ENGELBERG CENTER for Health Care Reform at BROOKINGS

Sentinel Initiative Public Workshop

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Risk of Intussusception after Rotavirus Vaccination:

Results of the Mini-Sentinel/PRISM* Study

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Sentinel Initiative Public Workshop

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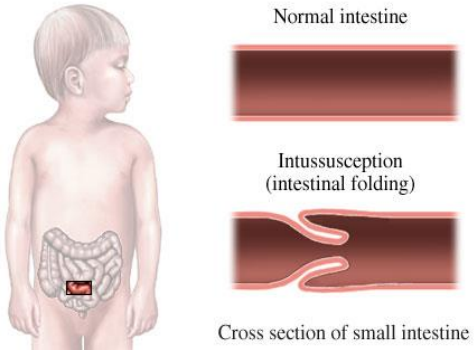


* Post-licensure Rapid Immunization Safety Monitoring

Background

- RotaShield, first vaccine for prevention of rotavirus infection in infants, licensed in 1998
  - Withdrawn in 1999 due to risk of intussusception, a form of bowel obstruction
  - Risk ≈ 1 – 2 excess cases per 10,000 vaccine recipients
- For RotaTeq and Rotarix, no increased risk in clinical trials of >60,000 children each
  - But post-licensure studies in other countries later suggested increased risk of intussusception after both
- In 2010, FDA's Center for Biologics Evaluation and Research (CBER) initiated this study to quantify the possible risk among U.S. infants

Source data and chart review

- Data partners: Aetna, HealthCore, Humana
- Date range: 2004 - mid-2011
- CPT-4 and ICD-9 codes to ID exposure and outcome:
  - CPT-4 codes 90680 (RotaTeq) and 90681 (Rotarix)
  - ICD-9 codes 560.0 (intussusception), 543.9; CPT-4 code 74283 (therapeutic enema…)
- Chart review to validate both outcome and exposure
  - Age range: 5-36 weeks, to cover recommended vaccination ages (2, 4, 6 mo.) plus follow-up time
  - Pediatrician adjudicators classified cases using Brighton Collaboration criteria

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

Design and analysis approaches

Primary:

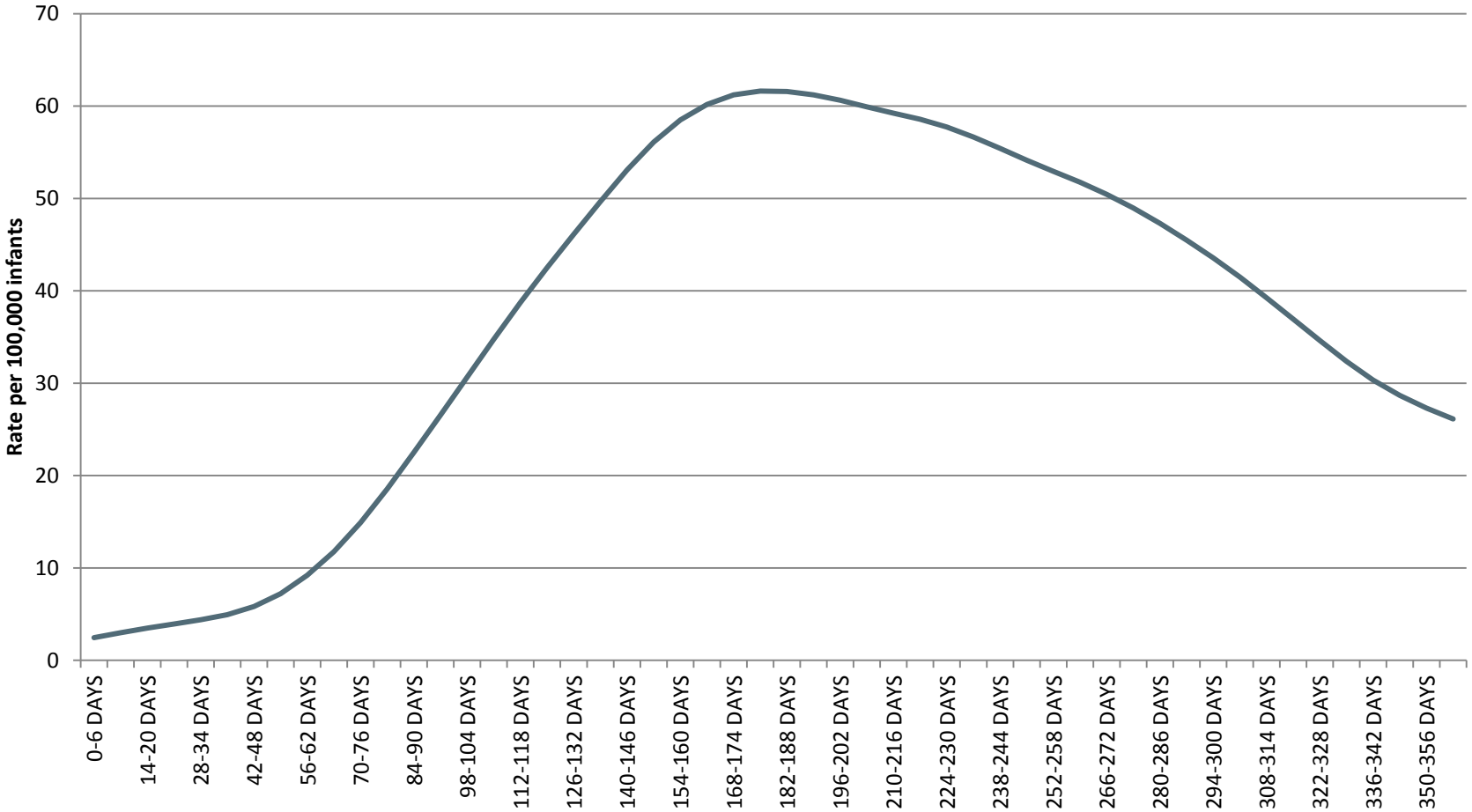
- Self-controlled risk interval (vaccinated infants only)—controls for fixed risk factors
  - Risk intervals: Days 1-7 and 1-21

Secondary:

- Cohort (all infants)—higher statistical power
  - Risk interval: Days 1-21 only

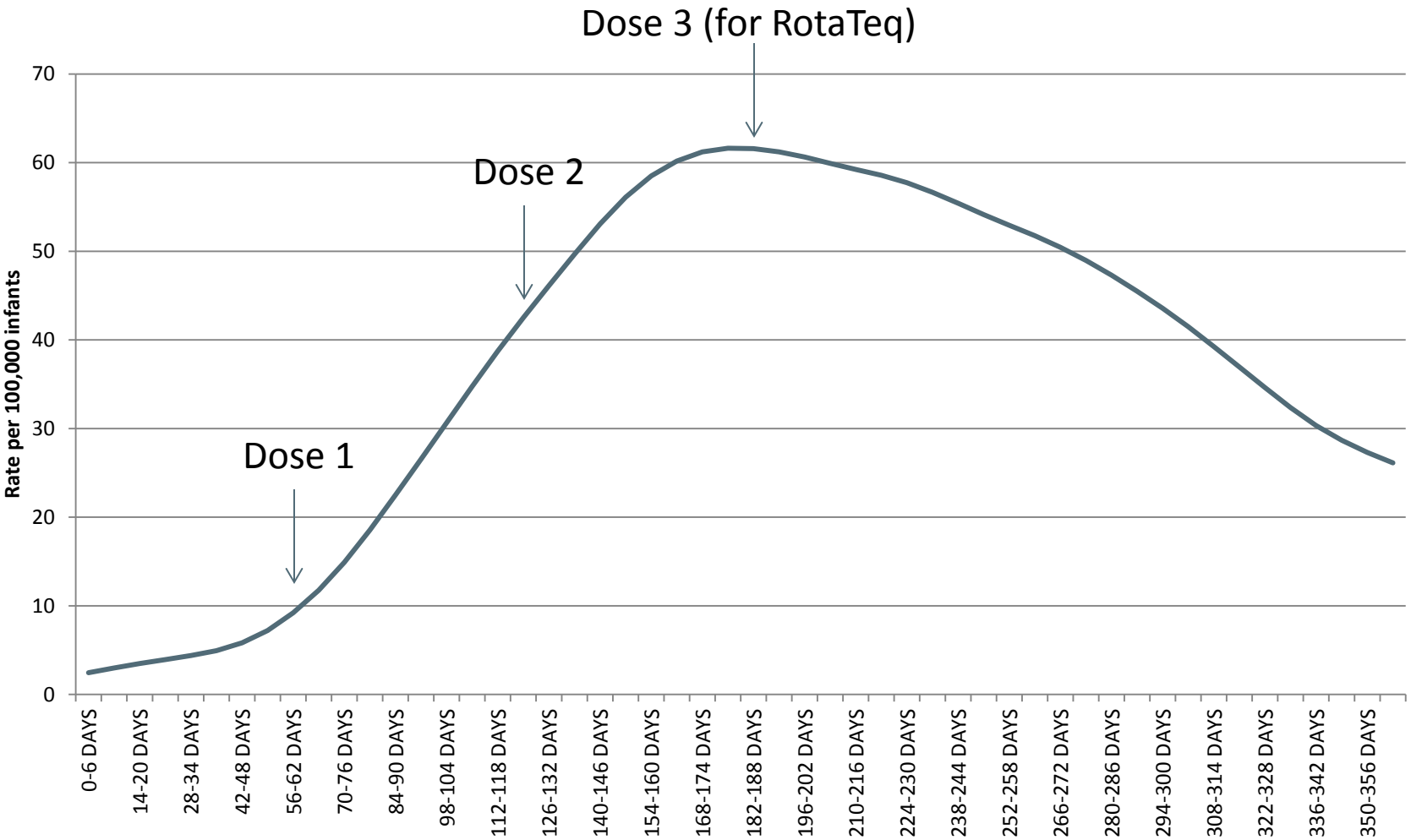
Also, temporal scan statistics

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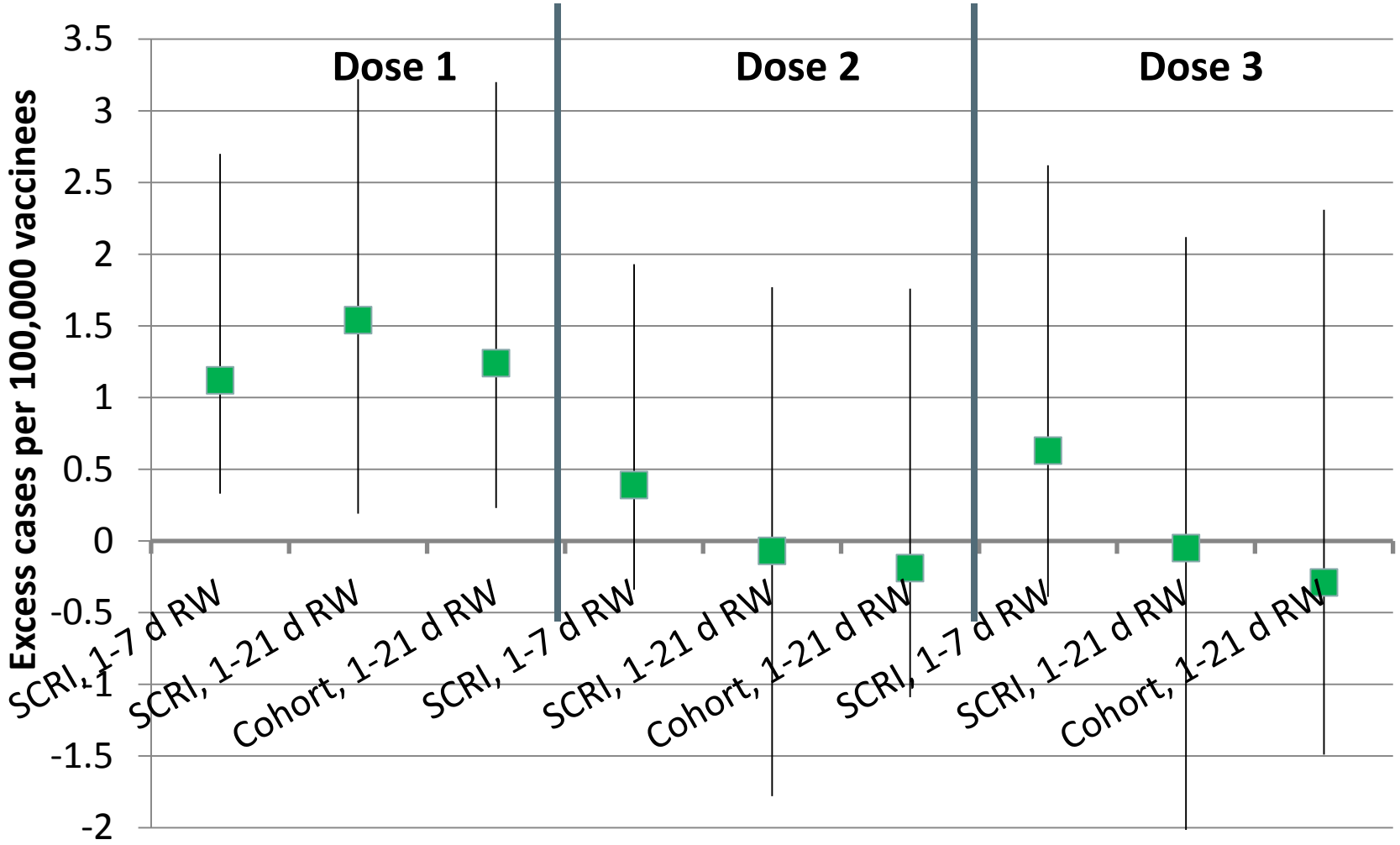
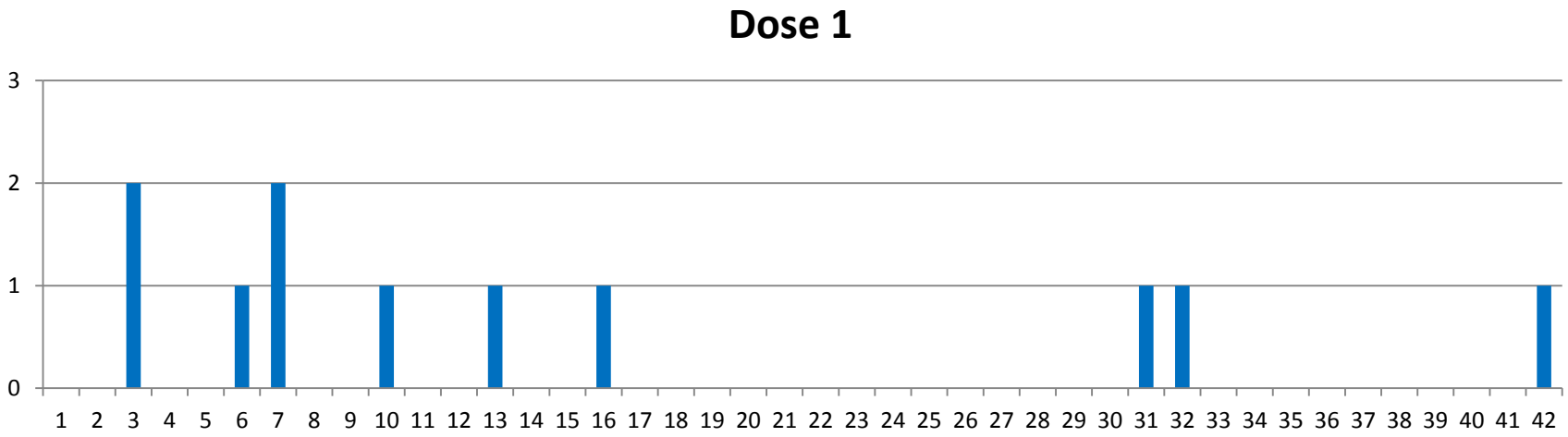
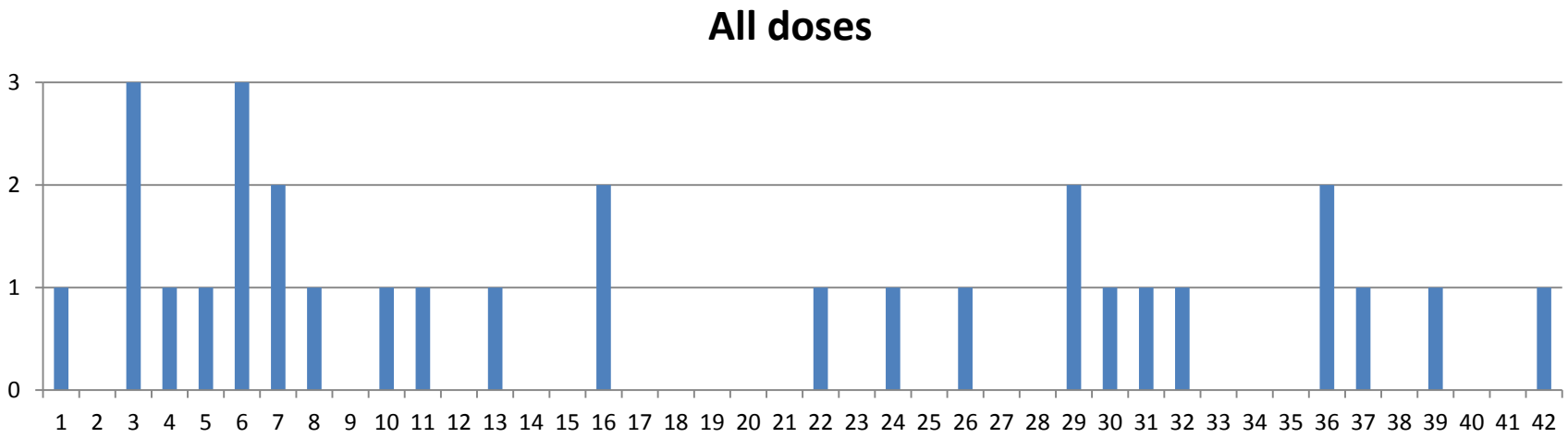
RotaTeq attributable risks by dose number, study design, and risk window



Confirmed IS onsets by day after **RotaTeq**

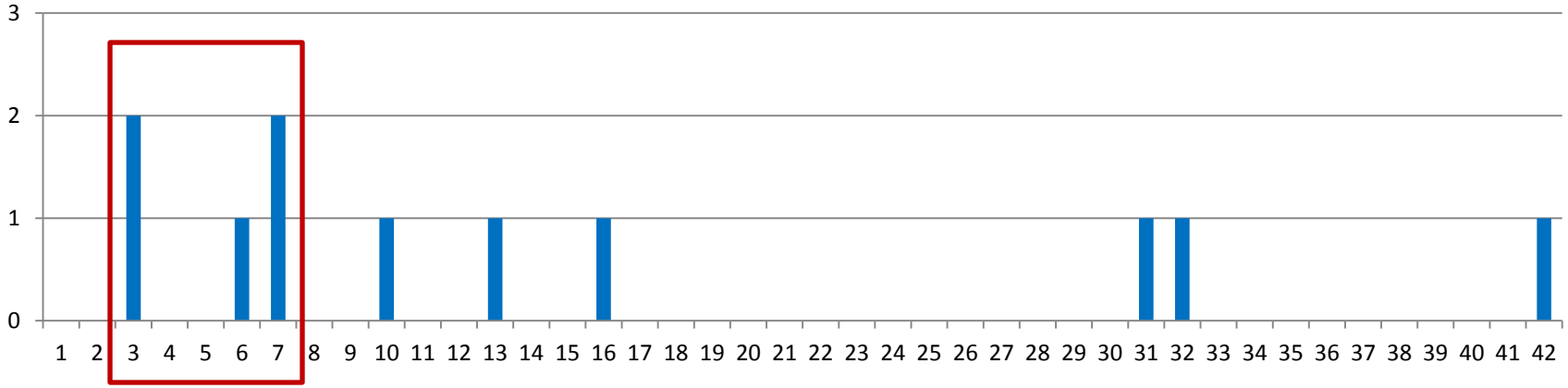




Confirmed IS onsets by day after **RotaTeq**

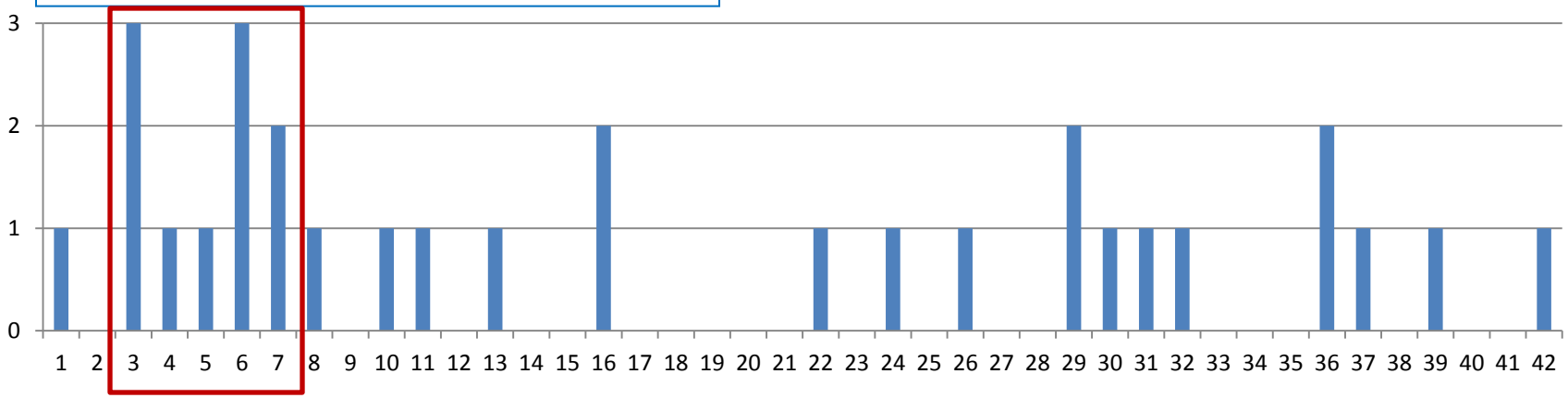
5 out of 11 cases, RR=9.7, p=0.008

Dose 1



10 out of 30 cases, RR=4.5, p=0.004

All doses

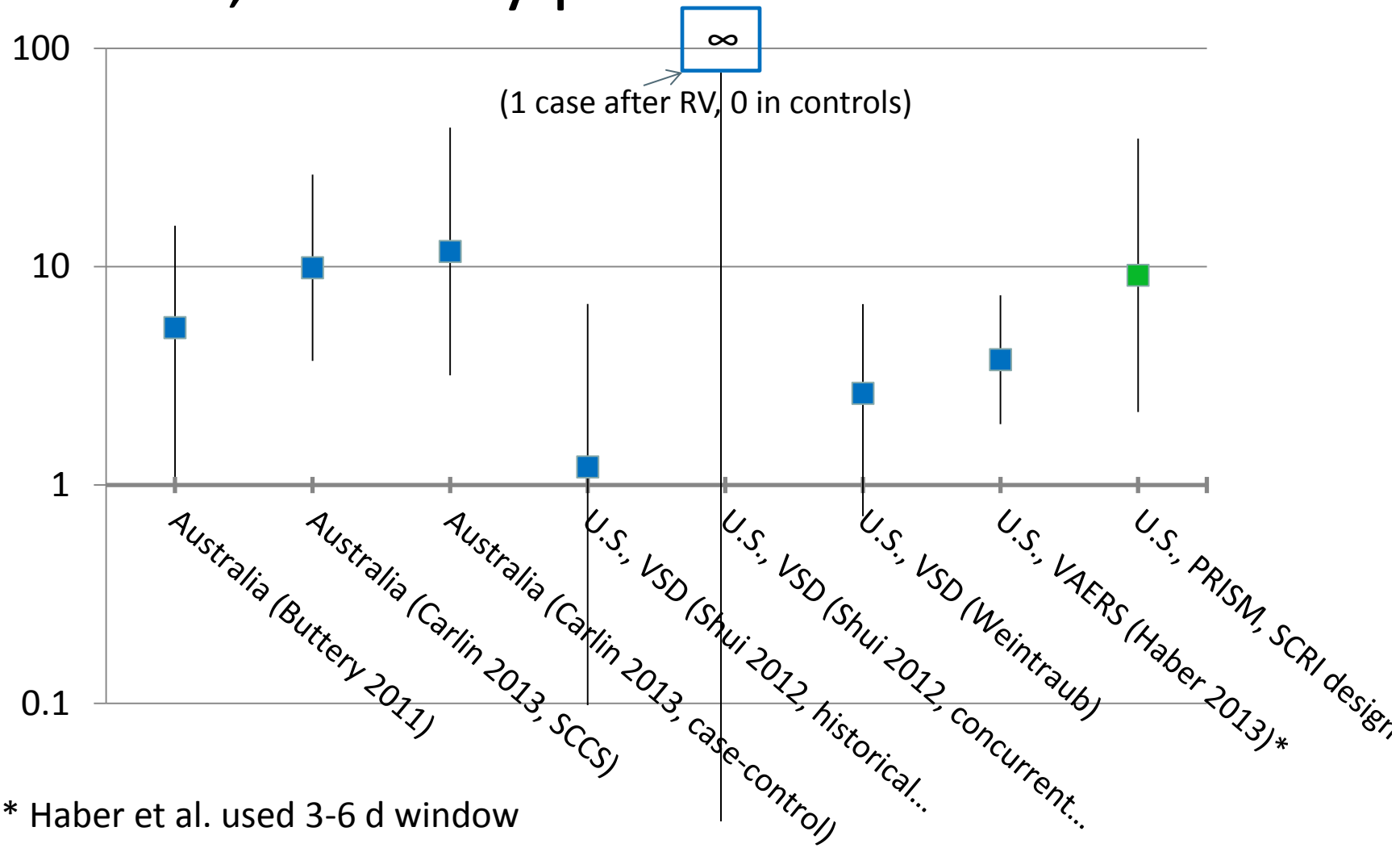


Conclusions: **RotaTeq**

- 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/ 100,000 (≈1/10 of risk associated with RotaShield)
- 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

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



* Haber et al. used 3-6 d window

RotaTeq label change

Warnings and Precautions (5.5)].

5.3 Intussusception

Following administration of a previously licensed live rhesus rotavirus reassortant vaccine, an increased risk of intussusception was observed.[1]

In a post-marketing observational study in the US cases of intussusception were observed in temporal association within 21 days following the first dose of RotaTeq, with a clustering of cases in the first 7 days. *[See Adverse Reactions (6.2)]*

In worldwide passive post-marketing surveillance, cases of intussusception have been reported in temporal association with RotaTeq. *[See Adverse Reactions (6.2)]*

5.4 Gastrointestinal Illness

Post-Marketing Observational Safety Surveillance Studies

The temporal association between vaccination with RotaTeq and intussusception was evaluated in the Post-licensure Rapid Immunization Safety Monitoring (PRISM) program[2], an electronic active surveillance program comprised of 3 US health insurance plans.

More than 1.2 million RotaTeq vaccinations (507,000 of which were first doses) administered to infants 5 through 36 weeks of age were evaluated. From 2004 through 2011, potential cases of intussusception in either the inpatient or emergency department setting and vaccine exposures were identified through electronic procedure and diagnosis codes. Medical records were reviewed to confirm intussusception and rotavirus vaccination status.

The risk of intussusception was assessed using self-controlled risk interval and cohort designs, with adjustment for age. Risk windows of 1-7 and 1-21 days were evaluated. Cases of intussusception were observed in temporal association within 21 days following the first dose of RotaTeq, with a clustering of cases in the first 7 days. Based on the results, approximately 1 to 1.5 excess cases of intussusception occur per 100,000 vaccinated US infants within 21 days following the first dose of RotaTeq. In the first year of life, the background rate of intussusception hospitalizations in the US has been estimated to be approximately 34 per 100,000 infants.[3]

CDC Provider Information with Rotavirus Vaccine Information Statement (VIS)

Risk of Intussusception Following Vaccination

Post-marketing studies indicate there is a small risk of intussusception from the currently licensed rotavirus vaccines. These studies on one or both of the vaccines were conducted in the United States, Australia, Mexico, and Brazil.

Two main studies in the U.S. have evaluated post-licensure risk following use of rotavirus vaccines.

- One study found an increased risk of intussusception during the first week following dose 1 and dose 2 of Rotarix. This study did not find a statistically significant increased risk of intussusception following RotaTeq.
- Another study found an increased risk of intussusception following the dose 1 of RotaTeq, primarily during the first week. No increased risk was detected following doses 2 or 3.

Studies in other countries have found increased risk of intussusception following both vaccines.

Though there are inconsistent findings across some studies and lack of precision in the risk estimates, the data indicate that both currently licensed rotavirus vaccines are associated with a small risk of intussusception. Monitoring is continuing in the U.S. and these risk estimates may change when additional data become available.

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CDC Provider Information with Rotavirus VIS

- CDC continues to recommend that all U.S. infants (following the age and precaution/ contraindication criteria) receive rotavirus vaccine. The benefits of either vaccine outweigh the small excess risk of intussusception.
- Parents should be made aware of the small risk of intussusception, the signs and symptoms of intussusception, and the need for prompt care if these develop.

Acknowledgments

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Data partners

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