Febrile Seizures After 2010–2011 Trivalent Inactivated Influenza Vaccine

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abstract

OBJECTIVES: In the Post-Licensure Rapid Immunization Safety Monitoring Program, we examined risk of febrile seizures (FS) after trivalent inactivated influenza vaccine (TIV) and 13-valent pneumococcal conjugate vaccine (PCV13) during the 2010–2011 influenza season, adjusted for concomitant diphtheria tetanus acellular pertussis-containing vaccines (DTaP). Assuming children would receive both vaccines, we examined whether same-day TIV and PCV13 vaccination was associated with greater FS risk when compared with separate-day vaccination.

METHODS: We used a self-controlled risk interval design, comparing the FS rate in a risk interval (0–1 days) versus control interval (14–20 days). Vaccinations were identified in claims and immunization registry data. FS were confirmed with medical records.

RESULTS: No statistically significant TIV-FS associations were found in unadjusted or adjusted models (incidence rate ratio [IRR] adjusted for age, seasonality, and concomitant PCV13 and DTaP: 1.36, 95% confidence interval [CI] 0.78 to 2.39). Adjusted for age and seasonality, PCV13 was significantly associated with FS (IRR 1.74, 95% CI 1.06 to 2.86), but not when further adjusting for concomitant TIV and DTaP (IRR 1.61, 95% CI 0.91 to 2.82). Same-day TIV and PCV13 vaccination was not associated with excess risk of FS when compared with separate-day vaccination (1.08 fewer FS per 100 000 with same day administration, 95% CI −5.68 to 6.09).

CONCLUSIONS: No statistically significant increased risk of FS was found for 2010–2011 TIV or PCV13, when adjusting for concomitant vaccines. Same-day TIV and PCV13 vaccination was not associated with more FS compared with separate-day vaccination.

WHAT'S KNOWN ON THIS SUBJECT: Previous studies found that 2010–2011 trivalent inactivated influenza vaccine (TIV) and 13-valent pneumococcal conjugate vaccine (PCV13) were associated with statistically significant increased risks of febrile seizures (FS) in the United States.

WHAT THIS STUDY ADDS: Estimated FS relative risks after TIV or PCV13 adjusted for DTaP were >1, although not statistically significant and lower than previous estimates. Same-day administration of TIV and PCV13 did not result in more FS compared with separate-day vaccination.

During the 2010–2011 influenza season in the United States, 2 complementary systems detected potentially increased risks of febrile seizures (FS): the Vaccine Adverse Event Reporting System and the Vaccine Safety Datalink (VSD).[1,2] US Food and Drug Administration (FDA) investigators conducted bimonthly disproportionate reporting analysis in the former, a spontaneous reporting system comanaged by the Centers for Disease Control and Prevention and FDA, to identify adverse events reported more frequently than expected after trivalent inactivated influenza vaccine (TIV). By November 23, 2010, disproportional reporting for FS was detected for Fluzone (Sanofi Pasteur Ltd) but not for other 2010–2011 TIV products.[2]

The VSD, an active surveillance system led by the Centers for Disease Control and Prevention and 8 medical care organizations, reported a statistically significant increased risk of seizures after 2010–2011 TIV during weekly sequential analysis.[1] Increased risks of FS were found in the week of November 14, 2010, using a cohort design with historical controls and in the week of December 26, 2010, using a self-controlled risk interval (SCRI) design. The risk of chart-confirmed FS was elevated 0 to 1 day after TIV, when compared with a control interval 14 to 20 days after vaccination, adjusting for concomitant 13-valent pneumococcal conjugate vaccine (PCV13). Because the study only included FS after TIV or PCV13 vaccines, the confounding and synergistic role of diphtheria tetanus acellular pertussis (DTaP) containing vaccines, the second most frequent vaccine coadministered with TIV, could not be assessed.

In a US population of children aged 6 to 59 months, the objective of this study was to examine whether there was an increased risk of confirmed FS in exposed periods after 2010–2011

TIV, or PCV13, compared with unexposed periods, while adjusting for concomitant DTaP-containing vaccines. Assuming that children would receive both vaccines, we also examined whether same-day receipt of 2010–2011 TIV and PCV13 would be associated with a greater risk of FS compared with separate-day receipt.

METHODS

Study Population

The study population was derived from the Post-Licensure Rapid Immunization Safety Monitoring Program (PRISM), a component of the FDA-sponsored Mini-Sentinel Pilot Initiative.[3–5] Children 6 to 59 months of age were eligible if they were enrolled in a health plan associated with 1 of 3 Mini-Sentinel Data Partners, Aetna, HealthCore, or Humana, during the study period (July 1, 2010–June 30, 2011). Children were included in the vaccinated cohort if they received at least 1 of the vaccine exposures (TIV, PCV13, DTaP-containing vaccines) during the study period and at a minimum, were enrolled in their health plan from 180 days before vaccination through 20 days after vaccination.

Study Design

We used a SCRI design, comparing the risk of an adverse event in a postvaccination risk interval to that in a control interval within the same individual.[6–8] The risk and control intervals for TIV, PCV13, and DTaP were defined as days 0 to 1 and 14 to 20, respectively, after each of these vaccinations.[1,9] We used a postvaccination control interval to avoid bias due to the healthy vaccinee effect, which occurs when providers or caregivers delay vaccination after the outcome under study.[10,11] Before conducting the study, we estimated 80% power to detect incidence rate ratios (IRRs) between 2.0 and 2.2 for TIV, PCV13, and DTaP-containing vaccines.

Outcomes

Potential FS were identified in claims-based data by the following *International Classification of Disease, Ninth Revision*, diagnosis codes in the inpatient or emergency department (ED) setting: 780.3, 780.31, 780.32, or 780.39.[1,12] Clinic visits were not included because they most likely indicate follow-up of previous seizures or treatment of seizure disorders.[12] We also excluded events with seizure codes in the previous 6 weeks (in any setting, including ambulatory care) to identify incident events.[13]

Adjudication of deidentified full-text medical records was conducted to confirm case status and date. Cases were excluded if the seizure visit could not be obtained; the visit was due to management of a known seizure disorder or of another non–seizure-related issue; or if the examining physician ruled out a suspected seizure. Each of the remaining cases was independently reviewed by 2 pediatricians blinded to vaccination timing and vaccines administered. A third pediatrician adjudicator, also blinded, reviewed cases where discrepancies in FS status or date of symptom onset were identified. These cases were rediscussed by the 3 adjudicators until consensus was achieved.

Case confirmation criteria included documentation of a seizure and fever (ie, 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 FS). We excluded cases with an underlying metabolic disorder, central nervous system infection/trauma, history of afebrile seizures, or focal seizures not associated with a complex FS.[14] Only confirmed FS were included in the main analysis. In a sensitivity analysis, we also analyzed cases that met adjudication criteria for seizure but had no clear documentation on presence or

absence of fever because true FS might lack such documentation.

Vaccine Exposures

Potential vaccine exposures were initially identified using claims data from the 3 participating data partners, as well as immunization registry data from 8 participating registries: Florida, Michigan, Minnesota, New York City, New York State, Pennsylvania, Virginia, and Wisconsin. Potential vaccination exposures were identified using codes specific to TIV, PCV13, DTaP, and DTaP-combination vaccines. We also used more general codes that did not specify whether influenza vaccines were live versus inactivated (influenza vaccine, not otherwise specified), as well as those that did not specify whether pneumococcal conjugate vaccines were 7-valent versus 13-valent (PCV, not otherwise specified). To confirm vaccinations, we obtained medical records of vaccinations visits and immunization histories.

All confirmed FS with vaccines identified in claims or registry data or in medical records were included in the main analysis. We excluded cases if live attenuated influenza vaccine (LAIV) or 7-valent pneumococcal conjugate vaccine (PCV7), rather than TIV or PCV13, was administered. We used the vaccination date in the medical record, if available. Otherwise, we used the vaccination date identified in electronic data. In a sensitivity analysis, cases without chart confirmation of vaccines (types and dates) were excluded.

Statistical Analysis

IRR Estimates

Conditional Poisson regression was used to estimate incidence rate ratios (IRRs) for FS comparing rates in exposed and unexposed intervals. We first implemented 3 bivariate models, each containing a term for TIV, DTaP-containing vaccines (described as DTaP in models) or

PCV13. Because a child's baseline risk for FS differs between the risk and control intervals,[15–17] which are spaced ∼3 weeks apart, we added adjustments for confounding by age and calendar time (in weeks) to each of the 3 models. Finally, the single primary analytic model contained TIV, DTaP, PCV13, and adjustments for calendar time and age. We adjusted for age and calendar time in splines by including unvaccinated person-time from the underlying PRISM cohort.

In exploratory analyses, we examined whether the IRR for FS after TIV might differ by concomitant administration of PCV13 and/or DTaP-containing vaccines. In separate exploratory analyses, we examined whether the IRR for FS after TIV might differ by age at vaccination (6–23 vs 24–59 months), previous history of FS, family history of seizures (among a first-degree relative), or influenza vaccine dose number.

AR Estimates for TIV, PCV13, and DTaP-Containing Vaccines and Estimates of Difference in ARs Comparing Same-Day Versus Separate-Day TIV and PCV13 Vaccination

We estimated age-specific (by weeks) attributable risks (ARs), comparing the difference in risk between exposed and unexposed intervals, for TIV, PCV13, and DTaP-containing vaccines. Assuming that children would receive both vaccinations, we also examined whether same-day receipt of TIV and PCV13 would be associated with a greater risk of FS when compared with separate-day vaccination. We calculated the difference in ARs comparing same-day versus separate-day vaccination. The potential impact of same-day vaccination of DTaP with TIV or PCV13 was not assessed because the IRR for DTaP was close to 1.0 and not statistically significant in the primary analysis. Methods for calculating ARs are described in Supplemental Appendix 1.

RESULTS

Approximately 1.9 million children aged 6 to 59 months of age were identified in the study population between July 1, 2010, and June 30, 2011. Of those, 842 325 received TIV, PCV13, and/or DTaP-containing vaccines during the study period and were enrolled continuously in their health plan from 180 days before vaccination through 20 days after vaccination. Using claims and immunization registry data, we identified 252 potential FS cases in the postvaccination intervals. One hundred fifty-two of the 216 potential cases with medical records available met confirmation criteria for FS (Fig 1). Of these, we excluded 5 cases with documentation of LAIV or PCV7 in the medical record and another 5 with medical records indicating that the FS did not occur in the post-vaccination intervals. The primary analytic dataset contained 142 confirmed FS cases, which occurred primarily in children <2 years of age and in the ED setting (Table 1). Sixty-eight were TIV-exposed, 71 were PCV13-exposed, and 59 were DTaP-exposed, with approximately one-third of children receiving ≥2 of these vaccines concomitantly. Vaccination confirmation rates ranged from 94% to 100%, when charts were available. (Supplemental Fig 3).

IRR Estimates

No statistically significant associations were found between TIV and risk of confirmed FS in our unadjusted or adjusted models, although the IRR point estimates for FS after TIV were >1 (Table 2, IRR adjusted for age, calendar time, and concomitant vaccinations 1.36, 95% confidence interval [CI] 0.78 to 2.39). We found a statistically significant association between PCV13 and risk of confirmed FS, adjusted for age and seasonality (IRR 1.74, 95% CI 1.06 to 2.86), but not when further adjusting for concomitant TIV and DTaP-containing vaccines (IRR 1.61, 95%
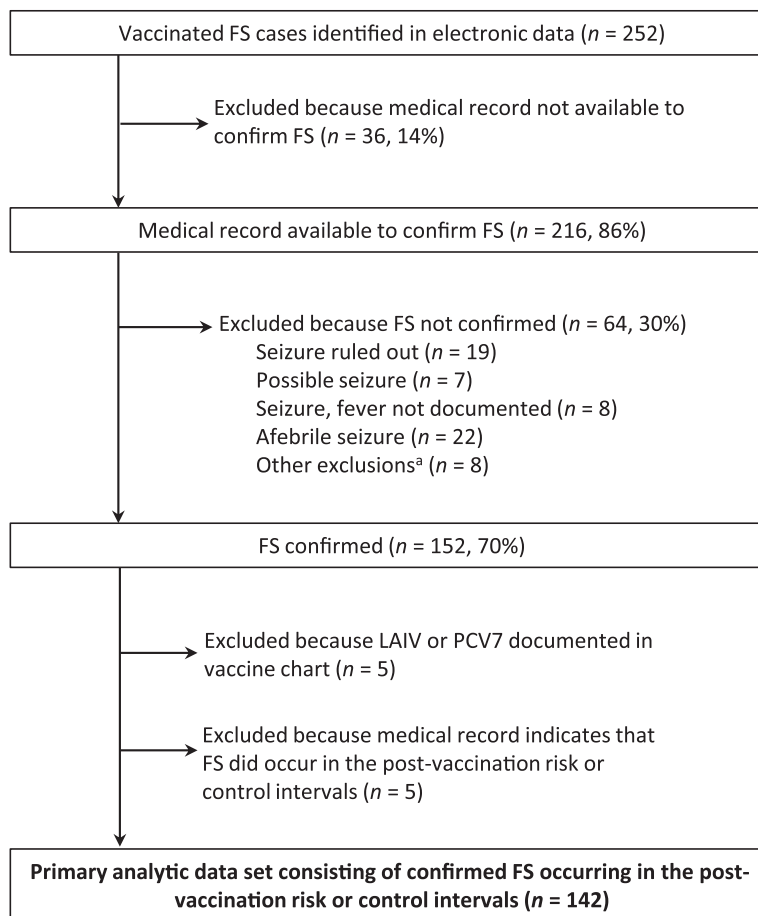
FIGURE 1
Case disposition status for vaccinated FS identified in electronic data. [a] Excluded due to seizure associated with metabolic disorder, central nervous system infection/inflammation, history of afebrile seizures, or focal seizures not associated with complex FS.

CI 0.91 to 2.82), although the IRR was similar. We found no statistically significant association between DTaP and risk of confirmed FS in our unadjusted or adjusted models, and the IRR was close to 1 when adjusting for age, calendar time, and concomitant vaccinations (IRR 1.02, 95% CI 0.53 to 1.96). Adjustments for age and calendar time had minimal effects on the IRR point estimates for FS after TIV, PCV13, and DTaP-containing vaccines, whereas adjustment for concomitant vaccines attenuated the IRR point estimates for all 3 vaccines, especially for DTaP-containing vaccines.

In exploratory analysis, we found no evidence to suggest that the IRR for FS after TIV differed by concomitant administration of PCV13 and/or DTaP. In separate models for each potential effect modifier, we also found no evidence to suggest that the IRR for FS after TIV differed by age at vaccination, previous FS, family history of seizures, or dose number.

AR Estimates

ARs for TIV, PCV13, and DTaP-containing vaccines varied by age (Fig 2) because of the varying baseline risk of FS. For each vaccine, the highest AR estimates were observed at 72 weeks (~17 months) of age, and the lowest AR estimates were observed at 260 weeks (~59 months) of age. ARs for TIV ranged from 0.24 to 1.83 per 100 000 doses. ARs for PCV13 ranged from 0.41 to 3.09 per 100 000 doses and ARs for DTaP-containing vaccines were

<0.20 per 100 000 doses for the entire age range.

We also calculated ARs based on the upper limit of the 95% CIs of the IRRs for TIV and PCV13. For TIV, the upper bound of the CI for the IRR translated to ARs that ranged from 0.93 per 100 000 doses at 260 weeks of age to 7.05 per 100 000 doses at 72 weeks of age. For PCV13, the corresponding estimates were 1.22 per 100 000 doses at 260 weeks and 9.23 per 100 000 doses at 72 weeks.

Difference in ARs Comparing Same-Day Versus Separate-Day TIV and PCV13 vaccination

Same day TIV and PCV13 vaccination was not significantly associated with an excess risk of FS compared with separate day vaccination. The difference in ARs comparing same-day versus separate-day vaccination was 1.08 fewer FS per 100 000 children with same-day vaccination (95% CI −5.68 to 6.09 per 100 000 children).

Sensitivity Analysis

In sensitivity analyses that included chart-confirmed FS and chart-confirmed seizures without clear chart documentation on the presence or absence of fever, the adjusted IRR estimates for TIV, PCV13, and DTaP-containing vaccines were similar to the primary results (Table 3). The results were also similar in sensitivity analyses requiring vaccinations to be chart-confirmed (Table 3).

DISCUSSION

The relative risk for FS after TIV was >1 in the 2010–2011 season, although not statistically significant regardless of whether the results were adjusted for age, calendar time, and other vaccinations. Furthermore, although PCV13 was associated with an increased risk for FS when adjusting for age and calendar time (but not concomitant vaccines), it was not significantly associated with FS when also adjusting for concomitant

TABLE 1 Characteristics of Confirmed FS Cases After TIV, PCV13, or DTaP-Containing Vaccines

Characteristic	Cases in Risk Interval, $n = 42$, n (%)[a]	Cases in Control Interval, $n = 100$, n (%)[b]
Age at vaccination (mo)		
6–11	6 (14)	12 (12)
12–15	12 (29)	38 (38)
16–23	10 (24)	28 (28)
24–35	11 (26)	16 (16)
36–47	1 (2)	2 (2)
48–59	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)
History of FS	10 (24)	15 (15)

[a] 0–1 d postvaccination.
[b] 14–20 d postvaccination.

DTaP and TIV. It is thus unclear whether PCV13 or TIV may have led to the observed increased risk of FS with PCV13 when not adjusting for concomitant DTaP and TIV; alternatively, it may have been due to an unmeasured time-varying confounder, such as other concomitant vaccines, or due to chance. Additionally, assuming that children would receive both TIV and PCV13, we did not find evidence to suggest that same-day vaccination with 2010–2011 TIV and PCV13 would be associated with a greater risk for FS when compared with separate-day vaccination.

Although we cannot rule out the possibility that increased risk of FS exists after TIV or PCV13, the ARs corresponding to the upper bounds of the CIs for the IRRs for TIV (2.4) and PCV13 (2.8) suggest that any increased risks, if present, would be modest. For TIV and PCV13 vaccinations, the upper bound of the confidence interval for the IRRs translate to ARs that range from ~1 per 100 000 doses at 59 months of age to ~7 to 9 per 100 000 doses at 17 months of age. Thus, the cumulative risk of FS across a child's lifetime would greatly exceed that of any transient increase in FS in the comparatively short risk intervals after TIV or PCV13 vaccination.

The associations of 2010–2011 TIV and PCV13 with risk of FS were also previously investigated in the VSD.[1] Like the PRISM study, the VSD study used a SCRI design with chart confirmation of FS, but there were slight differences from our study in exposure and outcome assessment.

Furthermore, in contrast to the VSD study, our study incorporated a larger sample size and adjustments for time-varying age, calendar time, and concomitant DTaP. The study populations may have also differed because PRISM consists of large national health insurers, whereas the majority of the VSD consists of more regional health plans with integrated health care systems. In the VSD study, TIV was significantly associated with risk of FS when adjusting for concomitant PCV13 (IRR 2.4, 95% CI 1.2 to 4.7); PCV13 was also significantly associated with risk of FS when adjusting for concomitant TIV (IRR 2.5 95% CI 1.3 to 4.7). Thus, in the VSD study, relative risks larger than 4.7 could be ruled out with 95% confidence for both vaccines. In this larger cohort of vaccinated children, our findings in PRISM now suggest that relative risks larger than 2.4 and 2.8 can be ruled out with 95% confidence for TIV and for PCV13, respectively.

This study had several strengths. First, the study had 80% power to detect IRRs between 2.0 and 2.2 for TIV, PCV13, and DTaP-containing vaccines. Second, we used a rigorous FS validation process that included adjudication blinded to vaccination timing by at least 2 pediatricians and by a third pediatrician if there was disagreement on case status or onset date. Third, the use of the SCRI design adjusted inherently for fixed confounders. By only including vaccinated children, we also avoided bias due to incomplete capture of vaccinations and the comparison of vaccinated to unvaccinated individuals. Fourth, we adjusted for

TABLE 2 Risk of Confirmed FS After TIV, PCV13, or DTaP-Containing Vaccines

Exposure	Cases in Risk Interval (0–1 d)	Cases in Control Interval (14–20 d)	Unadjusted IRR (95% CI)[a]	IRR, Adjusted for Age and Calendar Time (95% CI)[b]	IRR, Adjusted for Age, Calendar Time, and Other Vaccines (95% CI)[c]
TIV	20	48	1.46 (0.87 to 2.46)	1.54 (0.91 to 2.59)	1.36 (0.78 to 2.39)
PCV13	23	48	1.68 (1.02 to 2.76)	1.74 (1.06 to 2.86)	1.61 (0.91 to 2.82)
DTaP	17	42	1.42 (0.81 to 2.49)	1.43 (0.81 to 2.51)	1.02 (0.53 to 1.96)

[a] Only included FS cases vaccinated with TIV, DTaP-containing vaccines, or PCV13, as appropriate.
[b] Included FS cases vaccinated with TIV, DTaP-containing vaccines, or PCV13, as appropriate, and the PRISM population to estimate the age and time functions.
[c] Included all FS cases vaccinated with TIV, DTaP-containing vaccines, or PCV13 and the PRISM population to estimate the age and time functions.
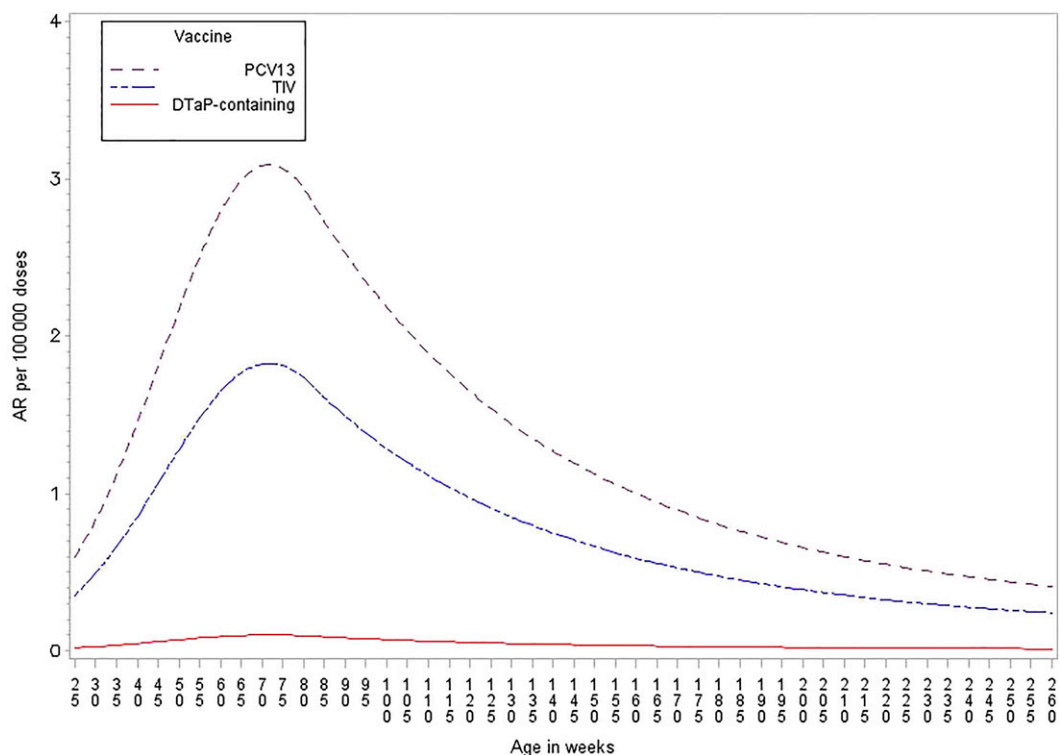
FIGURE 2
Attributable risk (AR) estimates for TIV, PCV13, and DTaP-containing vaccines.

time-varying age and seasonality using spline modeling of background rates in the PRISM population. Finally, we adjusted for concomitant vaccinations, including TIV, PCV13, and DTaP-containing vaccines.

Our study was subject to some limitations. First, we were unable to obtain seizure medical records for 14% of cases. However, we were able to obtain a similar proportion of medical records for cases in both the risk and control intervals (88% vs 85%),

minimizing bias due to differential ascertainment. Second, we were unable to obtain vaccination medical records for 9% of DTaP-containing vaccine and PCV13-exposed cases and for 21% of TIV-exposed cases. However, IRR estimates for FS after TIV, PCV13, and DTaP were similar when we excluded cases without vaccination confirmation. Third, we did not identify FS in the outpatient setting, which may have led to under

ascertainment of cases. However, a previous study using administrative data demonstrated that the vast majority of patients with postvaccination seizures presented for care in the ED or inpatient settings.[12] Fourth, statistical power to detect effect sizes representing less than a doubling of the incidence rate of FS after TIV or PCV13 was limited. However, this study provided the largest statistical power and yielded the most precise estimates published

TABLE 3 Sensitivity Analysis for Risk of Confirmed FS After TIV, PCV13, or DTaP-Containing Vaccines

Exposure	Sensitivity Analysis A: To Primary Analysis, Add Cases With Confirmed Seizure Without Fever Documentation in the Medical Record[a] IRR (95% CI), n = 147	Sensitivity Analysis B: From Primary Analysis, Require Confirmation of Influenza Vaccine, PCV, and DTaP-Containing Vaccines[b,c] IRR (95% CI), n = 119	Sensitivity Analysis C: From Primary Analysis, Require Confirmation of TIV, PCV13, and DTaP-Containing Vaccines[d] IRR (95% CI), n = 90
TIV	1.32 (0.76 to 2.28)	1.23 (0.65 to 2.34)	1.23 (0.58 to 2.58)
PCV13	1.68 (0.97 to 2.91)	1.62 (0.89 to 2.94)	1.58 (0.76 to 3.27)
DTaP	0.96 (0.50 to 1.84)	1.18 (0.59 to 2.38)	1.07 (0.48 to 2.37)

[a] Added to the primary analytic data set (n = 142) were 5 confirmed seizure cases without fever documentation in the medical record.

[b] Confirmation of influenza vaccine includes medical record documentation of TIV or influenza vaccine, not otherwise specified; confirmation of PCV includes medical record documentation of PCV13 or PCV, not otherwise specified.

[c] Excluded from the primary analytic data set (n = 142) were 16 confirmed FS cases without any vaccine medical 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.

[d] In addition to the individuals noted in footnote c, 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.

to date for the underlying relationship between TIV, PCV13, and FS in the 2010–2011 influenza season.[1] Fifth, a large portion of children received >1 vaccine of interest, making it difficult to distinguish between the independent effects of each vaccine and lessening statistical power in models adjusted for concomitant vaccines.

CONCLUSIONS

Each of the relative risk estimates for FS after TIV and PCV13, comparing exposed to unexposed intervals, were >1 in the 2010–2011 season. However, TIV and PCV13 were not significantly associated with FS in the primary analytic models adjusted for age, seasonality, and concomitant administration of each other and DTaP-containing vaccines. If increased risks for TIV or PCV13 were present, the relative risks would likely be lower than previously estimated and the corresponding ARs modest when compared with a child's lifetime risk of FS. Administration of TIV and PCV13 on the same day was not associated with increased risk of FS when compared with separate day vaccination. As of this writing, the US Advisory Committee on Immunization Practices continues to recommend influenza and pneumococcal conjugate vaccination in young children using the existing schedule.[18,19] The risk of FS after influenza vaccination merits continued monitoring in future influenza seasons, particularly given that vaccine formulations change yearly.

ABBREVIATIONS

CI: confidence interval
DTaP: diphtheria tetanus acellular pertussis
ED: emergency department
FDA: US Food and Drug Administration
FS: febrile seizures
IRR: incidence rate ratios
LAIV: live attenuated influenza vaccine
PCV13: 13-valent pneumococcal conjugate vaccine
PRISM: Post-licensure Rapid Immunization Safety Monitoring program
SCRI: self-controlled risk interval
TIV: trivalent inactivated influenza vaccine
VSD: Vaccine Safety Datalink

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