Rotavirus Vaccines: Progress & Challenges

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Outline

- Burden of rotavirus
- Withdrawn Rotashield vaccine
- Current vaccines – RotaTeq and Rotarix
- Remaining issues & challenges

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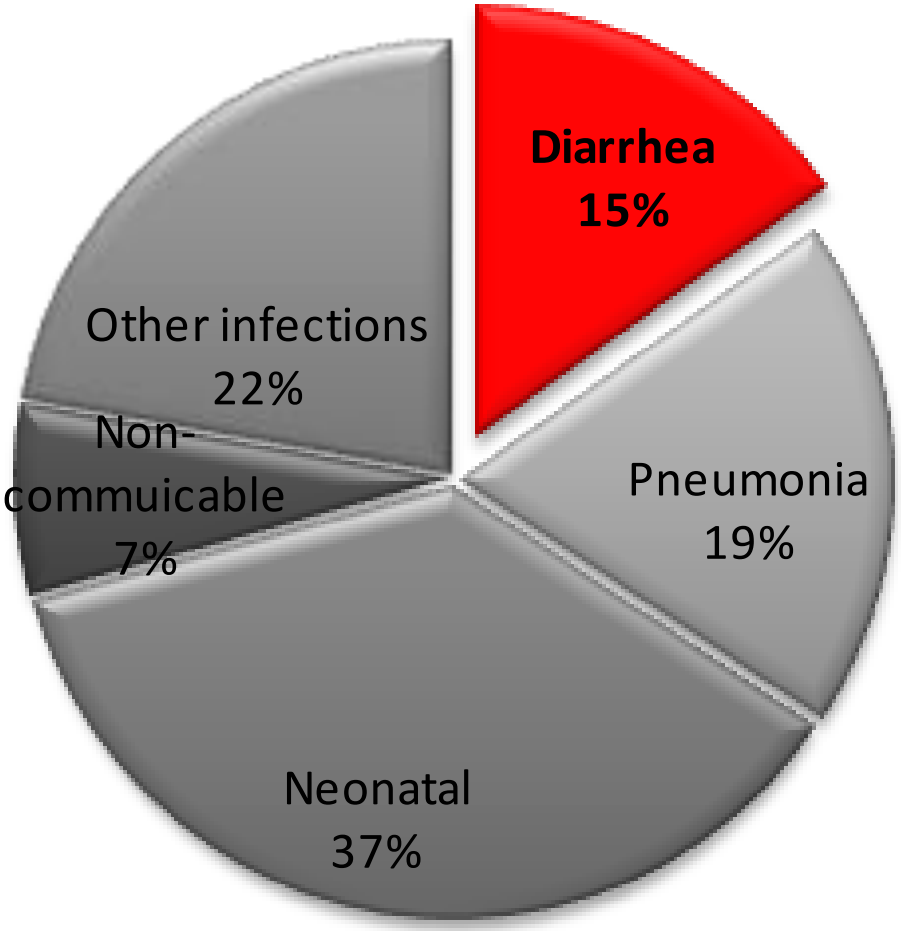
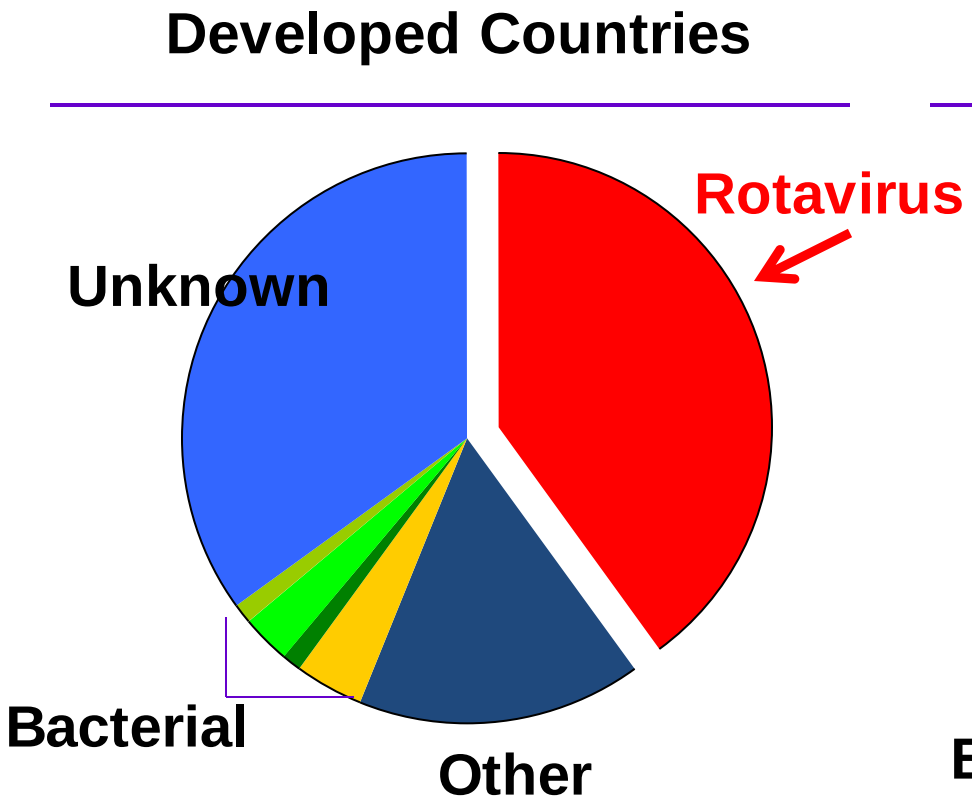
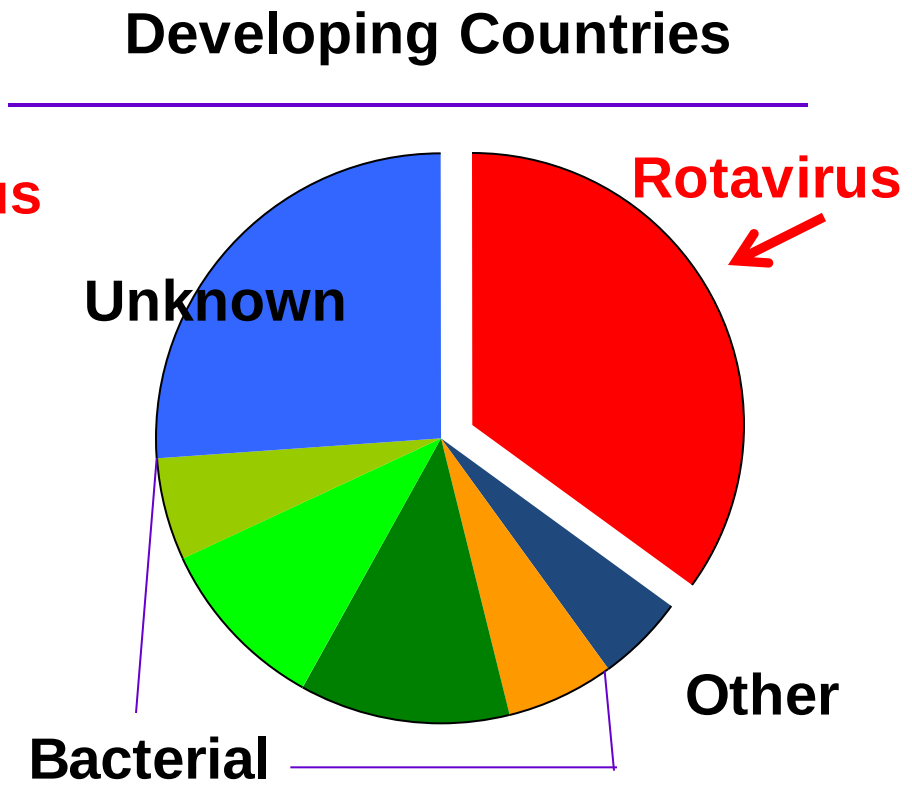
Diarrhea is a Leading Cause of Child Mortality Worldwide



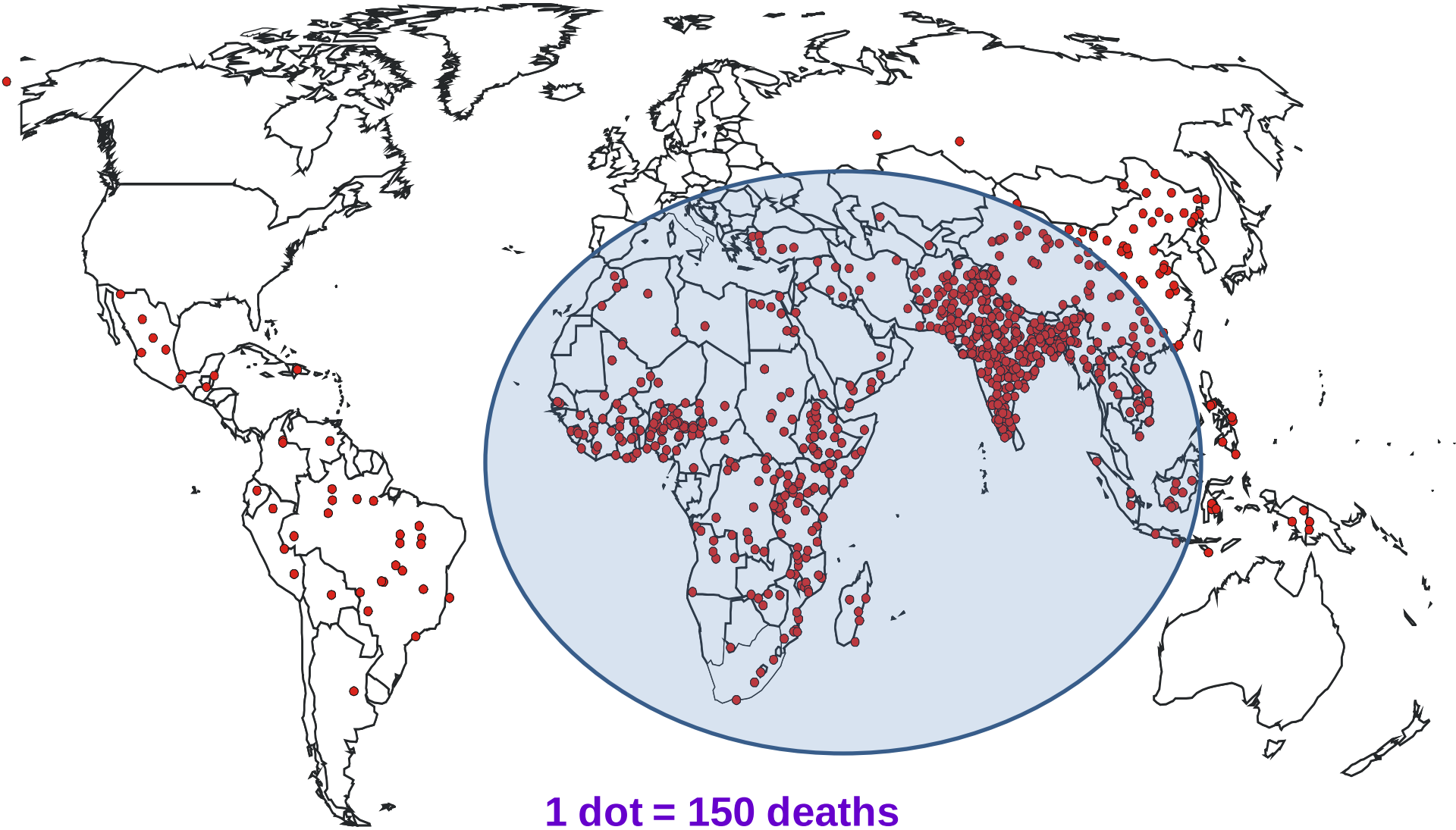
~ 700,000 deaths/year

Rotavirus is the Leading Cause Of Severe Diarrhea in Children <5 Years Globally





Rotavirus is a Major Cause of Child Mortality Worldwide -- ~200,000-250,000 Annual Deaths



1 dot = 150 deaths

Outline

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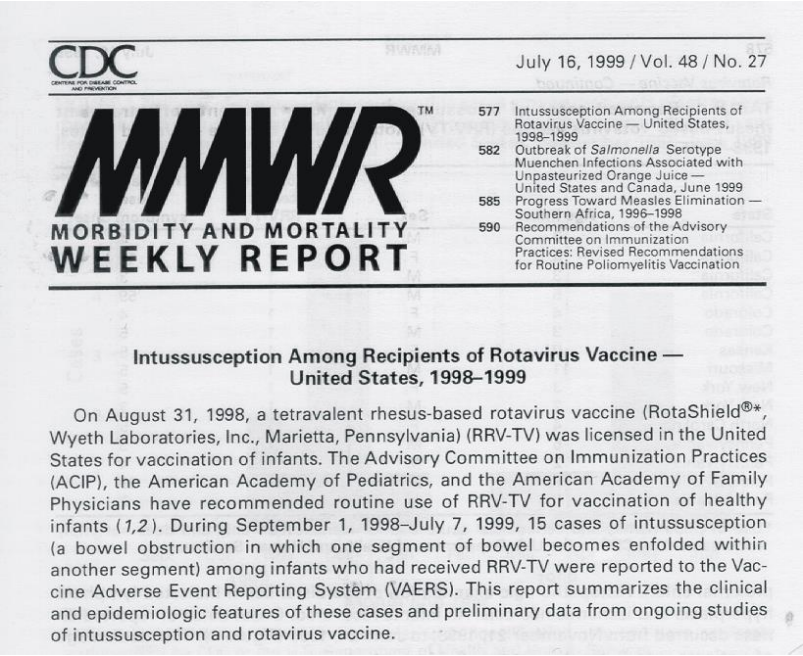
Rotashield Implemented in 1998 in US

A Setback – Rotashield Withdrawn Within 1 Year Because of Association with Intussusception



CDC

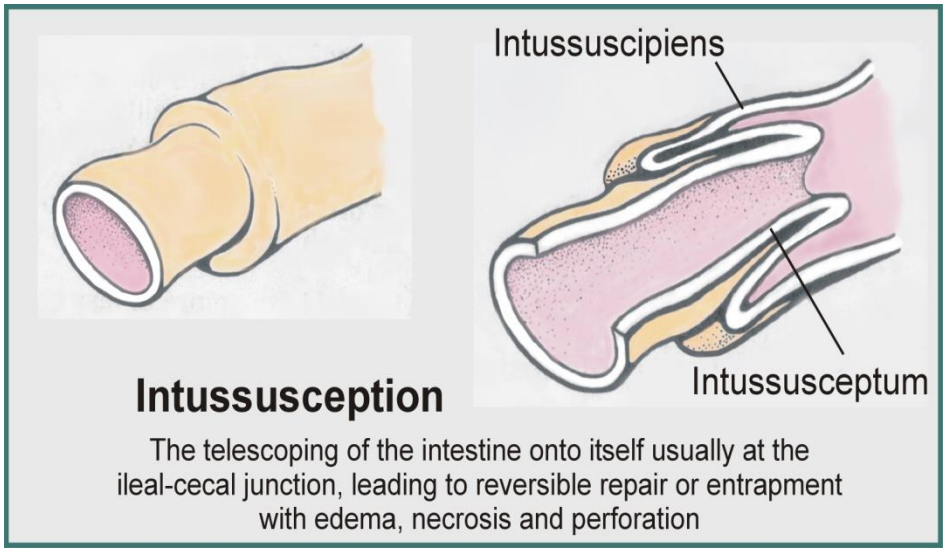
July 16, 1999 / Vol. 48 / No. 27

MMWR™

MORBIDITY AND MORTALITY WEEKLY REPORT

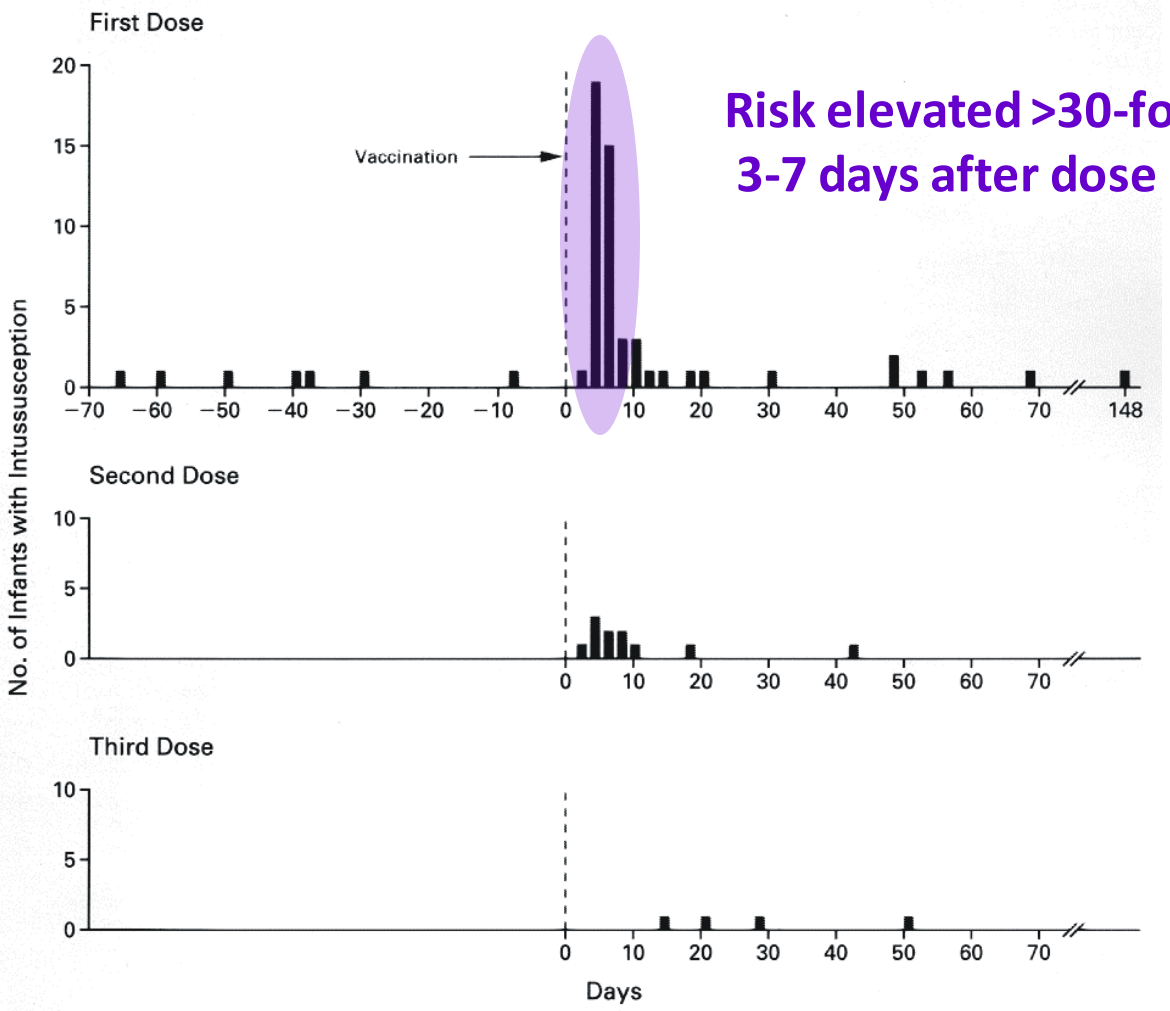
Intussusception Among Recipients of Rotavirus Vaccine — United States, 1998–1999

On August 31, 1998, a tetravalent rhesus-based rotavirus vaccine (RotaShield®*, Wyeth Laboratories, Inc., Marietta, Pennsylvania) (RRV-TV) was licensed in the United States for vaccination of infants. The Advisory Committee on Immunization Practices (ACIP), the American Academy of Pediatrics, and the American Academy of Family Physicians have recommended routine use of RRV-TV for vaccination of healthy infants (*1,2*). During September 1, 1998–July 7, 1999, 15 cases of intussusception (a bowel obstruction in which one segment of bowel becomes enfolded within another segment) among infants who had received RRV-TV were reported to the Vaccine Adverse Event Reporting System (VAERS). This report summarizes the clinical and epidemiologic features of these cases and preliminary data from ongoing studies of intussusception and rotavirus vaccine.



1 intussusception per 10,000 vaccinated infants

Intussusception Risk Greatest in First Week After Dose 1 of Rotashield



Risk elevated >30-fold during 3-7 days after dose 1

Murphy et al. NEJM 2001; 344:564-72.

The $100 million question

Will other oral rotavirus vaccines also cause intussusception?

Will Other Oral Rotavirus Vaccines Also Cause Intussusception?

- Unique features of the rhesus strain in Rotashield®
  - High replication and shedding (>80%)
  - Fever in >30% and some vomiting/diarrhea
- No apparent link between intussusception and natural rotavirus infection
- *Not possible to confirm absence of risk without large and expensive trials (~US $1 billion)*

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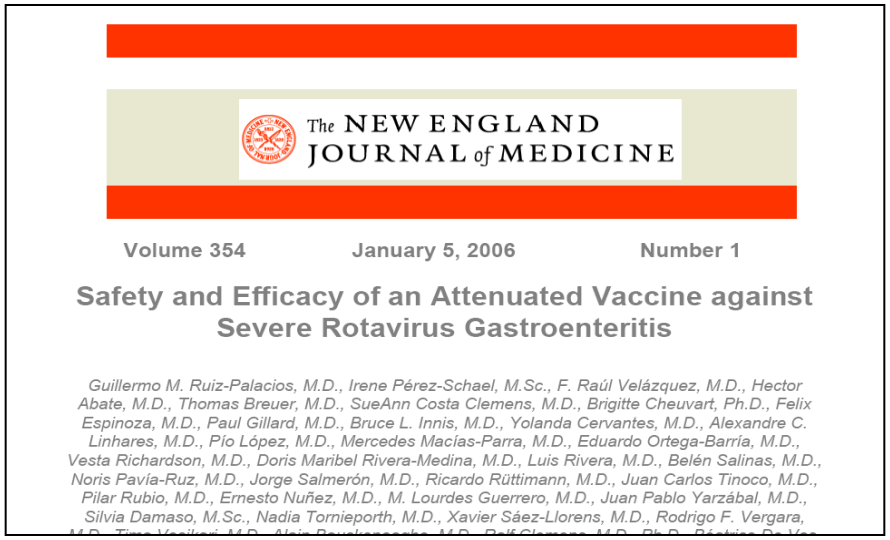
Two Oral Rotavirus Vaccines Licensed in 2006

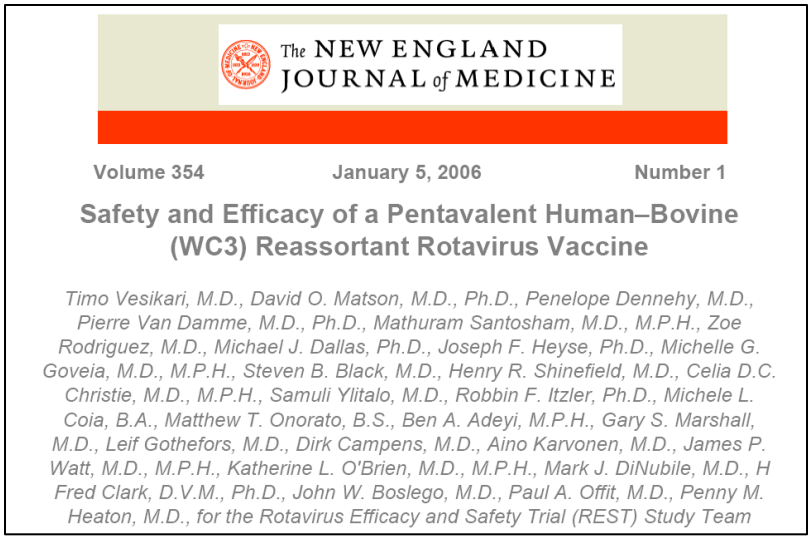


The NEW ENGLAND JOURNAL of MEDICINE

Volume 354 January 5, 2006 Number 1

Safety and Efficacy of an Attenuated Vaccine against Severe Rotavirus Gastroenteritis

Guillermo M. Ruiz-Palacios, M.D., Irene Pérez-Schael, M.Sc., F. Raúl Velázquez, M.D., Hector Abate, M.D., Thomas Breuer, M.D., SueAnn Costa Clemens, M.D., Brigitte Cheuvart, Ph.D., Felix Espinoza, M.D., Paul Gillard, M.D., Bruce L. Innis, M.D., Yolanda Cervantes, M.D., Alexandre C. Linhares, M.D., Pío López, M.D., Mercedes Macías-Parra, M.D., Eduardo Ortega-Barría, M.D., Vesta Richardson, M.D., Doris Maribel Rivera-Medina, M.D., Luis Rivera, M.D., Belén Salinas, M.D., Noris Pavía-Ruz, M.D., Jorge Salmerón, M.D., Ricardo Rüttimann, M.D., Juan Carlos Tinoco, M.D., Pilar Rubio, M.D., Ernesto Nuñez, M.D., M. Lourdes Guerrero, M.D., Juan Pablo Yarzábal, M.D., Silvia Damaso, M.Sc., Nadia Tornieporth, M.D., Xavier Sáez-Llorens, M.D., Rodrigo F. Vergara,



The NEW ENGLAND JOURNAL of MEDICINE

Volume 354 January 5, 2006 Number 1

Safety and Efficacy of a Pentavalent Human–Bovine (WC3) Reassortant Rotavirus Vaccine

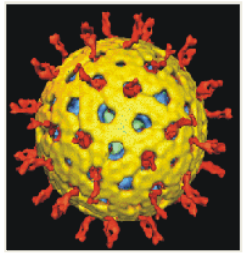
Timo Vesikari, M.D., David O. Matson, M.D., Ph.D., Penelope Dennehy, M.D., Pierre Van Damme, M.D., Ph.D., Mathuram Santosham, M.D., M.P.H., Zoe Rodriguez, M.D., Michael J. Dallas, Ph.D., Joseph F. Heyse, Ph.D., Michelle G. Goveia, M.D., M.P.H., Steven B. Black, M.D., Henry R. Shinefield, M.D., Celia D.C. Christie, M.D., M.P.H., Samuli Ylitalo, M.D., Robbin F. Itzler, Ph.D., Michele L. Coia, B.A., Matthew T. Onorato, B.S., Ben A. Adeyi, M.P.H., Gary S. Marshall, M.D., Leif Gothefors, M.D., Dirk Campens, M.D., Aino Karvonen, M.D., James P. Watt, M.D., M.P.H., Katherine L. O'Brien, M.D., M.P.H., Mark J. DiNubile, M.D., H Fred Clark, D.V.M., Ph.D., John W. Boslego, M.D., Paul A. Offit, M.D., Penny M. Heaton, M.D., for the Rotavirus Efficacy and Safety Trial (REST) Study Team

- Trials of 60-70,000 infants each
- No increased risk of intussusception
- Efficacy of 85%-98% against severe disease

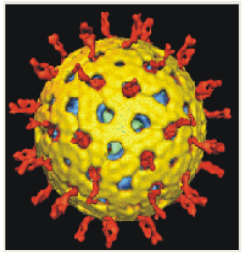
Vesikari et al and Ruiz-Palacios et al, NEJM 2006

RotaTeq (Merck & Co.)

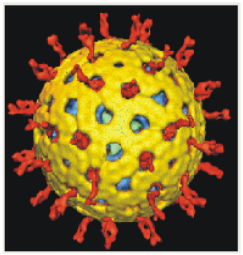
Bovine rotavirus with single human rotavirus gene substitution



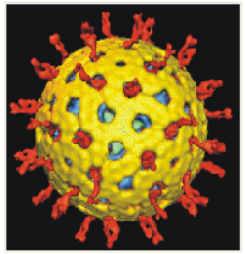
G1



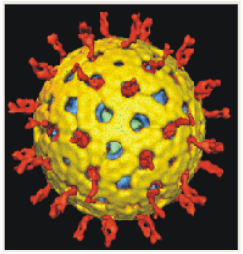
P[8]



G3



G2

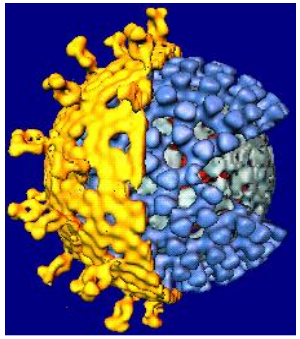


G4

3 doses

Rotarix (GSK)

Human rotavirus



G1P[8]

2 doses

2009 – WHO Global Recommendation

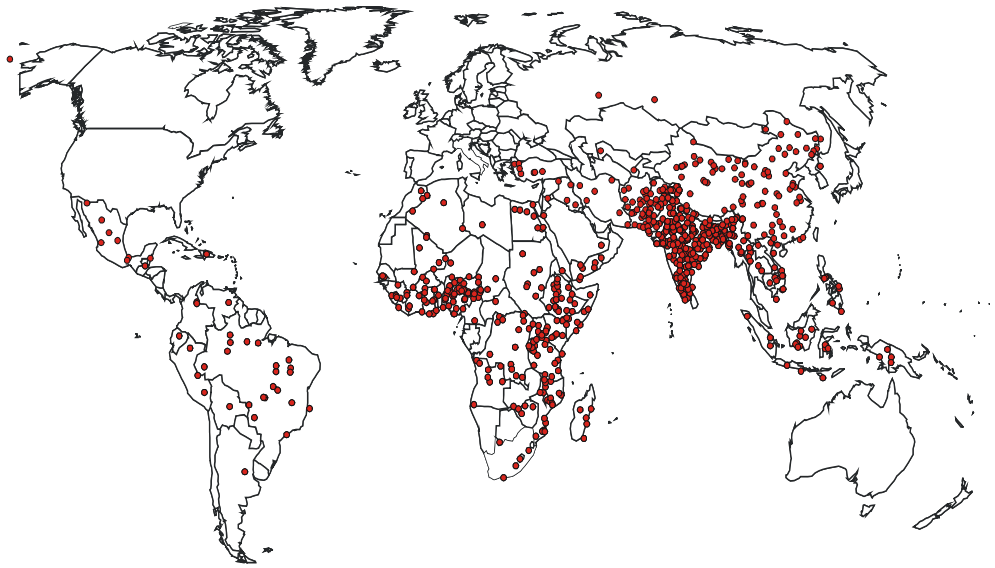
World Health Organization

PATH
A catalyst for global health

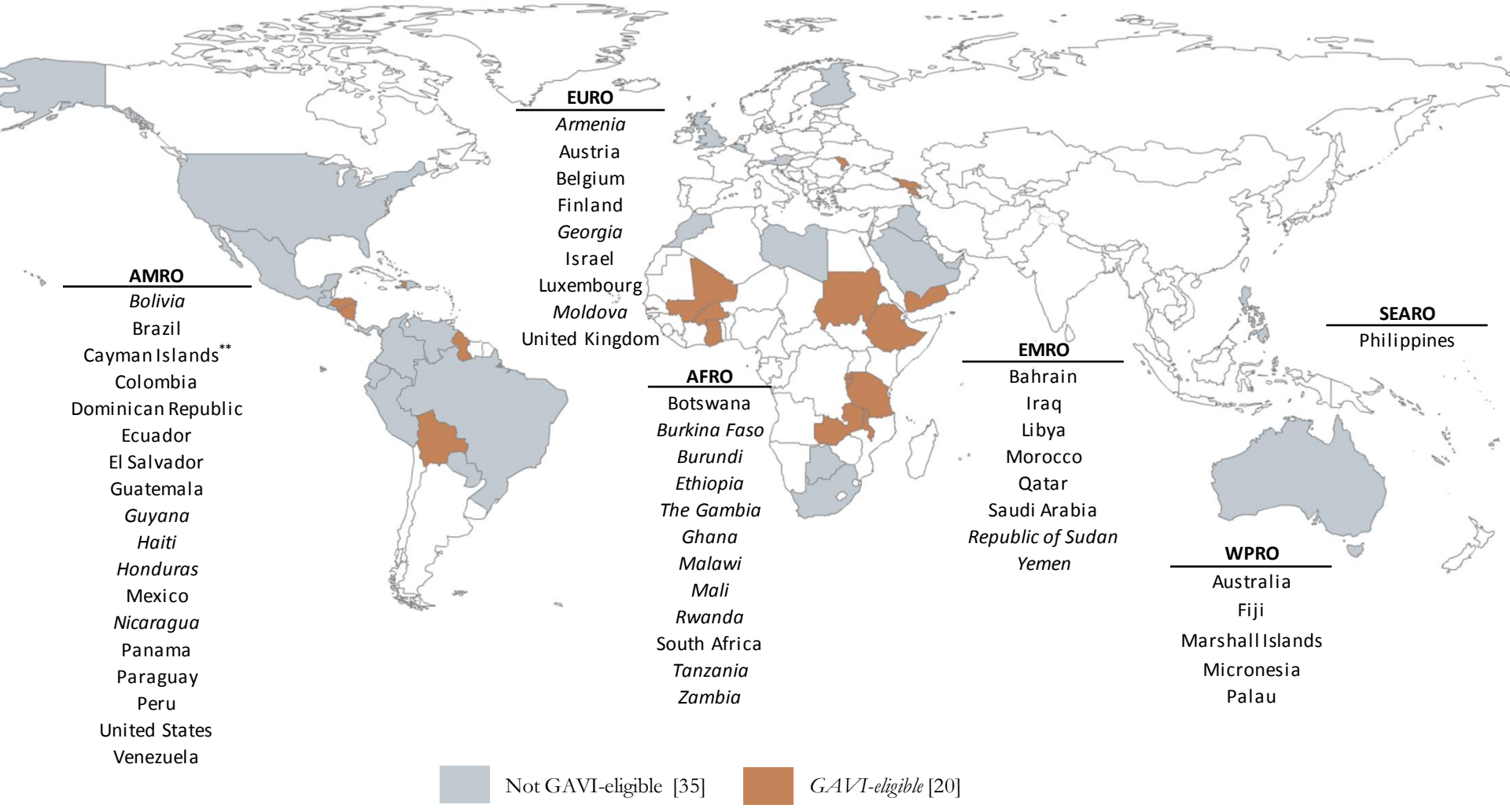
GAVI ALLIANCE

WHO Recommends Global Use of Rotavirus Vaccines

Decision Could Help Protect Millions of Children in Africa and Asia from Lethal Diarrheal Disease



National RV introductions by WHO region: 55 countries*



*National introductions by WHO region as of 28 March 2014
**Not a WHO member state
RV= rotavirus vaccine

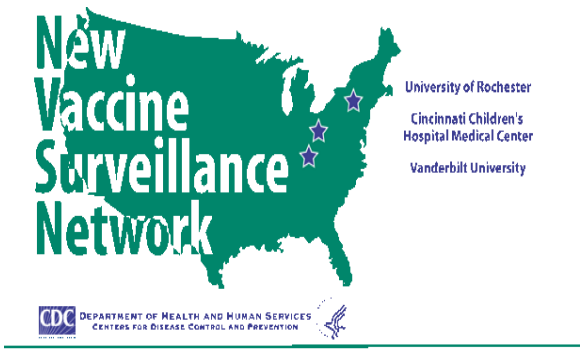
PATH

Rotavirus Vaccines in USA

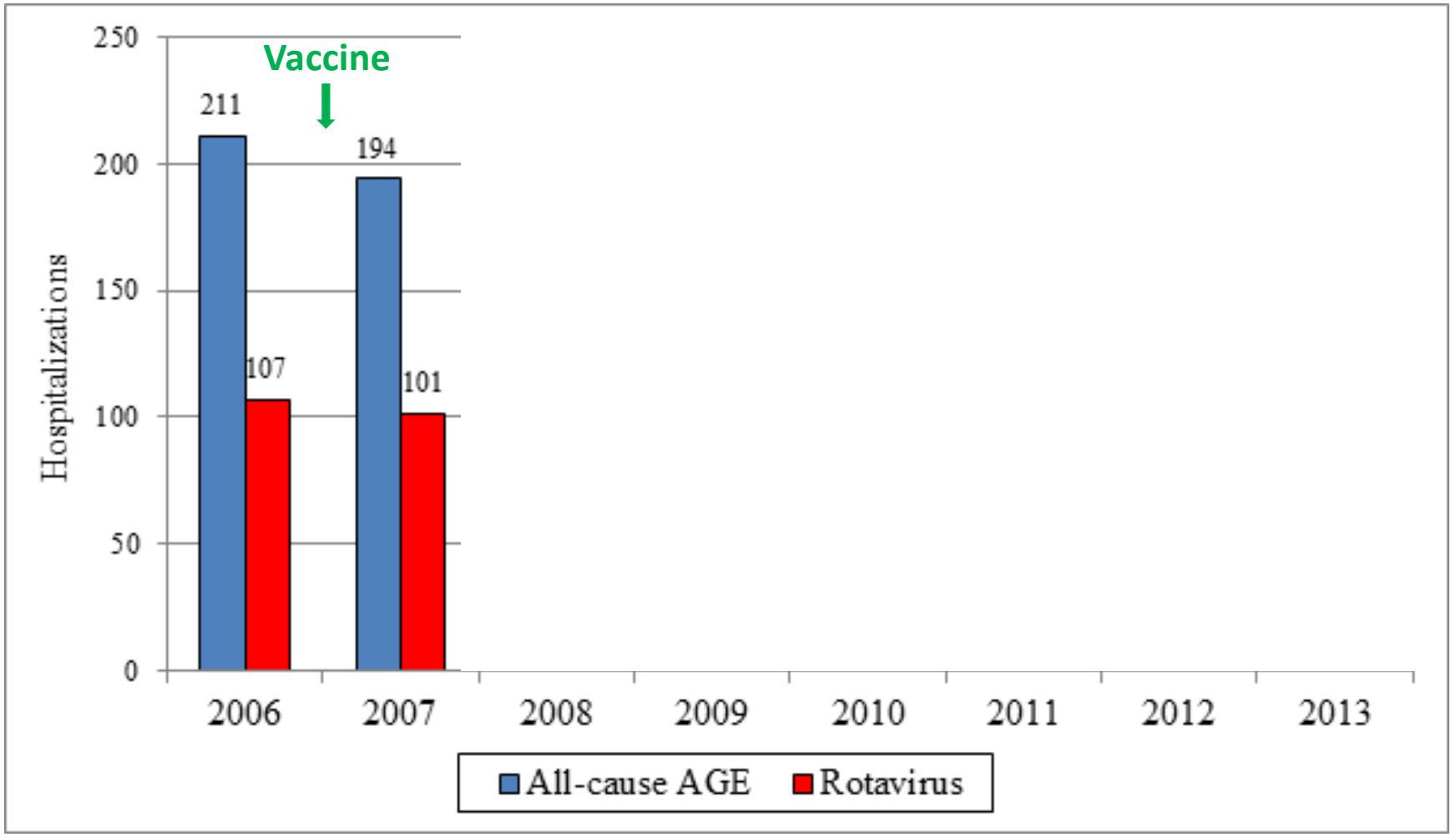
- Feb 2006 – RotaTeq recommended
- June 2008 – Rotarix recommended

Active Rotavirus Surveillance

- Active surveillance in 3 US counties
- Enrollment of inpatients, emergency room patients, and outpatients with AGE
- Fecal specimens obtained and tested for rotavirus



Impact on All-Cause and Rotavirus-Specific Gastroenteritis Hospitalizations in USA



Payne DC, unpublished 2014

Age-Specific Rotavirus Hospitalization Rate Reduction and Vaccine Coverage, USA

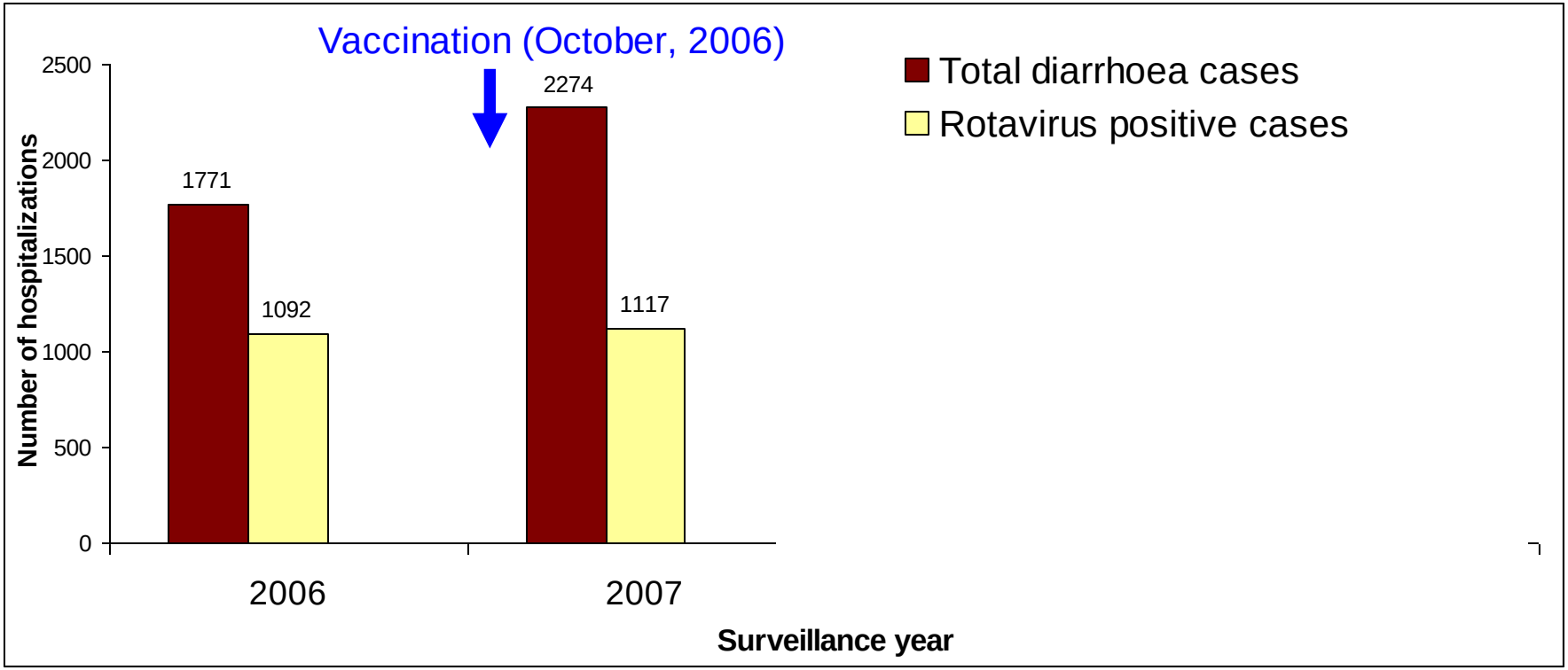
Age	Decline in rotavirus hospitalization rate (2008 vs. 2006)	Rotavirus vaccine coverage in 2008 (>=1 dose)
< 1 year	66%	56%
1 -< 2 years	95%	44%
2 -< 3 years	85%	<1%

This age cohort was ineligible to receive rotavirus vaccine

Herd immunity?

Impact on Rotavirus and All-Cause Gastroenteritis Hospitalizations in Children, El Salvador

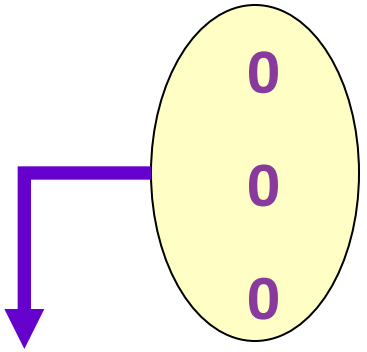
70-80% reduction in rotavirus hospitalizations children < 5 years



De Palma, BMJ, 2010

Herd Protection: Reduction in Rotavirus among UNVACCINATED Age Groups in El Salvador

Age	Decline in rotavirus hospitalization rate (2008 vs. 2006)	Rotavirus vaccine coverage in 2008 (>=1 dose)
< 1 year	84% (80 to 88)	76%
1 year	86% (82 to 89)	84%
2 years	65% (50 to 75)	0
3 years	41% (-7 to 68)	0
4 years	68% (29 to 85)	0



These age cohorts were ineligible to receive rotavirus vaccine

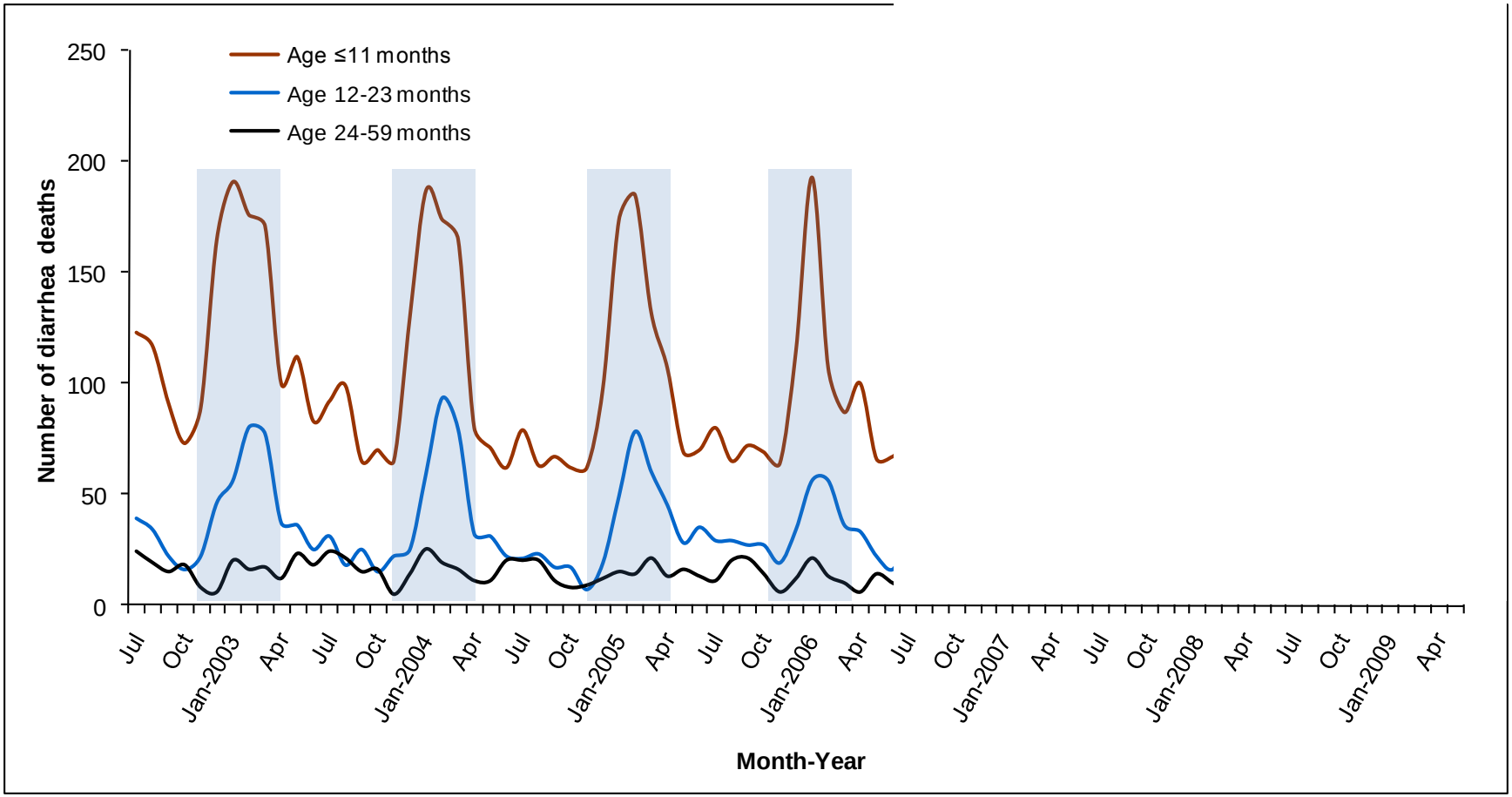
Yen et al, PIDJ 2011

First evidence of impact of vaccine on diarrhea mortality in Mexico

The NEW ENGLAND JOURNAL of MEDICINE

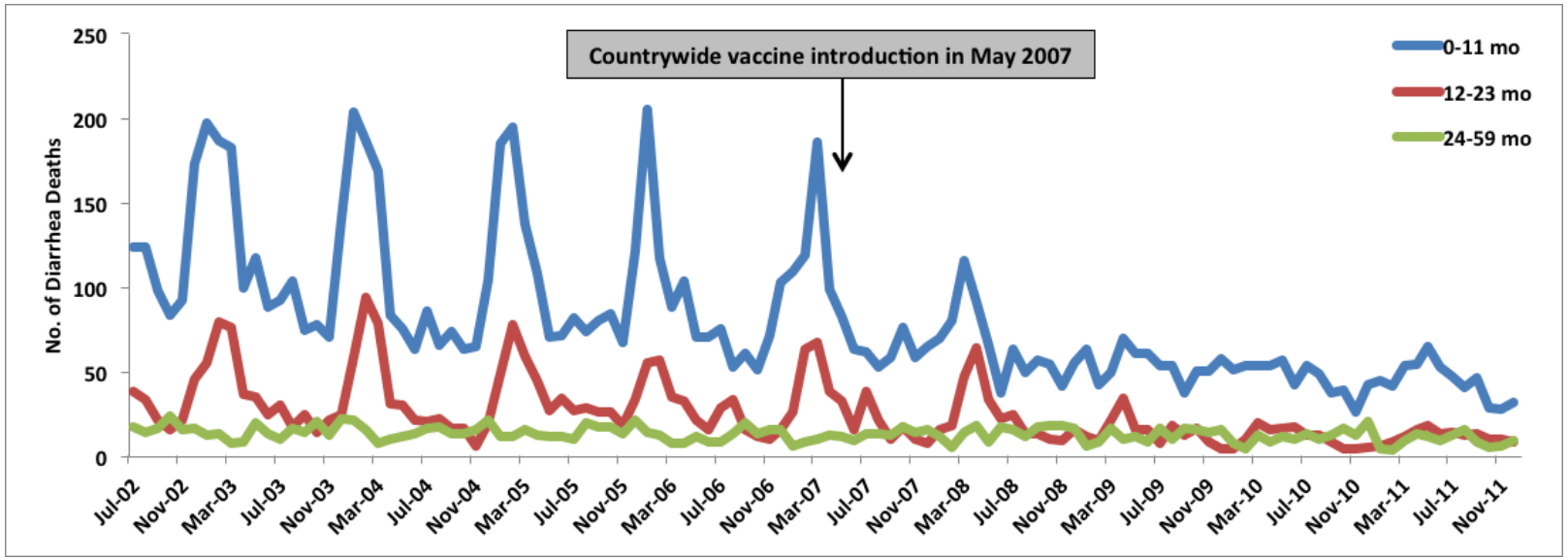
ORIGINAL ARTICLE

Effect of Rotavirus Vaccination on Death from Childhood Diarrhea in Mexico



Richardson et al, NEJM 2010

Mortality decline sustained for four years post vaccine implementation in Mexico



Rotavirus Vaccine Experience to Date

Borrowed from: http://dannybrown.me/wp-content/uploads/2011/01/success_baby.jpg

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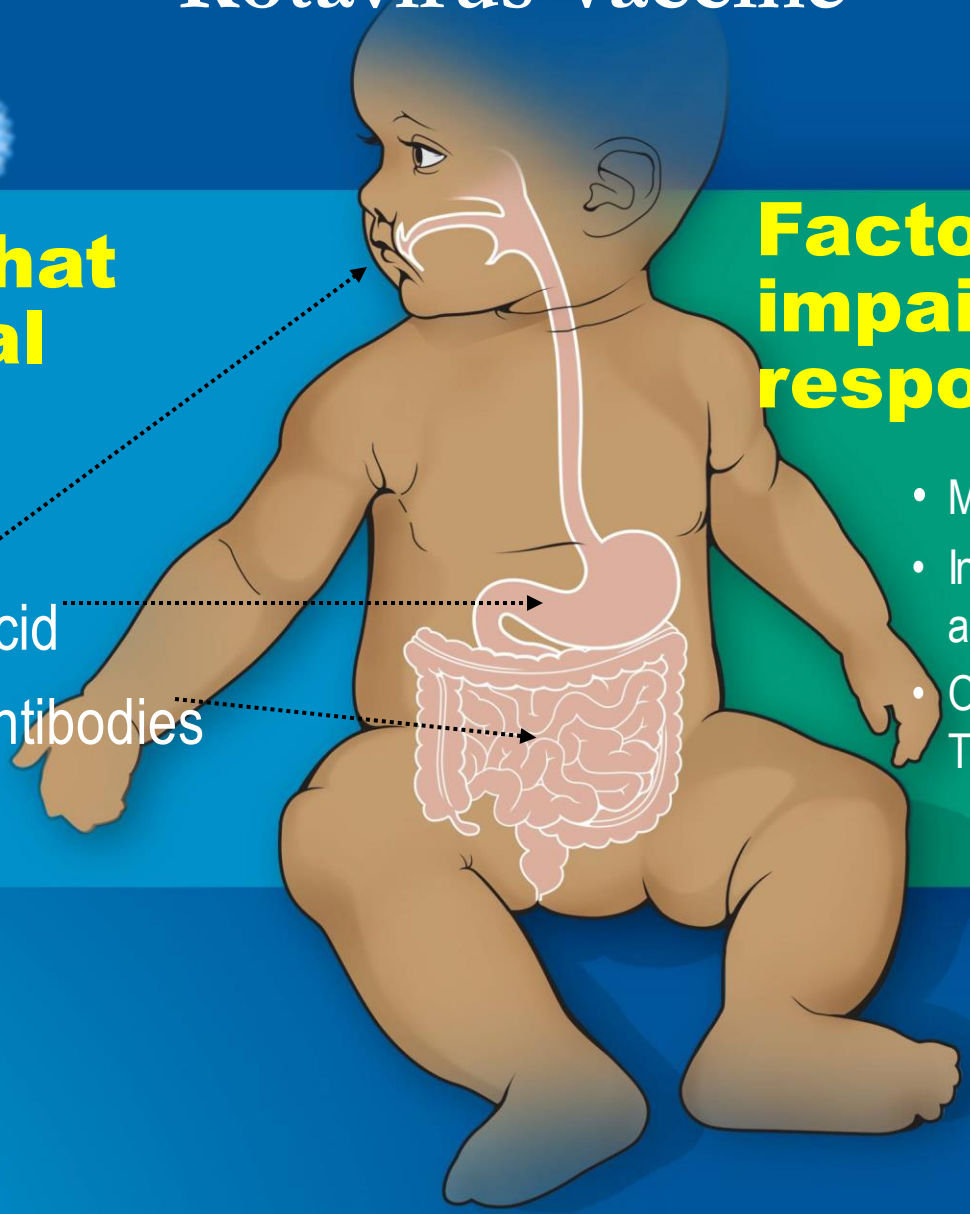
How well will live oral rotavirus vaccines work in the developing world?

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

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 28, 2010 VOL. 362 NO. 4

Effect of Human Rotavirus Vaccine on Severe Diarrhea in African Infants

Shabir A. Madhi, M.D., Nigel A. Cunliffe, M.B., Ch.B., Ph.D., Duncan Steele, Ph.D., Desirée Witte, M.D., Mari Kirsten, M.D., Cheryl Louw, M.D., Bagrey Ngwira, M.D., John C. Victor, Ph.D., M.P.H., Paul H. Gillard, M.D., Brigitte B. Cheuvart, Ph.D., Htay H. Han, M.B., B.S., and Kathleen M. Neuzil, M.D., M.P.H.

THE LANCET

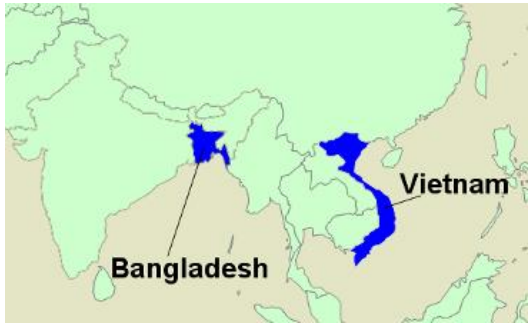
Volume 376 ■ Number 9741 ■ Pages 606-614 and 615-623 ■ 06 August 2010 www.thelancet.com

Efficacy of pentavalent rotavirus vaccine against severe rotavirus gastroenteritis in infants in developing countries in sub-Saharan Africa: a randomised, double-blind, placebo-controlled trial

George E Armah, Samba O Sow, Robert F Breiman, Michael J Dallas, Milagritos D Tapia, Daniel R Feikin, Fred N Binka, A Duncan Steele, Kayla F Laserson, Nana A Ansah, Myron M Levine, Kristen Lewis, Michele L Coia, Margaret Attah-Poku, Joel Ojwando, Stephen B Rivers, John C Victor, Geoffrey Nyambane, Abraham Hodgson, Florian Schödel, Max Ciarlet, Kathleen M Neuzil

Efficacy of pentavalent rotavirus vaccine against severe rotavirus gastroenteritis in infants in developing countries in Asia: a randomised, double-blind, placebo-controlled trial

K Zaman, Dang Duc Anh, John C Victor, Sunheang Shin, Md Yunus, Michael J Dallas, Goutam Podder, Vu Dinh Thiem, Le Thi Phuong Mai, Stephen P Luby, Le Huu Tho, Michele L Coia, Kristen Lewis, Stephen B Rivers, David A Sack, Florian Schödel, A Duncan Steele, Kathleen M Neuzil, Max Ciarlet



Moderate Efficacy of Rotavirus Vaccines in Africa and Asia

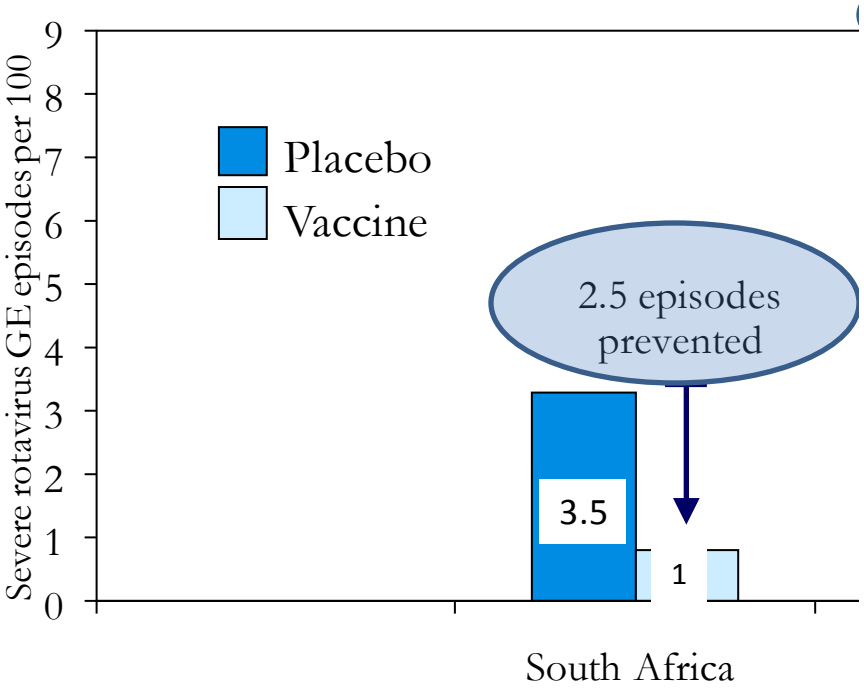
Vaccine	Region	Countries	Efficacy (95%CI)
RotaTeq	Africa	Ghana, Kenya, Mali	64% (40%-79%)
RotaTeq	Asia	Bangladesh, Vietnam	51% (13%-73%)
Rotarix	Africa	South Africa, Malawi	62% (44%-73%)

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

What does 50% efficacy mean?

Would you rather have 99% of my salary or 1% of Bill Gates'?

Despite Lower Efficacy, RV1 Prevented More Severe Rotavirus AGE in Malawi Because of Higher Burden



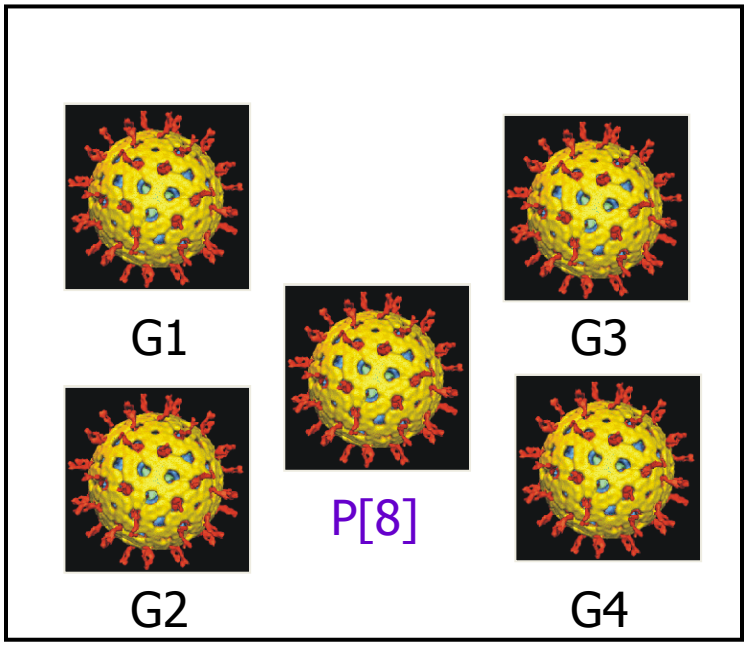
Efficacy 77%

Madhi et al. NEJM 2010

How well will vaccines protect against range of strains?

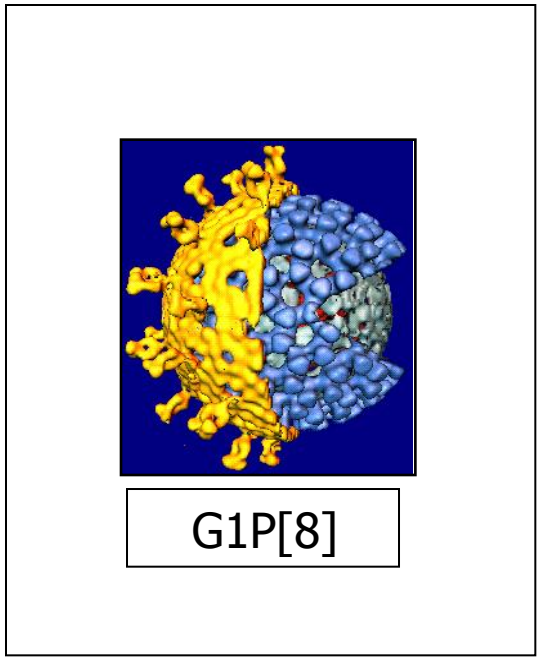
RotaTeq is Pentavalent & Rotarix is Monovalent

RotaTeq



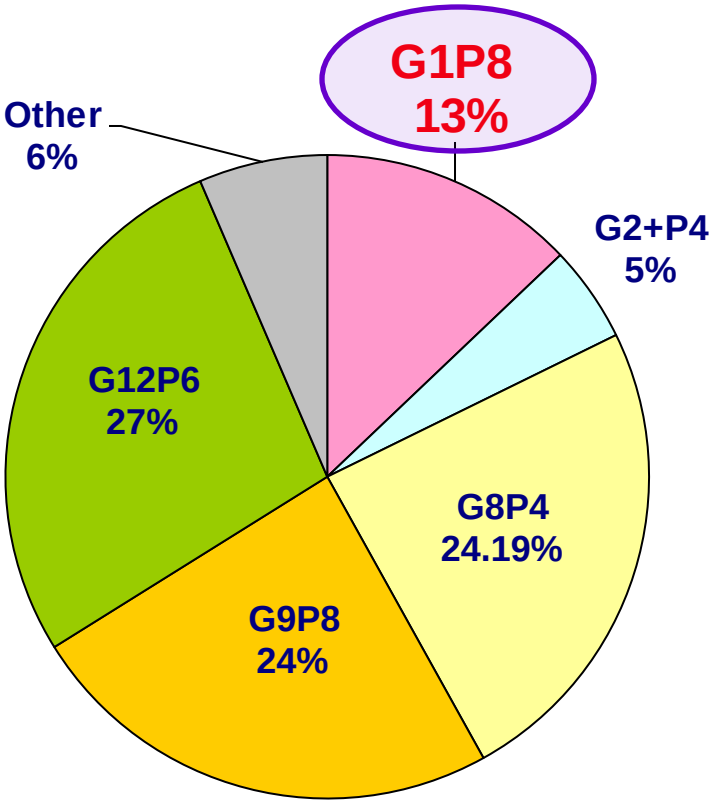
Five bovine-human rotavirus strains

Rotarix

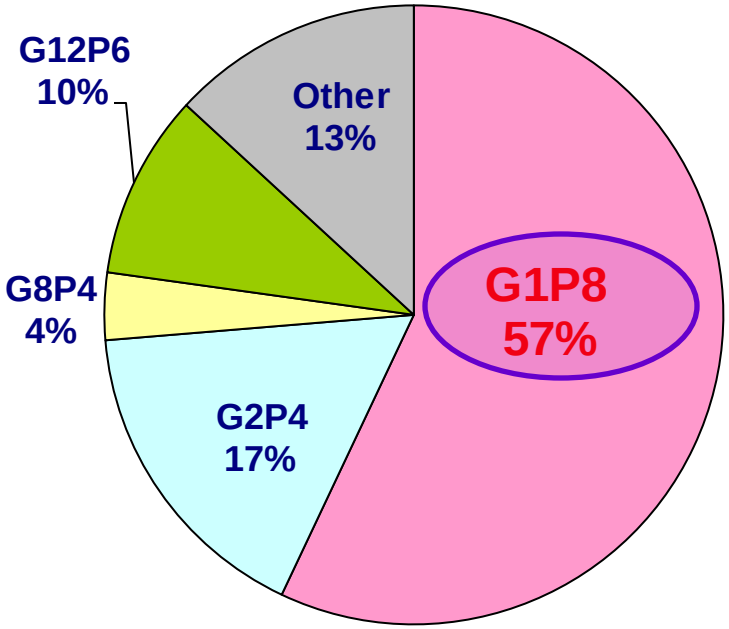


Single human rotavirus strain

Great Strain Diversity in African Rotarix Trial



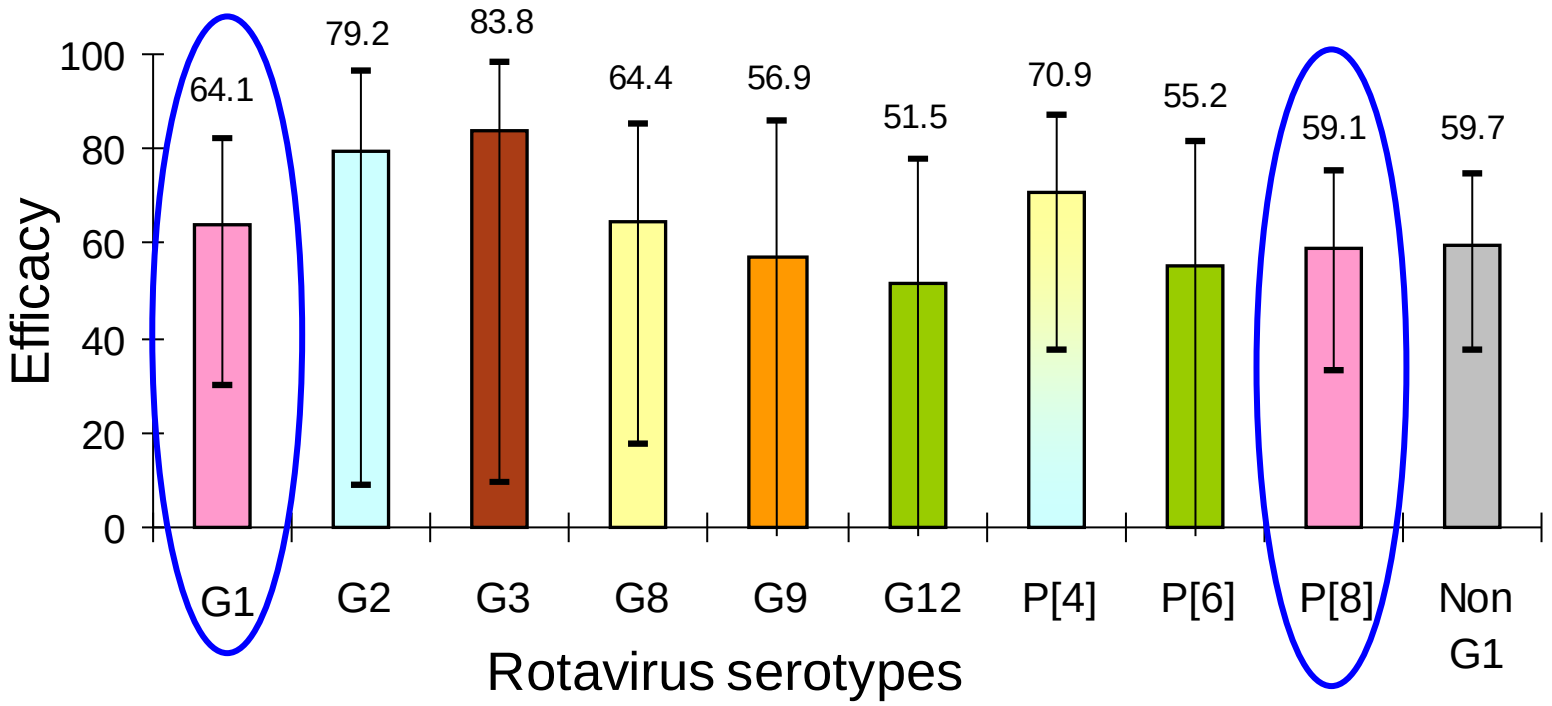
Malawi



South Africa

Madhi et al. NEJM 2010

Rotarix (G1P8) Efficacy Similar Against Disease Caused by Vaccine & Non-Vaccine Strains



Madhi et al. NEJM 2010

Increase in G2P4 Prevalence after Use of Rotarix (G1P8) in Brazil Raises Concern

Predominance of Rotavirus P[4]G2 in a Vaccinated Population, Brazil

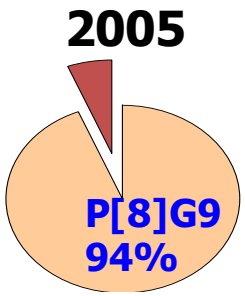
Gurgel et al, EID, 13(10), 2007

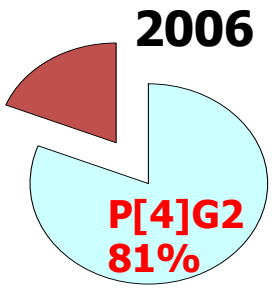
RAPID COMMUNICATION

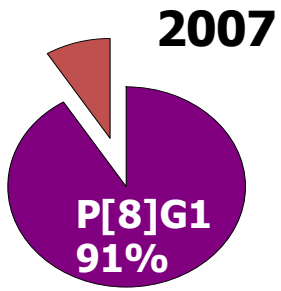
Apparent extinction of non-G2 rotavirus strains from circulation in Recife, Brazil, after the introduction of rotavirus vaccine

Nakagomi et al, Arch Vir 153(3); 2008

Is increasing prevalence of G2P[4] in Brazil caused by vaccine pressure or is it just natural variation?







El Salvador Rotarix, 2006 (opposite of Brazil)

Patel et al. EID 2009

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)

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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)

Will new Rotavirus Vaccines cause Intussusception?

Why Continue to Monitor Intussusception?

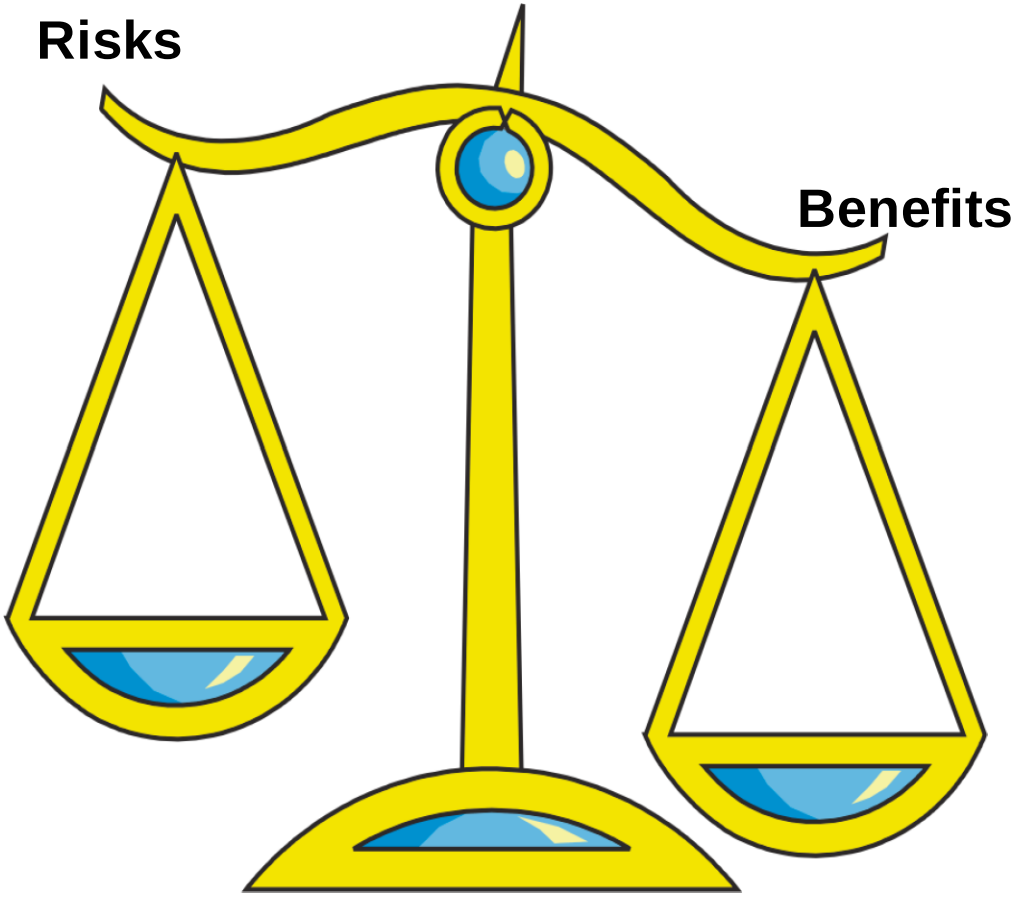
- Pre-licensure trials large
  - but powered to exclude large (~10-fold) increase in risk within 30-42 days of any dose

- Further monitoring to evaluate lower risk in shorter time periods after vaccination

Post-Licensure Intussusception Data

- Low risk of intussusception in many countries
  - US, Australia, Brazil, Mexico
  - ~1-6 excess cases per 100,000 vaccinated
  - With both vaccines

How does risk compare with benefits?



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)

*

2006-2013

Incredible years for new rotavirus vaccines!....

And great promise for the future!!

Many Opportunities Ahead -- Rotavirus Vaccines Implemented in Africa in 2012

GHANA

RWANDA

TANZANIA

MALAWI

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