims data to determine DTaP and Prevnar13 dose number in children who have continuous health plan enrollment since birth. We will report the source of dose number information (medical record vs. claims data).

follow-up. We will consider incorporating the uncertainty in the background rates used for age and seasonality adjustments if a method to do so is available.

To obtain offset terms that incorporate these differences in underlying rates of seizures by age in weeks and calendar time, using the background rates of seizures in the PRISM cohort, we will conduct Poisson regression modeling of the background incidence rate with age in months and calendar week in the 2010-2011 influenza season as covariates. The regression equation might look like the following:

λ (age, calendar weeks) = $\lambda_0 + \beta_1$*age + β_2*age^2 + β_3*calendar week + β_4* calendar week^2

Additional polynomials or splines could be considered during the art of model building. Categorical variables may be considered instead of continuous variables. Interaction terms may be considered if, for instance, the risk of seizures by calendar week varies by age. The model for the background rate of seizures will be fit and finalized prior to its application to age and seasonality adjustments in the primary analysis.

We will examine whether co-administration of DTaP containing vaccines and/or Prevnar 13, age, prior history of seizures, or family history of seizures modify the rate ratios by fitting an additional model for each potential effect modifier. In separate models examining for effect modification of age, prior history of seizures, or family history of seizures, we will include main effects terms for TIV and potential confounders, as well as an interaction term between TIV and the effect modifier of interest. For example, the model to examine whether age (6-23 vs. 24-59 months) is an effect modifier of the IRR for TIV would include main effect terms for TIV and potential confounders, as well as an interaction term between TIV and age category (24-59 vs. 6-23 months). To examine the role of effect modification by concomitant vaccines, we will build two models: (1) a model with main effect terms for TIV, DTaP, and PCV13, and two-way interaction terms of TIV with DTaP, TIV with Prevnar 13, and DTaP with Prevnar 13 and (2) a model with main effects for TIV, DTaP, and PCV13, two-way interaction terms of TIV with DTaP, TIV with Prevnar 13, and DTaP with Prevnar 13, and a three-way interaction term between TIV, DTaP, and Prevnar 13. We will also qualitatively test for effect modification of rate ratios by stratifying models by potential effect modifiers (i.e. running separate conditional Poisson regression models for each category of potential effect modifiers).

OBJECTIVE 2: Among TIV vaccinees, examine whether receipt of concomitant vaccines of interest is associated with an overall greater risk of febrile seizures when compared to vaccination on separate days by examining for effect modification by concomitant vaccines on the attributable risk scale.

2a. Study population

Objective 2 will use the same study population as Objective 1. In addition, we will obtain estimates of baseline rates of febrile seizures by age in months in the Objective 1 study population and historical PRISM population, regardless of vaccine exposure.

2b. Study design

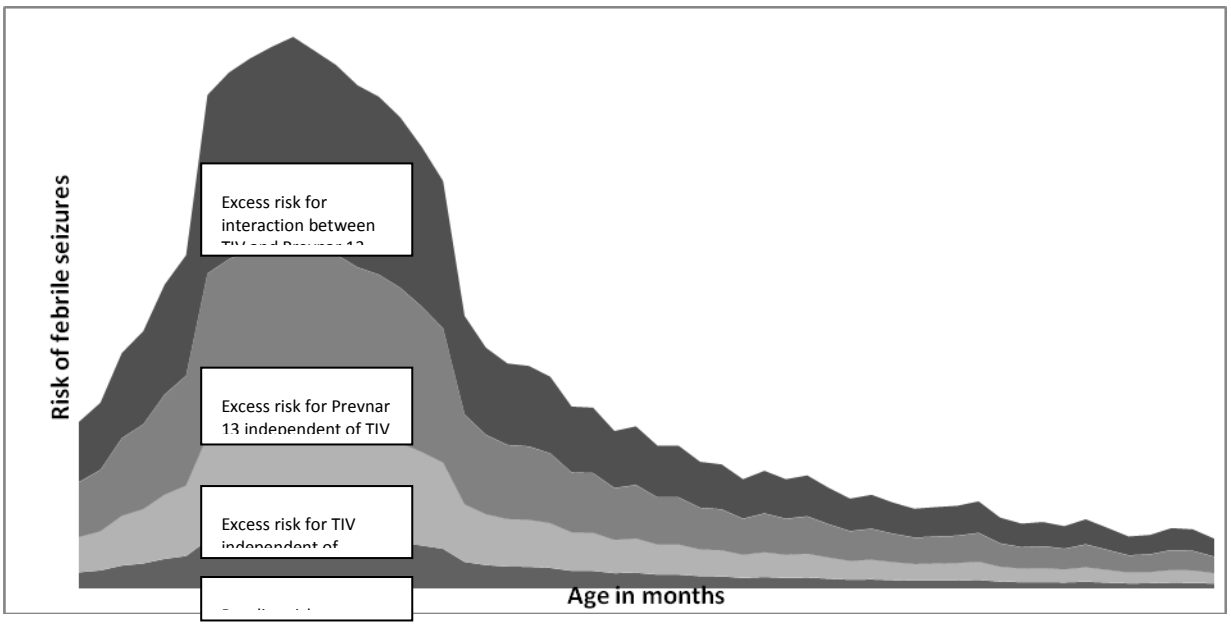
For Objective 2, to examine whether the overall risk of febrile seizures is elevated in children who receive other vaccines concomitantly with TIV as compared to separate day vaccination, we will use

attributable risk estimates calculated using the baseline rate of febrile seizures from the entire cohort and incidence rate ratio estimates from the self-controlled risk interval design in Objective 1 above.

The baseline rate of febrile seizures will be estimated by age in months using ICD9 codes in children ages 6-59 months in the Objective 1 study population and historical PRISM population, regardless of vaccination. This estimate based on ICD9 codes will then be corrected using age specific positive predictive value (PPV) estimates from medical record reviews. Attributable risk estimates by month of age and receipt of concomitant vaccines will be obtained by applying age specific baseline rates to incidence rate ratio estimates from Objective 1. For the purposes of the attributable risk calculations, the incidence rate ratios will be assumed to be constant across age unless there is evidence for effect modification by age.

As an example, if we are interested in whether same day receipt of TIV and Prevnar 13 is associated with an overall greater risk of febrile seizures, the null hypothesis is that the overall cumulative excess risk of febrile seizures in children who receive vaccines on separate days is equal to the cumulative excess risk of febrile seizures in children who receive both vaccines on the same day. Specifically (*Figure 4*), we would test whether the interaction risk between TIV and Prevnar 13 (i.e. the excess risk above and beyond the independent effect of TIV and of Prevnar 13 in children receiving concomitant TIV and PCV13) is greater than zero, where the interaction risk between TIV and Prevnar 13 is calculated as the area under the attributable risk curve for concomitant TIV and Prevnar 13 minus the area under the attributable risk curve for TIV without concomitant Prevnar 13 minus the area under the attributable risk curve for PCV13 without concomitant TIV. This example can be extended to accommodate more than one concomitant vaccine of interest.

Figure 4: Example of examining whether receipt of concomitant vaccines is associated with an overall greater excess risk of febrile seizures when compared to vaccination on separate days. Risks are stacked beyond the baseline risk, and the sum of three upper-most curves combined represents the total excess risk of febrile seizures for concomitant TIV and Prevnar 13.



2c. Statistical analyses

In the example described above in section 2b, to estimate the rate difference (i.e. excess cases per person day) by age in months for receipt of TIV without concomitant Prevnar 13, Prevnar 13 without concomitant TIV, and TIV with concomitant Prevnar 13, we would use incidence rate ratio estimates from conditional Poisson models from Objective 1 and apply age specific baseline rates using the formula (IRR-1)*p0, where IRR is the incidence rate ratio and p0 is the baseline rate by age in months. We would assume that the incidence rate ratio for each vaccine group is constant across age unless there is evidence of effect modification of the incidence rate ratios by age. We would estimate p0, the baseline rate of febrile seizure by age in months, using data from the Objective 1 study population and historical PRISM population; estimates of p0 would be obtained using ICD9 codes for seizures and applying the age specific estimates of PPV obtained from medical record reviews. We would then multiply the rate differences by the length of the risk interval to obtain the rate differences in excess cases per dose administered.

In this example, to examine whether the overall risk of febrile seizures is elevated in children who receive Prevnar 13 concomitantly with TIV when compared to separate day vaccination, we would test the hypothesis that the attributable risk for TIV without concomitant Prevnar 13 + attributable risk for Prevnar 13 without concomitant TIV equals the attributable risk for concomitant TIV and Prevnar 13. This approach can be further extended to examine the impact of other concomitant vaccines on risk of febrile seizures.

OBJECTIVE 3: To evaluate the positive predictive value of three alternative febrile seizures that use ICD9 data:

a. **ICD9 diagnosis code for seizure (780.3, 780.31, 780.32, or 780.39) in the inpatient or ED setting**
b. **ICD9 diagnosis code for febrile seizure (780.31) in the inpatient or ED setting**
c. **ICD9 diagnosis code for seizure (780.3, 780.31, 780.32, or 780.39) + ICD9 diagnosis code for medically attended fever (780.6, 780.60, 780.61, 780.62, or 780.63) on the same day in the inpatient or ED setting**

3a. Study population and study design

For Objective 3, we will use the medical record reviews conducted on potential febrile seizure cases in Objective 1. We will calculate the frequencies of chart confirmed cases of febrile seizure (primary case definition from Objective 1) that have

1) Any ICD9 code for seizures (780.3, 780.31, 780.32, or 780.39) in the ED or inpatient settings
2) ICD9 code for febrile seizures (780.31) in the ED or inpatient settings
3) Any ICD9 code for seizures + ICD9 code for medically attended fever on same day (780.6, 780.60, 780.61, 780.62, or 780.63) in the ED or inpatient settings

3b. Statistical analysis

For descriptive purposes, the positive predictive value (PPV) and corresponding 95% confidence interval for each of the three alternative febrile seizure definitions will be calculated as the proportion of chart confirmed febrile seizure cases that meet each respective definition. We will also estimate age specific PPVs for each of the definitions (6-11, 12-23, and 24-59 months).

OBJECTIVE 4: Using a self-controlled risk interval design, to explore whether the risk of <u>medically attended fever</u> identified in claims data is elevated following any 2010-11 TIV dose in the risk vs. control intervals, without medical record confirmation.

Although the clinical trials for each trivalent influenza vaccine differ slightly in design and definition for fever, the data (*Table 7*) suggest that fever after vaccination is variable by vaccine type. Of note while included in pre-licensure trials for Afluria, children less than 5 years of age were not included in ACIP recommendations for use of Afluria during the 2010-2011 season.

Table 7: Pre-licensure trial data on rates of fevers following TIV

Manufacturer	Product	Fever rate, 6–35 months	Fever rate, 36–59 months	Fever rate, 36 months to 8 years
CSL Biotherapies [5]	Afluria	23% (≥ 100.4°F)	---------	8-16% (≥ 100.4°F)
GlaxoSmithKline [21]	Fluarix	16% (≥ 100.4°F)	8% (≥ 100.4°F)	
Sanofi Pasteur [21]	Fluzone	11% (≥100.4°F)	9% (≥100.4°F)	12% (≥99.5°F)
Novartis Vaccines [22]	Fluvirin	Not available	2-3% (≥100.4°F)	---------

Given the increase in risk of febrile seizures following receipt of a TIV, particularly among children receiving concomitant Prevnar 13 vaccine, one may assume that the pathophysiologic explanation for this increased risk may relate to an increase in risk for fevers. In order to evaluate this hypothesis, we propose to explore whether the relative incidence of medically attended fevers following receipt of a TIV +/- concomitant vaccines is increased in the 0-1 days following vaccination compared to a control interval.

The results for Objective 4 will need to be interpreted in the context of the results for Objective 1 (i.e. risk of chart-confirmed febrile seizures following TIV) as shown in Table 8 below. The results from Objective 4 will be considered exploratory due to the study limitations, specifically poor sensitivity of codes for medically attended fever, lack of chart confirmation for outcomes, and inability to capture non-medically attended fevers.

Table 8: Potential scenarios when interpreting Objective 4 results in the context of Objective 1 results

		Objective 1: Statistically elevated risk of febrile seizures following TIV?	
Objective 4: Statistically elevated risk of medically attended fevers following TIV?		**Yes**	**No**
	Yes	A	-
	No	B	-

Objective 4 will only be conducted if we find a statistically elevated risk of febrile seizures following TIV. If scenario A (statistically elevated risks of both febrile seizures and fevers) were to occur, we would interpret this result to further support to our hypothesis that receipt of a TIV increases risk of febrile seizures due to an increase in risk for fevers. A result under scenario B might reflect the poor sensitivity of ICD9 diagnosis codes for medically attended fevers. Alternatively, fevers occurring in the absence of medical care seeking may also impact our ability to accurately assess risk for fevers, since our ICD9 diagnosis code data only capture medically attended fever. A less likely possibility would be that TIV results in a higher risk for seizures, whether febrile or afebrile, and that in the absence of an increased risk for medically attended fevers, we may want to consider further exploration of afebrile seizures as a potential outcome of interest in the future.

4a. Study population

Objective 4 will use a similar study population as Objective 1 (i.e., children 6-59 months of age experiencing an event of interest following TIV, DTaP, or PCV13 received during the study period and enrolled from 180 days prior to through 20 days after vaccination), except children will need to have experienced a medically attended fever event rather than a seizure event following vaccination.

4b. Study design

Similar to the design for Objective 1, we propose to use the self-controlled risk interval design to examine the null hypothesis that there is no association between receiving a TIV and medically attended fever in a pre-defined risk interval after vaccination. Exposed person time will consist of person time in the risk interval of 0-1 days post-vaccination and unexposed person time will consist of person time in a control interval beyond the risk interval (days 14-20). In order to adjust for confounding by co-administration with DTaP containing vaccines and Prevnar 13, we will collect information on medically attended fever in the similarly defined risk interval of 0-1 days post-vaccination and control interval of 14-20 days post-vaccination for these other vaccines, *regardless of co-administration with TIV.*

4c. Exposure

Exposure to TIV will be collected using the same vaccine codes as listed under Objective 1.

4d. Outcome

Medically attended fevers will be identified in the electronic data by any of the following ICD9 codes occurring in the inpatient, ED, or AV settings. Only codes that are the first in a 42-day period will be considered events. Fever events will not be chart confirmed.

Table 9: Codes to identify medically attended fevers

ICD9 code	Description
780.6	Fever and other physiologic disturbances of temperature regulation
780.60	Fever, unspecified
780.61	Fever presenting with conditions classified elsewhere
780.62	Postprocedural fever
780.63	Postvaccination fever

4e. Statistical analysis

Univariate and bivariate descriptive analyses in tables, histograms, and other graphs will be produced prior to hypothesis testing to characterize the TIV and medically attended fever data. This will include information on the age at time of vaccine and medically attended fever, sex, data partner, and manufacturer. We will examine the types and numbers of concomitant vaccines given on the same day as TIV in children who experienced medically attended fevers in the 0-1 days following vaccination.

Similar to the statistical method for Objective 1, we will we will use conditional Poisson regression to estimate incidence rate ratios, where the outcome is the occurrence of medically attended fever event, and the main exposure of interest is interval type with respect to receipt of a TIV (i.e., risk or control interval). To adjust for confounding by co-administration of DTaP containing vaccines and Prevnar 13, we will include main effect of each of these vaccines in the model. In addition, we will test for effect modification by concomitant vaccines by first entering two-way interaction terms of TIV with DTaP, DTaP with Prevnar 13, and TIV with Prevnar 13 and subsequently adding a three-way interaction between TIV, Prevnar 13, and DTaP.

OBJECTIVE 5: Using a self-controlled risk interval design, explore whether the risk of seizures identified in claims data is elevated following any 2010-11 live attenuated influenza vaccine dose in the risk vs. control intervals, without medical record confirmation.

No association has previously reported between live attenuated influenza vaccines and risk of febrile seizures. However in exploratory analysis, we will examine this association. Exposed person time will consist of person time in the risk interval of 1-3 days post-LAIV and unexposed person time will consist of person time in a control interval beyond the risk interval (days 14-20). Because LAIV is FDA approved for individuals 2 years and above, and the rates of seizures are lower in children older than 2 years of age, we will collect information on concomitant Prevnar 13 or DTaP containing vaccines, but will only use this information to adjust for confounding or examine for effect modification in the event that there is a statistically significant association between LAIV and seizures in univariate analysis.

5a. Study population

Objective 5 will use a similar study population as Objective 1 (i.e., children 6-59 months of age experiencing a seizure event following vaccine received during the study period with enrollment from 180 days prior to through 20 days after vaccination), except we will include children experiencing a seizure following LAIV rather than TIV, PCV13, or DTaP. Furthermore the age range will be restricted to 24-59 months of age because LAIV is not approved for use in children 6-23 months of age.

5b. Exposure

Exposure to LAIV will be collected in claims data using the relevant CPT code and any valid NDC code for LAIV and in immunization registry data using the relevant CVX code (*Table 10*).

Table 10: CPT and CVX codes used to identify LAIV. NDC codes will also be used to identify LAIV.

Description	CPT Code	Code Type
Influenza Virus Vaccine, live, for intranasal use	90660	CPT
Influenza virus vaccine, live, attenuated, for intranasal use	111	CVX

5c. Outcome

Seizure events will be identified in electronic data using the same codes listed under Objective 1. Only codes that are the first in a 42-day period will be considered events. Seizure events for this Objective will not be chart confirmed.

5d. Statistical analysis

Univariate and bivariate descriptive analyses in tables, histograms, and other graphs will be produced prior to hypothesis testing to characterize the LAIV and seizure data. This will include information on the age at time of vaccine and seizure, sex and data partner.

Similar to the statistical method for Objective 1, we will use conditional Poisson regression to estimate incidence rate ratios, where the outcome is the occurrence of seizure event and the main exposure of interest is interval type with respect to receipt of LAIV (i.e., risk or control interval).

VI. POWER CALCULATIONS

Based on the number of members in the participating health plans in October 2010 and coverage rates estimated from the 2009-2010 season, we estimate that roughly 270,000 and 590,000 TIV doses were administered to children ages 6-23 and 24-59 months, respectively during the 2010-2011 season. We performed univariate power calculations for a range of incidence rate ratios assuming that the rate of febrile seizures in the control interval will be similar to that found in the VSD study.

Table 11: Power calculations

Age group	Estimated number cases	Power by univariate incidence rate ratio for TIV					
		1.5	1.8	2.0	2.5	3.0	3.5
6-23 months	117	0.55	0.85	0.94	0.99	1	1
24-59 months	54	0.24	0.46	0.63	0.87	0.96	0.99
6-59 months	171	0.69	0.94	0.99	1	1	1

VII. DATA SET CREATION AND REGISTRY MAPPING

PRISM uses the Mini-Sentinel Common Data Model (MSCDM) to access data from the Mini-Sentinel Distributed Database (MSDD), which allows Data Partners to maintain control over patient-level data.

Data Partners extract and output data info eight files of standard format. The files relevant for the present study are: Enrollment, Demographic, Encounter, Procedure, Diagnosis, and Dispensing.

To obtain immunization data from state immunization registries, Data Partners will provide the registries with member identification information to allow the registries to match Data Partner members with registry immunization records. The registries will return immunization data (i.e. vaccination date, vaccine code, and manufacturer and lot number when available) for Data Partner members to the Data Partners. The Data Partners will then populate the MSCDM State Vaccine file that is linkable to the other files by the patient identification number. Immunization data from the claims-based Diagnosis, Procedure, and Dispensing files will be combined with the State Vaccine file into a single intermediate file. Duplicates will be eliminated using a method to be developed by PRISM programmers.

PRISM programmers will provide Data Partners with programs to be run on the patient-level files. The programs will produce aggregate data on vaccinations and seizures and fever events organized in strata defined by variables such as week of vaccination, type of vaccine, dose number, age, Data Partner, and sex, with counts of patients, vaccine doses, and seizure and fever events in particular strata. Data Partners will return the aggregate data for analysis at Harvard, using Mini-Sentinel's secure file transport methods.

VIII. INSTITUTIONAL REVIEW BOARD APPROVAL AND OTHER AUTHORIZATIONS

Per the privacy section on the Mini-Sentinel policies and procedures manual[23]:

4.1 Mini-Sentinel Activities Are Public Health Practice, Not Research

The HHS Office of Human Research Protections (OHRP) determined that the regulations administered by OHRP (45 CFR Part 46, "Common Rule") do not apply to the activities that are included in the FDA's Sentinel Initiative. FDA stated that this assessment also applies to Mini-Sentinel, as it is part of the Sentinel Initiative.

Additionally, FDA determined that Mini-Sentinel activities are public health activities in support of FDA's public health mission. It is therefore not necessary for the Collaborating Institutions to obtain approval from their respective Institutional Review Boards (IRBs) or Privacy Boards, or to obtain waivers of authorization under HIPAA, to participate in Mini-Sentinel activities (45 CFR §164.512(b)).

The HIPAA Privacy Rule permits covered entities the use and disclosure of protected health information (PHI) to public health authorities without patient authorization. Public health authorities include the FDA. The Operations Center and Collaborating Institutions are also public health authorities for purposes of the Mini-Sentinel pilot, because they are acting under contract with and under the authority of the FDA.

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