ENGELBERG CENTER for Health Care Reform at BROOKINGS

Brookings Roundtable on Active Medical Product Surveillance

Findings from a Mini-Sentinel Assessment: Rotavirus Vaccines and Risk of Intussusception

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July 23, 2013

Background

- RotaShield, first vaccine for prevention of rotavirus infection in infants, licensed in 1998
- RotaShield voluntarily withdrawn from market in 1999 due to observation of elevated risk of intussusception, a form of bowel obstruction
- RotaShield risk ≈ 1 – 1.5 excess cases per 10,000 vaccine recipients
- For RotaTeq and Rotarix, risk of intussusception assessed in clinical trials of > 60,000 children each; no increased risk for intussusception observed for either vaccine
- But post-licensure studies in other countries later suggested increased risk of intussusception after both Rotarix and RotaTeq
- In 2010, FDA's Center for Biologics Evaluation and Research (CBER) initiated this study to quantify the possible risk among U.S. infants

Risk of Intussusception after Rotavirus Vaccination: Results of a PRISM Study

W. Katherine Yih, PhD, MPH

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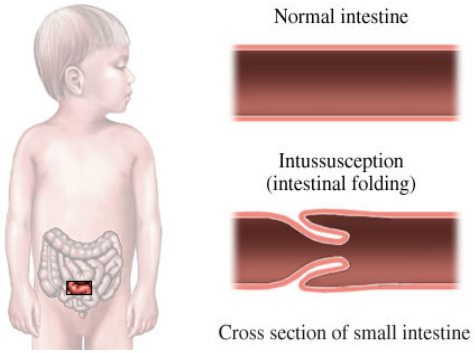
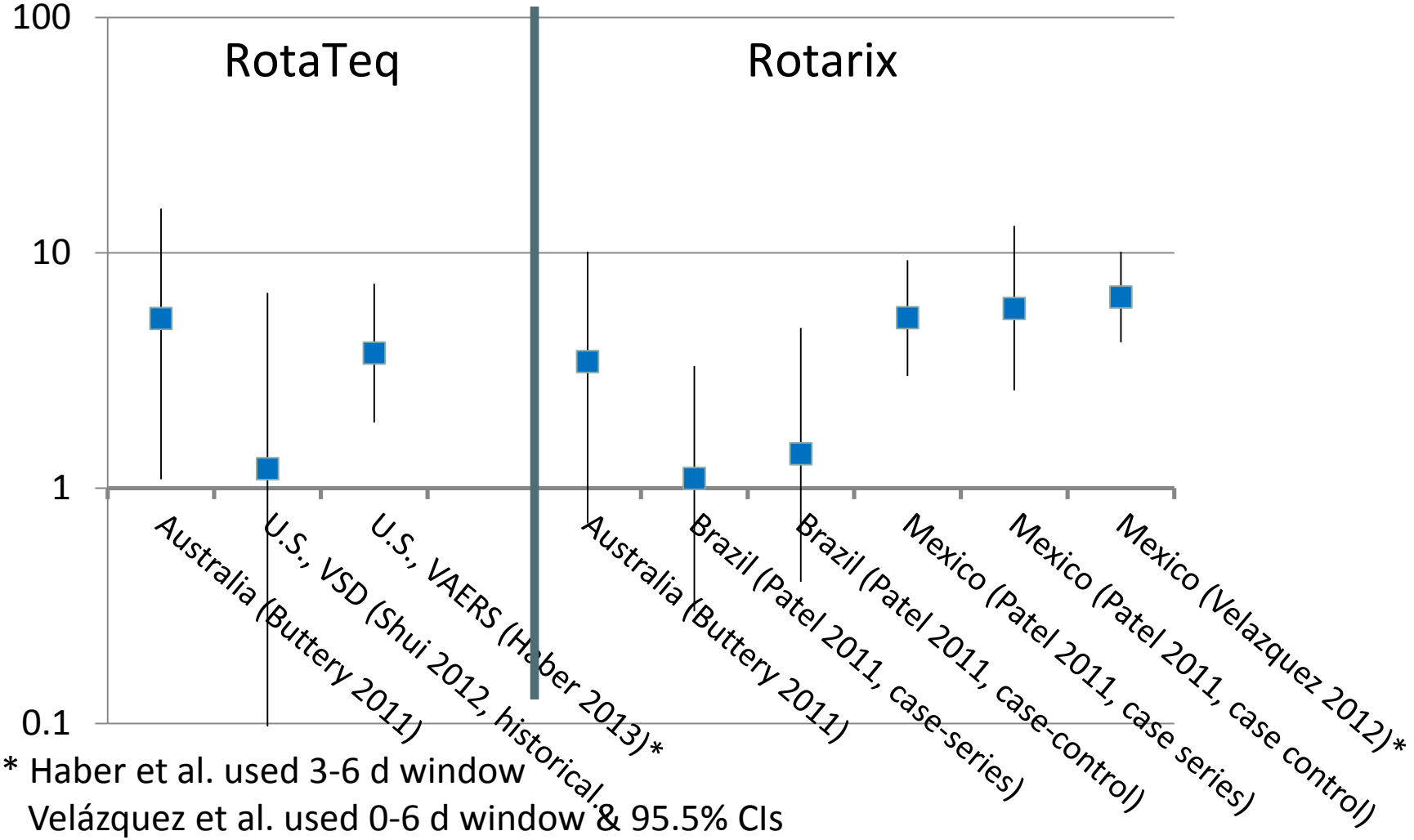


PRISM

- **P**ost-licensure **R**apid **I**mmunization **S**afety **M**onitoring system
- Largest vaccine safety surveillance program in U.S.
- PRISM data partners are national health insurance companies, which provide claims data
- Part of FDA-sponsored Mini-Sentinel pilot program developed to conduct active surveillance for medical product safety

Risk ratio estimates and 95% CI for Dose 1, ~1-7 day post-RV risk window*



* Haber et al. used 3-6 d window
Velázquez et al. used 0-6 d window & 95.5% CIs

Outline

1. Claims data
2. Chart review
3. Dose counts
4. Study designs
5. Attributable risk (AR) estimates
6. Temporal scan statistics
7. Conclusions
8. PRISM results compared to other studies

Data partners and date range

- Included in this study:
  - Aetna
  - HealthCore (Wellpoint)
  - Humana
- Date range varies by data partner
- Maximum period in this study:
  2004 – mid-2011

Identification of potential exposures and outcomes in electronic claims data

- Rotavirus vaccine exposure

  CPT-4 codes 90680 (RotaTeq) and 90681 (Rotarix)

- Intussusception

  First-ever of any of these in ED or inpatient setting:

  - ICD-9 code 560.0 (intussusception)
  - ICD-9 code 543.9 (unspecified diseases of appendix, including intussusception)
  - CPT-4 code 74283 (therapeutic enema, contrast or air, for reduction of intussusception or other intraluminal obstruction)

Chart review

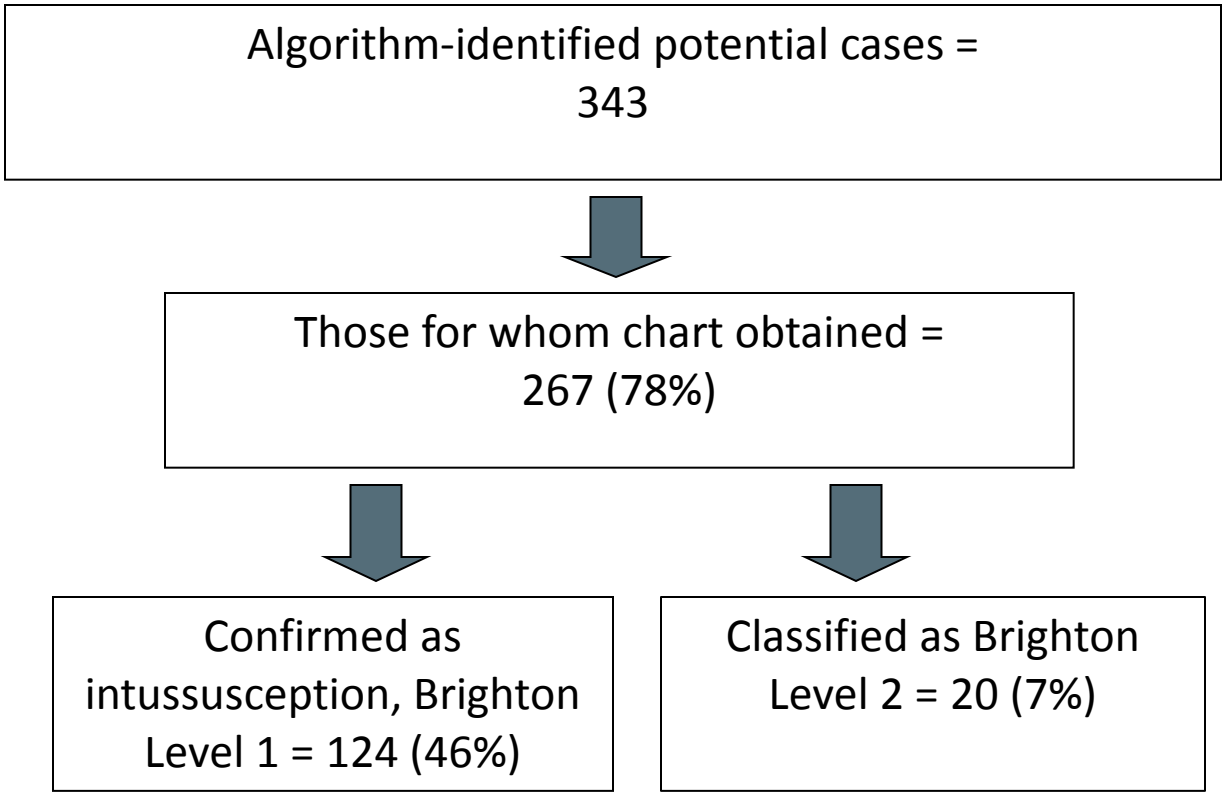
- Purposes
  - To confirm **intussusception** diagnoses
  - To confirm **rotavirus vaccination** status (specific vaccine, dose number, age) of intussusception cases
- Age range: 5-36 weeks, to cover recommended vaccination ages (2, 4, 6 mo.) plus follow-up time
- Reviewed charts of ostensibly vaccinated as well as unvaccinated cases
- Adjudicators of intussusception charts blinded to vaccination status

Brighton Collaboration criteria*

- Level 1 (requires direct observation of invagination of intestine or of highly specific features on ultrasound)
  - Surgical criteria and/or
  - Radiological criteria (using air/liquid contrast enema or ultrasound) and/or
  - Autopsy criteria
- Level 2
  - Clinical criteria, including “major” (more specific) ones
- Level 3
  - Clinical criteria but only “minor” (less specific) ones

* J Bines et al. *Vaccine* 2004;22:569-574

Intussusception confirmation



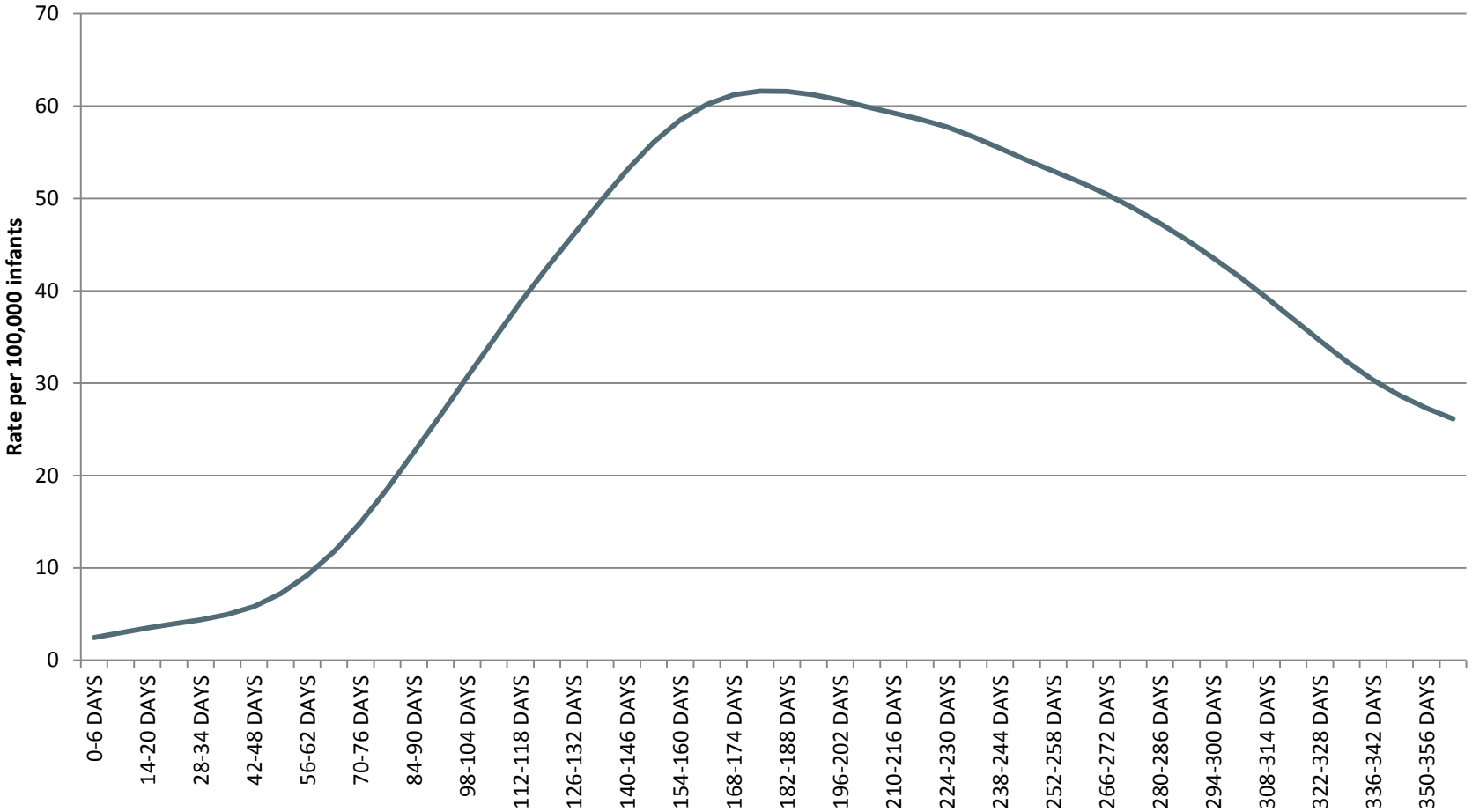
Potential cases are from whole population aged 5-36 weeks and include unexposed

Rotavirus vaccine doses in PRISM study

(for period for which charts reviewed, through 6/2011 maximum)

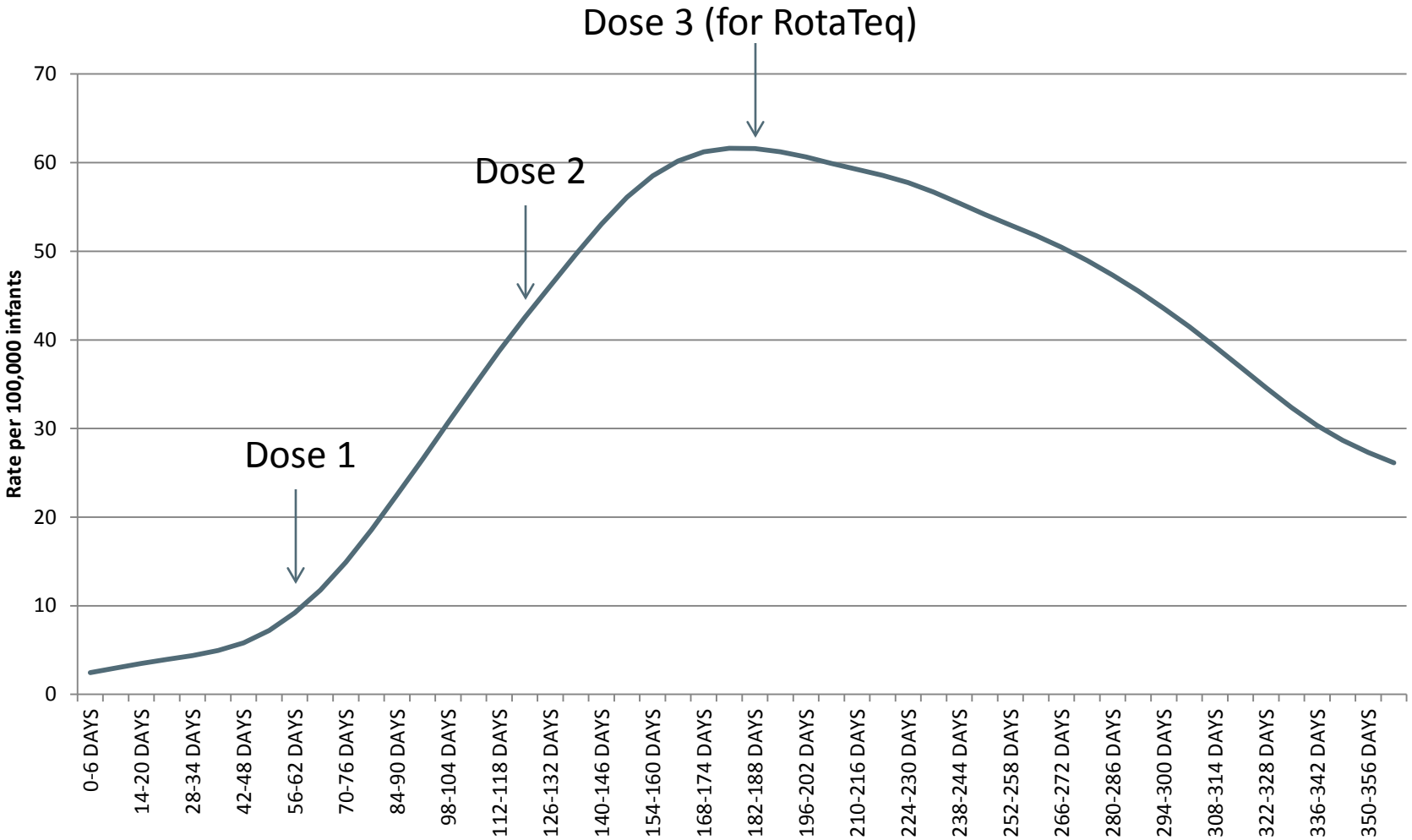
	1st doses	All doses
RotaTeq (3-dose series)	507,874	1,277,556
Rotarix (2-dose series)	53,638	103,098

Intussusception incidence by age



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

Intussusception incidence by age



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Design and analysis approaches

Primary:

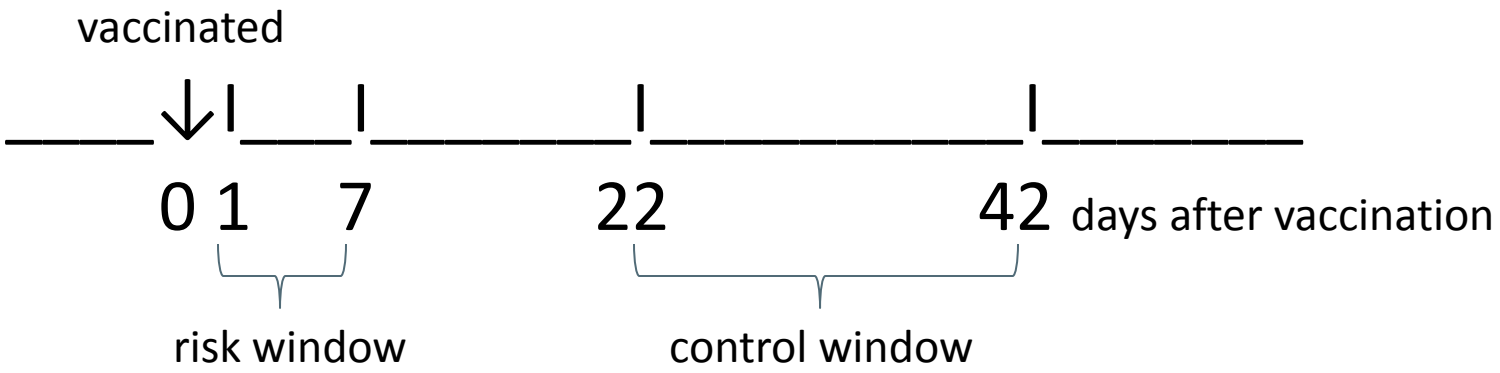
Self-controlled risk interval (vaccinated infants only)

Secondary:

Cohort (all infants)

Self-controlled risk interval design

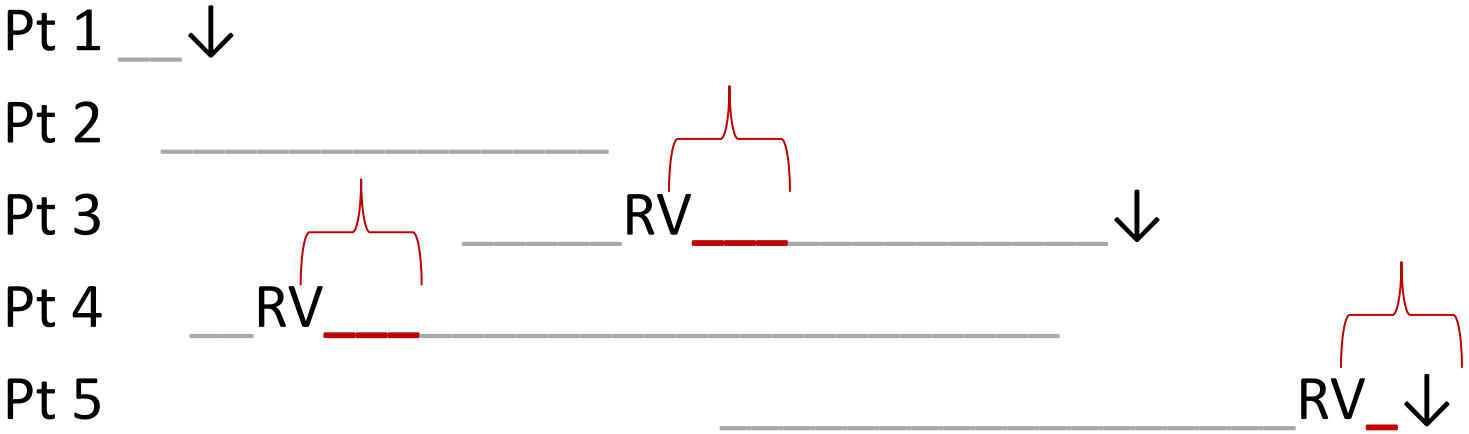
- Uses just vaccinated cases with intussusception in either pre-specified risk or control window
- Each subject serves as own control; adjusts for fixed (non-time-varying) confounders



- Analysis by logistic regression
  - **Adjust for age using age-specific incidence in offset term**

Cohort design

- Uses exposed and unexposed infant-time from cohort 5-36 weeks of age

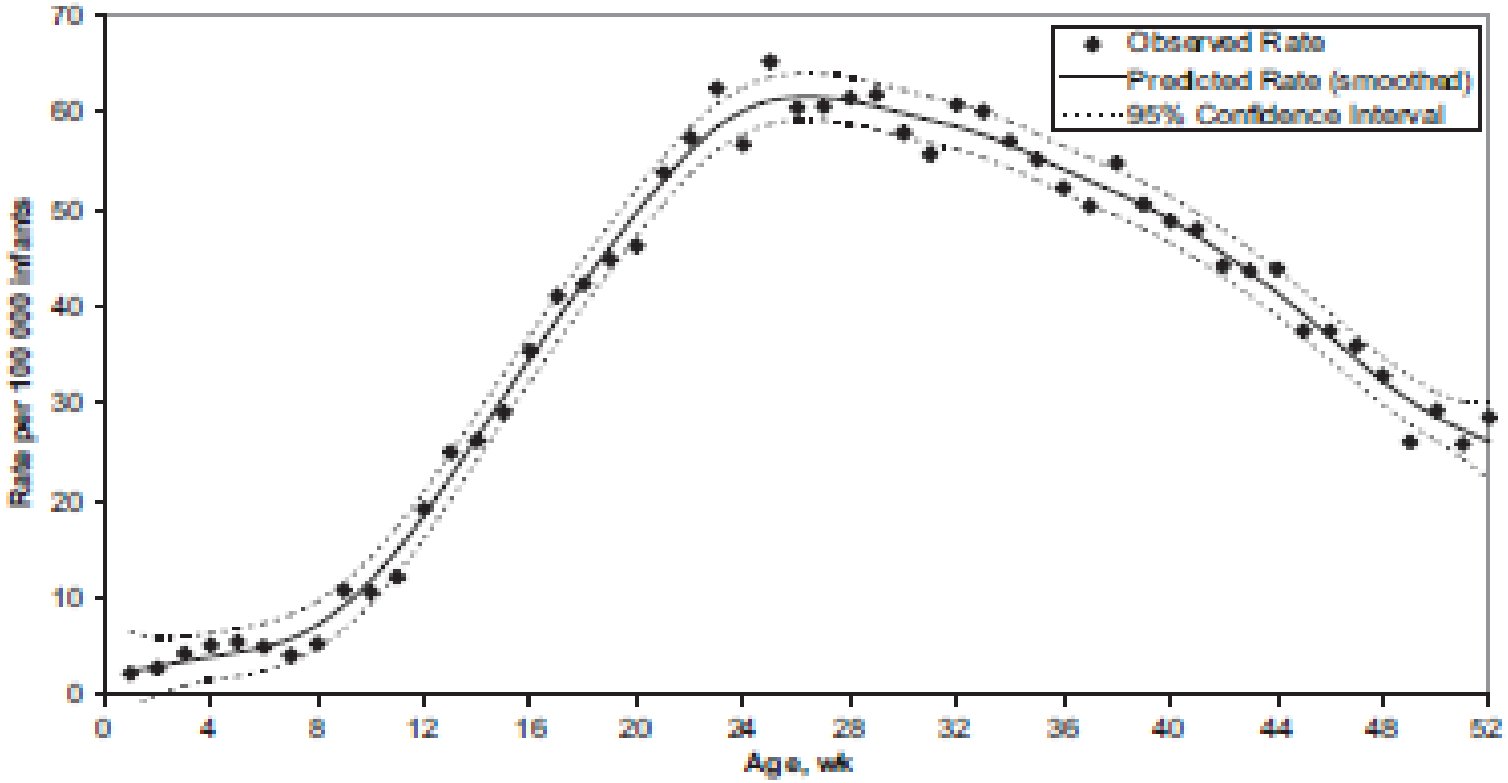


- Analysis by Poisson regression
  - **Adjust for age using polynomial function in model**

Complementarity of designs

Design	Pros	Cons
Self-controlled (SCRI) (pre-specified as primary)	Controls well for fixed risk factors	Requires accurate age-specific incidence for age adjustment
Cohort	Higher statistical power; extrinsic background rates not needed	Could be affected by residual confounding

Intussusception age-specific incidence from 11 years of U.S. HCUP data*



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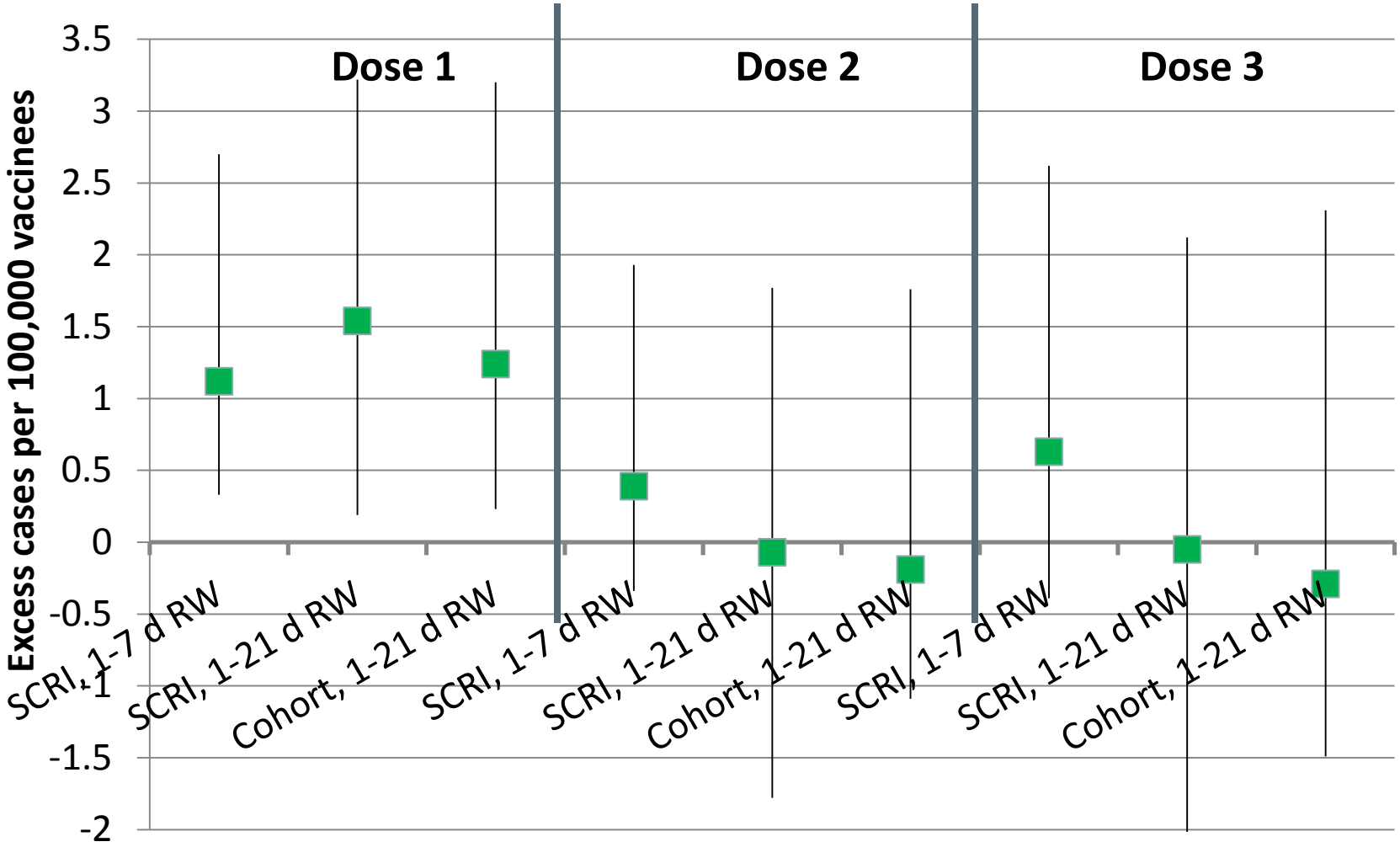
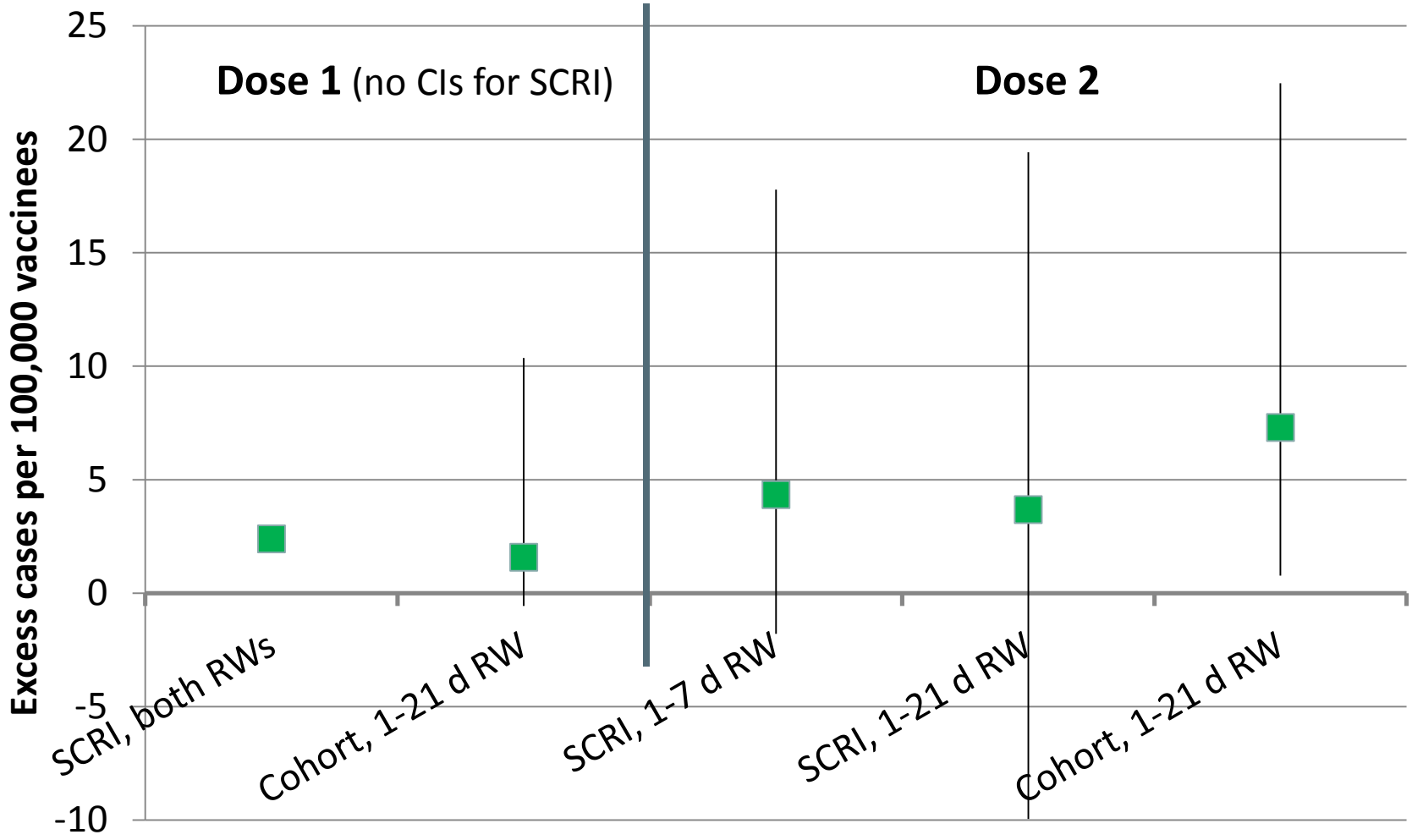
Dose-risk window combinations for each vaccine

Risk window → Dose ↓	1-7 days	1-21 days
1	SCRI (primary)	SCRI Cohort
2, 3	SCRI	SCRI Cohort

RotaTeq attributable risks by dose number, study design, and risk window



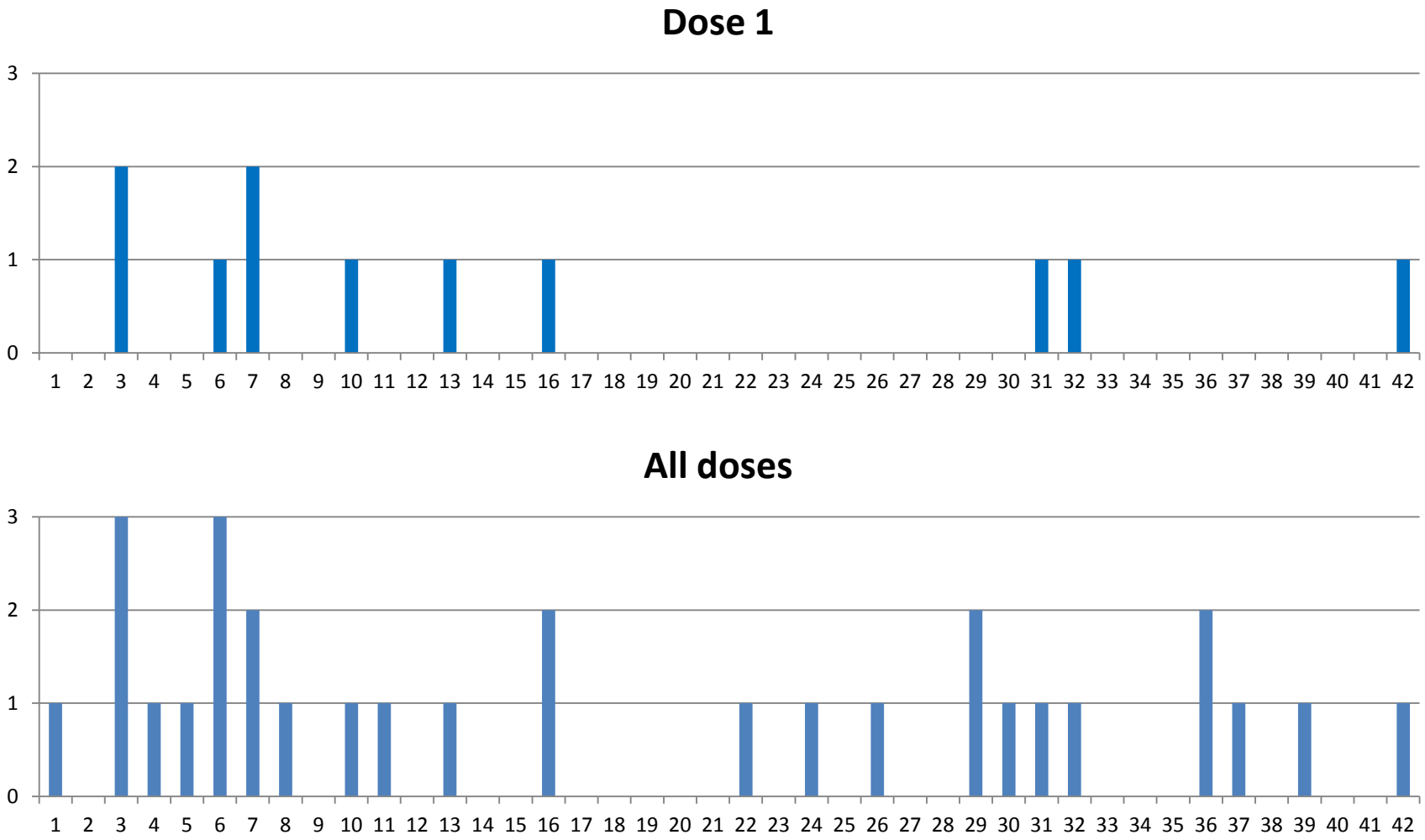
Rotarix attributable risks by dose number, study design, and risk window



Temporal scan statistics

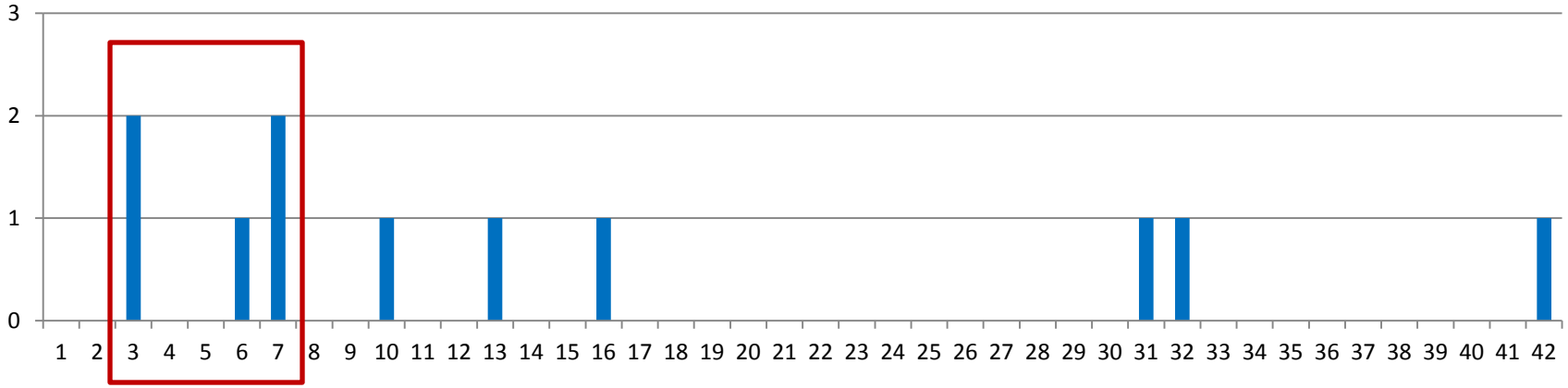
- Evaluated all potential risk windows…
  - starting 1-14 days after vaccination
  - ending 1-21 days after vaccination
- Adjusted for multiple testing (203 intervals considered)
- Adjusted for age using the age-specific incidence curve from Tate et al. and a randomization method
- Analyses conducted using SaTScan

Confirmed IS onsets by day after **RotaTeq**

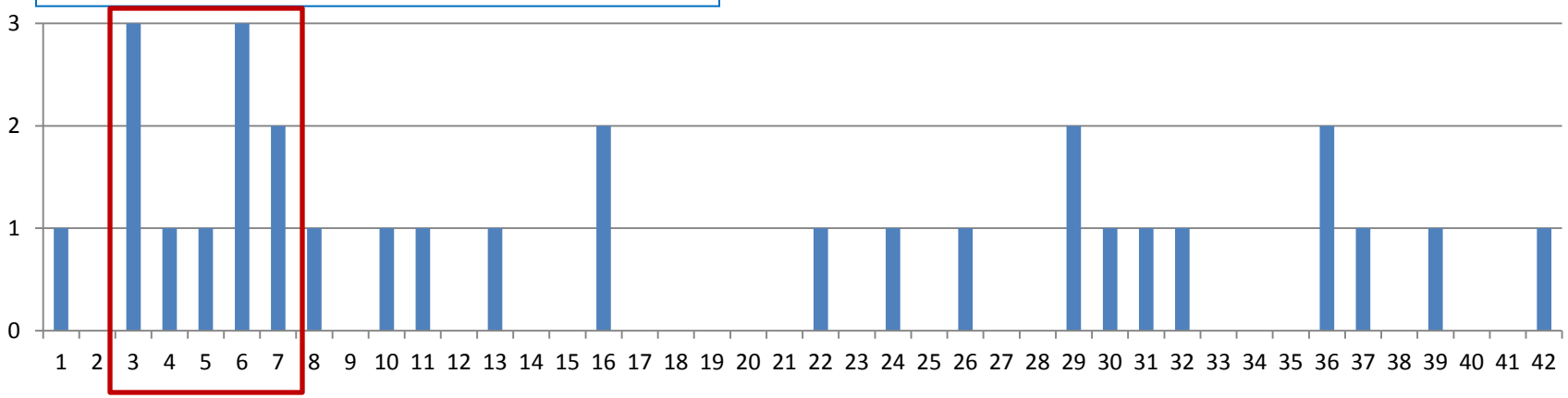


Confirmed IS onsets by day after **RotaTeq**

5 out of 11 cases, RR=9.7, p=0.008 **Dose 1**



10 out of 30 cases, RR=4.5, p=0.004 **All doses**



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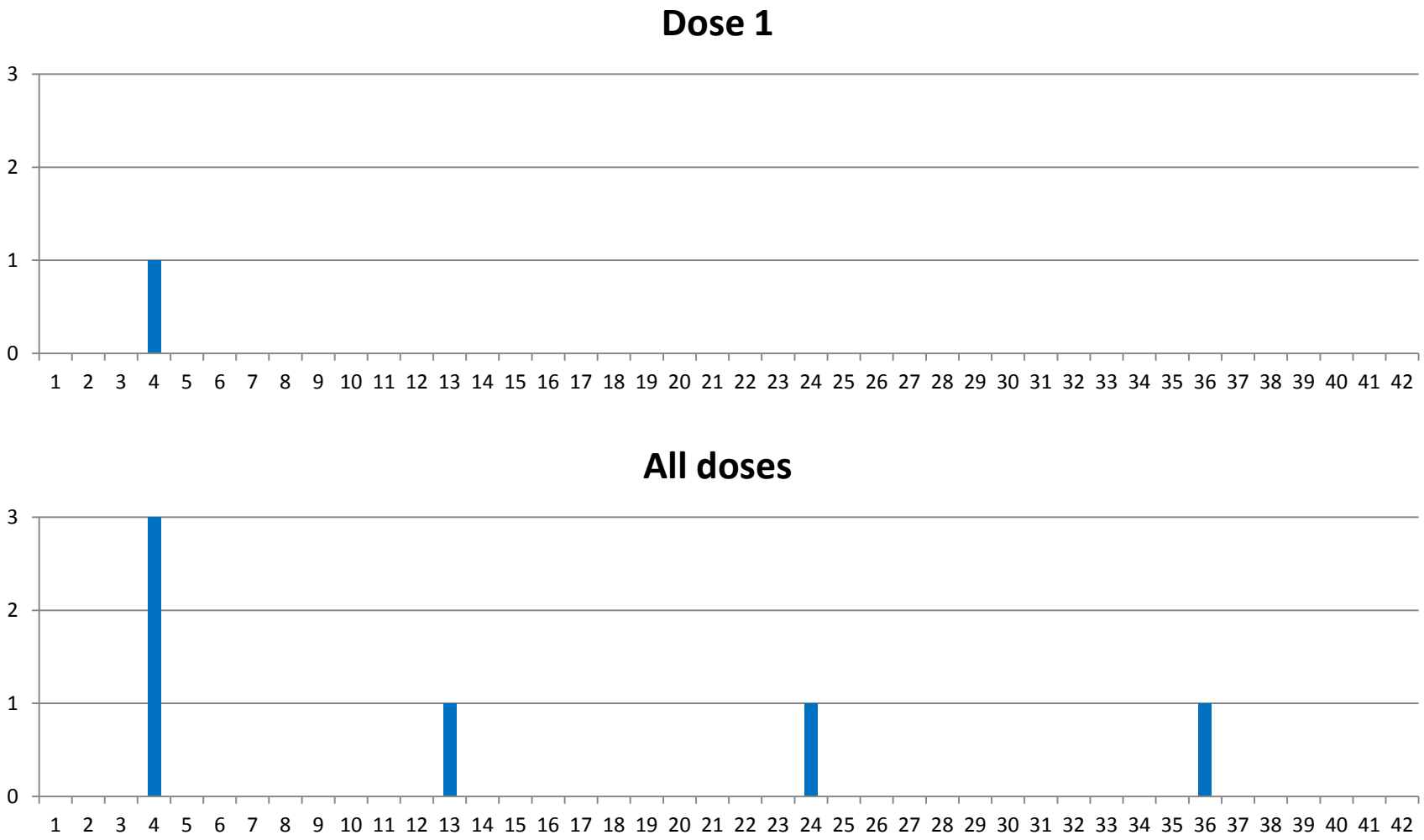

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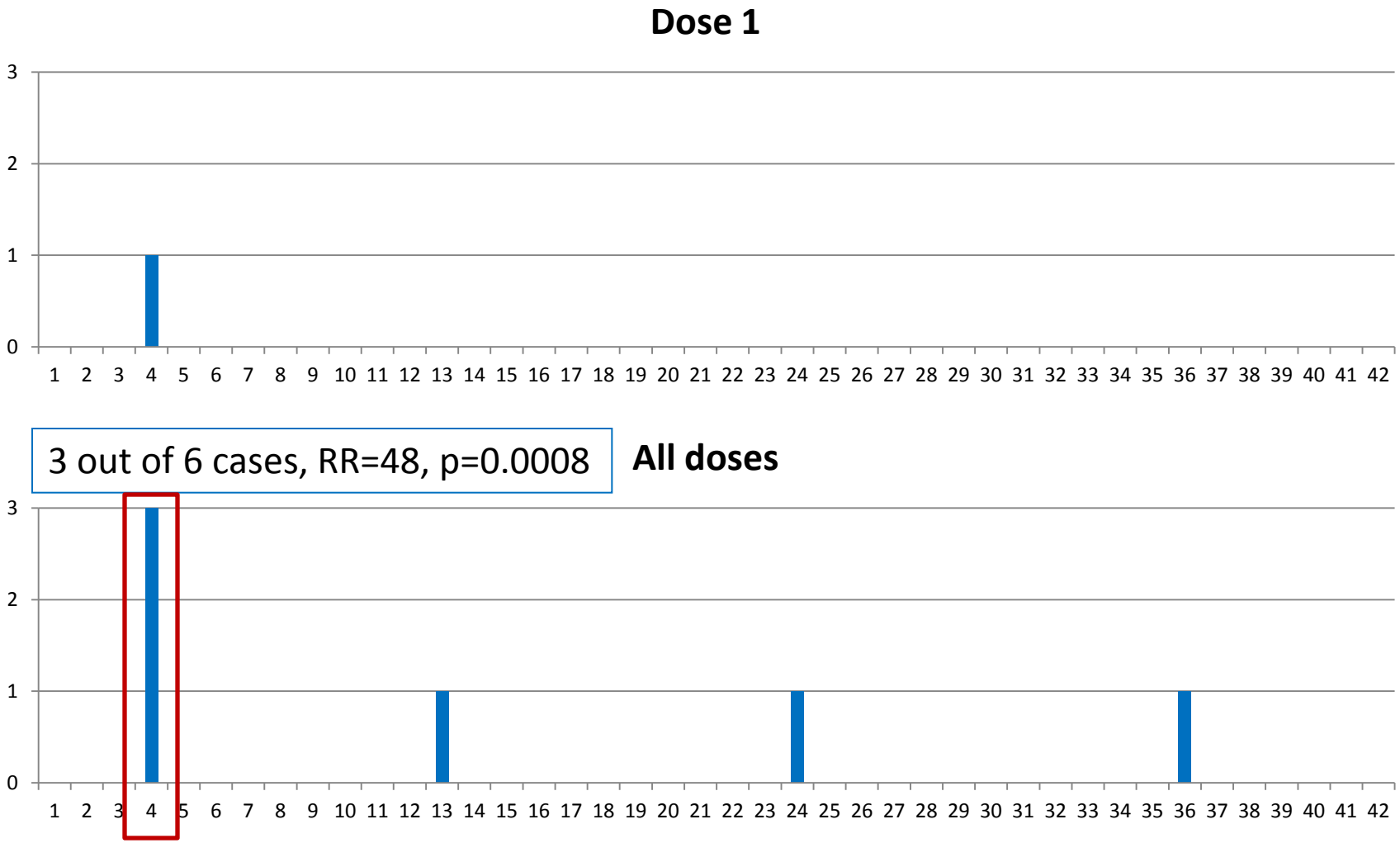


Conclusions: **RotaTeq**

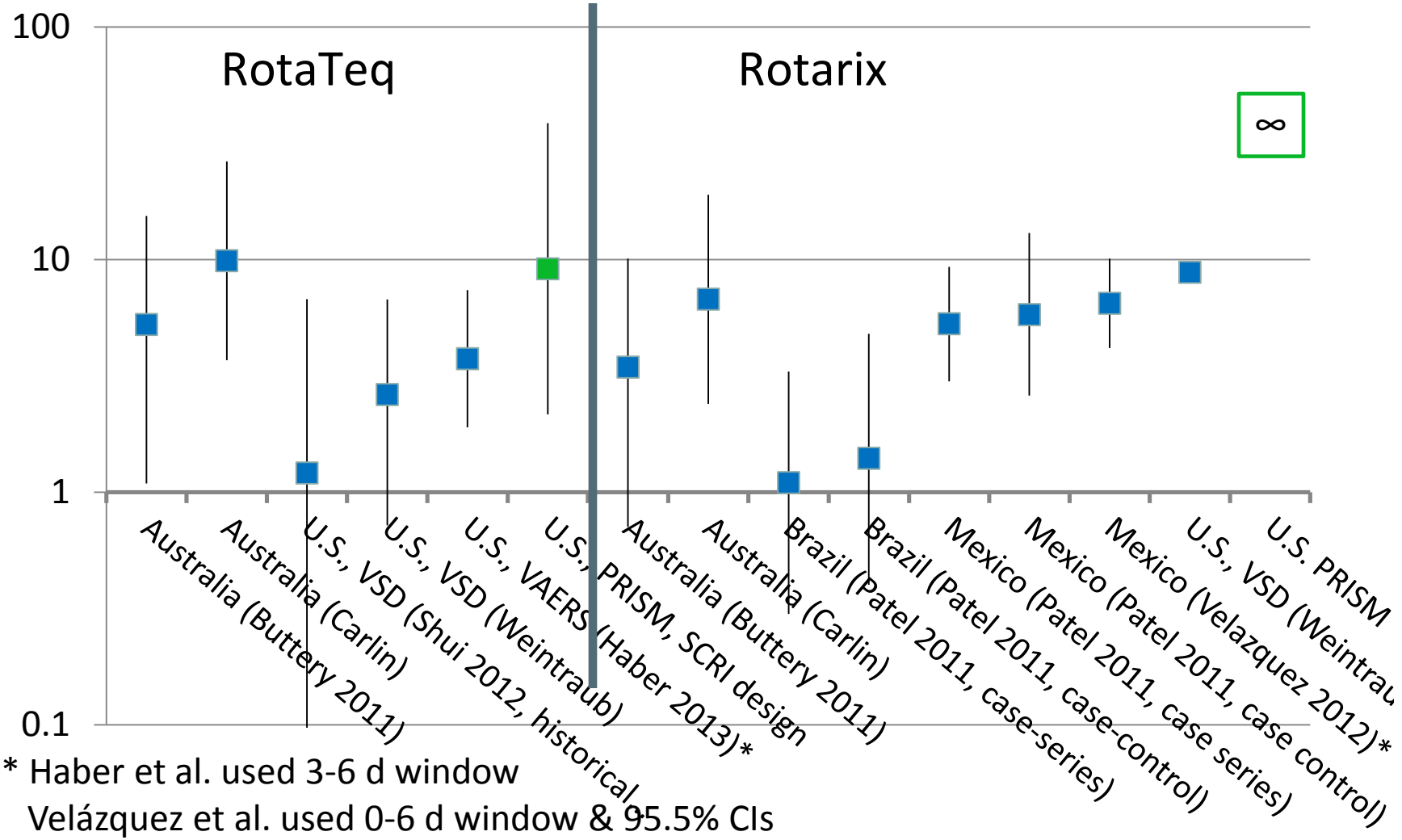
- Dose 1 associated with increased risk of intussus-ception in the 1-7 & 1-21 days after vaccination
- Statistically significant cluster found on Days 3-7 after vaccination (Dose 1 and all doses combined)
- All Dose 1 AR* point estimates in range of 1.1-1.5
- Lower and upper bounds of 95% CI of ARs*:
  - 0.2 excess cases/100,000 first-dose vaccinees (≈1/520,000)
  - 3.2 excess cases/100,000 first-dose vaccinees (≈1/30,000)

* attributable risk

Conclusions: **Rotarix**

- Low statistical power—103,098 total doses, 53,638 first doses, only 1 case in 1-42 d after first dose
- Statistically significant cluster found on Day 4 after vaccination (all doses combined)
- Other results also suggest increased risk but are inconclusive

Risk ratio estimates and 95% CI for Dose 1, ~1-7 day post-RV risk window*



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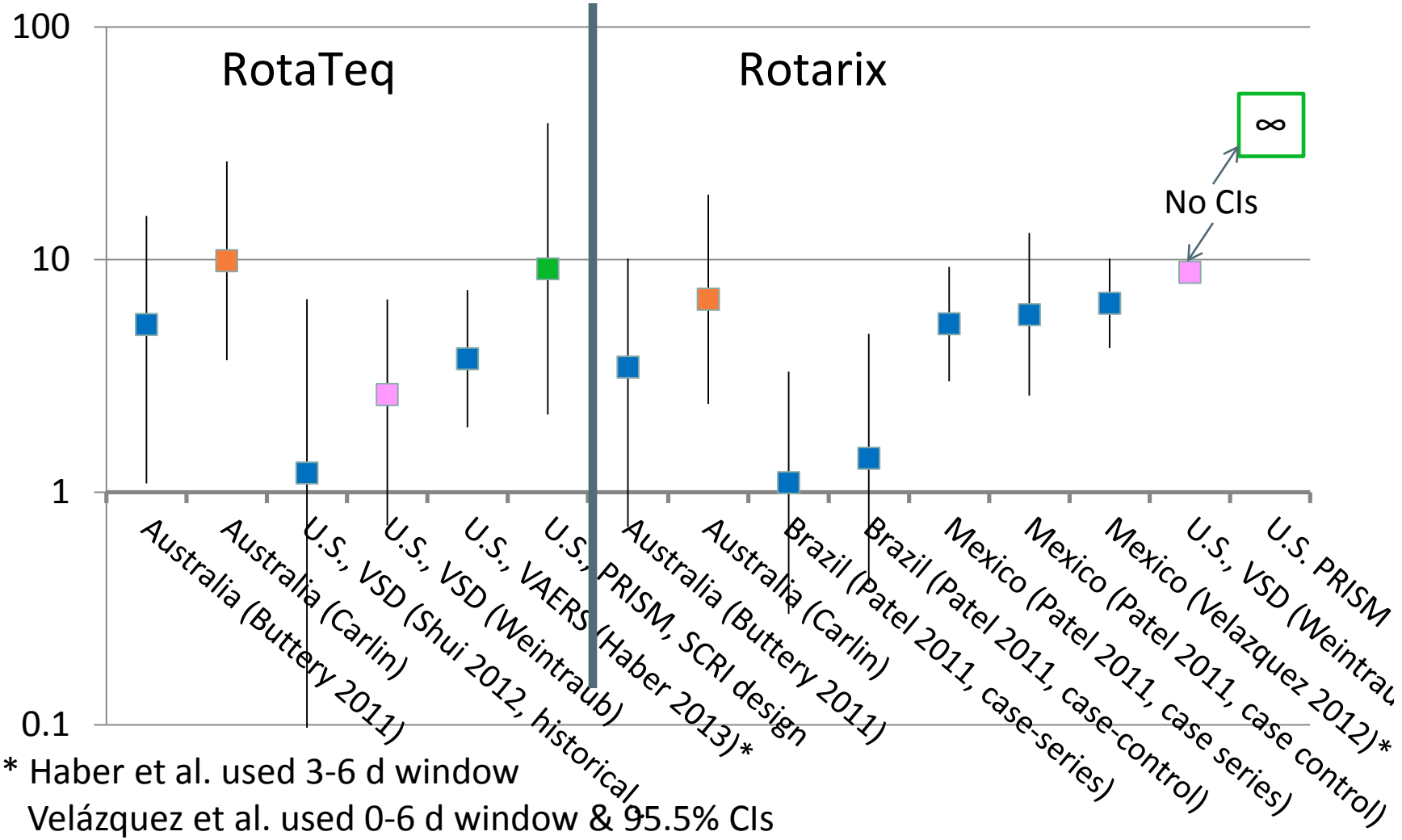

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Acknowledgments

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Others

Ed Belongia

Michael Silverman

Jacqueline Tate

Discussion