SENTINEL CBER FINAL REPORT

13-VALENT PNEUMOCOCCAL CONJUGATE VACCINATION AND KAWASAKI DISEASE DURING THE FIRST TWO YEARS OF LIFE

Prepared by: Meghan A. Baker[1], Bethany Baer[2], Martin Kulldorff[3], Lauren Zichittella[1], Rebecca Reindel[2], Sandra Feibelmann[1], Hana Lipowicz[1], Katherine Freitas[1], Robert Jin[1], W. Katherine Yih[1]

Author Affiliations: 1. Department of Population Medicine, Harvard Pilgrim Health Care Institute and Harvard Medical School, Boston, MA; 2. Center for Biologics Evaluation and Research, Food and Drug Administration, Silver Spring, MD; 3. Division of Pharmacoepidemiology and Pharmacoeconomics, Brigham and Women's Hospital, Boston, MA

October 24, 2018

The Sentinel System is sponsored by the U.S. Food and Drug Administration (FDA) to proactively monitor the safety of FDA-regulated medical products and complements other existing FDA safety surveillance capabilities. The Sentinel System is one piece of FDA's Sentinel Initiative, a long-term, multi-faceted effort to develop a national electronic system. Sentinel Collaborators include Data and Academic Partners that provide access to healthcare data and ongoing scientific, technical, methodological, and organizational expertise. The Sentinel Coordinating Center is funded by the FDA through the Department of Health and Human Services (HHS) Contract number HHSF223201400030I. This project was funded by the FDA through HHS Mini-Sentinel contract number HHSF223200910006I.

Sentinel CBER Final Report

13-Valent Pneumococcal Conjugate Vaccination and Kawasaki Disease During the First Two Years of Life

Table of Contents

I. INTRODUCTION

Although pre-licensure trials of both 7-valent pneumococcal polysaccharide-protein conjugate vaccine (PCV7 (Prevnar; Wyeth)) and 13-valent pneumococcal polysaccharide-protein conjugate vaccine (PCV13 (Prevnar13; Wyeth)) found no increased risk for serious adverse events,[1] post-licensure surveillance raised questions about a possible association between PCV13 and Kawasaki disease. Vaccine Safety Datalink (VSD) investigators monitored the safety of the PCV13 vaccine during the first 2 years of life with respect to 8 health outcomes of interest, including Kawasaki disease. A statistically significant result for Kawasaki disease after PCV13 was identified at the second of 12 group sequential tests. The investigators conducted an end-of-surveillance analysis restricted to chart-confirmed cases and found that the relative risk in the 0-28 days following vaccination with PCV13 compared with the same period after PCV7 was 2.38 (95% confidence interval (CI): 0.92, 6.38). Although this result was not statistically significant, the study authors noted that the possibility of an association between PCV13 and Kawasaki disease might deserve further investigation.[2] The Food and Drug Administration (FDA) completed a safety review of the first 18 months of licensure of PCV13 under the FDA Amendment Act of 2007 Section 915, which included an analysis of the VSD study results as well as an evaluation of the Vaccine Adverse Event Reporting System (VAERS) proportional reporting ratios (PRR) for Kawasaki disease. The review resulted in an FDA Postmarket Safety Evaluation Summary posting that stated that there had been reports of Kawasaki disease following administration of PCV13 and that the FDA intended to initiate a larger study of Kawasaki disease risk following PCV13 vaccination in the Post-licensure Rapid Immunization Safety Monitoring (PRISM) Program, a component of the FDA-sponsored CBER Sentinel Program.[3] The study protocol was developed in collaboration with the Centers for Disease Control and Prevention's (CDC's) Vaccine Safety Datalink (VSD) project. This report describes the now-completed PRISM study.

A. PCV13

Infection by *Streptococcus pneumoniae* is identified by the World Health Organization (WHO) as a major cause of pneumonia, bacteremia, and meningitis. Although over 90 pneumococcal serotypes have been identified, a small subset of serotypes account for the majority of disease.[4] Prior to licensure of the pneumococcal conjugate vaccine, young children were highly susceptible to pneumococcal disease, with an estimated 17,000 cases of invasive disease and 200 resulting deaths occurring annually in children ≤5 years of age in the United States. An additional 5 million cases per year of acute otitis media were believed to result from pneumococcal disease in children ≤5 years of age.[5]

In 2000, FDA licensed the first pneumococcal conjugate vaccine, PCV7, to protect young children against invasive disease caused by any of 7 strains of *Streptococcus pneumoniae*: 4, 6B, 9V, 14, 18C, 19F, and 23F. The routine vaccination schedule was 2, 4, 6, and 12-15 months of age.[6] Subsequently, inclusion of PCV7 in the recommended child immunization program resulted in decreased rates of invasive pneumococcal disease.[7] The CDC reported that rates of PCV7-type invasive pneumococcal disease in children under 5 years of age dropped from 80 cases per 100,000 to less than 1 case per 100,000 following the implementation of the PCV7 vaccine.[8] On February 24, 2010, FDA licensed a second vaccine, PCV13, to protect against 6 additional serotypes that accounted for much of the remaining invasive pneumococcal disease in young children.[9] Specifically, for children 6 weeks through 5 years of age, PCV13 is indicated for "active immunization for the prevention of invasive disease caused by *Streptococcus pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F" and "active immunization for the prevention of otitis media caused by *S. pneumoniae* serotypes 4, 6B, 9V, 14, 18C,

19F, and 23F."[10] The routine vaccination schedule for young children is the same as for PCV7: 2, 4, 6, and 12-15 months of age.[9] Full implementation of the transition from PCV7 to PCV13 came into effect in March 2010.[11] By July 2010, Pfizer reported that >90% of its private shipments of pneumococcal conjugate vaccines were for PCV13.[11] Children previously vaccinated with PCV7 finished their series with PCV13. A dose of PCV13 was recommended for children 14-59 months of age who had completed the 4-dose vaccination series with PCV7, and children with specified underlying medical conditions received a 5th dose until 71 months of age.[9]

B. KAWSAKI DISEASE

Kawasaki disease is an acute, self-limited vasculitis with a predilection for the coronary arteries and is the leading cause of acquired heart disease in children in the United States. The etiology of Kawasaki disease is unknown, although theories include an infectious cause or immunologic response triggered by an infectious agent.[12,13] No disease-specific laboratory test is available. Hence, the diagnosis of Kawasaki disease is based on a clinical case definition as described by the American Heart Association, which specifies that patients have fever lasting for ≥5 days (or fever until the date of administration of intravenous immunoglobulin) and at least 4 of the following 5 principal clinical features:[13,14]

1. Changes in the extremities (erythema of palms or soles; edema of hands or feet; and/or periungual desquamation in the subacute phase)
2. Polymorphous exanthem rash
3. Bilateral conjunctival injection without exudates
4. Changes in lips and oral cavity (inflamed lips or throat, strawberry tongue, or dry/cracking lips)
5. Cervical lymphadenopathy (at least 1 lymph node ≥ 1.5 cm in diameter)

If left untreated, approximately 25% of patients develop coronary artery aneurysms which may lead to additional cardiac complications including myocardial infarction, sudden death, or ischemic heart disease.[13-16] Intravenous immunoglobulin administration has been identified as a successful treatment in reducing coronary artery abnormalities in Kawasaki disease patients if promptly administered within 10 days of illness onset.[17]

Numerous factors have been shown to affect the incidence of Kawasaki disease in the United States. The illness presents most commonly in Americans of Asian and Pacific Island descent, with an incidence of 32.5/100,000 in children <5 years of age compared to 9.1/100,000 for non-Hispanic whites of the same age group.[13,18] In addition, Kawasaki disease is age-dependent, with 80% of cases occurring before 5 years of age and a peak incidence at 13-24 months of age.[19] Many studies have reported increased incidence of Kawasaki disease in males, with male to female ratios ranging from 1.5-1.7 : 1.[5,18,20-22] Seasonality is also believed to have some impact on incidence.[18]

II. METHODS

A. STUDY POPULATION AND DATA SOURCES

Six PRISM Data Partners contributed data to the study: Aetna, Inc.; Harvard Pilgrim Health Care; HealthCore (Anthem); Humana, Inc.; OptumInsight LifeSciences, Inc.; and Vanderbilt University School of Medicine, Department of Health Policy. The study population included infants and children from birth until 23.99 months of age who were members of any of the six Data Partners during 2010 to 2015 and who met one of two other enrollment criteria: 1) exposed to at least 1 dose of any PCV vaccine and continuously enrolled in the Data Partner from birth through at least 84 days after their first dose of any PCV vaccine or 2) unexposed to any PCV vaccine and continuously enrolled with the Data Partner from birth through at least 144 days of age (60 days, the time that many infants would receive dose 1, plus 84 days), with at least one documented health care visit between 14 and 150 days of age. Gaps of up to 45 days between birth and the start of enrollment were allowed.

To model Kawasaki disease risk by age for the age adjustment implemented in the primary analysis, we used the Kids' Inpatient Database for 2009, Healthcare Cost and Utilization Project (HCUP), Agency for Healthcare Research and Quality.[23]

B. EXPOSURE IDENTIFICATION

PCV13 was identified by codes for "PCV13" since January 1, 2010, including the Current Procedural Terminology (CPT) code 90670 and the National Drug Codes 00005197101, 00005197102, 00005197104, 00005197105. Unspecified PCV vaccine since September 1, 2010 was assumed to be PCV13 based on the date of approval for PCV13 and the fact that by July 2010, Pfizer reported that >90% of its private shipments of pneumococcal conjugate vaccines were for PCV13.[11] Unspecified PCV was identified by the CPT code 90669 and Healthcare Common Procedure Coding System codes G0009 and S0195.

C. OUTCOME IDENTIFICATION

Potential cases of Kawasaki disease were identified by the International Classification of Diseases 9th revision (ICD-9) code 446.1 and the International Classification of Diseases 10th revision (ICD-10) code M30.3 (acute febrile mucocutaneous lymph node syndrome) in the inpatient setting in any position (e.g., primary diagnosis, secondary diagnosis, etc.). We assumed that a confirmed or suspected case of Kawasaki disease would be admitted to a hospital to initiate treatment or undergo further clinical evaluation. Only the first code in 365 days in the inpatient setting for patients at least 365 days of age or the first ever code in the inpatient setting for those under 365 days of age were considered in order to exclude follow-up visits for Kawasaki disease.

D. MEDICAL RECORD REVIEW

Medical records of all potential Kawasaki disease cases (as identified by the above-described algorithm) occurring during the 70 days after PCV13 vaccination were requested. (The fact that Day 70 after vaccination (the maximum end of a control interval for the primary analysis) instead of Day 84 after vaccination was used as the limit was an inadvertent protocol violation. Because it is typical for some days to elapse between Kawasaki disease symptom onset and hospitalization, we had intended to capture and conduct chart review for potential cases through Day 84 in order to detect cases with symptom onset within 70 days of vaccination who were not hospitalized until Days 71-84.) In addition, records of potential cases without any known PCV vaccination were sought. Charts requested included the inpatient hospitalization record associated with the health care claim with Kawasaki disease

diagnosis code, as well as an outpatient follow-up visit for Kawasaki disease, including records of echocardiograms and angiograms.

Three board-certified pediatricians served as case adjudicators. First, 20 cases were double-adjudicated, using prespecified classification rules. The two independent reviews of each of the 20 cases were compared by the study team to discuss any discrepancies among reviewers and refine the classification rules. Once all discrepancies were resolved, the chart-review process continued with a single review of all remaining cases. The adjudicators were blinded to potential cases' vaccination history.

Diagnosis of Kawasaki disease was based on the American Heart Association diagnosis guidelines and the Centers for Disease Control and Prevention case definition.[13,24] Cases of confirmed Kawasaki disease were defined as those meeting one of the following criteria:

- ≥4 principal features and a fever (≥38.0˚C) persisting ≥5 days *or* until administration of IVIG if given before the 5th day of fever
- <4 principal features, fever (≥38.0˚C) of any duration, and coronary artery disease (aneurysm or dilation) detected by either echocardiography or coronary angiography.

Cases of possible Kawasaki disease were defined as those having evidence of 2 or 3 principal features and ≥ 5 days of fever. The possible Kawasaki disease category was of interest, as some principal clinical features are frequently absent in young infants,[13] and a large proportion of our study population was under 12 months of age. Inconclusive Kawasaki disease was defined as 1 principal feature and ≥ 5 days of fever.

For cases of Kawasaki disease without a prior PCV vaccination history in the administrative claims data, the immunization record was sought from the child's primary care provider for verification.

E. RISK INTERVALS

The primary risk interval (or risk "window") used in the analyses was Days 1-28 after any dose of PCV13, where Day 0 was the day of vaccination. This risk interval was also used in the VSD sequential analysis of PCV13[2] and is indirectly supported by evidence that, among siblings, more than one half of second Kawasaki disease cases in each family developed within 10 days of onset of symptoms in the first case, a finding consistent with a shared environmental trigger (or consecutive triggering infections with short incubation periods) and a relatively short latency period of days or weeks rather than months after exposure.[25] In a secondary analysis, we considered a post-vaccination risk interval of Days 1-42. The 42-day interval allowed us to address any concerns that, if PCV13 were associated with an increased risk of Kawasaki disease, the true period of increased risk might be longer than the first 28 days.

F. STATISTICAL ANALYSES

1. Overview

In the statistical analyses, we sought to examine and control for the confounding effect of age, as both PCV13 vaccination and the risk of Kawasaki disease are age-dependent. The analyses consisted of both age-adjusted and age-unadjusted self-controlled risk interval (SCRI) analyses using logistic regression, as well as age-adjusted cohort analyses using unconditional Poisson regression. One of the cohort analyses used a risk interval of Days 1-28, and the other used a risk interval of Days 1-42. These analyses are summarized in **Table 1** below and are discussed in greater detail in the subsections that follow.

Table 1. Statistical analysis methods used

1° vs. 2°	Design	Regression	Age adjustment	Risk interval
Primary	SCRI	Logistic	Offset term (from HCUP data)	Days 1-28
Secondary	SCRI	Logistic	None	Days 1-28
Secondary	Cohort	Unconditional Poisson	Internal, from study population	Days 1-28
Secondary	Cohort	Unconditional Poisson	Internal, from study population	Days 1-42

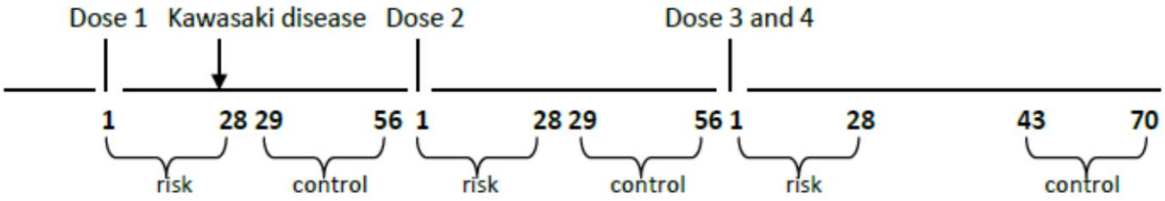
The pre-specified primary analysis was the SCRI analysis with confirmed Kawasaki disease cases and age adjustment based on external data. An originally planned secondary SCRI analysis where the age adjustment was to use data from the study population was not carried out, as the number and age distribution of the chart-confirmed cases proved insufficient to model Kawasaki disease by age.

No dose-specific analyses were conducted, i.e., all doses were pooled in analysis.

2. Self-Controlled Risk Interval Analyses

A major advantage of the SCRI design is that it inherently controls for all fixed (non-time-varying) potential confounders such as sex, race/ethnicity, and chronic predisposing conditions, by virtue of each subject serving as his/her own control. The null hypothesis with this design is that the risk of Kawasaki disease is the same on an average day in the risk interval as on an average day in the control interval. Adjustment for time-varying confounders such as age must be made explicitly. We used a risk interval of Days 1-28 post-vaccination and a 28-day-long comparison (control) interval following this risk interval. The originally specified comparison intervals were Days 29-56 for Doses 1 and 2 and Days 43-70 for Doses 3 and 4 (**Figure 1**). We considered the latter interval to be preferable due to uncertainty about the true period of vaccine-associated risk and the possibility that it might extend beyond 28 days after vaccination. However, the recommended ages of 2, 4, and 6 months for receipt of Doses 1, 2, and 3, respectively, made it necessary to fit the comparison interval for Doses 1 and 2 into a two-month period so as to avoid the control interval of one dose overlapping the risk interval of a subsequent dose. Confirmed and possible cases were assigned to risk or control intervals according to the timing of their adjudicated symptom onset.

Figure 1. Pre-specified risk and control intervals for SCRI design



Because the vaccinated potential cases selected for chart review included only those ascertained out to 70 days post-vaccination in the claims data, it was possible that some true cases with hospital admission dates beyond Day 70 but symptom onset within 70 days were missed. To address this, we conducted an additional set of analyses using Days 29-56 as the control interval for all four doses. We limited the cases analyzed in these post-hoc analyses to those for whom the Kawasaki disease hospital admission date minus the symptom onset date was less than or equal to 14 days, the difference between Day 70 and Day 56. The reason for this restriction was to avoid bias—without the restriction, all other things being equal, there would have tended to be more confirmed cases in the risk interval than in the control interval. This is because of the earlier timing of the risk interval relative to the control interval following the index PCV13 vaccination, which allows more follow-up time during which a potential case in the risk

interval could be ascertained (by means of their hospital admission date) compared to potential cases in the control interval.

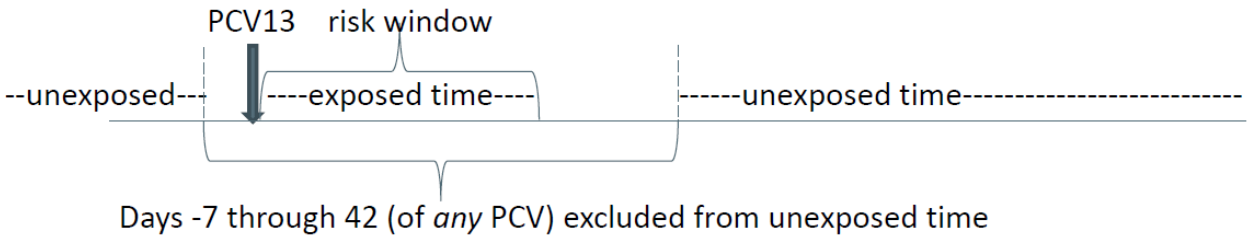
For the age-adjusted SCRI analyses, we first modeled the background risk of Kawasaki disease by age. To do this, we used Kawasaki disease counts from HCUP's Kids' Inpatient Database for 2009, which was the most recent year for which age by month was available. Using data for the range 2-35 months of age, we modeled Kawasaki disease occurrence by age, trying first-, second-, third-, fourth-, and fifth-order polynomial functions in successive Poisson models to determine the best-fitting function. The fourth-order function fit best according to the Akaike information criterion (AIC); and predicted values from this function were used to calculate offset terms for the cases in the logistic regression analysis in order to adjust for the differential risk of Kawasaki disease according to age in the risk and control intervals. These estimates were based on 1224 potential cases of Kawasaki disease identified based on claims in the HCUP dataset and were treated as known without error. Treating the background risk estimates as known without error has been shown to produce very similar results as when accounting for uncertainty in the estimates as long as the number of cases in the population used to estimate the background risk is greater than the number of cases in the SCRI analysis (Lingling Li, personal communication), as is the case in this study.

One set of SCRI analyses (a "set" included both age-adjusted and non-age-adjusted) used chart-confirmed cases of Kawasaki disease, while the other set included confirmed as well as possible cases per adjudicator determination.

3. Cohort Analysis

We used a cohort design with unconditional Poisson regression as a secondary analysis method, including cases and person-time from 2010 through a maximum of September 2015. Exposed person-time was defined as Days 1-28 or Days 1-42 after PCV13 vaccination, depending on the specific analysis (see **Table 1**, last two rows). Exposed cases were those occurring in the respective time period (Days 1-28 or 1-42). Unexposed time was defined as the time outside of the 7 days before through the 42 days after vaccination with either PCV13 or PCV7, including time from children not vaccinated with any PCV vaccine but with at least one documented healthcare visit. (We excluded the 7 days prior to vaccination in order to control for the healthy vaccinee effect and similar effects that could result from dependency of vaccination on one's health condition in the week prior.) Unexposed cases were those occurring in any unexposed time. **Figure 2** illustrates the categorization of exposed and unexposed person-time.

Figure 2. Illustration of segments of exposed and unexposed person-time for a PCV13-vaccinated child contributing person-time to the cohort analysis with the Days 1-28 risk interval. Person-time (and a Kawasaki disease case, if any) within the upward-pointing bracket is categorized as exposed, while person-time (and a Kawasaki disease case, if any) occurring outside of the downward-pointing bracket is categorized as unexposed. Person-time (and Kawasaki disease cases, if any) occurring during Days -7 through 0 and Days 29-42 of any PCV vaccination (in the downward-pointing bracket) was not included in the analysis.



We chose to use cohorts based on exposed and unexposed person-time in order to maximize the statistical power of the analyses and avoid the kind of confounding that often accompanies comparisons of vaccinated and unvaccinated children due to underlying differences in those two groups.

Data Partner, calendar year, sex, and age in weeks were included in the modeling. Age in weeks was modeled as a continuous variable; as with the HCUP data, we tried increasing orders of polynomial function (linear, quadratic, cubic, etc.) in successive models to determine the most appropriate, based on log-likelihood ratio, p-value, AIC, and biologic plausibility. The quartic (fourth-order) function was selected for the final model.

Due to the restrictions applied to potential cases for chart-review and the limited number of chart-confirmed cases available for modeling Kawasaki disease by age, we conducted the cohort analyses using potential cases based on the automated data only (i.e., not limited to chart-confirmed cases). There was no systematic difference in chart-confirmation ratio by age. However, given the overall case-confirmation ratio of 68% (reported in Results, **Section III.B**), this use of all potential cases as ascertained in the electronic data meant that there was some misclassification of the outcome. On conducting a chi-square test, we found no statistically significant difference in case-confirmation ratio by exposure status, suggesting that the misclassification was non-differential. The implications of this are discussed in the **Results** and **Discussion** sections.

4. Temporal Scan Analysis

To find any clustering of Kawasaki disease onsets within the 56 days after PCV13 vaccination, we used the temporal scan statistic, a self-controlled method that controls for multiple testing.[26,27] In order to avoid possible bias, as explained in the second paragraph of the SCRI analyses subsection above, we included only the confirmed cases with onsets during Days 1-56 post-vaccination for whom the difference between the hospital admission date and adjudicated symptom onset date was 14 days or less. All potential risk windows during the 56-day follow-up period that were between 1 and 28 days in length, inclusive, were evaluated.

III. RESULTS

A. VACCINE DOSES ADMINISTERED

A total of 6,177,795 doses of PCV13 vaccine were administered to the study population.

B. KAWASAKI DISEASE CASES

There were 206 potential cases of Kawasaki disease, all ascertained by the presence of the ICD-9 code 446.1, meeting the criteria for chart review. Medical records were obtained for 184 (89%) of these. Of the 184 cases for whom charts were obtained, 125 (68%) were determined by clinical adjudication to be confirmed Kawasaki disease, 29 (16%) were determined to be possible Kawasaki disease, 4 (2%) were considered inconclusive, 18 (10%) lacked the necessary information for adjudicators to make a determination, and 8 (4%) were ruled out (**Table 2**) as Kawasaki disease. The case confirmation proportion was thus 68% for Level 1 Kawasaki disease and 84% for Level 1 + Level 2.

Table 2. Disposition of potential cases meeting criteria for chart review

Category of case	Number	Proportion of the 184 cases for whom charts were obtained
Potential cases meeting criteria for chart review	206	
Potential cases whose charts were not obtainable	22	
Potential cases whose charts were obtained	184	
Level 1 (confirmed) Kawasaki disease	125	68%
Level 2 (possible) Kawasaki disease	29	16%
Level 3 (inconclusive) Kawasaki disease	4	2%
Potential cases whose charts contained insufficient information to make a determination	18	10%
Ruled out	8	4%

The distribution of confirmed cases by dose and risk vs. control interval are shown in the Appendix, **Table 4**.

C. SELF-CONTROLLED RISK INTERVAL ANALYSES

In the SCRI logistic regression analyses that used the pre-specified control windows, there were 43 confirmed cases in the risk window and 44 in the control window. No elevation in risk was observed in either the (primary) HCUP-age-adjusted analysis or the unadjusted analysis—the relative risks (RRs) were 1.07 (95% CI: 0.70, 1.63) and 0.98 (95% CI: 0.64, 1.49), respectively. Adding in the possible Kawasaki disease cases did not qualitatively change these findings—there were 53 confirmed or possible cases in the risk window and 53 in the control window, for a RR of 1.09 (95% CI: 0.75, 1.60) in the adjusted analysis and a RR of 1.00 (95% CI: 0.68, 1.46) in the unadjusted analysis (**Table 3**).

The post hoc SCRI logistic regression analyses that used Days 29-56 following vaccination as the control window for all doses and restricted cases for analysis to those where the difference between the hospital admission date and adjudicated symptom onset date was not greater than 14 days produced similar null results. There were 41 cases in the risk window and 50 in the control window, and the adjusted and unadjusted risk estimates for the confirmed cases were 0.89 (95% CI: 0.59, 1.34) and 0.81 (95% CI: 0.54, 1.24), respectively. When the possible cases were included with the confirmed cases,

there were 50 cases in the risk window and 61 in the control window, giving adjusted and unadjusted risk estimates of 0.89 (95% CI: 0.61, 1.29) and 0.82 (95% CI: 0.56, 1.19), respectively (**Table 3**).

Table 3. Results of SCRI analyses

Age-adjustment	Cases in RW	Cases in CW	KD*	RR (95% CI)
With Doses 1 & 2 CW = Days 29-56 and Doses 3 & 4 CW = Days 43-70:				
HCUP data	43	44	Level 1	1.07 (0.70, 1.63)
None	43	44	Level 1	0.98 (0.64, 1.49)
HCUP data	53	53	Level 1+2	1.09 (0.75, 1.60)
None	53	53	Level 1+2	1.00 (0.68, 1.46)
With all CWs = Days 29-56 and no cases where (KD admit – KD onset) > 14 days:				
HCUP data	41	50	Level 1	0.89 (0.59, 1.34)
None	41	50	Level 1	0.81 (0.54, 1.24)
HCUP data	50	61	Level 1+2	0.89 (0.61, 1.29)
None	50	61	Level 1+2	0.82 (0.56, 1.19)

* Level 1 = confirmed; Level 2 = possible

D. COHORT ANALYSES

The cohort for the analysis using the Days 1-28 risk window contained 80 potential Kawasaki disease cases (based on claims) in the risk window and approximately 474,000 exposed person-years (person-time in the risk window). The cohort for the analysis using the Days 1-42 risk window contained 145 potential cases in that risk window and approximately 711,000 exposed person-years. Both datasets had 598 potential cases in unexposed time and 2.7 million person-years of unexposed person-time, as unexposed time was defined the same way for both cohorts, namely as outside of Days -7 through 42 of PCV vaccination.

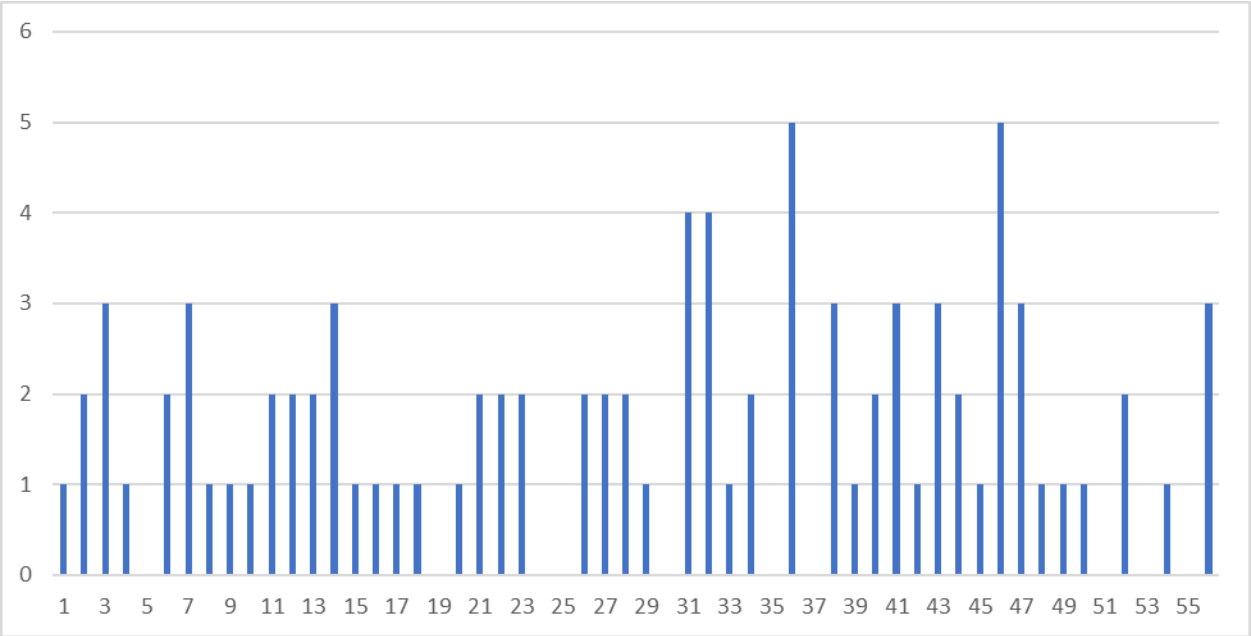
The risk estimates of potential Kawasaki disease in the risk window vs. in unexposed time were 0.84 (95% CI: 0.65, 1.08; p=0.18) for the Days 1-28 risk window and 0.97 (95% CI: 0.79, 1.19; p=0.80) for the Days 1-42 risk window.

The non-differential misclassification of the outcome entailed in not restricting the cohort analyses to chart-confirmed cases introduced noise, biasing the risk estimates toward the null. Given that the risk estimates were less than 1, unbiased estimates would have been somewhat lower than those observed.

E. TEMPORAL SCAN ANALYSIS

Figure 3 shows the temporal distribution of Kawasaki disease symptom onsets for the 91 confirmed cases during Days 1-56 post-PCV13 vaccination for which the difference between the hospital admission date and adjudicated symptom onset date was 14 days or less. The temporal scan statistical test found no statistically significant clustering of cases. The lowest p value of any grouping was 0.34.

Figure 3. Number of confirmed Kawasaki disease cases by day after PCV13 vaccination that adjudicated symptom onset occurred



IV. DISCUSSION

We found no evidence of an association between PCV13 vaccination and Kawasaki disease during the 1-28 days after vaccination in this large study, which included 87 confirmed cases in the primary SCRI analysis and approximately 700 potential cases and more than 3 million person-years in the secondary cohort analyses. These null results were robust to alternative methods of analysis and age-adjustment, alternative control intervals, and alternative levels of diagnostic certainty included (confirmed, confirmed and possible, and all cases conforming to the case-finding algorithm in the administrative claims data).

Our null results contrast with the elevated (albeit not statistically significant) point estimate of Kawasaki disease risk during Days 0-28 after PCV13 found by Vaccine Safety Datalink investigators (RR=2.38; 95% CI: 0.92, 6.38), who used historical rates of Kawasaki disease after PCV7 for comparison.[2] We consider our results to be more definitive because of (a) the primary, SCRI design's property of adjusting completely for potential confounders that do not vary over time, including race/ethnicity, and (b) the qualitatively similar results obtained in all our secondary analyses.

The possibility that any true period of increased risk might extend or be concentrated somewhat beyond 28 days post-vaccination was taken into consideration in several ways: (a) the primary SCRI analysis, which used a control interval of Days 43-70 for Doses 3 and 4, (b) a cohort analysis using a risk interval of Days 1-42, and (c) a temporal scan statistical analysis to detect clustering of onsets in any 1-to-28-day-long period during Days 1-56. No evidence for an increased risk after vaccination was found in any of these analyses.

The main limitation of the study was that we did not have the resources to conduct medical record review for all potential cases of Kawasaki disease during 2010-2015, of which there were 685, and thus had to restrict the potential cases undergoing chart review. This had two consequences: 1) We had too

few chart-confirmed cases to adequately model Kawasaki disease by age in the study population in one of the planned secondary analyses. However, our pre-specified primary analysis did not rely on the study population for age-adjustment but rather used external (HCUP) data for that purpose. For the analyses that did use the study population for age-adjustment (the two cohort analyses), we used the potential cases in the automated data instead of chart-confirmed cases in order to increase sample size. Although use of all the potential cases entailed non-differential misclassification of Kawasaki disease, biasing the risk estimates toward the null, unbiased risk estimates would not have indicated an association, given that the observed risk estimates were less than 1 (meaning unbiased estimates would have been even lower). 2) In applying criteria to limit the potential cases for chart review, potential cases with hospital admission during Days 71-84 after vaccination were unintentionally excluded. As a result, some true cases with symptom onset within 70 days of vaccination could have been missed. However, this would have led to a bias toward finding an increased risk in the (primary) SCRI analysis, where a Days 43-70 control interval was used for Doses 3 and 4. Yet no statistically significant elevated risk was found. In effect, the shorter follow-up period strengthens the null result. Moreover, the post hoc sensitivity analysis using a Days 29-56 control interval for all doses also produced null results.

Additional limitations: In the cohort (secondary) analyses, co-morbidities and other potential confounders other than Data Partner, calendar year, sex, and age were not adjusted for. Finally, all but the 20 pilot cases were adjudicated by a single adjudicator, and misclassification would have been more likely to occur in cases with a single adjudicator than with double adjudication. However, the 20 pilot cases were used to collectively resolve any discrepancies among adjudicators and refine the classification rules.

In summary, we found no evidence of an elevated risk of Kawasaki disease in the 4 weeks after PCV13 vaccination, nor any evidence of an elevated risk extending beyond 4 weeks. The consistency of the results across alternative designs, age-adjustment methods, control intervals, and levels of case confirmation included suggests that the null findings are highly robust.

V. ACKNOWLEDGEMENTS

Many thanks are due to the Data Partners who provided the data and medical records used in the analysis. These are Aetna, Blue Bell, PA (Annemarie Kline, Yihai Liu, Kevin Walsh, and Cheryl N. McMahill-Walraven); Harvard Pilgrim Health Care; HealthCore, Inc., Translational Research for Affordability and Quality, Alexandria, VA (Lauren Parlett, Jade Dinh, Amanda Marshall, Kevin Haynes, and Chunfu Liu); Humana, Inc., Comprehensive Health Insights, Miramar, FL (Vinit Nair, Yunping Zhou, and Mano Selvan); OptumInsight LifeSciences, Inc., Boston, MA (Nancy Lin, Judy Wong, Eva Ng, Ling Li, and Laura Karslake); Vanderbilt University School of Medicine, Department of Health Policy, Nashville, TN (Marie Griffin, Judy King, and J. Anthony Morrow); and the Division of TennCare of the Tennessee Department of Finance and Administration, which provided data to Vanderbilt. In addition, we would like to thank the physician adjudicators, James Antoon, Kecia Carroll, and Joseph Lazar; those aiding with chart review, Claudia Coronel-Moreno, Autumn Gertz, Tyler Jette, Margaret Johnson, and Ella Pestine; and those who contributed to the study in its early stages, David Cole, Grace Lee, and Megan Reidy.

VI. REFERENCES

1. Nuorti JP, Whitney CG. Prevention of pneumococcal disease among infants and children - use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine - recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recommendations and reports: Morbidity and mortality weekly report Recommendations and reports / Centers for Disease Control 2010;59:1-18.
2. Tseng HF, Sy LS, Liu IL, et al. Postlicensure surveillance for pre-specified adverse events following the 13-valent pneumococcal conjugate vaccine in children. Vaccine 2013;31:2578-83.
3. U.S. Food and Drug Administration, Postmarket Drug Safety Evaluation Summaries Completed from January 2012 through June 2012. https://wayback.archive-it.org/7993/20170111133823/http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/ucm355034.htm, accessed 2/27/2018.
4. World Health Organization (WHO), Pneumococcal disease. 2014. http://www.who.int/immunization/diseases/pneumococcal/en/, accessed 8/4/2015.
5. Han RK, Sinclair B, Newman A, et al. Recognition and management of Kawasaki disease. CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne 2000;162:807-12.
6. Wyeth. Prevnar (PCV7) package insert. https://www.fda.gov/downloads/biologicsbloodvaccines/vaccines/approvedproducts/ucm137038.pdf. Accessed May 11, 2018.
7. Invasive pneumococcal disease in children 5 years after conjugate vaccine introduction--eight states, 1998-2005. MMWR Morbidity and mortality weekly report 2008;57:144-8.
8. Centers for Disease Control and Prevention, Pneumococcal. 2014. http://www.cdc.gov/vaccines/pubs/surv-manual/chpt11-pneumo.html, accessed 3/28/2018.
9. Licensure of a 13-valent pneumococcal conjugate vaccine (PCV13) and recommendations for use among children - Advisory Committee on Immunization Practices (ACIP), 2010. MMWR Morbidity and mortality weekly report 2010;59:258-61.
10. Wyeth. Prevnar 13 (PCV13) package insert. https://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM201669.pdf. Accessed May 11, 2018.
11. Invasive pneumococcal disease and 13-valent pneumococcal conjugate vaccine (PCV13) coverage among children aged </=59 months---selected U.S. regions, 2010--2011. MMWR Morbidity and mortality weekly report 2011;60:1477-81.
12. Nakamura Y, Yashiro M, Uehara R, Oki I, Watanabe M, Yanagawa H. Monthly observation of the number of patients with Kawasaki disease and its incidence rates in Japan: chronological and geographical observation from nationwide surveys. Journal of epidemiology / Japan Epidemiological Association 2008;18:273-9.
13. Newburger JW, Takahashi M, Gerber MA, et al. Diagnosis, treatment, and long-term management of Kawasaki disease: a statement for health professionals from the Committee on Rheumatic Fever, Endocarditis and Kawasaki Disease, Council on Cardiovascular Disease in the Young, American Heart Association. Circulation 2004;110:2747-71.
14. McCrindle, BW, Rowley AH, Newburger JW, et al. Diagnosis, treatment, and long-term management of Kawasaki disease: a scientific statement for health professionals from the American Heart Association. *Circulation* 135.17 (2017): e927-e999.
15. Kato H, Sugimura T, Akagi T, et al. Long-term consequences of Kawasaki disease. A 10- to 21-year follow-up study of 594 patients. Circulation 1996;94:1379-85.

16. Dajani AS, Taubert KA, Gerber MA, et al. Diagnosis and therapy of Kawasaki disease in children. Circulation 1993;87:1776-80.
17. Furusho K, Kamiya T, Nakano H, et al. High-dose intravenous gammaglobulin for Kawasaki disease. Lancet. 1984; 2(8411):1055-8.
18. Holman RC, Belay ED, Curns AT, Schonberger LB, Steiner C. Kawasaki syndrome hospitalizations among children in the United States, 1988-1997. Pediatrics 2003;111:448.
19. Gedalia A. Kawasaki disease: an update. Current rheumatology reports 2002;4:25-9.
20. Hua W, Izurieta HS, Slade B, et al. Kawasaki disease after vaccination: reports to the vaccine adverse event reporting system 1990-2007. The Pediatric infectious disease journal 2009;28:943-7.
21. Luca NJ, Yeung RS. Epidemiology and management of Kawasaki disease. Drugs 2012;72:1029-38.
22. Mason WH, Takahashi M. Kawasaki syndrome. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 1999;28:169-85; quiz 86-7.
23. HCUP Kids' Inpatient Database (KID). Healthcare Cost and Utilization Project (HCUP). 2009. Agency for Healthcare Research and Quality, Rockville, MD. www.hcup-us.ahrq.gov/kidoverview.jsp, accessed 3/29/2018.
24. Centers for Disease Control and Prevention, Kawasaki Syndrome. http://www.cdc.gov/kawasaki/case-definition.html, accessed 5/13/2015.
25. Fujita Y, Nakamura Y, Sakata K, et al. Kawasaki disease in families. Pediatrics 1989;84:666-9.
26. Kulldorff M. A spatial scan statistic. Commun Stat Theory Methods 1997;26(6):1481–96.
27. Kulldorff M and Information Management Services Inc. SaTScanTM v9.3: Software for the spatial and space-time scan statistics. 2014. http://www.satscan.org, accessed 5/12/2015.

VII. APPENDIX

Table 4. Distribution of confirmed Kawasaki disease cases by PCV13 dose number and interval after vaccination of symptom onset

	No. in risk interval (Days 1-28)	No. in pre-specified control interval (Days 29-56 for Doses 1 & 2, Days 43-70 for Doses 3 & 4)	No. in post hoc control interval (Days 29-56 for all doses)
Including cases where (KD admit date - KD onset date) > 14 days:			
Dose 1	9	18	18
Dose 2	18	10	10
Dose 3	6	10	12
Dose 4	10	6	11
Total	**43**	**44**	**51**
Excluding cases where (KD admit date - KD onset date) > 14 days:			
Dose 1	9	17	17
Dose 2	16	10	10
Dose 3	6	10	12
Dose 4	10	6	11
Total	**41**	**43**	**50**