Using the Self-Controlled Risk Interval (SCRI) Method to Study Vaccine Safety

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Epidemiology of Vaccine Safety

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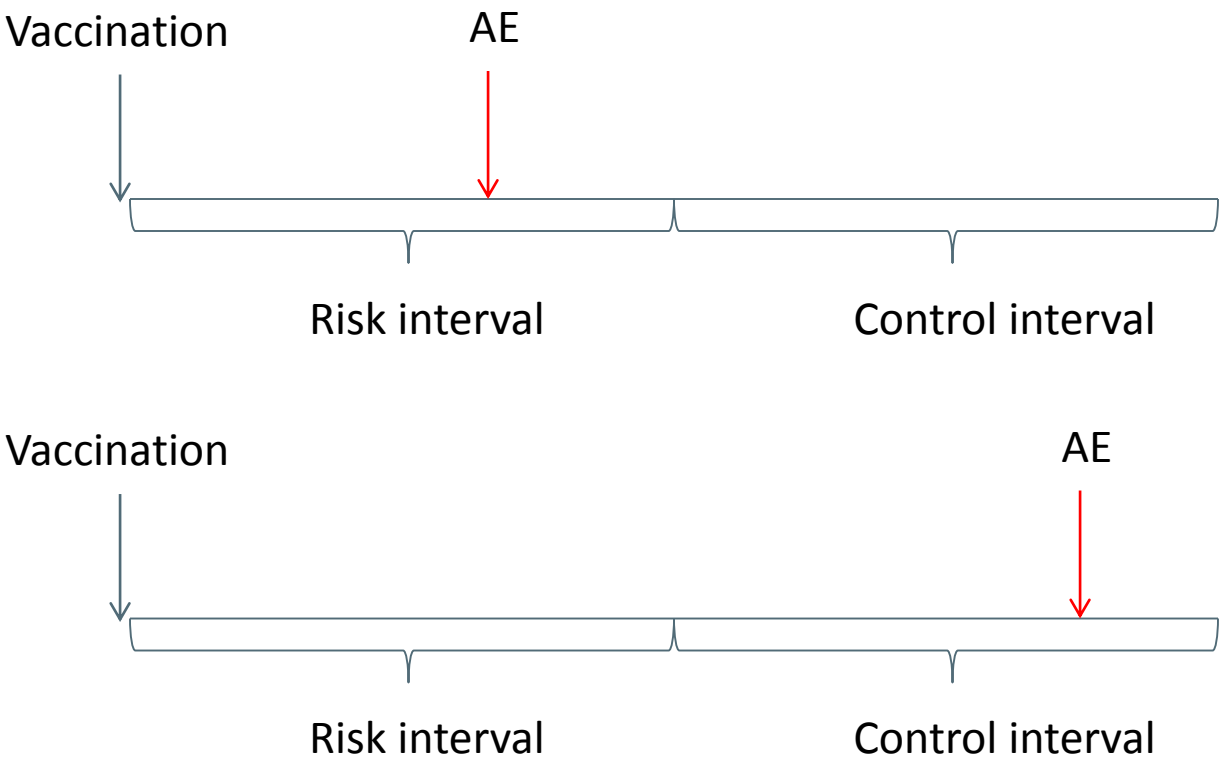
- Funding source: Food and Drug Administration

- I have no conflicts of interest

Self-controlled risk interval design

- Each individual contributes person-time in pre-specified risk and control intervals ("windows")



Self-controlled risk interval design

- Uses only vaccinated cases with the HOI in either pre-specified risk or control interval
- Each subject serves as own control—this adjusts for fixed confounders (e.g., sex, ethnicity, SES)
- Lengths of risk and control intervals are fixed but needn't be equal
- H_0: risk of outcome on average day in RW = risk of outcome on average day in CW

Self-controlled risk interval design

- Unadjusted RR point estimate is just as you'd expect
- Example 1:
  - Risk interval: Days 1-28
  - Control interval: Days 29-56
  - **13** events in risk interval, **9** in control interval
  - Unadjusted RR = 13/9 = 1.4
- Example 2:
  - Risk interval: Days 1-7
  - Control interval: Days 22-42
  - **13** events in risk interval, **9** in control interval
  - Unadjusted RR = (13*3)/9 = 4.3

Self-controlled risk interval design

- Advantages
  - Controls for fixed potential confounders
  - Uses only exposed cases, avoids bias affecting cohort studies when some exposed misclassified as unexposed
- Disadvantages
  - Less statistical power than cohort designs that use large amount of historical or concurrent data on unexposed
  - Any time-varying confounding must be explicitly controlled for

Two case studies

- Rotavirus vaccines (RV) and intussusception (IS)
- Quadrivalent HPV vaccine (Gardasil or “HPV4”) and venous thromboembolism (VTE)

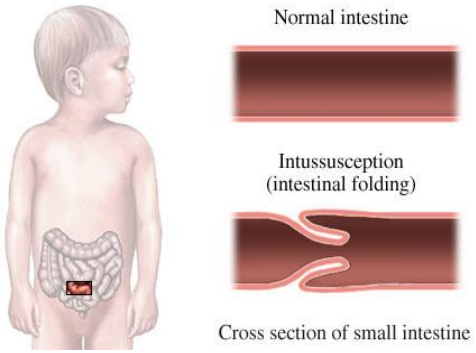
Data/surveillance system

- FDA-sponsored Sentinel Initiative (PRISM)
- Medical claims data from large health insurance companies
- 43 million people currently accruing new data (as of Jan. 2017)

Rotavirus vaccines & intussusception:

Motivation

- RotaShield licensed in 1998 but withdrawn in 1999 due to risk of intussusception (1-2 excess cases/10,000)
- For RotaTeq (2006) and Rotarix (2008), no increased risk observed in clinical trials of >60,000 children each, but post-licensure studies in other countries suggested increased risk after both
- FDA requested PRISM study to determine risk among U.S. infants



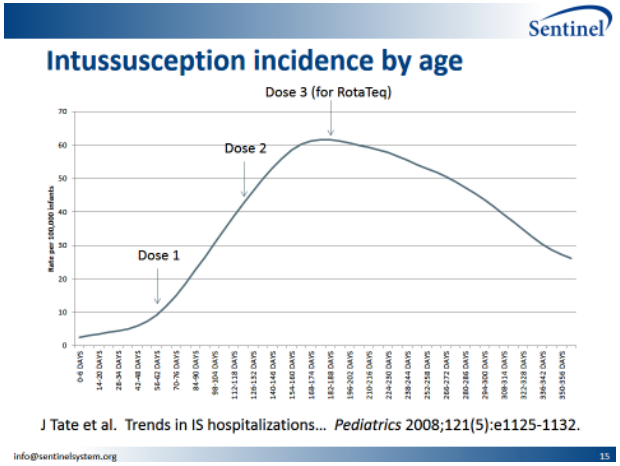
Rotavirus vaccines & intussusception:

Design

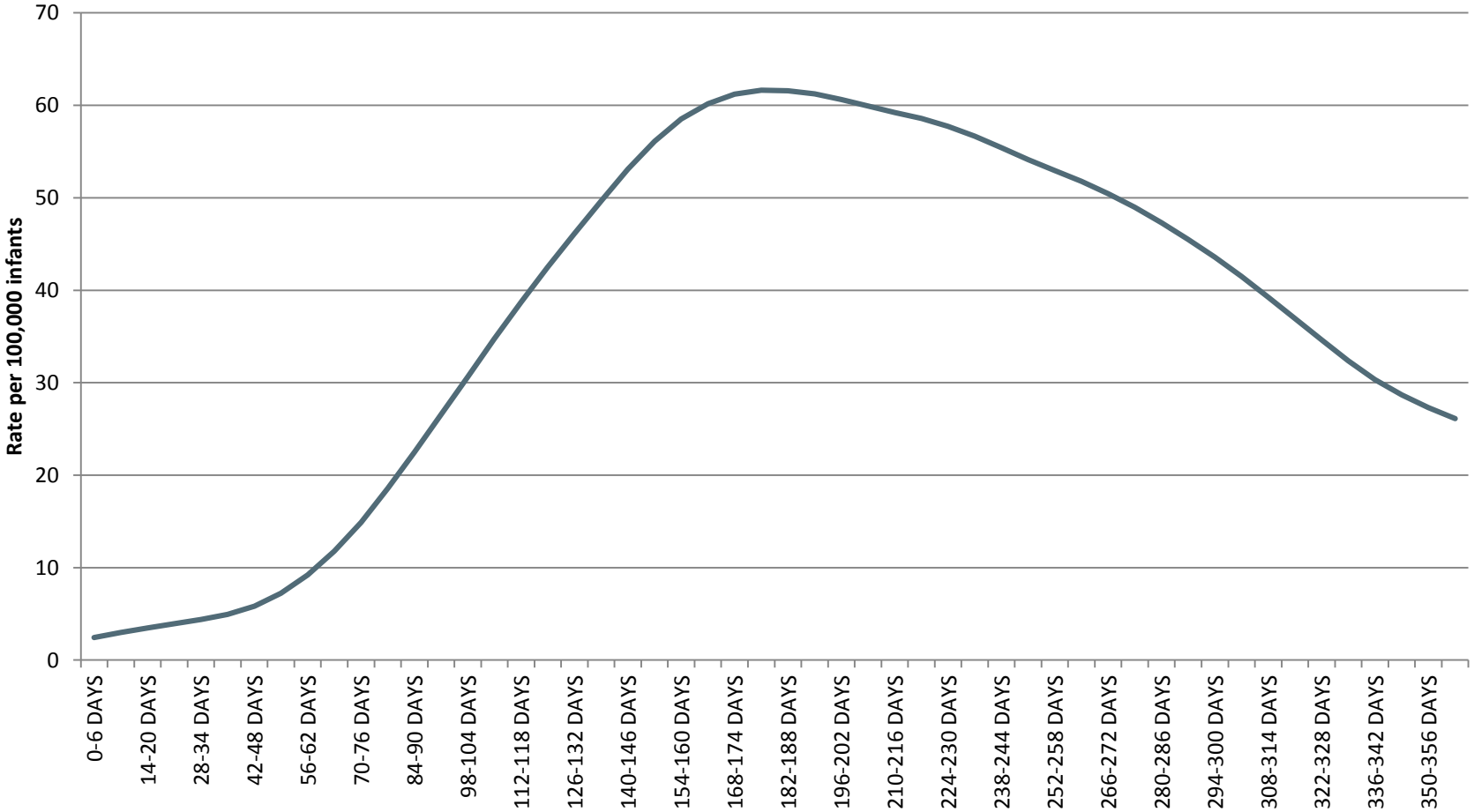
- Self-controlled risk interval (SCRI) (vaccinated infants only)—controls for fixed risk factors

  Risk intervals: Days 1-7 and 1-21

- Temporal scan statistics to look for clustering
- Confounding by **age**
- Explicitly controlled for age

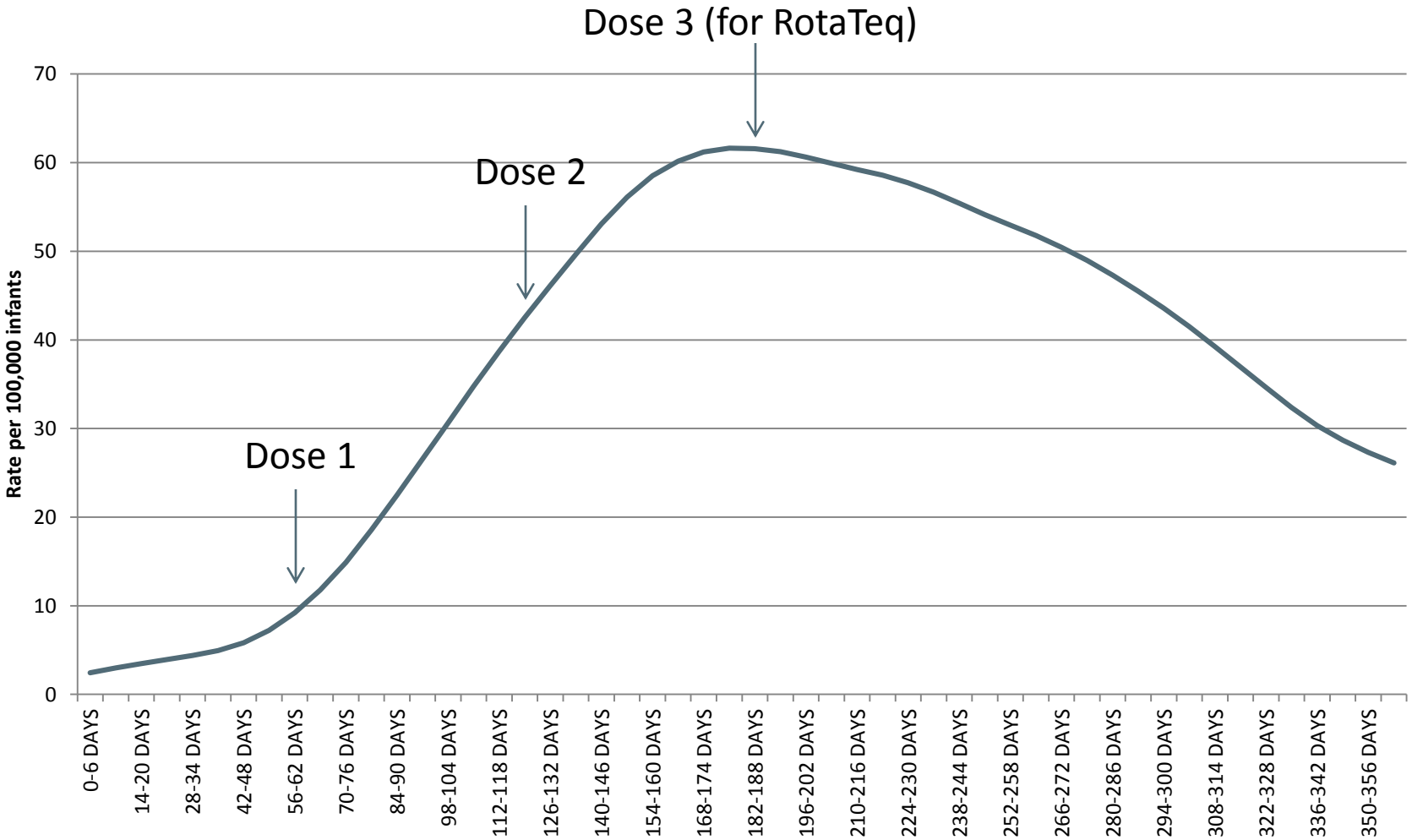


Intussusception incidence by age (from 11 years of U.S. HCUP data when rotavirus vaccine not used)



J Tate et al. Trends in IS hospitalizations… *Pediatrics* 2008;121(5):e1125-1132.

Intussusception incidence by age



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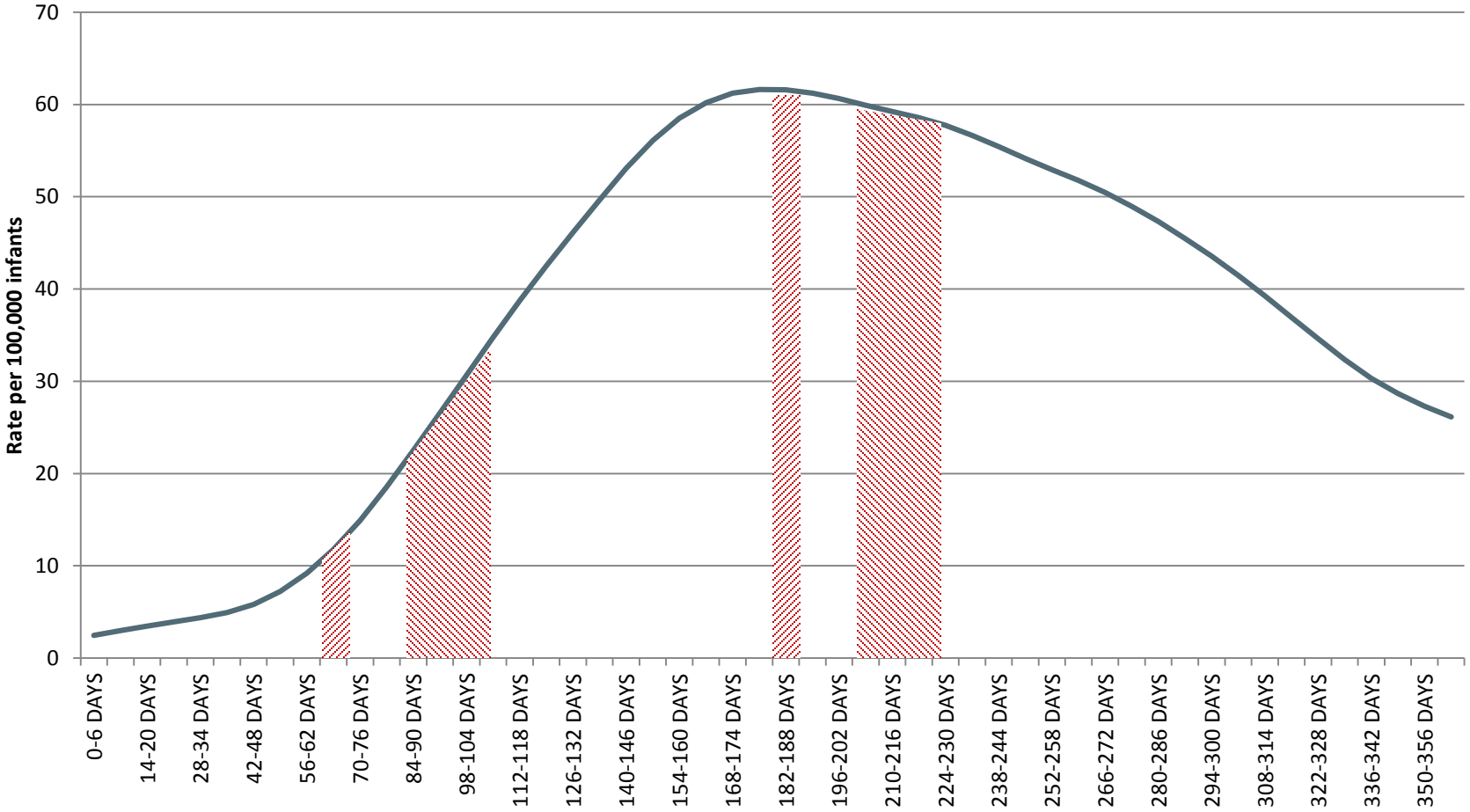
Adjustment for time-varying confounding

- Incorporate offset term into the logistic regression
- Offset adjusts for difference in background risk in RW and CW
- Each case has an offset term whose value depends on case's age at vaccination
- Offset = natural log (ln) of

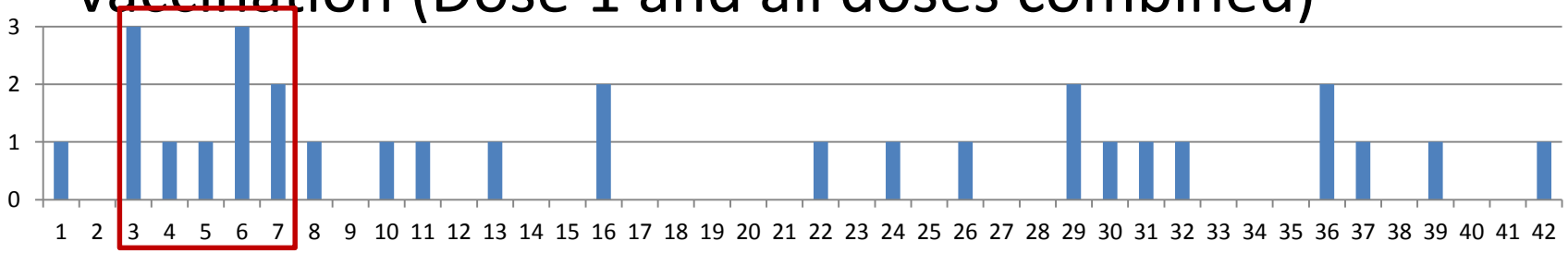
$$\frac{\text{Estimated cumulative baseline risk in RW}}{\text{Estimated cumulative baseline risk in CW}}$$

Background risk of intussusception in risk and control intervals for typically timed Doses 1 & 3



Rotavirus vaccines & intussusception:
RotaTeq results

- 507,874 Dose 1; 1,277,556 total doses
- Dose 1 associated with increased risk of intussus-ception in the 1-7 and 1-21 days after vaccination
- Statistically significant cluster found on Days 3-7 after vaccination (Dose 1 and all doses combined)



- All attributable risk point estimates in range of 1.1-1.5 excess cases per 100,000 first doses (≈1/10 of risk associated with RotaShield)

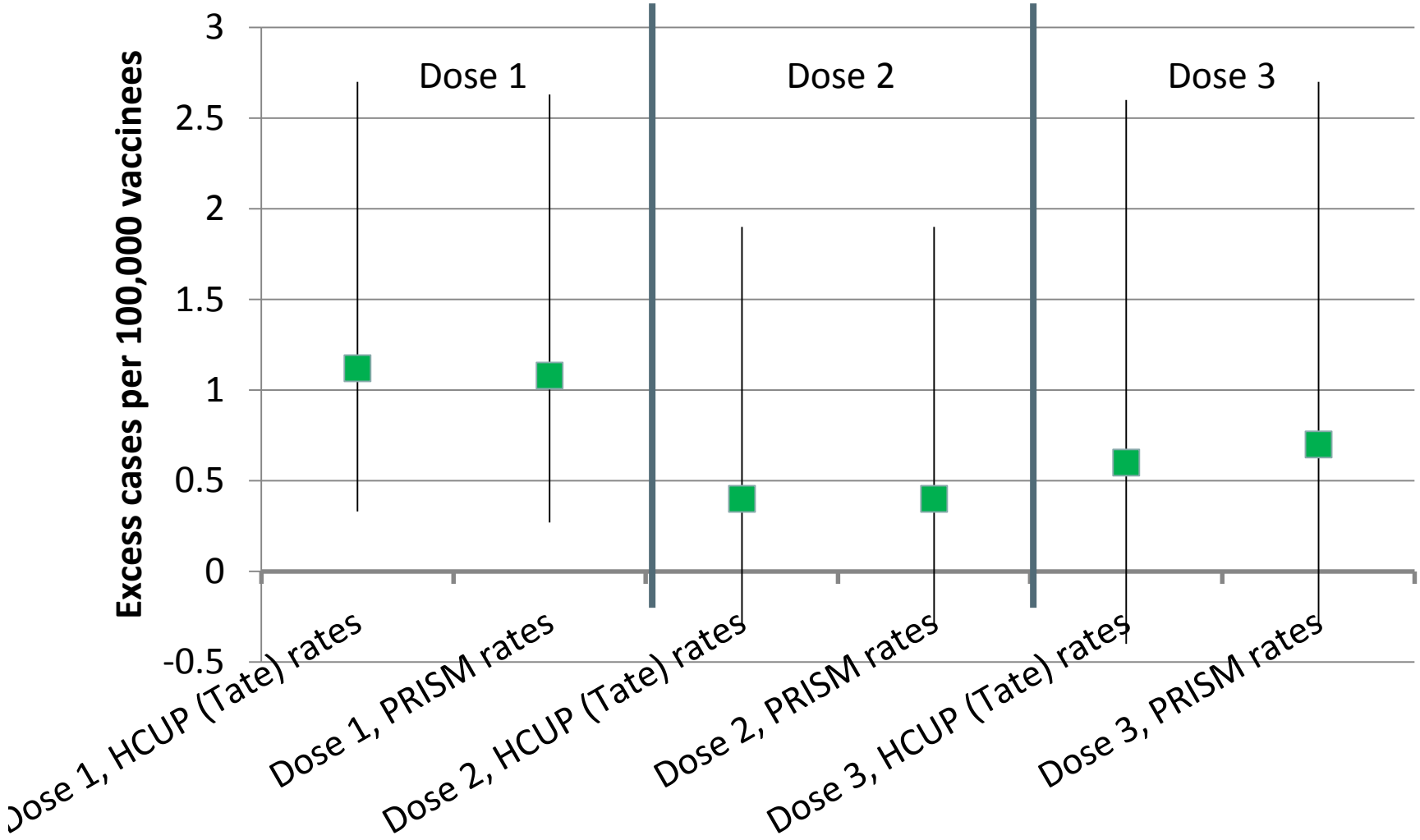
Critiques of our RV-IS age adjustment

1. HCUP **population different** from PRISM population, based on hospital discharge data, etc.
   - So HCUP age-specific incidence estimates could differ from true age-specific incidence in PRISM population

Response:

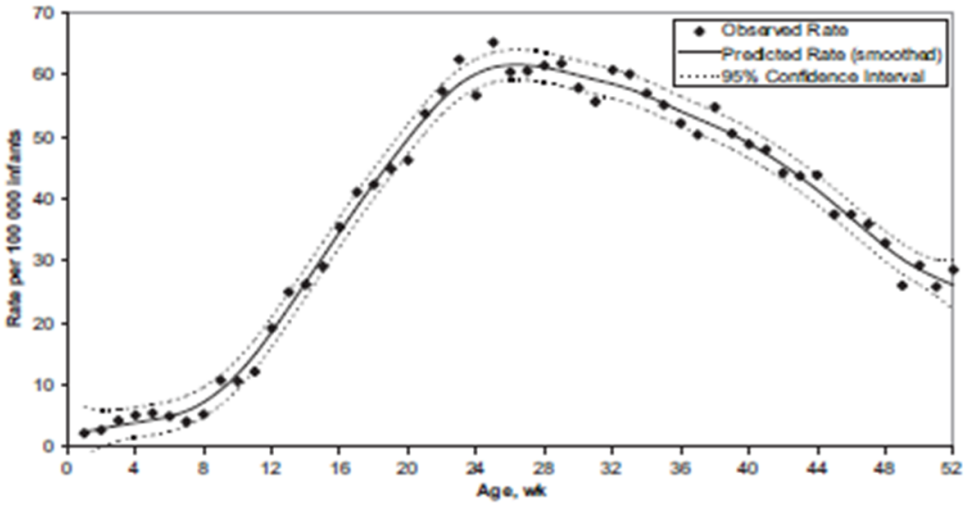
- HCUP estimates based on 3,463 cases, stable
- As long as curve correct in *relative* sense (x times higher or lower than HCUP curve), offset terms correct
- Conducted post hoc robustness analysis using modeled risk of intussusception in unexposed person-time of study population (with 97 confirmed cases)

RotaTeq attributable risks for Days 1-7 RW, by dose and age adjustment method



Critiques of our RV-IS age adjustment

2. **Uncertainty** in estimating age-specific background incidence **not taken into account**, rather incidence treated as known without error
   - Variance of rotavirus-intussusception RRs and ARs underestimated, confidence intervals too narrow



PEDIATRICS Volume 121, Number 5, May 2008 **e1129**

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Response (after rotavirus-intussusception study over):

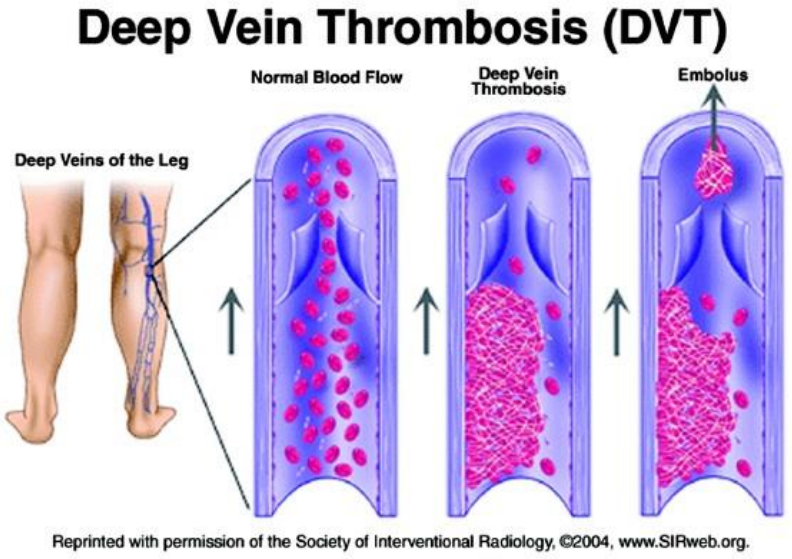
- Random adjustment method developed by M. Kulldorff for PRISM study of influenza vaccine and febrile seizures; accounts for uncertainty in baseline risk estimates
- L. Li conducted simulation study comparing performance of fixed adjustment and newer random adjustment

Comparison of fixed adjustment and random adjustment (*Lingling Li, 2015 ms.*)

- (Random adjustment takes into account **uncertainty** in estimating age-specific background incidence)
- Random adjustment performs well in general
- Fixed adjustment has comparable performance if no. in baseline data (n_b) ≥ no. in study (n_s)
- Rotavirus study met this condition: $n_b = 97$, $n_s \leq 30$

Gardasil & venous thromboembolism: Motivation

- Signal from VAERS, although 90% of the 31 had a known VTE risk factor (Slade et al., *JAMA* 2009)
- Signal from VSD, although all 5 had a known VTE risk factor (Gee et al., *Vaccine* 2011)
- FDA's Pediatric Advisory Committee requested PRISM study



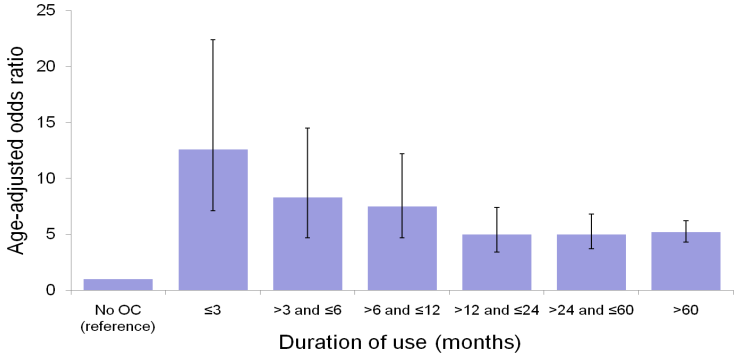
Gardasil & venous thromboembolism:

Design

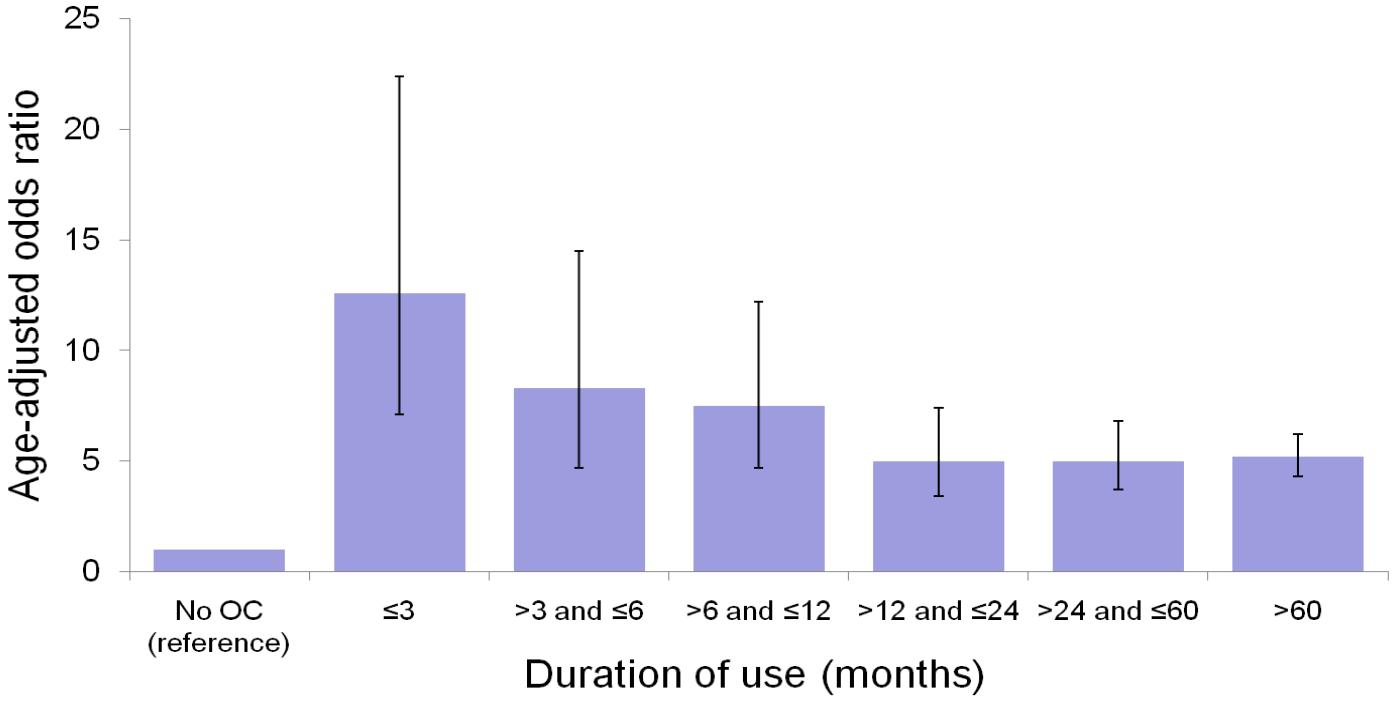
- Self-controlled risk interval (SCRI) (vaccinated infants only)—controls for fixed risk factors

  Risk intervals: Days 1-7 and 1-28

- Temporal scan statistics to look for clustering
- Confounding by **oral contraceptive (CHC) use**
- Explicitly controlled for duration of CHC use



VTE risk by duration of combined hormonal contraceptive (CHC) use



Vlieg et al. *BMJ* 2009;339:b2921

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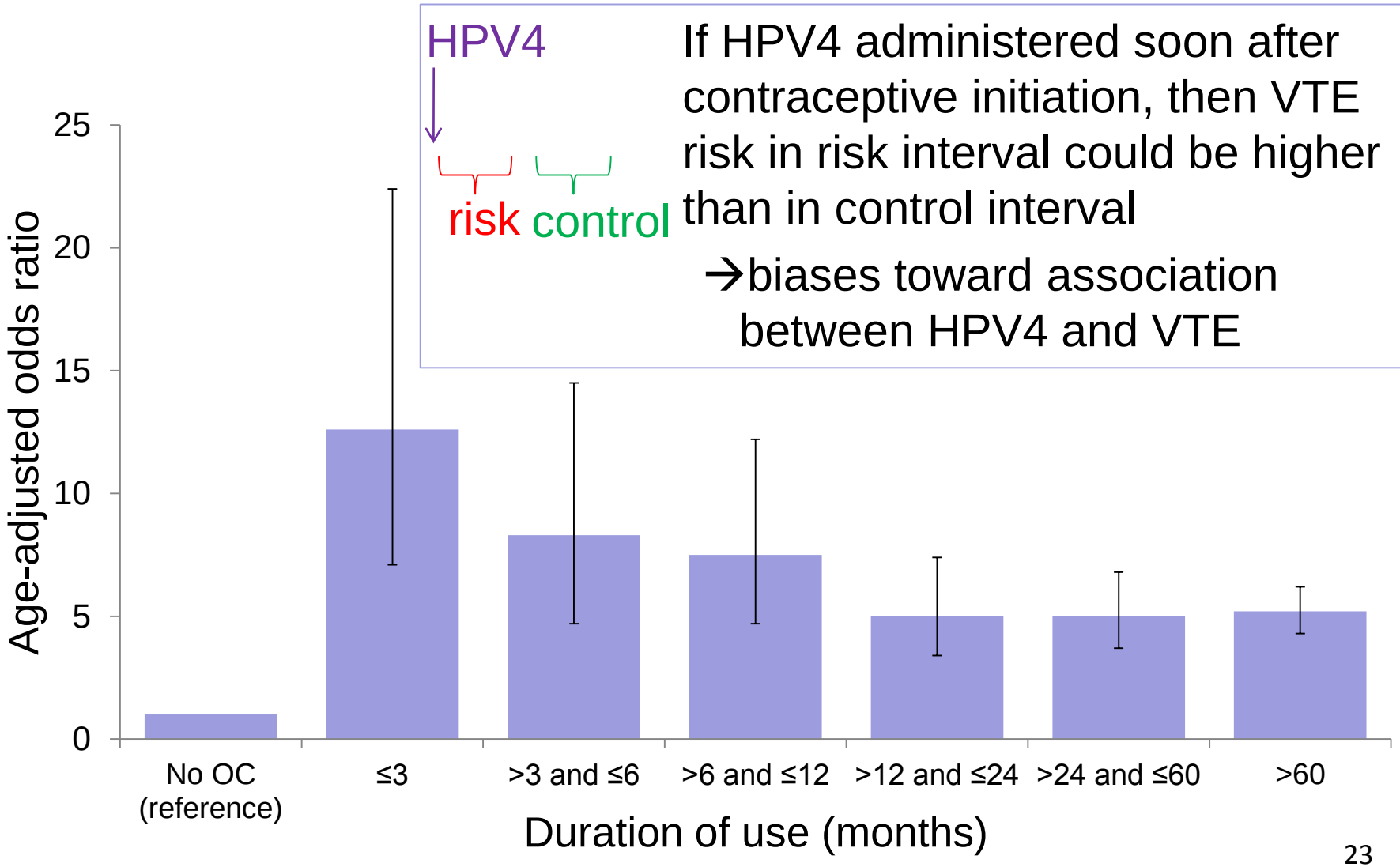

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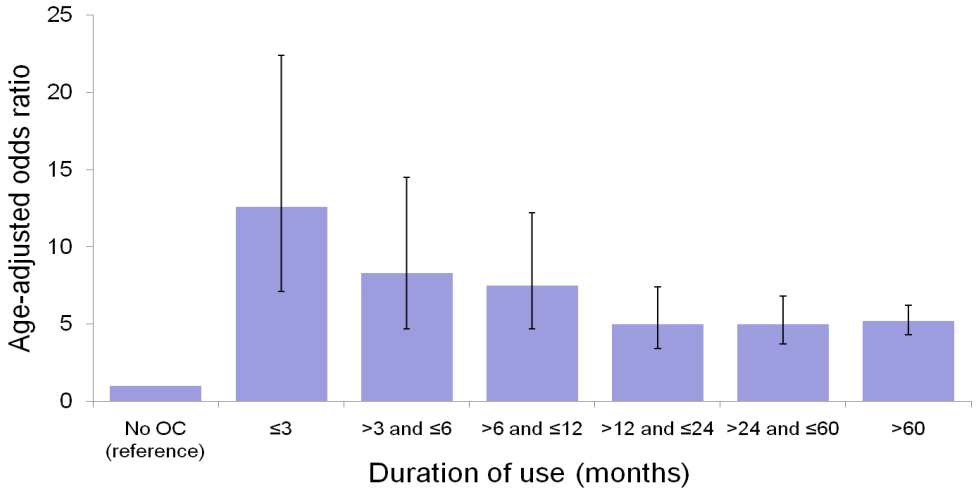
To adjust HPV4-VTE SCRI analysis…

Need to characterize VTE risk with changing duration of CHC use, with greater granularity than this:



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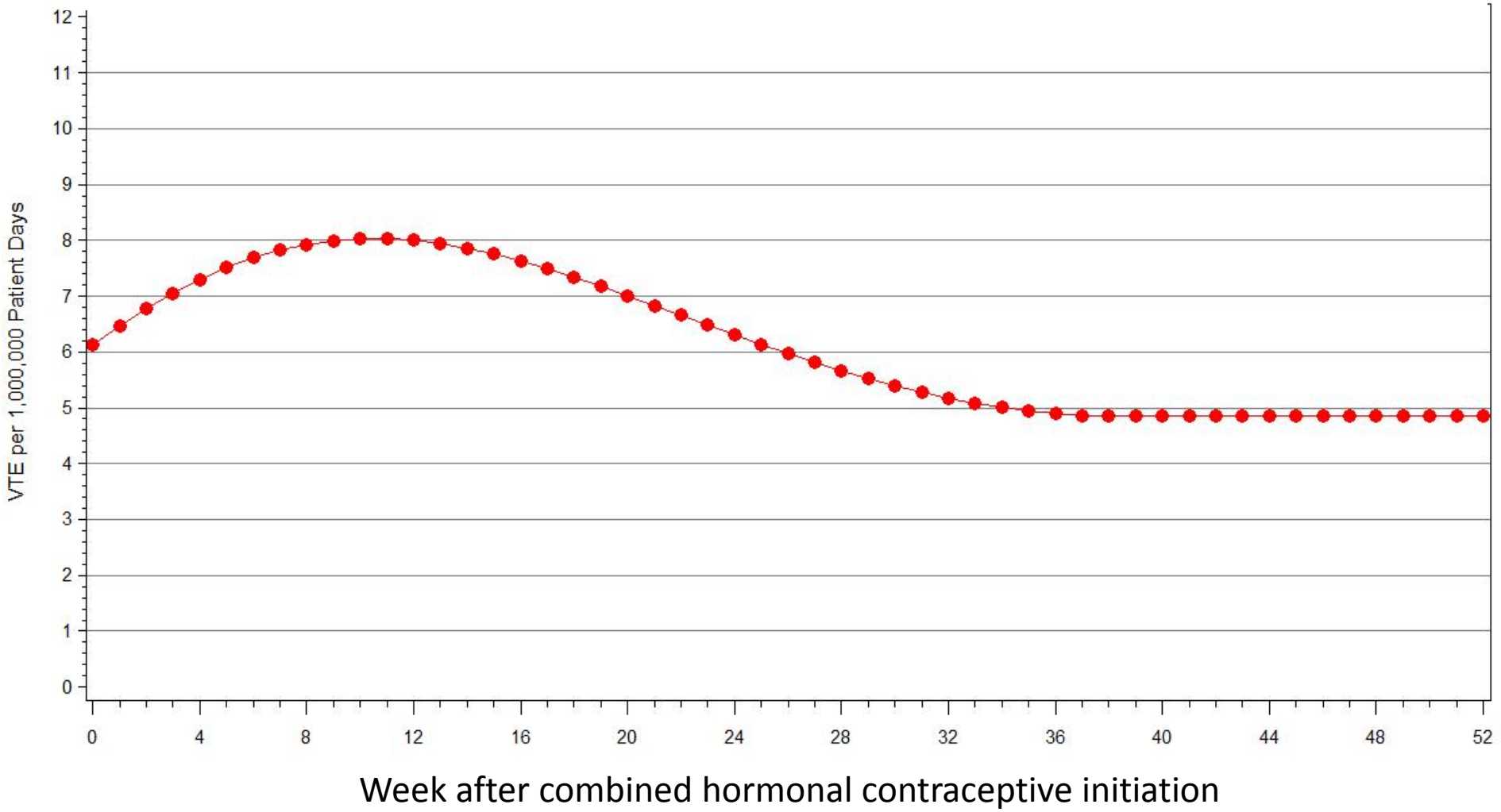
To adjust HPV4-VTE SCRI analysis…

- Use source population (in same time period plus from < 2006 if available)
- Identify CHC use
  - National Drug Codes in claims data
  - Generic names shared with Data Partners to add missing/homegrown codes
- Determine length of time on CHCs as of outcome
- Using Poisson regression, model risk of VTE by number of weeks on CHCs (adjusting for other relevant covariates, e.g., Data Partner, age, secular trends)

CHC-VTE modeling to adjust HPV4-VTE SCRI analysis

- Included in modeling:
  - ~9,000 potential cases of VTE
  - ~12 million person-years
- Model adjusted for Data Partner, age, whether and for how long on CHCs, estrogen dosage, and secular trends
- Point after CHC initiation at which VTE risk levels out:
  - Risk during 9-<12 mo. ≈ risk at ≥ 12 mo.
    - So considered VTE risk to plateau after 9.0 mo. on CHCs

Predicted VTE incidence by week after CHC initiation



Adjustment for time-varying confounding

- Incorporate offset term into the logistic regression
- Offset adjusts for difference in background risk in RW and CW
- Each case has an offset term whose value depends on case's ~~age~~ duration of CHC use at vaccination
- Offset = natural log (ln) of

$$\frac{\text{Estimated cumulative baseline risk in RW}}{\text{Estimated cumulative baseline risk in CW}}$$

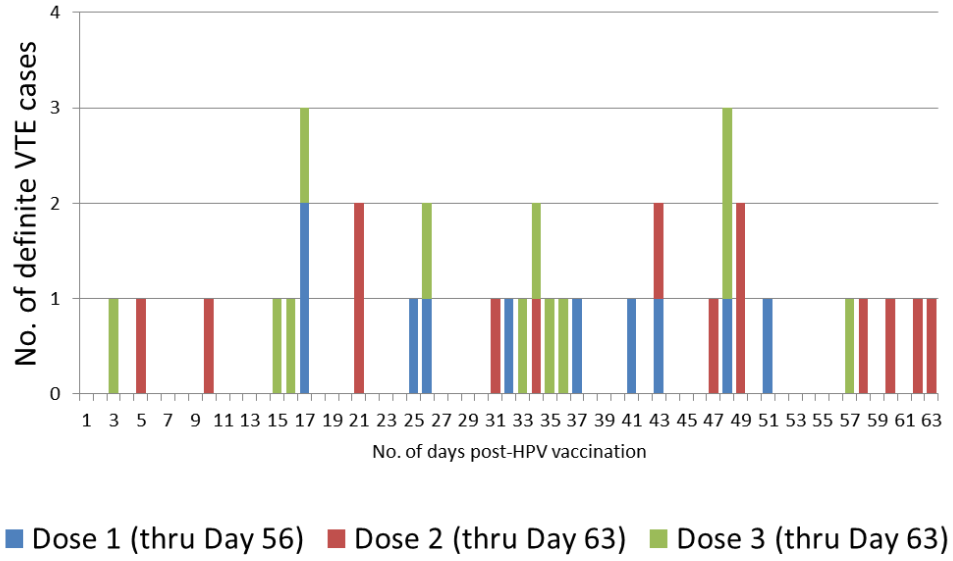
HPV4-VTE SCRI analyses without and with adjustment for CHC duration

A. Analyses with all definite VTE cases, with no adjustment for CHC use						
Dose	Days in RW	Cases in RW	Cases in CW	RR	95% CI lower bound	95% CI upper bound
1	1-28	4	5	0.60	0.15	2.27
2	1-28	4	8	0.50	0.13	1.59
3	1-28	5	4	1.25	0.33	5.05
All	1-28	13	17	0.70	0.33	1.44
1	1-7	0	5	0	--	--
2	1-7	1	8	0.50	0.03	2.73
3	1-7	1	4	1.00	0.05	6.76
All	1-7	2	17	0.43	0.07	1.51

B. Analyses with all definite VTE cases, with adjustment for CHC use						
Dose	Days in RW	Cases in RW	Cases in CW	RR	95% CI lower bound	95% CI upper bound
1	1-28	4	5	0.61	0.15	2.32
2	1-28	4	8	0.47	0.13	1.50
3	1-28	5	4	1.29	0.34	5.21
All	1-28	13	17	0.70	0.33	1.43
1	1-7	0	5	0	--	--
2	1-7	1	8	0.47	0.03	2.55
3	1-7	1	4	1.09	0.06	7.38
All	1-7	2	17	0.43	0.07	1.50

Gardasil & venous thromboembolism: Results

- 1,423,399 total doses
- No evidence of increased risk of VTE after Gardasil
  - SCRI analyses
  - Temporal scan analyses



Summary of the two case studies

	RV5 (RotaTeq) & intus-susception (IS) (> 1.2 M doses)	HPV4 (Gardasil) & venous thromboembolism (VTE) (> 1.4 M doses)
Design	SCRI	SCRI
Risk intervals	Days 1-7, 1-21	Days 1-7, 1-28
Control intervals	Days 22-42	Days 36-56 (Dose 1) Days 36-63 (Doses 2 & 3)
Time-varying confounder	Age	Duration of CHC (contraceptive) use
Method(s) of adjustment	Multiple, including using curve from *external* data treated as known with certainty	1) none, 2) using curve from *internal* data treated as known with certainty
Findings	Slightly increased risk of IS	No increased risk of VTE
Policy implications	Label change, no change in ACIP rec's	No change in label or ACIP rec's
Conclusions re. time-varying confounding	Adjustment crucial, but method didn't matter	Adjustment didn't matter

Conclusions

- Self-controlled risk interval design often a good choice for vaccine safety studies
  - Controls for fixed potential confounding
  - But power can be an issue when outcome is rare and/or effect size modest
- Control for time-varying confounding can be implemented in several ways
  - Random adjustment appropriate where internal data reasonably plentiful and individual-level data available
  - Otherwise, fixed adjustment (using either internal or comparable external data) is fine, as long as no. in baseline sample ≥ no. in SCRI sample (RW+CW)

Papers about the two PRISM studies

- Yih WK, Lieu TA, Kulldorff M, Martin D, McMahill-Walraven CN, Platt R, Selvam N, Selvan M, Lee GM, Nguyen M. Intussusception risk after rotavirus vaccination in U.S. infants. *N Engl J Med*. 2014;370:503-12.
- Yih WK, Greene SK, Zichittella L, Kulldorff M, Baker MA, de Jong JLO, Gil-Prieto R, Griffin MR, Jin R, Lin ND, McMahill-Walraven CN, Reidy M, Selvam N, Selvan MS, Nguyen MD. Evaluation of the risk of venous thromboembolism after quadrivalent human papillomavirus vaccination among US females. *Vaccine*. 2016;34:172-8.