Rotavirus Vaccines and Intussusception in the Vaccine Safety Datalink (VSD)

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on behalf of the Vaccine Safety Datalink

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The findings and conclusions in this presentation are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention

Vaccine Safety Datalink (VSD): Background

- Established in 1990
- A collaborative project among CDC and 9 medical care organizations
- Allows for planned immunization safety studies as well as timely investigations arising from
  - hypotheses from medical literature and pre-licensure
  - reports to the Vaccine Adverse Event Reporting System (VAERS)
  - changes in immunization schedules, or the introduction of new vaccines

VSD Sites: 2013

Collects medical care and vaccination data on more than 9.2 million members annually (3% of the US population)
Average yearly birth cohort ~ 96,000

CDC
Centers for Disease Control and Prevention

VSD Published Manuscripts Rotavirus Vaccine Safety

- No increased risk of intussusception has been found for Pentavalent Rotavirus vaccine (RV5) in VSD
  - 2010: In this study of 207,621 doses, we found no evidence that RV5 was associated with intussusception during days 1 to 30 after vaccine administration[1].
  - 2012: After 786,725 doses of RV5 vaccine administered, including more than 300,000 first doses, no increased risk of intussusception following RV5 in 1- to 30-day or 1- to 7-day risk windows[2].
    - An excess risk of 1 event per 65,287 RV5 vaccines following dose 1 can be reliably excluded
    - Cannot rule out the possibility of a lower-level risk

1. Belongia EA et al. Pediatr Infect Dis J 29: 1-5, 2010.
2. Shui IM et al. JAMA 307: 598-604, 2012.

Analysis Outline

Analysis	Comparison	Intussusception Case Definition
1. RV1 Rapid Cycle Analysis (RCA) surveillance	Historical background rate	ICD-9 coded medical visit
2. RV5 cohort update	Historical background rate	ICD-9 coded medical visit
3. RV1 compared to RV5	Concurrent vaccinated cohort	Brighton definition (chart confirmed)

Analysis 1: RV1 RCA Surveillance for Intussusception

Objectives

- Monitor for an increased risk of intussusception during **1-7 days** after receipt of RV1

Population

- 6 VSD sites*
- Infants 4 - 34 weeks of age
- Vaccinated April 2008 to March 2013
- Intussusception case definition
  - ICD 9 codes
    - 543.9 - other and unspecified disease of the appendix including intussusception
    - 560.0 - intussusception
  - Limited to first diagnosis from ER and Inpatient setting

*Northern and Southern California Kaiser, Group Health Cooperative, Northwest Kaiser, Kaiser Colorado and Marshfield Clinic

Analysis 1: RV1 RCA Surveillance for Intussusception

Methods

- A prospective cohort design was used to assess the risk of intussusception among children receiving RV1 compared to expected numbers of intussusception based on historical background rates

- The historical background rates were:
  - Stratified by age in weeks and VSD site
  - Restricted to recent years prior to RV1/RV5, 2001-2005

- Sequential analysis methods were utilized to:
  - Monitor the risk on a weekly basis
  - Maximized sequential probability ratio test (maxSPRT) was used to adjust for the repeated weekly testing

- ≥ 3 cases required to “signal”

Analysis 1: RV1 RCA Surveillance for Intussusception – Days 1-7

Dose	No. of Doses	Observed‡	Expected*	Obs/Exp	LLR€	Critical Value	AR per 100,000 Doses	1 Additional Case per
All Doses	207,955	6	0.716	8.376	7.469	2.565		
Dose 1	115,908	2	0.227	8.818	NA	2.151		
Dose 2	92,047	4	0.489	8.172	4.892	2.151		

‡ Observed includes non-confirmed cases identified in the inpatient and ER settings
*Expected based on historical background rates and adjusted for age in weeks and VSD site
€ Log Likelihood ratio

Preliminary

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Dose 1	115,908	2	0.227	8.818	NA	2.151	**1.53**	**65,374**
Dose 2	92,047	4	0.489	8.172	4.892	2.151	**3.81**	**26,217**

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Preliminary

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Attributable Risk 5.34 per 100,000 Infants
1 Additional Case of Intussusception for Every 18,713 Infants Vaccinated with RV1 Series

‡ Observed includes non-confirmed cases identified in the inpatient and ER settings
*Expected based on historical background rates and adjusted for age in weeks and VSD site
€ Log Likelihood ratio

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Analysis 1: RV1 RCA Surveillance for Intussusception – Days 8-30

Dose	No. of Doses	Observed‡	Expected*	Obs/Exp
All Doses	207,955	4	3.04	1.32
Dose 1	115,908	1	1.01	.99
Dose 2	92,047	3	2.03	1.48

‡ Observed includes non-confirmed cases identified in the inpatient and ER settings
*Expected based on historical background rates and adjusted for age in weeks and VSD site

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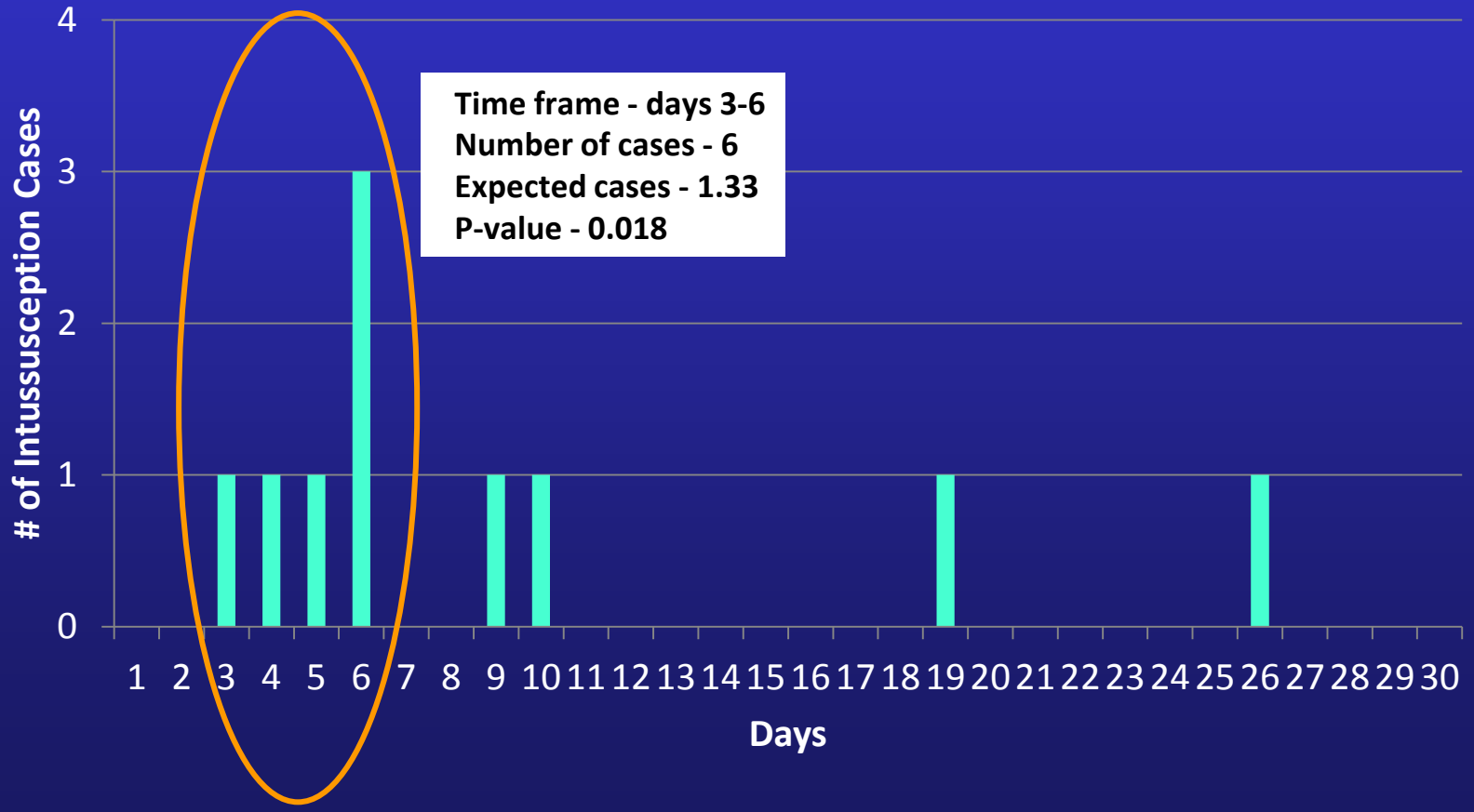
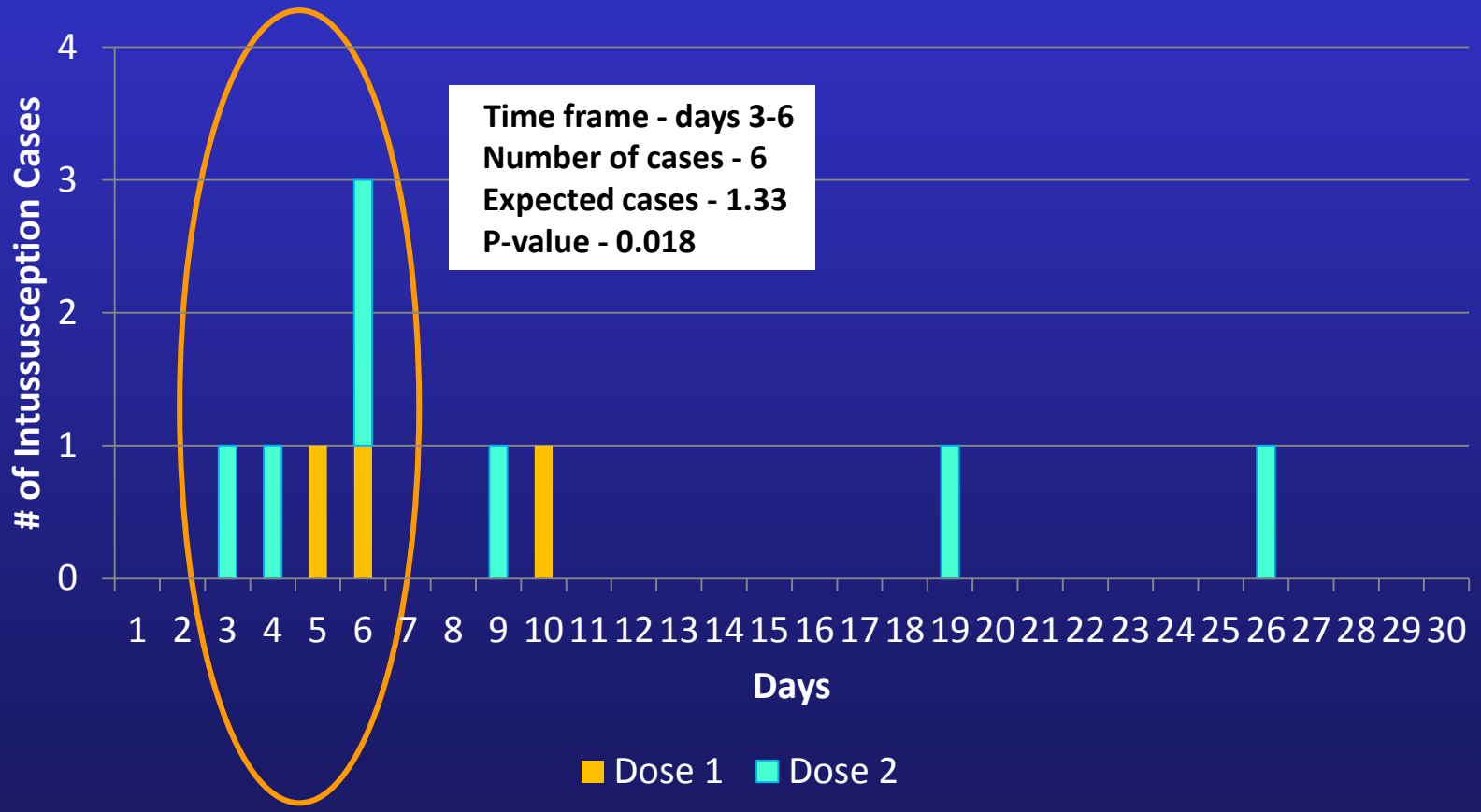
RV1 Cluster Analysis
of Intussusception Cases by Days Since Vaccination – All Doses



RV1 Cluster Analysis
of Intussusception Cases by Days Since Vaccination – All Doses



Analysis 2: RV5 Cohort Update

- This is an update to the VSD RV5 findings published by Shui et al in JAMA, Feb. 2012

- Methods are the same as analysis 1 except:
  - This analysis is of RV5 vaccination
  - The study period is May 2006 through March 2013
  - We conducted a one time analysis vs. weekly prospective surveillance

Analysis 2: RV5 Cohort Update

RV5 Doses	No. of Doses	Observed‡	Expected*	Obs/Exp	95% CI
All Doses	1,301,810	8	7.11	1.13	0.49- 2.22
Dose 1	493,560	4	1.52	2.63	0.72 - 6.74
Dose 2	427,297	0	2.37	0	0.00 - 1.26
Dose 3	380,953	4	3.2	1.25	0.34 - 3.20

‡ Observed includes non-confirmed cases identified in the inpatient and ER settings
*Expected based on historical background rates and adjusted for age in weeks and VSD site

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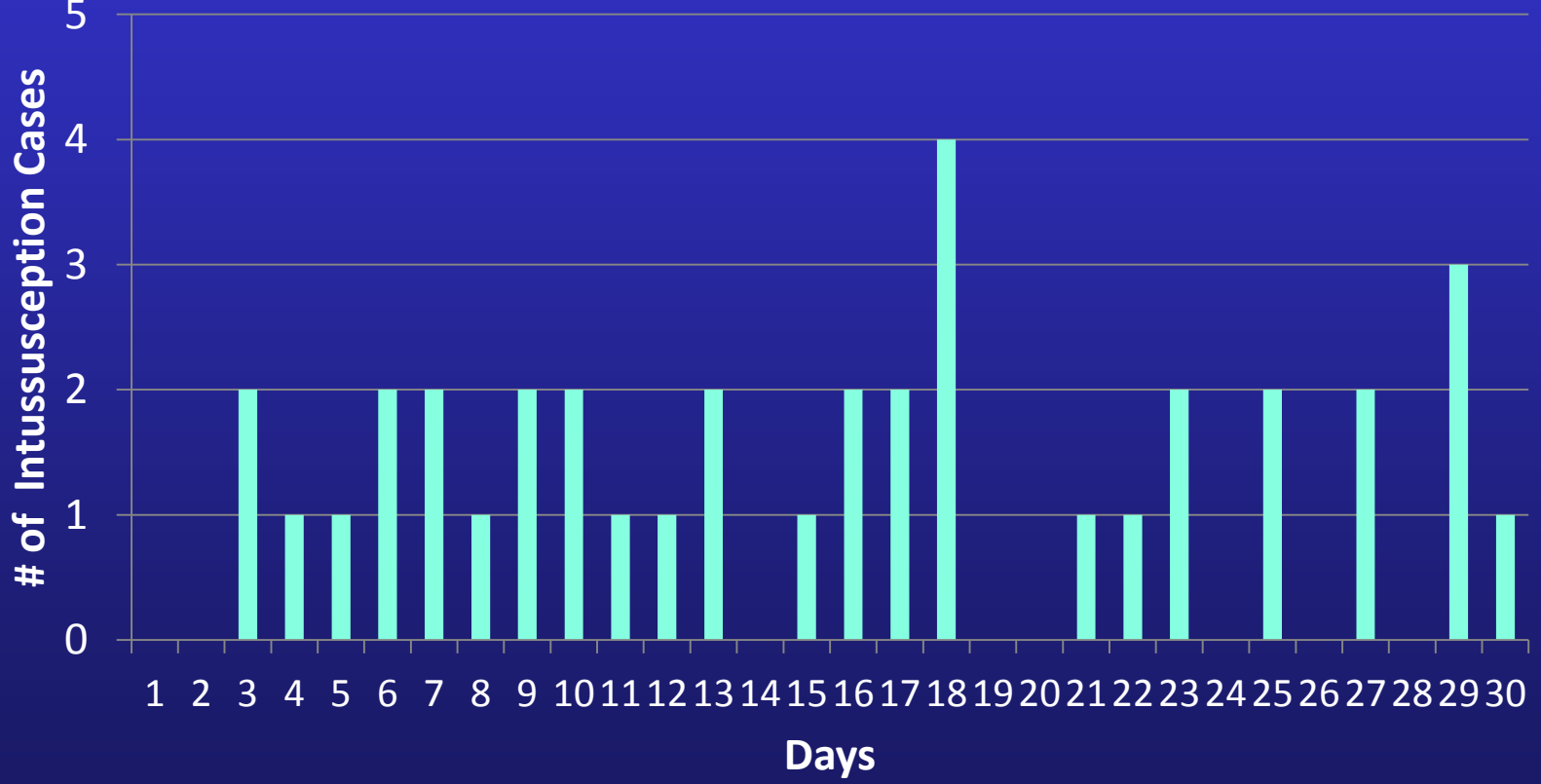
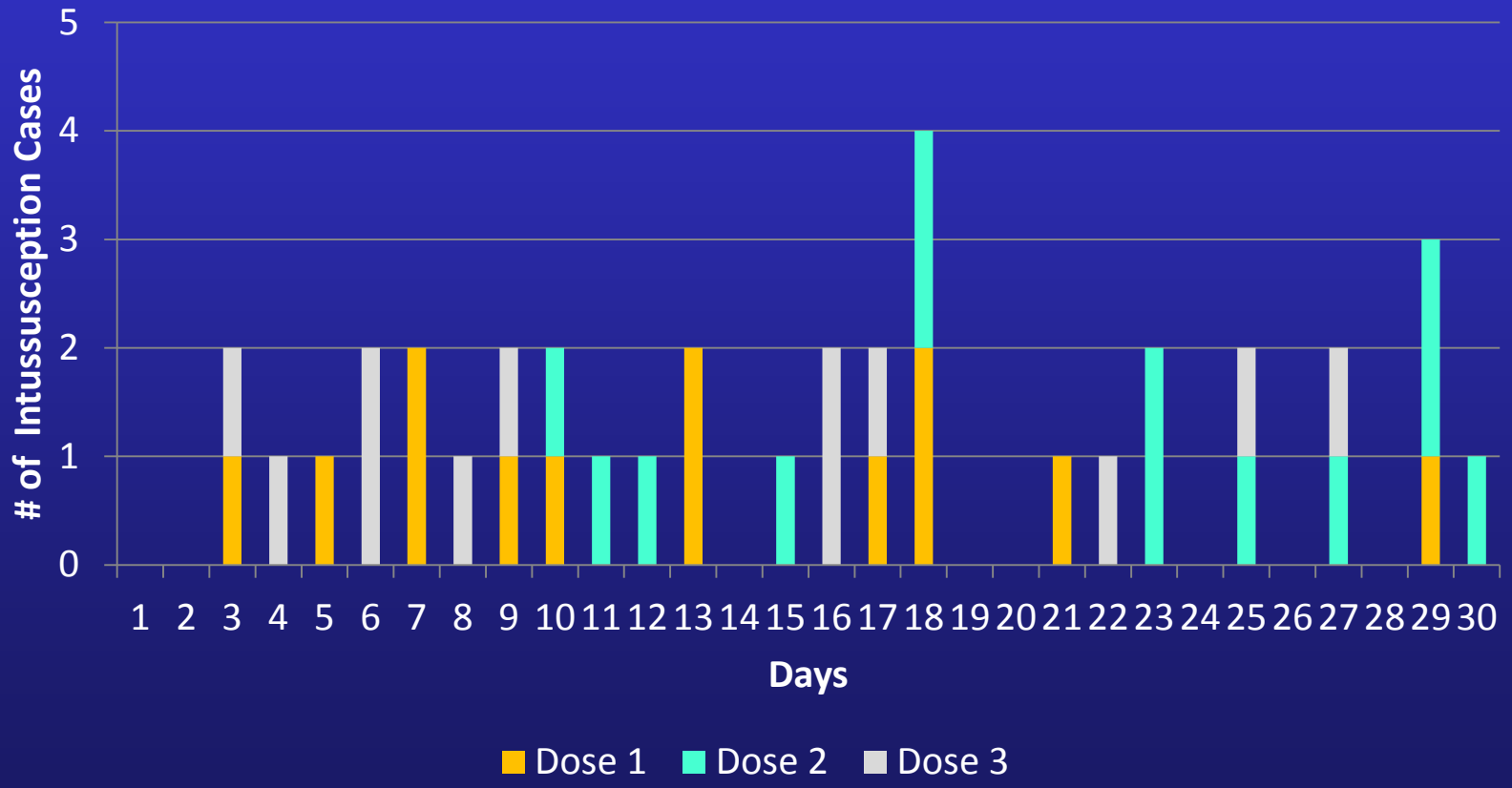
RV5 Cluster Analysis
of Intussusception Cases by Days Since Vaccination – All Doses



RV5 Cluster Analysis
of Intussusception Cases by Days Since Vaccination – by Dose



Analysis 3: RV1 Compared to RV5

- Reviewed medical charts on all cases of intussusception regardless of setting within 1-7 days of any RV1 or RV5 vaccination
- Cases were classified according to Brighton Collaboration case definition by 2 independent adjudicators.
  - Third review conducted if independent adjudicators disagreed
- Conducted an analysis on chart confirmed intussusception cases within 1-7 days following RV1 compared to RV5 vaccination
  - Brighton Collaboration Level 1 cases were included
  - Compared the risk of intussusception following RV1 to the risk following RV5 during the time period April 2008 to March 2013
  - Exact logistic regression

Chart Confirmed Intussusception Case Findings Days 1-7 Following Vaccination

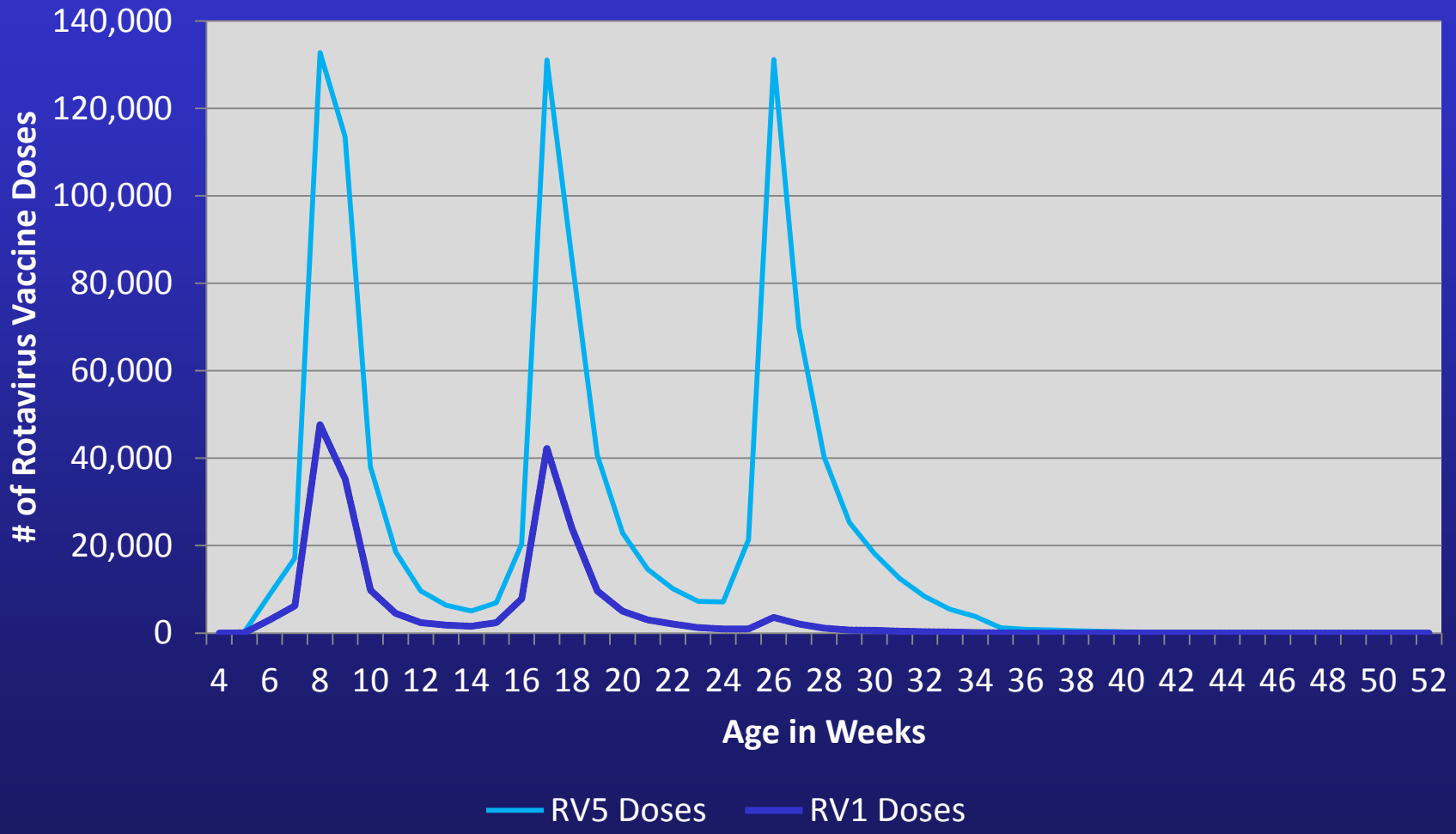
Intussusception	RV1	RV5
Total Cases Reviewed	7	9
Brighton Level 1	5 (71%)	6 (67%)
Surgical Criteria	2 *	1
Radiologic Criteria	3	5
Brighton Level 2	1(14%)	0(0%)
Not a Case	1(14%)	3(33%)
Total Confirmed Cases	6	6

*1 Case Required Bowel Resection

Chart Confirmed Intussusception Case Findings Days 1-7 Following Vaccination

Brighton Level 1 Cases	RV1 (n=5)	RV5 (n=6)
Age in Weeks Mean (range)	15 (8-19)	22 (8-30)
Male	0%	50%
Hospitalization	100%	100%
Length of Stay in Days (range)	1.6 (1-4)	1.5(1-2)
Death	0%	0%

Total Numbers of RV1 and RV5 Doses in the VSD by Week



Analysis 3: RV1 Compared to RV5 Brighton Level 1 Intussusception Cases

Dose	RV1 Doses	RV1 Confirmed Cases	RV5 Doses	RV5 Confirmed Cases
All Doses	207,955	5	999,123	6
Dose 1	115,908	2	355,994	2
Dose 2	92,047	3	345,025	0
Dose 3	0	0	298,104	4

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Analysis 3: Exact Logistic Regression Results for RV1 Compared to RV5 - Brighton Level 1 Intussusception Cases

Model	RR	95% CI	P-Value
Dose 1	3.07	0.22 – 42.37	0.509
Dose 2	undefined	2.19 – undefined	0.0187
Crude (Dose 1 & 2)	8.43	1.38 – 88.50	0.0173
Adjusting for Age and Site (Dose 1 & 2)	9.37	1.42 – 103.84	0.0163

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Analysis 3: Risk Difference for RV1 Compared to RV5 Brighton Level 1 Intussusception Cases

Dose	RV1 Risk per 100,000	RV5 Risk per 100,000	Risk Difference per 100,000	1 Additional Case per
Dose 1	1.73	0.56	1.16	85,933
Dose 2	3.26	0	3.26	30,682
Total			**4.42** **95% CI (0 – 8.89)**	**22,610** **95% CI (NA – 11,250)**

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Summary

- VSD study found a statistically significant elevated risk of intussusception following RV1 within 1-7 days of vaccination
  - The risk was increased following both doses of RV1
- After analyzing over 1.3 million doses, no significant increased risk was identified following RV5
- The increased risk for RV1 and intussusception was similar when we conducted both a historical and concurrent chart confirmed study design
  - Historical Comparison
    - Attributable Risk = 5.34 per 100,000 infants
    - 1 additional case for every 18,713 infants vaccinated with RV1 series
  - Concurrent RV5 Comparison – Brighton Level 1
    - Risk Difference = 4.42 per 100,000 infants
    - 1 additional case for every 22,610 infants vaccinated with RV1 series

Acknowledgements

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  - Claudia Vellozzi, MD, MPH
- Northern California Kaiser
- Southern California Kaiser
- Group Health Cooperative
- Northwest Kaiser
- Marshfield Clinic
- Kaiser Colorado

VSD Acronyms

Vaccine Safety Datalink	VSD
Distributed Data Model	DDM
Dynamic Data Files	DDF
Rapid Cycle Analysis	RCA

Group Health Cooperative, WA	GHC
Harvard Pilgrim Health Care, MA	HAR
HealthPartners Research Foundation, MN	HPM
Marshfield Clinic, WI	MFC
Kaiser Permanente of Colorado, CO	KPC
Northern California Kaiser Permanente, CA	NCK
Northwest Kaiser Permanente, OR	NWK
Southern California Kaiser Permanente	SCK