



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% 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

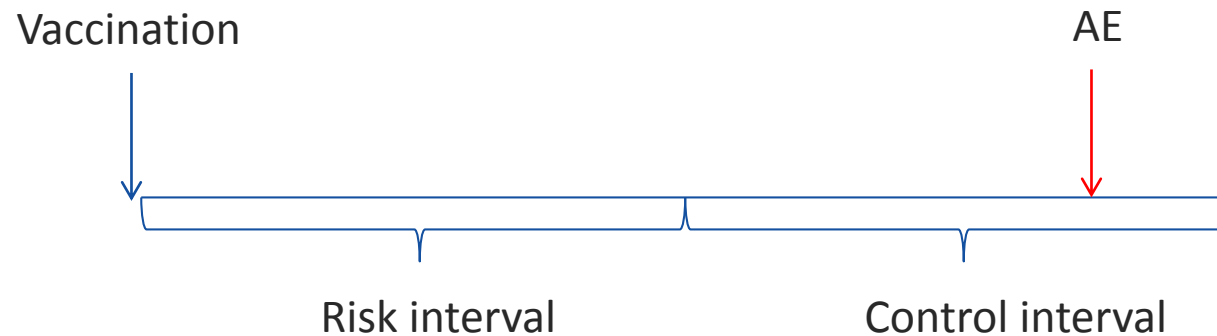
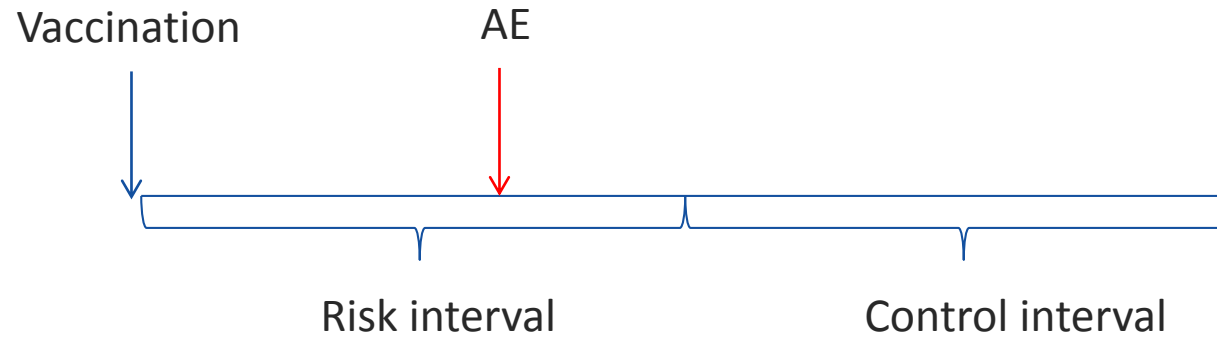
1° vs. 2°	Design	Regression	Age adjustment	Risk window
Primary	1. Self-controlled risk interval	Logistic	Offset term (from HCUP KID data)	Days 1-28
Secondary	"	"	None	"
Secondary	2. Cohort	Unconditional Poisson	Internal, from study population	Days 1-28
Secondary	"	"	"	Days 1-42

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

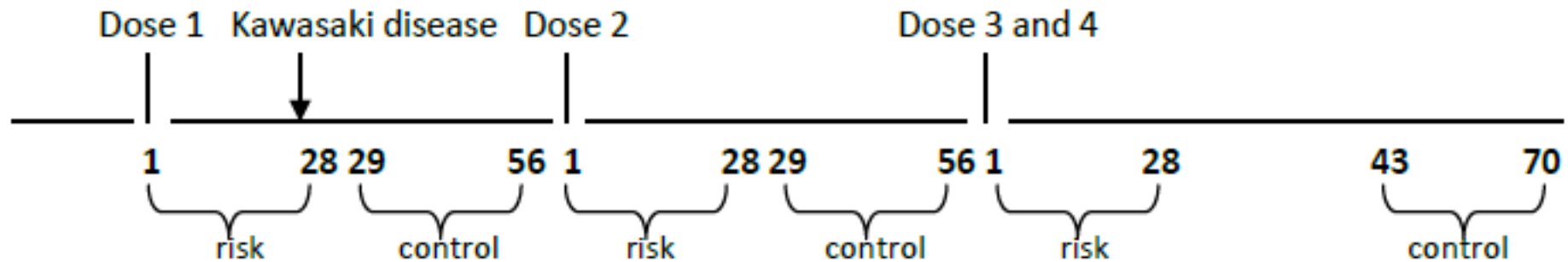
No dose-specific analyses

Self-controlled risk interval design

Uses only vaccinated cases with the outcome in either risk or control interval

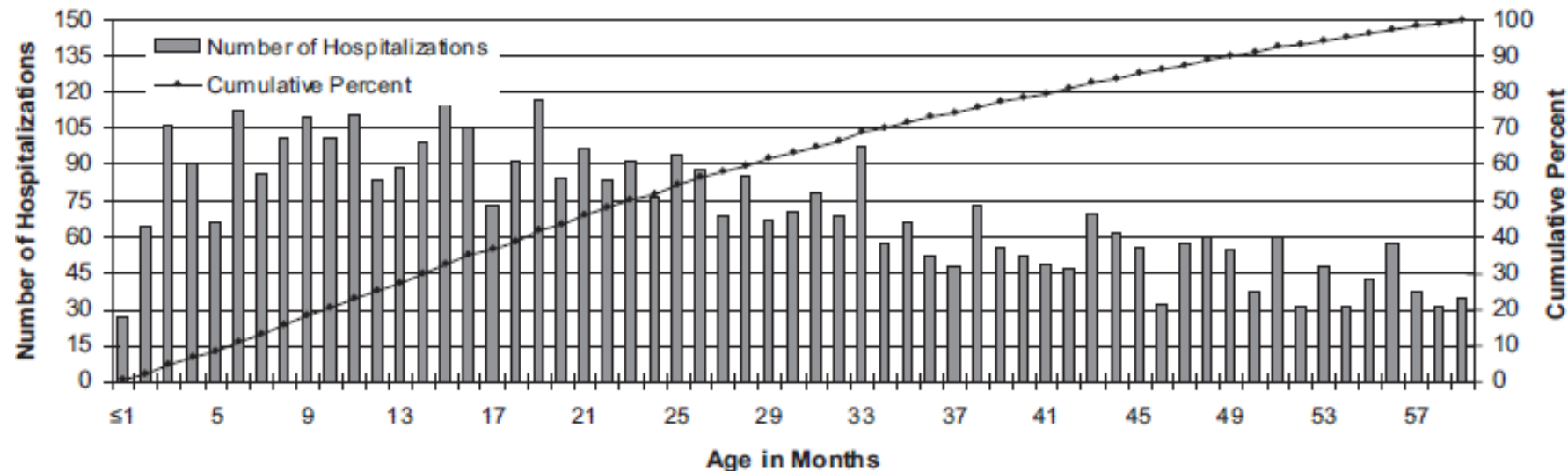


Pre-specified risk and control intervals for the PCV13 study



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)

Analyses conducted

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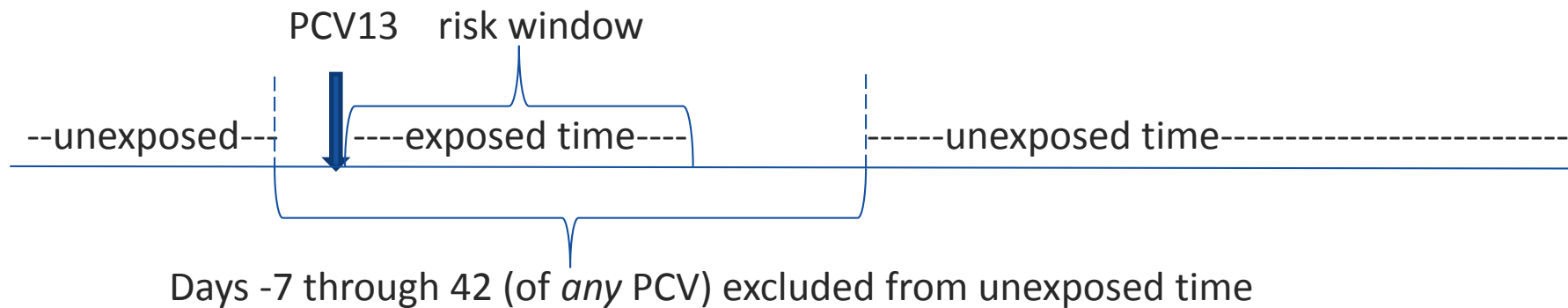
No dose-specific analyses

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



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

	1. Self-controlled risk interval design	2. Cohort design
Risk window	Days 1-28	1°: Days 1-28 2°: Days 1-42
Control window	Doses 1&2: Days 29-56 Doses 3&4: Days 43-70	Person-time outside of Days -7 through +42 of any PCV
Age adjustment	Used external data: HCUP KIDS data from 2009	Used internal data only
Case validation	Yes, 1° analysis used confirmed cases; a 2° analysis used possible cases also	No, used potential cases

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:

Category	Number	% of total	% of obtained
Total ascertained	206		
Charts obtained	184	89%	
Confirmed	125		68%
Possible	29		16%
Inconclusive	4		2%
Insufficient information	18		10%
Ruled out	8		4%

- Case confirmation:
 - 68% for confirmed
 - 84% for confirmed + possible

Analysis Results

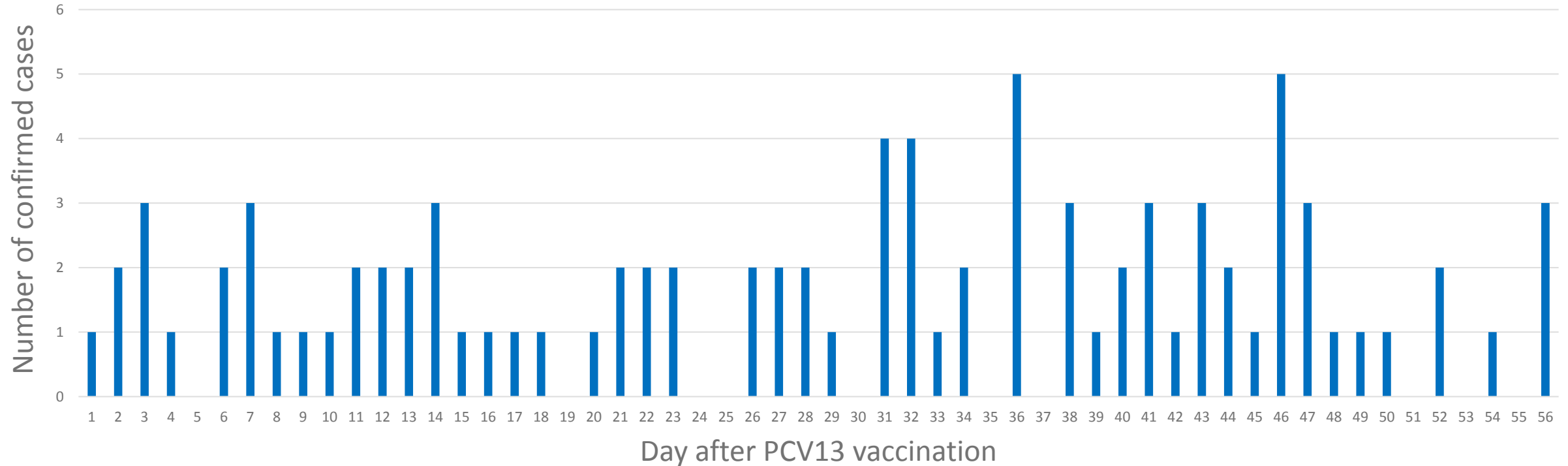
SCRI design (*with confirmed and possible cases*):

Age-adjustment	Cases in risk window	Cases in control window	Kawasaki disease level of diagnostic certainty	Relative risk (95% CI)
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)

Cohort design (*with all potential cases*):

Risk window	Cases in risk window	Cases in unexposed time	Exposed person-years	Unexposed person-years	Risk estimate (95% CI)
Days 1-28	80	598	~474,000	2.7 million	0.84 (0.65, 1.08)
Days 1-42	145	598	~711,000	2.7 million	0.97 (0.79, 1.19)

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

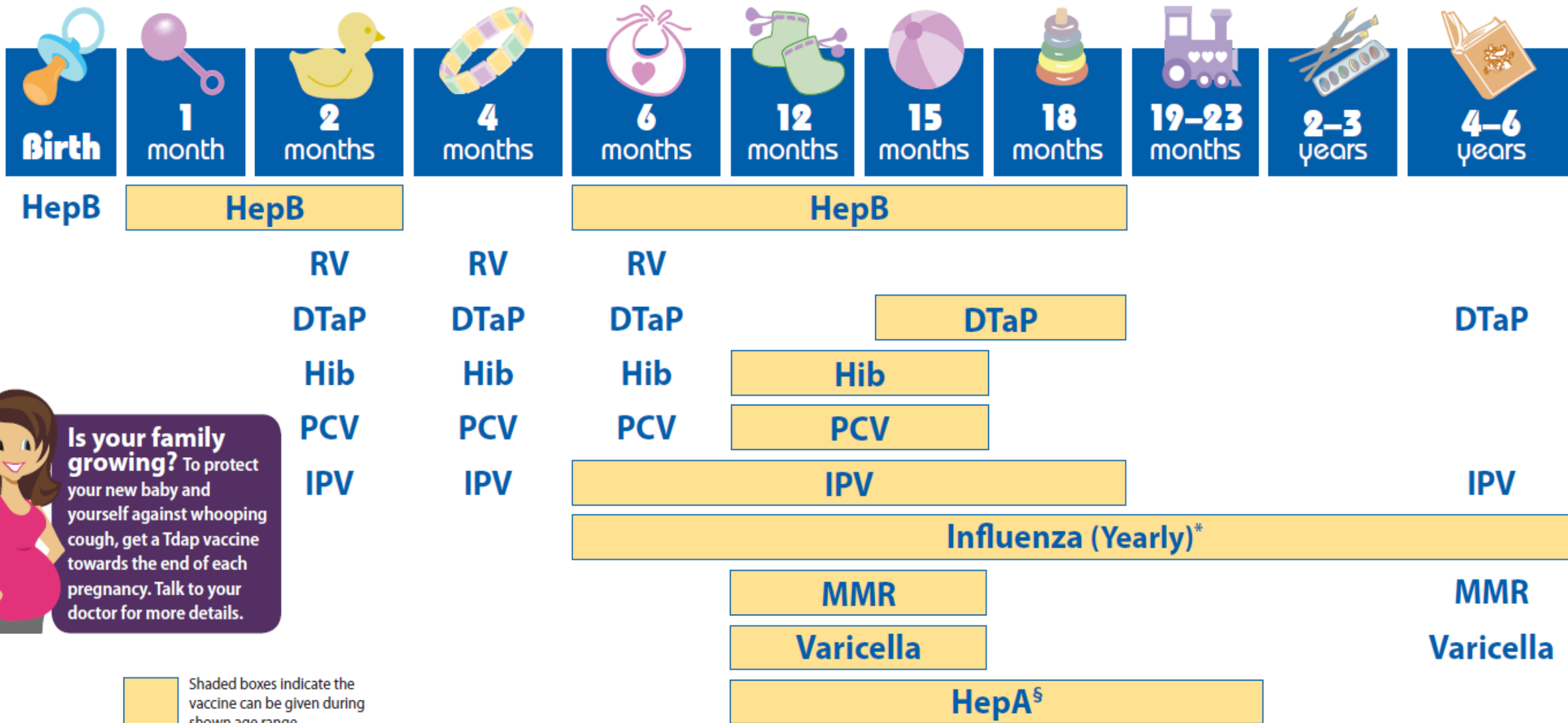
- No evidence of association found between PCV13 and Kawasaki onset during Days 1-28 after vaccination
- Strengths of the study:
 - a) Large—6 million doses, 87 confirmed cases in primary SCRI analysis
 - b) SCRI adjusts completely for time-fixed potential confounders, e.g., race/ethnicity
 - c) Qualitatively similar results obtained in all secondary analyses (with alternative methods of analysis and age-adjustment, varying levels of diagnostic certainty)

Extras

Pneumococcal conjugate vaccines (PCV)

- 2/17/2000: FDA licensed 7-valent PCV (PCV7) (Pneumovax; 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) (Pneumovax 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



Is your family growing? To protect your new baby and yourself against whooping cough, get a Tdap vaccine towards the end of each pregnancy. Talk to your doctor for more details.

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

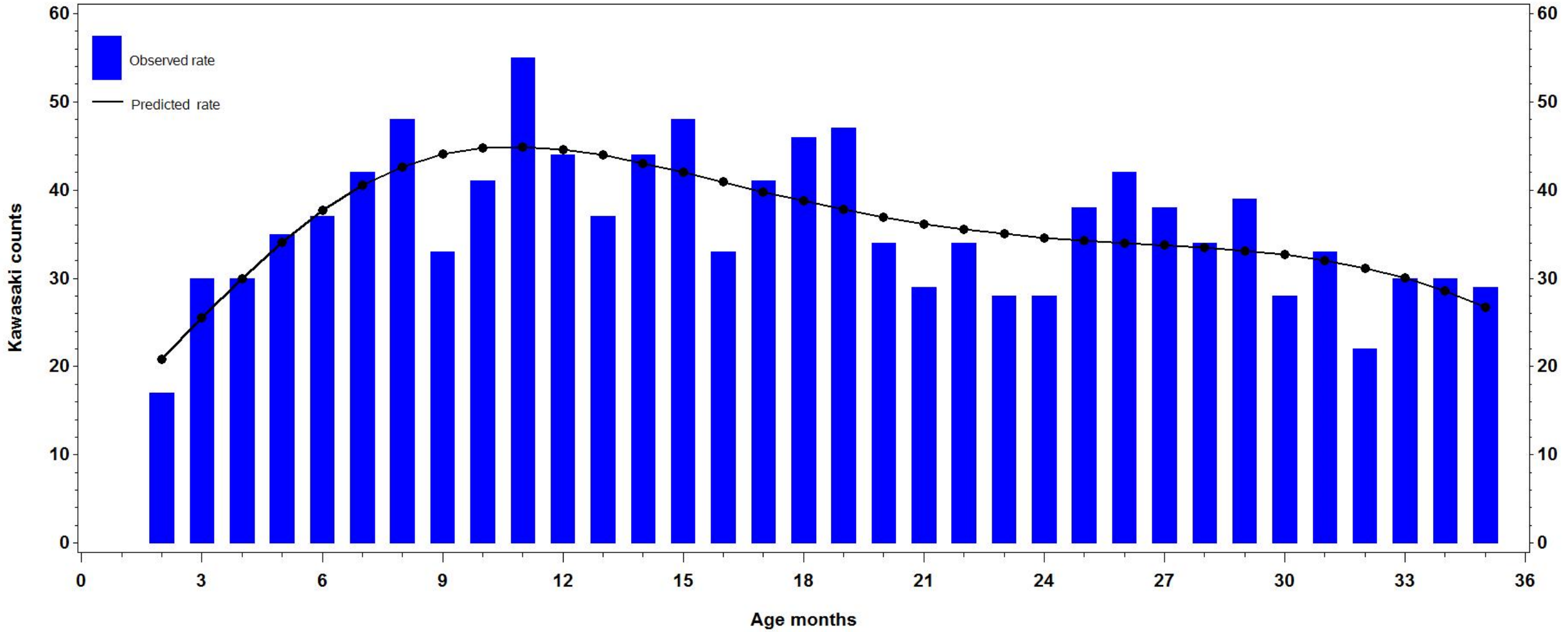
Epidemiology

- 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 $\approx 1.5:1$
- 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: $\text{Kawasaki_count} = \text{Agemonth} \text{Agemonth}^2 \text{Agemonth}^3 \text{Agemonth}^4$



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