13-Valent Pneumococcal Conjugate Vaccine (PCV13) and Kawasaki Disease

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Disclaimer

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- No relationships to disclose
Background: Post-licensure reports of Kawasaki disease after PCV13

- Vaccine Adverse Event Reporting System (VAERS)
- Vaccine Safety Datalink (VSD): Signal emerged during PCV13 sequential analysis, then:
  - End-of-surveillance analysis using chart-confirmed cases
  - Kawasaki disease in Days 0-28 after PCV13 vs. after PCV7
  - Relative risk: \(2.38 (95\% \text{ CI}: 0.92, 6.38)\)*
- FDA’s 18-month review cited these VAERS and VSD results, proposed a larger study in PRISM/Sentinel

Methods

• Study population
  – Children aged 0-23.99 months in 6 PRISM data partners
  – Data from 2010-2015
• Identifying exposure and outcome
  – PCV identified via CPT, NDC, and HCPCS codes
  – Kawasaki disease identified via ICD-9 code 446.1 and ICD-10 code M30.3
    • Inpatient setting
    • First code in 365 days (to exclude follow-up visits)
• Case adjudication
  – Based on American Heart Association guidelines
  – Selection criteria:
    • KD admit date within 70 days after PCV13 dose, or
    • KD in children not receiving PCV vaccines
### Analyses conducted

<table>
<thead>
<tr>
<th>1° vs. 2°</th>
<th>Design</th>
<th>Regression</th>
<th>Age adjustment</th>
<th>Risk window</th>
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<tr>
<td>Primary</td>
<td>1. Self-controlled risk interval</td>
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<td>Days 1-42</td>
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3. **Temporal scan statistics** used in a 2° analysis: evaluated all potential risk windows 1 to 28 days in length during 56-day follow-up

No dose-specific analyses
Self-controlled risk interval design

Uses only vaccinated cases with the outcome in either risk or control interval
Pre-specified risk and control intervals for the PCV13 study
Self-controlled risk interval design

• Each subject serves as own control—this adjusts for *time-fixed* confounders (e.g., sex, ethnicity, SES)

• Any time-varying confounding requires adjustment

• Kawasaki disease risk varies by age*

• Age-adjustment used Healthcare Cost & Utilization Project Kids’ Inpatient Database (HCUP KID)

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3. Temporal scan statistics used in a 2° analysis:
evaluated all potential risk windows 1 to 28 days in length during 56-day follow-up

No dose-specific analyses
Cohort design

- Started with entire eligible population, identified exposed and unexposed person-time, then any KD events therein
Cohort design

• Definition of “exposed”—two alternatives:
  – Within Days 1-28 of PCV13
  – Within Days 1-42 of PCV13

• Definition of “unexposed”: 
  – Not within Days -7-42 of any PCV

PCV13 risk window

Days -7 through 42 (of any PCV) excluded from unexposed time
Modeling KD risk by age for cohort analyses

• To have enough cases to model KD risk by age, used all potential cases, not just chart-confirmed
  – No systematic difference in chart-confirmation ratio by age
  – Some bias toward null from using all potential cases
• Included data partner, calendar year, sex, and age
### Summary of Methods

<table>
<thead>
<tr>
<th>1. Self-controlled risk interval design</th>
<th>2. Cohort design</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk window</td>
<td>1°: Days 1-28</td>
</tr>
<tr>
<td></td>
<td>2°: Days 1-42</td>
</tr>
<tr>
<td>Control window</td>
<td>Person-time outside of Days -7 through +42 of any PCV</td>
</tr>
<tr>
<td>Doses 1&amp;2: Days 29-56</td>
<td>Person-time outside of Days -7 through +42 of any PCV</td>
</tr>
<tr>
<td>Doses 3&amp;4: Days 43-70</td>
<td>Person-time outside of Days -7 through +42 of any PCV</td>
</tr>
<tr>
<td>Age adjustment</td>
<td>Used internal data only</td>
</tr>
<tr>
<td>Used external data: HCUP KIDS data from 2009</td>
<td>Used internal data only</td>
</tr>
<tr>
<td>Case validation</td>
<td>Yes, 1° analysis used <strong>confirmed</strong> cases; a 2° analysis used <strong>possible</strong> cases also</td>
</tr>
</tbody>
</table>

3. Temporal scan statistics used in a 2° analysis: evaluated all potential risk windows 1 to 28 days in length during 56-day follow-up
Results

• Doses of PCV13 in study population: 6,177,795

• Kawasaki disease cases:

<table>
<thead>
<tr>
<th>Category</th>
<th>Number</th>
<th>% of total</th>
<th>% of obtained</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total ascertained</td>
<td>206</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Charts obtained</td>
<td>184</td>
<td>89%</td>
<td></td>
</tr>
<tr>
<td>Confirmed</td>
<td>125</td>
<td>68%</td>
<td>89%</td>
</tr>
<tr>
<td>Possible</td>
<td>29</td>
<td>16%</td>
<td>16%</td>
</tr>
<tr>
<td>Inconclusive</td>
<td>4</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>Insufficient information</td>
<td>18</td>
<td>10%</td>
<td>10%</td>
</tr>
<tr>
<td>Ruled out</td>
<td>8</td>
<td>4%</td>
<td>4%</td>
</tr>
</tbody>
</table>

• Case confirmation:
  – 68% for confirmed
  – 84% for confirmed + possible
## Analysis Results

### SCRI design *(with confirmed and possible cases)*:

<table>
<thead>
<tr>
<th>Age-adjustment</th>
<th>Cases in risk window</th>
<th>Cases in control window</th>
<th>Kawasaki disease level of diagnostic certainty</th>
<th>Relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCUP data</td>
<td>43</td>
<td>44</td>
<td>Level 1</td>
<td>1.07 (0.70, 1.63)</td>
</tr>
<tr>
<td>None</td>
<td>43</td>
<td>44</td>
<td>Level 1</td>
<td>0.98 (0.64, 1.49)</td>
</tr>
<tr>
<td>HCUP data</td>
<td>53</td>
<td>53</td>
<td>Level 1+2</td>
<td>1.09 (0.75, 1.60)</td>
</tr>
<tr>
<td>None</td>
<td>53</td>
<td>53</td>
<td>Level 1+2</td>
<td>1.00 (0.68, 1.46)</td>
</tr>
</tbody>
</table>

### Cohort design *(with all potential cases)*:

<table>
<thead>
<tr>
<th>Risk window</th>
<th>Cases in risk window</th>
<th>Cases in unexposed time</th>
<th>Exposed person-years</th>
<th>Unexposed person-years</th>
<th>Risk estimate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days 1-28</td>
<td>80</td>
<td>598</td>
<td>~474,000</td>
<td>2.7 million</td>
<td>0.84 (0.65, 1.08)</td>
</tr>
<tr>
<td>Days 1-42</td>
<td>145</td>
<td>598</td>
<td>~711,000</td>
<td>2.7 million</td>
<td>0.97 (0.79, 1.19)</td>
</tr>
</tbody>
</table>
Distribution of onsets of confirmed cases after PCV13 vaccination

- Temporal scan statistics:
  - No statistically significant clustering of cases
  - Lowest p-value of any grouping: 0.34
Conclusions

• No evidence of association found between PCV13 and Kawasaki onset during Days 1-28 after vaccination

• Strengths of the study:
  a) Large—6 million doses, 87 confirmed cases in primary SCRI analysis
  b) SCRI adjusts completely for time-fixed potential confounders, e.g., race/ethnicity
  c) Qualitatively similar results obtained in all secondary analyses (with alternative methods of analysis and age-adjustment, varying levels of diagnostic certainty)
Pneumococcal conjugate vaccines (PCV)

• 2/17/2000: FDA licensed 7-valent PCV (PCV7) (Prevnar; Wyeth)
  – Rates of invasive pneumococcal disease in children under 5 years of age (of serotypes targeted by vaccine) dropped sharply

• 2/24/2010: FDA licensed 13-valent PCV (PCV13) (Prevnar 13; Wyeth) to protect against 6 additional serotypes

• > 90% of Pfizer’s private shipments of PCV were PCV13 by 7/2010
# 2013 Recommended Immunizations for Children from Birth Through 6 Years Old

<table>
<thead>
<tr>
<th>Age Range</th>
<th>Immunizations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth</td>
<td>HepB</td>
</tr>
<tr>
<td>1 month</td>
<td>HepB</td>
</tr>
<tr>
<td>2 months</td>
<td>RV DTaP Hib</td>
</tr>
<tr>
<td>4 months</td>
<td>RV DTaP Hib</td>
</tr>
<tr>
<td>6 months</td>
<td>RV DTaP Hib</td>
</tr>
<tr>
<td>12 months</td>
<td>PCV IPV</td>
</tr>
<tr>
<td>15 months</td>
<td>IPV</td>
</tr>
<tr>
<td>18 months</td>
<td>IPV</td>
</tr>
<tr>
<td>19–23 months</td>
<td>DTaP DTaP</td>
</tr>
<tr>
<td>2–3 years</td>
<td>DTaP</td>
</tr>
<tr>
<td>4–6 years</td>
<td>DTaP</td>
</tr>
<tr>
<td></td>
<td>Influenza (Yearly)*</td>
</tr>
<tr>
<td></td>
<td>MMR</td>
</tr>
<tr>
<td></td>
<td>Varicella</td>
</tr>
<tr>
<td></td>
<td>HepA§</td>
</tr>
</tbody>
</table>

*Shaded boxes indicate the vaccine can be given during shown age range.

Kawasaki Disease (KD)

- Acute, self-limited febrile illness of unknown etiology that predominantly affects children < 5 years of age
- KD can result in inflammation, dilation and aneurysms of the medium-sized arteries, particularly the epicardial coronary arteries
- Timely initiation of treatment with intravenous immunoglobulin (IVIG) has reduced the incidence of coronary artery aneurysms from 25% to ≈4%
Clinical criteria of Kawasaki disease

• ≥ 5 days fever
• 4 of the following:
  – Bilateral conjunctival injection
  – Oral mucosal changes
  – Peripheral extremity changes
  – Rash
  – Cervical lymphadenopathy
Epidemiology

- The estimated incidence in North America is ≈25 cases per 100,000 children <5 years of age per year
  - The highest relative risk is in Asian children, especially of Japanese ancestry
  - The ratio of males to females is ≈1.5:1
- Coronary artery aneurysms from KD account for 5% of acute coronary syndromes in adults <40 years of age
- KD is the leading cause of acquired heart disease in children in developed countries


Data for age adjustment

- Healthcare Cost and Utilization Project Kids’ Inpatient Database (HCUP KID) was pre-specified as source of KD background rates
- Used most up-to-date HCUP KID data containing month-of-age, 2009
- Modeled KD by age using polynomial functions (in successive models)
- Ultimately chose 4th-order polynomial function to obtain offset terms for age adjustment
KID 2009 Kawasaki rate for 2-35 months of age
Model 4: Kawasaki_count = Agemonth + Agemonth^2 + Agemonth^3 + Agemonth^4

- Observed rate
- Predicted rate
Using offset terms to adjust for age in SCRI

- Each KD case in the SCRI analysis (i.e., occurring in a risk or control window (RW or CW)) gets an offset term.
- Offset term corresponds to:
  - age at index PCV13 vaccination, and
  - dose number (because determines control window)
    (CW for Dose 1 or 2: Days 29-56; CW for Dose 3 or 4: Days 43-70)
- Whether case in RW or CW has no bearing on offset term.
- Offset term =
  $$\ln \left( \frac{\text{estimated cumulative baseline risk in RW}}{\text{estimated cumulative baseline risk in CW}} \right)$$
Addressing possibility of risk window > 28 days

- **SCRI** pre-specified control windows meant to address this (Doses 1&2: Days 29-56; Doses 3&4: Days 43-70)
  - Results null

- **Cohort** with Days 1-42 risk window
  - Results null

- **Temporal scan**, Days 1-56
  - Results presented earlier