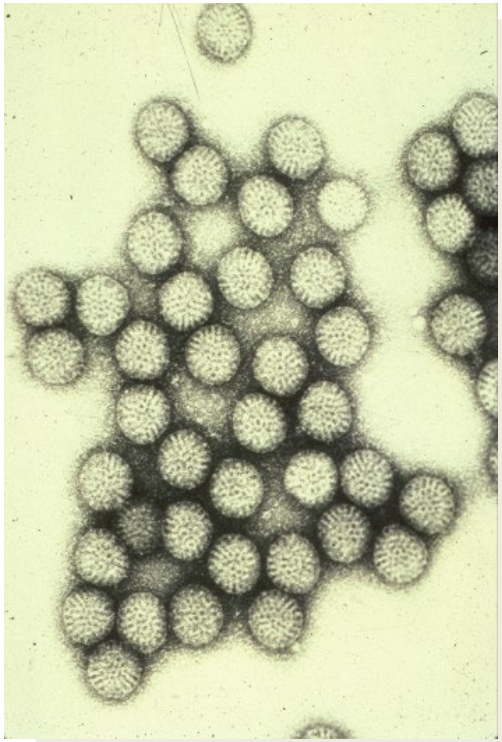
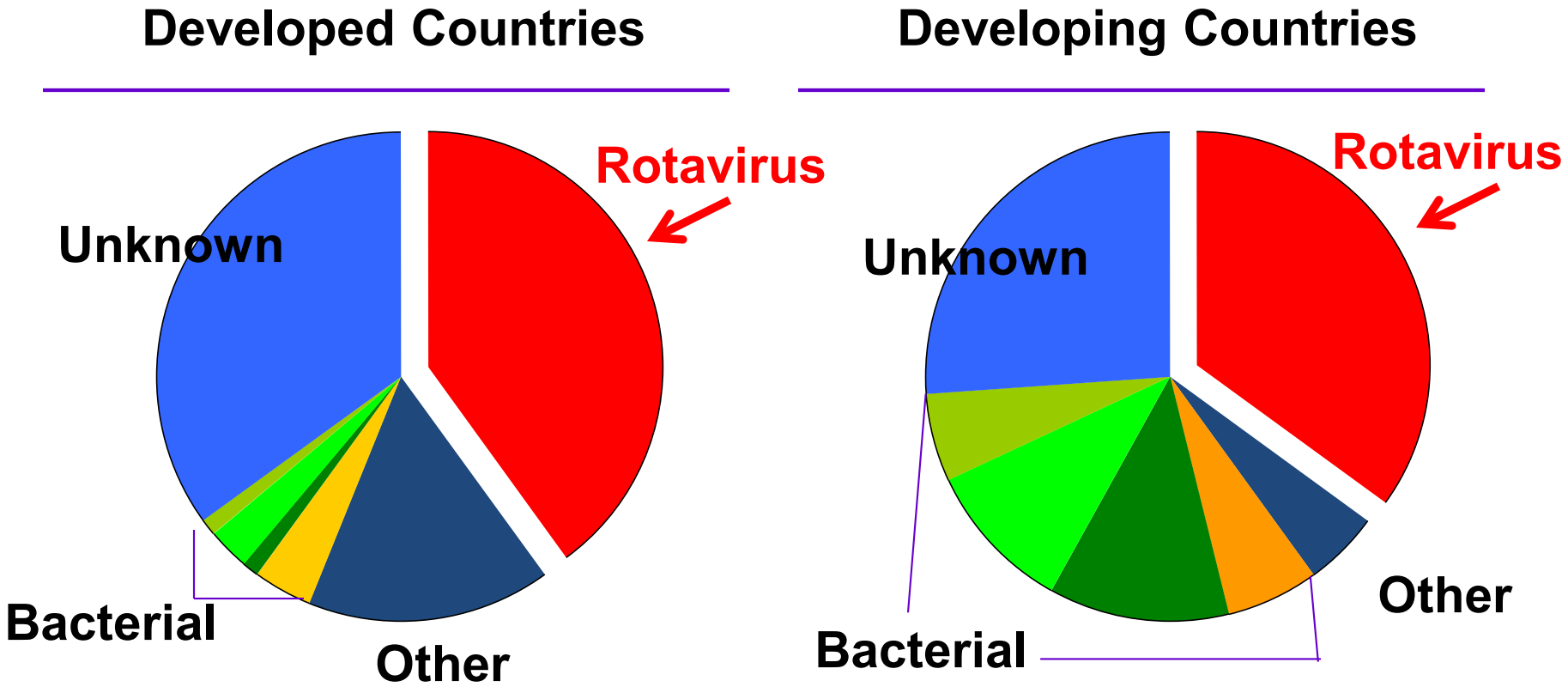
# Rotavirus & Norovirus Vaccines

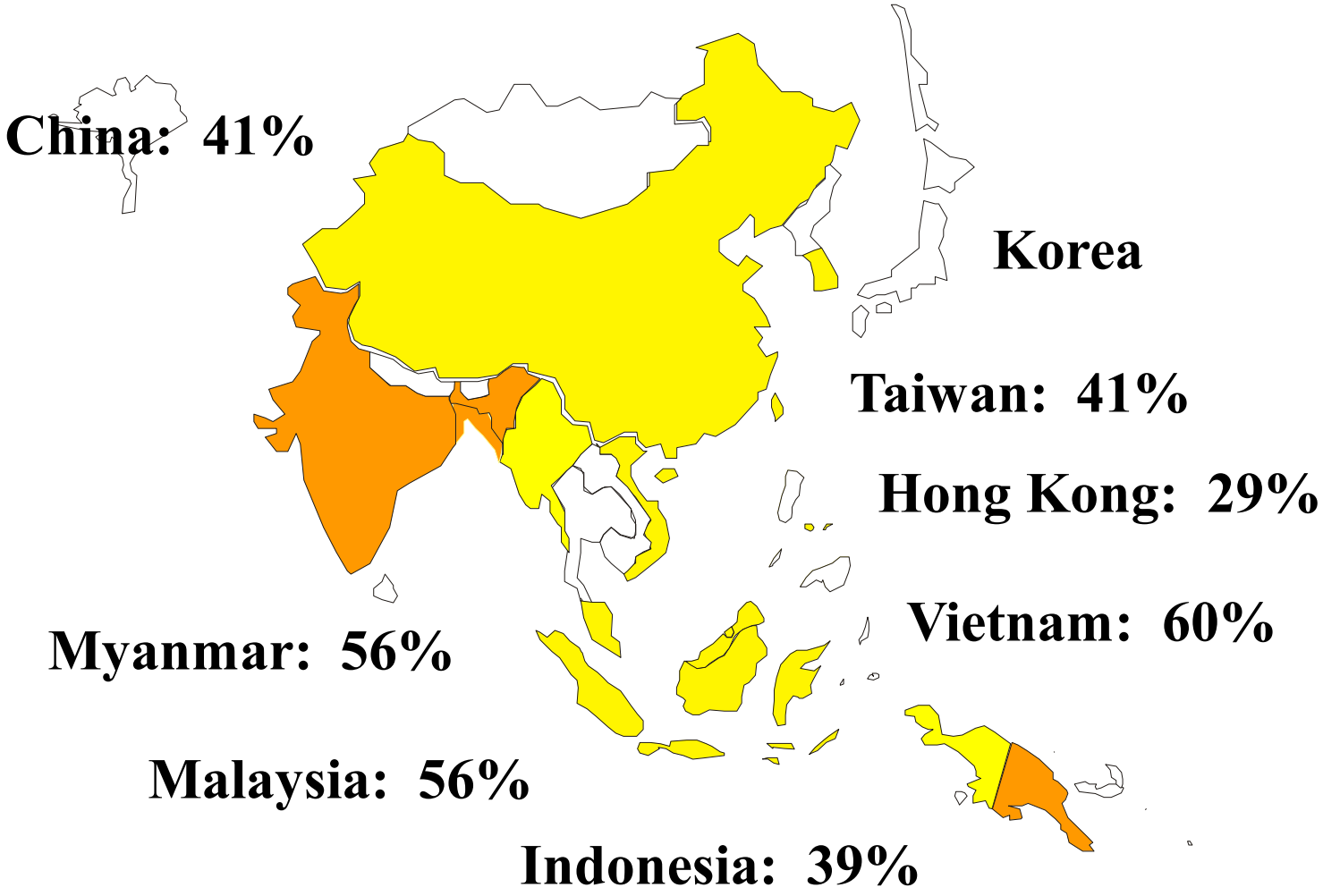


Umesh D. Parashar
Chief, Viral Gastroenteritis Branch
CDC, Atlanta, USA
uparashar@cdc.gov

# Rotavirus is the leading cause of diarrhea hospitalizations in children <5 years globally

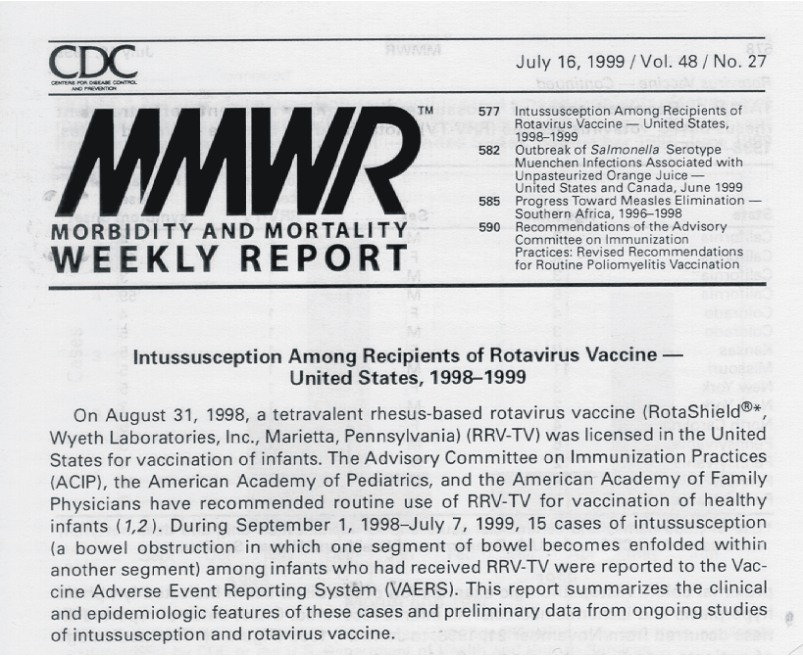


# Proportion of diarrhea hospitalizations due to rotavirus in the Asian Rotavirus Network



# First rotavirus vaccine licensed in 1998 in US

# A setback – Vaccine withdrawn within 1 year because it caused intussusception



CDC

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

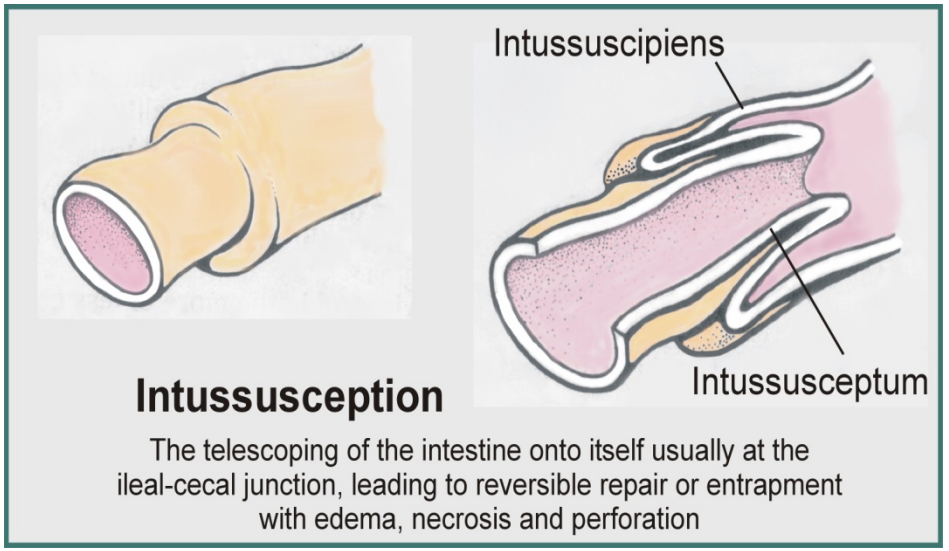
MMWR™

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 case per 10,000 vaccinated infants*

# Two new rotavirus vaccines licensed in 2006

| RotaTeq™ (Merck&Co., Inc.) | Rotarix™ (GlaxoSmithKline) |
|---|---|
| 3 oral doses beginning at 6 weeks   | 2 oral doses beginning at 6 weeks   |

- Large trials (~70,000 infants) in US, Europe, and South America
- ***No increased risk of intussusception!***

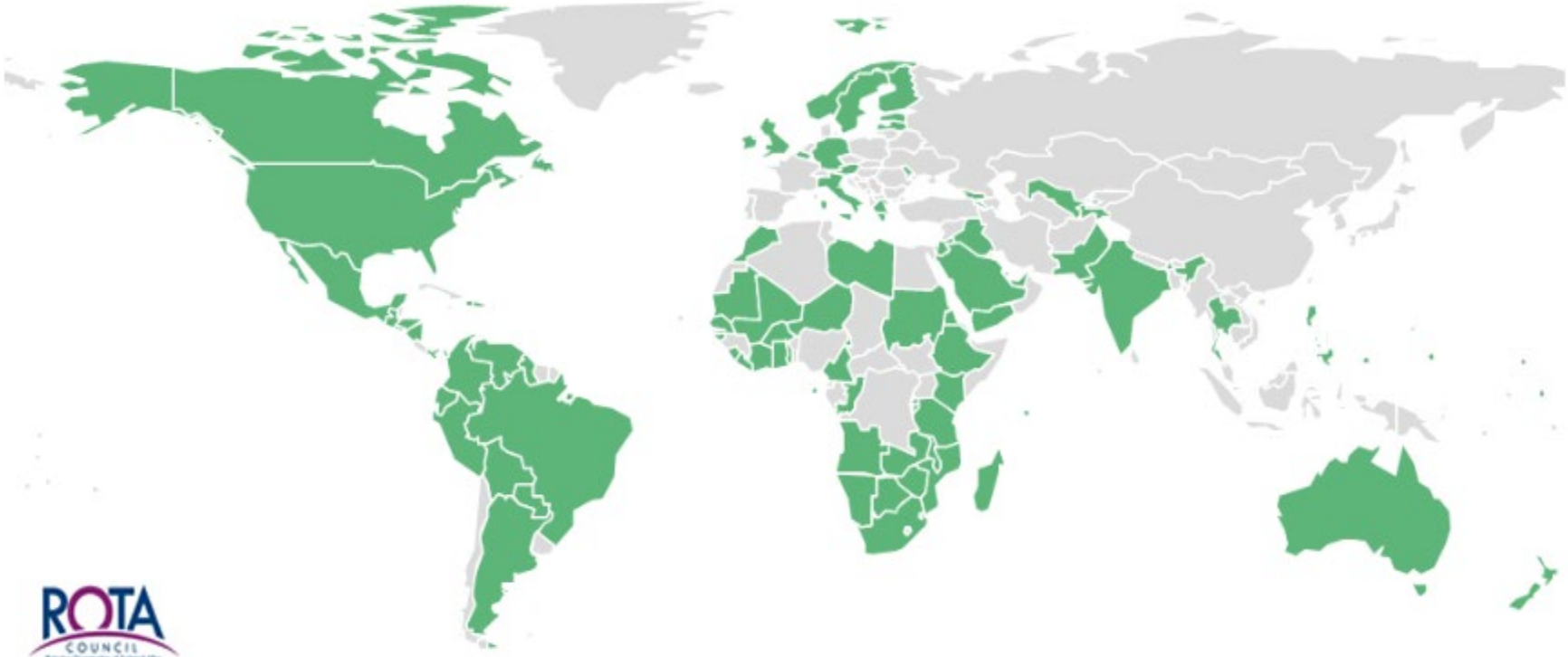
Vesikari et al and Ruiz-Palacios et al, NEJM 2006

# 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%) |
| Rotarix | Asia | 96% (85%-99%) |
| RotaTeq | Europe/US | 98% (88%-100%) |

Vesikari et al and Ruiz-Palacios et al, NEJM 2006
Vesikari et al, Lancet, 2007.

# 98 countries have implemented national rotavirus vaccination programs

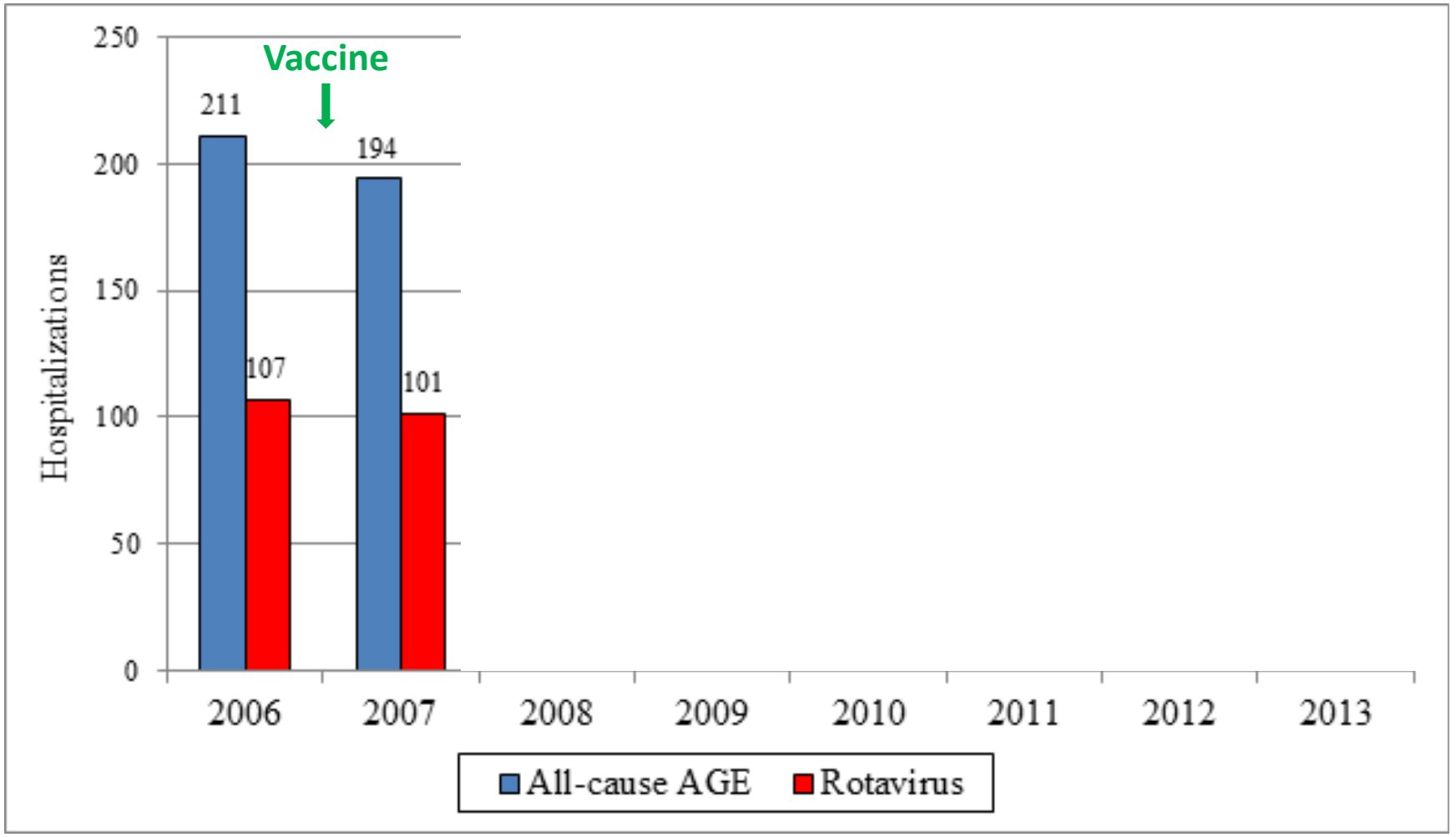


ROTA COUNCIL

VIEW-hub

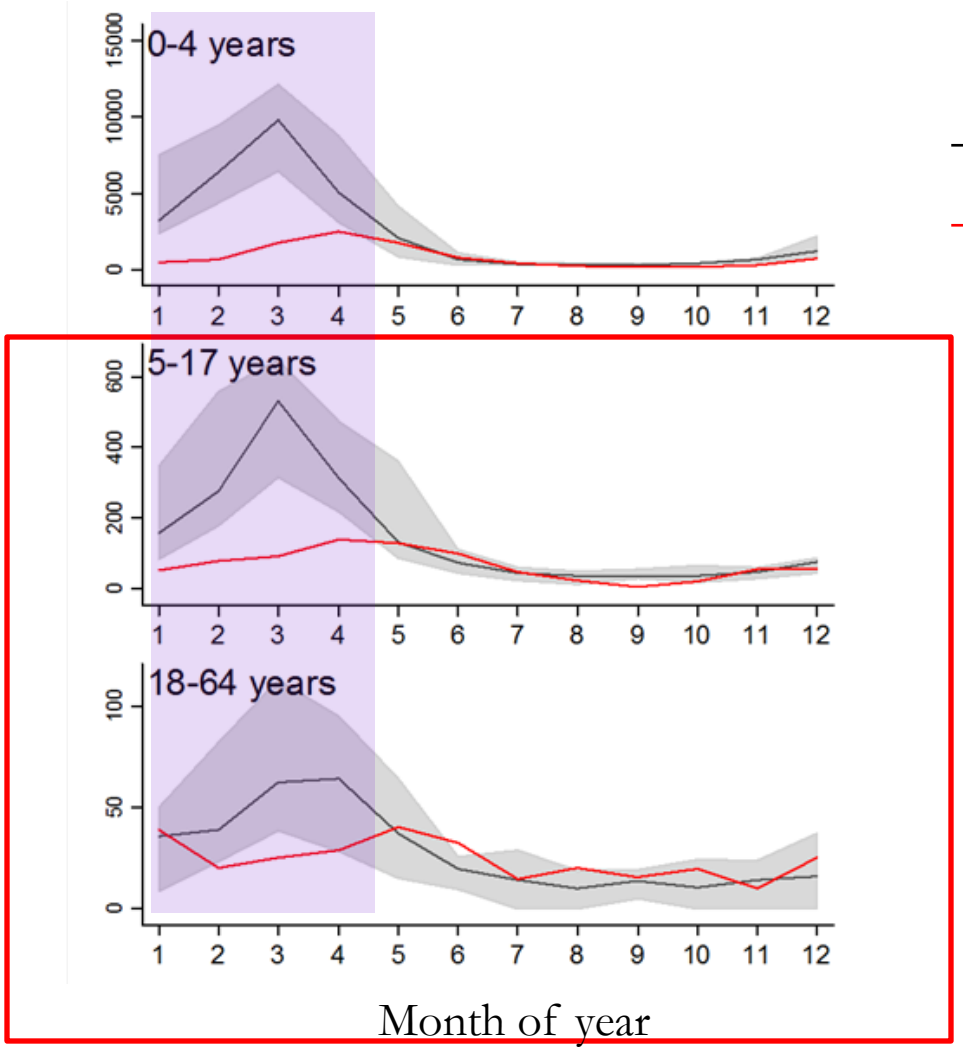
# How well will vaccines perform in routine use?

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




Payne DC et al, unpublished data

# Unexpectedly, reduction in AGE hospitalizations seen in older unvaccinated children and adults in the US



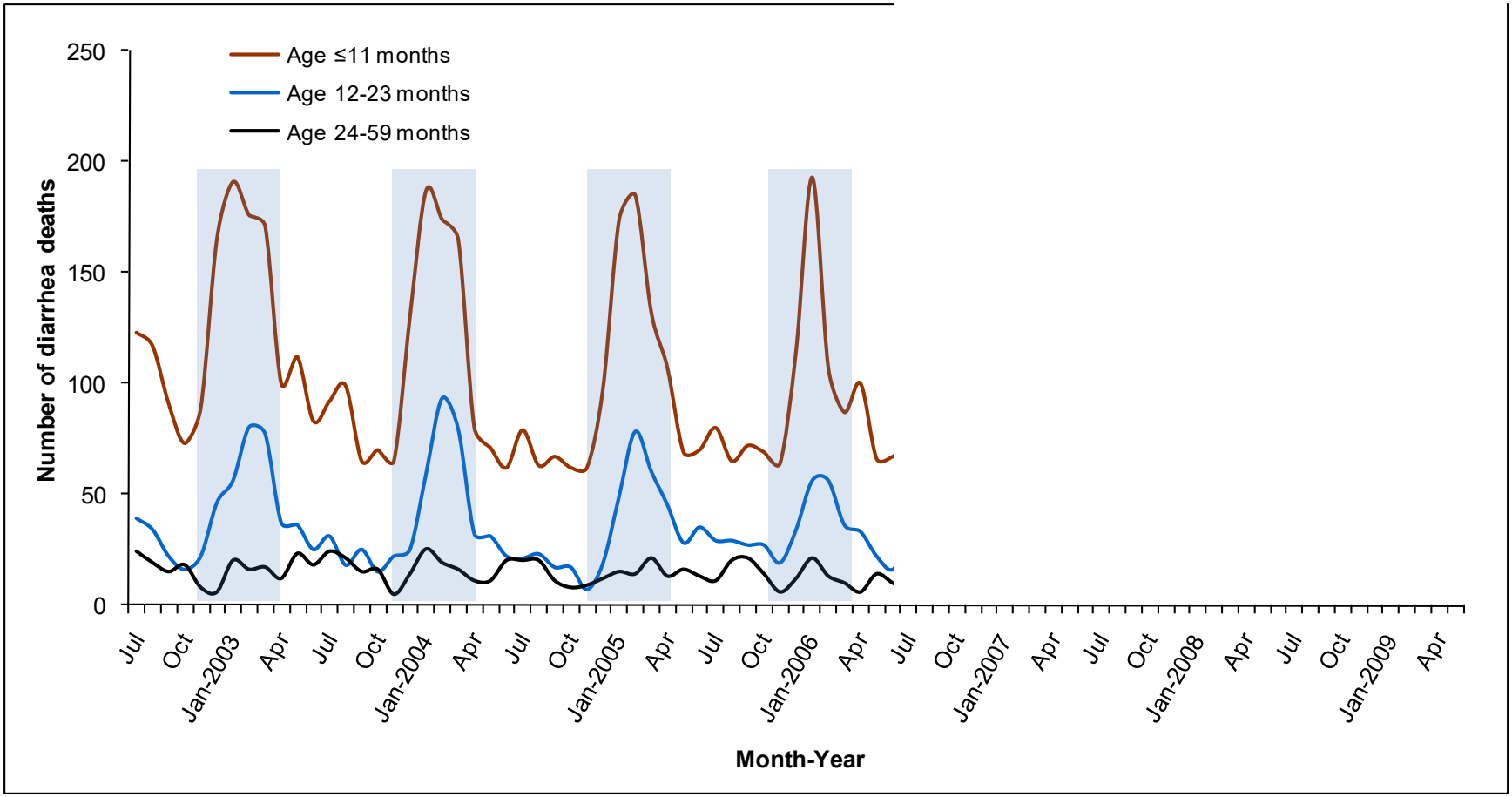

Lopman et al. JID 2011

Gastanaduy et al JAMA 2013

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

# Effect of Rotavirus Vaccination on Death from Childhood Diarrhea in Mexico




Richardson et al, NEJM 2010

# Reduced risk of childhood seizures associated with rotavirus vaccination

Vaccinated children had ~20% reduction in risk of seizures requiring hospitalization or ED care compared with unvaccinated children during the year following vaccination

## Protective Association Between Rotavirus Vaccination and Childhood Seizures in the Year Following Vaccination in US Children

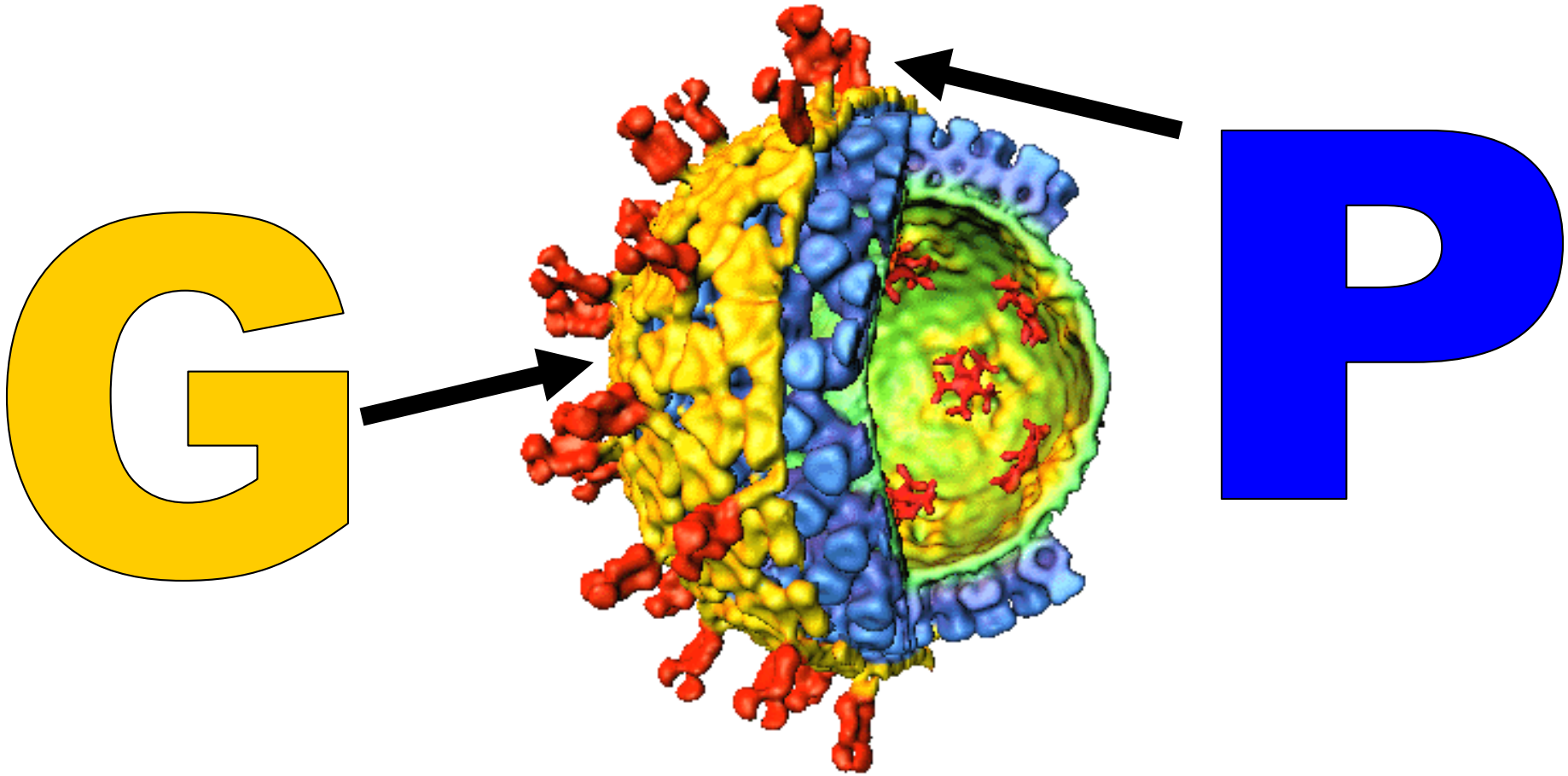
**Daniel C. Payne,[1] James Baggs,[2] Danielle M. Zerr,[3,4] Nicola P. Klein,[5] Katherine Yih,[6] Jason Glanz,[7] Aaron T. Curns,[1] Eric Weintraub,[8] and Umesh D. Parashar[1]**

[1]Epidemiology Branch, Division of Viral Diseases, National Center for Immunization and Respiratory Diseases, and [2]Prevention and Response Branch, Division of Healthcare Quality Promotion, National Center for Zoonotic and Emerging Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia; [3]Department of Pediatrics, University of Washington, Seattle; [4]Seattle Children's Research Institute, Washington; [5]Kaiser Permanente Vaccine Study Center, Kaiser Permanente, Oakland, California; [6]Department of Population Medicine, Harvard Medical School and Harvard Pilgrim Health Care Institute, Boston, Massachusetts; [7]Institute for Health Research, Kaiser Permanente Colorado, Denver; and [8]Immunization Safety Office, Division of Healthcare Quality Promotion, National Center for Zoonotic and Emerging Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia


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

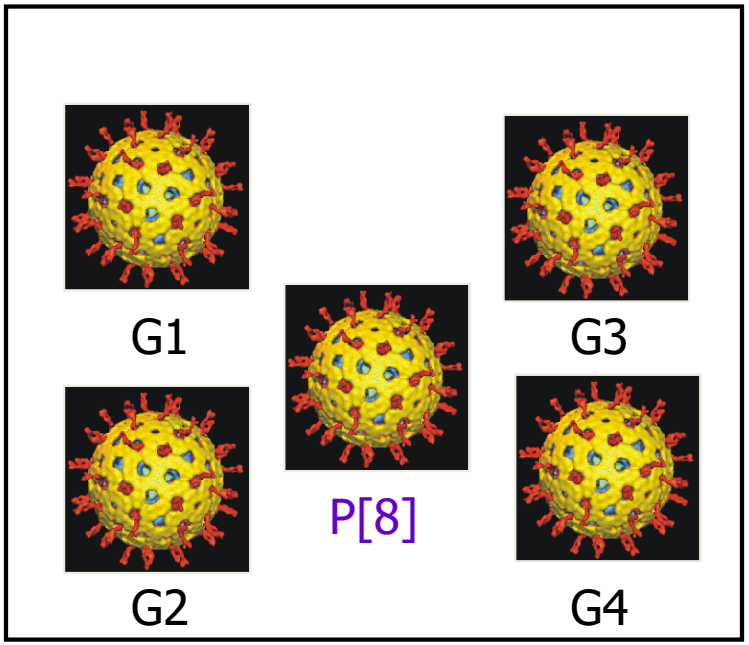
# How well will vaccines protect against range of rotavirus strains?

# Two outer capsid proteins (G and P) determine rotavirus strain type



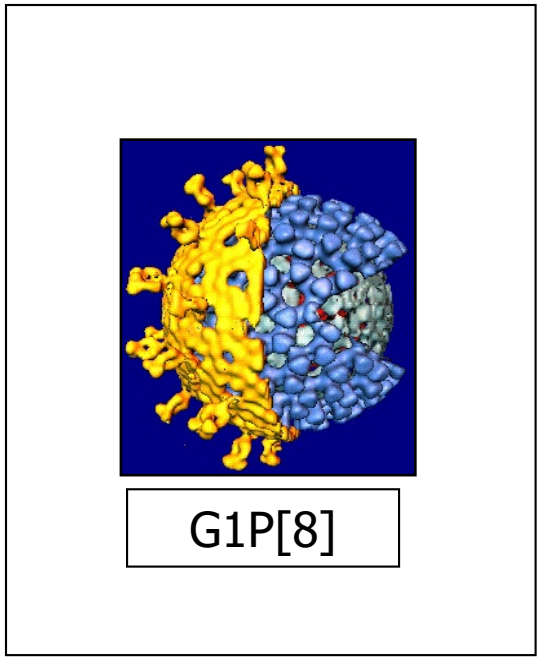
# RotaTeq is pentavalent & Rotarix is monovalent

## RotaTeq



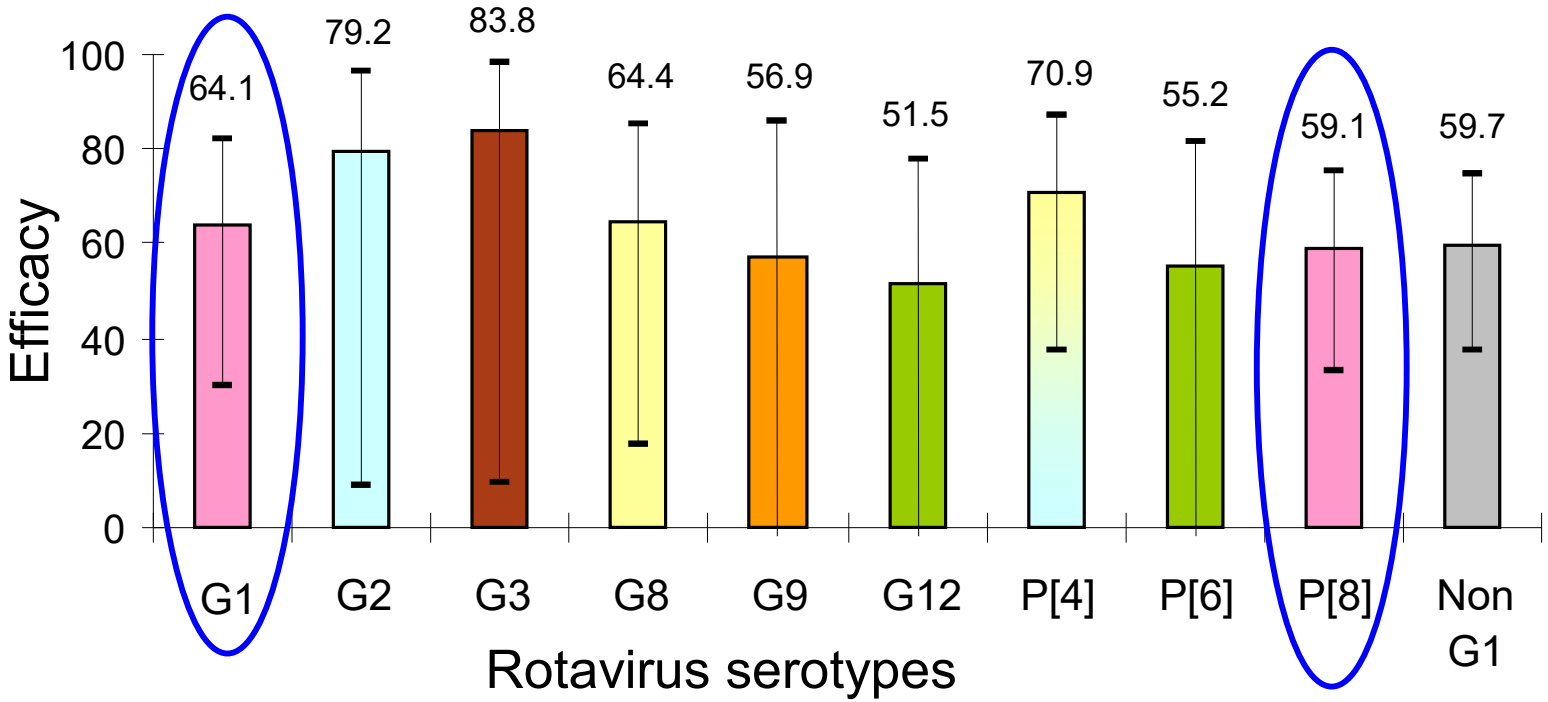

Five bovine-human rotavirus strains

## Rotarix




Single human rotavirus strain

# Monovalent rotarix (G1P8) efficacy similar against vaccine & non-vaccine strains in Africa




Madhi et al. NEJM 2010

# Increase in G2P4 after implementation of monovalent Rotarix (G1P8) in Brazil

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

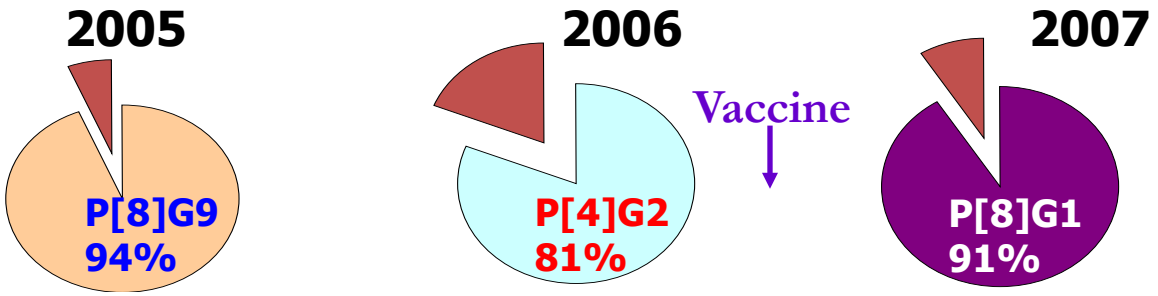
**Gurgel et al, EID, 13(10), 2007*

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?

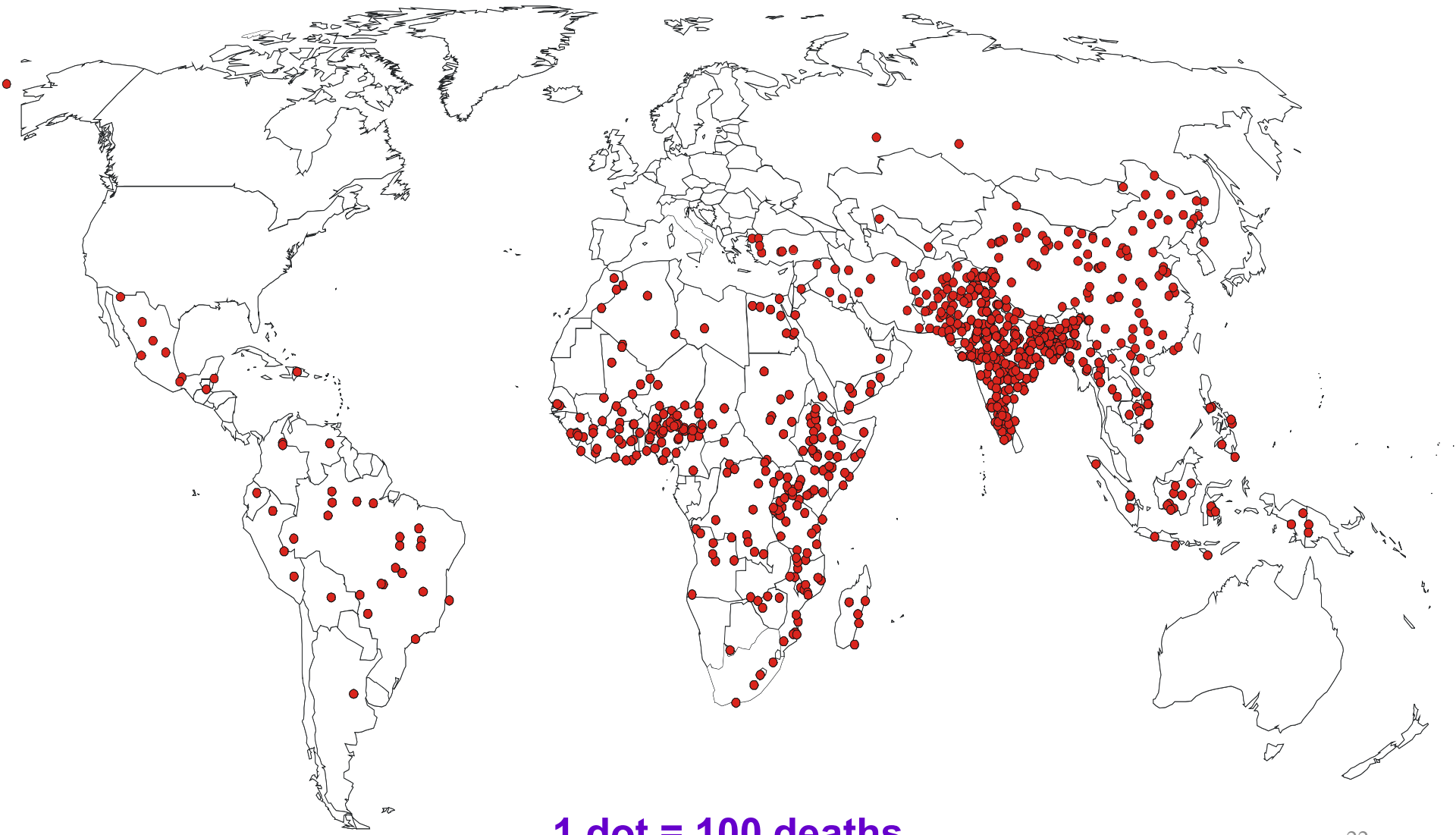



**El Salvador**
**Rotarix, 2006**
**(opposite of Brazil)**

Patel et al. EID 2009

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

# The vast majority of the ~200,000 annual deaths from rotavirus occur in developing countries



1 dot = 100 deaths

# Moderate efficacy seen in trials in low income African and Asian countries

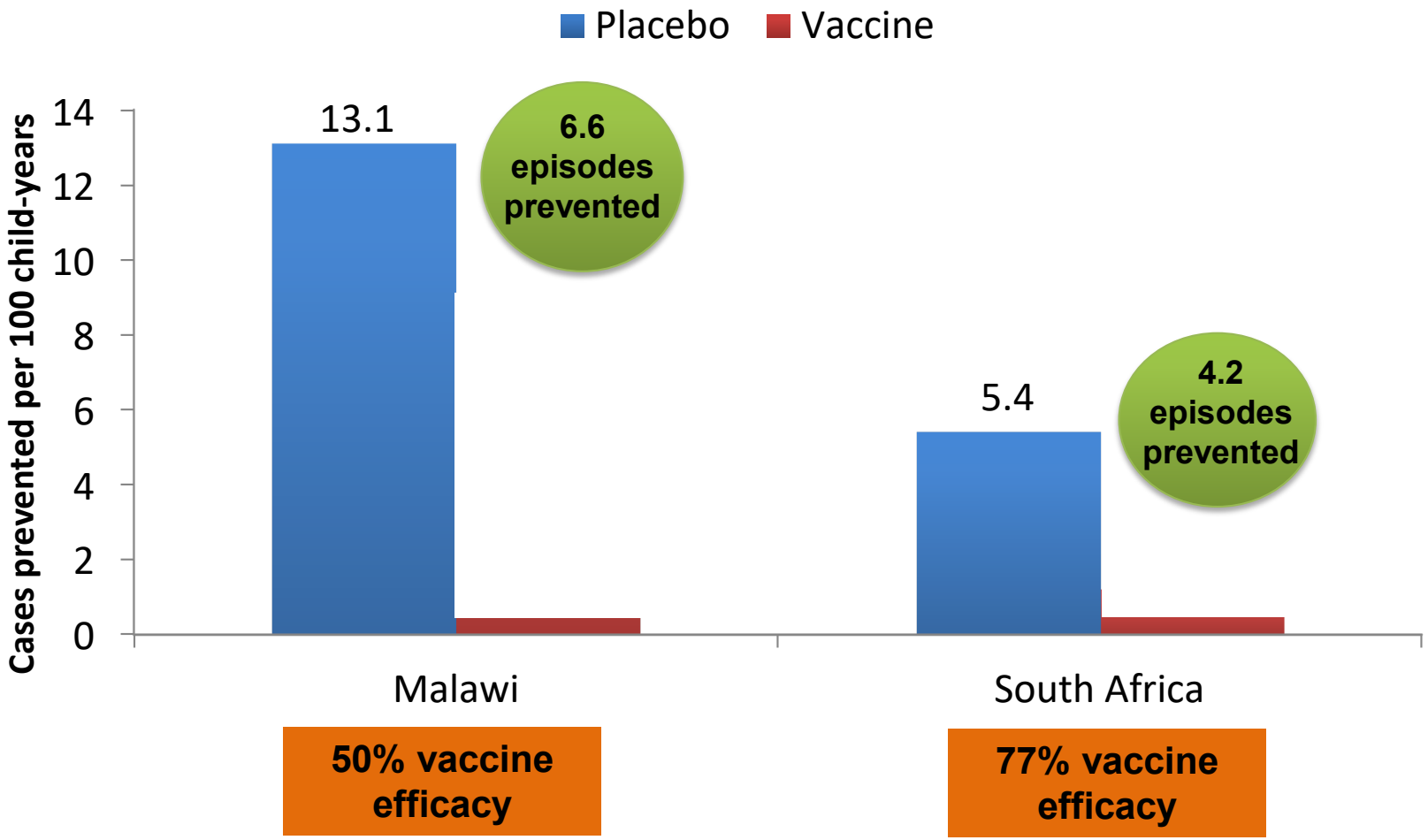
| Vaccine | Region | Efficacy (95%CI) |
|---|---|---|
| RotaTeq | Africa | 64% (40%-79%) |
| RotaTeq | Asia | 51% (13%-73%) |
| Rotarix | Africa | 62% (44%-73%) |

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

# What does 50% efficacy mean?

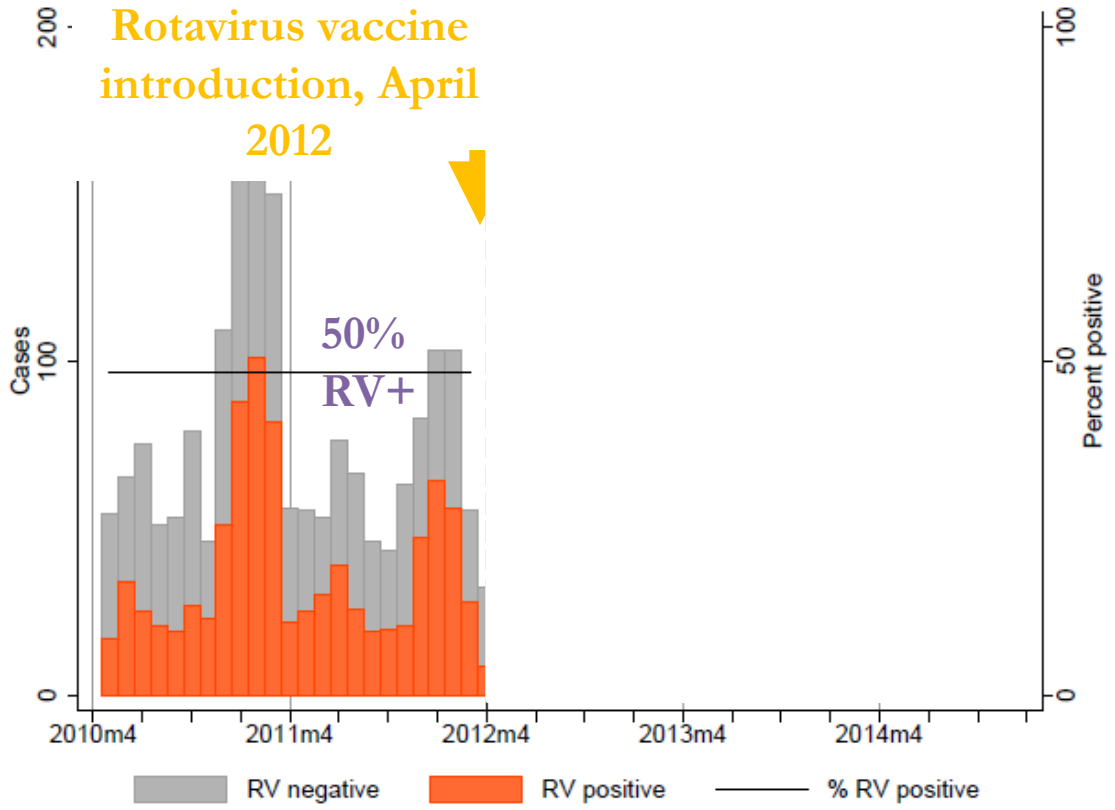
***Would you rather have 99% of my salary or 1% of Bill Gates'?***

# Despite lower efficacy, rotavirus vaccines prevent more disease in high burden settings




Madhi, NEJM 2010

# Decline in rotavirus hospitalizations after vaccine implementation in Ghana




Armah et al CID 2016

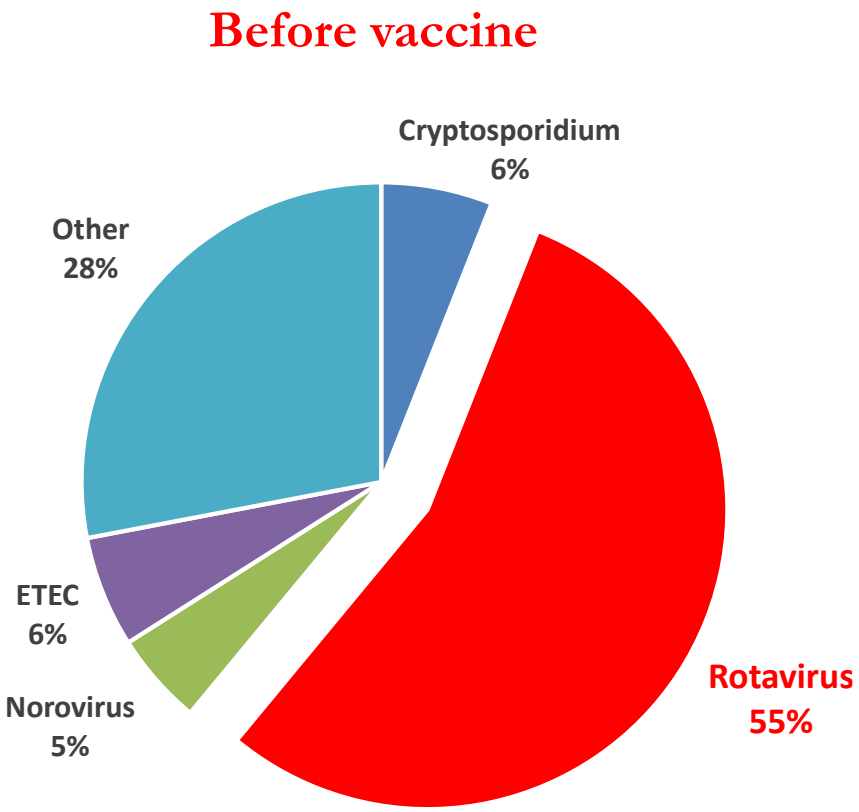
Lancet Global Health

# Impact of monovalent rotavirus vaccine on diarrhoea-associated post-neonatal infant mortality in rural communities in Malawi: a population-based birth cohort study

- **Diarrhea-associated mortality declined by 31% (95% CI, 1%-52%)**
- **Vaccine effectiveness against diarrhea mortality 34% (95% CI, -28%-66%)**

Bar-Zeev et al, Lancet Global Health 2018

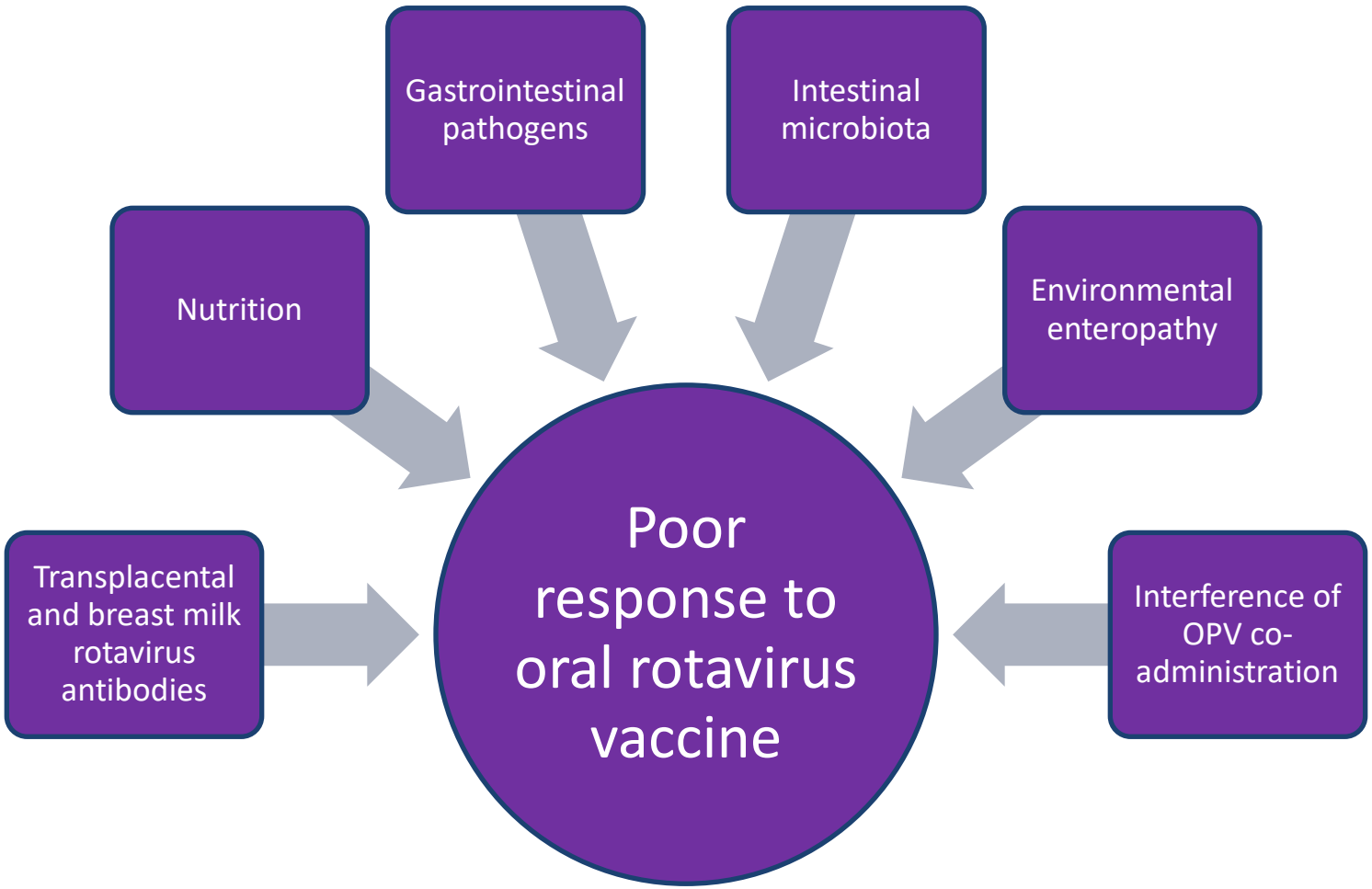
# Rotavirus remains the leading cause of severe diarrhea in developing countries after rotavirus vaccine introduction



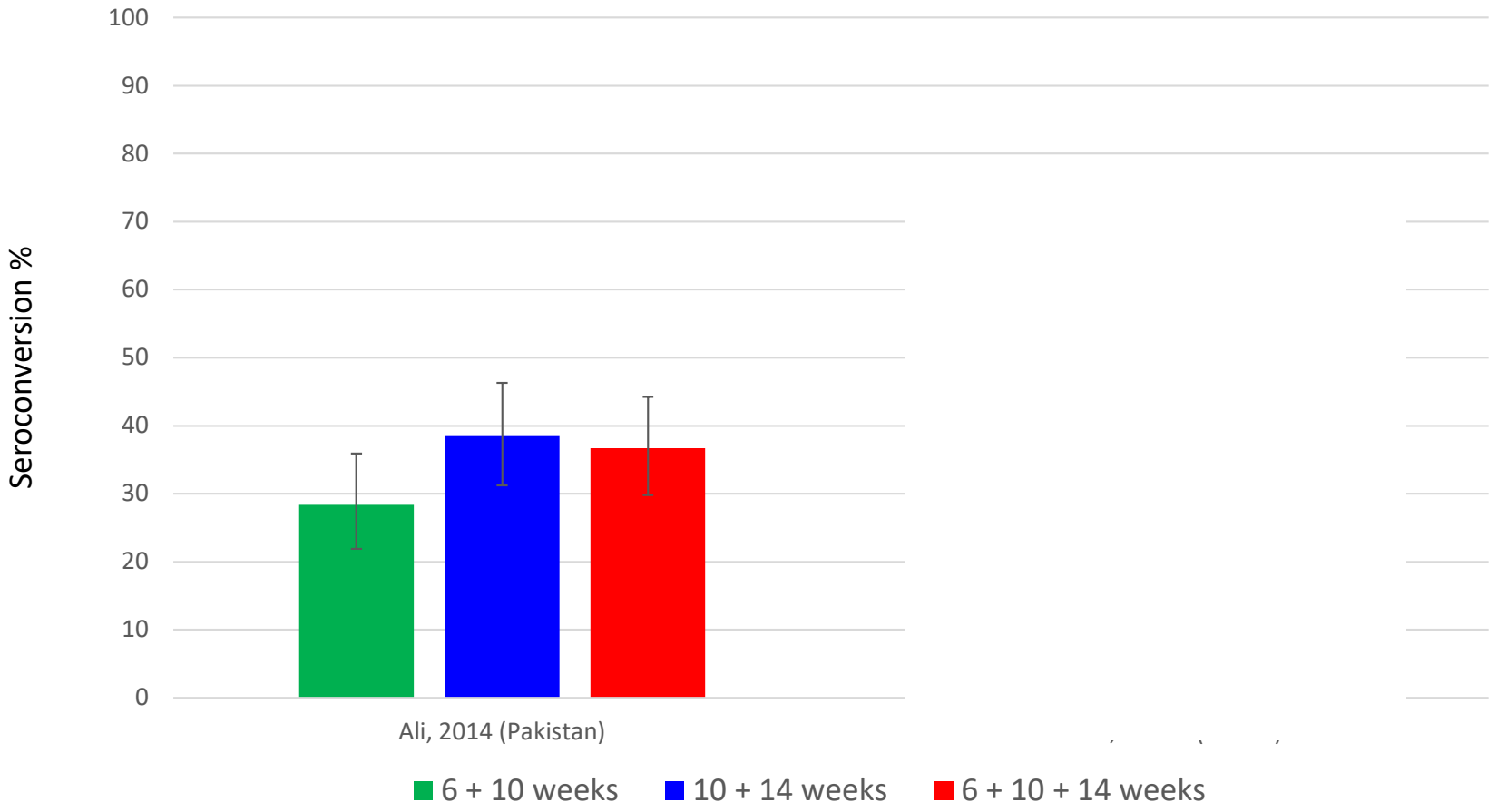

Plats Mills et al JID 2017

# How can we improve rotavirus vaccine performance in developing countries?

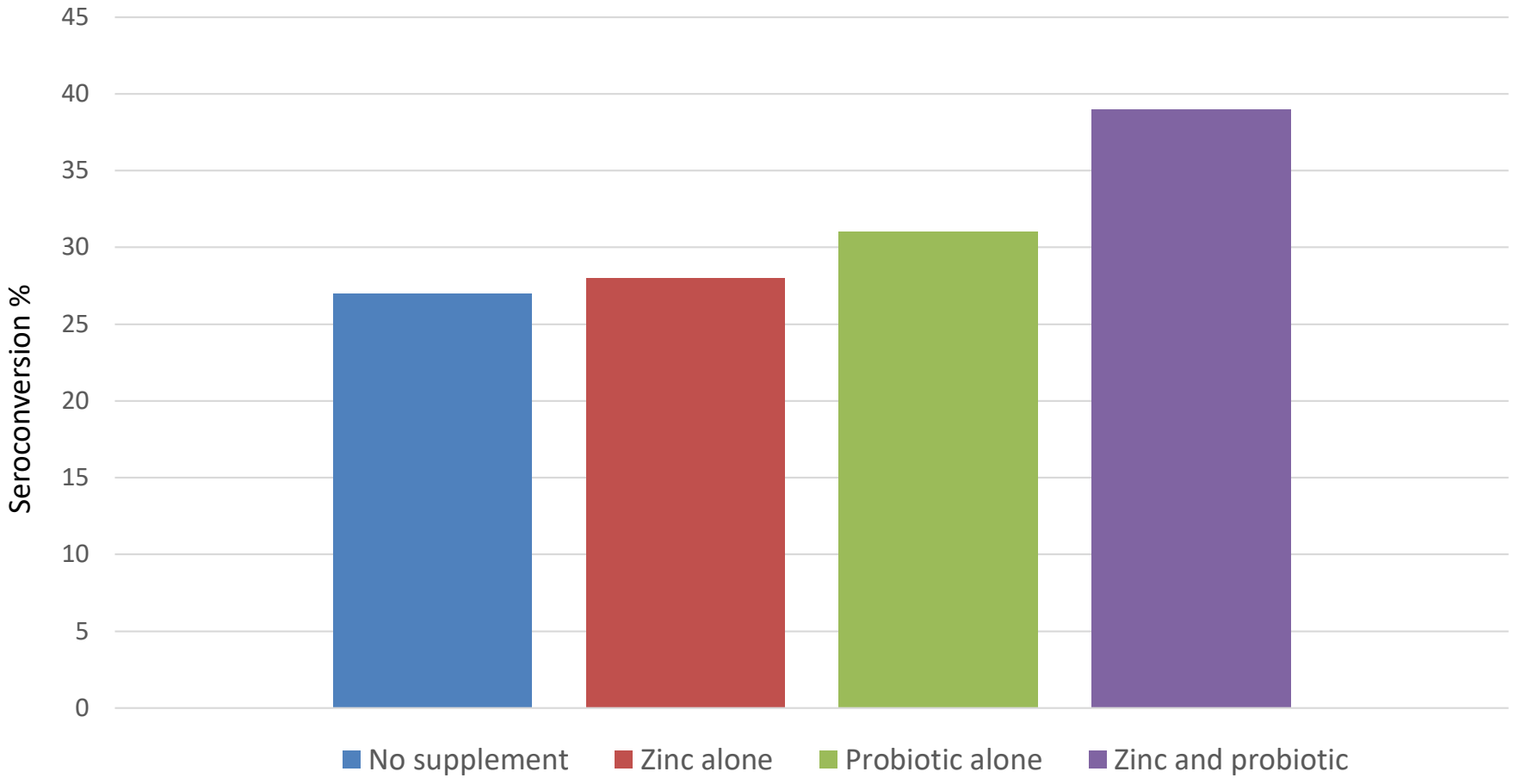
# Multiple factors affect rotavirus vaccine efficacy



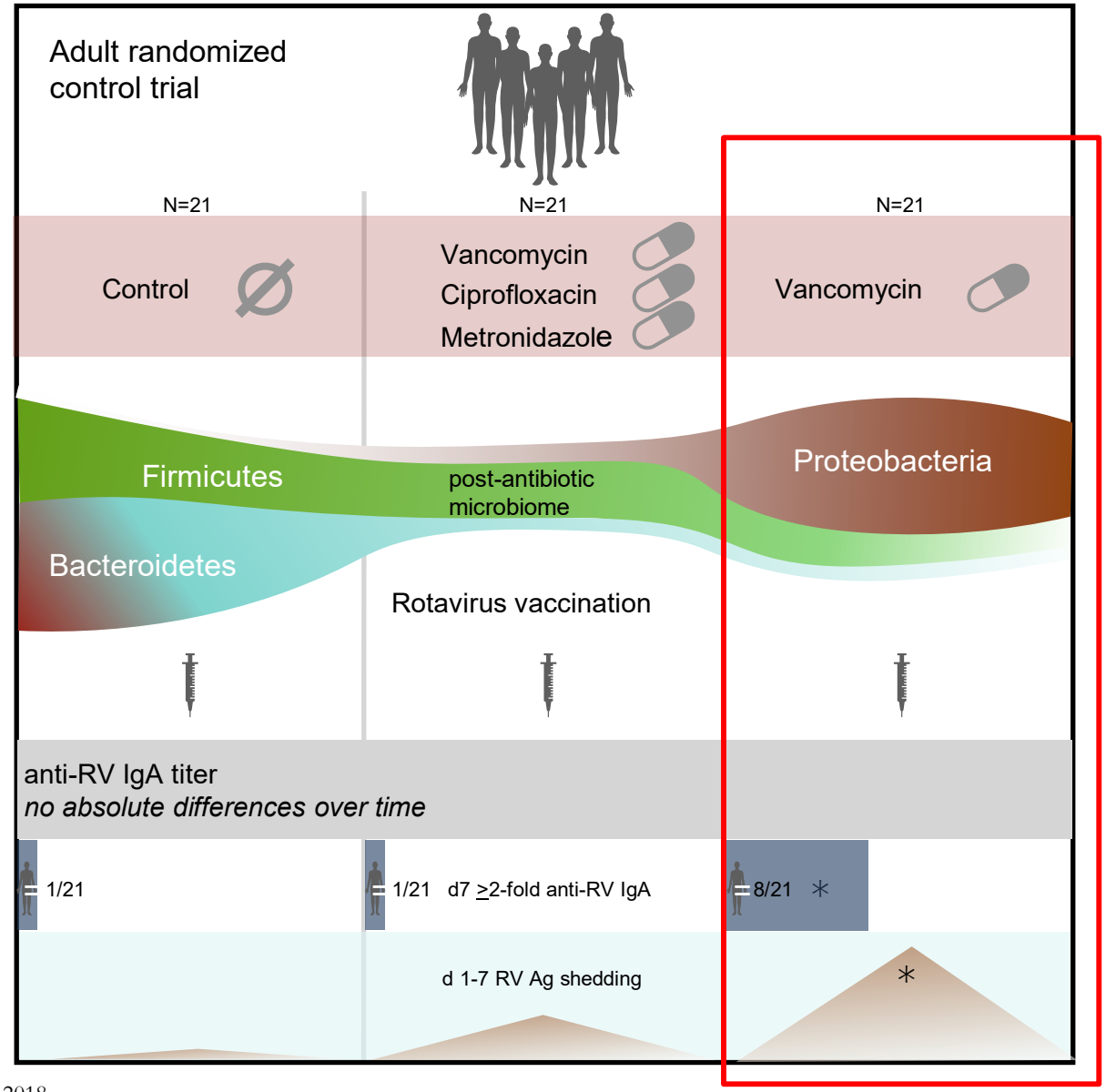
# Delaying 2-dose schedule or adding 3rd dose slightly improved Rotarix vaccine response



# Supplementing with both Zn and probiotics slightly improved vaccine response



# Antibiotic microbiome modulation alters RV immunogenicity




Harris et al, Cell Host Microbe, 2018

# Like polio – Injectable rotavirus vaccine?

## Safety and immunogenicity of a parenteral P2-VP8-P[8] subunit rotavirus vaccine in toddlers and infants in South Africa: a randomised, double-blind, placebo-controlled trial

Michelle J Groome, Anthonet Koen, Alan Fix, Nicola Page, Lisa Jose, Shabir A Madhi, Monica McNeal, Len Dally, Iksung Cho, Maureen Power, Jorge Flores, Stanley Cryz

Vaccine 36 (2018) 2233–2236

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Short communication

## The future control of rotavirus disease: Can live oral vaccines alone solve the rotavirus problem? ☆

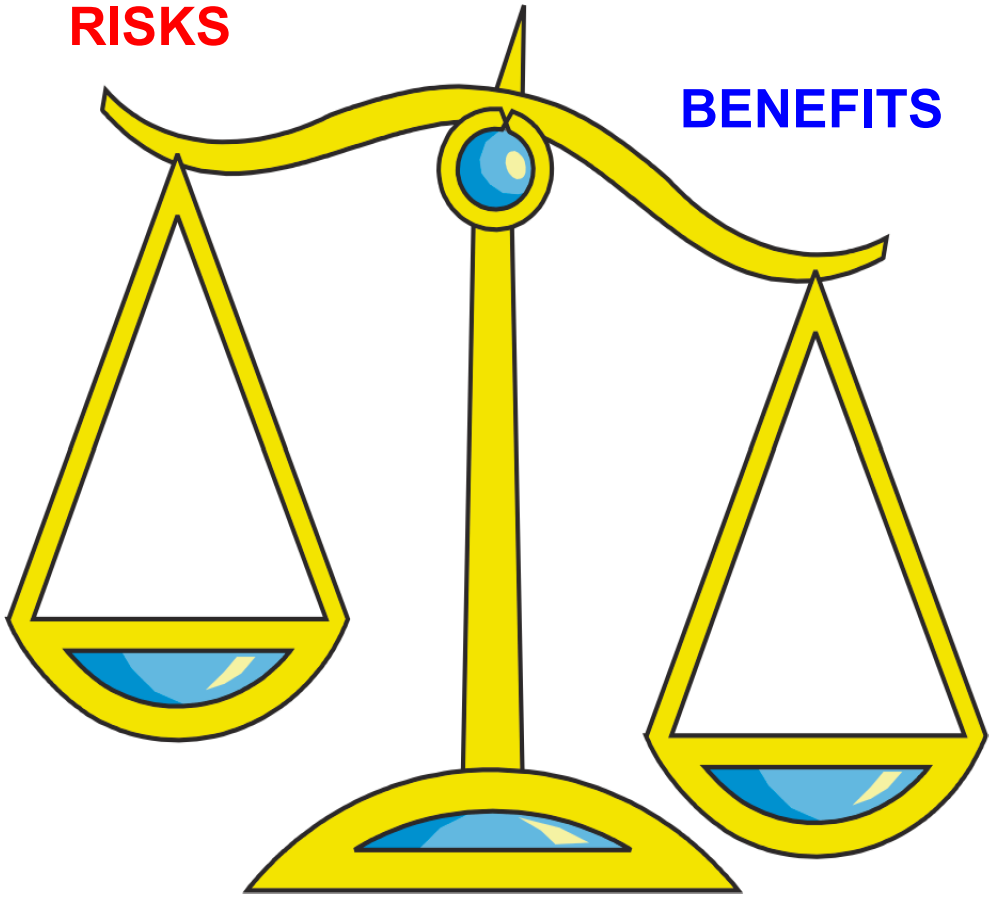
Roger I. Glass [a,b,*], Baoming Jiang [b], Umesh Parashar [b]

[a] Fogarty International Center, National Institutes of Health, Bethesda, MD, USA
[b] Viral Gastroenteritis Branch (proposed), Division of Viral Diseases, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, Atlanta, GA, USA

# Will new rotavirus vaccines cause intussusception?

# Low risk of intussusception in several high & middle income countries (Mexico, US, Australia, UK)

- ~1-6 cases per 100,000 vaccinated
- Similar risk with both vaccines


RISKS
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) |

*

# No intussusception risk in large study in 7 low income African countries!

The NEW ENGLAND JOURNAL of MEDICINE

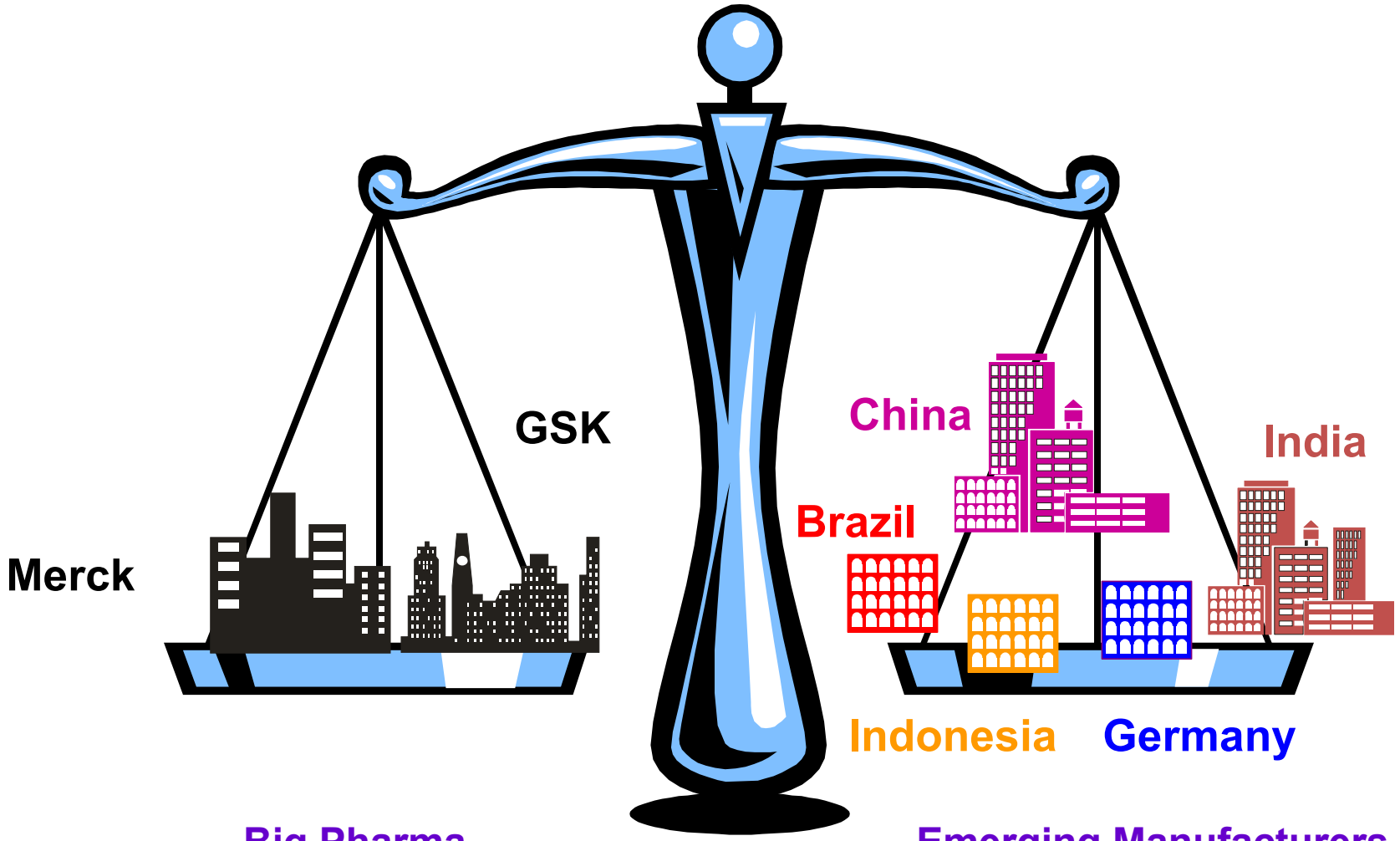
ORIGINAL ARTICLE

## Evaluation of Intussusception after Monovalent Rotavirus Vaccination in Africa

J.E. Tate, J.M. Mwenda, G. Armah, B. Jani, R. Omore, A. Ademe, H. Mujuru, E. Mpabalwani, B. Ngwira, M.M. Cortese, R. Mihigo, H. Glover-Addy, M. Mbaga, F. Osawa, A. Tadesse, B. Mbuwayesango, J. Simwaka, N. Cunliffe, B.A. Lopman, G. Weldegebriel, D. Ansong, D. Msuya, B. Ogwel, T. Karengera, P. Manangazira, B. Bvulani, C. Yen, F.R. Zawaira, C.T. Narh, L. Mboma, P. Saula, F. Teshager, H. Getachew, R.M. Moeti, C. Eweronu-Laryea, and U.D. Parashar, for the African Intussusception Surveillance Network*

NEJM. April 2018

# Who Will Supply Rotavirus Vaccine to the World?



# Two Indian-made rotavirus vaccines pre-qualified for global use in 2018

**Prime Minister Modi**

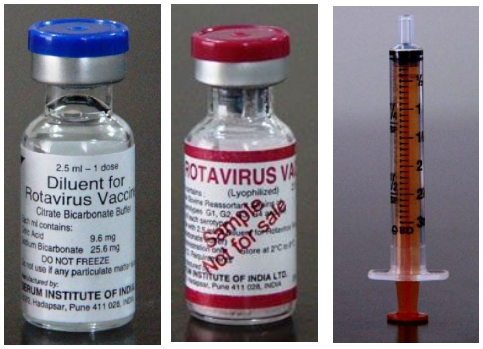
***"Government of India will provide a rotavirus vaccine to all Indian children"***

# Rotavac and RotaSIIL were pre-qualified by WHO in 2018

Bharat Biotech
Lead Innovation


ROTAVAC™, Bharat Biotech

(derived from a single Indian neonatal strain of human rotavirus) G9P11




POONAWALLA GROUP

RotaSIIL™, Serum Institute

(Reassorted bovine-human rotavirus) Genetically engineered vaccine consisting of 5 different strains to protect against the 5 most common human rotaviruses G1,2,3,4 & 9

# Efficacy of various rotavirus vaccines similar in developing countries

| Vaccine | Efficacy (95% CI) | |
|---|---|---|
| | Asia | Africa |
| RotaTeq | 51 (13-73) | 64 (40-79) |
| Rotarix | -- | 62 (44-73) |
| Rotavac | 56 (37-70) | -- |
| Rotasiil | 37 (11-54) | 67 (50-78) |

# Global implementation of rotavirus vaccines

ROTA COUNCIL

VIEW-hub

# Norovirus Vaccines

# Norovirus is the leading cause of AGE outbreaks

SECTIONS HOME SEARCH International New York Times TRY TIMES

U.S. Added 292,000 Jobs in December, Capping Year of Steady Growth

A New Economic Era for China Goes Off the Rails

VW Refuses to Give U.S. States Documents in Emissions Inquiries

BUSINESS DAY

## *Chipotle Is Subpoenaed in Criminal Inquiry Over Norovirus Outbreak*

By RACHEL ABRAMS JAN. 6, 2016


## 57 sick; norovirus strikes Scottish swimmers

POSTED: JULY 22ND, 2012 - 12:52AM BY DOUG POWELL

Swimming is dangerous is Scotland too - and not always because of monsters.

*Over 50 people took ill after taking part in an open water swimming event at Strathclyde Loch.*

*They suffered sickness, stomach cramps and diarrhoea following the race which attracted 70 entrants from across Scotland.*

*None of those affected are thought to have been hospitalised, however, the loch has now been closed to water sports and boating.*

*Some of those who fell sick tested positive for norovirus. Experts believe heavy rain prior to the event may have contaminated the water.*

*A Motherwell Masters Amateur Swimming Club source said six members of their club took part and were "very ill." They had to seek medical advice following the event and some were off work for a week, she added.*

*The event, the Western Districts Open Water Swimming Championships, took place on June 23.*

## Hundreds laid low after eating Valentine's Day oysters

By DAILY MAIL REPORTER
**UPDATED:** 05:23 EST, 11 March 2010

Share View comments

Hundreds of diners have fallen ill after eating oysters - many around Valentine's Day - at restaurants across the country.

The oysters from British and Irish suppliers are believed to have been contaminated with the winter vomiting bug, norovirus.

A similar problem led to the closure of Heston Blumenthal's awardwinning Fat Duck restaurant in Bray, Berkshire, last March.


**Love sick: Hundreds of couples who ate oysters around Valentine's Day contracted a winter vomiting bug (file photo)**

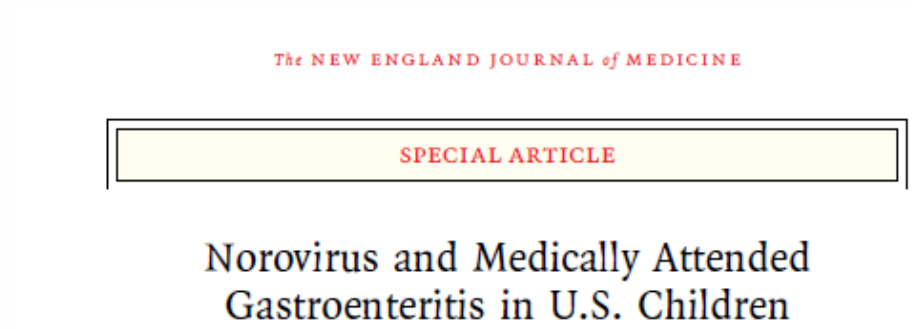
SmartBrief

SmartBrief > Advertising & Marketing > Animal Health SmartBrief > Related Stories

## Butterflies in your stomach this Valentine's? Or is that the norovirus?

Just imagine — it's Valentine's Day and you and your special someone are about to enjoy a nice dinner together. There's a little music playing, soft candlelight, and you even have butterflies in your stomach ... or at least that's what you think they are, until you start feeling nauseated. ...

# Norovirus is the leading cause of severe AGE in US children after rotavirus vaccine implementation



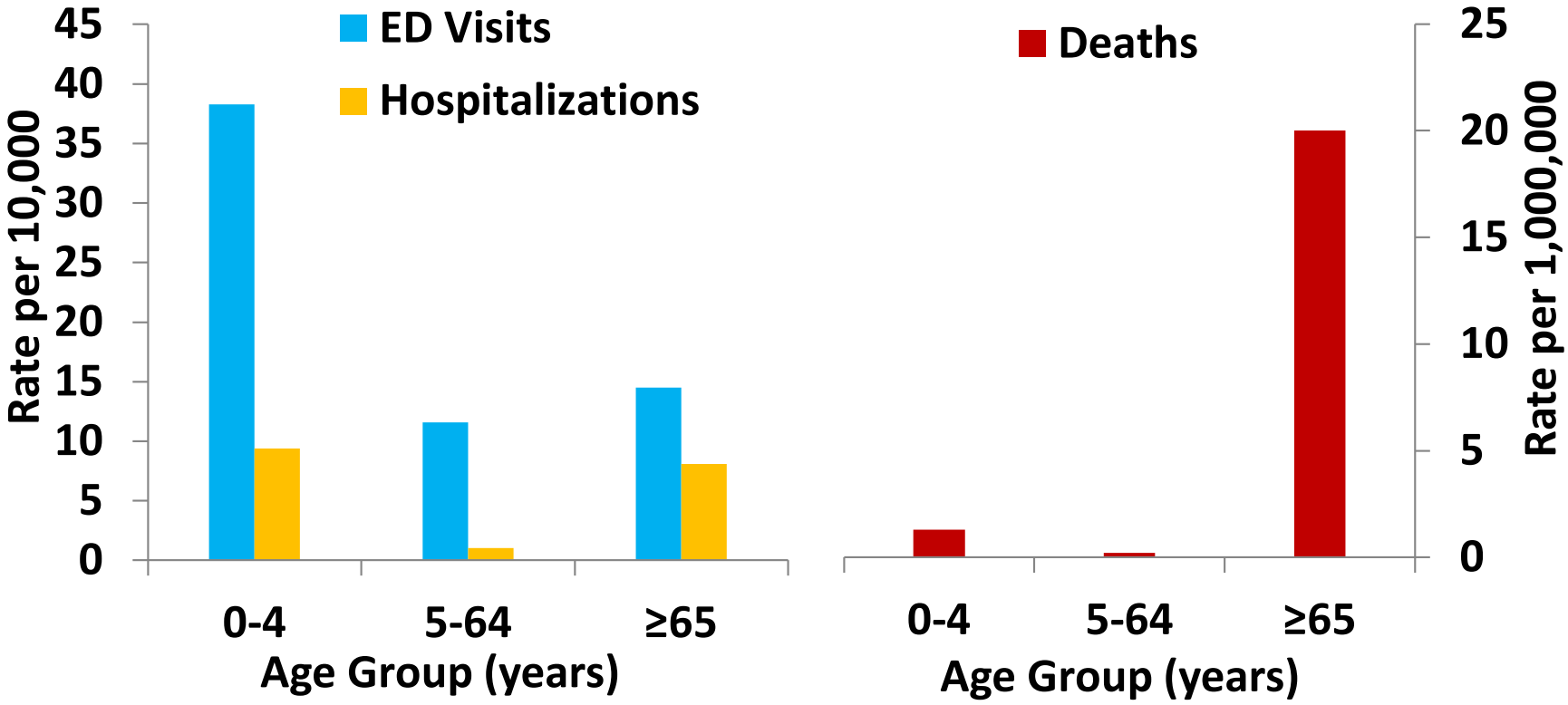
The NEW ENGLAND JOURNAL of MEDICINE

SPECIAL ARTICLE

Norovirus and Medically Attended Gastroenteritis in U.S. Children

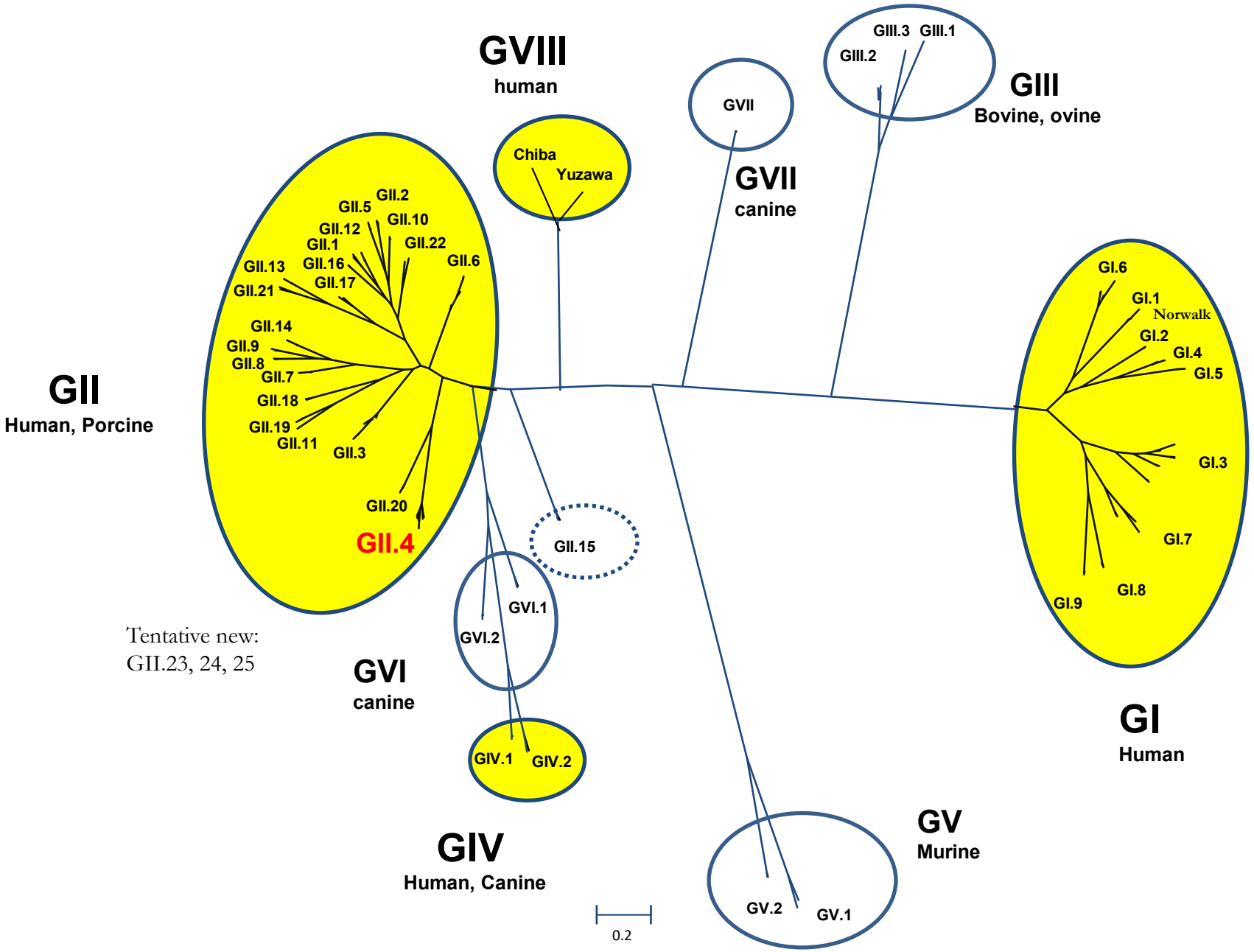
- 21% of severe AGE episodes caused by norovirus
- ~1 million annual pediatric medical care visits
  - $273 million in health care costs

# Norovirus causes severe disease in both young children & the elderly




Hall 2013 EID

# Noroviruses are genetically diverse




Tentative new:
GII.23, 24, 25

# Norovirus Vaccine Candidates in Human Trials

| | **Bivalent VLP (Takeda pharma)** | **Adenoviral vector (Vaxart)** |
|---|---|---|
| **Norovirus antigen** | GI.1 and GII.4 consensus VLP | GI.1 VP1 |
| **Route of admin** | Intramuscular, previously intranasal | Oral (pill) |
| **Status** | Phase 2b | Phase 1 |

# Intra-nasal monovalent GI.1 VLP vaccine efficacy (Takeda)

| Endpoint | Vaccine (N=43) | Placebo (N=41) | % Reduction (95% CI) |
|---|---|---|---|
| Norovirus infection | 60.5% | 82.1% | 26% (1%, 45%) |
| Norovirus AGE | 36.8% | 69.2% | 47% (15%, 67%) |

Atmar 2011 NEJM

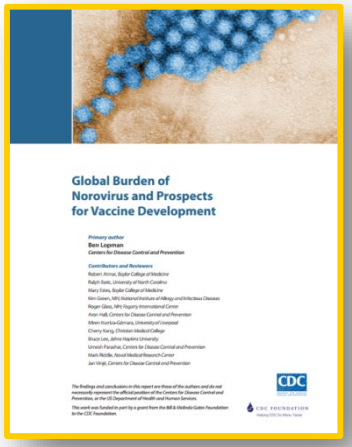
# Intra-muscular bivalent GI.1, GII.4 vaccine efficacy (Takeda)

| Norovirus AGE Severity | Vaccine (N=50) | Placebo (N=48) | % Reduction (95% CI) |
|---|---|---|---|
| Any | 20.0% | 37.5% | 47% (-4%, 73%) |
| Mod-severe | 6.0% | 18.8% | 68% (-11%, 91%) |
| Severe | 0% | 8.3% | 100% |

Bernstein 2015 JID

# Challenges for a norovirus vaccine

1. Whom to target – Children? Elderly?
2. Protection against multiple genotypes?
3. Need to be updated to keep up with viral evolution?
4. Need for different vaccine formulations for different age groups?




http://www.cdc.gov/norovirus/downloads/global-burden-report.pdf

# Major breakthrough in 2016

INFECTIOUS DISEASE

## Replication of human noroviruses in stem cell–derived human enteroids

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The major barrier to research and development of effective interventions for human noroviruses (HuNoVs) has been the lack of a robust and reproducible in vitro cultivation system. HuNoVs are the leading cause of gastroenteritis worldwide. We report the successful cultivation of multiple HuNoV strains in enterocytes in stem cell–derived, nontransformed human intestinal enteroid monolayer cultures. Bile, a critical factor of the intestinal milieu, is required for strain-dependent HuNoV replication. Lack of appropriate histoblood group antigen expression in intestinal cells restricts virus replication, and infectivity is abrogated by inactivation (e.g., irradiation, heating) and serum neutralization. This culture system recapitulates the human intestinal epithelium, permits human host-pathogen studies of previously noncultivatable pathogens, and allows the assessment of methods to prevent and treat HuNoV infections.

Human noroviruses (HuNoVs) are the most common cause of epidemic and sporadic cases of acute gastroenteritis worldwide, and are the leading cause of food-borne gastroenteritis (*1*–*3*). Since the introduction of rotavirus vaccines, HuNoVs have become the predominant gastrointestinal pathogen within pediatric populations in developed countries (*4*). HuNoVs are highly contagious, with rapid person-to-person transmission directly through the fecal-oral route



SARAH ZHANG SCIENCE 09.02.16 8:00 AM

## THE SECRET TO A BREAKTHROUGH IN FIGHTING NOROVIRUS? HUMAN BILE