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Post licensure surveillance of influenza vaccines in the Vaccine Safety Datalink in the 2013–2014 and 2014–2015 seasons

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Abstract

Purpose—The changes in each year in influenza vaccine antigenic components as well as vaccine administration patterns may pose new risks of adverse events following immunization (AEs). To evaluate the safety of influenza vaccines annually administered to people ≥ 6 months, we conducted weekly post licensure surveillance for seven pre-specified adverse events following receipt of influenza vaccines during the 2013–2014 and 2014–2015 seasons in the Vaccine Safety Datalink (VSD).

Methods—We used both a historically-controlled cohort design with the Poisson-based maximized sequential probability ratio test (maxSPRT) and a self-controlled risk interval (SCRI) design with the binomial-based maxSPRT. For each adverse event outcome, we defined the risk interval on the basis of biologic plausibility and prior literature. For the historical cohort design, numbers of expected adverse events were calculated from the prior seven seasons, adjusted for age and site. For the SCRI design, a comparison window was defined either before vaccination or after vaccination, depending on each specific outcome.

Results—An elevated risk of febrile seizures 0–1 days following trivalent inactivated influenza vaccine (IIV3) was identified in children aged 6–23 months during the 2014–2015 season using the SCRI design. We found the relative risk (RR) of febrile seizures following concomitant administration of IIV3 and PCV13 was 5.3 with a 95% CI 1.87–14.75. Without concomitant PCV

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13 administration, the estimated risk decreased and was no longer statistically significant (RR: 1.4; CI: 0.54 – 3.61).

Conclusion—No increased risks, other than for febrile seizures, were identified in influenza vaccine safety surveillance during 2013–2014 and 2014–2015 seasons in the VSD.

Keywords

vaccine safety; pharmacoepidemiology; febrile seizures; PCV13

INTRODUCTION

Routine annual influenza vaccination for all persons aged >6 months has been recommended by the Centers for Disease Control and Prevention (CDC) and Advisory Committee on Immunization Practices (ACIP) since 2010.[1] Influenza vaccines often contain different antigens in different seasons, based on predictions for circulating influenza viruses. The changes in vaccine antigenic components as well as vaccine administration patterns may pose new risks of adverse events following immunization (AEs); thus, annual post licensure vaccine safety surveillance is essential.

Since 2009 post licensure surveillance of AEs following seasonal influenza vaccines has been routinely conducted in the Vaccine Safety Datalink (VSD) using electronic health record data from multiple integrated healthcare organizations. During the 2010–2011 influenza season, an elevated risk of febrile seizures was detected in children 6–59 months of age following vaccination with trivalent inactivated influenza vaccine (IIV3), using sequential near real-time rapid cycle analysis (RCA).[2] In addition, in the 2011–2012 influenza season, an elevated risk of seizures in children 6–23 months of age following IIV3 was also identified through sequential monitoring. However, in the 2012–2013 season, when the vaccine components were changed no associations were found between influenza vaccines and increased risks for pre-specified AEs, including seizures, Guillain–Barré syndrome (GBS), encephalitis, or anaphylaxis.[3]

In the 2013–2014 season, a quadrivalent influenza vaccine became available. This vaccine included a second influenza type B strain in addition to the one type B and two type A strains included in the trivalent vaccine. Specifically, the trivalent IIV (IIV3) for 2013–2014 contained antigens from an A/California/7/2009 (H1N1)-like virus, an H3N2 virus antigenically like the cell-propagated prototype virus A/Victoria/361/2011, and a B/Massachusetts/2/2012-like virus, while quadrivalent (IIV4) vaccines contained the additional B/Brisbane/60/2008-like virus antigens.[4] For the 2014–2015 season, U.S.-licensed trivalent and quadrivalent influenza vaccines contained the same vaccine virus strains as those in the 2013–2014 vaccines.[5] To monitor the safety of influenza vaccines in a timely manner during the 2013–2014 and 2014–2015 influenza seasons, we performed a near real-time RCA for IIV3 and IIV4, as well as the live attenuated influenza vaccine (LAIV) utilizing electronic health record data from multiple VSD sites that are updated weekly. This report describes the methods and provides the results of influenza vaccine safety surveillance during these two seasons.

METHODS

Data sources

The VSD is a collaboration between the CDC and nine integrated healthcare delivery organizations.[6] The VSD population included over eight million individuals in 2010, which represented 2.6% of the total US population.[7] VSD population can be representative of the general US population demographically and socioeconomically. The electronic health care database includes demographic data on immunization history and diagnosis codes for medical visits during health plan members' enrollment. Diagnosis codes from ambulatory, urgent care, emergency department, and inpatient encounters use the International Classification of Diseases, Ninth Revision (ICD-9) standard. Six integrated healthcare organizations (hereafter referred to as "sites") who joined the infrastructure task order participated in this analysis and contributed dynamic weekly data files: Kaiser Permanente of Northern California, Oakland, California (NCK); Kaiser Permanente of Colorado, Denver, Colorado (KPC); Marshfield Clinic Research Foundation, Marshfield, Wisconsin (MFC); Northwest Kaiser Permanente, Portland, Oregon (NWK); Group Health Cooperative, Seattle, Washington (GHC); and Kaiser Permanente of Southern California, Pasadena, California (SCK).

Institutional review boards at CDC and each participating VSD site approved the study and determined that informed consent was not required.

Vaccines and outcomes

During the 2013–2014 and 2014–2015 influenza seasons, both IIV3 and IIV4 were available for persons aged 6 months and older (Table 1). A quadrivalent live attenuated influenza vaccine (LAIV4) was available for persons aged 2 through 49 years. A trivalent recombinant hemagglutinin vaccine (RIV3) was also available for persons aged 18–49 years. For persons aged 65 years and older, a trivalent high dose inactivated influenza vaccine was also available. An IIV3 intradermal was available for persons aged 18 through 64 years. We monitored AE outcomes following only the first doses for all these influenza vaccines. For IIV3, IIV4 standard dose and LAIV4, we monitored seven outcomes: acute disseminated encephalomyelitis (ADEM), anaphylaxis, Bell's palsy, encephalitis, GBS, febrile seizures, and transverse myelitis. ICD-9 codes for these seven outcomes are listed in Table 2. These seven outcomes were selected based on the safety concerns from pre-licensure clinical trials as well as reports to the Vaccine Adverse Event Reporting System (VAERS). The outcomes monitored were clinically well defined with relatively acute onset, and serious enough to results in a medical visit.[8] Post-vaccination risk intervals for each outcome were chosen based on their biologic plausibility and the prior literature (Table 2).[2,3,9] Age groups that were monitored for each outcome are also listed in Table 2. Because of small numbers of vaccine recipients and small AE numbers, we did not conduct formal statistical analyses for IIV3 high dose, RIV3, and IIV3 intradermal; however, we monitored the number of doses administered and the number of events for all seven pre-specified outcomes except febrile seizures because these presentations are licensed for adults only.

Study design and statistical methods

We used both a historically controlled cohort design and a self-controlled risk interval (SCRI) design[10] to sequentially monitor the occurrence of all seven outcomes following IIV3, IIV4, and LAIV4. The historically controlled design provides sufficient power to detect rare AE outcomes. An advantage of the SCRI design is that it accounts for any time-invariant confounders, such as gender and patients' underlying health condition, because the same individual serves as his/her own control.[11] In the historical design, the observed number of AEs in the pre-specified risk window were summed for all the individuals and compared with the expected number of AEs based on outcome rates computed among IIV3 vaccinees in prior seasons (2005–2006 through 2012–2013), stratified by VSD site. The Poisson maximized sequential probability ratio test (maxSPRT)[10] was applied weekly and used to detect any elevated risks following vaccination. Upper limits on the length of surveillance were defined in terms of the expected number of events accrued under the null hypothesis. We pre-specified the upper limit for each outcome based on the number of AEs from the historical data. The sequential method binomial maxSPRT[9] was used with the SCRI design to monitor any potential signals weekly. The number of cases in the risk interval was compared with the number of cases in a pre-vaccination or post-vaccination control interval. Critical values for signaling a potential elevated risk of an AE were calculated using the exact numerical algorithm described in Kulldorff *et al.* based on an alpha level of 0.05.[10] We defined a "signal" as a log likelihood ratio test statistic that exceeded the critical value. We reported and refined all the signals identified using both historically controlled and self-controlled methods.

Each week, we compiled and analyzed cumulative immunization and AE data accrued through the previous week. Analyzing data in this near-real time manner raises two key complications: (i) Outcome risk windows may not have fully elapsed for some vaccinees at the time of each analysis (i.e. partially elapsed window), and (ii) Information captured in the health care organization databases may not be complete because some data (e.g. AEs that occur outside the health care system as well as health care claims from other institutions) may not populate in the electronic database on the same week they occur in practice (i.e. late arriving). Usually, the lag between an AE occurrence and its appearance in the database differs by site and specific medical care setting (i.e. inpatient, emergency department, outpatient). To account for partially elapsed risk windows and late-arriving data, we adopted previously described methods.[12] Briefly, for the historically controlled design, we reduced the expected number of AEs if the risk window had only partially elapsed. For the SCRI design with a pre-vaccination comparison window, when the end of a surveillance week truncated the risk window, we also truncated the control window to maintain a fixed ratio between the two time window lengths. For the SCRI design with a post-vaccination control window, AEs occurring in later weeks in the risk window were ignored if the corresponding week had not yet elapsed in the comparison window. To account for potentially late-arriving AE data (i.e. time lag between a diagnosis time and the appearance in the data), we adjusted the expected number of AEs for the historically controlled design for the inpatient setting based on the site-specific proportion of inpatient data estimated to have been received by that week. For the SCRI design, a site's inpatient data were included only after we received 95% estimated data accrual to avoid an imbalance between risk and control windows.

A statistical signal identified during sequential monitoring does not necessarily represent a true elevated risk because of various reasons, such as incorrect case identification. Therefore, we conducted further assessments to determine if a detected signal truly indicated a potential increased risk of the AE. Trained abstractors at each site used a standardized chart review form to confirm whether an AE case coded in the database was a true incident case. For the outcomes that signaled, we also performed an end-of-season analysis after all the data had been collected and data lags were no longer an issue. This was a one-time analysis and different from the analyses that were performed sequentially to avoid violating the sequential design and type 1 error.

RESULTS

Weekly data were collected during surveillance periods from June 30, 2013 through April 19, 2014 and from 29 June 2014 through 9 April 2015 (Figure 1). More than 3.7 million and 3.4 million first doses of IIV3 were administered during the 2013–2014 and 2014–2015 seasons (Table 3), respectively. The number of IIV4 vaccinees increased dramatically from the 2013–2014 season (N = 23990) to the 2014–2015 season (N = 251271), with the majority of doses administered in the youngest age group (<5 year-olds). More doses of LAIV were administered during the 2014–2015 season than in the 2013–2014 season (307967 vs. 219093). There was also a slightly higher number of females than males receiving all types of influenza vaccines in this study.

For the 2013–2014 influenza season, we did not find a statistically significant elevated risk following IIV3, IIV4, or LAIV for any of the seven pre-specified AEs. For the 2014–2015 influenza season, the historically controlled analyses detected a significantly increased risk of Bell's palsy following IIV4 for the age group ≥50 years old with a relative risk (RR) of 11.3 on 1 October 2014 after 23271 doses were administered. To follow up on this preliminary signal, we conducted medical chart review of the five cases detected. Only one of these cases was confirmed to be a true incident case. Among the other four cases, one had a history of Bells palsy, two had disease onset prior to vaccination, and one was miscoded. Based upon the additional chart review information and the lack of any signal throughout the surveillance period using the SCRI design, it was determined to be a false signal. Additionally, on 3 December 2014, both the historical-controlled and SCRI analyses signaled for an elevated risk of encephalitis following 2691270 doses of IIV3 among individuals >6 months old, with a total of 17 cases observed (compared to 7.8 expected) with an estimated RR = 2.18 for historical comparators and RR = 2.62 for self-controlled time periods respectively. After medical record review of the 17 cases, only one was confirmed to be a true incident case, compared to 7.8 expected, and thus this was determined not to be a true encephalitis signal. The following week on 10 December 2014, we identified a potential elevated risk for seizures following 43641 doses of IIV3 among children 6–23 months old using the SCRI study design. We found five cases in the risk window and one case in the comparison window, with a relative risk of 17.5. We did not perform medical chart review of febrile seizure cases because the ICD-9 code has previously been shown to have a high positive predictive value for true febrile seizures, and this outcome has signaled and been evaluated in previous seasons.[13]

End-of-season analysis for febrile seizures

Because only one febrile seizure was observed in the comparison window for IIV3 in the 2014–2015 season, we combined the data from both seasons to conduct an end-of-season analysis. In the 2010–2011 season we found that concomitant administration of IIV3 and PVC13 was associated with an increased risk of febrile seizures in young children[2]; thus, we used the SCRI design to determine whether concomitant administration of IIV3 or IIV4 with PCV13 significantly increased the risk of febrile seizures in the risk window 0–1 days after IIV vaccination compared to the control time period 14–20 days after vaccination for children aged 6–23 months. We found the RR of febrile seizures following concomitant administration of IIV3 and PCV13 was 5.3 with a 95%CI 1.87–14.75 (Table 4). Without concomitant PCV 13 administration, the estimated risk decreased and was no longer significant (RR: 1.4; CI: 0.54–3.61). Similarly, we found a much higher relative risk for IIV4 administered concomitantly with PCV13 than without PCV13 (12.3 vs. 0.6; CI: 2.5–58.9 vs. 0.07–4.85) for children aged 6–23 months for the season of 2014–2015. For the season 2013–2014, we did not perform the analysis for IIV4 because there were very few doses (<1000) of IIV4 administered for this age group.

DISCUSSION

We conducted weekly safety surveillance of influenza vaccines IIV3, IIV4, and LAIV for 2013–2014 and 2014–2015 influenza seasons. No association was found between IIV (IIV3 or IIV4) and GBS, anaphylaxis, ADEM, or transverse myelitis in persons >6 months of age in either our historical or self-controlled design analyses in either season. Statistical signals were identified for Bell's palsy following IIV4 for people >50 years of age and encephalitis following IIV3 for people >6 months of age, but both were determined to be false signals after chart review found that the majority of these cases were not incident cases. No association was found between LAIV and seizures for individuals aged 24–59 months old. Since 2009,[9] VSD has been conducting RCA for influenza vaccines in each influenza season using sequential methodology. The success of RCA depends on timely data updates (i.e. weekly) from each data source. Currently, VSD is the only system that provides dynamic data files and data are refreshed weekly. FDA Sentinel System was built on a quarterly data basis, and their recent pilot RCA study for influenza vaccines was using data as recent as 6 weeks old.[14]

The signal identified using the SCRI design in 2014–2015 between IIV3 and seizures in children 6–23 months of age is similar in direction to findings from the 2010–2011 season in the VSD, which found a 2.4-fold increased risk of febrile seizures among 6- to 59-month-old children.[2] However, the historically controlled cohort design did not detect a signal for seizures and IIV3 throughout the 2014–2015 season. One possible explanation is that the historical rate used in the historically controlled cohort design might not reflect the expected baseline seizure rate in the absence of vaccination. The background rate may also have been falsely elevated because it included the rate of seizures following IIV vaccinees during the 2010–2011 season and 2011–12 seasons; seasons for which an increased risk of febrile seizure was identified. The SCRI finding of no signal for febrile seizures for IIV3 during the 2013–2014 season and no signal for febrile seizures for IIV4 during the

2014–2015 season, which included all of the same strains as IIV3, raised questions of validity. However, in our end of season analysis, the RR of febrile seizure for IIV3 and IIV4 were very similar when the analysis was restricted to IIV doses given without any other concomitant vaccine. The sequential analysis included all IIV doses without controlling for concomitant vaccines, and the difference observed between IIV3 and IIV4 during the 2014–2015 season surveillance (i.e. signal versus no signal) could have been because of differences in concomitant vaccination patterns between the two groups.

The VSD 2010–2011 influenza vaccine end-of-season analysis found that the risk of febrile seizure following IIV3 differed by receipt of concomitant PCV13 vaccine.[2] The relative risk comparing exposed to unexposed intervals was lower for children receiving IIV3 without concomitant PCV13 and higher when both vaccines were given together. Our combined end-of-season analysis for 2013–2014 and 2014–2015 was consistent with the 2010–2011 season's findings and further demonstrates that this pattern of greater risk with concomitant IIV and PCV13 vaccination can also occur in a season in which IIV is not associated with an independently increased risk of febrile seizure.

This study is subject to several limitations. First, both the Poisson-based maxSPRT, used with the historically controlled cohort design, and binomial-based maxSPRT, used with the SCRI design, require pre-specified upper limits in terms of the expected and observed number of AEs. If we incorrectly specified this input, the critical value may have been set too low or too high, thus affecting the time to signal. Second, we made adjustments for the delay in inpatient data accrual; however, this adjustment was based on the best estimates from each site from seasons 2005–2006 through 2012–2013, which may not accurately reflect the situation in either the 2013–14 and 2014–15 seasons. Third, because of limited sample size, during rapid cycle analyses we were unable to assess whether the elevated risk of febrile seizures associated with influenza vaccine was because of concomitant PCV13 or other concomitant vaccines; in the end-of-season analysis, however, we found that increased risk was only evident when inactivated influenza vaccines were administered at the same time as pneumococcal conjugate vaccines (i.e. IIV3 and concomitant PCV13 increased the risk of febrile seizure by 5.25-fold and IIV4 and concomitant PCV13 increased the risk of febrile seizures by 12.3-fold).

One strength of this surveillance study is that we simultaneously used both the historically controlled cohort design and SCRI design to monitor the same seven AEs following influenza vaccines. It provided an opportunity to capture a potential elevated risk of AEs as early as possible, because one method may signal earlier than the other because of the different design mechanisms. For rare outcomes, the historically controlled cohort design is likely to signal earlier than the SCRI design, because it uses historical rates as the baseline and has greater statistical power. In addition, the historically controlled cohort is less impacted by data lags because we only need to collect data for the risk window, rather than for both risk and comparison windows as in the SCRI design. However, if the baseline risk is estimated to be higher than the true baseline risk, this would falsely obscure a signal. The SCRI design, which uses the binomial-based maxSPRT, does not require estimation of the baseline risk, and is superior in dealing with time-invariant confounders. By conducting two different analyses simultaneously, we gain the advantages of both methods.

In summary, an elevated risk of febrile seizures in the 0–1 days following the first dose IIV3 was identified during the 2014–2015 season in children aged 6–23 months in the VSD. In an analysis combining the data from two seasons the relative risk of febrile seizures comparing exposed to unexposed time periods was significantly elevated for IIV3 and IIV4 with concomitant PCV13 vaccination and not for IIV3 or IIV4 alone. Similar findings have been observed in previous seasons. No new safety concerns were identified in influenza vaccine safety surveillance during 2013–2014 and 2014–2015 seasons in the VSD. The VSD will continue to monitor the safety of influenza vaccines in future influenza seasons.

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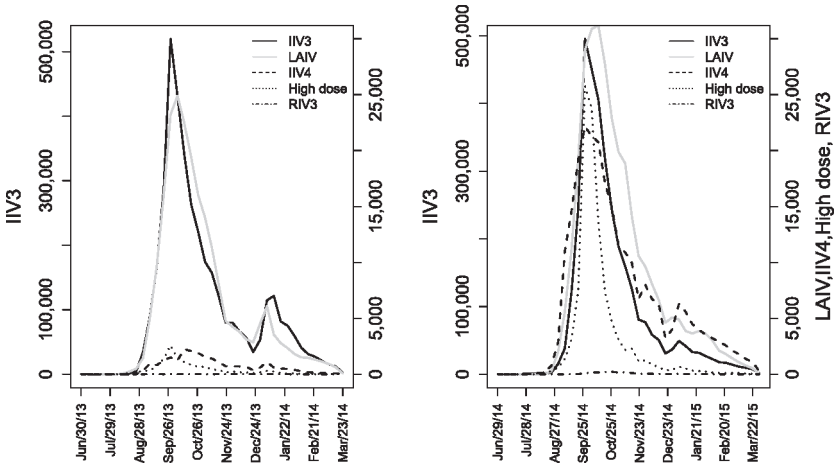

Figure 1.

Weekly uptake of influenza vaccines influenza trivalent inactivated influenza vaccine (IIV3), quadrivalent inactivated influenza vaccine (IIV4), live attenuated influenza vaccine (LAIV), IIV3 high dose, and trivalent recombinant hemagglutinin vaccine (RIV3) for seasons 2013–2014 (left) and 2014–2015 (right)

Table 1.

Influenza vaccines available for the 2013–2014 and 2014–2015 seasons by age group and whether a statistical analysis was performed

Vaccines	Age group	Statistical analysis
IIV3	≥6 months	Yes
IIV4	≥6 months	Yes
LAIV4	2–49 years	Yes
RIV3	18–49 years	No
IIV3 high	≥65 years	No
IIV3 intradermal	18–64 years	No

Table 2.

Seven pre-specified adverse events following vaccination under surveillance

Outcome	ICD-9 diagnosis codes	Setting	Risk interval (days after vaccination)	Control interval (for binomial, days before or after vaccination)	Age group(s)
ADEM	323.61	Inpatient, ED*, outpatient	1 – 21	−56 – −15	>6 months
Anaphylaxis	995.0, 999.4	Inpatient, ED, outpatient	0 – 2	7–9	>6 months
Bell's palsy	351.0	Inpatient, ED, outpatient	1 –42	−56 – −15	<18 years, 18–49 years, ≥50 years
Encephalitis	323.5, 323.6, 323.8, 323.9, 341.2	Inpatient, ED, outpatient	1 –21	−56 – −15	>6 months
GBS	357.0	Inpatient, ED, outpatient	1 – 42	43 – 260	>6 months
Seizure	780.3, 780.31, 780.39	Inpatient, ED, outpatient	0 – 1 for IIV; 0 – 7 for LAIV	14 – 20 for IIV; 15 – 29 for LAIV	6–23 months, 24–59 months
Transverse myelitis	341.2, 323.52	Inpatient, ED, outpatient	1 –21	−56 – −15	>6 months

*ED: emergency department.

Table 3.

Number of first doses of IIV and LAIV administered in the Vaccine Safety Datalink by site, age, and sex

Season	Characteristic	IIV3	High dose	Intradermal	IIV4	RIV3	LAIV
2013–2014		*N* = 3 786 868	*N* = 13 071	*N* = 3386	*N* = 23 990	*N* = 174	*N* = 219 093
	Site						
	A	1 457 980	3960	0	0	0	76 771
	B	204 230	321	0	4	0	10 836
	C	100 868	972	0	0	27	6531
	D	226 244	511	195	2346	37	23 695
	E	1 517 157	3251	2028	20 360	96	74 606
	F	280389	4056	1163	1280	14	26 654
	Age						
	<5 years	289 009	26	0	1739	1	44 521
	5–17 years	490 917	31	27	7145	1	150 369
	18–49 years	1 135 619	366	1854	7297	110	23 118
	50–64 years	913 643	470	1233	4447	47	730
	65–84 years	850 478	10 457	247	2997	14	297
	>85 years	107 202	1721	25	365	1	58
	Sex						
	Male	1 659 992	5750	1205	10 910	40	103 258
	Female	2 126 795	7320	2181	13 080	134	115 833
	Unknown	81	1	0	0	0	2
2014–2015		*N* = 3 429 406	*N* = 103 121	*N* = 5167	*N* = 251 271	*N* = 1593	*N* = 307 967
	Site						
	A	1 292 443	77 779	1353	1823	211	117 939
	B	190173	354	.	18 475	.	13 715
	C	81 936	1829	.	.	59	7714
	D	246 135	9181	275	48 772	332	31 478
	E	1 433 409	4818	2438	84 235	114	104 955
	F	185 310	9160	1101	97 966	877	32 166
	Age						

Season	Characteristic	IIV3	High dose	Intradermal	IIV4	RIV3	LAIV
	<5 years	140 940	84	2	107 755	2	71 256
	5–17 years	401 986	136	31	16 069	40	207 713
	18–49 years	1 109 183	754	2768	45 596	785	27 752
	50–64 years	896 228	1315	1893	35 509	572	734
	65–84 years	796 014	76 644	421	40 715	178	429
	≥85 years	85 055	24 188	52	5627	16	83
	Sex						
	Male	1 484 652	44 702	3444	113 714	507	160 935
	Female	1 944 446	58 335	1716	137 405	1080	147 015
	Unknown	308	84	7	152	6	17

Table 4.

End of season analysis for febrile seizures following IIV3 for the combined two seasons and IIV4 for the 2014—2015 season among 6- to 23- month-old children

	Cases in risk window	Cases in comparison window	Relative risk	Confidence interval
IIV3				
With PCV 13 and other vaccines	9	6	5.25	1.87 – 14.75
Without PCV13	6	15	1.4	0.54 – 3.61
IIV3 only *	3	7	1.5	0.39 – 5.80
IIV4				
With PCV 13 and other vaccines	7	2	12.3	2.50 – 58.90
Without PCV13	1	6	0.6	0.07 – 4.85
IIV4 only *	1	3	1.2	0.12 – 11.20

* Only includes IIV3 or IIV4 given alone without any other vaccine.