

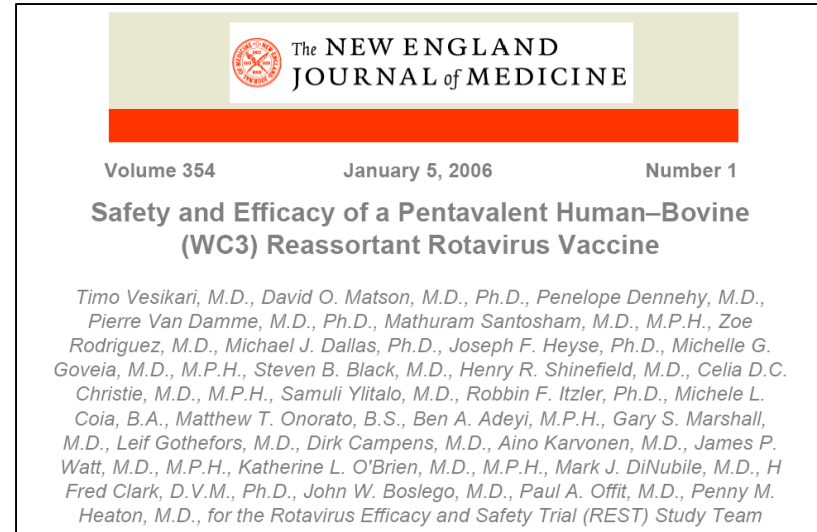
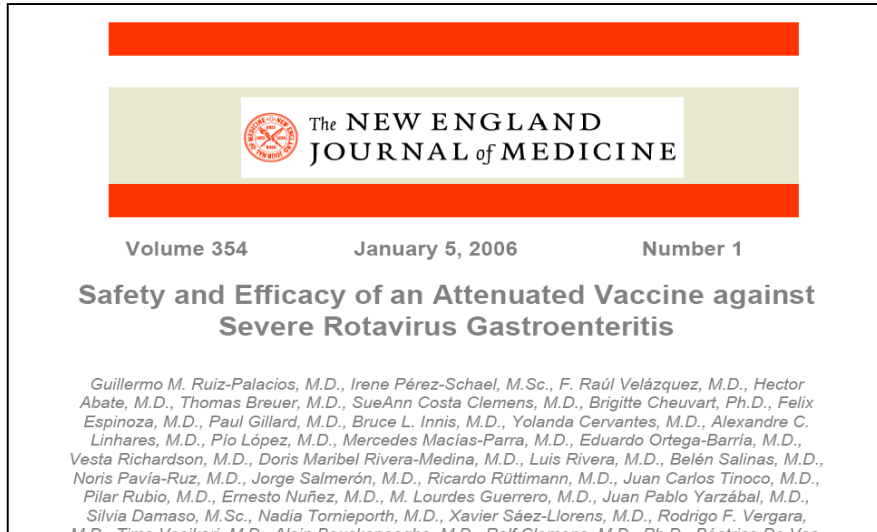
Rotavirus Vaccines -- Current Status & Value of a Correlate of Protection



Umesh D. Parashar
CDC, Atlanta, GA

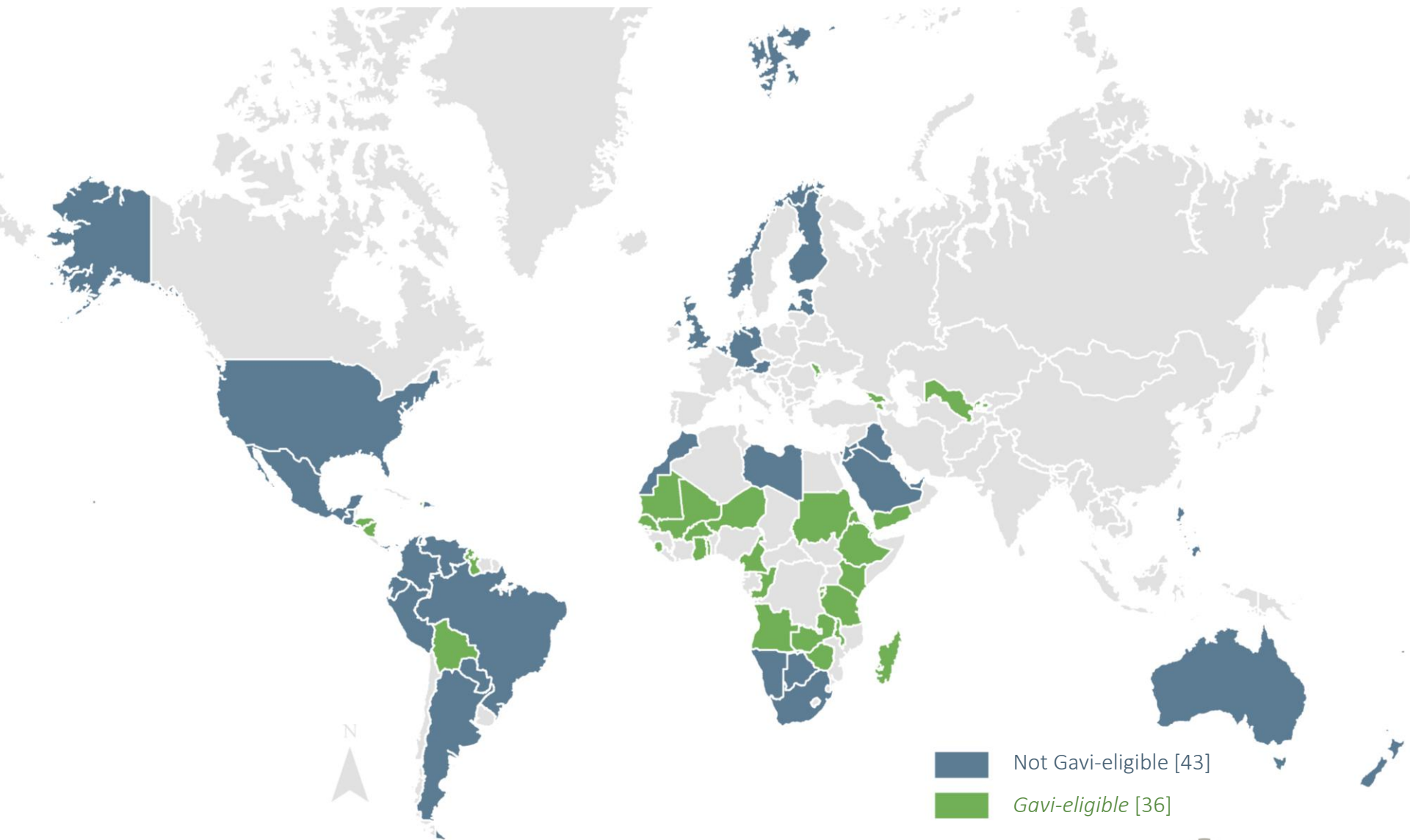


Two New Rotavirus Vaccines Licensed in 2006



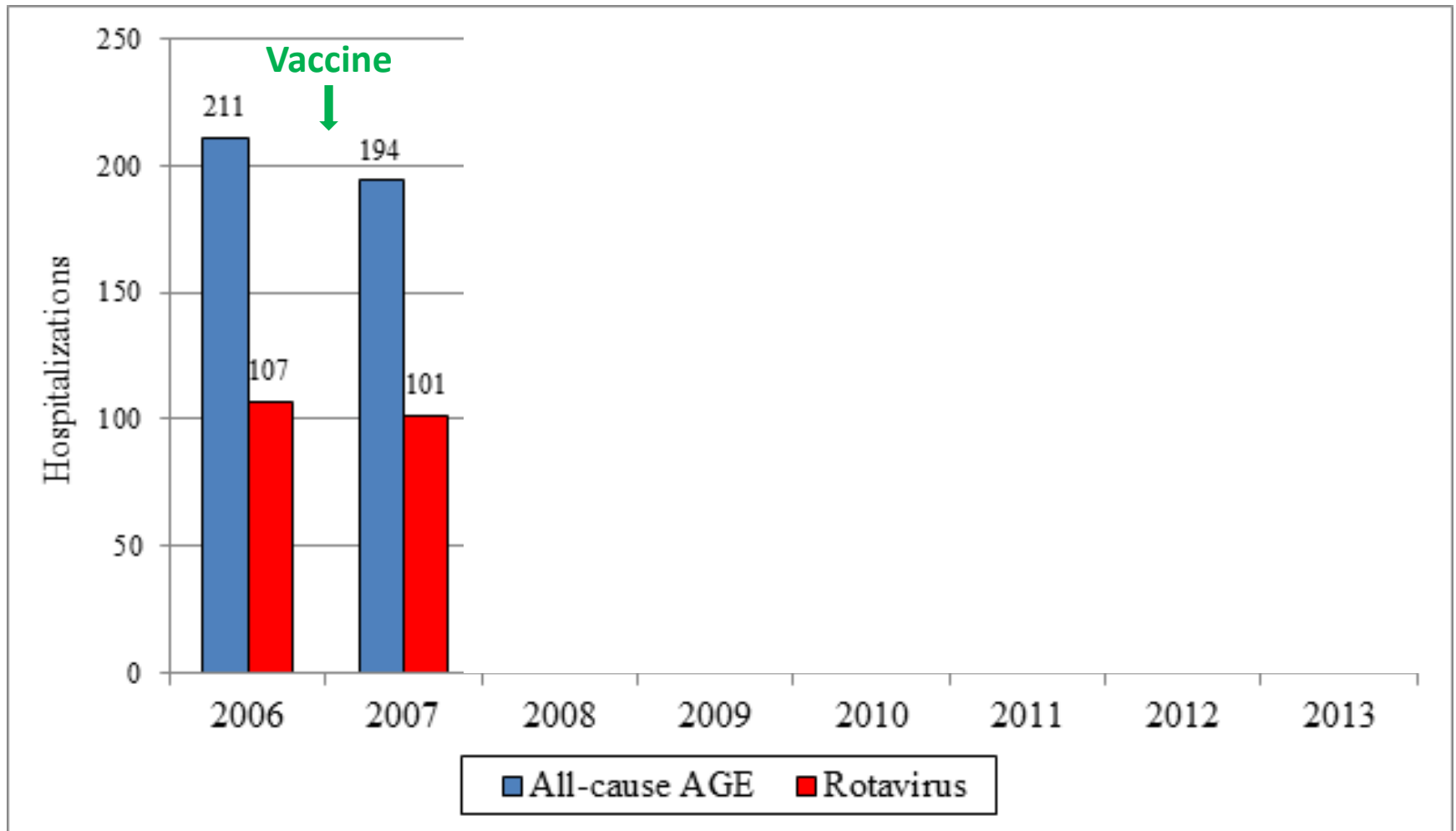
- Efficacy of 85%-98% against severe disease in Europe and Americas

National RV introductions, 79 countries*



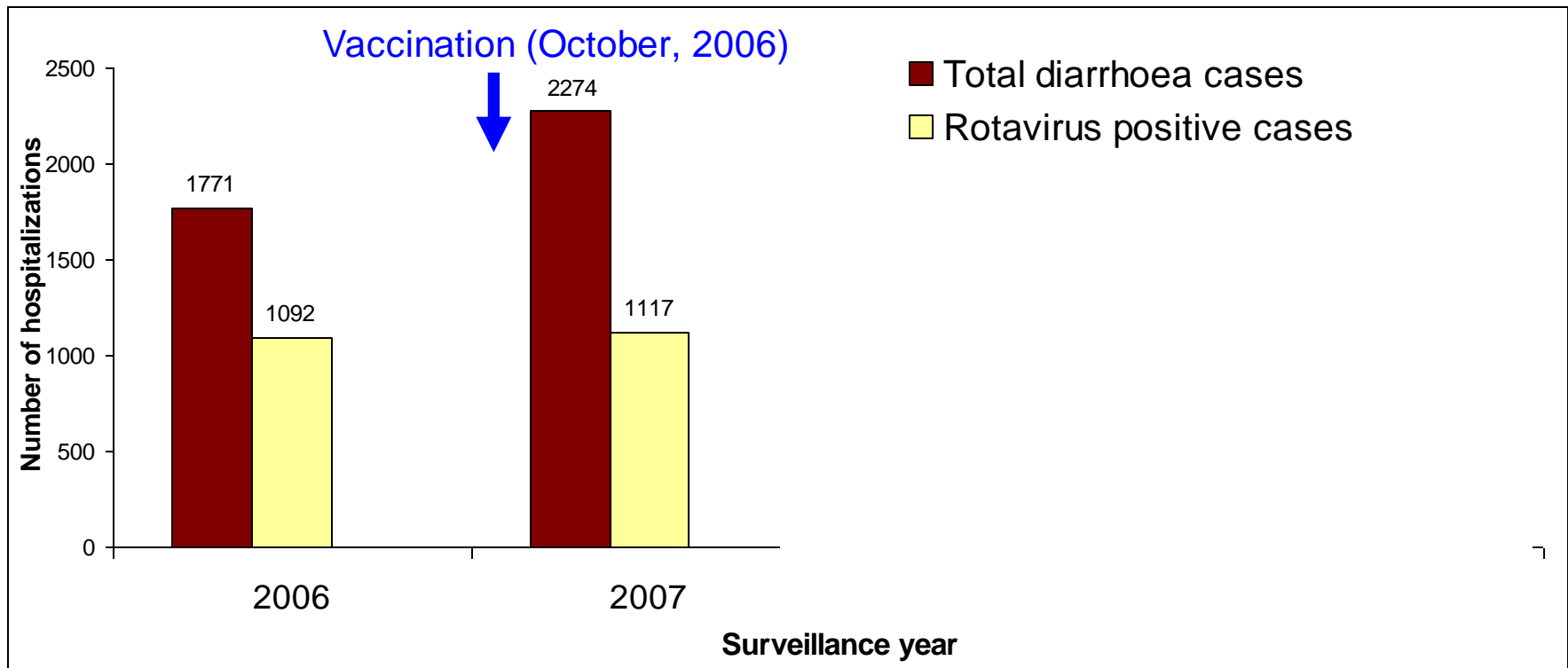
*As of Oct 1, 2015

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



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

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



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

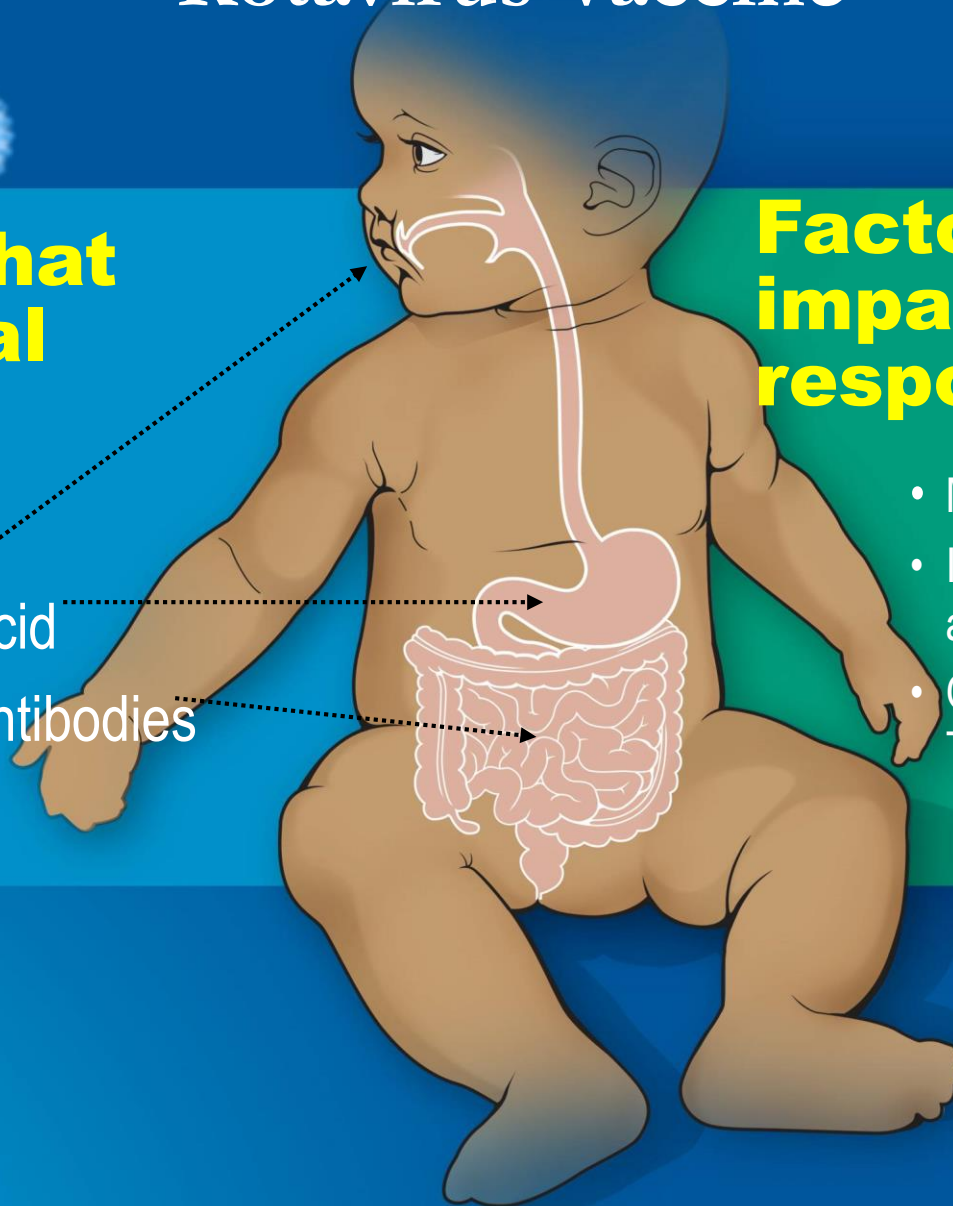
Hurdles to Immunization for a Live Oral Rotavirus Vaccine

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

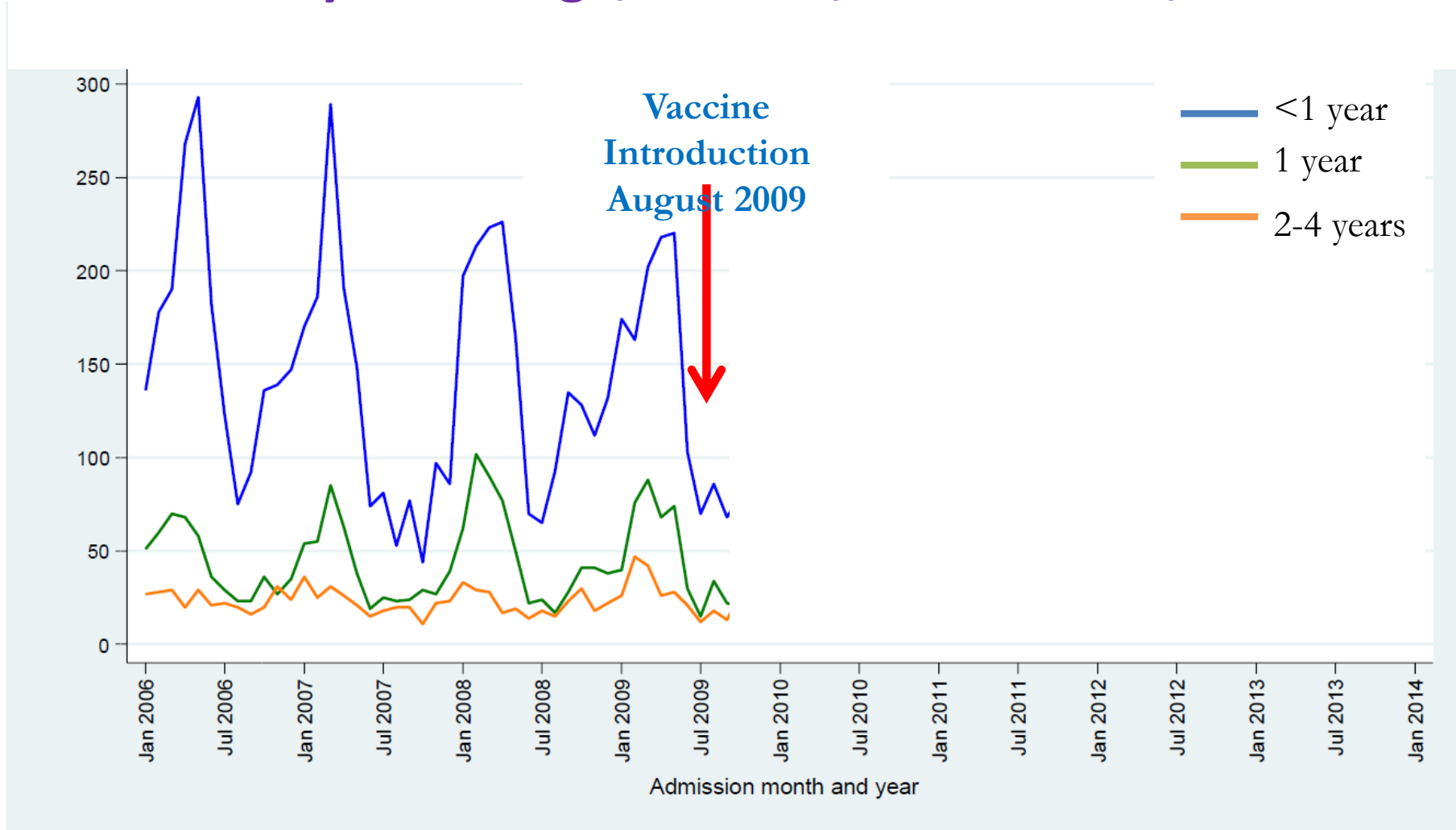


Moderate Efficacy of Rotavirus Vaccines in Africa and Asia

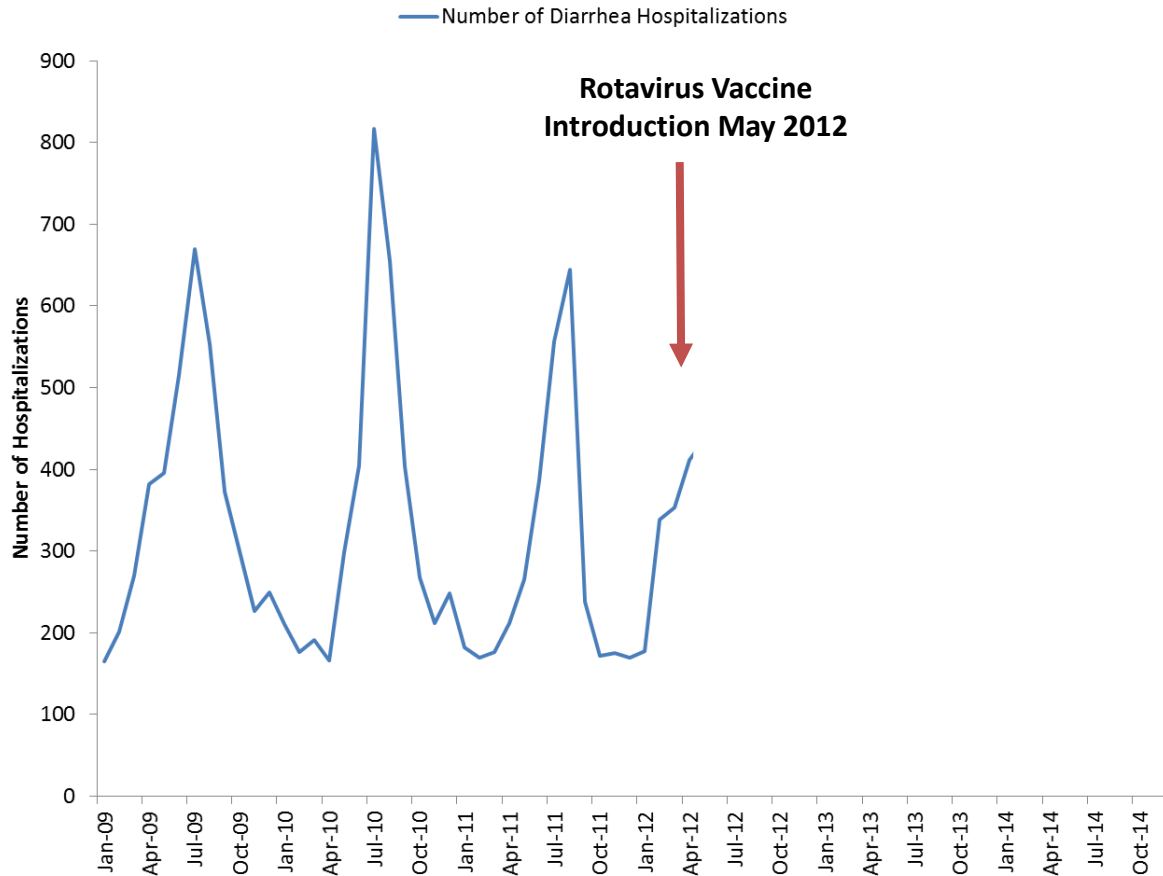
Vaccine	Region	Countries	Efficacy (95%CI)
RotaTeq	Africa	Ghana, Kenya, Mali	64% (40%-79%)
RotaTeq	Asia	Bangladesh, Vietnam	51% (13%-73%)
Rotarix	Africa	South Africa, Malawi	62% (44%-73%)

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

Monthly count of diarrhea hospitalizations among children <5 years of age, Soweto, South Africa, 2006-2013



Diarrhea hospitalizations by month among children <5 years of age at 24 district hospitals, Rwanda, 2009-2014

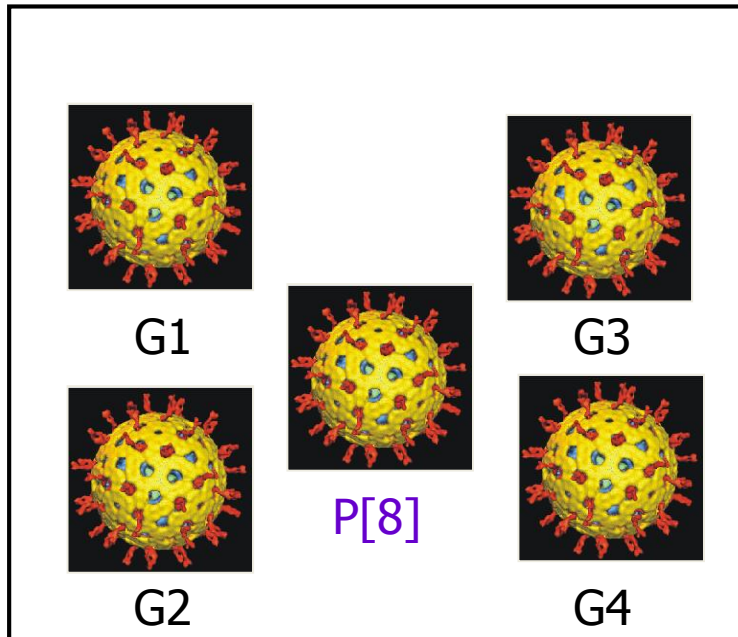


Annual reductions of 17%-23% in diarrhea hospitalizations following rotavirus vaccine introduction

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

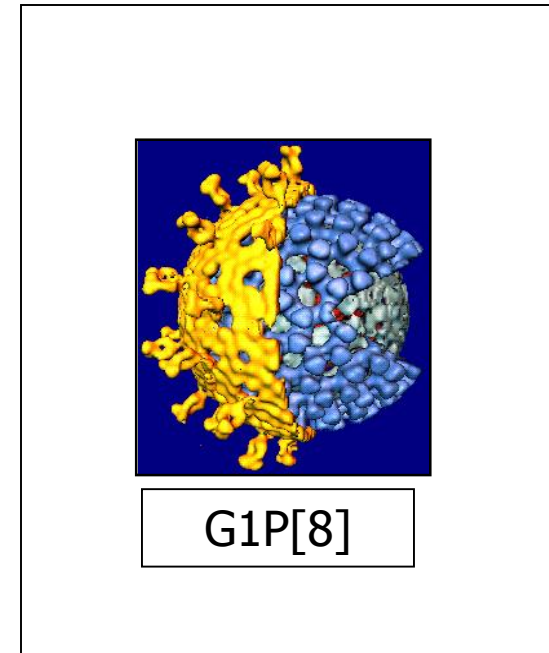
RotaTeq is Pentavalent & Rotarix is Monovalent

RotaTeq



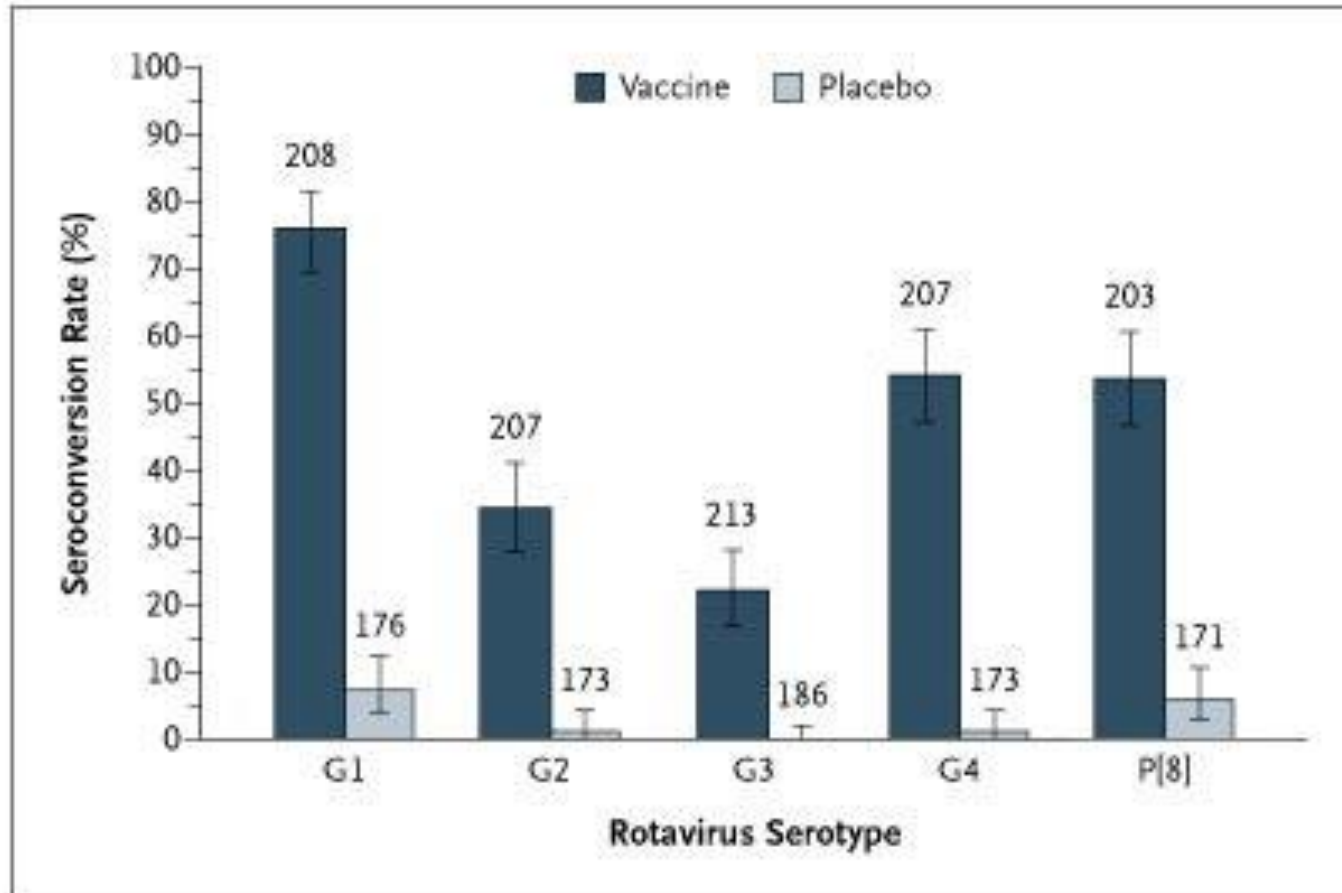
Five bovine-human
rotavirus strains

Rotarix



Single human
rotavirus strain

Seroconversion rates for serum neutralizing antibodies differed against human serotypes in RotaTeq, REST Trial

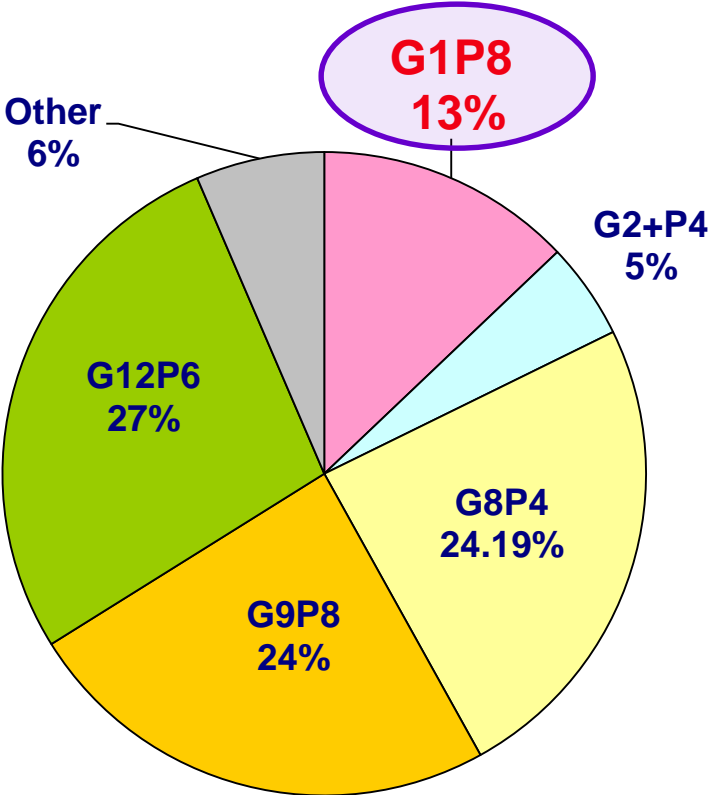


RotaTeq efficacy was similar against different G types

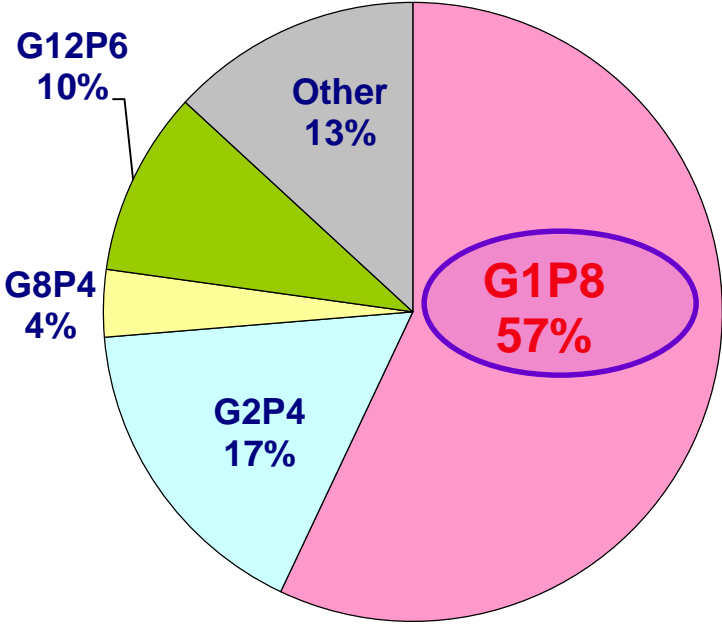
Table 2. Reduction in the Numbers of Hospitalizations and Emergency Department Visits in the Per-Protocol Population of the Large-Scale Study, According to G Serotype Identified in the Subject's Stool.*

Serotype	No. of Cases of Rotavirus Gastroenteritis		Percent Rate Reduction (95% CI)
	Vaccine Group (N=34,035)	Placebo Group (N=34,003)	
G1	16	328	95.1 (91.6–97.1)
G2	1	8	87.6 (<0–98.5)
G3	1	15	93.4 (49.4–99.1)
G4	2	18	89.1 (52.0–97.5)
G9	0	13	100.0 (67.4–100.0)
G12	0	1	100.0 (<0–100.0)

Great Strain Diversity in African Rotarix Trial

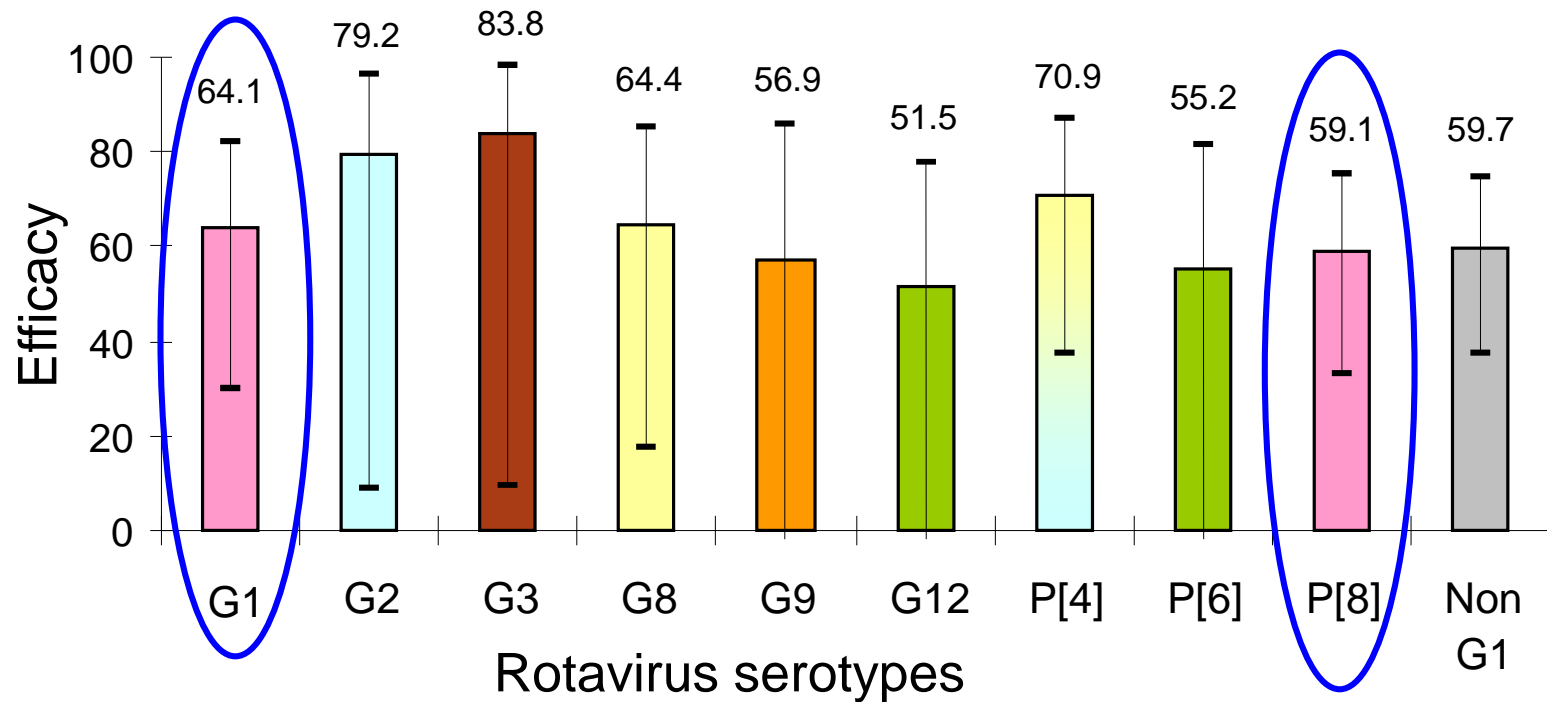


Malawi



South Africa

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



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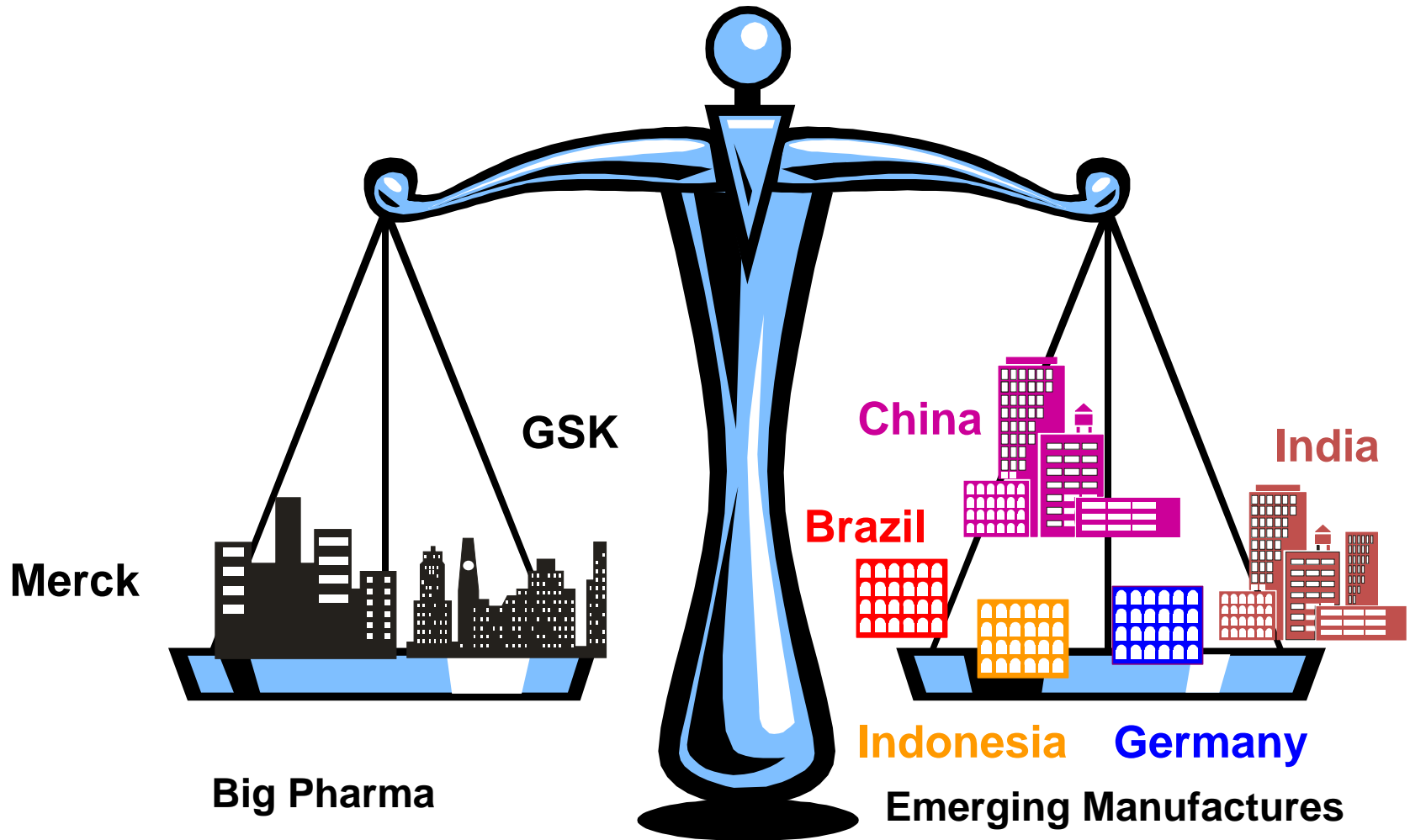
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High Rotarix (G1P8) Effectiveness against Non-Vaccine Strains in Several Countries

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)

Value of a Correlate of Protection

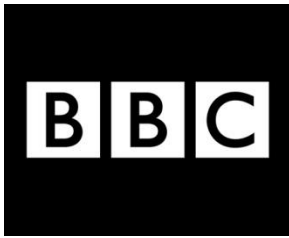
Key Issue – Vaccine Supply and Cost



Efficacy of a monovalent human-bovine (116E) rotavirus vaccine in Indian infants: a randomised, double-blind, placebo-controlled trial

Nita Bhandari, Temsunaro Rongsen-Chandola, Ashish Bavdekar, Jacob John, Kalpana Antony, Sunita Taneja, Nidhi Goyal, Anand Kawade, Gagandeep Kang, Sudeep Singh Rathore, Sanjay Juvekar, Jayaprakash Muliylil, Alok Arya, Hanif Shaikh, Vinod Abraham, Sudhanshu Vrati, Michael Proschan, Robert Kohberger, Georges Thiry, Roger Glass, Harry B Greenberg, George Curlin, Krishna Mohan, G V J A Harshavardhan, Sai Prasad, T S Rao, John Boslego, Maharaj Kishan Bhan, for the India Rotavirus Vaccine Group†*

Endpoints	ROTAVAC N= 4354	Placebo N= 2187	Vaccine Efficacy % (95% CI)	p value
Severe RV GE requiring hospitalization# or supervised rehydration therapy\$				
Till 2 yrs of age	92 (2%)	102 (5%)	55.6% (40.5, 66.8)	<0.0001
Till 1 yr of age	57 (1%)	65 (3%)	56.3% (36.7, 69.9)	<0.0001



Drug firms cut vaccine prices to the developing world*

	United States	PAHO	GAVI / UNICEF
GSK	\$120 – \$200/child	\$15/child	\$5/child [up to 125 M doses; over 5 yrs]
Merck	\$120 – \$200/child	\$15.45/ child	\$10.50/child [for volume over 30 M]
Bharat Biotech	–	–	~ \$3/ child

- **3 doses/child: Merck, Bharat Biotech**
- **2 doses/child: GSK**
- * **Applies to GAVI tenders**

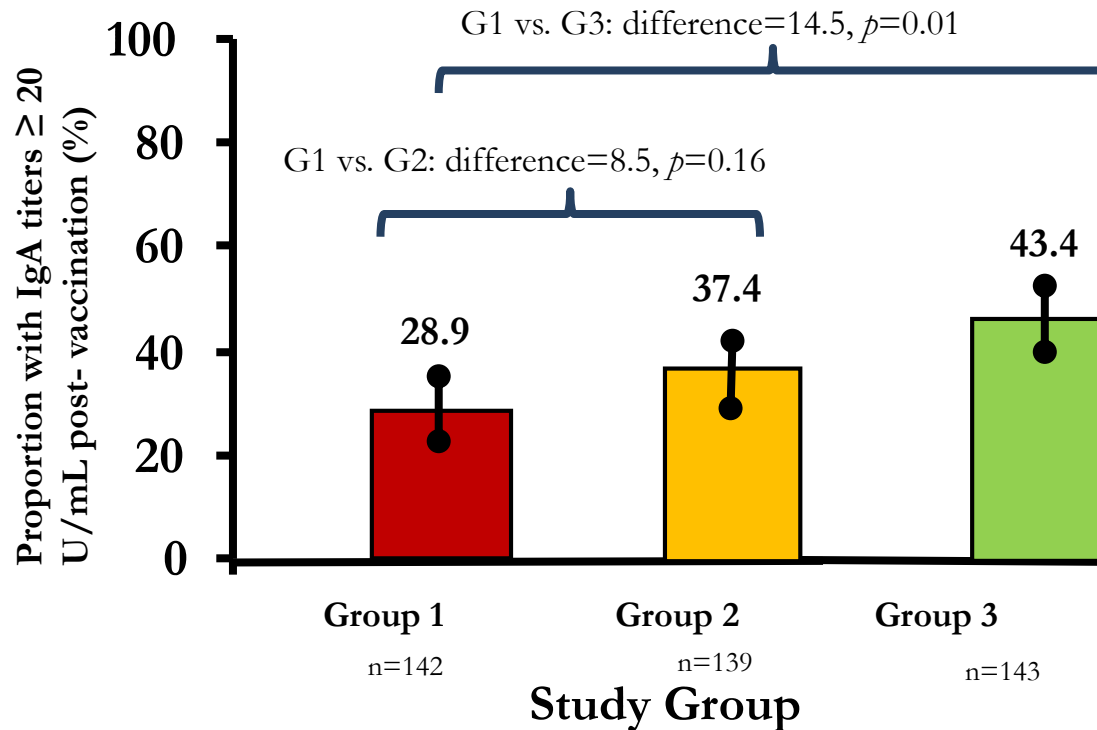
How will we license future rotavirus vaccines?

- All trials to date have been placebo controlled and relied on clinical endpoint
- Placebo controlled trials ethically complex given widespread global rollout of vaccine
- Non-inferiority studies with clinical endpoints large and expensive to conduct
- An immunologic correlate will simplify testing

Testing of interventions to improve rotavirus vaccine performance in developing countries

- Additional doses of vaccine
 - 3rd dose of RV1
 - Booster dose at 9 month of life
- Alternate vaccination schedules
 - Delaying vaccination to reduce interference with maternally acquire antibody
- Supplementation with micronutrients (e.g., zinc) or probiotics

Immunogenicity of Different RV1 Schedules in Ghana

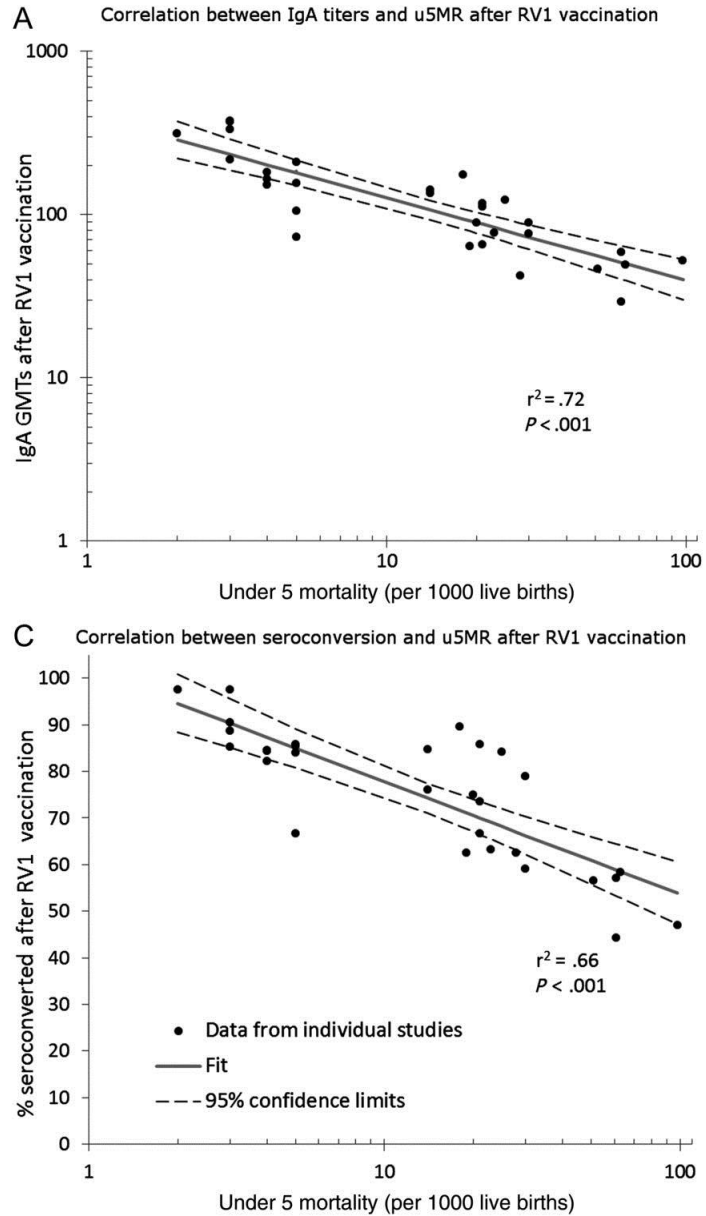


Group 1 – 2 RV1 doses at 6 and 10 weeks
Group 2 – 2 RV1 doses at 10 and 14 weeks
Group 3– 3 RV1 doses at 6, 10, and 14 weeks

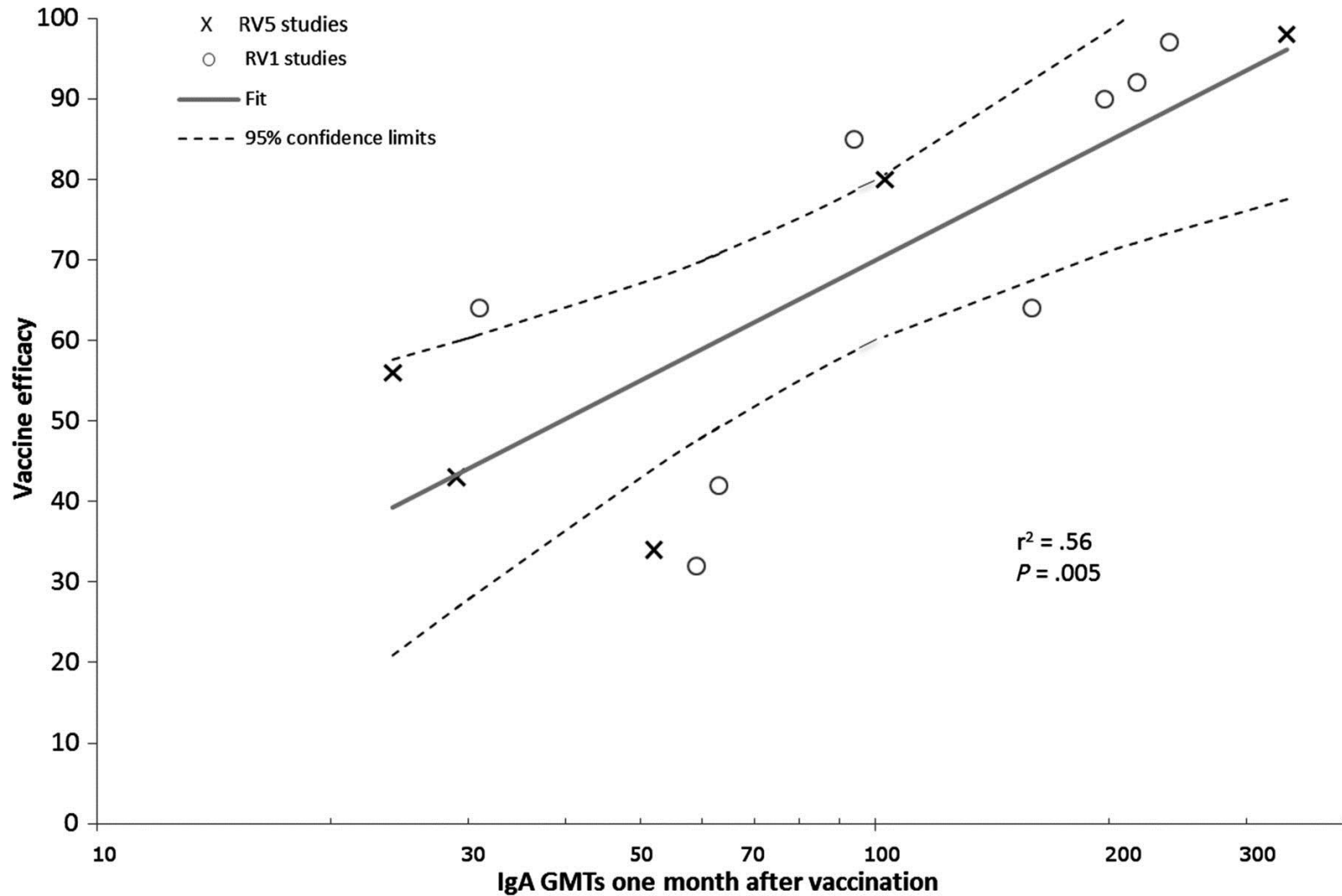


Serum IgA as a Correlate?

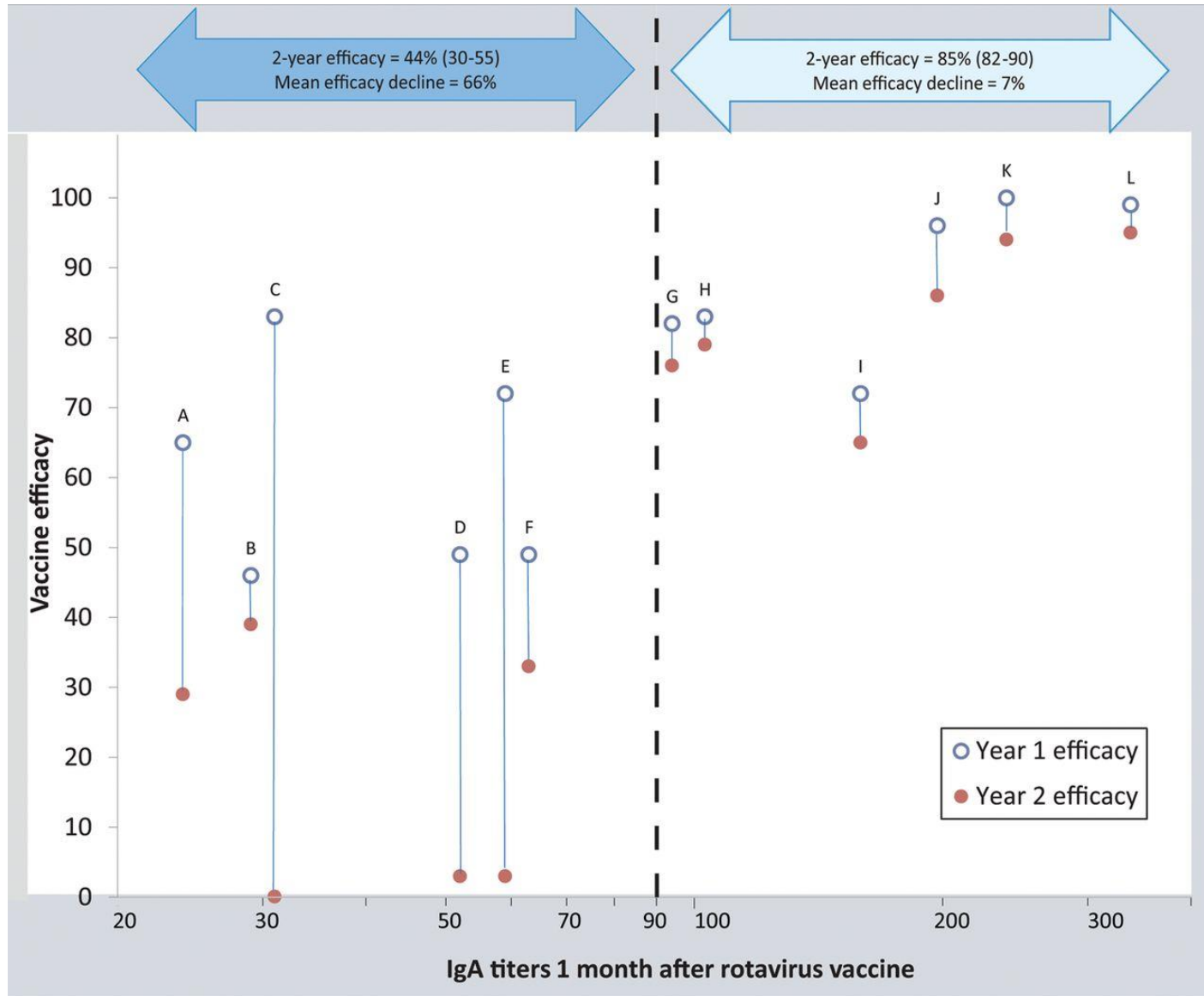
Relationship between under-5 child mortality and immune response to rotavirus vaccination



Relationship between anti-rotavirus serum IgA geometric mean titers/concentrations and rotavirus vaccine efficacy



Decline in vaccine efficacy between year 1 (open circles) and year 2 (solid circles) after rotavirus vaccination, by location and titers rotavirus IgA geometric mean titers/concentrations



Summary

- Good impact of rotavirus vaccination
 - Efficacy lower in developing countries, but still substantial impact
 - Evidence of heterotypic protection
- Correlate of protection will
 - Simplify testing of future rotavirus vaccines
 - Help test interventions to improve vaccine performance