SENTINEL CBER/PRISM SURVEILLANCE REPORT

INFLUENZA VACCINES AND FEBRILE SEIZURES IN THE 2013-2014 AND 2014-2015 INFLUENZA SEASONS

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Sentinel CBER/PRISM Surveillance Report

Influenza Vaccines and Febrile Seizures in the 2013-2014 And 2014-2015 Influenza Seasons

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I. BACKGROUND

An increased risk of febrile seizures was noted in children 6 months to 4 years of age in the 24 hours following a trivalent inactivated influenza vaccine (TIV) manufactured by CSL Biotherapies during the 2010 Southern Hemisphere influenza season in Australia.[1] This finding prompted the U.S. Advisory Committee on Immunization Practices (ACIP) to recommend that Afluria® (an antigenically equivalent U.S.-licensed vaccine manufactured by CSL Biotherapies) should not be used in children ages 6 months through 8 years. The FDA also updated the Warnings and Precautions section 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 seizures among young children, predominantly those less than 5 years of age, in Australia.[2,3] Subsequently, the FDA approved use of Afluria was changed from 6 months of age and older to 5 years of age and older. The finding in Australia was the first associating influenza vaccination with increased risk of febrile seizures. Several studies conducted in the U.S. in seasons prior to 2010-11 did not suggest an elevated risk of seizures following influenza vaccination.[4-7]

A study conducted in the Vaccine Safety Datalink (VSD) among U.S. children ages 6-59 months to assess the risk of febrile seizures 0-1 days following TIV in the 2010-2011 season found an incidence rate ratio (IRR) of 2.4 (95% CI 1.2, 4.7) for TIV adjusted for concomitant 13-valent pneumococcal conjugate vaccine (PCV13) and an IRR of 2.5 (95% CI 1.3, 4.7) for PCV13 adjusted for concomitant TIV.[8] The IRR for febrile seizures after concomitant TIV and PCV13 was 5.9 (95% CI 3.1, 11.3). This study prompted further investigation in the Post-Licensure Rapid Immunization Safety Monitoring program (PRISM), a component of the FDA-sponsored Sentinel program. A study among the same age group and using the same risk interval receiving same day vs separate day administration of TIV and PCV13 and/or diphtheria tetanus and pertussis (DTaP) containing vaccines in the 2010-2011 season was conducted showing no statistically significant association between TIV administration and febrile seizures.[9,10] Using a self-controlled risk interval (SCRI) design, Kawai and colleagues reported IRRs of 1.36 (95% CI 0.78, 2.39) for TIV, 1.02 (95% CI 0.53, 1.96) for DTaP, and 1.61 (95% CI 0.91, 2.82) for PCV13, after adjusting for concomitant vaccination, age, and calendar time. In addition, same day vaccination with TIV and PCV13 did not show a statistically significant association with febrile seizures when compared to separate day vaccination.

During the 2013-2014 influenza season, Yih and colleagues evaluated the risk of seizures in children after influenza vaccination using a prospective sequential analysis within PRISM.[11] A statistical signal was identified at the 7th "look" in children 6-23 months who received inactivated (trivalent or quadrivalent) influenza vaccine (IIV) with concomitant PCV13, where the comparison group was IIV vaccinees from historical seasons prior to the widespread use of PCV13. The cumulative number of observed events in the risk interval (0-1 days) was 9 and the expected count was 3 (relative risk [RR] 3.0). By the last, 10th look, there were 12 cases observed and 4.5 expected with a RR of 2.7. In contrast, the primary SCRI analysis conducted within the study did not reveal any statistical signals, with 4 events in the risk interval and 10 events in the control interval (14-20 days) for a RR of 1.4. Additionally, no statistical signal was identified for seizures in children 6-23 months without concomitant PCV13 in either design.

Lacking data on the risk of seizures in PCV13 vaccinees not receiving IIV, the PRISM prospective surveillance study was unable to determine whether the signal, if real, was due to the PCV13 vaccine entirely, or due to some interaction between the 2013-14 IIV and PCV13.

The overall objective for the present study was to evaluate the statistical signal for seizures among children 6 months through 23 months of age after concomitant IIV and PCV13 vaccination that was identified in current-versus-historical sequential analysis during the 2013-14 season. Using PRISM electronic data from two influenza seasons with the same IIV strain composition, 2013-14 and 2014-15, and using a SCRI design, we conducted a follow-up analysis with the primary aims:

1. To estimate the relative risk (RR) of febrile seizures following any IIV dose in the 2013-2014 and 2014-2015 seasons for children ages 6 through 23 months using a self-controlled risk interval design, adjusting for confounding by concomitant vaccination with PCV13, age, and seasonality.
2. To estimate the RR of febrile seizures following any PCV13 dose in the 2013-14 and 2014-15 seasons for children ages 6 through 23 months using a self-controlled risk interval design, adjusting for confounding by concomitant vaccination with IIV, age, and seasonality.
3. To explore whether the RR of febrile seizures after IIV is modified by concomitant vaccination with PCV13.

II. METHODS

A. STUDY POPULATION

The associations between IIV and febrile seizures were examined in PRISM, a component of the FDA-sponsored Sentinel program. The Data Partners participating in the activity included HealthCore, Aetna, Optum, and Humana. The population consisted of children 6 through 23 months of age who were members of any of the participating Data Partners for all or a portion of the period of interest, July 1, 2013 to June 30, 2015, capturing two influenza seasons with the same IIV strain composition. Children were included in the study if they received a dose of IIV or PCV13 during the study period and, at a minimum, were enrolled in medical coverage from 180 days prior to vaccination through 20 days after vaccination. An enrollment criterion of 180 days prior to vaccination was used to optimize the ability to identify history of seizure and patient comorbidities, while balancing power considerations.

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 6-23 month age range.

B. EXPOSURE

Of the inactivated influenza vaccines available for use in children during the seasons under study, Fluzone Quadrivalent® (approved June 7, 2013) and Fluzone® were the only FDA-approved IIV for use in children 6 through 23 months of age, the population of interest. Any age-appropriately administered dose of Fluzone® or Fluzone Quadrivalent® or a 'generic' code for influenza vaccination was included as an exposure. We excluded those influenza vaccinations that were administered outside of the approved age range.

Exposures to IIV, PCV13 and DTaP were identified using claims data from the Data Partners. CPT (Current Procedural Terminology), Healthcare Common Procedure Coding System (HCPCS), National Drug Codes (NDC), and International Classification of Diseases, 9th Edition (ICD-9) procedure codes were used, please see the **Appendix**.

C. OUTCOME

Potential cases of febrile seizure were identified in the electronic data using two case definitions, both based on ICD-9 diagnosis codes. The narrow case definition was the primary definition and included 780.31 (febrile seizure [simple], unspecified) or 780.32 (complex febrile seizures) in the inpatient or emergency department (ED) setting. In the 2010-11 PRISM study, this case definition had a positive predictive value of 91% and accounted for >90% of the chart-confirmed febrile seizure cases.[10] Only cases having codes that were the first in a 42-day period (occurring in any setting) were included to avoid follow-up visits for seizure episodes.

A broad case definition was included for sensitivity analyses to mirror the sequential surveillance analysis where the signal was found and to increase power.[11] Potential cases of febrile seizure were identified in electronic data by any of the following ICD-9 diagnosis codes occurring in the inpatient or ED setting: 780.3 (seizure), 780.31 (febrile seizure [simple], unspecified), 780.32 (complex febrile seizure), or 780.39 (other seizure). Similar to the narrow definition, only cases having the first seizure code without a qualifying code in the 42-days prior (occurring in any setting) were included.

D. STUDY DESIGN

We used the SCRI design to assess the IRR of febrile seizures after influenza vaccine and PCV13 exposure. Because the SCRI 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 bias from exposure misclassification resulting from individuals receiving influenza vaccines in non-traditional settings, which may not be captured in claims data.

Exposed person-time was defined as the risk interval of 0-1 days post-vaccination and unexposed person-time consisted of person-time in a control interval, 14-20 days post-vaccination. In order to adjust for confounding by co-administration with PCV13 and/or DTaP containing vaccines, we collected information on febrile seizures in the same 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 IIV. This control interval was selected for the following 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 and PRISM studies and enables this study to directly add to the existing safety information, and (c) this interval 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.[8,10] The unequal lengths of the risk and control intervals are accounted for in the analysis.

E. POTENTIAL CONFOUNDERS AND EFFECT MODIFIERS

In the primary analytic model that assessed the IIV-febrile seizures and PCV13-febrile seizures associations, we adjusted for age in weeks, calendar time, and concomitant administration of PCV13 or IIV vaccine. The risk of febrile seizures is known to vary by age, and seasonality may be used as a proxy for circulating viral infections which may also alter the risk of febrile seizures.[10,12,13] Adjustments for age and calendar time were made using background rates from vaccinated and unvaccinated children, as described in the next section. A secondary model additionally adjusted for concomitant DTaP; this model was considered secondary since no indication of an increased risk of seizures from DTaP had been observed in the Kawai et al. study of the 2010-2011 season[10] and since inclusion of the covariate was expected to negatively impact power due to anticipated low case numbers. Additional secondary

models assessed the IIV-febrile seizures and PCV13-febrile seizures associations without adjustments for age, calendar time, or concomitant vaccination. Finally, an exploratory analysis assessed whether the relative risk of febrile seizures after IIV is modified by concomitant vaccination with PCV13.

F. STATISTICAL ANALYSIS

We used conditional Poisson regression to estimate IRRs for febrile seizures in the risk vs. control intervals following vaccination. We first implemented two bivariate models including a term for IIV or PCV13. To each of these models, we added calendar time (in weeks) and age (in weeks), as described below. The primary analytic models included terms for IIV, PCV13 and adjustments for calendar time and age. A secondary analytic model included adjustment for DTaP.

To adjust for time-varying age and seasonality, we included unvaccinated person-time from the underlying cohort of children ages 6-23 months during the study period into our models. A quadratic spline function with a single knot for age in weeks and a cubic spline function with 7 knots for calendar week were included in the primary analytic model. Prior to including age and calendar time in the model with exposures of interest, we determined the age and calendar time risk functions using data from the underlying PRISM cohort, independent of vaccination. 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 IIV, 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 age range. 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 as this model resulted in both the lowest AIC value and best fit. We fit a series of models for calendar week with quadratic and cubic splines. We allowed the number of knots to range from 4 to 8, with knots equally spaced across the range of calendar weeks over the two seasons. 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 and best fit.

Concomitant PCV13 vaccine was considered a possible effect modifier on the multiplicative scale of the IRR for IIV. To examine the possibility of effect modification, we built models with main effect terms for IIV and PCV13, and a two-way interaction term of IIV with PCV13. We also explored the possibility of effect modification by influenza vaccine season and by IIV type (trivalent versus quadrivalent) by including an interaction term between IIV and season and vaccine type. Finally, we ran models stratifying by IIV and PCV13, PCV13 and IIV.

For descriptive purposes, we estimated attributable risks (AR) for IIV and PCV13 by age in weeks. The attributable risk was calculated for each age using the formula, AR=(IRR-1)*p0*2, where 2 is the length of the risk interval in days and p0 is the baseline rate per person-day estimated in electronic data in the PRISM population. 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.

Finally, in a sensitivity analysis, we repeated the primary analysis assessing the IRR of febrile seizures after IIV using an alternative definition for febrile seizures, the broad definition, to be consistent with the sequential analysis activity.[11]

III. RESULTS

A. DOSES OF IIV AND PCV13 VACCINES AND FEBRILE SEIZURES

During the study period from July 1, 2013 through June 30, 2015, 735,425 children from 6 to 23 months of age had at least 180 days of continuous enrollment in the study--357,543 females, 377,817 males, and 65 with unknown sex. Of these, 355,486 received at least one dose of IIV and 581,868 received at least one dose of PCV13 during the study period.

We identified 321 episodes of febrile seizures during risk or control intervals, 202 febrile seizures among children exposed to IIV and 173 febrile seizures among children exposed to PCV13 (**Table 1**). Seventy febrile seizure episodes occurred in the 6-11 month age group, 162 in the 12-15 month age group, and 89 in the 16-23 month age group. Approximately equal numbers of febrile seizures were found in the 2013-2014 season and 2014-2015 season, 155 and 166 respectively. The majority of the febrile seizure events were evaluated in the ED setting.

B. ASSOCIATIONS OF IIV AND PCV13 VACCINES WITH FEBRILE SEIZURES

In the adjusted and unadjusted analyses, IIV was not significantly associated with risk of febrile seizures, defined as at least one code for febrile convulsions (**Table 2**). Fifty-one cases occurred during the risk interval and 151 cases occurred in the control interval, and the IRR adjusted for age, calendar time and PCV13 was 1.12 (95% CI 0.80, 1.56). Additional adjustment for concomitant DTaP-containing vaccines did not appreciably change the results, IRR 1.06 (95% CI 0.75, 1.49).

PCV13 was significantly associated with risk of febrile seizures in the unadjusted and adjusted analyses. The IRR adjusted for age, calendar time and IIV was 1.80 (95% CI 1.29, 2.52) with 57 cases identified in the risk interval and 116 cases identified in the control interval. Additional adjustment for concomitant DTaP-containing vaccines slightly attenuated the point estimate IRR 1.56 (95% CI 1.09, 2.25).

C. EXPLORATORY ANALYSIS OF IIV-FEBRILE SEIZURES ASSOCIATION

In the model that included IIV, PCV13, age, and calendar time, the p-value for the 2-way interaction of IIV*PCV13 was 0.10, the exponentiated estimate for the interaction term was 1.93 (95% CI 0.88, 4.24). Although there was no clear evidence for effect modification by concomitant PCV13, the study was not powered to assess this. Therefore, we ran an analysis restricted to children receiving IIV without concomitant PCV13 (IRR 0.94 [95% CI 0.63, 1.42]), PCV13 without concomitant IIV (IRR 1.54 [95% CI 1.04, 2.28]) and IIV and PCV13 administered on the same day (IRR 2.80 [95% CI 1.63, 4.83]) (**Table 3**), while adjusting for age and calendar time. While PCV13 alone appears to have an increased risk of febrile seizures, the stratified IRRs suggest that there may be a synergistic effect between IIV and PCV13 despite the lack of statistical significance of the IIV*PCV13 interaction term. Specifically, the IRR of PCV13 and IIV is greater than that of PCV13 alone, possibly driven by an interactive effect.

Based on the model with the 2-way interaction of IIV*PCV13, we also estimated the IRRs for IIV without concomitant PCV13, PCV13 without concomitant IIV, and concomitant IIV and PCV13 (0.94 [95% CI 0.63, 1.42], 1.53 [95% CI 1.03, 2.28] and 2.80 [1.62, 4.82] respectively). Results were similar to when we restricted analyses to each of these groups.

Finally, we found no evidence that the risk of febrile seizures following IIV was different between the two seasons or by the number of strains in the vaccine (p-values for the interaction terms 0.64 and 0.70 respectively, **Table 4**).

D. ATTRIBUTABLE RISK ESTIMATES FOR PCV13 VACCINES

Attributable risk (AR) estimates of PCV13 vaccine varied by age (**Figure 1**) due to the varying baseline risk of febrile seizures, with the highest estimates at 65 weeks of age (5.16 per 100,000 doses) and the lowest estimates at 25 weeks of age (0.33 per 100,000 doses).

E. SENSITIVITY ANALYSIS

In a sensitivity analysis, we included nonspecific PCV vaccine codes in addition to the specific PCV13 vaccine code. Only three additional cases were included. Using PCV vaccine codes (specific PCV13 combined with nonspecific PCV) the IRR for febrile seizures adjusted for age, calendar time and IIV was consistent with the primary analysis 1.80 (95% CI 1.30, 2.51).

When the broad definition for febrile seizures (i.e. at least one code for febrile convulsion or other convulsion) was used, results were consistent with the narrow definition, and IIV was not significantly associated with the risk of febrile seizures (**Table 5**). When the broad definition for febrile seizures was used, PCV13 remained significantly associated with the risk of febrile seizure; however, the effect estimate was attenuated.

IV. DISCUSSION

We found no evidence for an increased risk of febrile seizures following IIV in unadjusted models or adjusted models (IRR adjusted for age, calendar time, and concomitant PCV13 1.12 [95% CI 0.80, 1.56]). We did find evidence for an increased risk of febrile seizures following PCV13 in both the unadjusted and adjusted models (IRR adjusted for age, calendar time and concomitant IIV 1.80 [95% CI 1.29, 2.52]). Although there was no clear evidence for effect modification as the interaction term between IIV and PCV was not statistically significant, the stratified analyses of IIV and PCV13 suggest that concomitant administration of IIV with PCV13 may increase the risk of febrile seizures to a greater degree than expected based on the independent effects of PCV13 alone. Finally, the highest attributable risk of febrile seizures associated with PCV13 was only 5.16 per 100,000 doses at 65 weeks of age.

The lack of association between febrile seizures and IIV persisted in an adjusted analysis where we added adjustment for concomitant DTaP administration. In exploratory evaluations of the risk of febrile seizures after IIV administration, we also found no evidence that the risk differed by season or by number of strains in the vaccine. Additional sensitivity analyses including a more inclusive definition of febrile seizures consistently found no evidence for association. The lack of association is consistent with prior evaluations.[10,14]

For PCV13, on the other hand, a statistically significant excess risk of febrile seizures was found both in unadjusted analyses and when adjusting for age, calendar year and concomitant administration of IIV. The risk remained statistically significant when we added adjustment for administration of DTaP. In a stratified analysis, administration of PCV13 alone was associated with febrile seizures, and concomitant administration of PCV13 and IIV had an elevated risk. However, the study was not powered to evaluate the possibility of a multiplicative effect of the two vaccines. The attributable risk of febrile seizures was highest at 65 weeks of age. Notably, this occurs during a period when PCV13 is recommended, 12-15 months (52-65 weeks) of age. However, the attributable risk was low compared to the 2 to 5% overall risk of febrile seizures among children between the ages of 6 and 60 months.[15] Therefore, these findings should be considered in the context of the importance of preventing pneumococcal infections and associated complications.

The association between the pneumococcal conjugate vaccine and febrile seizures is consistent with prior studies including a recent publication by Duffy et al. that noted an independent risk of febrile seizures with PCV7.[10,14,16] The authors also evaluated the association between PCV13 and febrile seizures; however, the power was limited due to the fact that few doses of PCV13 were administered during the study period. The prior PRISM study found an increased risk of febrile seizures after PCV13 that was statistically significant when adjusting for age and seasonality[10] but not when also adjusting for concomitant IIV and DTaP. The point estimates from that study (1.74 [adjusted for age and seasonality] and 1.61 [adjusted for age, seasonality and concomitant TIV and DTaP]) were similar to the point estimates found in the current evaluation. The fact that the current study includes two influenza seasons, rather than one, increases the power and ability to detect a statistically significant association. The current evaluation is also consistent with the statistical signal detected in the prospective sequential analysis in PRISM during the 2013-2014 season, in which a signal for an elevated risk of febrile seizures was identified at the 7th "look" among children 6-23 months of age who received IIV with concomitant PCV13 but not in those receiving IIV without PCV13.[15]

This study had a number of strengths. We included a large nationally representative insured study population and included two years of data. Combining two seasons was possible because of the same influenza virus strain composition of IIV, and this increased the power to evaluate the possible association between febrile seizures and IIV and/or PCV13. The use of the self-controlled risk interval design adjusted inherently for fixed confounders and avoided bias from misclassification of exposure because it only included vaccinated cases. Despite the short time period comprised by the risk and control windows, we adjusted for time-varying age and calendar time using spline modeling of background rates in the PRISM population. Finally, we were able to adjust for some concomitant vaccinations, including DTaP-containing vaccines, PCV13, and IIV. The study results were robust to adjustments for age, calendar time, and concomitant vaccines with IIV or PCV13.

Limitations of the study include the fact that cases of febrile seizure were not validated using medical record review. However, based on prior validation activities in PRISM, we expect that the febrile seizure definition had a positive predictive value (PPV) of approximately 91%.[10] We included a broader definition of febrile seizures as a sensitivity analysis, but this definition only had a PPV of 70% in a prior evaluation in the PRISM population. Vaccination confirmation rates ranged from 94-100% in the prior study identifying TIV, PCV13, and DTaP vaccinations[10], and we expect that these rates would have been similar.

Although PRISM is one of the largest cohorts used to evaluate vaccine safety, this study was not powered to determine if same day IIV and PCV13 vaccine synergistically increased the risk of febrile seizures. The potential for additional concomitant vaccinations for which this study did not control is an additional limitation. Between the ages of 6 to 24 months of age, the Advisory Committee on Immunization Practices also recommends vaccination with Measles-Mumps-Rubella, Hepatitis B, Rotavirus, Haemophilus influenza, Inactivated Polio, Varicella, and Hepatitis A vaccines.[17] We carefully selected the control interval for our study (14-20 days post-vaccination) to avoid overlap with the risk window of febrile seizure following a Measles-Mumps-Rubella-Varicella Combination Vaccine (7-10 day post-vaccination).[18] This study did not collect data on vaccines other than PCV13, DTaP, and IIV, so we are unable to incorporate additional concomitant vaccinations in the analysis.

V. CONCLUSIONS

In conclusion, we did not find evidence of an elevated risk for febrile seizures in children 6-23 months of age following IIV vaccination during the 2013-2014 and 2014-2015 seasons. However, we did find an elevated risk of febrile seizures following administration of the PCV13 vaccine. The attributable risk from PCV13 was dependent on age, with the highest estimates occurring at 65 weeks of age (5 febrile seizures per 100,000 doses). Evidence for an interactive effect wherein same-day IIV boosts the risk of seizures from PCV13 (or vice versa) was equivocal. The risk of seizures after PCV13 or concomitant PCV13 and IIV is low compared to a child's lifetime risk of febrile seizures from other causes, and these findings should be assessed in the context of the importance of preventing both influenza and pneumococcal infections in young children.

VI. TABLES AND FIGURES

Figure 1. Attributable risk (AR) estimates for PCV13 by age in week

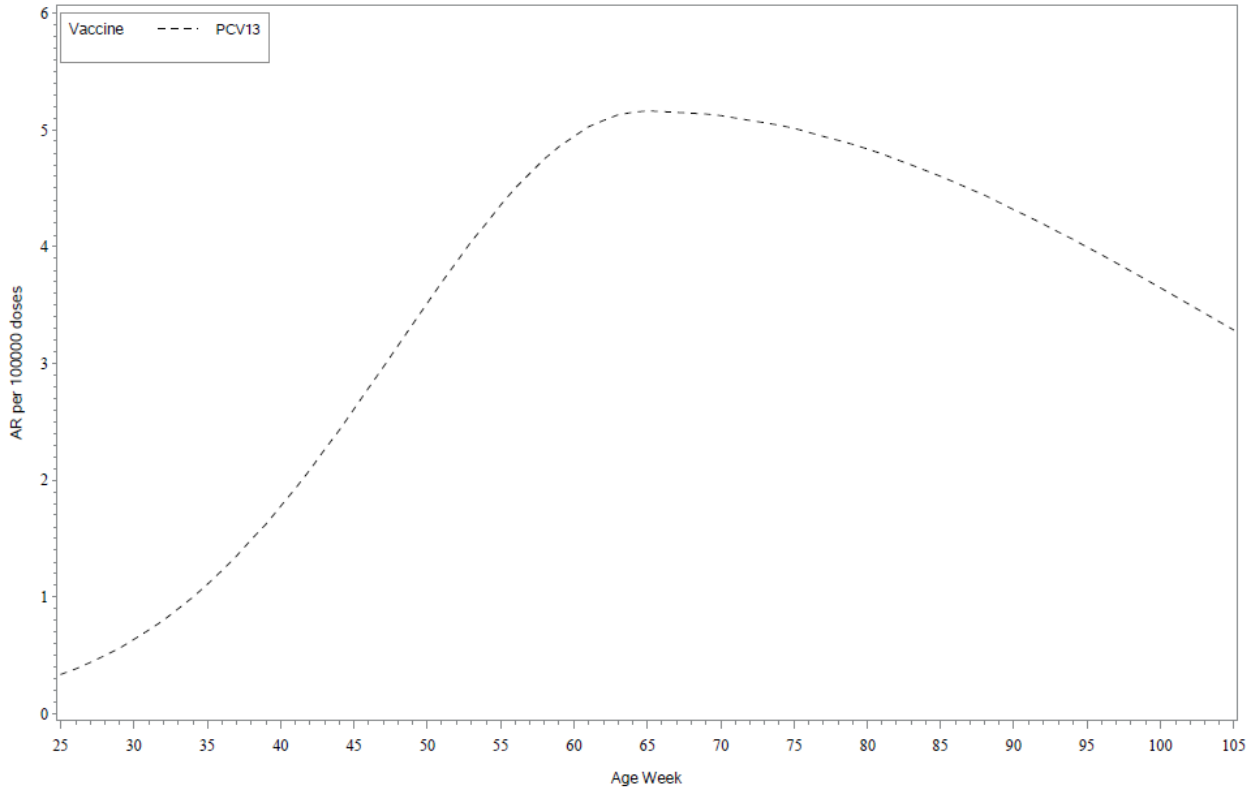

Table 1. Characteristics of febrile seizure cases by administration of IIV and PCV13

Characteristic	Cases in risk interval following IIV (%) N=51	Cases in control interval following IIV (%) N=151	Cases in risk interval following PCV13 (%) N=57	Cases in control interval following PCV13 (%) N=116
Age at vaccination				
6-11 months	14 (27%)	39 (26%)	12 (21%)	20 (17%)
12-15 months	22 (43%)	58 (38%)	38 (67%)	75 (65%)
16-23 months	15 (29%)	54 (36%)	7 (12%)	21 (18%)
Setting of diagnosis				
ED	45 (88%)	140 (93%)	55 (96%)	109 (94%)
Inpatient	6 (12%)	11 (7%)	2 (4%)	7 (6%)
Season				
2013-2014	27 (53%)	73 (48%)	32 (56%)	49 (42%)
2014-2015	24 (47%)	78 (52%)	25 (44%)	67 (58%)
Concomitant vaccines received				
IIV or PCV13	29 (57%)	119 (79%)	35 (61%)	84 (72%)
IIV and PCV13	22 (43%)	32 (21%)	22 (39%)	32 (28%)

Table 2. Risk of febrile seizure following IIV and PCV13 vaccines

Exposure	Cases in risk interval (0-1 day)	Cases in control interval (14-20 days)	Unadjusted IRR (95% CI)	IRR, adjusted for age and calendar time (95% CI)	Primary analysis: IRR, adjusted for age, calendar time, and IIV or PCV13 vaccines (95% CI)
IIV	51	151	1.18 (0.86, 1.62)	1.33 (0.96, 1.82)	**1.12 (0.80, 1.56)**
PCV13	57	116	1.72 (1.25, 2.36)	1.87 (1.36, 2.57)	**1.80 (1.29, 2.52)**

Table 3. Exploratory analysis: Risk of febrile seizures following IIV without PCV13, PCV13 without IIV and concomitant IIV and PCV13

Exposure	Cases in risk interval (0-1 day)	Cases in control interval (14-20 days)	Unadjusted IRR (95% CI)	IRR, adjusted for age and calendar time (95% CI)
IIV without PCV13	29	119	0.85 (0.57, 1.28)	0.94 (0.63, 1.42)
PCV13 without IIV	35	84	1.46 (0.98, 2.16)	1.54 (1.04, 2.28)
IIV and PCV13	22	32	2.41 (1.40, 4.15)	2.80 (1.63, 4.83)

Table 4. Exploratory analysis: Risk of febrile seizures following IIV stratified by season and number of vaccine strains

Exposure	Cases in risk interval (0-1 day)	Cases in control interval (14-20 days)	Unadjusted IRR (95% CI)	IRR, adjusted for age and calendar time (95% CI)	IRR, adjusted for age, calendar time, and PCV13 vaccines (95% CI)
Season 2013-2014	27	73	1.29 (0.83, 2.01)	1.42 (0.91, 2.21)	1.20 (0.76, 1.90)
Season 2014-2015	24	78	1.08 (0.68, 1.70)	1.23 (0.78, 1.95)	1.03 (0.64, 1.66)
IIV3	18	56	1.12 (0.66, 1.91)	1.25 (0.73, 2.12)	1.03 (0.59, 1.78)
IIV4	33	95	1.22 (0.82, 1.81)	1.37 (0.92, 2.04)	1.17 (0.78, 1.77)

Table 5. Sensitivity Analysis: Risk of febrile seizures using a broad definition following IIV and/or PCV13 vaccines

Exposure	Cases in risk interval (0-1 day)	Cases in control interval (14-20 days)	Unadjusted IRR (95% CI)	IRR, adjusted for age and calendar time (95% CI)	IRR, adjusted for age, calendar time, and IIV or PCV13 vaccines (95% CI)
IIV	64	207	1.08 (0.82, 1.43)	1.18 (0.89, 1.56)	1.04 (0.77, 1.39)
PCV13	71	169	1.47 (1.11, 1.94)	1.57 (1.19, 2.07)	1.55 (1.16, 2.07)

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IX. APPENDIX

Appendix Table. Exposure to IIV, PCV13, and DTaP vaccines identified using claims codes data

Vaccine Code Description	Code	Procedure Code Type[1]
Influenza virus vaccine, trivalent split virus, preservative free, for children 6-35 months of age, for intramuscular use	90655	CPT
Influenza virus vaccine, trivalent split virus, for children 6-35 months of age, for intramuscular use	90657	CPT
Influenza virus vaccine, quadrivalent, split virus, preservative free, when administered to children 6-35 months of age, for intramuscular use	90685	CPT
Influenza virus vaccine, quadrivalent, split virus, when administered to children 6-35 months of age, for intramuscular use	90687	CPT
Administration of influenza virus vaccine	G0008	HCPCS
Diphtheria, tetanus toxoids, and acellular pertussis vaccine, haemophilus influenza Type B, and poliovirus vaccine, inactivated (DTaP - Hib - IPV), for intramuscular use	90698	CPT
DIPTHERIA, PERTUSS(ACELL), TETANUS, POLIO VACC/HIB CONJ-TET/PF		NDC
Diphtheria, tetanus toxoids, acellular pertussis vaccine, Hepatitis B, and poliovirus vaccine, inactivated (DTaP-HepB-IPV), for intramuscular use	90723	CPT
HEP B VIRUS, RCMB/DIPTH, PERTUS(ACELL), TET, POLIO VACCINE/PF		NDC
HEP B VIRUS, RCMB/DIPTH, PERTUS(ACELL), TET, POLIO VACCINE/PF		NDC
HEP B VIRUS, RCMB/DIPTH, PERTUS(ACELL), TET, POLIO VACCINE/PF		NDC
HEP B VIRUS, RCMB/DIPTH, PERTUS(ACELL), TET, POLIO VACCINE/PF		NDC
HEP B VIRUS, RCMB/DIPTH, PERTUS(ACELL), TET, POLIO VACCINE/PF		NDC
HEP B VIRUS, RCMB/DIPTH, PERTUS(ACELL), TET, POLIO VACCINE/PF		NDC
HEPATITIS B VIRUS, RCMB/DIPTH, PERTUS(ACELL), TET, POLIO VACCINE		NDC
HEPATITIS B VIRUS, RCMB/DIPTH, PERTUS(ACELL), TET, POLIO VACCINE		NDC
DIPHTH, PERTUSS(ACELL), TET PED		NDC
DIPHTHERIA, PERTUSSIS(ACELL), TETANUS PED VACC/PF		NDC
DIPHTHERIA, PERTUSSIS(ACELL), TETANUS PED VACC/PF		NDC

[1] Procedure code definitions: CPT = Current Procedural Terminology; HCHPS = Healthcare Common Procedure Coding System; NDC = National Drug Code; ICD-9 = International Classification of Diseases, 9th Edition

Vaccine Code Description	Code	Procedure Code Type[1]
DIPHTHERIA, PERTUSSIS(ACELL), TETANUS PED VACC/PF		NDC
DIPHTHERIA, PERTUSSIS(ACELL), TETANUS PED VACC/PF		NDC
DIPHTHERIA, PERTUSSIS(ACELL), TETANUS PED VACC/PF		NDC
DIPHTHERIA, PERTUSSIS(ACELL), TETANUS PED VACC/PF		NDC
DIPHTHERIA, PERTUSSIS(ACELL), TETANUS PED VACC/PF		NDC
DIPHTHERIA, PERTUSSIS(ACELL), TETANUS PED VACC/PF		NDC
DIPHTHERIA, PERTUSSIS(ACELL), TETANUS PED VACC/PF		NDC
DIPHTHERIA, PERTUSSIS(ACELL), TETANUS PED VACC/PF		NDC
DIPHTHERIA, PERTUSSIS(ACELL), TETANUS PED VACC/PF		NDC
DIPHTH, PERTUSS(ACELL), TET PED		NDC
DIPHTH, PERTUSS(ACELL), TET PED		NDC
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 (DTaP), for use in individuals younger than seven years, for intramuscular use	V068	ICD-9
Pneumococcal conjugate vaccine, 13 valent, for intramuscular use	90670	CPT
PNEUMOCOCCAL 13-VALENT CONJUGATE VACCINE (DIPHTHERIA CRM)/PF		NDC
PNEUMOCOCCAL 13-VALENT CONJUGATE VACCINE (DIPHTHERIA CRM)/PF		NDC
DIPHTH, PERTUSS(ACELL), TET PEDDAPTACELDAPTACEL VACCINE		NDC
DIPHTHERIA, PERTUSSIS(ACELL), TETANUS PED VACC/PFDAPTACELDAPTACEL VACCINE		NDC
DIPHTHERIA, PERTUSSIS(ACELL), TETANUS PED VACC/PFDAPTACEL DTAPDAPTACEL DTAP VACCINE		NDC
DIPTHERIA, PERTUSS(ACELL), TETANUS, POLIO VACC/HIB CONJ-TET/PFPENTACELPENTACEL VIAL		NDC
HAEMOPHILUS B CONJUGATE VACCINE (TETANUS TOXOID CONJUGATE)/PFPENTACEL ACTHIB COMPONENTPENTACEL ACTHIB COMPONENT VIAL		NDC
DIPHTHERIA, PERTUSSIS(ACELL), TETANUS, POLIO VACCINE/PFPENTACEL DTAP-IPV COMPONENTPENTACEL DTAP-IPV COMPONENT VL		NDC
DIPHTHERIA, PERTUSSIS(ACELL), TETANUS PED VACC/PFINFANRIXINFANRIX VACCINE VIAL		NDC
DIPHTHERIA, PERTUSSIS(ACELL), TETANUS PED VACC/PFINFANRIX PFINFANRIX PF VACCINE SYRINGE		NDC
DIPHTHERIA, PERTUSSIS(ACELL), TETANUS PED VACC/PFINFANRIXINFANRIX VACCINE VIAL		NDC
DIPHTHERIA, PERTUSSIS(ACELL), TETANUS PED VACC/PFINFANRIXINFANRIX VACCINE VIAL		NDC
DIPHTHERIA, PERTUSSIS(ACELL), TETANUS PED VACC/PFINFANRIX PFINFANRIX PF VACCINE SYRINGE		NDC
DIPHTHERIA, PERTUSSIS(ACELL), TETANUS PED VACC/PFINFANRIXINFANRIX VACCINE SYRINGE		NDC
DIPHTHERIA, PERTUSSIS(ACELL), TETANUS PED VACC/PFINFANRIX PFINFANRIX PF VACCINE SYRINGE		NDC
DIPHTHERIA, PERTUSSIS(ACELL), TETANUS PED VACC/PFINFANRIX PFINFANRIX PF VACCINE SYRINGE		NDC
DIPHTHERIA, PERTUSSIS(ACELL), TETANUS PED VACC/PFINFANRIX PFINFANRIX PF VACCINE SYRINGE		NDC

Vaccine Code Description	Code	Procedure Code Type[1]
HEP B VIRUS, RCMB/DIPTH, PERTUS(ACELL), TET, POLIO VACCINE/PFPEDIARIXPEDIARIX 0.5 ML VIAL		NDC
HEP B VIRUS, RCMB/DIPTH, PERTUS(ACELL), TET, POLIO VACCINE/PFPEDIARIXPEDIARIX 0.5 ML SYRINGE		NDC
HEP B VIRUS, RCMB/DIPTH, PERTUS(ACELL), TET, POLIO VACCINE/PFPEDIARIXPEDIARIX 0.5 ML SYRINGE		NDC
HEP B VIRUS, RCMB/DIPTH, PERTUS(ACELL), TET, POLIO VACCINE/PFPEDIARIXPEDIARIX 0.5 ML SYRINGE		NDC
HEP B VIRUS, RCMB/DIPTH, PERTUS(ACELL), TET, POLIO VACCINE/PFPEDIARIXPEDIARIX 0.5 ML SYRING		NDC
HEP B VIRUS, RCMB/DIPTH, PERTUS(ACELL), TET, POLIO VACCINE/PFPEDIARIXPEDIARIX 0.5 ML SYRINGE		NDC
DIPHTHERIA, PERTUSSIS(ACELL), TETANUS, POLIO VACCINE/PFKINRIXKINRIX VIAL		NDC
DIPHTHERIA, PERTUSSIS(ACELL), TETANUS, POLIO VACCINE/PFKINRIXKINRIX VIAL		NDC
DIPHTHERIA, PERTUSSIS(ACELL), TETANUS, POLIO VACCINE/PFKINRIXKINRIX TIP-LOK SYRINGE		NDC
DIPHTHERIA, PERTUSSIS(ACELL), TETANUS, POLIO VACCINE/PFKINRIXKINRIX TIP-LOK SYRINGE		NDC
DIPHTHERIA, PERTUSSIS(ACELL), TETANUS, POLIO VACCINE/PFKINRIXKINRIX TIP-LOK SYRINGE		NDC
DIPHTHERIA, PERTUSSIS(ACELL), TETANUS, POLIO VACCINE/PFKINRIXKINRIX TIP-LOK SYRINGE		NDC
DIPHTHERIA, PERTUSSIS(ACELL), TETANUS PED VACC/PFINFANRIXINFANRIX VACCINE VIAL		NDC
DIPHTHERIA, PERTUSSIS(ACELL), TETANUS PED VACC/PFINFANRIXINFANRIX VACCINE VIAL		NDC
DIPHTH, PERTUSS(ACELL), TET PEDINFANRIXINFANRIX VACCINE SYRINGE		NDC
DIPHTH, PERTUSS(ACELL), TET PEDINFANRIXINFANRIX VACCINE SYRINGE		NDC
HEPATITIS B VIRUS, RCMB/DIPTH, PERTUS(ACELL), TET, POLIO VACCINEPEDIARIXPEDIARIX 0.5 ML VIAL		NDC
HEPATITIS B VIRUS, RCMB/DIPTH, PERTUS(ACELL), TET, POLIO VACCINEPEDIARIXPEDIARIX 0.5 ML SYRINGE		NDC
INFLUENZA VIRUS VACCINE TVS 2013-2014 (6 MOS-35 MOS)/PFFLUZONE PEDI 2013-2014FLUZONE PEDI 2013-2014 SYRINGE		NDC
INFLUENZA VIRUS VACCINE TVS 2013-2014 (6 MOS-35 MOS)/PFFLUZONE PEDI 2013-2014FLUZONE PEDI 2013-2014 SYRINGE		NDC
INFLUENZA VIRUS VACCINE TRI-SPLIT 2013-14 (6 MOS AND OLDER) FLUZONE 2013-2014FLUZONE 2013-2014 VIAL		NDC
INFLUENZA VIRUS VACCINE TRI-SPLIT 2013-14 (6 MOS AND OLDER) FLUZONE 2013-2014FLUZONE 2013-2014 VIAL		NDC
INFLUENZA VIRUS VACCINE TRIVALENT 2014-15 (6 MOS AND OLDER) FLUZONE 2014-2015FLUZONE 2014-2015 VIAL		NDC
INFLUENZA VIRUS VACCINE TRIVALENT 2014-15 (6 MOS AND OLDER) FLUZONE 2014-2015FLUZONE 2014-2015 VIAL		NDC
INFLUENZA VIRUS VACCINE QUAD VS 2013-2014 (6 MOS-35 MOS)/PFFLUZONE PEDI 2013-2014FLUZONE PEDI 2013-2014 SYRINGE		NDC
INFLUENZA VIRUS VACCINE QUAD VS 2013-2014 (6 MOS-35 MOS)/PFFLUZONE PEDI 2013-2014FLUZONE PEDI 2013-2014 SYRINGE		NDC

Vaccine Code Description	Code	Procedure Code Type[1]
INFLUENZA VIRUS VACCINE QUADRIVAL 2014-15 (6 MOS-35 MOS)/PFFLUZONE QUAD PEDI 2014-2015FLUZONE QUAD PEDI 2014-15 SYR		NDC
INFLUENZA VIRUS VACCINE QUADRIVAL 2014-15 (6 MOS-35 MOS)/PFFLUZONE QUAD PEDI 2014-2015FLUZONE QUAD PEDI 2014-15 SYR		NDC
INFLUENZA VIRUS VACCINE QUADRIVAL 2014-2015 (6 MOS & OLDER) FLUZONE QUAD 2014-2015FLUZONE QUAD 2014-2015 VIAL		NDC
INFLUENZA VIRUS VACCINE QUADRIVAL 2014-2015 (6 MOS & OLDER) FLUZONE QUAD 2014-2015FLUZONE QUAD 2014-2015 VIAL		NDC
PNEUMOCOCCAL 13-VALENT CONJUGATE VACCINE (DIPHTHERIA CRM)/PFPREVNAR 13PREVNAR 13 SYRINGE		NDC
PNEUMOCOCCAL 13-VALENT CONJUGATE VACCINE (DIPHTHERIA CRM)/PFPREVNAR 13PREVNAR 13 SYRINGE		NDC
PNEUMOCOCCAL 13-VALENT CONJUGATE VACCINE (DIPHTHERIA CRM)/PFPREVNAR 13PREVNAR 13 SYRINGE		NDC