Monitoring of Intussusception after Rotavirus Vaccines—United States, Vaccine Adverse Event Reporting System (VAERS), 2006-2012

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Vaccine Adverse Event Reporting System (VAERS) (co-managed CDC and FDA)[1]

Strengths

- Rapid signal detection
- Can detect rare adverse events
- Generates hypothesis
- Encourages reports from healthcare providers and accepts reports from patients and others
- Data available to the public

Limitations

- Reporting bias (e.g., underreporting, stimulated reporting)
- Inconsistent data quality and completeness
- Not designed to assess if vaccine caused an adverse event
- Lack of unvaccinated comparison group

1. VAERS website: http://vaers.hhs.gov

VAERS Post Licensure Experience

- 2008 analysis from VAERS, suggested clustering of intussusception reports during 3-6 days after the first dose of RotaTeq (RV5) and after ~ 9 million doses of RV5 were distributed in the US*

* Haber et al. Pediatrics 2008 121(6):1206-1212

Study Objectives

- To update evaluation of temporal clustering of intussusception reports to VAERS after RotaTeq (RV5)
- To present descriptive data of VAERS intussusception reports after Rotarix (RV1)

Method:
Clinical assessment

- **We assessed all intussusception (IS) reports among infants< 1 year of age reported to VAERS during**
  - February 2006-April 2012 for RV5 and
  - February 2008-December 2012 for RV1
- **All IS reports were verified using the Brighton Collaboration Level 1 case definition for intussusception***
- **Vaccine history and dose number were ascertained via immunization records**

***Brighton case definition Level 1 : Documented on autopsy, surgery or radiologically; Tapiainen T, Vaccine 2006 24(9); 1483-7**

Method (cont.)
statistical Method

- **Self-controlled risk interval (SCRI) analysis[1]**
  - Conditional Poisson regression to estimate the daily reporting ratio (DRR) of IS comparing average daily reports 3-6 versus 0-2 days after vaccination
- **Reporting rate differences were calculated based on DRRs and background rates of intussusception[2]**
  - The excess number of events in the United States was estimated based on number of births per year and vaccine coverage similar to that of a mature vaccination coverage of diphtheria tetanus acellular pertussis (DTaP) vaccine
- **Few reports were submitted after Rotarix (RV1), allowing only a descriptive analysis**

[1] Weldeselassie YG, et al. Use of the self-controlled cases-series methods in vaccine safety studies. Epidemiol Infect 2011;139 (12):1805-17 [2] Background rates from VSD hospital discharge data and ER visits for intussusception during 2000-2006, when no rotavirus vaccine was in use in the US

Results: Intussusception (IS) Reports after RotaTeq (RV5) and Rotarix (RV1) Vaccines, VAERS 2006-2012

RotaTeq

- ~ 47 million doses distributed in the US*
- 6,989 total RV5 reports
- 657 (9.4%) IS
- 584 (89%) confirmed IS
- 182 (31%) after dose 1
  - 60 (33%) within 0-6 days

Rotarix

- ~7.4 million doses distributed in the US**
- 678 total RV1 reports
- 71 (21%) IS
- 66 (93%) confirmed IS
- 31 (47%) after dose 1
  - 13 (42%) within 0-6 days

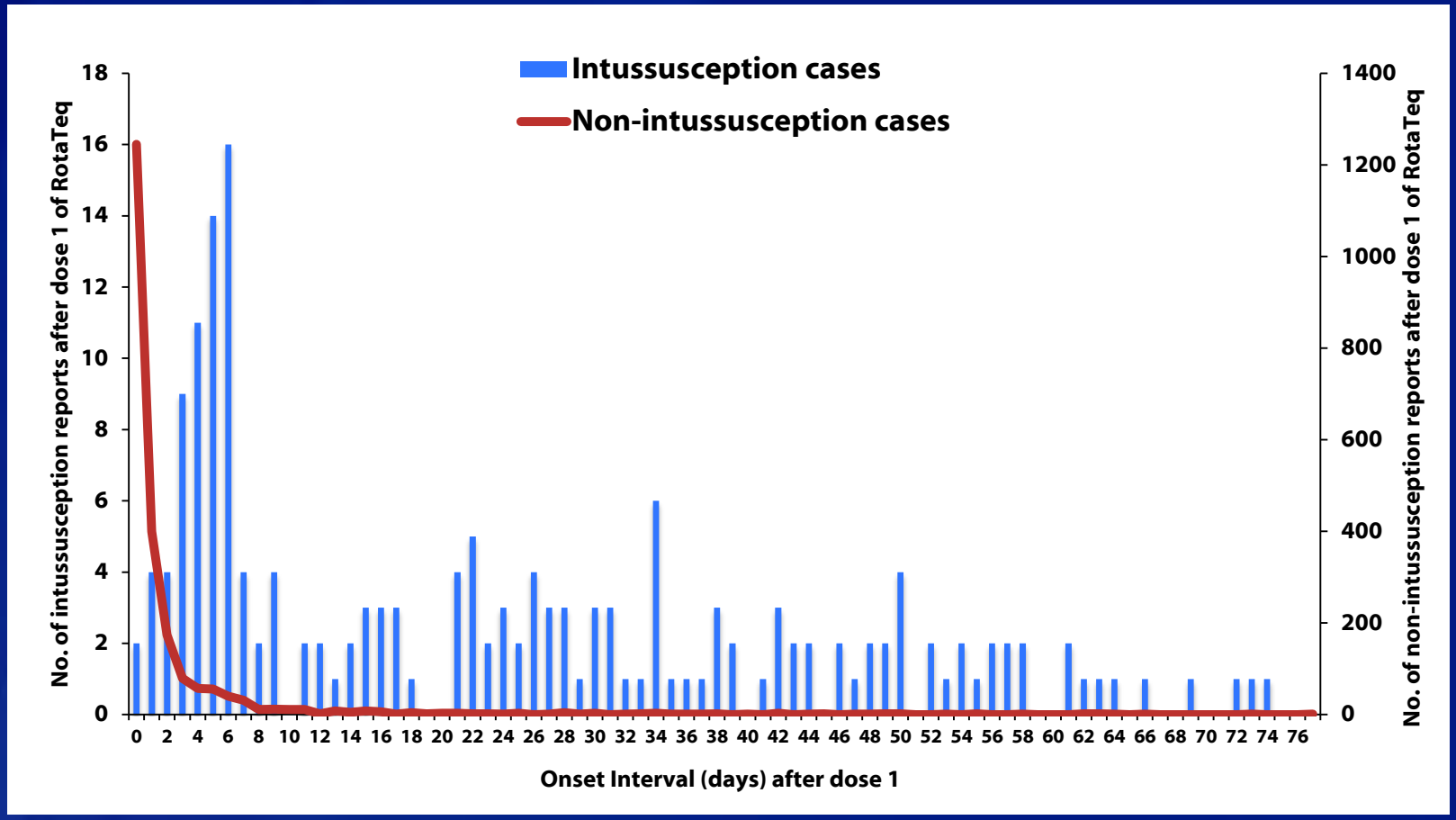
*Merck unpublished data , April 13, 2012
**GSK unpublished data, February 15, 2013

Results (cont.)
All Intussusception Reports after RotaTeq (RV5) and Rotarix (RV1) Vaccines, VAERS 2006-2012

	RotaTeq	Rotarix
	N (%)	N (%)
Total confirmed* intussusception cases	584	66
Hospitalized	544 (93)	64 (97)
Surgery	266 (45.5)	37 (56)
Bowel resection	73/266 (28.6)	3/37 (8)
Death	2 (0.3)	0

* Confirmed based on Brighton criteria level 1

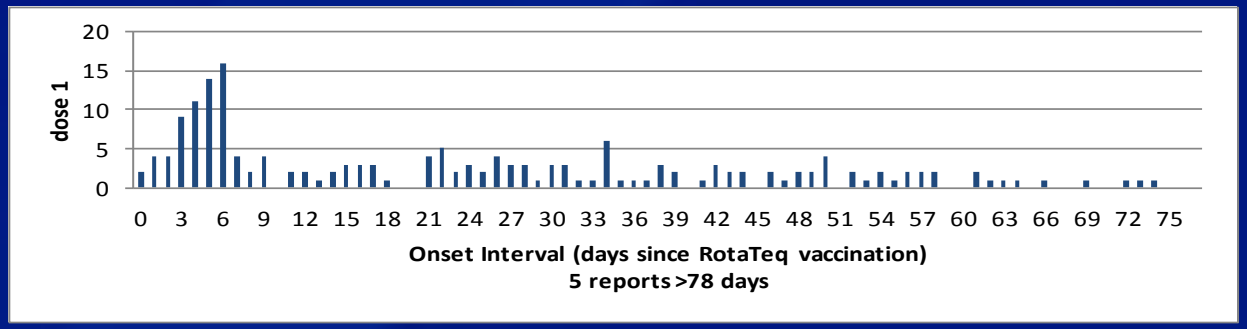
Number of reports to VAERS* of intussusception cases and non-intussusception cases after dose 1 of RotaTeq (RV5), onset interval† in days—United States, 2006-2012



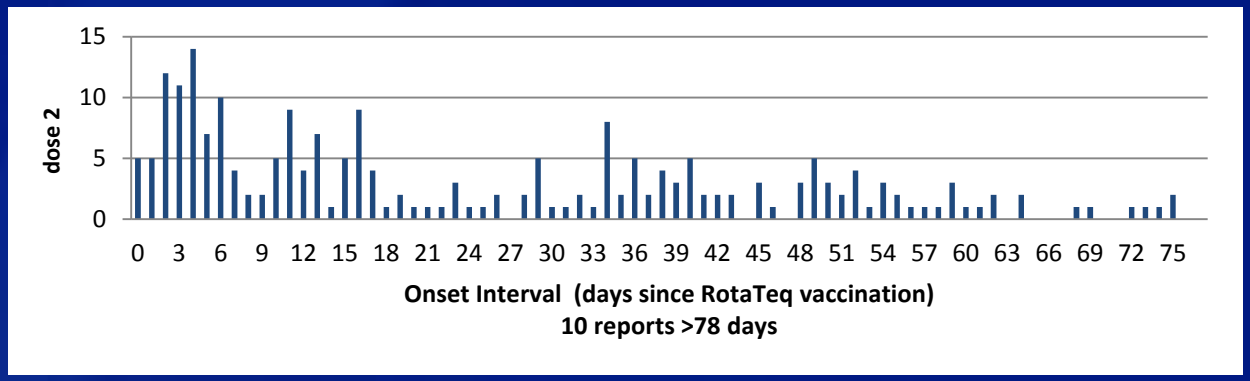
* Vaccine Adverse Event Reporting System

† Days after vaccination ; Total of 182 intussusception events, with 5 intussusception reports >78 days ranging from 79 to 399 days after vaccination

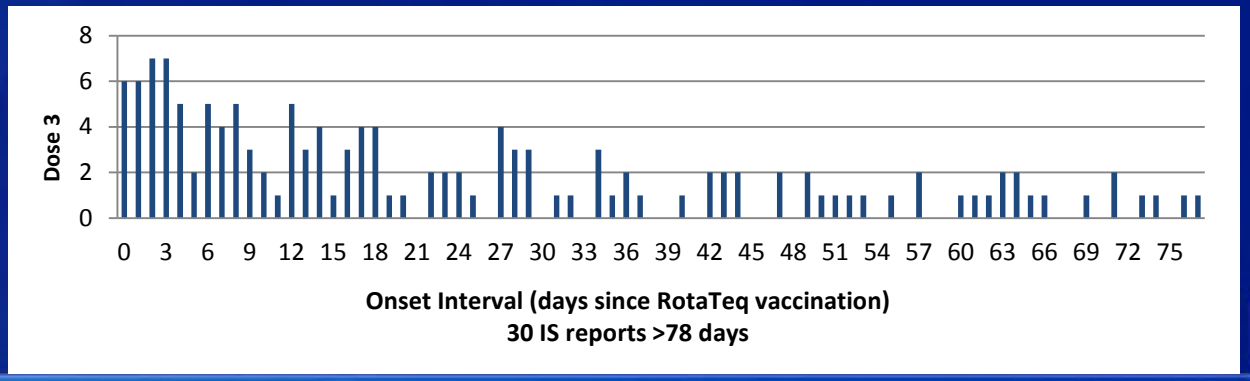
Number of reports to VAERS* of intussusception cases after RotaTeq (RV5) and onset interval† in days by dose—United States, February 1, 2006—April 30, 2012.



N=182



N=233

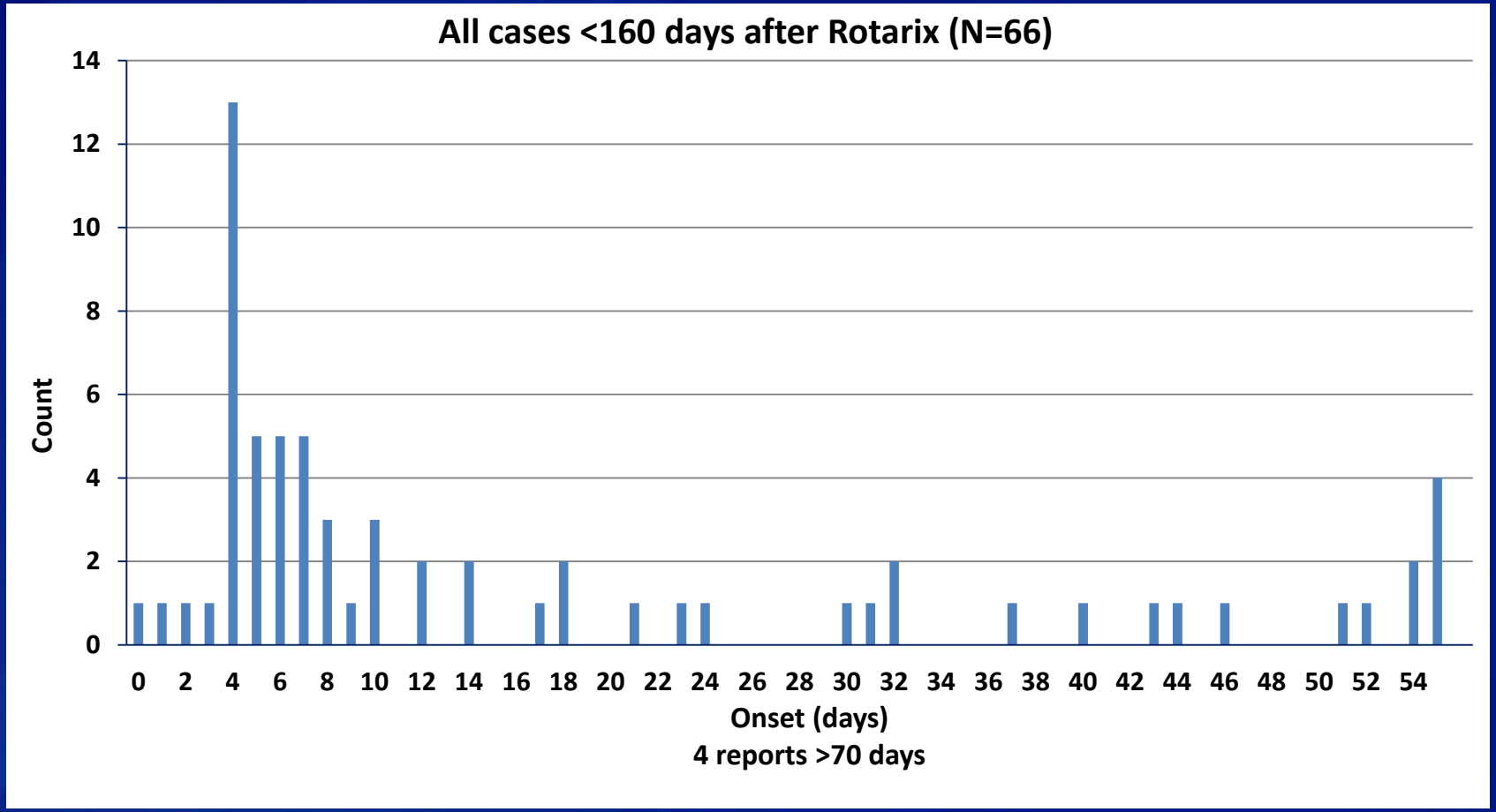


N=169

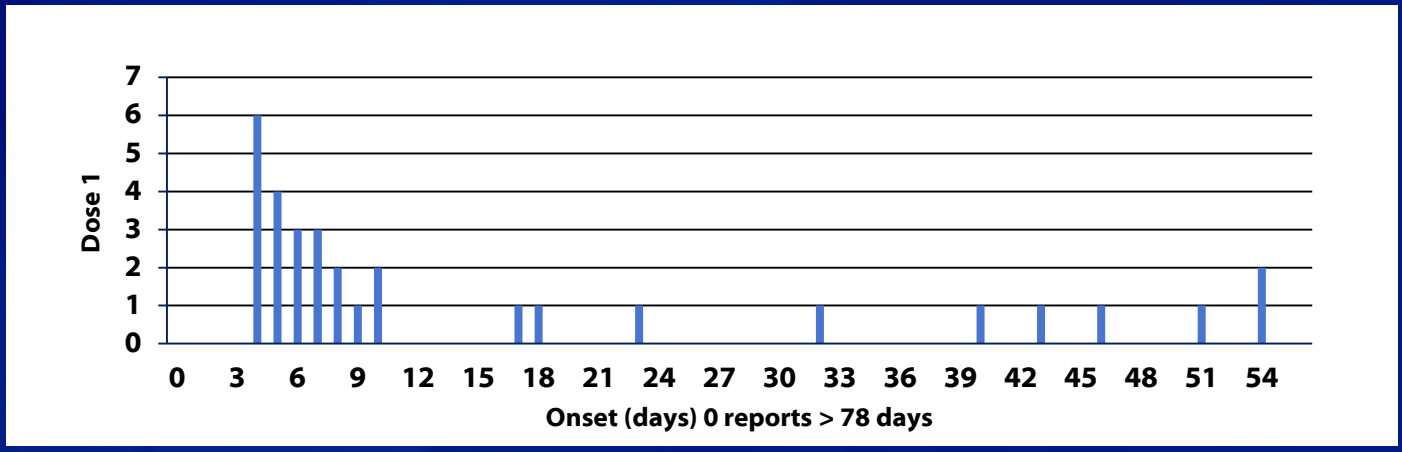
* Vaccine Adverse Event Reporting System.

† Denotes vaccination dose most recently administered before onset of intussusception.

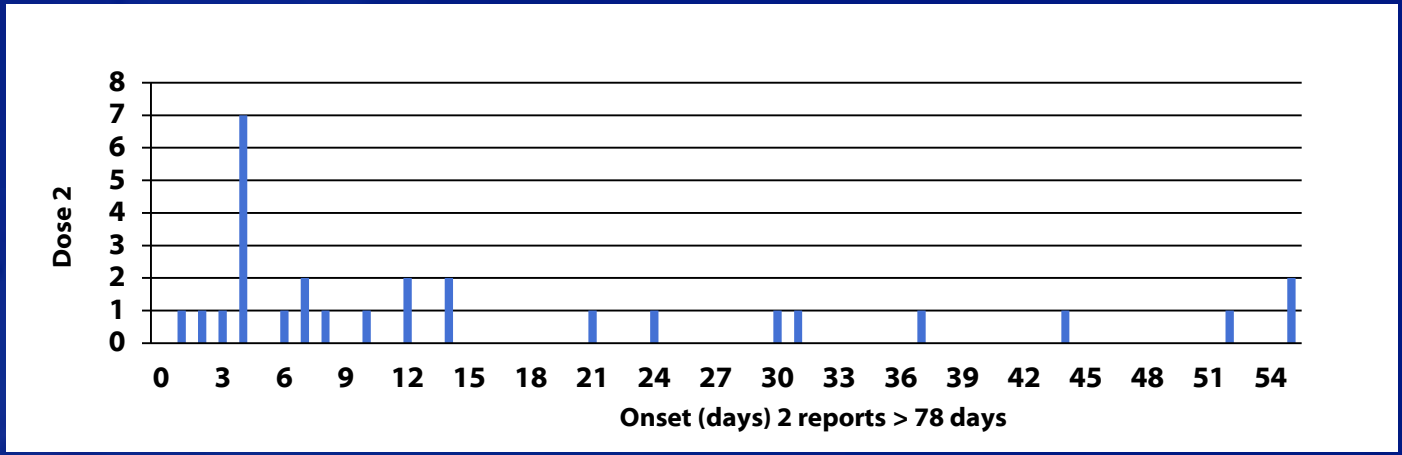
Number of reports to VAERS* of intussusception events after Rotarix vaccination, by onset interval in days United States, April 1, 2008—December 30, 2012



Number of reports to VAERS* of intussusception cases after Rotarix (RV1) by dose and onset interval† in days



N=31



N=29

*Vaccine Adverse Event Reporting System. Six reports after dose 3 (not shown)

†Denotes vaccination dose most recently administered before onset of intussusception

Results: Daily Reporting ratios and excess risk of intussusception after RotaTeq (RV5) using the self-controlled risk interval analysis for VAERS data, by dose

	Number of cases 3-6 days	Number of cases 0-2 days	Daily Reporting Ratio (95% CI)	p value	Excess risk per 100,000 infants (95% CI)	Excess cases in the US per year* related to RV5 vaccine
Dose 1	50	10	3.75 (1.90, 7.39)	<0.001	0.74 (0.24, 1.71)	30.1 (9.8, 69.9)
Dose 2	42	22	1.43 (0.85, 2.40)	0.1	0.21 (-0.07, 0.68)	8.3 (-2.9, 26.9)
Dose 3	19	19	0.75 (0.40, 1.42)	0.3	-0.16 (-0.38, 0.27)	-5.5 (-13.2, 9.3)

*Combining all three doses, the excess risk was 0.79 events (95% CI = -0.04, 1.62) per 100,000 vaccinations, translating to 33 additional events per year (95% CI = 0, 66) in the United States under a fully mature rotavirus vaccination program

http://pediatrics.aappublications.org/content/early/2013/05/08/peds.2012-2554

Limitation:
Self Control Risk interval (SCRI) method

- **Applying SCRI method to VAERS generally violates a key criterion of self-control designs that ascertainment of cases should not be influenced by exposure history; however,**
  - Analysis was limited to a narrow time window of 0-6 days and 0-2 day interval as the comparison time period
  - Since reporting efficiency is likely to be greatest in the first few days after vaccination, using the 0-2 day window as the comparison period should result in conservative relative risk estimates

- **Lower reporting of cases in days 0-2 after dose 1 could occur due to a possible healthy vaccinee bias; however,**
  - The presence of a significant signal after the first dose but not the second or third dose argues against this bias

Discussion

- **We observed a persistent clustering of reported intussusception events 3-6 days after the first dose of RV5 vaccination**
- **This clustering could potentially translate to 33 additional events per year (95% CI = 0, 66) in the US which is outweighed by the benefits of rotavirus vaccination***
  - ~40,000 diarrhea hospitalizations prevented annually in the US since rotavirus vaccine introduction
- **We were not able to quantify the risk after RV1 due to small number of reports in the US**

*Cortese M. et al. ACIP, October 2010