ASSESSMENT OF FEBRILE SEIZURES AFTER TRIVALENT INFLUENZA VACCINES DURING THE 2010-2011 INFLUENZA SEASON IN THE POST-LICENSURE RAPID IMMUNIZATION SAFETY MONITORING PROGRAM

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May 15, 2014

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. BACKGROUND

During the 2010 Southern Hemisphere influenza season in Australia, an increased risk of febrile seizures was found in children 6 months to less than 5 years of age in the 24 hours following a trivalent inactivated influenza vaccine (TIV) manufactured by CSL Biotherapies (Fluvax ®, Fluvax Junior ®)[1]. As a result, in the summer of 2010, the U.S. Advisory Committee on Immunization Practices (ACIP) recommended that Afluria® (an antigenically equivalent vaccine manufactured by CSL Biotherapies) should not be used in children ages 6 months to 8 years. However, the ACIP recommendations stated that Afluria could be used in children 5 to 8 years of age if they had medical conditions that increased the risk for influenza complications and no other licensed influenza vaccines were available. The FDA also 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, Fluvirin, Fluarix, and Fluzone were FDA approved and recommended by ACIP for use in a portion of or the full age range of 6 months through 5 years, with Fluzone being the only FDA approved and ACIP recommended 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].

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 find a statistically significant 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, FDA investigators conducted bimonthly disproportional reporting analysis in the Vaccine Adverse Event Reporting System (VAERS), a spontaneous reporting system co-managed by the CDC and FDA, to identify adverse events reported more frequently than expected following TIV[11]. By November 23, 2010, disproportional reporting for febrile seizures was detected for Fluzone but not for other 2010-2011 TIV products. In a subsequent analysis conducted on December 10, 2010 the disproportional reporting persisted. Over 80% of the disproportionally reported febrile seizure cases occurred in children less than 2 years of age. 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, the Vaccine Safety Datalink (VSD), a collaboration between CDC and 8 medical care organizations, conducted weekly near real-time surveillance for seizures in approximately 200,000 children ages 6 months through 4 years. The VSD used 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 significant increased risks of seizures following receipt of a TIV (all TIVs were combined) 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 for weekly sequential analysis. After the potential cases following TIV were chart confirmed, an analysis of all TIV products combined, 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® (13-valent pneumococcal conjugate vaccine, PCV13, manufactured by Pfizer), (IRR for TIV, adjusted for concomitant PCV13=2.4, 95% CI 1.2, 4.7). Of note, the VSD analysis contained febrile seizure cases who had been vaccinated with TIV or PCV13. As a result, main effect estimates for DTaP-containing vaccines and their confounding or synergistic role could not be evaluated.

The primary purpose of the present study is to examine the risk of confirmed febrile seizures following a 2010-2011 TIV in children ages 6-59 months while adjusting for concomitant PCV13 and DTaP-containing vaccines in a larger population of vaccinated children in the U.S. We address the following aims:

1. To estimate the relative risk of febrile seizures among children 6-59 months of age following any TIV dose in the 2010-2011 season, adjusted for confounding by concomitant vaccines. Also, we will *explore* whether the relative risk of febrile seizures 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 febrile seizures or family history of seizures
    d. Vaccine product type (i.e. manufacturer)
    e. Dose number in the 2010-2011 season

2. Among TIV vaccinees, to 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 on the attributable risk scale.

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

    a. ICD9 diagnosis code for seizure [780.3], febrile seizure (simple), unspecified [780.31], complex febrile seizure [780.32], or other seizure [780.39] in the inpatient or ED setting
    b. ICD9 diagnosis code for febrile seizure (simple), unspecified [780.31] or for complex febrile seizure [780.32] in the inpatient or ED setting
    c. ICD9 diagnosis code for seizure [780.3] or other seizure [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

4. To 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 using electronic data only

II. METHODS

A. Study Population

The associations between TIV and confirmed febrile seizures and between LAIV and seizure without medical record confirmation were examined in the Post-Licensure Rapid Immunization Safety Monitoring program (PRISM), a component of the FDA-sponsored Mini-Sentinel pilot program. The study population consisted of children 6-59 months of age who were members enrolled in a health plan associated with one of three participating Mini-Sentinel Data Partners, Aetna, HealthCore, or Humana, during the period of interest (July 1, 2010 to June 30, 2011). Within this overall population (N= 1,946,265), children were included if they received a TIV, LAIV, PCV13, or DTaP-containing vaccine during the study period and at a minimum, were enrolled in their health plan from 180 days prior to vaccination through 20 days after vaccination. To estimate the risk of febrile seizure by age and calendar-time for confounding adjustment, we also included person time contributed by vaccinated and unvaccinated children during the study period within the 6-59 month age range.

B. Study Design

We used 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 influenza vaccines and febrile seizure in a pre-specified risk interval after vaccination.7,13 The risk interval for TIV was defined as days 0-1 post-vaccination, while the control interval was defined as days 14-20 post-vaccination.13,14 The length and placement of the risk interval for TIV was selected based on the recommendation of the Risk interval Working Group of the Clinical Immunization Safety Assessment (CISA) Network, which cited data from VAERS demonstrating that the majority of febrile seizure cases occurred on day 0 or 1 following TIV.14 We also collected information on febrile seizures in the similarly defined risk and control intervals following DTaP-containing vaccines and PCV13, regardless of concomitant administration of TIV, to adjust for concomitant administration of these vaccines in the analytic model. The risk interval for LAIV was defined as 1-3 days post-vaccination14, while the control interval as days 14-20 post-vaccination. The length and placement of the risk interval for LAIV was also based on the recommendation of CISA, which cited VAERS data suggesting that the onset of febrile seizure was slightly later than that following TIV.

The self-controlled risk interval 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 person-time in the exposed (i.e., the risk interval) and unexposed (i.e., the control interval) intervals within the same individual, it implicitly controls for bias due to time invariant confounders, such as race and socioeconomic status. Additionally, by only including vaccinated individuals, it avoids bias from 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).

C. Vaccine Exposures

Exposure to LAIV, TIV, PCV13, and DTaP-containing vaccines were identified using claims data from the Data Partners and immunization registry data (i.e., immunization information systems, or "IIS") from any of eight participating registries: Florida, Michigan, Minnesota, New York City, New York State, Pennsylvania, Virginia, and Wisconsin. CPT, HCPCS, NDC, ICD9-diagnosis codes were used to identify vaccines in claims data while CVX codes were used to identify vaccines in immunization registry data (Appendix 1-3). ICD9-diagnosis codes for identifying vaccine exposure were only used if the ICD9-diagnosis code for "vaccination not carried out" (V64.0*) was not present on the same day.

Exposures to TIV, PCV13 and DTaP were identified using claims and immunization registry codes for TIV or influenza vaccine not otherwise specified (influenza vaccine NOS); PCV13 or pneumococcal conjugate vaccine not otherwise specified (PCV NOS) after January 1, 2011; and DTaP. We also obtained medical records of visits where vaccines were administered. If these visit records were not available, we further obtained immunization records (i.e. history of vaccines given). We considered the vaccine of interest confirmed by medical records if it was documented in the visit record or in the immunization history. We considered TIV confirmed if influenza vaccine without further specification or TIV was documented in the medical record and PCV13 confirmed if PCV without further specification or PCV13 was documented in the medical record. If only an immunization history was available and the vaccine was not documented, we considered the medical record of vaccination unobtainable because we could not verify whether the immunization history was complete.

Our main analysis included all TIV, PCV13 and DTaP exposures identified using claims, immunization registry or medical record data. We excluded from all analyses vaccine exposures that were chart confirmed as LAIV or PCV7, rather than TIV or PCV13. We used the date of vaccination available in the medical record, if available; otherwise we used the date of vaccination identified in electronic records. In a sensitivity analysis, we also required medical record documentation of TIV and PCV13.

D. Outcomes

Potential cases of febrile seizure were identified in electronic data by any of the following ICD9 diagnosis codes occurring in the inpatient or emergency department (ED) setting: 780.3 [seizure], 780.31 [febrile seizure (simple), unspecified], 780.32 [complex febrile seizure], or 780.39 [other seizure]. Of note, we did not use 780.33 [post-traumatic seizure]. We did not include events that had another seizure code in the 42-day period prior (in any setting, including ambulatory care) in order to avoid including follow-up visits for seizure episodes.

Chart review was conducted for potential cases of febrile seizure following TIV, DTaP, or PCV13. Case status and date of occurrence was determined by adjudication based on review of de-identified full text medical records of the event. Cases were excluded if a medical record for the seizure could not be obtained or if initial examination of the medical record revealed that the visit was due to management of a known seizure or other non-seizure related issue or if the examining physician ruled out a suspected seizure. Each of the remaining potential febrile seizure cases was independently reviewed by two pediatricians. A third adjudicator, also a pediatrician, reviewed the case if there was lack of consensus between the two primary adjudicators regarding case status or date of occurrence. Clinical adjudicators were blinded to vaccination history.

Cases were determined to be confirmed febrile seizures if documentation in the medical records described a seizure and evidence of fever (i.e., a measured temperature >38 C or tactile fever within 24 hours of a seizure, or a physician's diagnosis of a concomitant febrile illness and a seizure, or a physician's diagnosis of a febrile seizure). We excluded potential cases if they had an underlying metabolic disorder, CNS infection/trauma, history of afebrile seizures, or if they were described as focal seizures that were not associated with a complex febrile seizure. We also excluded cases where documentation was insufficient to confirm the occurrence of a seizure or if the treating clinician recorded uncertainty regarding a seizure diagnosis in the medical records. In a sensitivity analysis, we also analyzed potential cases that met adjudication criteria for seizure but had no clear documentation of either the presence or absence of fever in the medical record.

Medical records were considered unobtainable if after a minimum of 5 requests (using a combination of letters, emails, faxes, or phone calls), we received no response from the provider. We also considered records unobtainable if (1) the provider declined participation; (2) the provider was reached but the chart could not be found at the provider site (e.g., no record for the date of service of interest existed or the charts had been destroyed or lost); or (3) it was determined that the provider could not be contacted using the information on file (e.g., clinic had relocated, or provider was no longer affiliated with the facility or was deceased).

E. Effect Modifiers

Age, history of febrile seizures, family history of seizures (among a first-degree relative), and influenza vaccine dose number were considered as potential effect modifiers in exploratory analysis. A patient was considered to have a prior history of febrile seizures or family history of seizures if these were documented in the medical record. We determined TIV dose number based on information available from the medical record and from claims data, if they had continuous health plan enrollment from the beginning of the influenza season.

If manufacturer was not specified in the medical record, we obtained manufacturer information from product specific claims codes (i.e., NDC codes). If none of the above data sources were available for obtaining manufacturer information, we inferred manufacturer based on medical record descriptions or claims codes corresponding to a single FDA-approved product (e.g., documentation of 'influenza virus vaccine, split virus, preservative free, for children 6-35 months of age, for intramuscular use' in medical records or claims data).

III. STATISTICAL ANALYSIS

Conditional Poisson regression was used to estimate incidence rate ratios (IRRs) for seizures in the risk vs. control intervals following vaccination. We first implemented three bivariate models, each containing a term for TIV, DTaP, or PCV13. To each of these three models, we then added calendar time (in weeks) and age (in weeks), as described further in the next paragraph. Finally, the single primary analytic model contained terms for TIV, DTaP, PCV13, along with adjustments for calendar time and age.

To adjust for time-varying age (in weeks) and seasonality (calendar week number), we included unvaccinated person-time from the underlying cohort of children ages 6-59 months of age during the

study period into our models. A quadratic spline function with a single knot for age in weeks and a quadratic spline function with 6 knots for calendar week were included in the primary analytic model.

Prior to including age and calendar time into the model with exposures of interest, we had previously determined the age and calendar time risk functions using data from the underlying PRISM cohort, independent of vaccination, as follows. To be included in the model, each person-day was required to have at least 42 days of continuous enrollment in the immediately preceding period since the definition of seizure used a 42-day washout period. Person-time was also required to be unexposed to TIV, DTaP, and/or PCV13 in the 0-1 days prior and to be unexposed to MMR or MMRV in the 5-12 days prior. We examined the fit of quadratic and cubic splines for modeling age in weeks and calendar week using the Akaike Information Criteria (AIC). To determine the function for age, we fit a series of models with quadratic splines and cubic splines, all using a single knot. We allowed the placement of the knot to vary over the range of age. For each polynomial type used for spline modeling (quadratic and cubic), we identified the model with knot placement that resulted in the lowest AIC value and plotted both curves with raw rates for evaluating fit. We then proceeded to model calendar week, with all models from this point forward containing a quadratic spline with a single knot for age in weeks. We fit a series of models for calendar week with quadratic and cubic splines. We allowed the number of knots to range from 3 to 7, with knots equally spaced across the range of calendar weeks. For each polynomial type used for spline modeling (quadratic and cubic), we identified the number of knots that resulted in the lowest AIC value and selected the calendar time function that produced the lowest AIC.

In the primary analysis, we also conducted a test for effect modification of TIV by concomitant administration of PCV13 on the additive scale. Specifically, we examined the hypothesis,$AR_{TIV+PCV13} - AR_{TIV,} - AR_{PCV13}=0$, where $AR_{TIV+PCV13}$ is the attributable risk for concomitant TIV and PCV13, AR_{TIV} is the attributable risk for TIV without concomitant PCV13, and AR_{PCV13} is the attributable risk for PCV13 without concomitant TIV. The described difference in ARs represents the excess risk or reduction in risk when comparing same day vs. separate day vaccination. To calculate the differences in AR, we first calculated the attributable risk estimates for TIV without concomitant PCV13, PCV13 without concomitant TIV, and TIV with concomitant PCV13 vaccinees using the formula AR= (IRR-1)*p0*2*PPV, where 2 is the length of the risk interval in days , p0 is the baseline rate per person day estimated in electronic data in the PRISM population, and PPV is the positive predictive value of seizure codes determined from chart review of control interval cases in this study. The IRRs and PPVs were assumed to be constant across all ages, as statistical tests revealed that the IRRs and the case confirmation rate did not differ by age (6-23 months vs. 24-59 months of age). The IRRs were based on the effect estimates for TIV, PCV13, and TIV*PCV13 from the conditional Poisson model containing these three terms, age, and calendar time**.** We then calculated the difference in ARs, as described earlier. To construct confidence intervals for the difference in ARs, we simulated 10 million independent samples of the IRRs for TIV, PCV13, and TIV*PCV13 from a 3-dimensional joint distribution estimated from the conditional Poisson regression. For each sample, the difference in AR between same day vs. separate day vaccinees was calculated, with the 95% confidence lower and upper limits corresponding to the 2.5% and 97.5% percentiles from the 10 million simulated samples.

For descriptive purposes, we estimated attributable risks for TIV, PCV13, and DTaP by age in weeks. The attributable risk was calculated for each age using the same formula as described earlier, (IRR-1)*po*2*PPV. IRRs were estimated using the main analytic model, which included TIV, PCV13, DTaP, age, and calendar time. Age-specific baseline rates were estimated using a model that only included the quadratic spline function for age that was used in the main analytic model.

In exploratory analyses, concomitant PCV13 and DTaP-containing vaccines were considered as possible effect modifiers of the IRR for TIV (i.e., effect modifiers on the multiplicative scale). To examine the role of effect modification by concomitant vaccines on the IRR scale, we built 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 PCV13, and DTaP with PCV13 and (2) a model with those terms and a three-way interaction term between TIV, DTaP, and PCV13.

In further exploratory analysis, age at vaccination (6-23 vs. 24-59 months), and prior history of febrile seizures were considered as potential effect modifiers of the IRR for TIV. In separate models examining for effect modification of the IRR for TIV by age, prior history of febrile seizures, and influenza vaccine dose number, we included 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) was an effect modifier of the IRR for TIV included 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).

IV. RESULTS

A. Doses of LAIV, TIV, PCV13, and DTaP-Containing Vaccines

During the study period from July 1, 2010 through June 30, 2011, 618,204 TIV doses, 138,077 LAIV doses, 497,979 PCV13 doses, and 518,758 doses of DTaP-containing vaccines were administered among children 6-59 months of age. Of the TIV doses, 472,145 were first 2010-11 TIV doses and 146,059 were second 2010-11 TIV doses.

B. Overview of Case Disposition

Figure 1 illustrates the disposition of all vaccinated febrile seizure cases identified in electronic data. In electronic data, we identified 252 potential febrile seizures with exposure to TIV, PCV13, or DTaP-containing vaccine in 0-1 or 14-20 days prior to the seizure. After excluding potential cases due to lack of seizure medical records, failure to meet adjudication criteria for febrile seizure, documentation of LAIV or PCV7 on the index date, or reassignment of seizure or vaccination date, a total of 142 confirmed febrile seizure cases in the post-vaccination risk or control intervals of interest were available in the primary analysis. The details of medical record confirmation of seizures and of vaccinations are described further below.

C. Febrile Seizure Events

Because this study incorporated chart confirmation, the strategy to identify potential febrile seizure cases placed a higher priority on sensitivity than specificity. As a result, our study included ICD-9 codes for seizure [780.3], febrile seizure (simple), unspecified [780.31], complex febrile seizure [780.32], or other seizure [780.39]. Of the 252 electronically identified potential cases of febrile seizures with potential exposure to TIV, DTaP, or PCV13, 216 potential cases (86%) had medical records of seizure-related visits obtained from healthcare providers (Figure 1). We were equally like to obtain medical records of seizure-related visits among cases in the risk and control intervals (88 % vs. 85%,

respectively). One hundred fifty-two potential cases met criteria for febrile seizures, for a total positive predictive value of 70% (Table 1).

To inform future automated analysis using the distributed database, we calculated the positive predictive value of three alternative automated case definitions that used ICD9 data (Table 1). The first definition was restricted to codes for febrile convulsions (simple), unspecified or for complex febrile convulsions in the inpatient or ED setting. The second required a code for medically attended fever on the same day as codes for convulsions or other convulsions, all of which were required to occur in the inpatient or ED settings, in the absence of either code for febrile convulsions. The third required a code for convulsions or other convulsions in the inpatient or ED setting, in the absence of a code for febrile convulsions or medically attended fever on the same day in the inpatient or ED settings. The second definition provided the highest positive predictive value (91%), with only a slight decrease in number of confirmed cases. Codes for convulsions or other convulsions in the absence of codes for febrile convulsions yielded very low positive predictive values, regardless of whether medically attended fever was required on the same day.

D. Vaccine Exposures

Figure 2 shows the results of validation of potential exposure to TIV, PCV13, and DTaP-containing vaccines identified in claims or immunization registry data in confirmed cases of febrile seizures.

Of the 72 confirmed febrile seizure cases with potential exposure to TIV identified in claims or IIS data, 57 (79%) had medical records of influenza vaccination obtained (Figure 2a). Of those with influenza vaccination records that were obtainable, 56 (98%) had TIV (defined as either TIV or influenza vaccine, not otherwise specified documented) confirmed. Of the 15 cases with unobtainable medical records of influenza vaccination, 8 did not have any vaccination record of any type (whether of the visit or an immunization history) available, while 7 had only an immunization history available, without documentation of influenza vaccination in the immunization history. We excluded one case with LAIV documented in the medical record.

Of the 78 confirmed febrile seizure cases with potential exposure to PCV13 identified in claims or IIS data, 71 (91%) had medical records of PCV obtained (Figure 2b). Of those with medical records of vaccination obtained, 67 (94%) had PCV13 (defined as PCV13 or PCV, not otherwise specified documented) confirmed. All 7 cases whose medical records of PCV were unobtainable did not have an immunization history or a record of the vaccination visit. We excluded four cases with PCV7 documented in the medical record.

Of the 64 cases with potential exposure to DTaP-containing vaccines identified in claims or IIS data, 58 (91%) had medical records of DTaP-containing vaccine obtained (Figure 2c). Of those with medical records of DTaP-containing vaccine available, all 58 (100%) had DTaP-containing vaccine confirmed. All 6 cases whose medical records of DTaP-containing vaccine were unobtainable did not have an immunization history or a record of the vaccination visit available.

After incorporating the dates of vaccination and seizure from medical records where available, we also excluded five cases with vaccination dates that occurred outside of the intervals of interest (0-1 or 14-20 days before confirmed seizure onset), for a total of 142 cases included in the primary analysis. Among confirmed febrile seizure cases with potential PCV13 exposure in the 0-1 and 14-20 days prior, Appendix 4 illustrates the distribution of PCV type documented in electronic data and medical records.

E. Characteristics of Confirmed Febrile Seizures

Table 2 shows the characteristics of confirmed febrile seizure cases in cases overall, while Table 3 shows the characteristics of confirmed febrile seizure by vaccination status. Cases occurred primarily in children less than 2 years of age and were seen primarily in the ED setting. TIV was commonly administered concomitantly with other vaccines, with 11% of cases receiving TIV with PCV13 and 14% of cases receiving TIV with DTaP-containing vaccine.

F. Associations of TIV, PCV13, and DTaP-Containing Vaccines with Febrile Seizure Risk

Table 4 shows the results of the primary analysis, which includes confirmed febrile seizure cases and includes adjustments for age and calendar time. In the adjusted and unadjusted analysis, TIV and DTaP were not significantly associated with risk of febrile seizure. Adjustments for age and calendar time had minimal effects on the point estimates for TIV and DTaP-containing vaccines, while adjustment for concomitant vaccines attenuated the point estimates. PCV13 was significantly associated with risk of febrile seizures in the unadjusted analysis and the age and calendar time-adjusted analysis. However, it was not significantly associated with the risk of febrile seizures in the analysis further adjusted for concomitant vaccines. Similar to TIV and DTaP-containing vaccines, adjustment for age and calendar time had minimal impact on the point estimate for PCV13, while adjustment for concomitant vaccines attenuated the point estimate.

G. Attributable Risk Estimates for TIV, DTaP-Containing Vaccines, and PCV13

ARs for TIV, PCV13, and DTaP-containing vaccines varied by age (Figure 3) due to the varying baseline risk of febrile seizures, with the highest estimates at 72 weeks of age and the lowest estimates at 260 weeks of age. ARs for TIV ranged from 0.2 to 1.8 per 100,000 doses. ARs for PCV13 ranged from 0.4 to 3.1 per 100,000 doses and ARs for DTaP-containing vaccine were less than 0.2 per 100,000 doses for the entire age range.

We also calculated ARs based on the upper bound of the confidence intervals for the IRR estimates. For TIV, the upper bound of the confidence interval for the IRR translates to ARs that range from 0.93 per 100,000 children at 260 weeks to 7.05 per 100,000 children at 72 weeks. For DTaP-containing vaccines, the upper bound translates to ARs that range from 0.64 per 100,000 children at 260 weeks to 4.87 per 100,000 at 72 weeks; for PCV13, the corresponding estimates would be 1.22 per 100,000 children at 260 weeks to 9.23 per 100,000 children at 72 weeks.

H. Exploratory Analysis of TIV-Febrile Seizures Association

Effect Modification of IRR by Concomitant Vaccines, Age, Prior History of Febrile Seizures, and Dose Number

When we added two-way interactions of TIV*DTaP, TIV*PCV13, DTaP*PCV13 to the model with TIV, PCV13, DTaP, age, and calendar time, all p-values for the 2-way interactions were not significant (p=0.57, 0.60, 0.23, respectively). Furthermore, in the model in which two-way interactions of TIV*DTaP, TIV*PCV13, DTaP*PCV13 and a three-way interaction of TIV*DTaP*PCV13 were added, the p-value for the three-way interaction (p=0.56) was not statistically significant.

When we created three separate models, each building upon a model with TIV, DTaP-containing vaccines, PCV13, age, and calendar time, with the addition of an interaction term between TIV and age at vaccination (6-23 vs. 24-59 months), TIV and history of febrile seizures, and TIV and dose number, the p-values for the interaction terms were not statistically significant (p=0.11, 0.10, and 0.50, respectively).

Product Type Among TIV-Exposed Cases

Of the 68 TIV-exposed confirmed cases, Sanofi Pasteur was specified or inferred in 62 cases (Appendix 5). Manufacturer was not specified and could not be inferred for the remaining 6 TIV-exposed cases.

Effect modification of AR for TIV by Concomitant PCV13

Based on our estimate of the AR for concomitant TIV and PCV13 minus the AR for TIV without concomitant PCV13 minus the AR for PCV13 without concomitant TIV, same day vaccination was associated with 1.08 fewer febrile seizures per 100,000 vaccinated children when compared to separate day vaccination. However, this result was not statistically significant (point estimate, -1.08, 95% CI -5.68, 6.09).

I. Sensitivity Analysis for TIV-Febrile Seizures Association

In a sensitivity analysis that included cases without clear documentation of the presence or absence of fever in the medical record, the adjusted IRR estimates for TIV, DTaP-containing vaccines, and PCV13 were similar (Table 5). The results were also similar in sensitivity analyses that required vaccination to be confirmed in the medical record (Table 5).

J. LAIV-Seizures Association

In the SCRI analysis examining the LAIV-seizures association, without medical record confirmation, 4 cases occurred in the risk interval and 7 cases occurred in the control interval. LAIV was not significantly associated with risk of seizure (IRR= 1.33, 95% CI 0.39, 4.55).

V. DISCUSSION

This study includes 142 confirmed febrile seizure cases occurring in the post-vaccination periods of interest following 618,204 TIV doses, 497,979 PCV13 doses, and 518,758 doses of DTaP-containing vaccines administered among children 6-59 months of age during the study period from July 1, 2010 through June 30, 2011. We found a statistically significant excess risk of confirmed febrile seizures following PCV13 when adjusting for age and seasonality but not for concomitant vaccines (IRR 1.74, 95% CI 1.06, 2.86). We did not find statistically significant associations between PCV13 and febrile seizures when further adjusting for concomitant vaccines, although the IRR was similar (IRR 1.61, 95% CI 0.91, 2.82). No statistically significant associations were found between TIV or DTaP-containing vaccine with risk of confirmed febrile seizures in our adjusted models. While we cannot rule out the possibility that increased risks exist, the upper bounds of the confidence intervals for the IRRs for TIV (upper bound=2.39), DTaP-containing vaccines (upper bound=1.96), and PCV13 (upper bound=2.82) suggest that any increased risks, if present, are modest. For TIV, the upper bound of the confidence interval for the IRR translates to ARs that range from 0.93 per 100,000 children at 260 weeks to 7.05 per 100,000 children at 72 weeks. Ninety-one percent of TIV-exposed cases in this study were specified or inferred to

have Fluzone exposure. Evaluation of the attributable and relative risks for other TIV products is not possible since we could not infer from the available information which product, among those approved for use in age 6-59 months, was administered for the remaining nine percent of TIV-exposed cases. It is possible that these administrations involved Fluzone as well. For DTaP-containing vaccines, the upper bound translates to ARs that range from 0.64 per 100,000 children at 260 weeks to 4.87 per 100,000 at 72 weeks; for PCV13, the corresponding estimates would be 1.22 per 100,000 children at 260 weeks to 9.23 per 100,000 children at 72 weeks. We did not find evidence to suggest that same day TIV and PCV13 vaccination was associated with an increased risk of febrile seizures when compared to separate day vaccination in the 2010-11 season. We also did not find an association between LAIV and risk of seizure without medical record confirmation, though we were likely underpowered due to low case numbers.

Our medical record validation of seizures identified in ICD9 coded data provides information regarding the validity of specific automated case definitions for identifying febrile seizures which have not been investigated in prior vaccine safety studies. Use of all seizure codes without post-traumatic seizures yielded a moderate positive predictive value (PPV=70%). Restriction to codes for simple and complex febrile seizures yielded a much higher positive predictive value (PPV=91%). Thus, investigators conducting future automated surveillance using ICD9 codes to identify febrile seizures should consider restricting to codes for febrile seizures. If resources permit, signal evaluation should be performed with medical record review of cases coded with all seizure codes except for post-traumatic seizures.

This study had several notable strengths. First, it included a large nationally representative study population, and it had 80% power to detect IRRs between 2.0 and 2.2 for TIV, DTaP-containing vaccines, and PCV13. Second, to minimize outcome misclassification, we used a rigorous febrile seizure validation process that included adjudication blinded to vaccination status by at least two pediatricians and by a third pediatrician if there was disagreement on case status or date of onset. Third, the febrile seizure case definition used for this study was consistent with the current American Academy of Pediatrics Clinical Practice Guideline[15]. Fourth, we made equivalent efforts to confirm vaccination for all three vaccine classes included in the analysis. Fifth, the use of the self-controlled risk interval design adjusted inherently for fixed confounders and avoided misclassification of exposure because it only included vaccinated cases. Sixth, we adjusted for time-varying age and calendar time using spline modeling of background rates in the PRISM population. Finally, we adjusted for multiple concomitant vaccinations, including DTaP-containing vaccines and PCV13. The study results were robust to adjustments for age, calendar time, and concomitant vaccines.

A number of limitations are worth noting. First, while we were able to obtain the seizure medical record in the vast majority (86%) of cases, we were nonetheless unable to obtain them for all cases. However, we were able to obtain medical records of seizure visits at a similar rate between risk and control intervals (88% vs. 85%) and Data Partners were blinded to vaccination and timing of vaccination when obtaining charts. Thus, our findings are unlikely to be affected by differential obtainment rates with respect to vaccination timing. Second, while we were able to obtain the medical record of vaccination in 88% of cases, we were unable to obtain them for all cases. However, in instances where the medical record of vaccination was obtained, we confirmed nearly all vaccinations. Furthermore, when we excluded cases without vaccine confirmation, results were very similar. Third, our statistical power to detect effect sizes representing less than a doubling of incidence rate was limited. However, this study provided the largest statistical power and yielded the narrowest confidence intervals published to date for the estimation of the underlying relationship between TIV, PCV13, and febrile seizures in the 2010-

11 influenza season. Given the large sample size and the likely modest effect sizes (as evidenced by the confidence intervals for the IRRs), marked improvements in precision are unlikely with further study.

The associations of TIV and PCV13 with risk of febrile seizures were previously investigated in the Vaccine Safety Datalink. In that study, the IRR for TIV adjusted for concomitant PCV13 was 2.4 (95% CI 1.2, 4.7) while the IRR for PCV13 adjusted for concomitant TIV was 2.5 (95% CI 1.3, 4.7). Although the VSD and PRISM studies used self-controlled risk interval designs, there were differences in exposure assessment, outcome assessment, adjustment for time-varying age, adjustment for calendar time, and adjustment for concomitant vaccinations. Additionally, random error could have contributed to the differing results. The reported results are not inconsistent since the point estimates from both studies are both above 1 and that the confidence intervals overlap. In addition, the data from both studies suggest that higher magnitudes of increased risk can be ruled out. The confidence intervals in PRISM suggest with 95% confidence that relative risks larger than 2.4 and 2.8 can be ruled out for TIV and for PCV13, respectively. The VSD data suggest that relative risks larger than 4.7 can be ruled out with 95% confidence for both vaccines.

VI. CONCLUSIONS

In conclusion, we did not find evidence of a statistically significant elevated risk for febrile seizures in children 6-59 months of age following TIV, PCV13 or DTaP-containing vaccine during the 2010-2011 season. Ninety-one percent of TIV exposed-cases were specified or inferred to have Fluzone exposure, with the remaining cases having indeterminate product type. While we cannot rule out the possibility of increased risks with TIV, PCV13, or DTaP-containing vaccines, they are likely modest if they exist. No evidence was found to suggest that same day TIV (91% identified as Fluzone) and PCV13 vaccination increased the risk of febrile seizures when compared to separate day vaccination in the 2010-11 season. Continued monitoring of febrile seizures following vaccination may be warranted in future influenza seasons, particularly since vaccine formulations change yearly.

VII. ACKNOWLEDGEMENTS

Mini-Sentinel/PRISM is funded by the Food and Drug Administration through Department of Health and Human Services Contract Number HHSF223200910006I, Task Order Number HHSF22301005T.

We thank Sarah Henrickson and Sangeeth Gnanasekaran for adjudication, and David Cole and Robert Jin for statistical analysis. In addition, we gratefully acknowledge the contributions of the following people and organizations: Mini-Sentinel Operations Center: Meghan Baker, Carolyn Balsbaugh, Claudia Coronel-Moreno, Ashleigh Goff, Patricia Kennedy, Linda Pointon, Megan Reidy, Robert Rosofsky, Diana Santiago, and Katherine Yih; FDA Centers for Biologics and Evaluation: Wei Hua and Michael D. Nguyen. Aetna: Carolyn Jevit, Carolyn Neff, Claire Spettell, Joaquim Fernandes, and Yihai Liu; HealthCore: Chunfu Liu, Tosmai Puenpatom, Marcus Wilson, and Amanda Rodriguez; Humana: Vinit Nair and Qianli Ma; TTM: Tom Stacy; Verisk Health: Faith Woodhouse and Katie Kennedy.

We gratefully acknowledge the contribution to the vaccination data gained from matching with eight Immunization Information Systems, and the assistance provided by the staff listed below.

Florida: Susan, Lincicome, Pete Garner

Michigan: Ian Hancke, Bea Salada

Minnesota: Emily Emerson, Diana Jaeger

New York City: Rezaul Kabir, Vikki Papadouka

New York State: Michael Flynn, Munyaradzi Masawi, Megan Meldrum

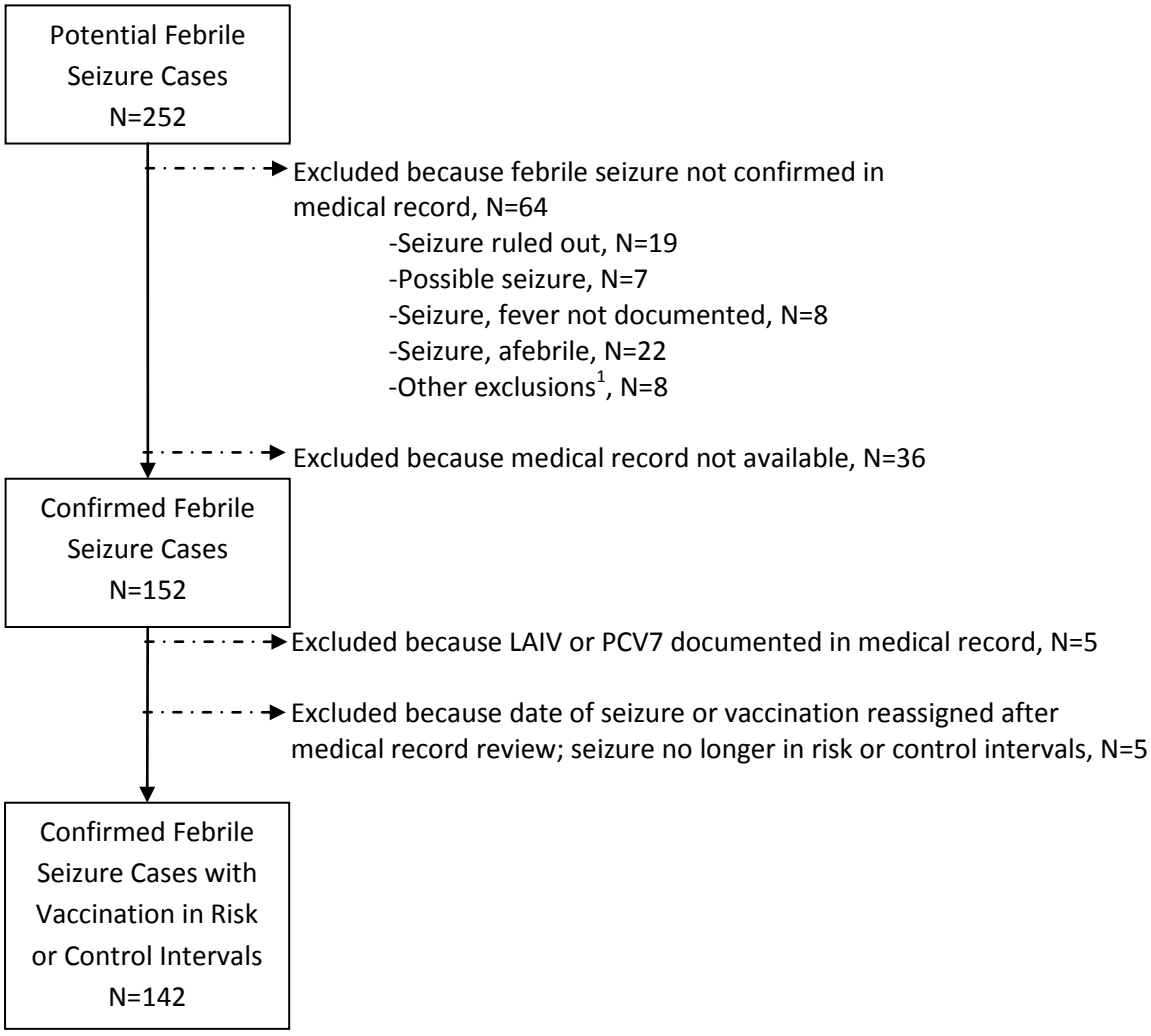
Pennsylvania: Frank Caniglia, Zachary Runkle

Virginia: Greg Dennis

Wisconsin: Daniel Hopfensperger, Thomas Maerz

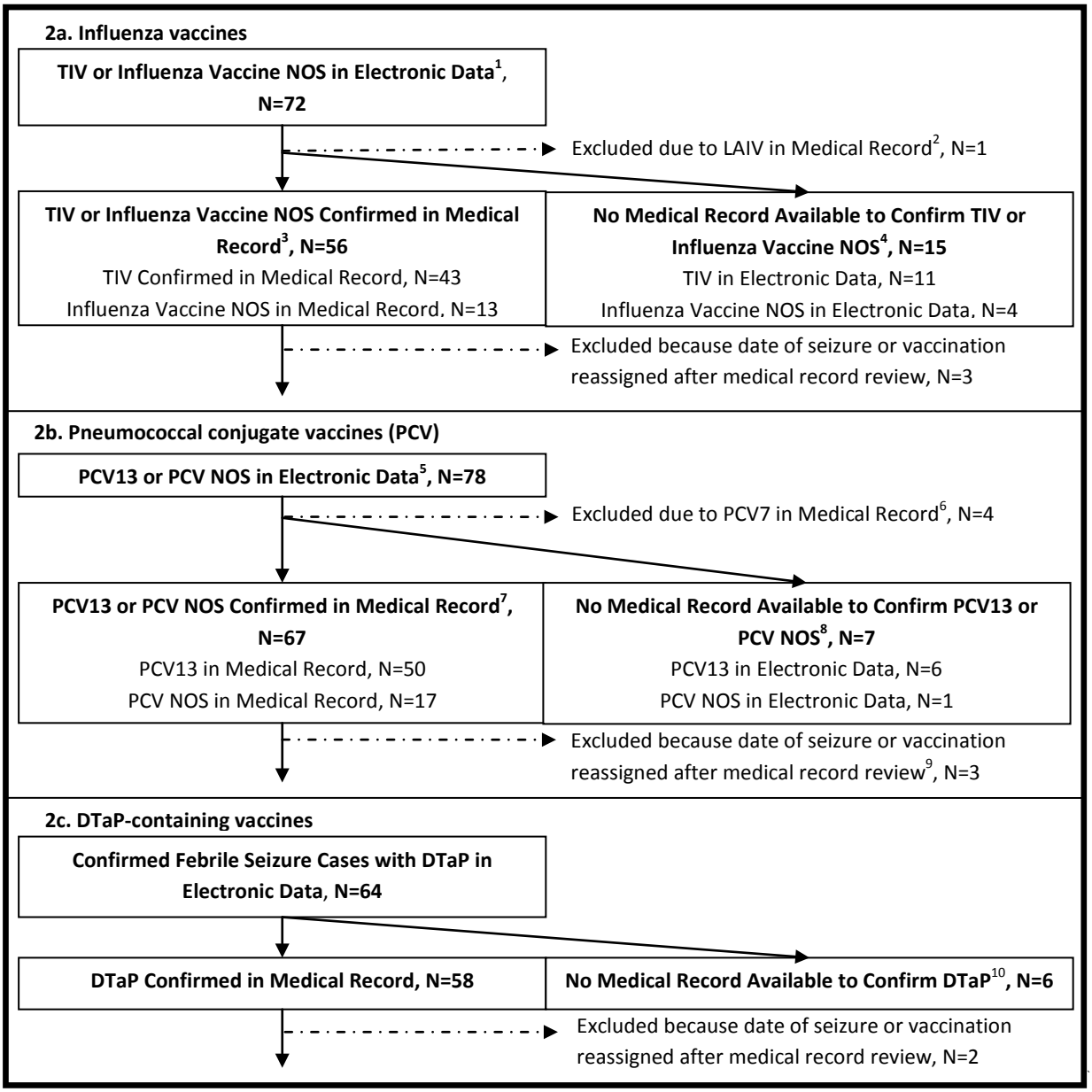
VIII. TABLES AND FIGURES

Figure 1: Case disposition of vaccinated febrile seizure cases



[1] Excluded due to seizure associated with metabolic disorder, CNS inflammation/infection, history of afebrile seizures, or focal seizure not associated with complex febrile seizure

Figure 2: Overall availability of influenza vaccine (Figure 2a), PCV (Figure 2b), and DTaP-containing vaccine (Figure 2c) information in electronic data and medical records.



[1] "Influenza vaccine NOS" represents influenza vaccine, not otherwise specified regarding vaccine type (i.e., TIV vs. LAIV). Potential exposure to TIV was identified in electronic data using claims or immunization registry codes for TIV or influenza vaccine NOS. Codes for LAIV were not used.

[2] The case with LAIV in the medical record was identified with a code for influenza vaccine NOS in electronic data.

[3] Of the 43 cases with TIV in the medical record, all but 3 were identified with TIV in electronic data. Of the 13 cases with influenza vaccine NOS in the medical record, all but 1 had TIV in electronic data.

[4] Of the 15 cases without medical records available to confirm influenza vaccination, 8 did not have any vaccination record of any type (whether of the visit or of an immunization history) available, while 7 had only an immunization history available without documentation of influenza vaccination in the immunization history.

[5] "PCV NOS" represents PCV not specified otherwise specified regarding vaccine type (i.e., PCV13 vs. PCV7). Potential exposure to PCV13 was identified in electronic data using claims or immunization registry codes for PCV13 or pneumococcal vaccine NOS. Codes for PCV7 were not used.

[6] Of the 4 cases with PCV7 in the medical record, all were identified with PCV13 codes in electronic data. These cases were excluded from the analysis, regardless of concomitant vaccinations.
[7] Of the 50 cases with PCV13 in the medical record, all but one was identified with PCV13 in electronic data. Of the 17 cases with PCV NOS in the medical record, all were identified with PCV13 in electronic data.
[8] All 7 cases without medical records available to confirm PCV had neither an immunization history nor a vaccine visit record available.
[9] Two cases with PCV13 or PCV NOS based on electronic data were completely excluded from the analysis due to reassignment of vaccination or seizure date. One case with PCV13/PCV NOS and TIV/influenza vaccine NOS based on electronic data was considered unexposed to PCV13 in the intervals of interest due to reassignment of PCV date based on the medical record; however, this case was included in the analytic dataset and considered TIV-exposed because date of influenza vaccine was confirmed in the medical record.
[10] All 6 cases without medical records available to confirm DTaP had neither an immunization history nor a vaccine visit record available.

Figure 3: Attributable risk estimates for DTaP-containing vaccines, TIV, and PCV13 by age in weeks

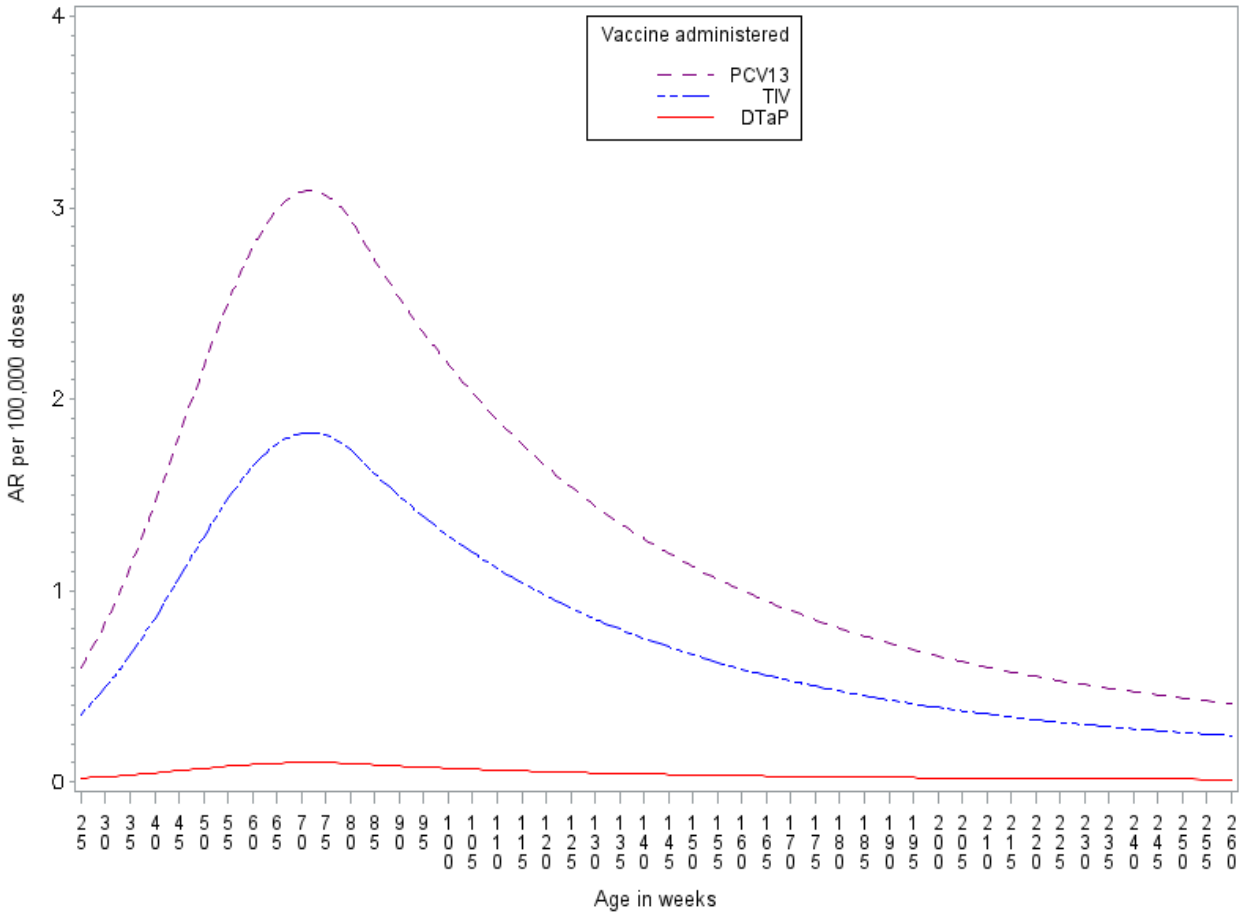


Table 1: Positive predictive value of ICD-9 Code definitions for febrile seizures

Definition of Febrile Seizure Based on ICD-9 Diagnosis Codes Identified in the Inpatient or ED Setting	Number of Potential Cases Meeting Febrile Seizure Adjudication Criteria	Number Potential Cases Identified Using Definition	Positive Predictive Value (95% CI)
Code for seizure [780.3], febrile seizure (simple), unspecified [780.31], complex febrile seizure [780.32], or other seizure [780.39]	152	216	0.70 (0.64, 0.76)
Code for febrile seizure (simple), unspecified or for complex febrile seizure [1]	140	154	0.91 (0.85, 0.95)
Codes for seizure or other seizure, and for medically attended fever [780.6, 780.60, 780.61, 780.62, 780.63] on same day, without simple/unspecified or complex febrile seizure	1	5	0.20 (0.01, 0.72)
Code for seizure or other seizure, without medically attended fever and without simple/unspecified or complex febrile seizure on same day	11	57	0.19 (0.10, 0.32)

[1] Two potential cases were identified with a code for complex febrile seizure while 152 potential cases were identified with a code for simple febrile seizure.

Table 2: Characteristics of confirmed febrile seizure cases following TIV, DTaP-containing vaccines, and PCV13

Characteristic	Cases in risk interval (0-1 day) N=42	Cases in control interval (14-20 days) N=100
Age at vaccination		
6-11 months	6 (14%)	12 (12%)
12-15 months	12 (29%)	38 (38%)
16-23 months	10 (24%)	28 (28%)
24-35 months	11 (26%)	16 (16%)
36-47 months	1 (2%)	2 (2%)
48-59 months	2 (5%)	4 (4%)
Setting of diagnosis		
ED	40 (95%)	90 (90%)
Inpatient	2 (5%)	10 (10%)
Concomitant vaccines received		
TIV + PCV13 + DTaP	3 (7%)	5 (5%)
TIV + PCV13, no DTaP	2 (5%)	6 (6%)
TIV + DTaP, no PCV13	2 (5%)	10 (10%)
PCV13 + DTaP, no TIV	8 (19%)	12 (12%)
TIV, no PCV13, no DTaP	13 (31%)	27 (27%)
PCV13, no DTaP, no TIV	10 (24%)	25 (25%)
DTaP, no TIV, no PCV13	4 (10%)	15 (15%)
Prior history of febrile seizures	10 (24%)	15 (15%)

Table 3: Characteristics of confirmed febrile seizure cases by administration of TIV, PCV13, and DTaP-containing vaccines[1]

Characteristic	Cases in risk interval following TIV (% column) N=20	Cases in control interval following TIV (% column) N=48	Cases in risk interval following PCV13 (% column) N=23	Cases in control interval following PCV13 (% column) N=48	Cases in risk interval following DTaP (% column) N=17	Cases in control interval following DTaP (% column) N=42
Age at vaccination						
6-11 months	3 (15%)	10 (21%)	4 (17%)	4 (8%)	4 (24%)	4 (10%)
12-15 months	2 (10%)	16 (33%)	9 (39%)	26 (54%)	5 (29%)	15 (36%)
16-23 months	7 (35%)	12 (25%)	4 (17%)	5 (10%)	6 (35%)	20 (48%)
24-35 months	7 (35%)	8 (17%)	5 (22%)	10 (21%)	1 (6%)	2 (5%)
36-59 months	1 (5%)	2 (4%)	1 (4%)	3 (6%)	1 (6%)	1 (2%)
Setting of diagnosis						
ED	18 (90%)	43 (90%)	22 (96%)	42 (88%)	15 (88%)	37 (88%)
Inpatient	2 (10%)	5 (10%)	1 (4%)	6 (12%)	2 (12%)	5 (12%)

[1] The sum of the number of cases in the risk interval across the three vaccines does not equal the number of cases in the risk interval following TIV, PCV13, and/or DTaP vaccines (Table 2) because cases may have received more than one of these vaccines. The same is true for the sum of the number cases in the control interval across the three vaccines.

Table 4: Risk of confirmed febrile seizure following TIV, PCV13, and/or DTaP-containing vaccines

Exposure	Cases in risk interval (0-1 day)	Cases in control interval (14-20 days)	Unadjusted IRR[1]	IRR, adjusted for age and calendar time (95% CI)[2]	IRR, adjusted for age, calendar time, and other vaccines (95% CI)[3]
TIV	20	48	1.46 (0.87, 2.46)	1.54 (0.91, 2.59)	1.36 (0.78, 2.39)
DTaP	17	42	1.42 (0.81, 2.49)	1.43 (0.81, 2.51)	1.02 (0.53, 1.96)
PCV13	23	48	1.68 (1.02, 2.76)	1.74 (1.06, 2.86)	1.61 (0.91, 2.82)

[1] Only included febrile seizure cases vaccinated with TIV, DTaP-containing vaccines, or PCV13, as appropriate.
[2] Included febrile seizure cases vaccinated with TIV, DTaP-containing vaccines, or PCV13, as appropriate, and the PRISM population to estimate the age and time functions.
[3] Included febrile seizure cases vaccinated with TIV, DTaP-containing vaccines, or PCV13 and the PRISM population to estimate the age and time functions.

Table 5: Sensitivity analysis for risk of confirmed febrile seizure following TIV, PCV13, and/or DTaP-containing vaccines

	Primary Analysis	**Sensitivity Analysis, Difference from Primary Analysis Noted**		
	Adjusted for age, calendar time, and other vaccines N=142	Sensitivity Analysis A: From primary analysis, add cases with confirmed seizure without fever documentation in the medical record[1] N=147	Sensitivity Analysis B: From primary analysis, remove cases without chart-confirmed influenza vaccine (TIV or influenza, not otherwise specified), PCV (PCV13 or PCV, not otherwise specified) or DTaP-containing vaccines[2] N=119	Sensitivity Analysis C: From primary analysis, remove cases without chart-confirmed TIV, PCV13, or DTaP-containing vaccines[3] N=90
Exposure	**IRR (95% CI)**	**IRR (95% CI)**	**IRR (95% CI)**	**IRR (95% CI)**
TIV	1.36 (0.78, 2.39)	1.32 (0.76, 2.28)	1.23 (0.65, 2.34)	1.23 (0.58, 2.58)
DTaP	1.02 (0.53, 1.96)	0.96 (0.50, 1.84)	1.18 (0.59, 2.38)	1.07 (0.48, 2.37)
PCV13	1.61 (0.91, 2.82)	1.68 (0.97, 2.91)	1.62 (0.89, 2.94)	1.58 (0.76, 3.27)

[1] Added to the primary analytic data set were 5 confirmed seizure cases without fever documentation in the medical record.
[2] Excluded from the primary analytic data set were 16 confirmed febrile seizure cases without any vaccine records (either of the visit or an immunization history) obtained and 7 confirmed febrile seizure cases whose influenza vaccination medical record was considered unobtainable because lack of influenza vaccination on the index date in the immunization history.
[3] In addition to the individuals noted in footnote 2, this analysis also excluded 13 cases with influenza, not otherwise specified, documented in the medical record and 16 cases with PCV, not otherwise specified, documented in the medical record from the primary analytic data.

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X. APPENDIX

Appendix 1. Vaccine codes to identify potential administration of TIV. NDC codes were also used to identify potential administration of TIV.

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
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

Appendix 2. Vaccine codes to identify potential administration of PCV13. NDC codes were also used to identify potential administration of PCV13.

Description	Code	Code Type
Pneumococcal conjugate vaccine, 13 valent, for intramuscular use	90670	CPT
Pneumococcal conjugate vaccine, 13 valent	133	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	ICD9 Diagnosis
Need for prophylactic vaccination and inoculation against streptococcus pneumoniae [pneumococcus] and influenza	V06.6	ICD9 Diagnosis

Appendix 3. Vaccine codes to identify potential administration of DTaP-containing vaccines. NDC codes were also 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
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

Appendix 4. Status of pneumococcal vaccination in medical record among confirmed febrile seizure cases with claims or immunization registry codes for PCV13 or pneumococcal vaccination, not otherwise specified (i.e., PCV NOS). In this report, only codes for PCV13 or PCV NOS were used to identify potential PCV13 exposure.

	Pneumococcal Conjugate Vaccine Based on Claims or Immunization Registry Data	
Pneumococcal Conjugate Vaccine Based on Medical Record	PCV13	PCV NOS
PCV7	4	0
PCV13	49[a]	1[a]
PCVNOS	17[a]	0
No Medical Record Obtained	6[a]	1[a]

[a] Cases were eligible for the primary analytic dataset if they had medical record documentation of PCV13, PCVNOS, or if a medical record was not available to confirm receipt of PCV13. We excluded cases with PCV7 documented in the medical record or in electronic data. Further exclusions are described in Figure 2.

Appendix 5. Source of manufacturer among TIV-exposed cases. The list below represents the hierarchy of methods used to assign manufacturer, since multiple sources were available for some cases.

Priority of Source	Source of manufacturer	N (% column) N=68	Manufacturer specified or inferred
1	Specified in medical record	20 (29.4%)	Sanofi Pasteur
2	Determined from product-specific claims codes (i.e., NDC codes)	1 (1.5%)	Sanofi Pasteur
3	Inferred from medical record documentation of inactivated influenza vaccine for child 6-35 months of age[a]	9 (13.2%)	Sanofi Pasteur
4	Inferred from claims codes for inactivated influenza vaccine for child 6-35 months of age[a]	32 (47.1%)	Sanofi Pasteur
Not applicable	Could not be determined or inferred from medical record or claims data	6 (8.8%)	-------

[a] Only TIV products manufactured by Sanofi Pasteur were approved and recommended for use in children 6-35 months of age during the 2010-11 influenza season.