

# Summary of Intussusception Risk and Benefits of Rotavirus Vaccination in the United States

Margaret M. Cortese, MD  
CAPT, USPHS  
Centers for Disease Control and Prevention

ACIP Meeting  
June 20, 2013



# Outline

- Trends in intussusception hospitalizations
- Summary of attributable risk estimates
- Rotavirus vaccine impact in the United States
- Estimates of benefits and intussusception risk of rotavirus vaccination in the United States
- Recommendations

# Trends in Intussusception Hospitalizations

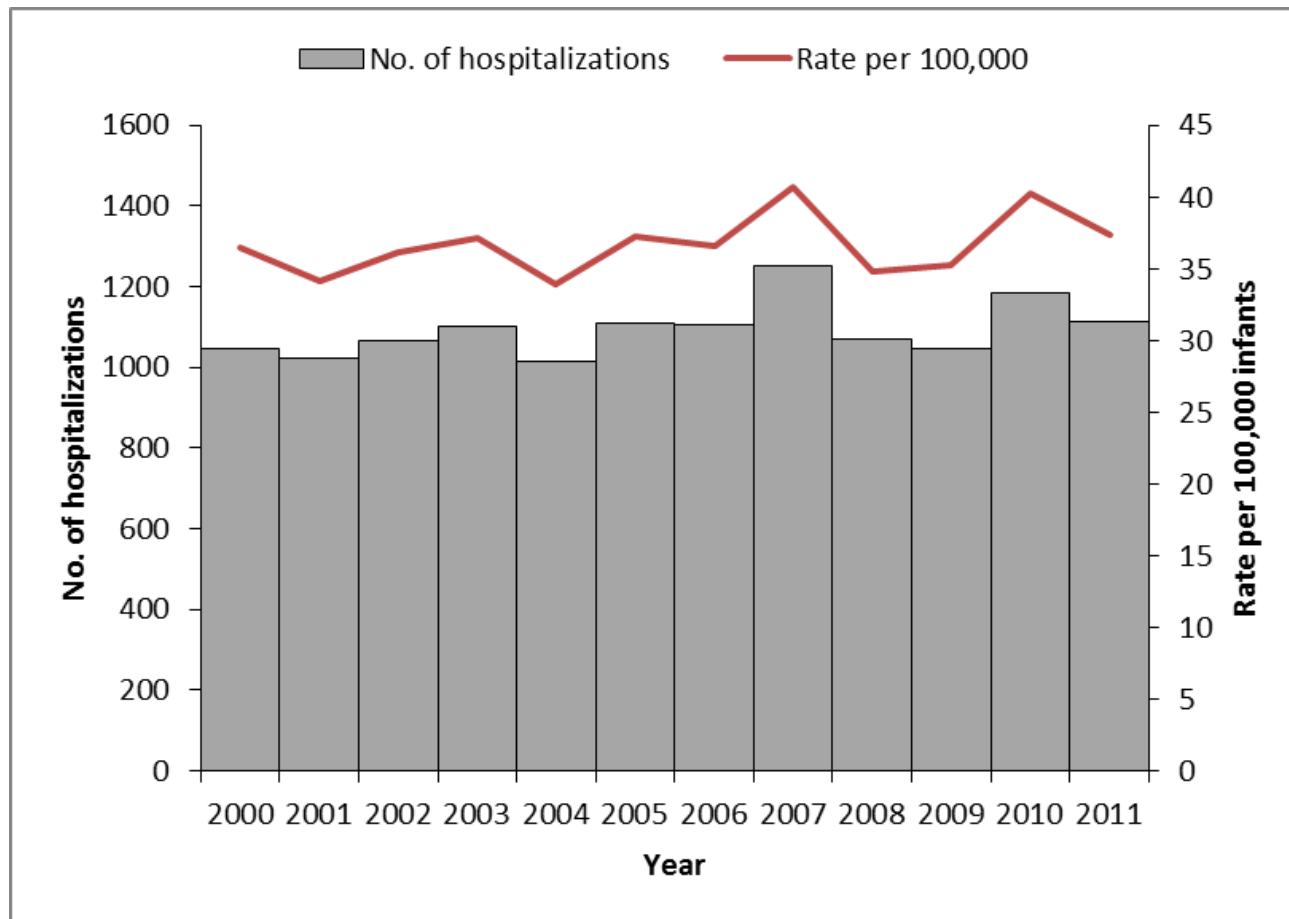
# Trends in Intussusception Hospitalizations among US infants

- State Inpatient Databases (SID) of the Healthcare Cost and Utilization Project (HCUP)
  - Hospital discharge data provided by 26 states for 2000–2011
  - 75% of US birth cohort represented
- ICD-9-CM code for intussusception (560.0) listed as a discharge diagnosis
- Population data, National Center for Health Statistics

Yen C, Tate J, Steiner C et al J Inf Dis 2012; Tate J, Steiner C et al, Preliminary

# Trends in Intussusception Hospitalizations among US infants, 2000–2011

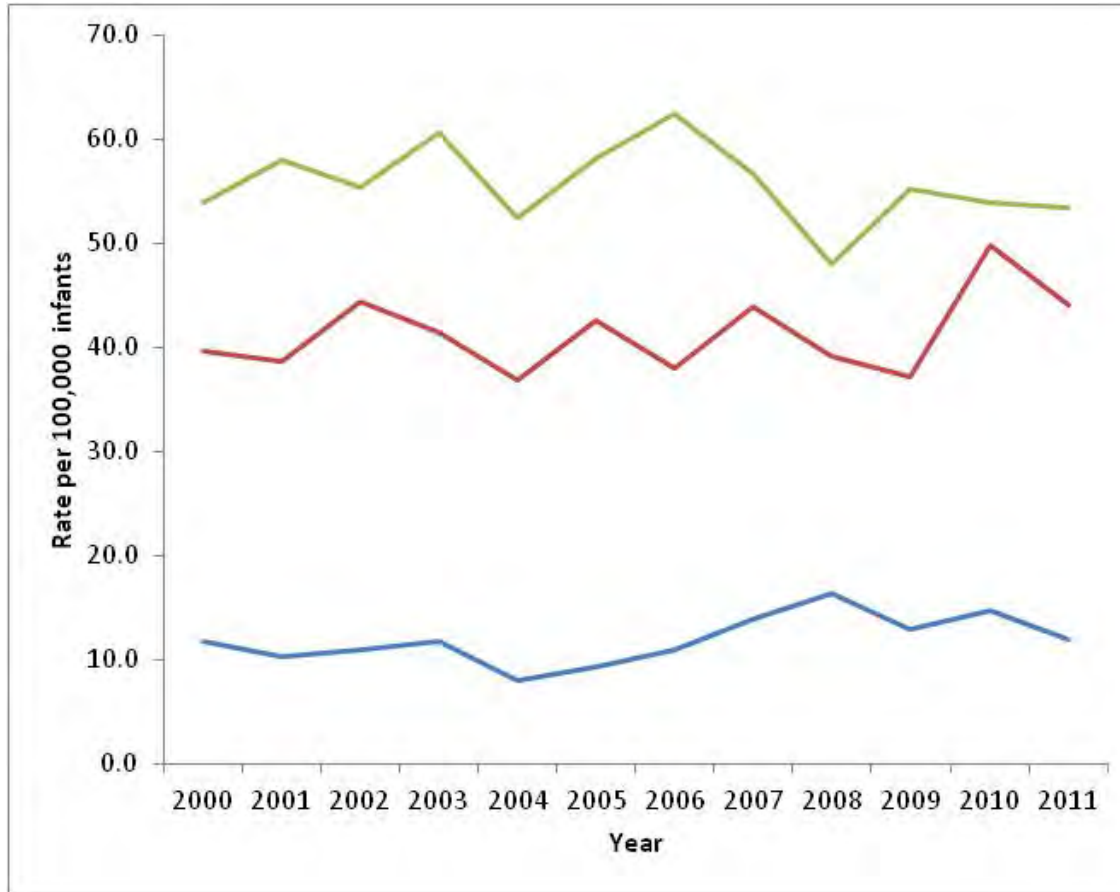
## Age <12 months



Yen C, Tate J, Steiner C et al J Inf Dis 2012; Tate J, Steiner C et al, Preliminary

# Trends in Intussusception Hospitalizations among US infants, 2000–2011

## By Specific Age Group



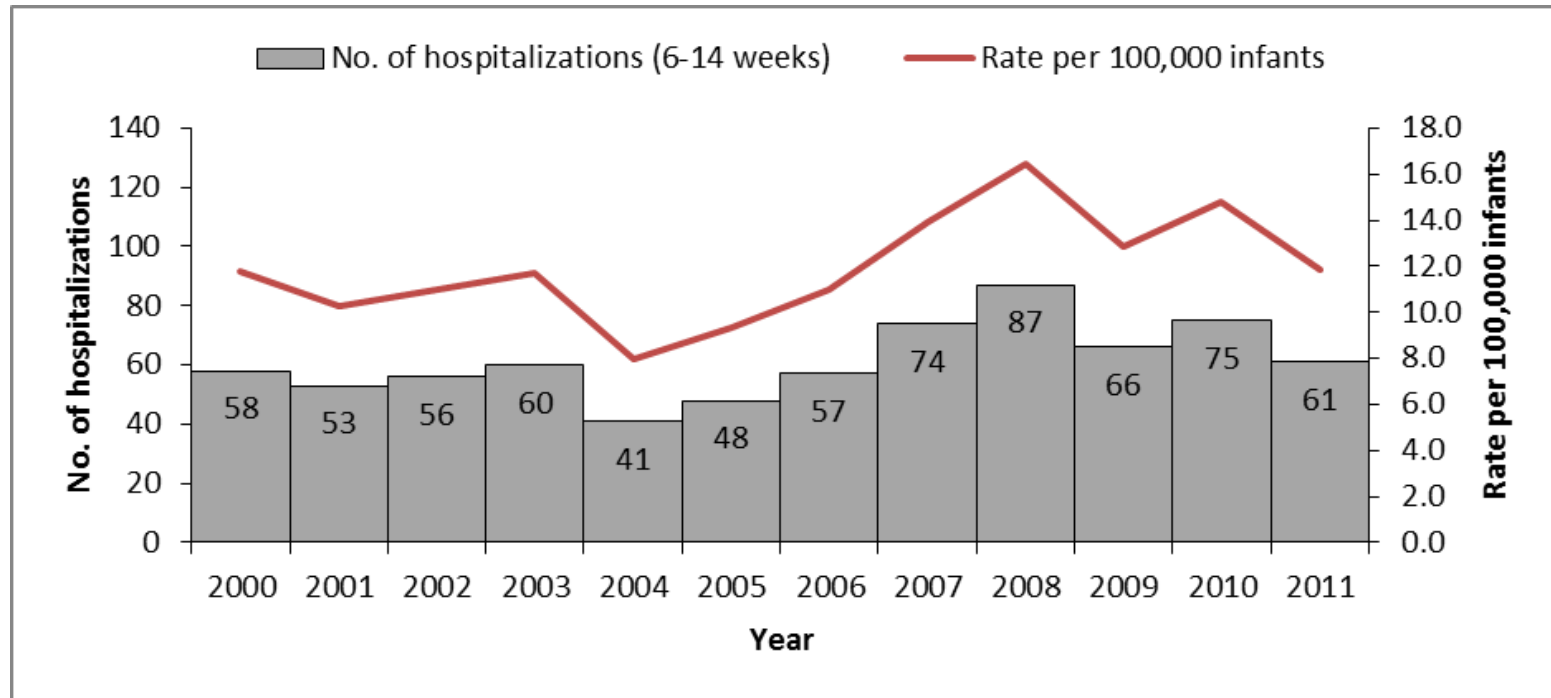
Age 25–34 weeks (Dose 3)

Age 15–24 weeks (Dose 2)

Age 6–14 weeks (Dose 1)

# Trends in Intussusception Hospitalizations among US infants, 2000–2011

## Age 6–14 weeks



Yen C, Tate J, Steiner C et al J Inf Dis 2012; Tate J, Steiner C et al, Preliminary

# Summary of Attributable Risk Estimates



# Attributable Risk Estimates: United States

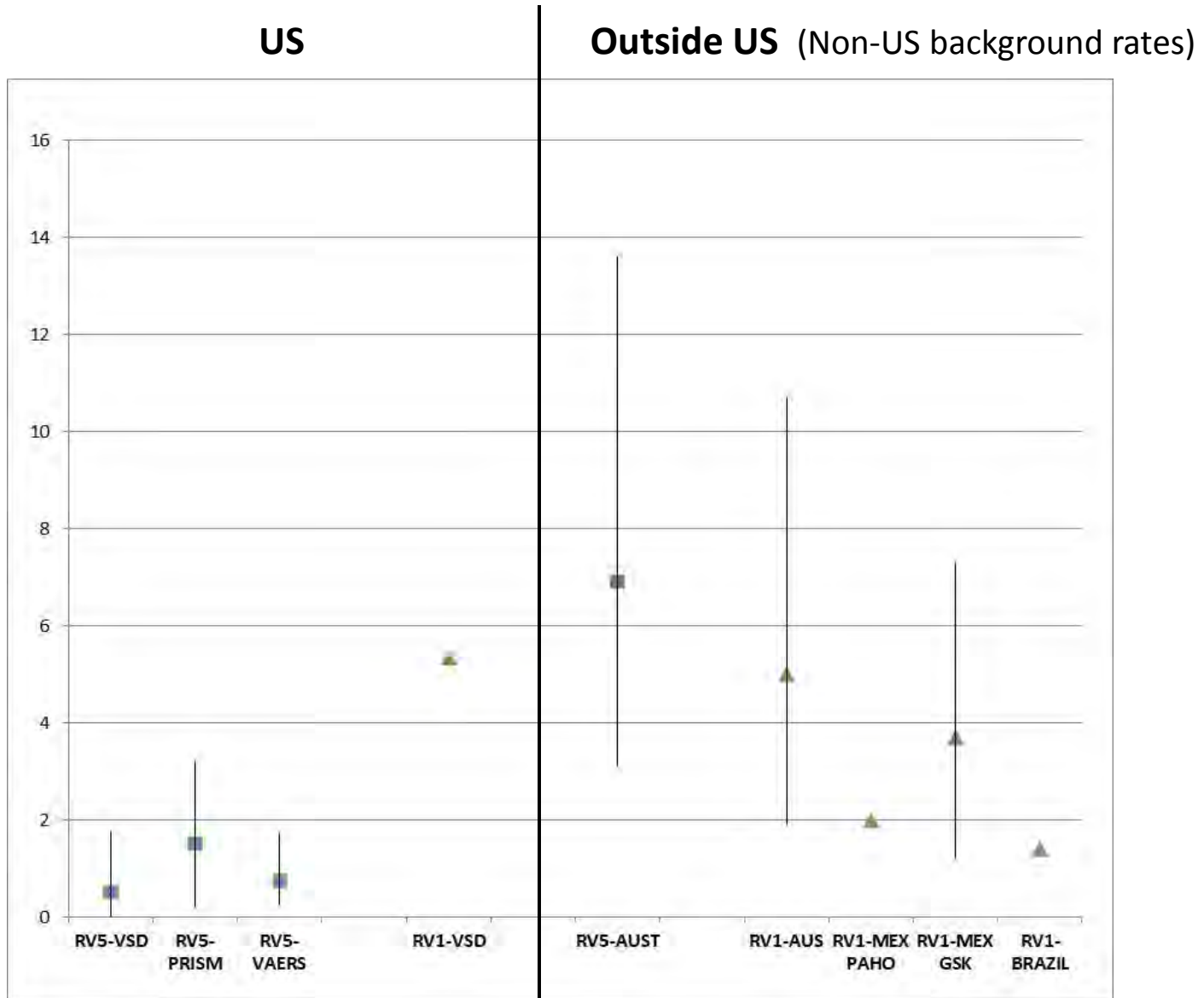
Study population; Investigators	Methods; ~Doses in population	AR calculation based on risk detected with this dose:	Attributable Risk (US population)	95% CI
<b>RV5 (RotaTeq): US</b>				
<b>US: VSD pop</b> CDC/VSD Weintraub E et al	O/E; expected from historical rates  Total doses: 1.30 million; Dose 1: 494,000	<b>No significant risk detected;</b> AR estimate from DOSE 1: Days 1-7	<b>No significant risk detected;</b> point estimate <b>0.5 per 100,000 vaccinated infants</b>  or  1 per 199,000 vaccinated infants	<b>CI: 0 –1.77 cases per 100,000 vaccinated infants</b>  or CI: 1 per 56,000 to (infinite) vaccinated infants
<b>US: PRISM pop</b> FDA/Harvard Pilgrim  Yih K et al	Self-controlled risk interval; cohort study  Total doses: 1.28 million; Dose 1: 508,000	<b>DOSE 1:</b> Days 1-7 or 1-21	Point estimates <b>1.1 to 1.5 cases per 100,000 vaccinated infants</b>  or 1 per 67,000 vaccinated infants 1 per 91,000 vaccinated infants	<b>CI: 0.2–3.20 cases per 100,000 vaccinated infants</b>  or CI: 1 per 30,000 to 520,000 vaccinated infants
<b>US: VAERS;</b> National, passive reports CDC Haber P et al	Self-controlled risk interval	<b>DOSE 1:</b> Days 3-6	<b>0.74 cases per 100,000 vaccinated infants</b>  or  1 per 135,000 vaccinated infants	<b>CI: 0.24–1.71 cases per 100,000 vaccinated infants</b>  or CI: 1 per 58,000 to 417,000 vaccinated infants
<b>RV1 (Rotarix): US</b>				
<b>US: VSD pop</b> CDC/VSD Weintraub E et al	O/E; expected from historical rates  Total doses: 208,000 Dose 1: 116,000 Dose 2: 92,000	<b>DOSE 1:</b> Days 1-7 <b>DOSE 2:</b> Days 1-7	<b>5.34 cases per 100,000 vaccinated infants</b>  or  1 per 19,000 vaccinated infants	Not available   Not available

# Attributable Risk Estimates: Outside US

Study location; Investigators	Methods	AR calculation based on risk detected with this dose:	Attributable Risk (non-US population)	95% CI
<b>RV5 (RotaTeq): OUTSIDE US</b>				
<b>AUSTRALIA</b>	Self-controlled case-series; case-control	From SCCS <b>DOSE 1:</b> Days 1-7 and 8-21 <b>DOSE 2:</b> Days 1-7	<b>6.9 cases per 100,000 vaccinated infants</b>	<b>CI: 3.1–13.6 cases per 100,00 vaccinated infants</b>
Univ Melbourne/NCIRS Carlin J et al			or  1 per 14,000 vaccinated infants	CI: 1 per  7,000 to 32,000 vaccinated infants
<b>RV1 (Rotarix): OUTSIDE US</b>				
<b>AUSTRALIA</b>	Self-controlled case-series; case-control	From SCCS <b>DOSE 1:</b> Days 1-7 and 8-21 <b>DOSE 2:</b> Days 1-7	<b>5.0 cases per 100,000 vaccinated infants</b>	<b>CI: 1.9–10.7 cases per 100,000 vaccinated infants</b>
Univ Melbourne/NCIRS Carlin J et al			or  1 per 20,000 vaccinated infants	or CI: 1 per 9,000 to 53,000 vaccinated infants
<b>MEXICO</b>	Self-controlled case-series; case-control	From SCCS <b>DOSE 1:</b> Days 1-7	<b>1.9 cases per 100,000 vaccinated infants</b>	Not available
PAHO/CDC Patel M et al			or  1 per 51,000 vaccinated infants	Not available
<b>MEXICO</b>	Self-controlled case-series	<b>DOSE 1:</b> Days 0-6	<b>3.7 cases per 100,000 vaccinated infants</b>	<b>CI: 1.2–7.3 cases per 100,000 vaccinated infants</b>
GSK Velazquez FR et al			or  1 per 27,000 vaccinated infants	or CI: 1 per 14,000 to 83,000 vaccinated infants
<b>BRAZIL</b>	Self-controlled case-series; case-control	From SCCS <b>DOSE 2:</b> Days 1-7	<b>1.4 cases per 100,000 vaccinated infants</b>	Not available
PAHO/CDC Patel M et al			or  1 per 69,000 vaccinated infants	Not available

# Attributable Risk Estimates

## Excess IS cases per 100,000 Vaccinated Infants



# Rotavirus Vaccine Impact in the United States

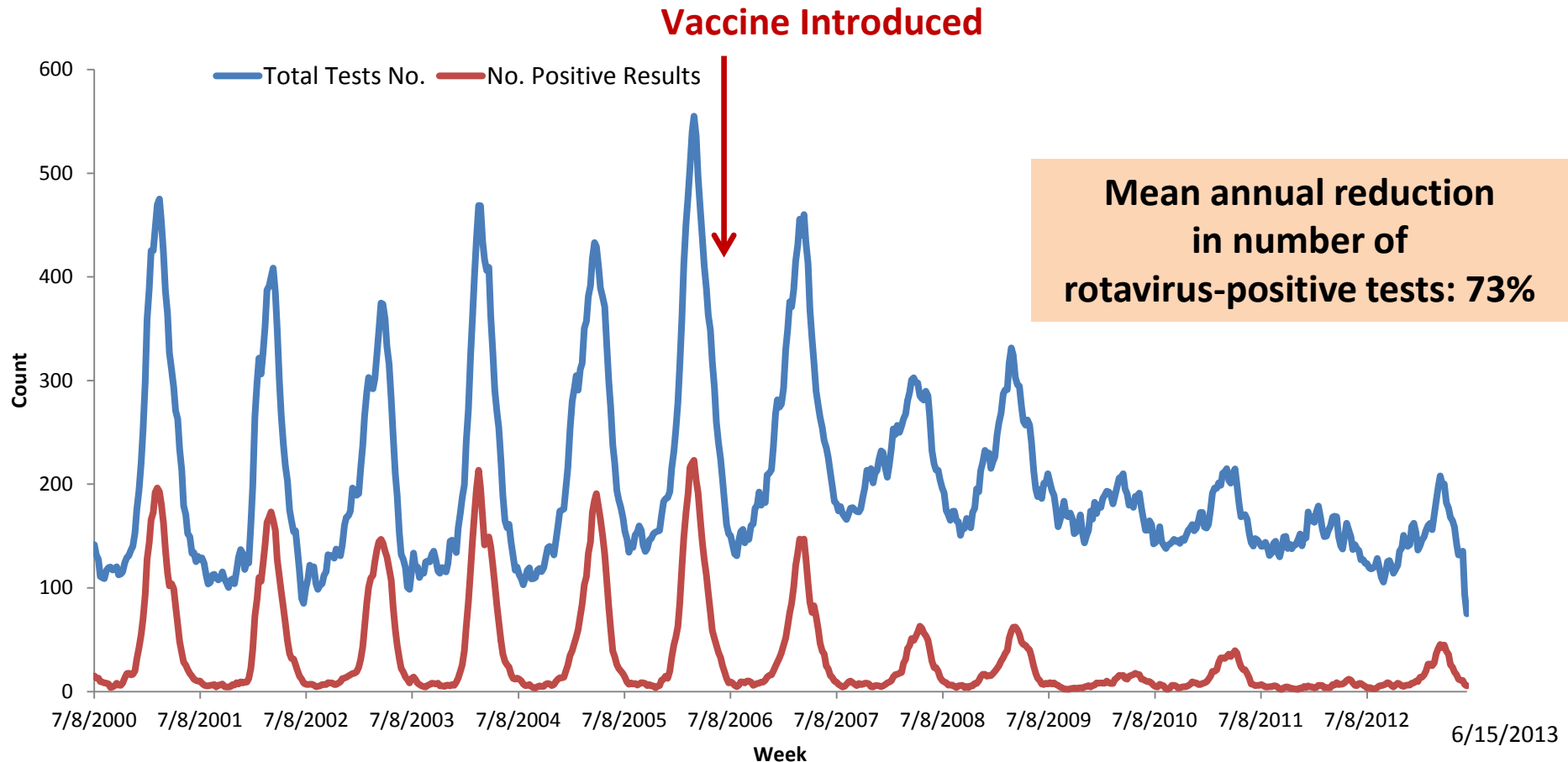
# National Laboratory Surveillance for Rotavirus Testing



- Weekly reporting (passive)
  - Number of rotavirus tests performed
  - Number testing positive
- Since 1991, 22 labs have reported continuously

# Rotavirus Tests at Reporting Laboratories

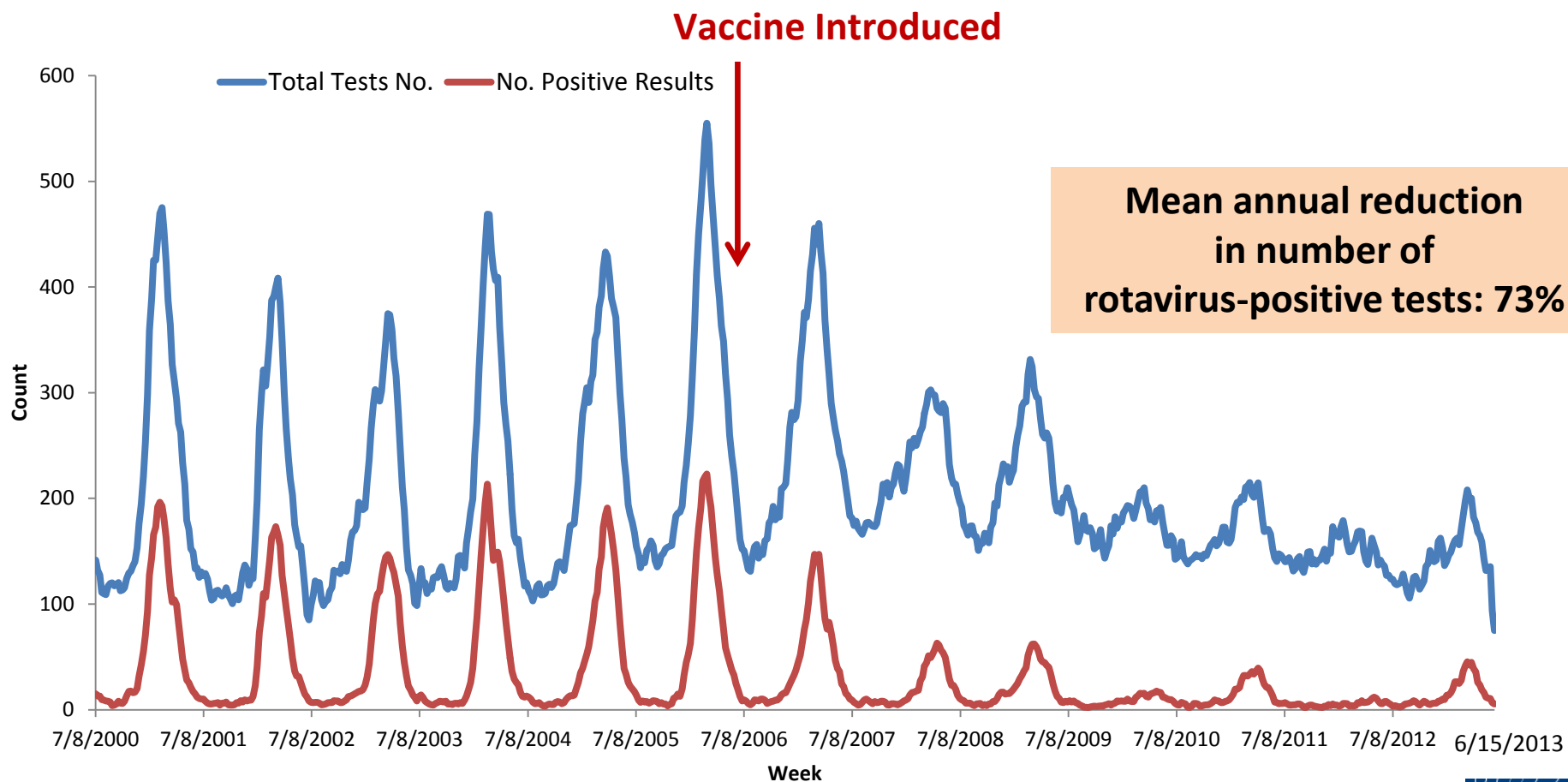
## Number of tests and number rotavirus-positive July 2000–June 2013



Tate, J, Haynes A, Payne D et al PIDJ 2013; Tate J et al, Preliminary

# Rotavirus Tests at Reporting Laboratories

## Number of tests and number rotavirus-positive July 2000–June 2013

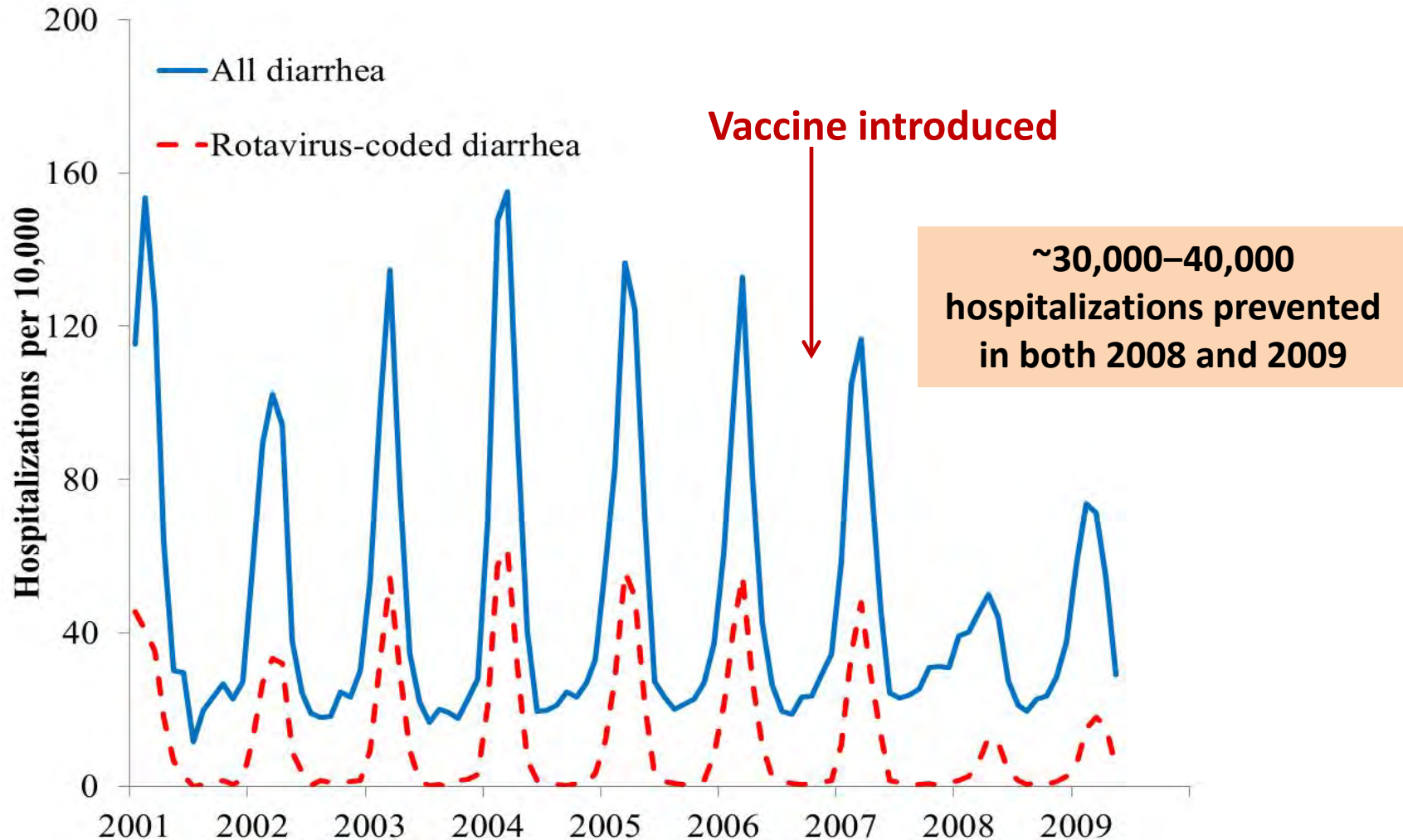


Tate, J, Haynes A, Payne D et al PIDJ 2013; Tate J et al, Preliminary

# Hospitalization Data from MarketScan Database

## Diarrhea and Rotavirus-coded Hospitalizations

### Children aged <5 yrs, 2001-2009





# Estimated National Reduction in Diarrhea-associated Hospitalizations Post-Rotavirus Vaccine Introduction

## US Children aged <5 years

### Administrative Data

	<b>Reduction in 2008</b>	<b>Reduction in 2009</b>	<b>Reduction in 2010</b>
Study 1	36,890	27,965	
Study 2	37,697	39,099	
Study 3	50,665	49,381	69,753

Study 1: Cortes J, Curns AT, Tate JE et al N Engl J Med 2011

Study 2: Desai R, Curns AT, Steiner CA et al Clin Inf Dis 2012: 55

Study 3: Gastanaduy PA, Curns AT, Parashar UD, Lopman BL (submitted)

# Active Rotavirus Surveillance



DEPARTMENT OF HEALTH AND HUMAN SERVICES  
CENTERS FOR DISEASE CONTROL AND PREVENTION

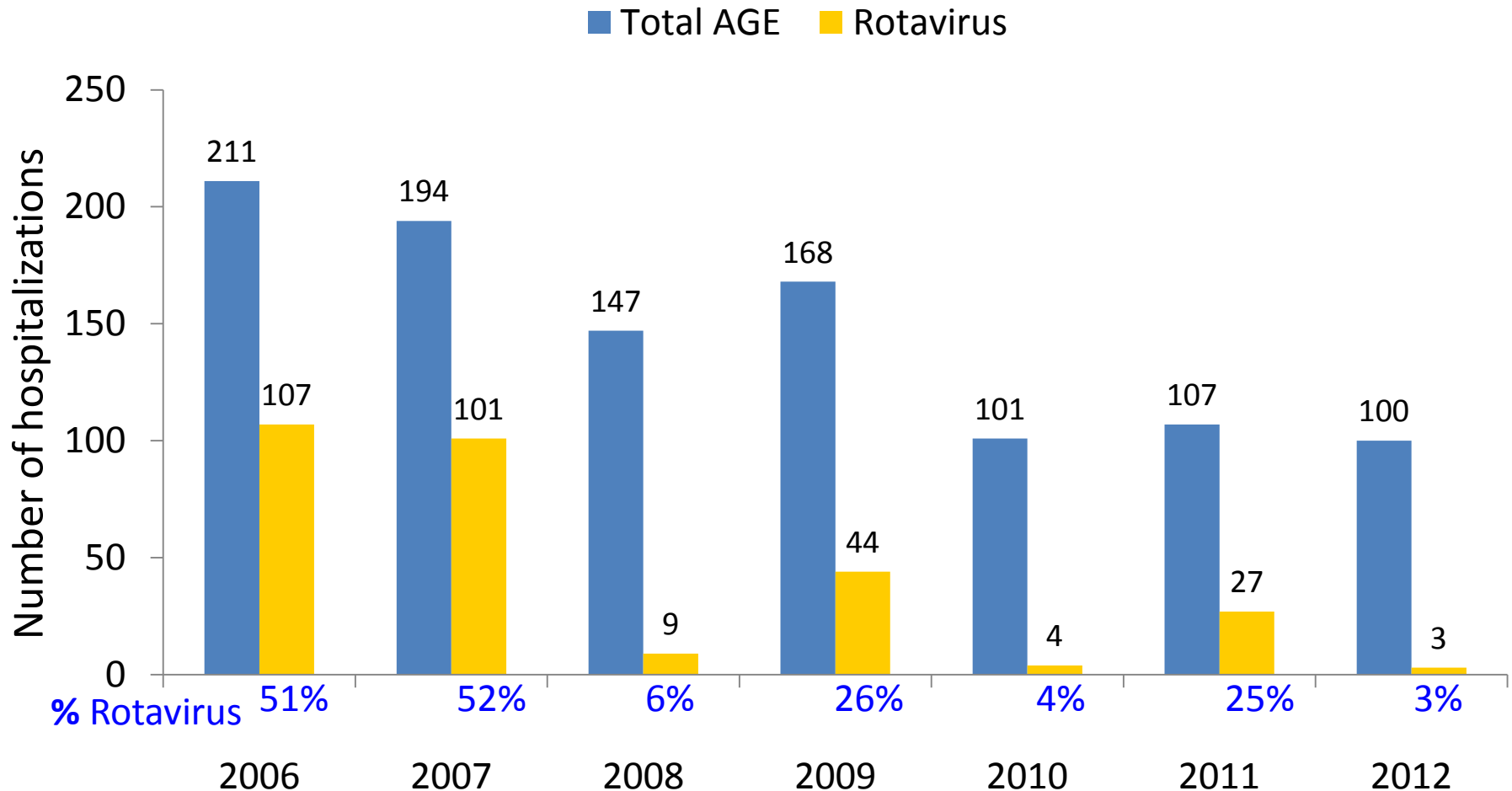


# Active Rotavirus Surveillance at 3 Children's Hospitals

- Prospective surveillance for acute gastroenteritis (AGE) among children aged <3 years, since 2006
- Hospitalizations, emergency department care
- Stool specimens tested for rotavirus
- Epidemiologic and clinical data collected

# Active Rotavirus Surveillance at 3 Children's Hospitals, January–June, 2006–2012

## Gastroenteritis and Rotavirus-confirmed Hospitalizations



# RV5 Vaccine Effectiveness against Rotavirus Hospitalizations/Emergency Department Care

	<b>RV5</b> Study A	<b>RV5</b> Study B	<b>RV5</b> Study C	<b>RV5</b> Study D	<b>RV5</b> Study E
3 doses	<b>89%</b> (70, 96)	<b>87%</b> (71, 94)	<b>90%</b> (84, 94)	<b>84%</b> (78,98)	<b>92%</b> (75, 97)
2 doses	<b>82%</b> (15, 96)	<b>88%</b> (66, 96)	<b>90%</b> (75, 96)	<b>78%</b> (65, 86)	<b>84%</b> (1, 99)
1 dose	<b>65%</b> (-11, 89)	<b>74%</b> (37, 90)	<b>66%</b> (16, 86)	<b>70%</b> (50, 82)	NA

Study A: Boom J et al. Pediatrics 2010;155:e199. Study B: Staat M et al. Pediatrics 2011;128:e267  
 Study C: Cortese M et al. Pediatrics 2011;128:e1474. Study D: Payne P et al. Clin Inf Dis 2013. Study E: Cortese M et al. Pediatrics 2013. Control group = Rotavirus-test negative children. Point estimate and 95% CI

# RV1 Vaccine Effectiveness against Rotavirus Hospitalizations/Emergency Department Care

	<b>RV1 Study D</b>	<b>RV1 Study E</b>
<b>2 doses</b>	<b>70%</b> (39, 86)	<b>91%</b> (80, 95)
<b>1 dose</b>	<b>57%</b> (-45, 87)	<b>53%</b> (-41, 84)

Study D: Payne D et al. Clin Inf Dis 2013. Study E: Cortese M et al. Pediatrics 2013  
Control group = Rotavirus-test negative children. Point estimate and 95% CI

# Estimates of Benefits and Intussusception Risk of Rotavirus Vaccination in the United States

# Estimate of Benefits: Inputs

## Rotavirus Burden and Vaccination

<b>Birth cohort (2009)</b>		<b>4.26 million</b>
<b>Rotavirus burden in unvaccinated cohort to age 5 years</b>	<b>Deaths</b>	<b>33</b>
	<b>Hospitalizations</b>	<b>71,175</b>
	<b>ED visits</b>	<b>226,126</b>
<b>Rotavirus vaccine coverage</b>	<b>1 dose</b>	<b>96%</b>
	<b>2 doses</b>	<b>93%</b>
	<b>3 doses</b>	<b>82%</b>
<b>Rotavirus vaccine effectiveness</b>	<b>Hospitalization/death</b>	
	<b>1 dose</b>	<b>66%</b>
	<b>2 doses</b>	<b>90%</b>
	<b>3 doses</b>	<b>92%</b>
	<b>ED visit</b>	
	<b>1 dose</b>	<b>55%</b>
	<b>2 doses</b>	<b>79%</b>
<b>3 doses</b>	<b>81%</b>	



# Estimate of Benefits: Results

## Rotavirus Disease Prevented with Vaccination

Rotavirus Events	Without vaccine	With vaccine	Number (%) prevented with vaccination
Deaths	33	19	14 (42%)
Hospitalizations	71,175	17,731	53,444 (75%)
ED visits	226,126	56,117	169,949 (75%)

# Estimate of Risk : Input

## IS risk in one vaccinated birth cohort

IS risk from vaccination	AR low-high range from US point estimates
Proportion of total IS cases managed as short-stay/ED patients	22%
Proportion of hospitalized IS cases that require surgery	53% (or 37% of total IS cases)
Proportion of hospitalized IS cases that die	0.3%

# Estimate of Risk: Results

## Excess Intussusception

**Baseline IS cases in infants** **1856**

### Excess IS cases and outcomes

<b>Updated</b>	<b>IS cases: total</b>	<b>45–213</b>
	<b>IS cases: hospitalized</b>	<b>35–166</b>
	<b>IS with surgery</b>	<b>18–88</b>
	<b>IS resulting in death</b>	<b>0.1–0.5</b>
<hr/>		
<b>PIDJ</b>	<b>IS cases: total</b>	<b>58</b>
	<b>IS cases: hospitalized</b>	<b>45</b>
	<b>IS with surgery</b>	<b>24</b>
	<b>IS resulting in death</b>	<b>0.2</b>

# Benefits vs. Risks: Summary of Estimates

## One vaccinated birth cohort to age 5 years

	Events	Rotavirus gastroenteritis sequelae prevented with vaccination	Excess intussusception cases and sequelae with vaccination	Rotavirus outcome prevented per 1 excess IS outcome
<b>Updated</b>	<b>Hospitalization</b>	<b>53,444</b>	<b>35–166</b>	<b>322–1,530 : 1 excess hosp IS case</b> <b>251–1,191 : 1 excess IS case</b>
	<b>Emergency Department Total</b>	<b>169,949</b>	<b>10–47</b> <b>45–213</b>	<b>3,603–17,118 : 1 excess ED IS case</b>
	<b>Surgery</b>	<b>---</b>	<b>18–88</b>	
	<b>Death</b>	<b>14</b>	<b>0.1–0.5</b>	<b>28–134 : 1</b>
<b>PIDJ</b>	<b>Hospitalization</b>	<b>53,444</b>	<b>45</b>	<b>1093 : 1 excess hosp IS case</b> <b>850 : 1 excess IS case</b>
	<b>Emergency Department Total</b>	<b>169,949</b>	<b>13</b> <b>58</b>	<b>12,115 : 1 excess ED IS case</b>
	<b>Surgery</b>	<b>---</b>	<b>24</b>	
	<b>Death</b>	<b>14</b>	<b>0.2</b>	<b>71 : 1</b>

In last column, for updated results, low-high ratio results were obtained by dividing rotavirus outcomes prevented by high-low excess intussusception outcomes caused. In PIDJ publication, ratio results are from Monte Carlo simulations.

# Recommendations

- CDC continues to recommend that all US infants (following the age and precaution/contraindication criteria) receive rotavirus vaccine. The benefits of RV5 and RV1 outweigh the small excess risk of intussusception.
- Parents and providers need to be aware of the small risk of intussusception, the signs and symptoms of intussusception, and the need for prompt care if these develop.

# Next Steps

- Monitoring will continue through the established safety monitoring systems to further quantitate the intussusception risk following each vaccine. When additional results become available, they will be presented to ACIP.
- CDC communication materials (including VIS) are being updated
  - FDA approved revised labeling for RV5
- GRADE review of the available safety data will be performed and presented at a future ACIP meeting.

**THANK YOU**