Studying Rotavirus Vaccines and Intussusception in Mini-Sentinel

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Rotavirus vaccines

- Live, attenuated, oral vaccines for infants, multiple doses
- Rotashield licensed in August 1998
- In 1999, Rotashield voluntarily withdrawn due to increased risk of intussusception
  - Excess risk: 1-2 cases/10,000 vaccine recipients
  - Risk highest 3-7 days after Dose 1
- RotaTeq (2006) and Rotarix (2008) licensed after clinical trials with >60,000 infants

Post-licensure studies, RotaTeq & Rotarix Dose 1, 1-7 d after vaccination

1st author, date	Site, system	1st doses	No. of cases	RR (95% CI)
RotaTeq				
Buttery 2011	Australia	115,657	3	5.3 (1.1, 15)
Haber (abstract) 2011	U.S., VAERS	n.a.	66	1.5 (0.96, 2.3)
Shui 2012	U.S., VSD	309,844	1	1.2 (0.03, 6.8)
Rotarix				
Buttery 2011	Australia	163,709	3	3.5 (0.7, 10)
Patel 2011	Mexico	n.a.	24	5.3 (3.0, 9.3) 5.8 (2.6, 13)
Velázquez 2012	Mexico	n.a.	56	6.5 (95.5% CI 4.2, 10)

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Rotavirus vaccine doses in Mini-Sentinel study (for period for which charts reviewed, through 6/2011 maximum)

	1st doses	All doses
RotaTeq	507,874	1,277,556
Rotarix	53,638	103,098

Intussusception case-finding algorithm

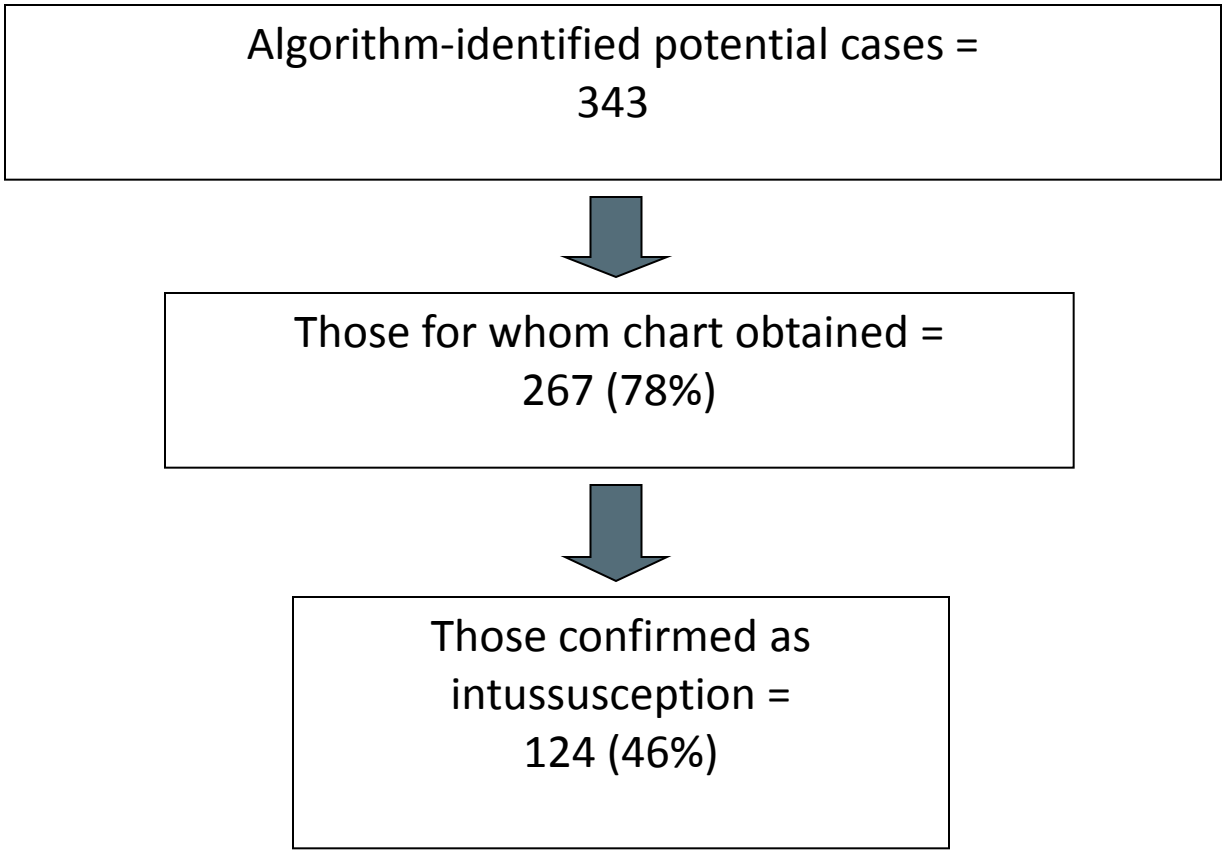
First-ever of any of these in ED or inpatient setting:

- ICD-9 560.0 (intussusception)
- ICD-9 543.9 (unspec. diseases of appendix, including intussusception)
- CPT 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** (specific vaccine, dose, age) of intussusception cases
- Standardized chart abstraction and adjudication forms
- Pediatrician adjudicators reviewed chart material to determine if cases found by algorithm truly intussusception
- Adjudicators blinded to vaccination status

Chart review metrics

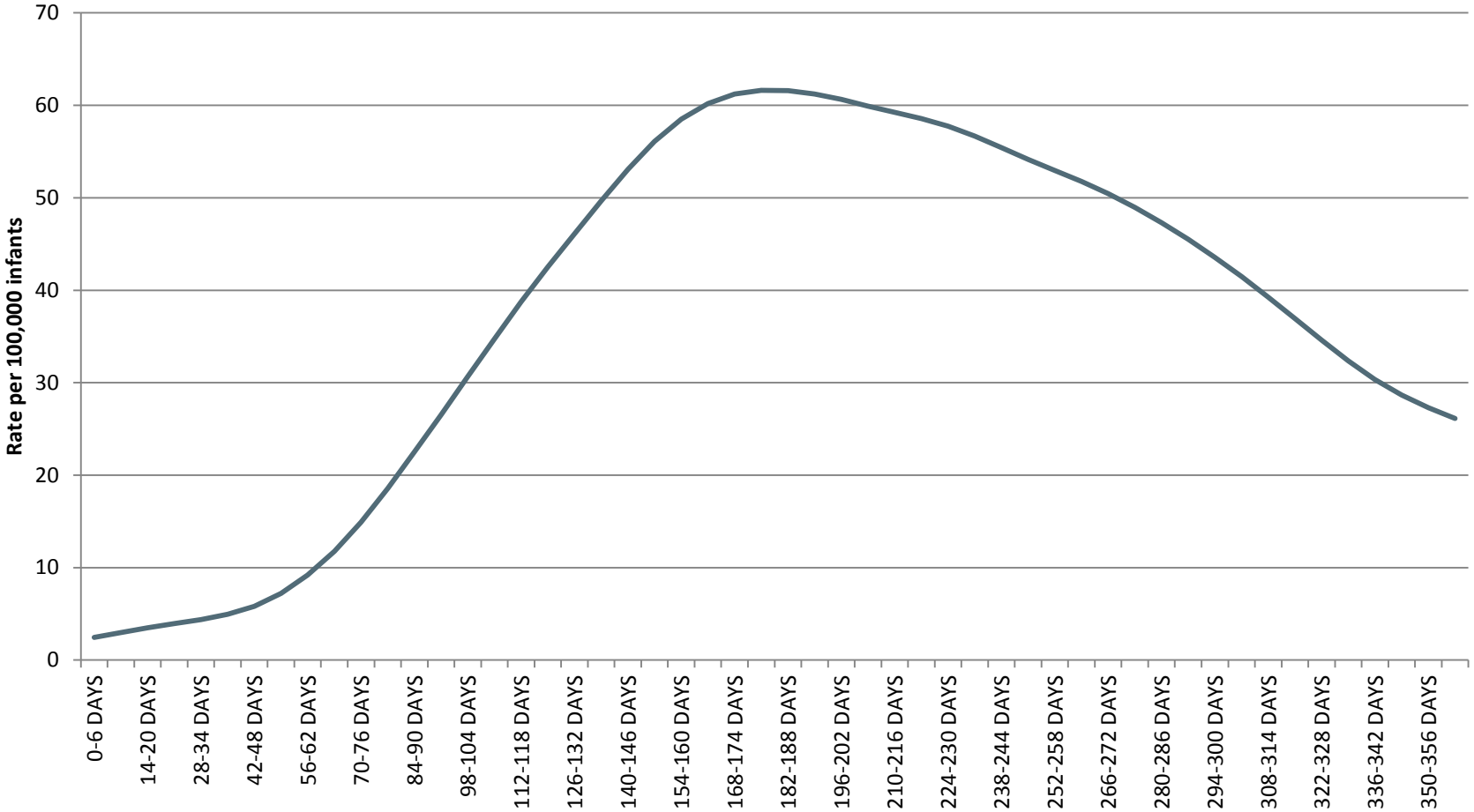


Cases are from whole infant population and include unexposed

Designs and analysis approaches

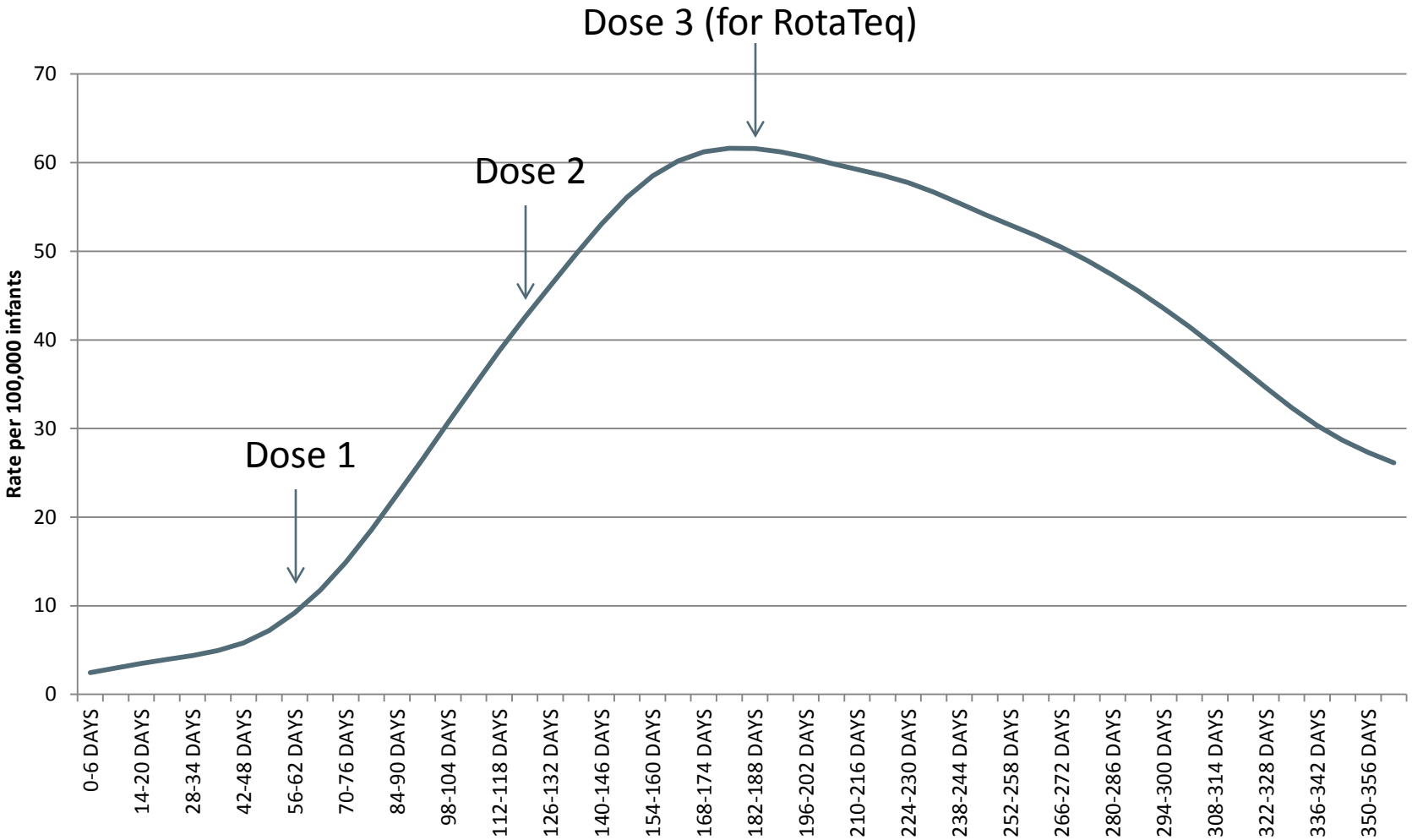
- Vaccinated infants only (self-controlled risk interval)
  - Uses just vaccinated cases with intussusception in either pre-specified risk interval or comparison interval
  - Analysis by logistic regression
- All infants (cohort)
  - Uses exposed and unexposed person-time of whole infant population
  - Analysis by Poisson regression

Intussusception incidence by age



from Tate et al. *Pediatrics* 2008;121:e1125-e1132

Intussusception incidence by age



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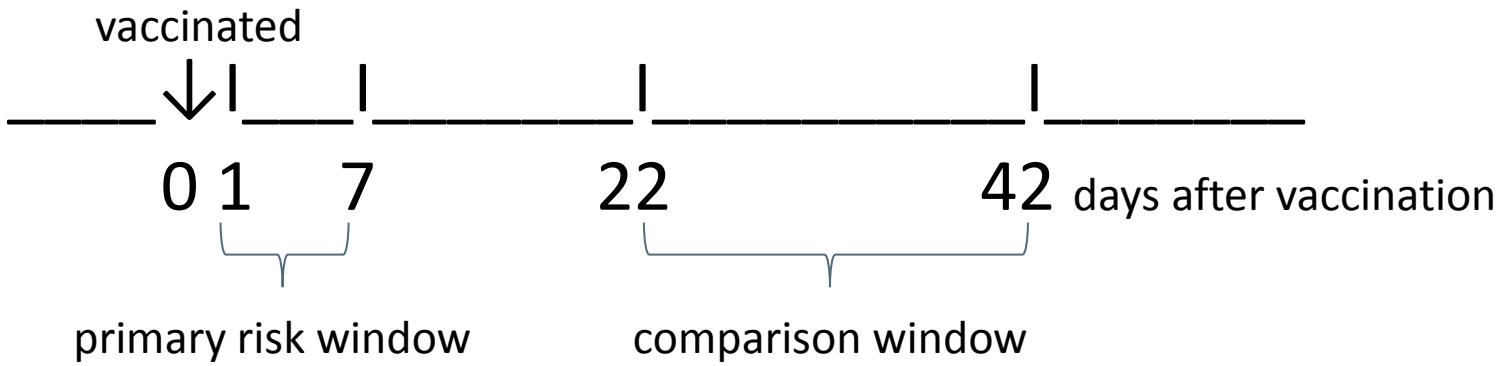
Self-controlled risk interval design

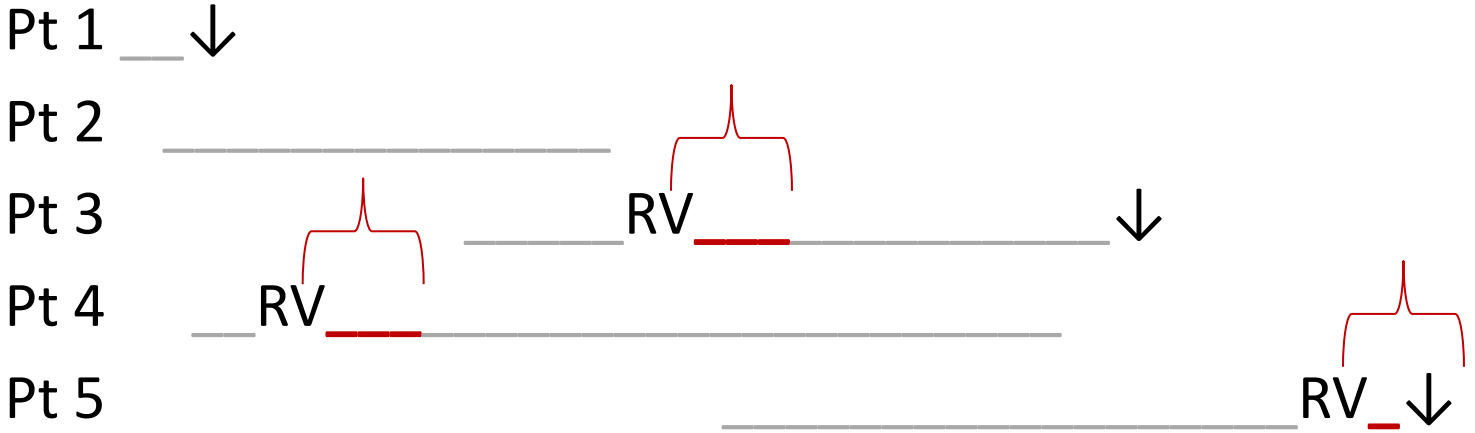
- Each subject serves as own control; adjusts for individuals' characteristics that don't change



- Adjust for age-specific risk of intussusception using logistic regression with offset term

Cohort design

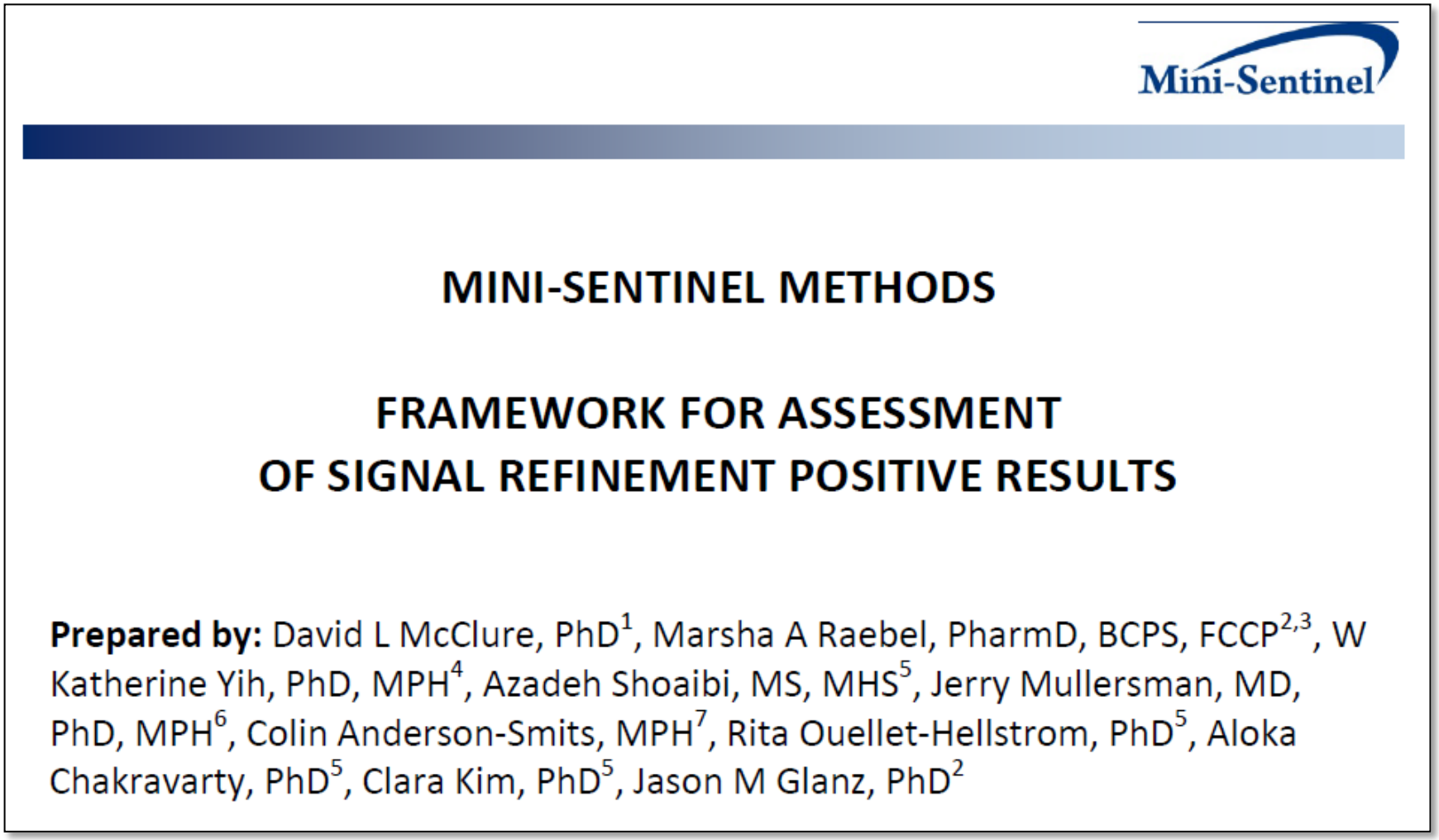
- Uses exposed and unexposed person-time in 1st year of life from whole population



- Adjust for age-specific risk of intussusception using Poisson regression with polynomial risk function

Complementarity of designs

Design	Pros	Cons
Self-controlled	Controls well for fixed risk factors, e.g. race/ethnicity	Requires accurate age-specific incidence for age adjustment
Cohort	Higher statistical power; extrinsic background rates not needed	Could be affected by residual confounding



www.mini-sentinel.org/work_products/Statistical_Methods/Mini-Sentinel_Methods_Framework-for-Assessment-of-Signal-Refinement-Positive-Results.pdf

Concern	To address concern
1. Data validity	Examine descriptive statistics in detail
2. Systematic bias	
a. Misclassification	
i. Of exposure	Review charts to confirm RV exposure (type, dose number) Use 2 risk windows, 1-7 d and 1-21 d
ii. Of outcome	Review charts to confirm intussusception
b. Selection bias	Use exposed and unexposed person-time from same people (with self-controls and with the cohort)
c. Confounding	Use SCRI analysis to adjust for fixed risk factors Use multivariate adjustment in regression modeling Age: Adjust for age in all analyses, using either age-specific incidence from literature or in M-S data

List of concerns adapted from Mini-Sentinel Framework for Assessment of Positive Results (1st of 2 slides)

Concern	To address concern
3. Magnitude of influence of systematic error on risk estimates	Quantitative bias analysis Examples:
	Re-do analyses including possible cases (neither confirmed nor ruled out)
	Re-do analyses taking into consideration cases whose charts were not obtained

Additional secondary analysis: examine pattern in timing of onset after vaccination, using age-adjusted temporal scan statistics

Adapted from Mini-Sentinel Framework for Assessment of Positive Results
(2nd of 2 slides)

- Final results available by fall 2013