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Postlicensure surveillance for pre-specified adverse events following the 13-valent pneumococcal conjugate vaccine in children

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ABSTRACT

Although no increased risk was detected for serious adverse events in the prelicensure trials for the 13-valent pneumococcal vaccine, Prevnar 13® (PCV13), continued monitoring of rare but serious adverse events is necessary. A surveillance system using cohort study design was set up to monitor safety of PCV13 immediately after it was included in the childhood immunization program in the United States. The exposed population included children of 1 month to 2 years old who received PCV13 from April, 2010 to January, 2012 from the eight managed care organizations participating in the Vaccine Safety Datalink Project in the United States. The historical unexposed population was children of the same age who received the 7-valent pneumococcal conjugate vaccine Prevnar 7® (PCV7) in 2007 (or 2005 depending on the outcome of interest) to 2009. The risk of pre-specified adverse events in the risk window following PCV13 was repeatedly compared to that in the historical comparison group. The number of doses included in the study was 599,229. No increased risk was found for febrile seizures, urticaria or angioneurotic edema, asthma, thrombocytopenia, or anaphylaxis. An increased risk for encephalopathy was not confirmed following the medical record review. The relative risk for Kawasaki disease in 0–28 days following vaccination was 1.94 (95% confidence interval: 0.79–4.86), comparing PCV13 to PCV7. Comparing to PCV7 vaccine, we identified no significant increased risk of pre-specified adverse events in the Vaccine Safety Datalink study cohort. The possible association between PCV13 and Kawasaki disease may deserve further investigation.

1. Introduction

While the 7-valent pneumococcal conjugate vaccine Prevnar 7® (PCV7) is successful in countries with routine immunization programs, a significant disease burden still exists globally due to serotypes not included in PCV7 [1–4]. In February 2010, the 13-valent pneumococcal conjugate vaccine, Prevnar 13® (PCV13), was approved by the United States (US) Food and Drug Administration because the new vaccine provides additional protection to serotypes not covered in PCV7 and compatible with other routine childhood vaccinations. It became the only new pneumococcal conjugate vaccine to be approved in the US for prevention of invasive diseases caused by the serotypes in the vaccine and prevention of otitis media caused by the 7 original serotypes [5].

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PCV13 is approved for use in children six weeks to <5 years of age and licensed as a four-dose series that is indicated for use at 2, 4, 6, and 12 to 15 months of age [6]. For children ≤15 months of age, PCV13 replaced PCV7 in the vaccination schedule. A catch up dose (i.e., one additional PCV13 dose for children who have been fully vaccinated with 4 doses of PCV7) is recommended for children at 14–59 months of age. Children with an underlying medical condition may receive the vaccine before 6 years of age, and children 6–18 years of age who are at increased risk for pneumococcal disease may receive a single dose of the vaccine [7].

Safety monitoring was conducted in the prelicensure trials for PCV13, and no increased risk was detected for serious adverse events [8]. Nevertheless, rare but serious adverse events such as anaphylaxis, or angioneurotic edema following PCV7 reported from postlicensure studies and the Vaccine Adverse Events Reporting System warrant further study in PCV13 [9–12]. In this study, we present results from our monitoring of the occurrence of pre-specified events following PCV13 immediately after it was included in the U.S. childhood immunization program using the surveillance method developed in the Vaccine Safety Datalink Project [13,14].

2. Materials and methods

2.1. Subjects and settings

The study monitored the risk of pre-specified adverse events following PCV13 in children of 1 month–2 years of age for 90 weeks. The study population included children at any of the eight managed care organizations participating in the Vaccine Safety Datalink Project who were vaccinated with PCV13 [14]. Vaccination records and medical encounters were identified from electronic data prepared by each organization. The Institutional Review Boards of each organization approved this study.

2.2. Pre-specified adverse events

Computerized data were used to identify children with any of the following events: (1) febrile seizures, (2) encephalopathy, (3) urticaria and angioneurotic edema, (4) asthma, (5) anaphylaxis, (6) thrombocytopenia and (7) Kawasaki disease (Table 1). Cases except thrombocytopenia were identified by diagnoses that were coded according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes. Thrombocytopenia was identified using platelet laboratory data because of its accuracy over ICD-9-CM codes at VSD settings.

These events of interest were selected based on PCV13 clinical trial safety data, PCV7 reports in the Vaccine Adverse Event Reporting system and post-licensure safety studies. Febrile seizures, urticaria, angioneurotic edema, and anaphylaxis were observed in the PCV13 clinical trials [6]. Also, 94 cases of febrile seizure, 4 serious cases of encephalopathy, and 14 cases of cases of thrombocytopenia following PCV7 were reported to the Vaccine Adverse Events Reporting System data from 2000 to 2002 [12]. Incidence of asthma was found to be higher among PCV7 recipients than the comparison group in clinical trials and postmarketing surveillance studies of PCV7 [10,11]. Finally, while a recent study found no statistically significant association between Kawasaki disease and PCV7 vaccination [15] there were 29 cases of Kawasaki disease following PCV7 reported to Vaccine Adverse Events Reporting System from 1990 to 2007 [16]. Although an analysis of these reports found no elevation of this risk, we chose to include this condition in the current study.

Risk windows were also defined for each event. These are pre-specified time periods following vaccination in which the risk of events can hypothetically be affected by vaccination and vary depending on the event of interest (Table 1). Shorter windows were defined for events with more immediate onset. Also, in order to identify incident cases, only the first event documented within a specified time interval for that individual was counted. For example, an incident event of encephalopathy was defined as the first episode in 12 months.

2.3. Statistical methods

In this study, the cumulative risk of a pre-specified adverse event in the risk window following PCV13 was sequentially compared to that following PCV7, which was aggregated in a 3-year (or 5-year for anaphylaxis and encephalopathy) period from 2007 (or 2005) to 2009. Twelve repeated group sequential tests were designed to span a period up to 90 weeks (from April 25, 2010 to January 14, 2012) while the overall type I error was maintained at 5%. Tests were conducted at time points that were evenly-spaced based on the number of vaccine doses administered required to ensure 80% statistical power of detecting a pre-specified relative risk of 2–4. Each week, aggregated number of vaccine doses administered and number of diagnoses with pre-specified adverse events from each participating site were combined and accumulated until the required number of doses for each test had been reached. At each of the time points tested, relative risks comparing the PCV13 and PCV7 groups and log likelihood ratios test statistics were calculated [17,18]. A non-flat O'Brien–Fleming threshold for log likelihood ratios, which is wider at earlier time points and narrows later as more observations are accumulated, was used in order to minimize false positives at the early phase of the surveillance [19]. The null hypothesis was rejected if the log likelihood ratios reached the threshold. The null hypothesis of no difference in risk between the two vaccines was not rejected if the log likelihood ratios never reached the threshold after all twelve tests were performed.

For common events, vaccine dose in the series and age-stratified analyses were performed. The dose-in-the-series stratified analysis was performed by restricting to doses given within a pre-specified age range (first dose: 1 month to less than 4; second dose: 3 months to less than 6; third dose: 5 months to less than 12; fourth dose: 12–24 months). The age-stratified analysis ignored the dose-specific information and divided age into 4 groups: 1 to less than 4 to months, 4 to less than 6 months, 6 to less than 12 months, and 12–24 months. In addition, to avoid duplicate records, if the number of days between two PCV13 or two PCV7 records was less than 28 days, the second record was excluded from the analysis.

If a signal, defined as a statistically significant increased risk, was detected, medical records of events in the risk window identified by automated data were abstracted and reviewed by investigators to validate presumptive diagnosis and confirm the signal. An analysis comparing the risk of events following PCV13 and PCV7 using chart-confirmed cases was conducted. For the study, diagnoses for cases without increased risk were not reviewed.

3. Results

The number of vaccine doses of PCV13 included in the study was 599,229. The results of age- and dose-in-the-series-specific analyses, including the number of doses of PCV13 per test at a given time point, the number of observed adverse events based on automated data cumulated during monitoring period, the relative risk of adverse events compared to PCV7, and the planned relative risk detectable with 80% power, are presented in Table 2. There was no signal for febrile seizures, urticaria or angioneurotic edema, asthma, thrombocytopenia, and anaphylaxis after 12 group sequential tests were completed. There were two signals of an increased risk, one for encephalopathy at the eighth test after 63

Table 1
International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9) codes and lab values for pre-specified adverse events following 13-valent pneumococcal conjugate vaccine vaccination.

Adverse event group	ICD-9 codes & descriptions or lab value[a]	Exclusions (exclude if code below appears on same day as adverse event code or lab value)	Risk window[b]	Settings	First diagnosis in what period[c]
Neurological outcomes					
Febrile seizure	780.3 convulsions, 780.31 febrile convulsions (simple), unspecified, 780.32 complex febrile convulsions, 780.39 other convulsions	345 (epilepsy & recurrent seizure)	0–7 days	Inpatient, emergency department (ED)	First in 42 days
Encephalopathy	348.3 encephalopathy, not elsewhere classified, 348.30 encephalopathy, unspecified, 348.31 metabolic encephalopathy, 348.39 other encephalopathy	None	1–28 days	Inpatient, ED	First in 1 year
Immunological outcomes					
Urticaria & angioneurotic edema (angioedema)	708.0 allergic urticaria, 708.1 idiopathic urticaria, 708.9 urticaria, unspecified, 995.1 angioneurotic edema	None	0–7 days	Inpatient, ED	First in 42 days
Asthma	493 Asthma, 466.1 acute bronchiolitis, 786.07 wheezing, 786.09 respiratory distress/insufficiency, 519.1 other diseases of trachea & bronchus	None	0–7 days	Inpatient, ED	First in 42 days
Anaphylaxis	999.4 Anaphylactic shock due to serum, 995.0 other anaphylactic shock	None	0–1 day	Inpatient, ED, outpatient	First in 2 days
Thrombocytopenia I	Two platelet counts of ≤50,000 within 7 days of each other (not necessarily consecutive)	Known illnesses causing thrombocytopenia: 140.0–208.0 (malignant neoplasms), 228 (hemangioma and lymphangioma, any site), 279 (disorders involving the immune mechanism), 283 (acquired hemolytic anemias), 284 (aplastic anemia and other bone marrow failure syndromes), 286.6 (defibrination syndrome), 570 (acute and subacute necrosis of liver), 571 (chronic liver disease and cirrhosis), 742.59 (other specified anomalies of spinal cord)	1–28 days	Platelet, Inpatient, ED, Outpatient	First in 6 months
Thrombocytopenia II	Two platelet counts of ≤100,000 within 7 days of each other (not necessarily consecutive)	Same as above	1–28 days	Platelet, inpatient, ED, outpatient	First in 6 months
Kawasaki disease	446.1 acute febrile mucocutaneous lymph node syndrome (MCLS)	None	1–28 days	Inpatient, ED, outpatient	First in 1 year

[a] See ICD-9-CM Official Guidelines for Coding and Reporting (http://www.cdc.gov/nchs/data/icd9/icdguide10.pdf); for 3-digit codes, include all 4th and 5th digits with that code; for 4 digit codes, include all 5th digits with that code.
[b] The pre-defined risk period after vaccination.
[c] A diagnosis is considered as an incident event if it is the first one within the past window period, ranging from 2 days to 1 year for various adverse events.

weeks of monitoring (relative risk = 3.05) and another for Kawasaki disease at the second test after 18 weeks of monitoring (relative risk = 4.24) (Table 2). The encephalopathy signal was further investigated by conducting medical record review.

Medical records of patients with an encephalopathy diagnosis within 1–28 days of vaccination with PCV13 and PCV7 were reviewed by medically trained investigators. There were 6 children with an encephalopathy diagnosis in the PCV13 group versus 8 in the PCV7 group. Medical record review found that only 2 of the 6 children with an encephalopathy diagnosis had confirmed encephalopathy in the PCV13 group, and both had causes unrelated to PCV13. One of them was a child with developmental delay whose encephalopathy symptoms were present before PCV13 vaccination. The other was a child with hypoxic ischemic encephalopathy after a near-drowning event. There were 2 confirmed encephalopathy cases with onset after vaccination in the PCV7 group as well. The increased risk of encephalopathy following PCV13 was not confirmed following medical record review.

The Kawasaki disease signal was identified at an early stage of the study. At the second group sequential test, there were 7 children with a diagnosis of Kawasaki disease within 1–28 days of PCV13 vaccination. In order to avoid a spurious conclusion about the association based on a small number of patients and doses included in that stage of the analysis, the study team decided to continue monitoring and accumulate the maximal number of doses for an end-of-study analysis. The window for searching for automated

Table 2
Required number of doses per test, detectable relative risk, and results of the last group sequential test for adverse events following the 13-valent pneumococcal conjugate vaccine.

Adverse event	No. of doses per test[b]	No. of observed events	Relative risk	No. of group sequential test/last week of monitoring	Detectable relative risk[e]
Febrile seizures					
Age 1 < 4 months	12,800	12	1.29	12th/week 85 (no signal)	2
Age 4 < 6 months	8100	9	0.91	12th/week 70 (no signal)	2
Age 6 < 12 months	5300	12	1.04	12th/week 43 (no signal)	2
Age 12–24 months	2200	10	0.99	12th/week 14 (no signal)	2
Dose 1	10,700	10	1.11	12th/week 84 (no signal)	2
Dose 2	8100	8	0.87	12th/week 69 (no signal)	2
Dose 3	7500	15	1.13	12th/week 61 (no signal)	2
Dose 4	2200	11	1.06	12th/week 22 (no signal)	2
Encephalopathy	52,500	6	3.05	8th/week 63 (signaled)	3
Encephalopathy[a]	52,500	6	3.13	8th/week 63 (signaled)	3
Urticaria, angioneurotic edema					
Age 1 < 4 months	8000	1	0.34	12th/week 55 (no signal)	3
Age 4 < 6 months	6300	5	1.73	12th/week 55 (no signal)	3
Age 6 < 12 months	8100	8	0.86	12th/week 65 (no signal)	2
Age 12–24 months	5300	12	1.29	12th/week 28 (no signal)	2
Dose 1	6900	1	0.34	12th/week 57 (no signal)	3
Dose 2	10,800	6	1.89	12th/week 89 (no signal)	3
Dose 3	7500	9	0.96	12th/week 61 (no signal)	2
Dose 4	7500	16	1.35	12th/week 61 (no signal)	2
Asthma					
Age 1 < 4 months	2200	8	0.69	12th/week 18 (no signal)	2
Age 4 < 6 months	2200	7	0.72	12th/week 22 (no signal)	2
Age 6 < 12 months	2200	9	0.67	12th/week 22 (no signal)	2
Age 12–24 months	2200	10	0.95	12th/week 14 (no signal)	2
Dose 1	2200	10	0.85	12th/week 20 (no signal)	2
Dose 2	2200	7	0.73	12th/week 22 (no signal)	2
Dose 3	2200	5	0.45	12th/week 21 (no signal)	2
Dose 4	2200	6	0.60	12th/week 20 (no signal)	2
Anaphylaxis	34,000	0	–	12th/week 61 (no signal)	4
Anaphylaxis[a]	31,000	0	–	12th/week 56 (no signal)	4
Thrombocytopenia I[c]	43,000	4	0.43	12th/week 83 (no signal)	2
Thrombocytopenia II[d]	30,900	4	0.42	12th/week 60 (no signal)	2
Kawasaki disease	52,500	7	4.24	2nd/week 18 (signaled)	2

[a] Background risk using 5 years of PCV7 data (2005–2009).
[b] Total number of doses approximately equal to the number of dose per test multiplied by the number of the group sequential tests.
[c] Two platelet counts of ≤50,000 within 7 days of each other (not necessarily consecutive).
[d] Two platelet counts of ≤100,000 within 7 days of each other (not necessarily consecutive).
[e] Pre-specified detectable relative risk with 80% power.

diagnoses of Kawasaki disease was expanded to 56 days following vaccination to capture cases with disease onset within 28 days of vaccination but labeled with a diagnosis later due to evolving symptoms and laboratory findings. Medical records of these potential cases were abstracted at the VSD sites and reviewed by one of the investigators (SMM) to confirm the diagnosis and determine the date of onset. The diagnosis of complete and incomplete Kawasaki disease was based upon the clinical and laboratory criteria described in the Clinical Report from the American Academy of Pediatrics and the American Heart Association [20]. Patients with confirmed Kawasaki disease with onset 0–28 days following vaccination were included in the final analysis.

The results of the end-of-study analysis for Kawasaki disease following PCV13 are presented in Table 3. When 599,229 doses of PCV13 vaccine had been administered, there were 30 diagnoses of Kawasaki disease in the 1–56 days following vaccination, compared to 49 diagnoses of Kawasaki disease, among 1,067,691 doses of PCV7 vaccine. After reviewing the medical records, there were 5 confirmed complete cases and 7 confirmed incomplete cases with onset 0–28 days following PCV13 vaccination, compared to 5 confirmed complete Kawasaki cases, 4 confirmed incomplete cases, and 2 possible cases in the PCV7 group. One of the possible Kawasaki disease cases had less than 3 laboratory criteria and a normal echo cardiogram, but had a consult with a Kawasaki disease expert. The other possible case met four out of five clinical criteria, but had inadequate information on "possible pyelonephritis", making it impossible to confirm or reject the diagnosis. The risk of Kawasaki disease was 0.84 or 1.03 per 100,000 doses in the PCV7 group, depending on whether possible cases were included. It was 2.00 per 100,000 doses in the PCV13 group. The relative risk was 1.94 (95% confidence interval (CI): 0.79–4.86), if the two possible patients were included in the analysis. The estimated relative risk remained similar after controlling for age, sex, and season (relative risk 1.97, 95% CI: 0.79–4.94). This relative increase would translate to a risk difference of 0.97 (95% CI: −0.44 to 2.39) per 100,000 doses of PCV13 vaccine (Table 3).

4. Discussion

In this study, conducted soon after the PCV13 vaccine was approved by the Food and Drug Administration and adopted in the US childhood immunization program, we found no signal of excess risk of febrile seizures, urticaria and angioneurotic edema, asthma, anaphylaxis, or thrombocytopenia compared with PCV7. The increased risk of encephalopathy was not confirmed after medical record review. The early signal of Kawasaki disease in the 28 days following vaccination was further evaluated by conducting an end-of-study analysis, using chart confirmed cases. Compared to PCV7, there was a non-significant 2-fold increased risk of Kawasaki disease following PCV13.

Table 3
Comparison of the risk of Kawasaki disease (KD) following vaccination with 13- and 7-valent pneumococcal conjugate vaccines (PCV13 and PCV7).

	No. of doses	No. of KD diagnoses (1–56 days)	Onset of KD in 0–28 days			Risk (per 100,000 doses) (95% confidence interval, CI)	Relative risk (95% CI)[c]	Risk difference (per 100,000 doses) (95% CI)[d]
			Confirmed complete KD	Confirmed incomplete KD	Possible KD			
PCV13	599,229	30	5	7	0	2.00 (1.03–3.50)	2.38 (0.92, 6.38)[a]	1.16 (−0.23, 2.55)[a]
PCV7	1,067,691	49	5	4	2	0.84 (0.39–1.60)[a] 1.03 (0.51–1.84)[b]	1.94 (0.79, 4.86)[b]	0.97 (−0.44, 2.39)[b]

[a] Based on confirmed complete and incomplete cases only.
[b] Based on confirmed complete and incomplete cases plus possible KD cases.
[c] Exact 95% confidence interval.
[d] Approximate 95% confidence interval with continuity correction.

The possibility of an association between Kawasaki disease and the conjugated pneumococcal vaccine was first evaluated in the post-licensure observational safety surveillance study conducted by Center et al. at Northern California Kaiser Permanente [15]. In that study, several pre-specified secondary safety outcomes in PCV7 vaccinees were compared with a historic control population of *Haemophilus influenzae* type b (Hib)-immunized infants. An increase in Kawasaki disease hospitalizations was noted among PCV7 recipients and a post hoc evaluation of all cases of Kawasaki disease in vaccinees and historic controls was undertaken. In the control group, there were 17 cases of Kawasaki disease, compared to 42 cases among PCV7 recipients at any time during the observation period (Unadjusted relative risk = 2.02, 95% CI = 1.16, 3.63). After controlling for sex, race, age at first dose, length of follow-up, and season, the relative risk of hospitalization for Kawasaki disease was not significantly different between cohorts (relative risk = 1.67; 95% CI = 0.93, 3.00). The authors concluded that there was no association between Kawasaki disease and PCV7.

In this study, we observed an approximately 2-fold increased risk of Kawasaki disease within 28 days following PCV13 vaccination, compared to that in the PCV7 group. Although both our study and Center et al's study failed to find a significant increased risk of Kawasaki following PCV13 or PCV7, there were two important distinctions between the two studies. First, Kawasaki cases were not adjudicated in their study [15]. Second, in our study, the risk period was pre-specified at 28 days while in their study it was not pre-specified and the follow-up period was not clearly described in their report [15].

No increased risk of febrile seizures was identified in any age group in this study. Another recent Vaccine Safety Datalink study by Tse et al. had found that trivalent inactivated influenza vaccine and PCV13 were each associated with an increased risk of febrile seizures independent of concomitant receipt of the other in children ages 6–59 months [21]. These authors used a self-controlled risk interval design in which they compared the risk of seizures in the 0–1 days versus 14–20 days following a trivalent inactivated influenza vaccine. Importantly, they found the risk differences were highest following receipt of TIV and PCV13 concomitantly. While both studies examined the association between PCV13 and febrile seizure, precautions need to be taken when comparing the results. First, the designs of the two studies were different: The current study was a surveillance activity using a sequential test method which ended when all planned tests were completed, while Tse et al.'s study was a confirmation study that employed a self-controlled risk interval design. Second, the comparison groups were different: The current study used a historical comparison group exposed to PCV7 while the other study used a different comparison window within the same person. Third, the age groups were different: The children were ages 1 month-2 years in this study while they were 6–59 months in Tse et al.'s study. Fourth, the current study used automated febrile seizure cases while Tse et al.'s study used chart confirmed cases. Finally, the risk window in the current study was 0–7 days while it was 0–1 day in the other study. One thing to note is if we used data accumulated over 90 weeks, we observed that the risk for febrile seizure for children 6–24 months of age receiving PCV13 and influenza vaccine concomitantly was 1.35 times (95% CI: 0.93–2.00) higher than the risk in their counterparts receiving PCV7 and influenza vaccine concomitantly. The risk of febrile seizure was comparable between PCV13 and PCV7 groups if the influenza vaccine was not administered concomitantly. More studies are needed to further examine this issue.

Some methodological issues in the current study are worth mentioning. First, covariates were not adjusted for in the analysis because individual level data were not available at each sequential test. There is no compelling reason to believe the distribution of potential risk factors for the outcomes to be significantly different between the PCV13 cohort and PCV7 cohort because PCV13 was recommended to replace PCV7 in the childhood vaccination program. Although uncontrolled bias resulting from confounding is possible, it is expected to be minimal. Second, although the detectable relative risk with 80% power for most conditions was designed to be as low as 2, for some rare conditions like urticaria and angioneurotic edema in younger age group, encephalopathy, and anaphylaxis, the detectable relative risk was set higher at 3 or 4. This was so that we could complete the sequential tests in a reasonable timeframe in order to provide timely safety information on the new vaccine to the public. If a smaller detectable relative risk were set for rare conditions, an extended period of monitoring would be required, which would compromise the purpose of conducting a surveillance study. Although the detectable relative risk was higher for rare conditions, no case of anaphylaxis was observed during the monitoring period and the encephalopathy signal could be detected at week 63 (although it was subsequently excluded on chart review). Third, diagnostic patterns and the prevalence of outcome may change over time. For example, the Kawasaki disease signal following PCV13 could have been due to better recognition/diagnosis over time, but we checked and found no significant change in the pattern of Kawasaki disease diagnosis across all VSD sites over the study period. Fourth, the adverse events under investigation were pre-specified and unexpected outcomes were not studied. Finally, misclassification of exposure and event status is possible because the study relied primarily on electronic medical record data. Medical records were reviewed only when there was statistically significant increased risk. Thus, false negative results might potentially be overlooked.

5. Conclusions

In conclusion, safety surveillance at VSD is not intended to provide conclusive evidence of causality. Rather, it is a method to quickly detect potential associations between a vaccine and an adverse event so that a thorough investigation can be planned [13]. In this study, we identified potential signals for encephalopathy and Kawasaki disease following PCV13 vaccination. Evaluation these signals through medical record review failed to confirm the PCV13 associated encephalopathy, however the association of Kawasaki disease and PCV13 may deserve further investigation. Based on 90 weeks of data including approximately 600,000 doses of PCV13 collected at the Vaccine Safety Datalink Project, we identified no significant increased risk of pre-specified adverse events associated PCV13 vaccine comparing to PCV7 vaccine.

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Disclaimer

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Conflict of interest

Hung Fu Tseng, Lina Sy, and Steven Jacobsen report support from Novartis Vaccine. Steven Jacobsen reports serving as an unpaid consultant for Merck. Allison Naleway reports support from GSK. Roger Baxter reports support from Merck, Novartis, Sanofi, GSK, and Pfizer. Others report no potential conflict of interest.

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