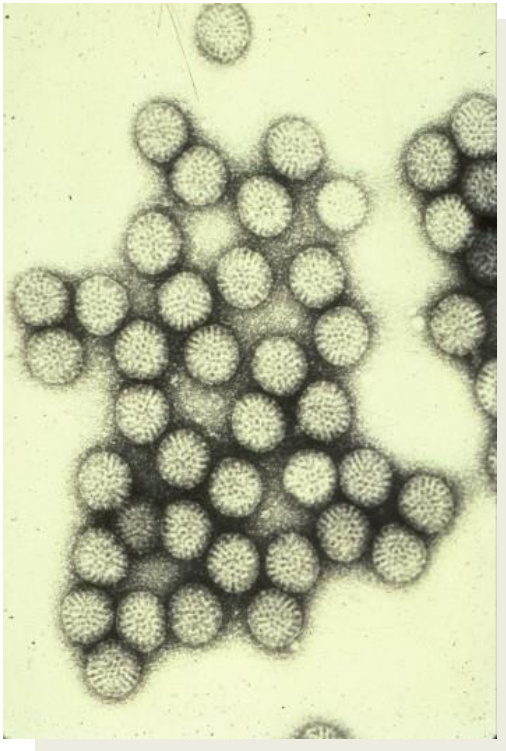


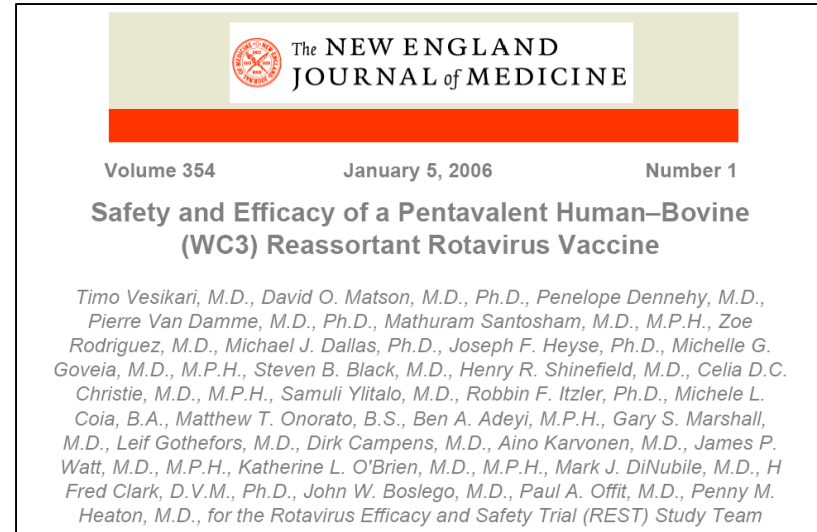
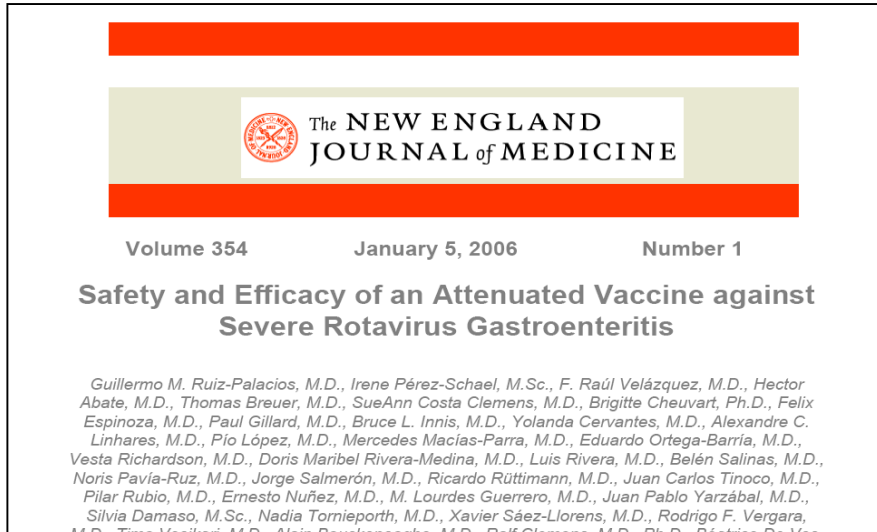
# Value of post-licensure data to assess public health value – Example of rotavirus vaccines



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# Two New Rotavirus Vaccines Licensed in 2006



- Large trials (60-70,000 infants) in US, Europe, and Latin America
- No increased risk of intussusception

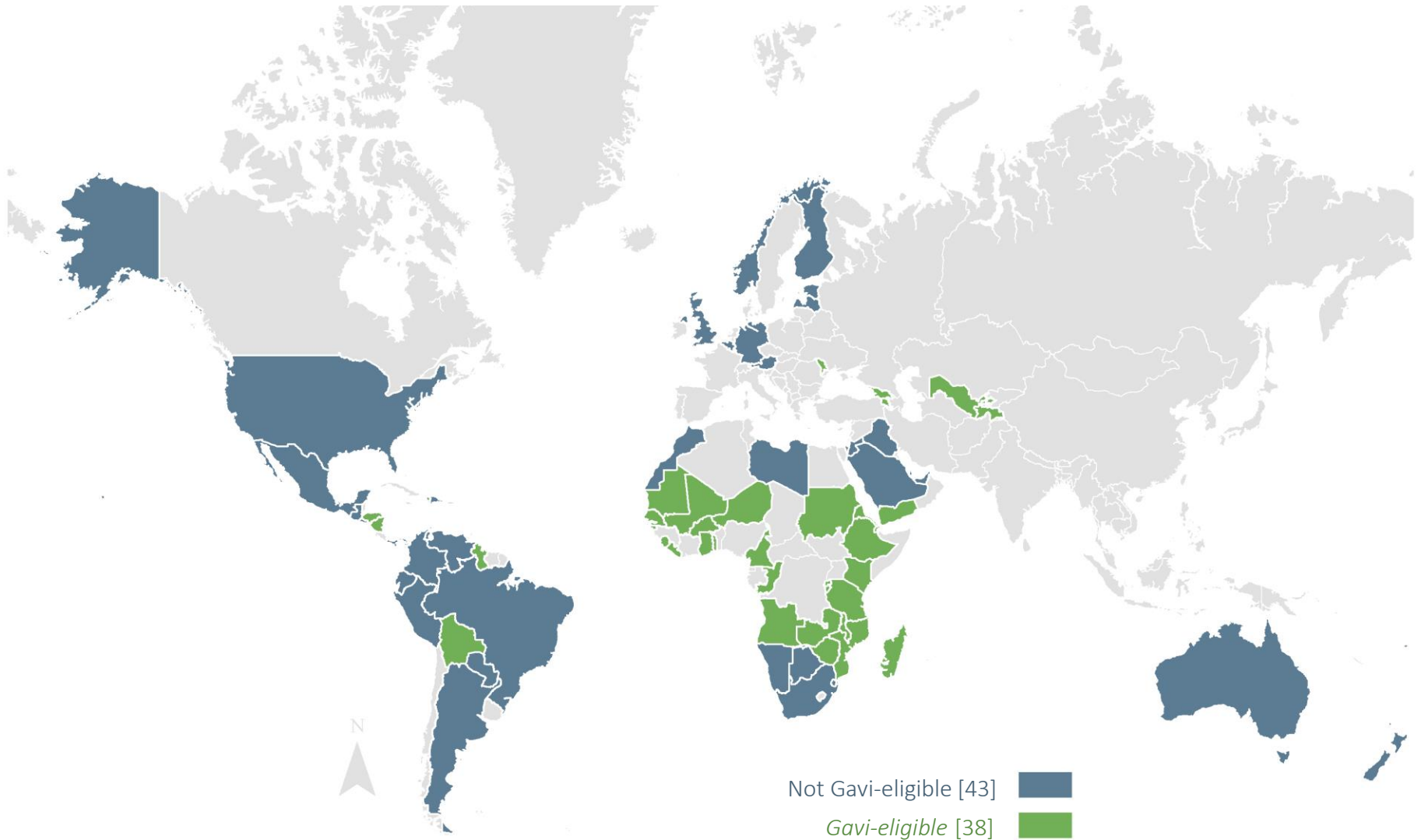
# High Efficacy of Both Vaccines in Trials in High/Middle Income Countries

Vaccine	Region	Efficacy (95%CI)
Rotarix	Europe	96% (90%-99%)
Rotarix	Latin America	85% (72%-92%)
RotaTeq	Europe/US	98% (88%-100%)

Vesikari et al and Ruiz-Palacios et al, NEJM 2006

Vesikari et al, Lancet, 2007.

# National RV introductions, 81 countries\*



\*As of May 1, 2016

**How well will vaccines perform  
in routine use?**

# Rotavirus Vaccines in USA

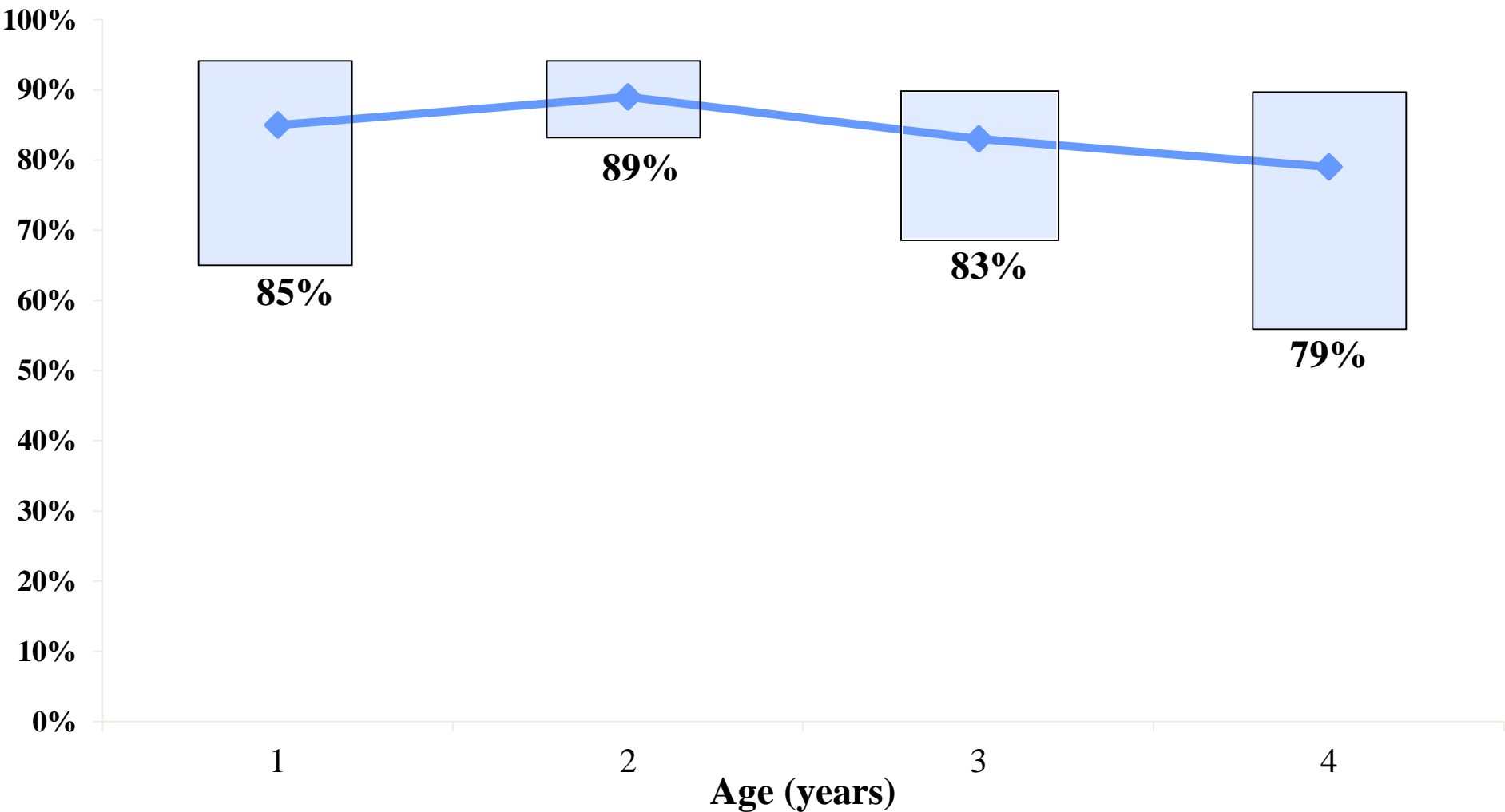
- Feb 2006 – RotaTeq recommended
- June 2008 – Rotarix recommended



# High effectiveness of RotaTeq against severe Rotavirus Disease in US infants

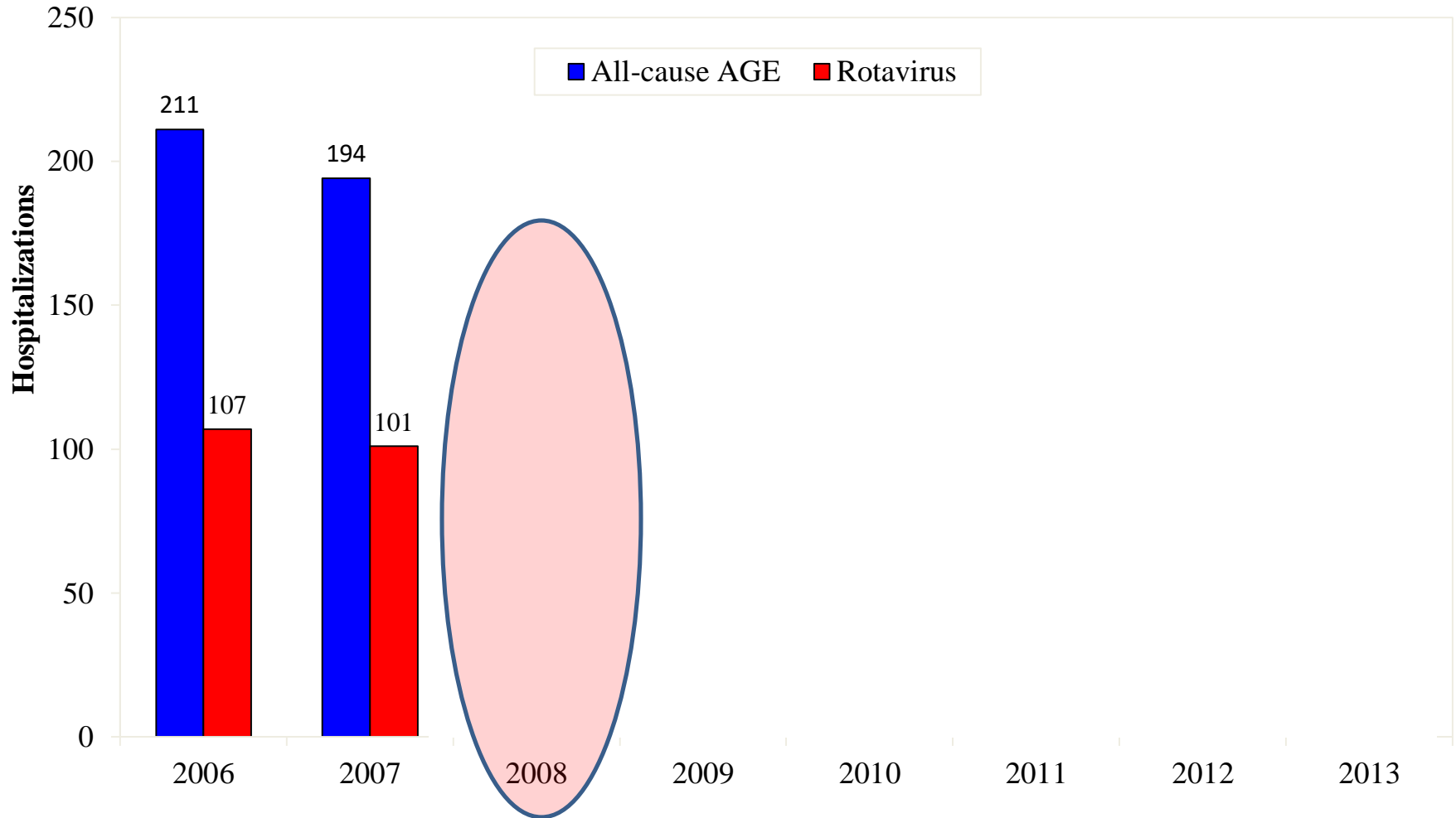
	<b>Study 1</b> Boom et al, 2010	<b>Study 2</b> Staat et al, 2011	<b>Study 3</b> Cortese et al, 2011	<b>Study 4</b> Payne et al, 2013	<b>Study 5</b> Cortese et al, 2013
<b>3 doses</b>	<b>89%</b> (70, 96)	<b>87%</b> (71, 94)	<b>90%</b> (84, 94)	<b>84%</b> (78, 98)	<b>92%</b> (75, 97)
<b>2 doses</b>	<b>82%</b> (15, 96)	<b>88%</b> (66, 96)	<b>90%</b> (75, 96)	<b>78%</b> (65, 86)	<b>84%</b> (1, 99)
<b>1 dose</b>	<b>65%</b> (-11, 89)	<b>74%</b> (37, 90)	<b>66%</b> (16, 86)	<b>70%</b> (50, 82)	<b>NA</b>

# Sustained RotaTeq effectiveness over 4 years of life





# Impact of vaccination on all cause acute gastroenteritis and rotavirus AGE hospitalizations in US children



# Decline in rotavirus hospitalization rate in 2008 and vaccine coverage by age

Age	Decline in rotavirus hospitalization rate (2008 vs. 2006)	Rotavirus vaccine coverage in 2008 (>=1 dose)
< 1 year	66%	56%
1 -< 2 years	95%	44%
2 -< 3 years	85%	<1%

*This age cohort was ineligible to receive rotavirus vaccine*

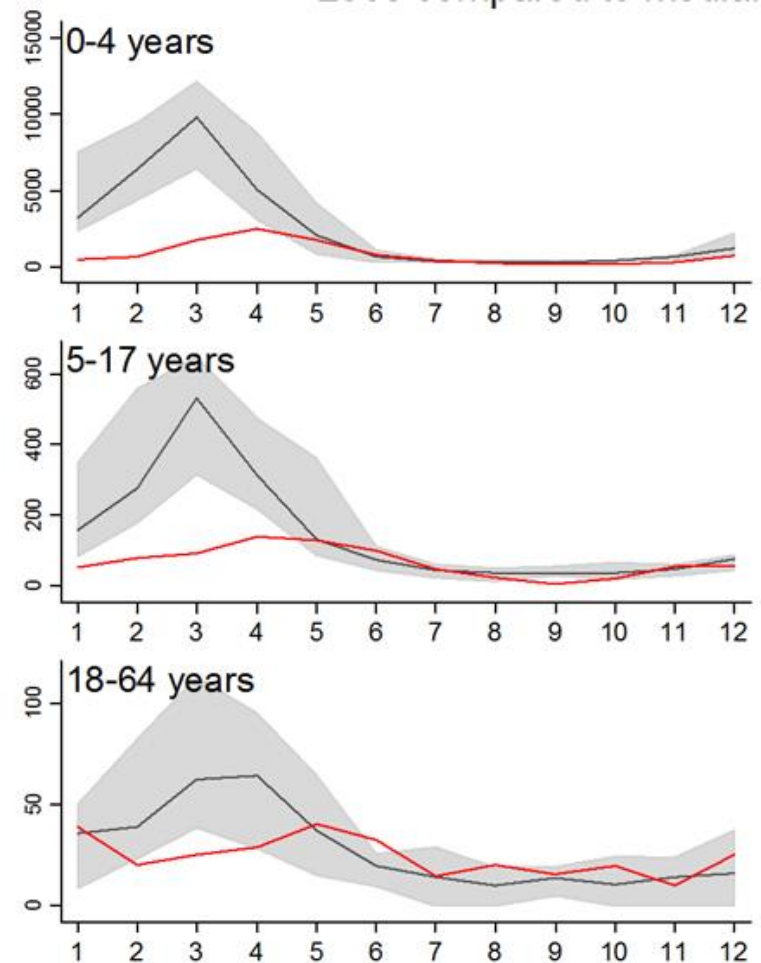
**Herd Protection?**

# Reduction in gastroenteritis hospitalizations in older children and young adults in the US

Estimated Rotavirus Hospitalizations  
2008 vs. 2000–2006 (median and range)

Age 0-4 years: ~56,000  
hospitalizations averted  
(\$162 million)

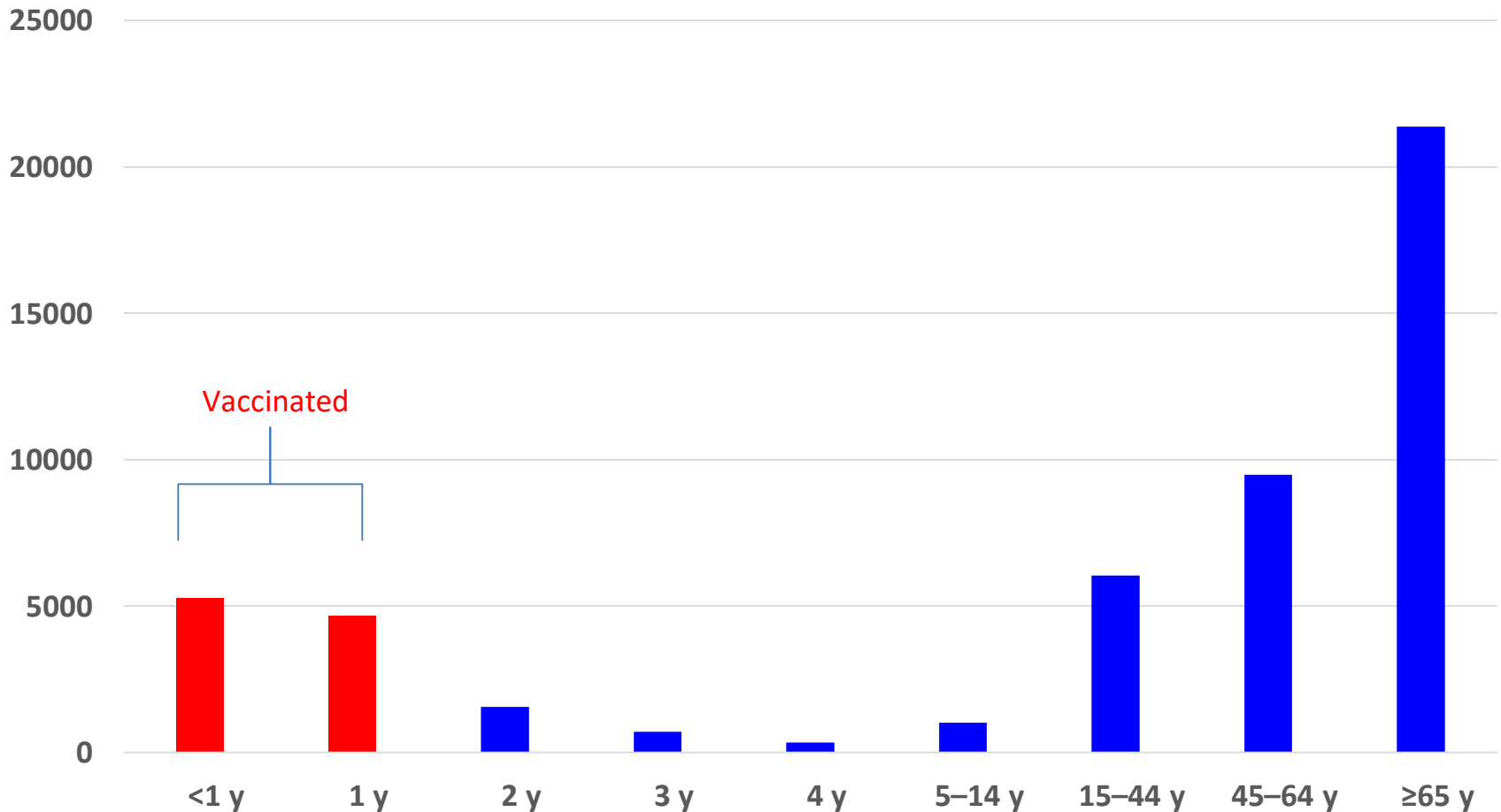
Age 5-24 years: ~10,000  
hospitalizations averted  
(\$42 million)



Lopman et al. JID 2011

Gastanaduy et al JAMA 2013

# Number of gastroenteritis hospitalizations averted by age group in UK



**Will vaccination save lives?**



**How well will live oral rotavirus vaccines  
work in the developing world?**

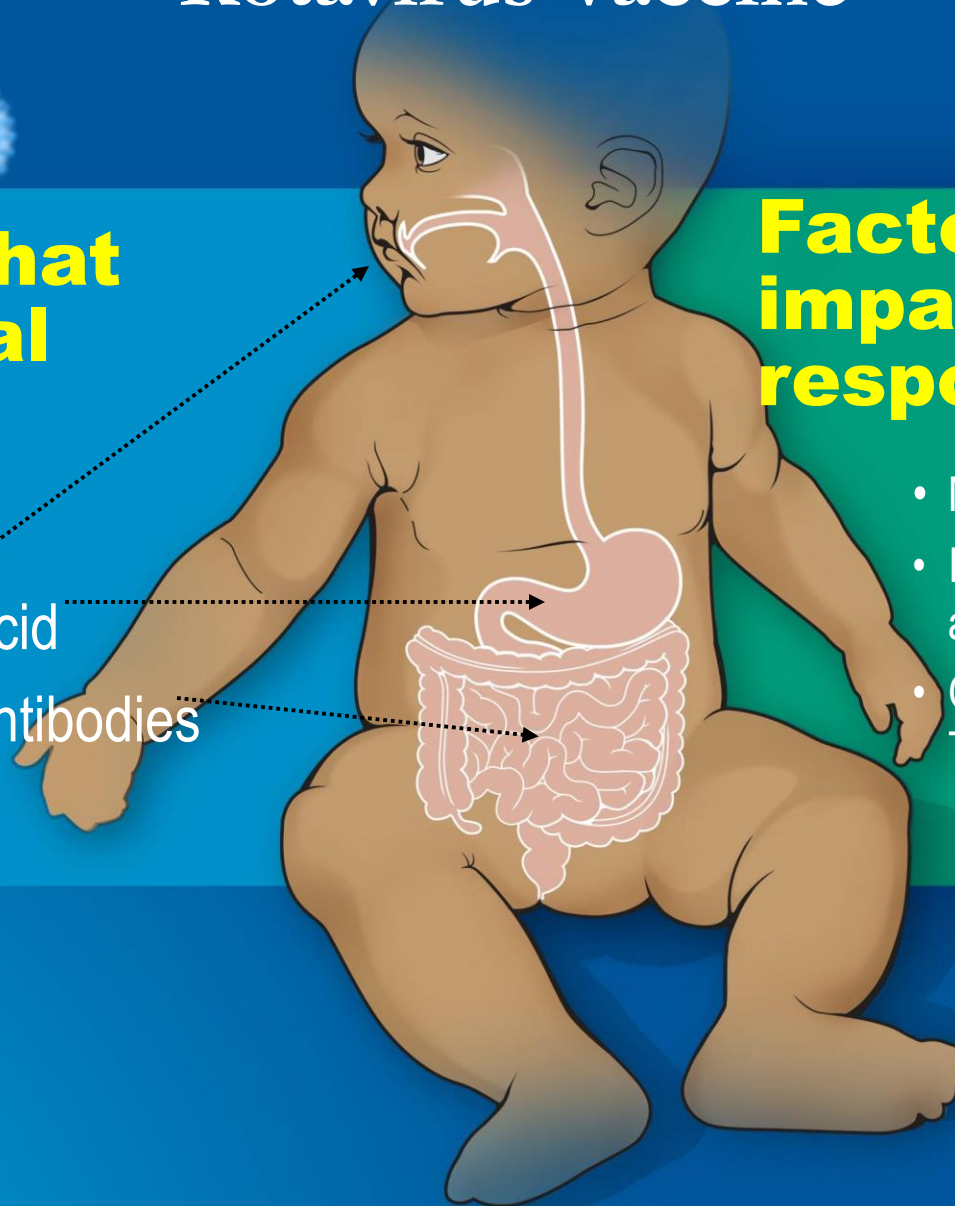
# Hurdles to Immunization for a Live Oral Rotavirus Vaccine

## Factors that lower viral titer

- Breast milk
- Stomach acid
- Maternal antibodies
- OPV

## Factors that impair immune response

- Malnutrition - Zn, Vit A
- Interfering microbes- viruses and bacteria
- Other infections- HIV, malaria, TBC



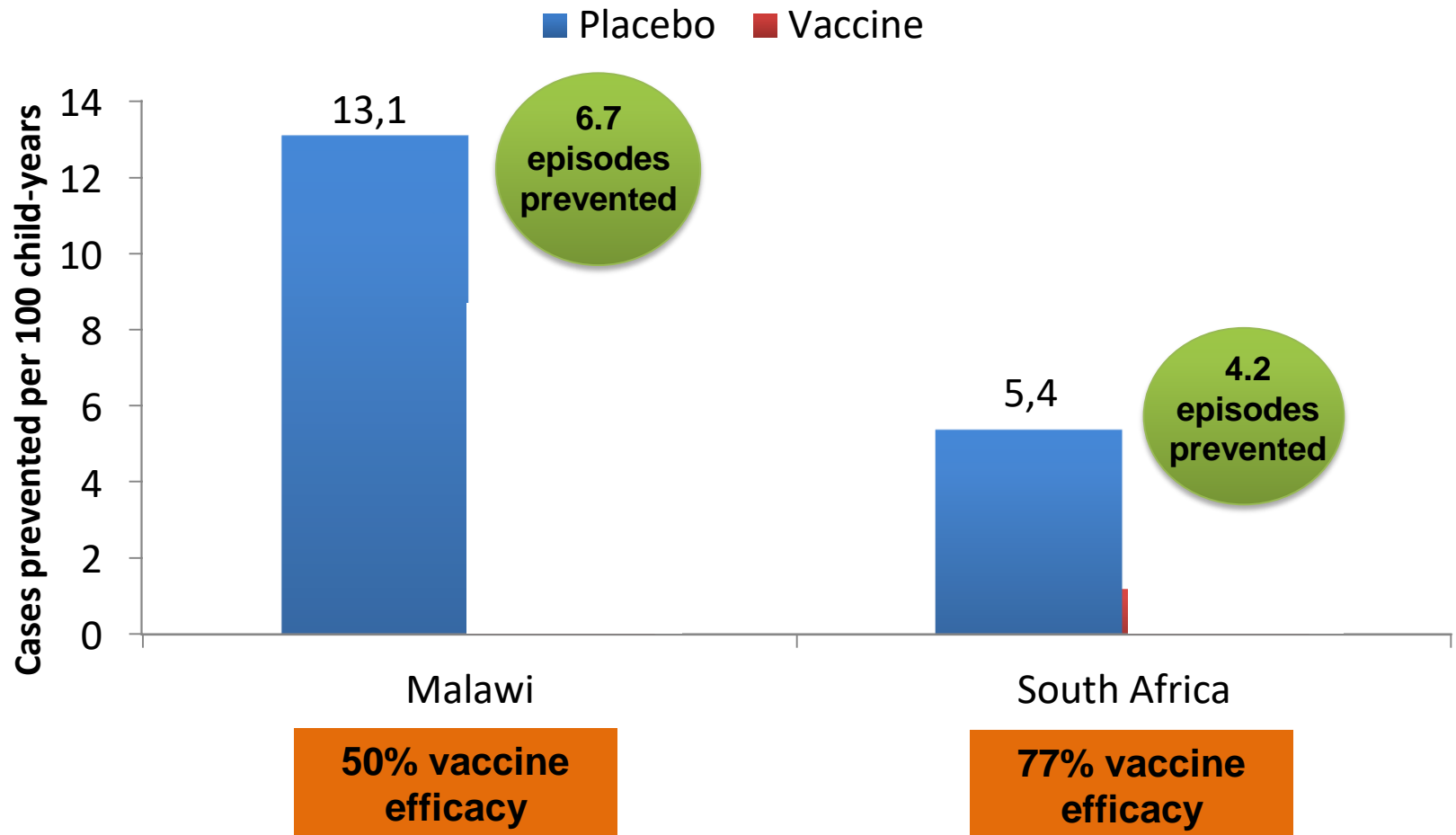


# Moderate Efficacy of Rotavirus Vaccines in Africa and Asia

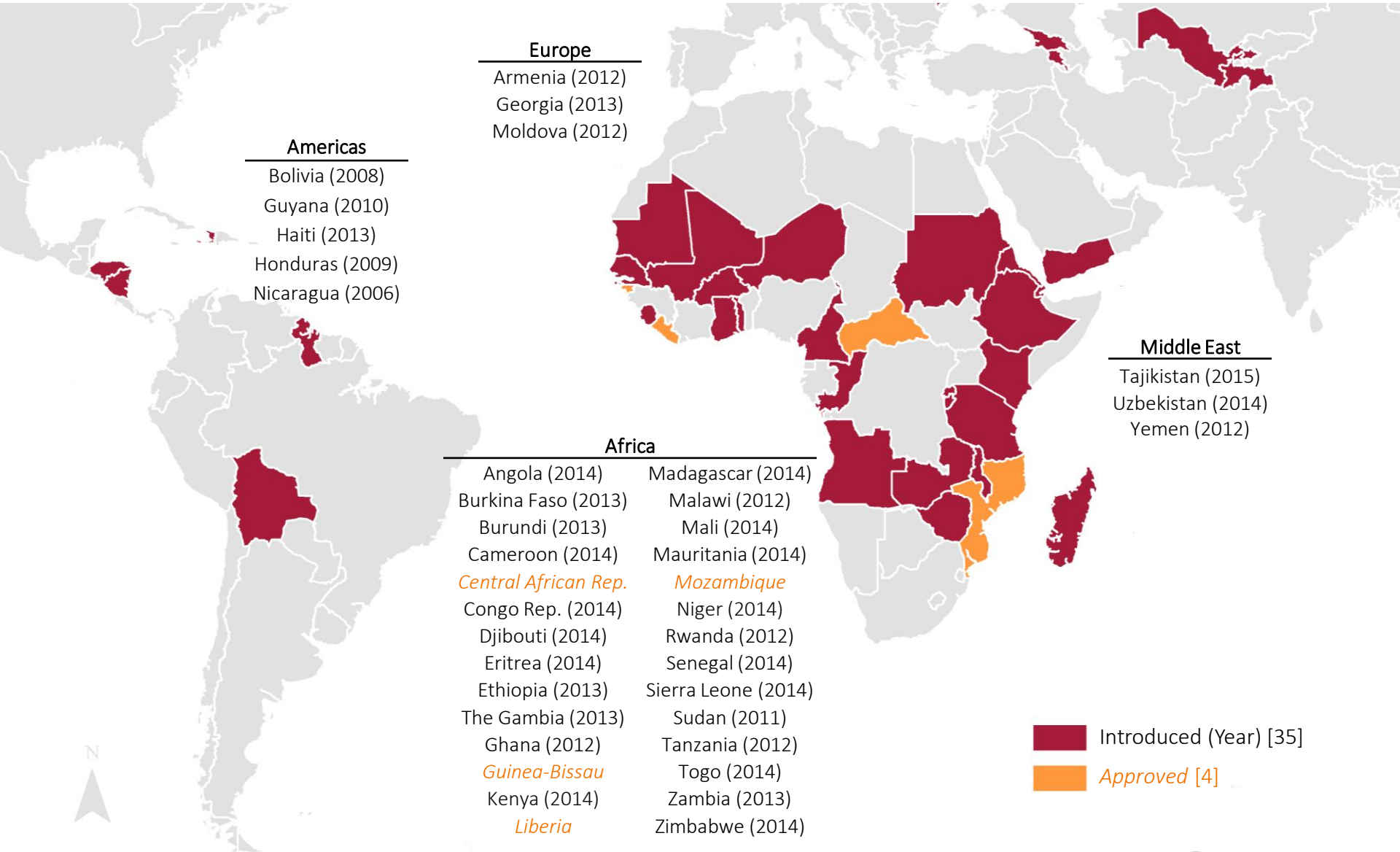
Vaccine	Region	Countries	Efficacy (95%CI)
RotaTeq	Africa	Ghana, Kenya, Mali	64% (40%-79%)
RotaTeq	Asia	Bangladesh, Vietnam	51% (13%-73%)
Rotarix	Africa	South Africa, Malawi	62% (44%-73%)

Armah et al. Lancet 2010  
Zaman et al. Lancet 2010  
Madhi et al NEJM 2010

# Rotavirus vaccines prevent more disease, despite lower vaccine efficacy, in higher burden settings



# GAVI-supported RV introductions, 35 countries\*



- Americas**
- Bolivia (2008)
  - Guyana (2010)
  - Haiti (2013)
  - Honduras (2009)
  - Nicaragua (2006)

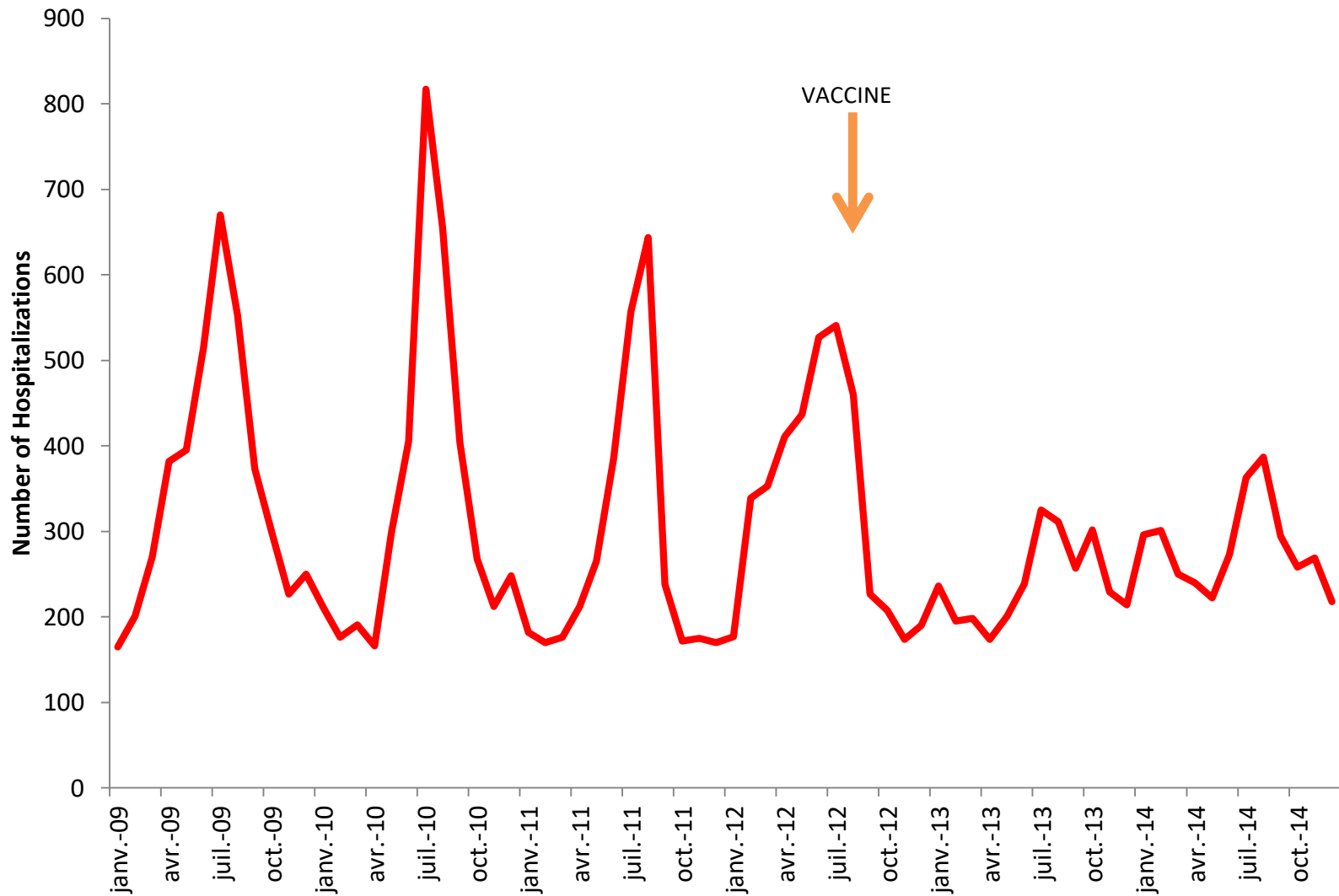
- Europe**
- Armenia (2012)
  - Georgia (2013)
  - Moldova (2012)

- Africa**
- Angola (2014)
  - Burkina Faso (2013)
  - Burundi (2013)
  - Cameroon (2014)
  - Central African Rep.*
  - Congo Rep. (2014)
  - Djibouti (2014)
  - Eritrea (2014)
  - Ethiopia (2013)
  - The Gambia (2013)
  - Ghana (2012)
  - Guinea-Bissau*
  - Kenya (2014)
  - Liberia*
  - Madagascar (2014)
  - Malawi (2012)
  - Mali (2014)
  - Mauritania (2014)
  - Mozambique*
  - Niger (2014)
  - Rwanda (2012)
  - Senegal (2014)
  - Sierra Leone (2014)
  - Sudan (2011)
  - Tanzania (2012)
  - Togo (2014)
  - Zambia (2013)
  - Zimbabwe (2014)

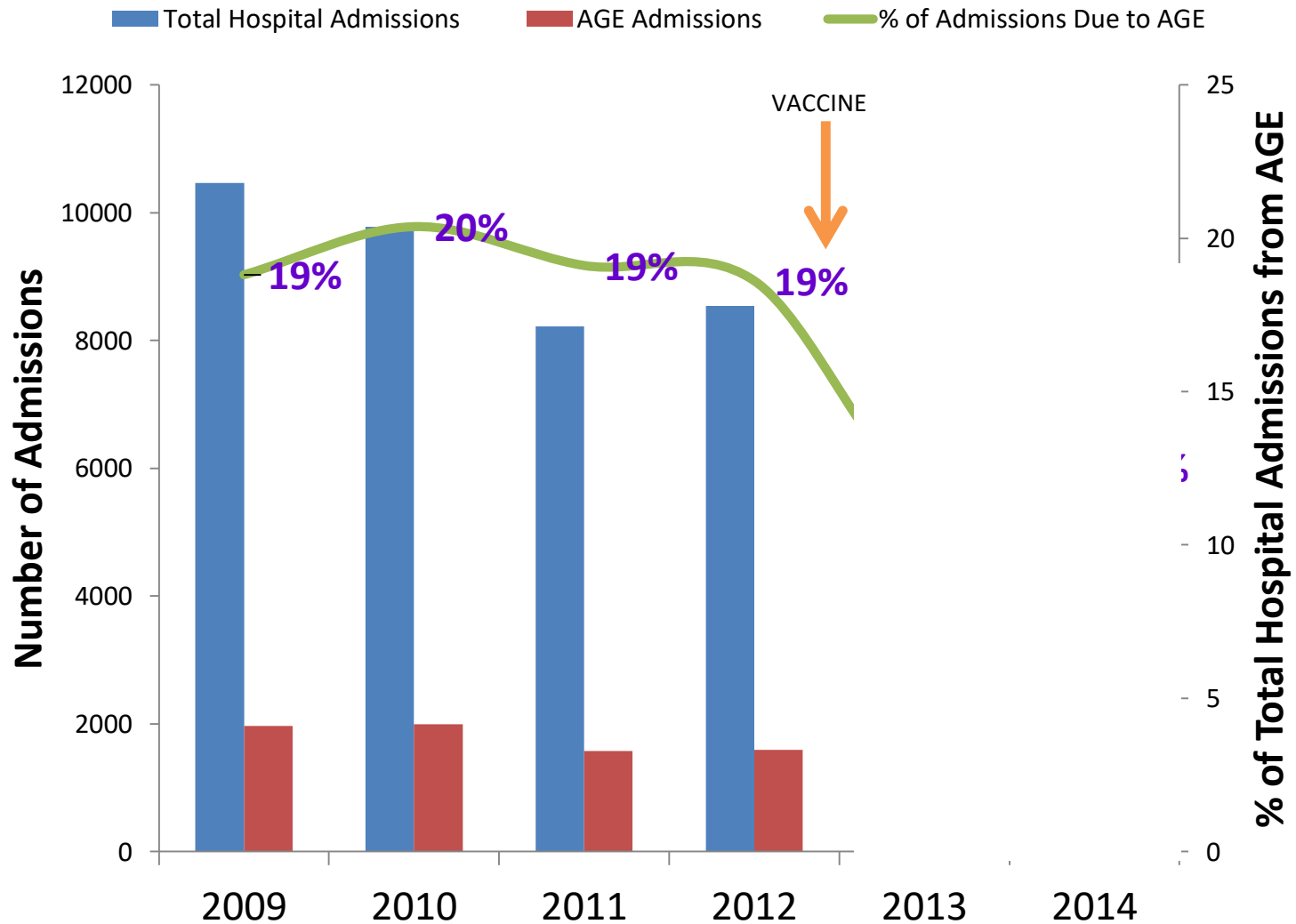
- Middle East**
- Tajikistan (2015)
  - Uzbekistan (2014)
  - Yemen (2012)

Introduced (Year) [35]  
 *Approved [4]*

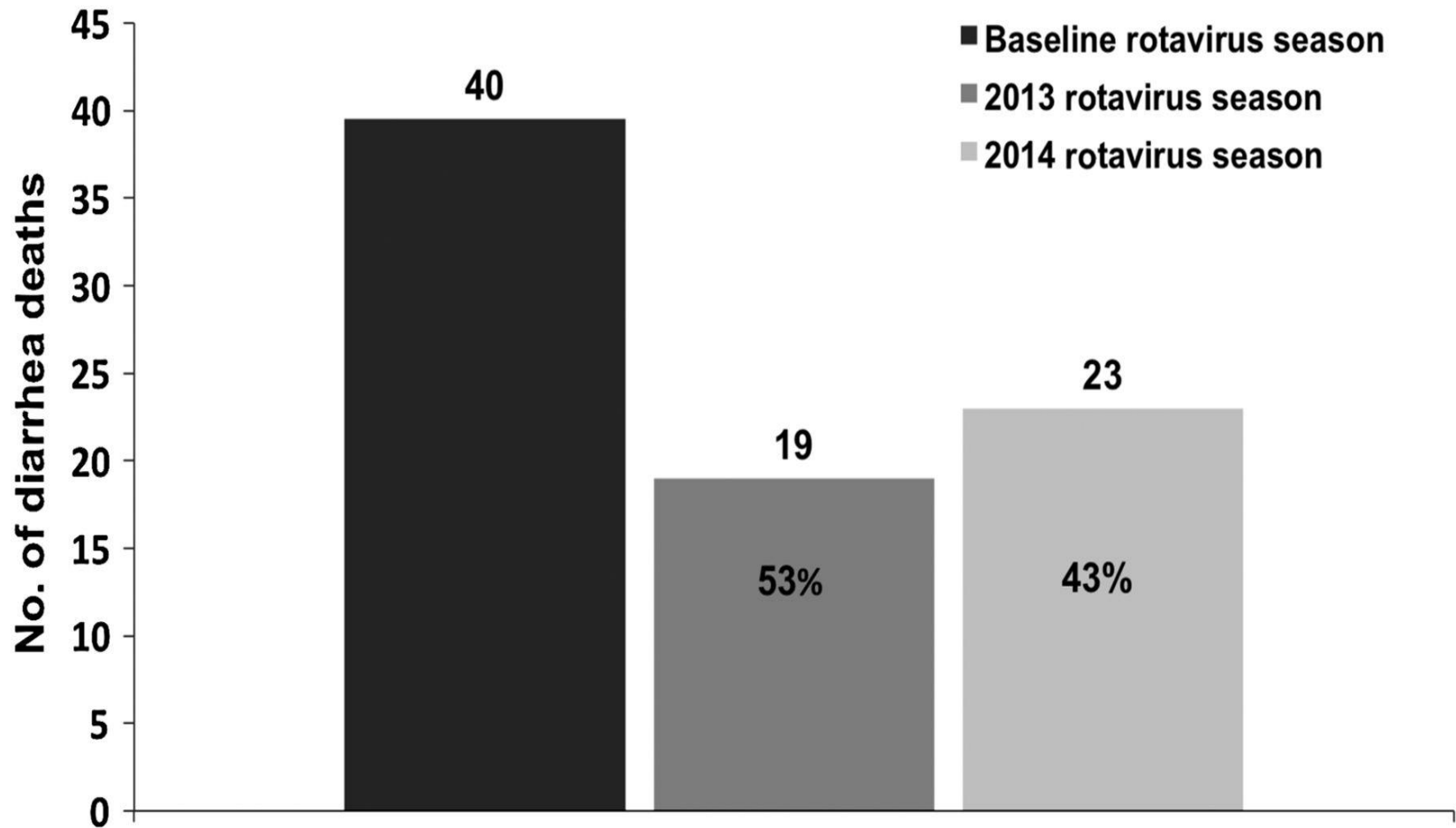
# Decline in childhood diarrhea hospitalizations at 27 district hospitals in Rwanda after rotavirus vaccine introduction



# Decline in proportion of childhood hospitalizations caused by diarrhea in Rwanda



# Reduction in all-cause gastroenteritis-related deaths among infants at 4 hospitals in Botswana after rotavirus vaccine implementation



**What is the economic impact of  
vaccination?**

# Cost-effectiveness of rotavirus vaccination in Malawi



- Prospective cohort N=530
- Household & Societal perspective
  - Itemised household expenditures
  - Post-discharge home visit
  - Detailed socioeconomic data
- Government perspective
  - Detailed costing of individual healthcare actually received

→ avert 54,000 child deaths

→ US\$19 per DALY averted



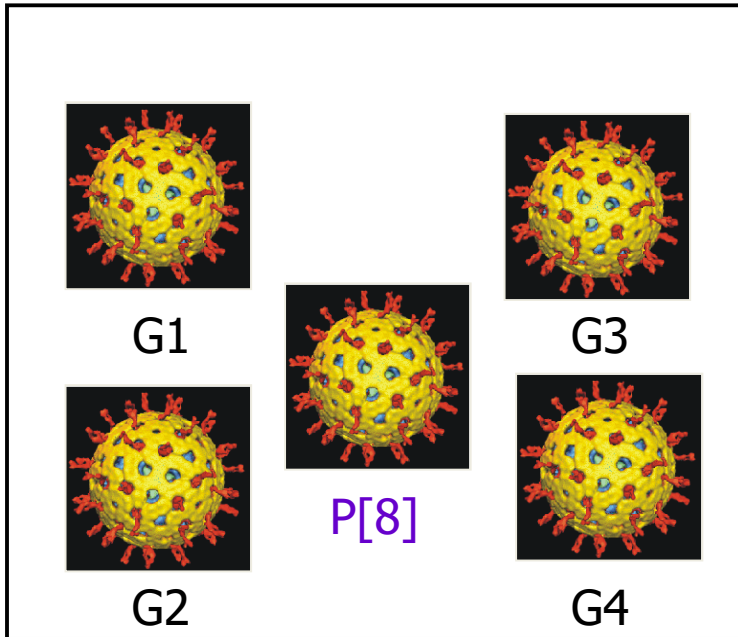
**\$143 per DALY averted**



**How well will vaccines protect  
against range of strains?**

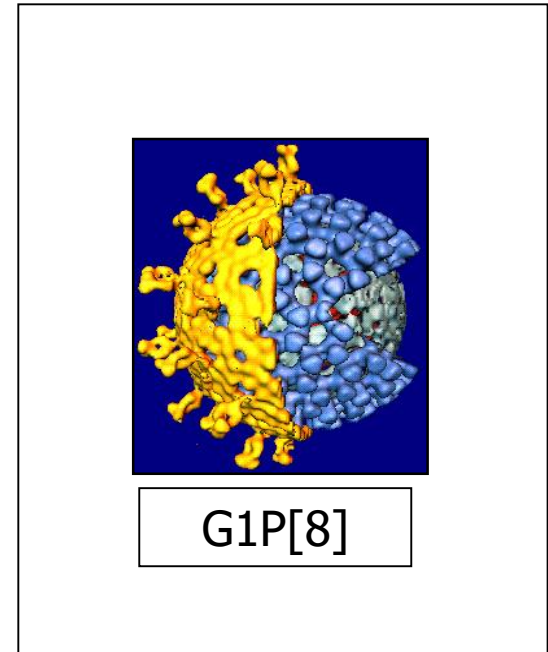
# RotaTeq is Pentavalent & Rotarix is Monovalent

## RotaTeq



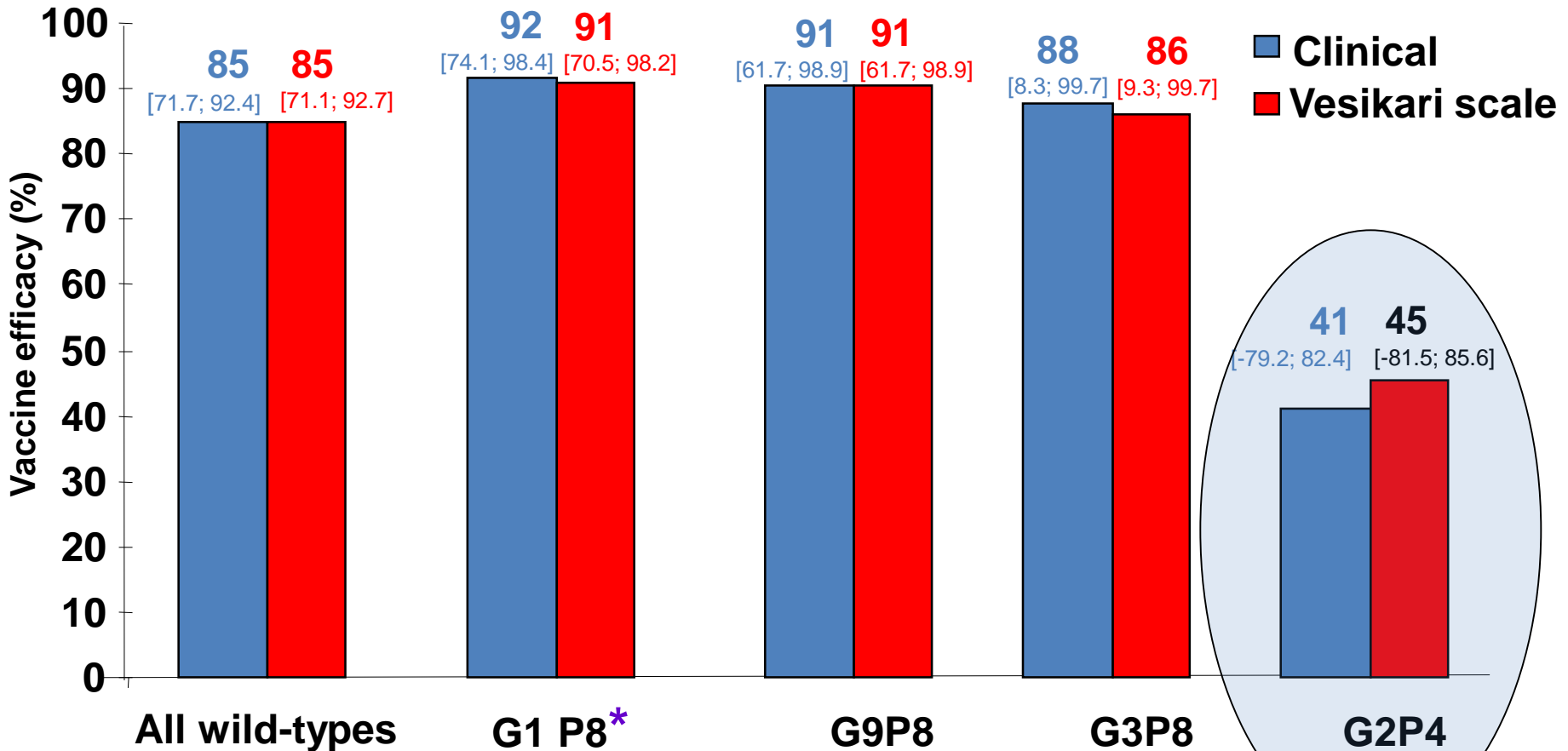
Five bovine-human rotavirus strains

## Rotarix



Single human rotavirus strain

# Rotarix (G1P8): Serotype Specific Efficacy in Latin America



\* Homotypic strain

# High Rotarix (G1P8) Effectiveness against Non-Vaccine Strains in Several Countries

Country	Post-vaccine strains	Vaccine Effectiveness (95% CI)
Brazil	G2P[4]	85% (54, 95)

# High Rotarix (G1P8) Effectiveness against Non-Vaccine Strains in Several Countries

Country	Post-vaccine strains	Vaccine Effectiveness (95% CI)
Brazil	G2P[4]	85% (54, 95)
Mexico	G9P[4]	94% (16, 100)

# High Rotarix (G1P8) Effectiveness against Non-Vaccine Strains in Several Countries

Country	Post-vaccine strains	Vaccine Effectiveness (95% CI)
Brazil	G2P[4]	85% (54, 95)
Mexico	G9P[4]	94% (16, 100)
Bolivia	G9P[8]	84% (64, 92)
	G2P[4]	71% (19, 90)
	G3P[8]	92% (60, 98)
	G9P[6]	87% (-10, 98)

**Do rotavirus vaccines  
cause intussusception?**

# Post-Licensure Intussusception Data

- Mexico, Brazil, US, and Australia have reported a low risk of intussusception
  - ~1-6 cases per 100,000 vaccinated
  - With both vaccines
- **Key Question** – How does the risk compare with benefits of vaccination?



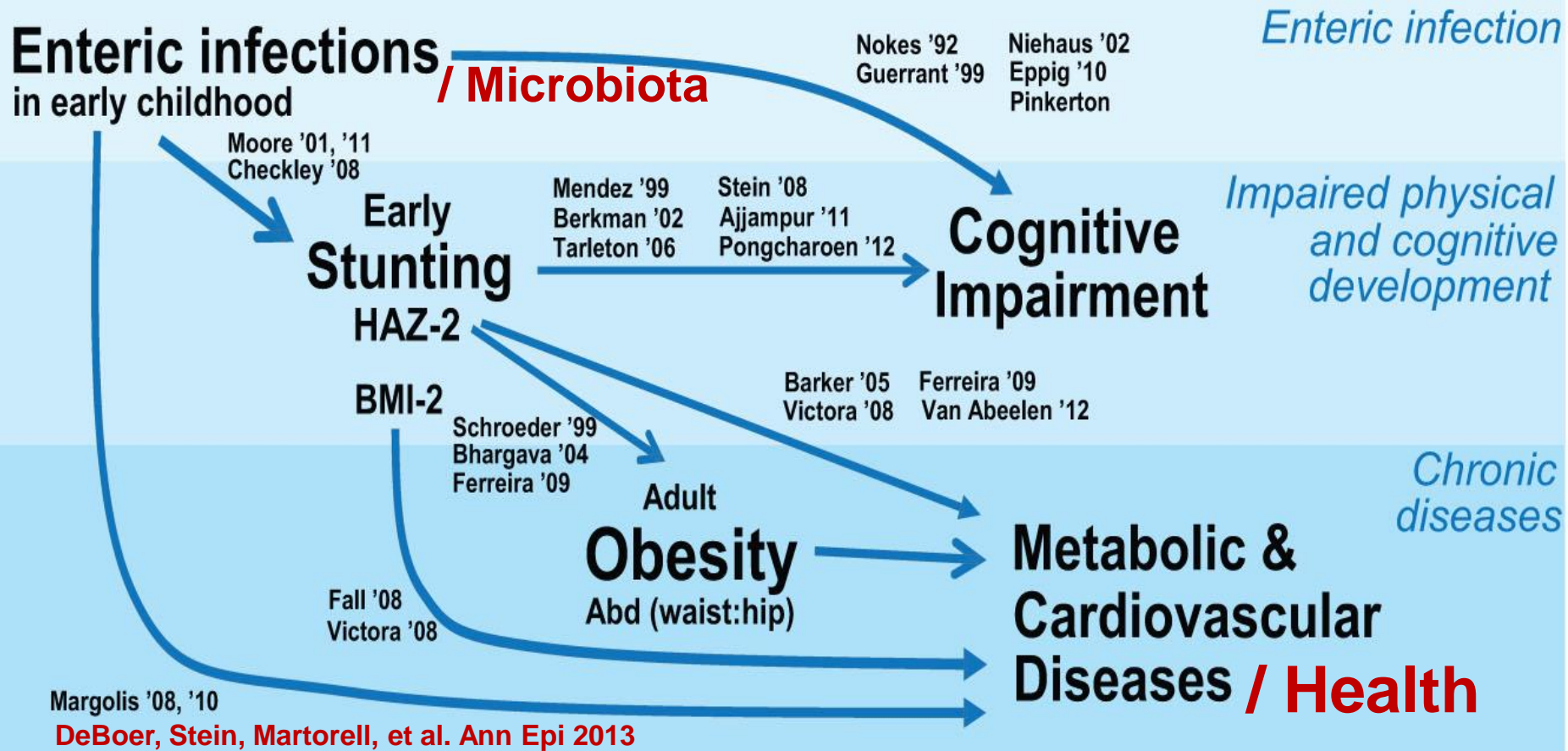
# Benefits vs. Risks of Vaccination

	Diarrhea Hospitalizations (Deaths) Prevented	Intussusception Cases (Deaths) Caused
Mexico	11,600 (663)	41 (2)
Brazil	69,600 (640)	55 (3)
Australia	7,000 (0)	6 (0)
US	53,000 (16)	48 (0)

\*

**Are there other, unmeasured benefits  
of vaccination?**

# The triple burden of enteric infections, stunted growth and development and chronic diseases



# Post-licensure data has provided key evidence

- ✓ **Indirect benefits** to unvaccinated groups
- ✓ Reduction of **diarrhea mortality**
- ✓ **High impact despite lower efficacy** in low income settings
- ✓ **Broad protection** against range of strains
- ✓ **Benefits outweigh risks** of vaccination