Rotavirus Vaccines: Update on Intussusception

Marietta Vázquez, MD

Chair, ACIP Rotavirus Vaccines Work Group

June 20, 2013

Main Rotavirus Vaccine Phase III Trials

- Large size, to permit evaluation of intussusception (IS)
- No increased risk identified

Study	Time after dose	IS in Vaccine Arm	IS in Placebo Arm	RR (95% CI)
RV5: Finland/US	Days 1-42 Doses 1, 2, 3 combined	6/34,837	5/34,788	1.6 (0.4-6.4)
RV1: Latin America	Days 1-30 Doses 1, 2 combined	6/31,673	7/31,552	0.85 (0.30-2.42)

- Post-marketing monitoring important

Rotavirus Vaccines in the United States

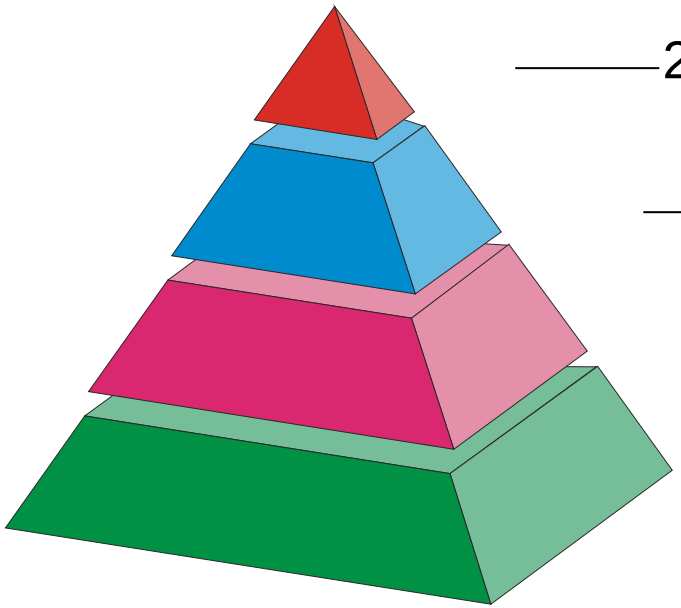
- Feb 2006 – RV5 (RotaTeq) recommended
- June 2008 – RV1 (Rotarix) recommended

ACIP Recommended Ages and Intervals

	RV5 (RotaTeq)	RV1 (Rotarix)
Number of doses in series	3	2
Recommended ages for doses	2, 4 and 6 months	2 and 4 months
Minimum age for Dose 1	6 weeks	
Maximum age for Dose 1	14 weeks 6 days	
Minimum interval between doses	4 weeks	
Maximum age for last dose	8 months 0 days	

US Rotavirus Disease Burden in Pre-Vaccine Period

One US birth cohort followed to age 5 yrs



20–60 deaths

55,000–70,000 hospitalizations

205–272,000 emergency room visits

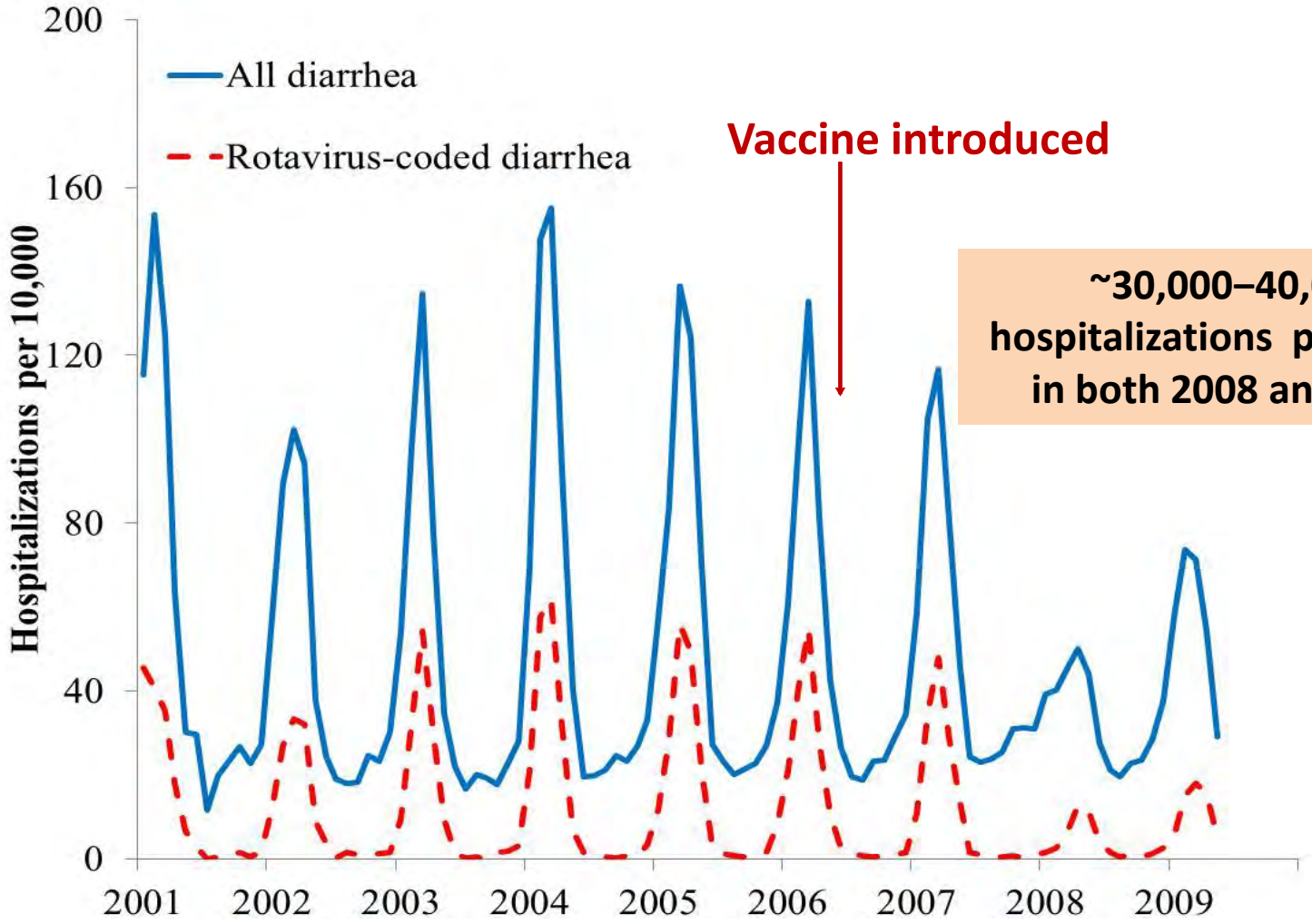
410,000 outpatient/office visits

2.7 million episodes

Hospitalization Data from MarketScan Database

Diarrhea and Rotavirus-coded Hospitalizations

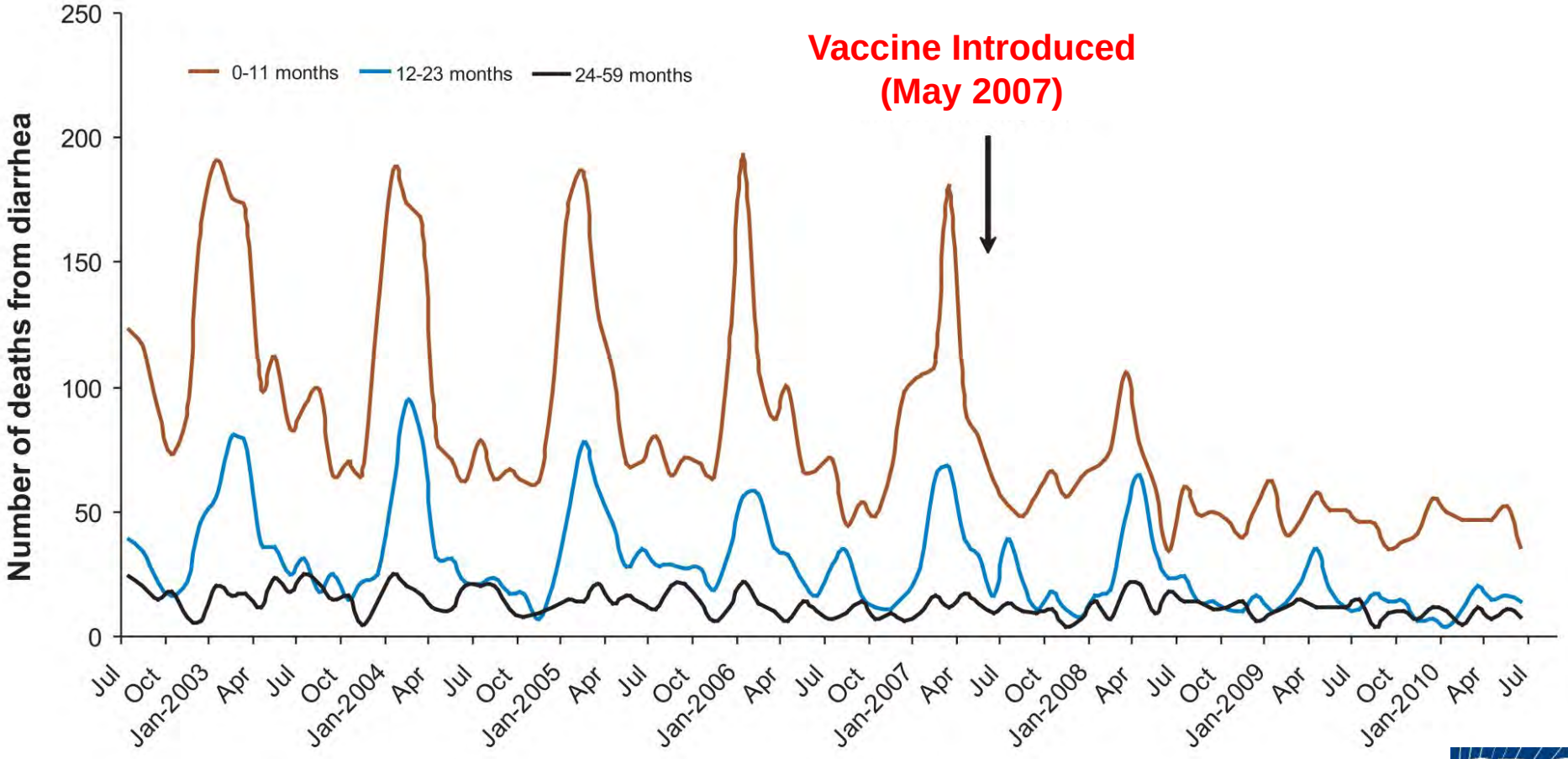
Children aged <5 yrs, 2001-2009



~30,000–40,000 hospitalizations prevented in both 2008 and 2009

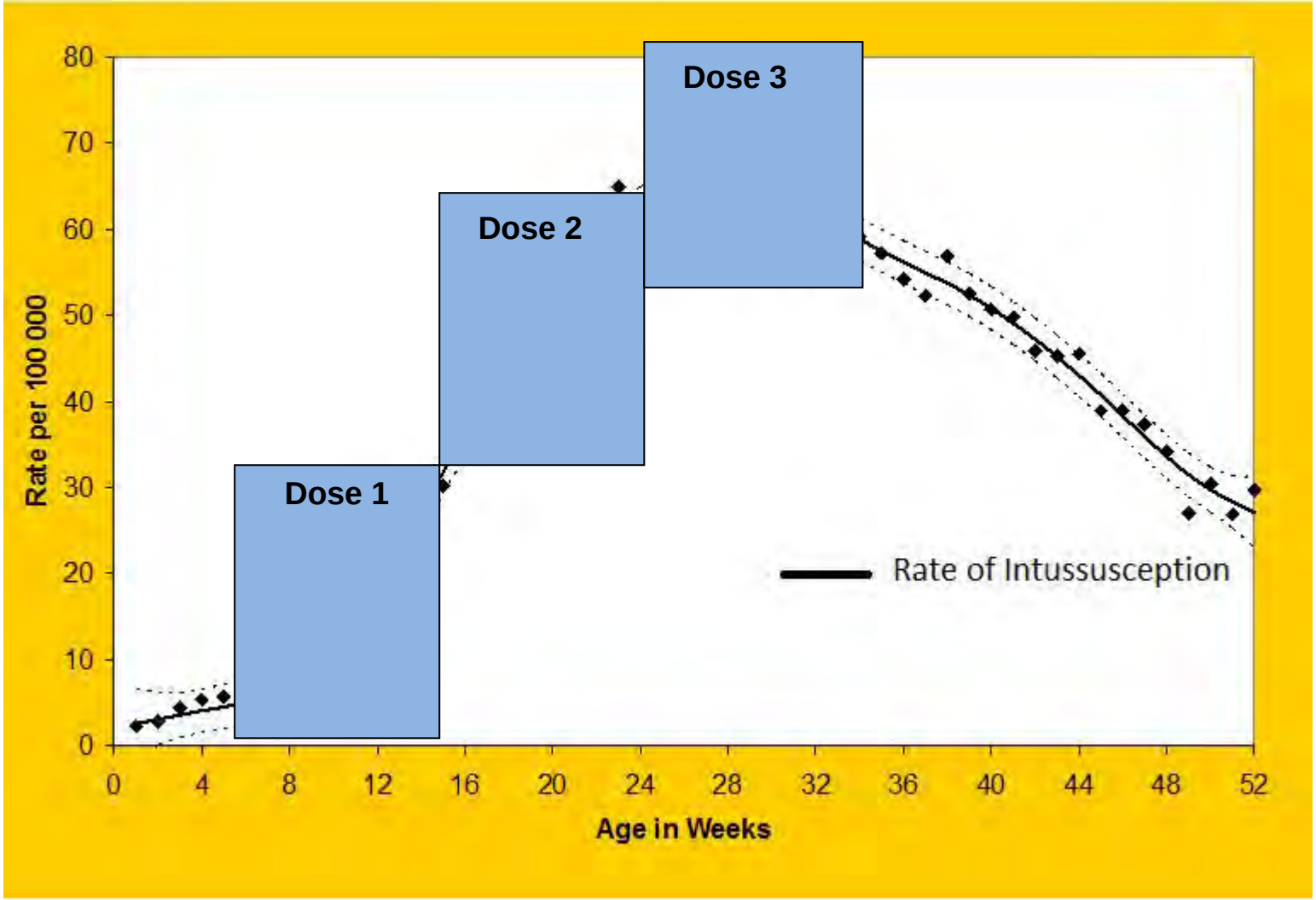
Cortes J, Curns A, Tate, J et al N Engl J Med 2011

Large Reductions in Diarrhea Deaths after Vaccine Introduction in Mexico



Richardson V J et al N Engl J Med 2010; Richardson V, Parashar U, Patel M N Engl J Med 2011

Background Rate of Intussusception Hospitalizations
US infants, 1993-2004



Tate et al. Pediatrics 2008; 121;e1125-e1132

Brighton Criteria: Level 1
Highest level of diagnostic certainty

- SURGICAL
  - Demonstration of invagination of intestine at surgery (in absence of another primary cause such as volvulus or pyloric stenosis);

  or
- RADIOGRAPHIC
  - Demonstration of invagination of intestine by air or liquid contrast enema; *or*
  - Demonstration of an intra-abdominal mass by abdominal ultrasound with specific criteria, that is proved to be reduced by hydrostatic enema on post-reduction ultrasound;

  or
- AUTOPSY
  - Demonstration of invagination of intestine at autopsy

Post-marketing Intussusception Studies
ACIP Meeting, October 2010

RV5 (RotaTeq)

Study Population Investigators	Methods	Results (selected)	RR	95% CI
US: VSD pop CDC/VSD Shui I et al JAMA 2012	Expected IS cases from historical rates	**DOSE 1** 1-7 days	(Standardized incidence ratio) 1.21	 0.03, 6.75
US: Insured pop Merck Loughlin et al Pediatr Inf Dis J 2011	Controls: concurrent DTaP recipients	**DOSE 1,2,3 combined** 1-7 days (exploratory) 0-30 days	 RR 2.8 RR 0.8	 0.3, 139.5 0.2, 3.5
Australia APSU/PAEDS Buttery J et al Pediatr Inf Dis J 2011	Expected IS cases from historical rates	**DOSE 1** Age 1 - <3 months 1-7 days	 RR 5.26	 1.1, 15.4

*Final study results presented in table. In October 2010, some study results were not finalized.

Post-marketing Intussusception Studies
ACIP Meeting, October 2010

RV1 (Rotarix)				
Study Population Investigators	**Methods**	**Results (selected)**	**Incidence Rate Ratio**	**95% CI**
Mexico/Brazil PAHO/CDC Patel M et al N Engl J Med 2011	Self-controlled case series (+ case-control)			
	Mexico	**DOSE 1** 1-7 days	IRR 5.3	3.0, 9.3
	Brazil	**DOSE 2** 1-7 days	IRR 2.6	1.3, 5.2
Mexico GSK Velazquez FR et al Pediatr Inf Dis J 2012	Self-controlled case series	**DOSE 1** 0-6 days	IRR 6.49	4.17, 10.09
Australia APSU/PAEDS Buttery J et al Pediatr Inf Dis J 2011	Expected IS cases from historical rates	**DOSE 1** Age 1 - <3 months 1-7 days	(Relative Risk) RR 3.45	0.71, 10.1

*Final study results presented in table. In October 2010, some study results were not finalized.

Actions Taken

- Performed and presented to ACIP analysis of potential intussusception risk vs. benefits of rotavirus vaccination in the United States
  - If risk existed at level similar to that in Mexico (PAHO/CDC study)
- Communication material developed and distributed
  - VIS updated
  - FDA approved revised labeling for RV1 that incorporated Mexico study results (GSK study)
- Proposal initiated to add intussusception to the general Table category of rotavirus vaccines of the Vaccine Injury Table
- Monitoring continued through established safety monitoring systems

Update on Intussusception

- US VSD Eric Weintraub
- US VAERS Penina Haber
- US PRISM Katherine Yih
- Australia Peter McIntyre
- US Summary Margaret Cortese
- Discussion

Members of ACIP Rotavirus Vaccines Work Group

- ACIP Members
  - Chair: Marietta Vázquez
  - Doug Campos-Outcalt
  - Mark Sawyer
- Designated Federal Officer (CDC)
  - Margaret Cortese
- Ex Officio Members
  - Ralph LeBlanc (FDA)
  - Jennifer Read (FDA)
- Liaison Representatives
  - Penny Dennehy (PIDS)
  - Stanley Grogg (AOA)
  - Kathy Neuzil (IDSA)
  - Elizabeth Rosenblum (AAFP)
  - Rodney Willoughby (AAP)
- Invited Consultants
  - Evan Anderson
  - Geoffrey Evans
  - Samuel Katz
  - Edgar Marcuse
  - John Modlin