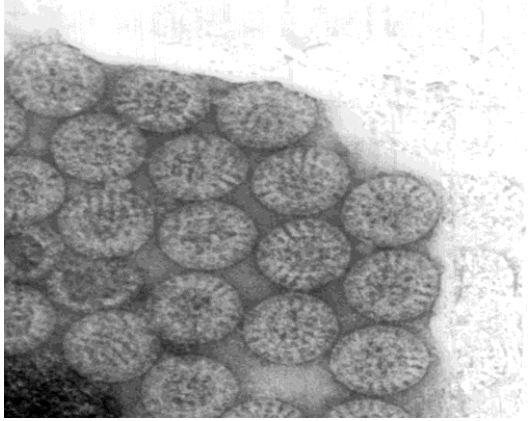
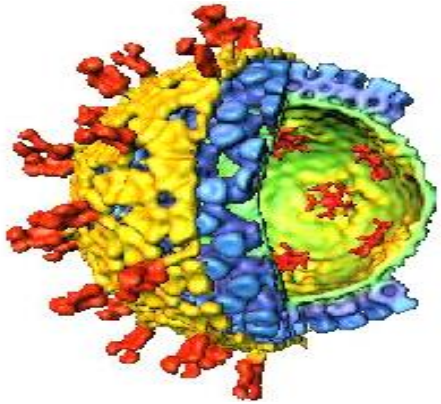




An update on rotavirus vaccines

Gagandeep Kang

Outline

- Introduction
- Licensed vaccines and how they work
- Impact of vaccines in LMICs
- Interchangeability of currently licensed vaccines
- Correlates of protection
- Determinants of response
  - EED and the role of the microbiota
- Non-living vaccine candidates in development

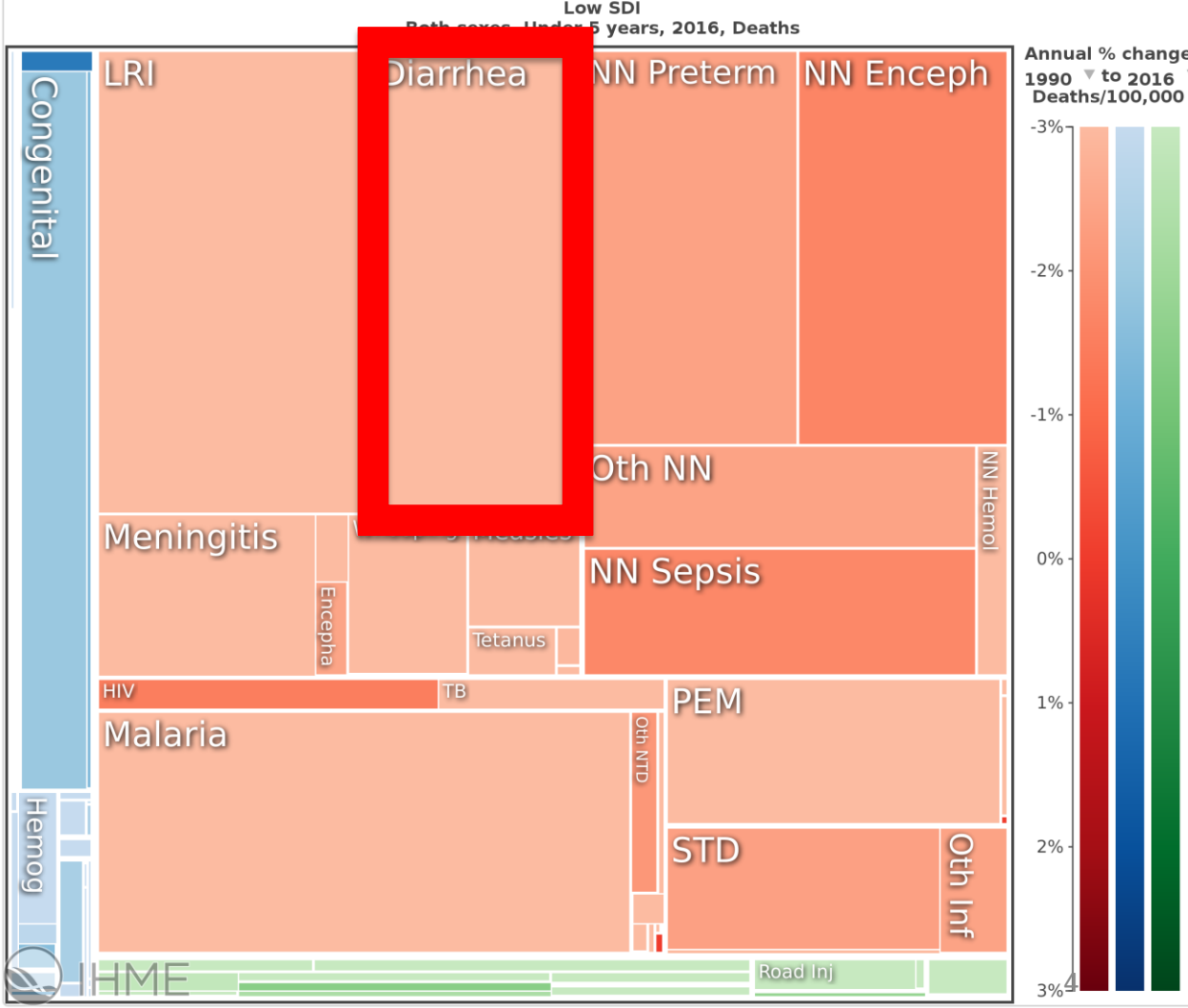
Outline

- Introduction
- Licensed vaccines and how they work
- Impact of vaccines in LMICs
- Interchangeability of currently licensed vaccines
- Correlates of protection
- Determinants of response
  - EED and the role of the microbiota
- Non-living vaccine candidates in development

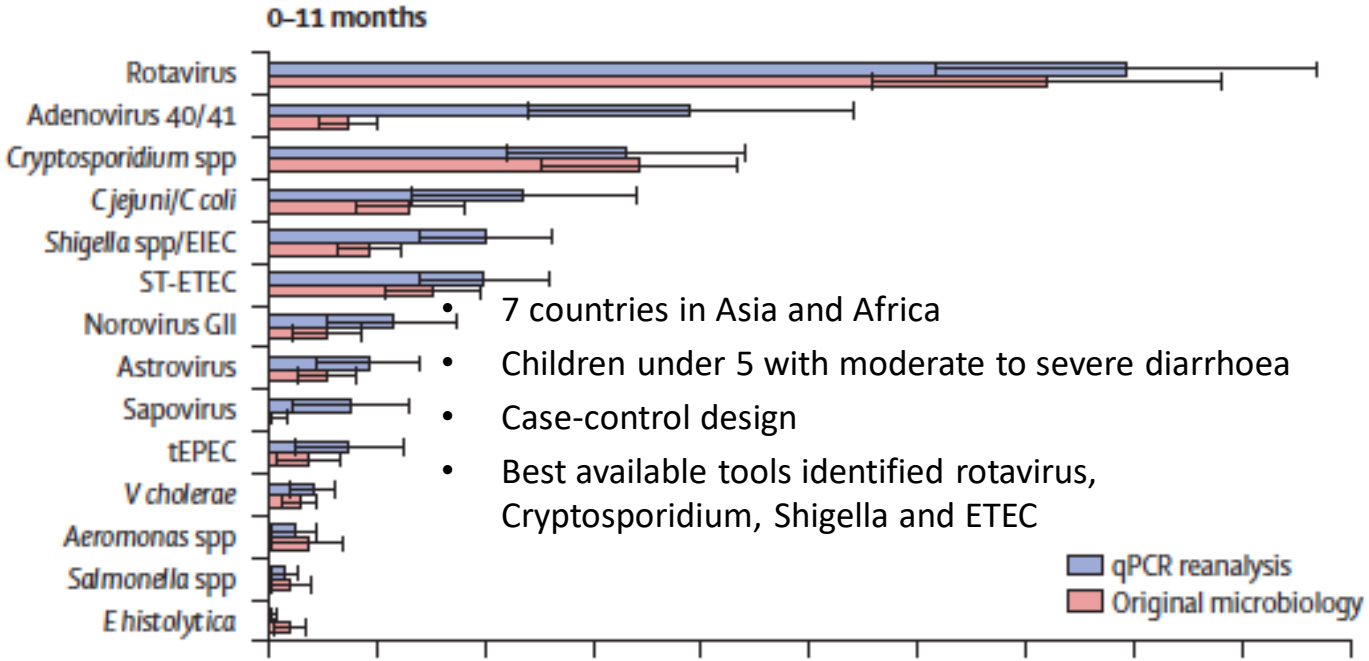
Introduction

- Deaths, <5 years
- 10. 2% (8.92% to 11.49%)
- -5.04% annual change

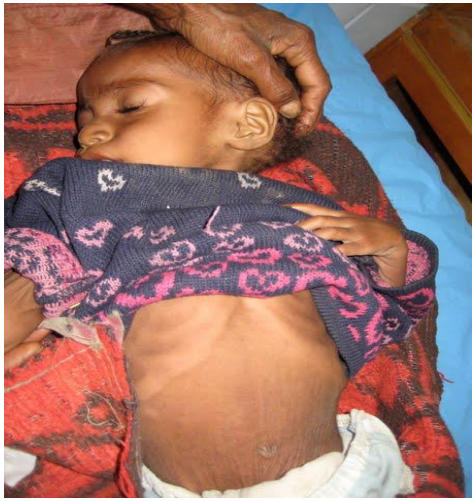
IHME, 2016



Rotavirus is the commonest cause of acute dehydrating gastroenteritis in young children



- 7 countries in Asia and Africa
- Children under 5 with moderate to severe diarrhoea
- Case-control design
- Best available tools identified rotavirus, Cryptosporidium, Shigella and ETEC

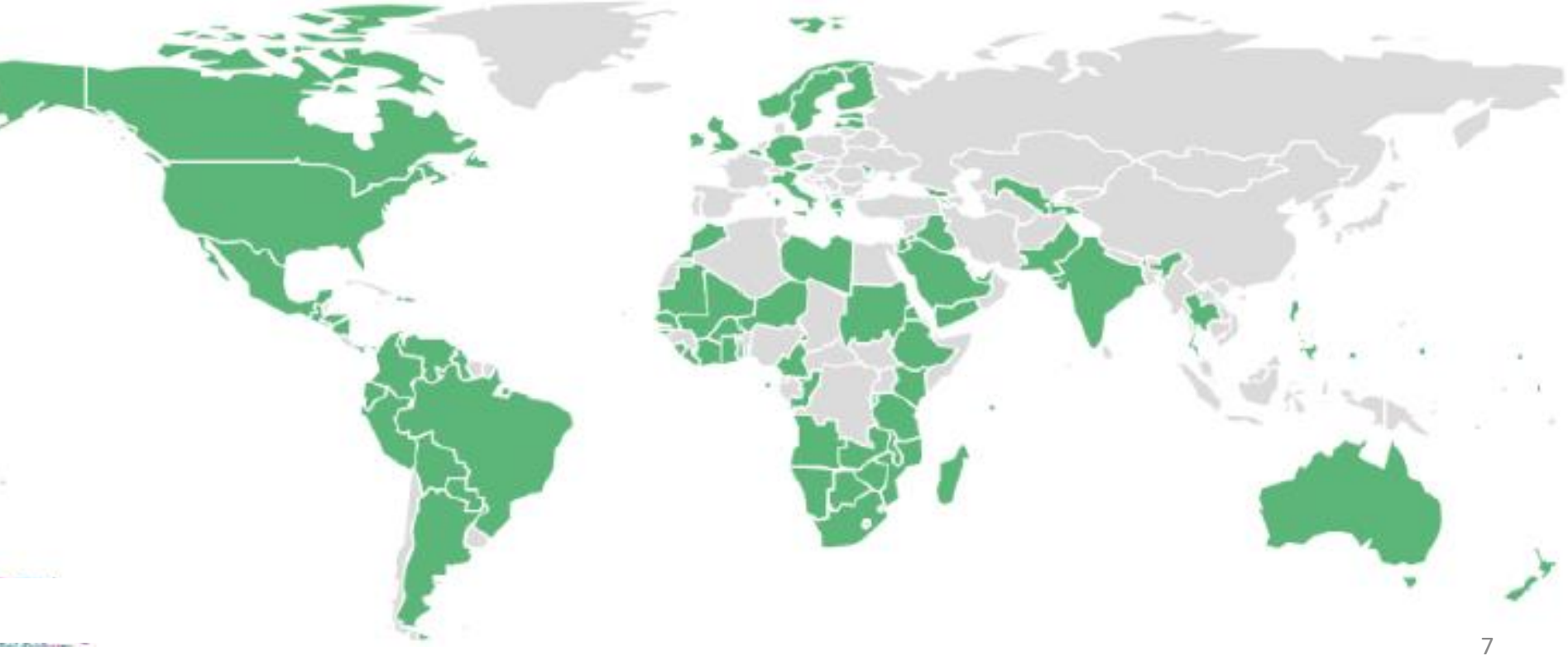


Liu et al, Lancet 2016

Rotavirus is democratic, and hygiene delays but does not prevent infection

- Rotavirus cannot be treated with antibiotics or other drugs
- Prompt **treatment with oral rehydration therapy (ORT) can be effective** in treating mild infections
- But many of **the world's poorest children do not have access to ORT**, despite the fact that it is effective and inexpensive
- **IV fluids may be required** if ORT is not administered, given too late or dehydration is too severe
- **Rotavirus prevention by vaccination is key to improving child survival**

93 countries with 86 with nationwide introductions in December 2017



Outline

- Introduction
- Licensed vaccines and how they work
- Impact of vaccines in LMICs
- Interchangeability of currently licensed vaccines
- Correlates of protection
- Vaccines that work and not so much
- Determinants of response
  - EED and the role of the microbiota
- Non-living vaccine candidates in development

Rotavirus vaccines	Rotarix (GSK)	Rotateq (Merck)	Rotavac (Bharat Biotech)	RotaSIIL (Serum)	Rotavin (Polyvac)	LLR (Lanzhou)	Rotashield (Wyeth, Biovirx)
Licensure	Several countries, 2006	Several countries, 2006	India, 2014	India, 2017	Vietnam, 2012	China, 2000	Several countries, 1998
Pre-qual	Yes	Yes	Yes	No	No	No	No
Strains	Monovalent, human derived G1P8	Pentavalent, WC3 G6P5 bovine, reassortants G1-4, P8	Monovalent, human neonatal derived G9P11	Pentavalent, UK Bovine G6P5, reassortants G1-4, G9	Monovalent, human G1P8	Monovalent, lamb G10P12	Tetravalent, RRV G3P3 rhesus backbone, reassortants G1, 2, 4
No of doses	Two	Three	Three	Three	Two	One per year for 3 yr	Three (two neonatal)
Age first dose	6 weeks	6 weeks	6 weeks	6 weeks	6 weeks	2-36 mon	6 weeks
Dosage	10^6 of live attenuated human G1P[8] particles	2.0-2.8 x 10^6 infectious units per reassortant	10^5 FFU of live rotavirus	$10^{5.6}$ infectious units per reassortant	$10^{6.3}$ of live attenuated human G1P[8] particles	>5.5 log $CCID_{50}$	1 x 10^5 plaque-forming units (pfu) of each component

What do vaccine efficacy data show?

- Few head to head studies in the same population
- Efficacy trial data indicates that mono- and multivalent vaccines have similar efficacy in broadly similar settings

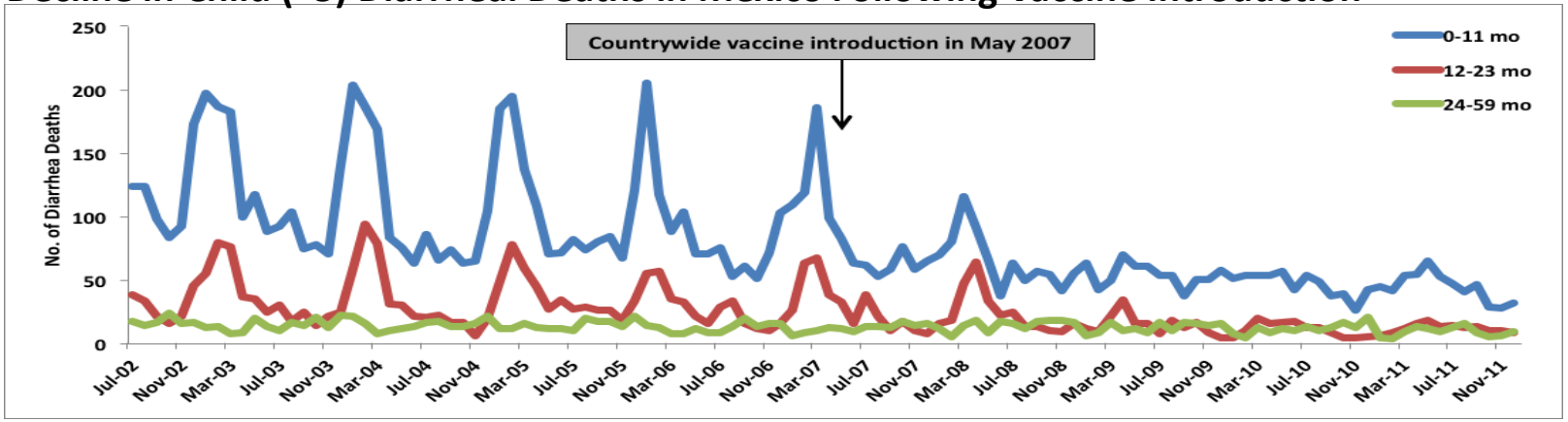
Setting	Vaccine	Schedule	1st yr efficacy	2nd yr efficacy	Combined
Latin America	RV1	2, 4 months	83% (67-92)	79% (66-87)	**81%** (71-87)
Europe	RV1	3, 5 months	96% (90-99)	86% (76-92)	**90%** (85-94)
Asia (HIC)	RV1	3, 5 months	96% (85-100)		
USA, Finland	RV5	2, 4, 6 months	**98%** (88-100)		
South Africa	RV1	10, 14 weeks	**72%** (40-8)	--	32% (-71-75)
South Africa	RV1	6, 10, 14 wks	**82%** (55-94)	--	85% (35-98)
Malawi	RV1	10, 14 wks	**49%** (11-72)	3% (-101-53)	34% (-2-58)
Malawi	RV1	6, 10, 14 wks	**50%** (11-72)	33% (-49-71)	42% (9-64)
Africa	RV5	6, 10, 14 wks	**64%** (40-79)	**20%** (-16-44)	39% (19-55)
Ghana	RV5	6, 10, 14 wks	65% (36-82)	29% (-65-71)	56% (28-73)
Kenya	RV5	6, 10, 14 wks	83% (26-98)	-55% (-1753-82)	64% (-6-90)
Mali	RV5	6, 10, 14 wks	1% (-432-82)	19% (-23-47)	18% (-23-45)
Asia	RV5	6, 10, 14 wks	**51%** (13-73)	**46%** (1-71)	48% (22-66)
Vietnam	RV5	6, 10, 14 wks	72% (-45-97)	65% (-48-94)	64% (8-91)
Bangladesh	RV5	6, 10, 14 wks	46% (-1-72)	39% (-18-70)	43% (10-64)
India	Rotavac	6, 10, 15 wks	56% (37-70)	49% (17-68)	55% (40-66)

Outline

- Introduction
- Licensed vaccines and how they work
- Impact of vaccines in LMICs – South America, Africa and India
- Interchangeability of currently licensed vaccines
- Correlates of protection
- Determinants of response
  - EED and the role of the microbiota
- Non-living vaccine candidates in development

Impact on mortality in Mexico

Decline in Child (<5) Diarrheal Deaths in Mexico Following Vaccine Introduction

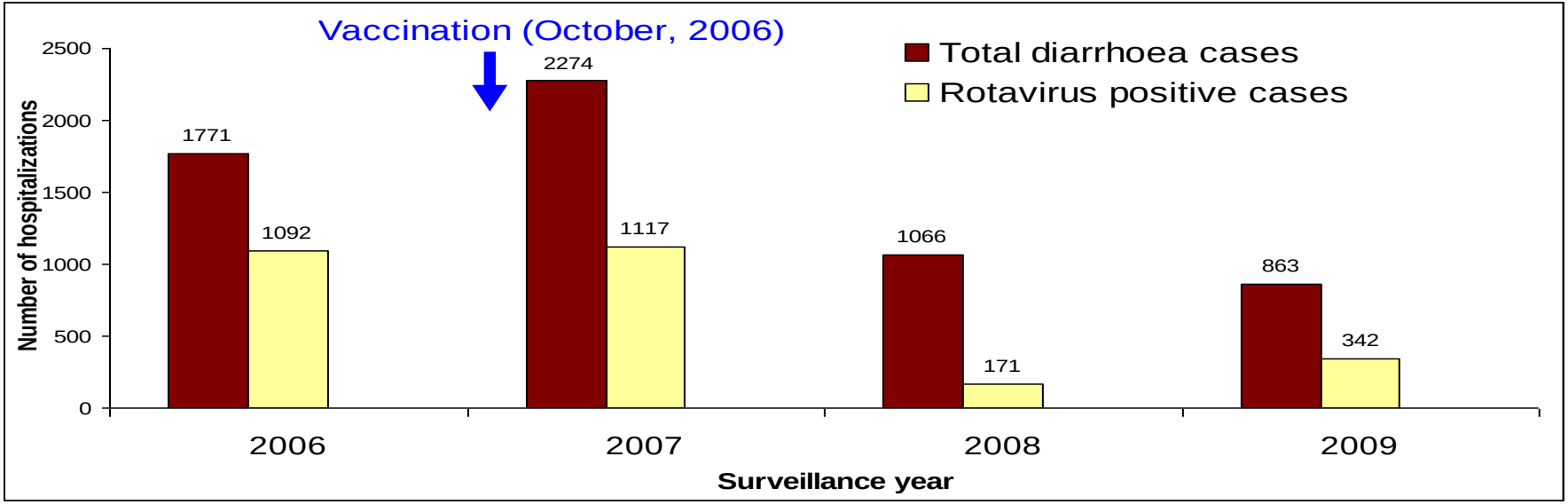


- Reduction in deaths of **>50%** sustained across all regions.
- Reduction in deaths of **35%** seen in just the first year.

Gastañaduy et al, Pediatrics, 2013
Richardson et al, NEJM, 2010

Impact on rotavirus and all-cause gastroenteritis hospitalizations in El Salvador

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

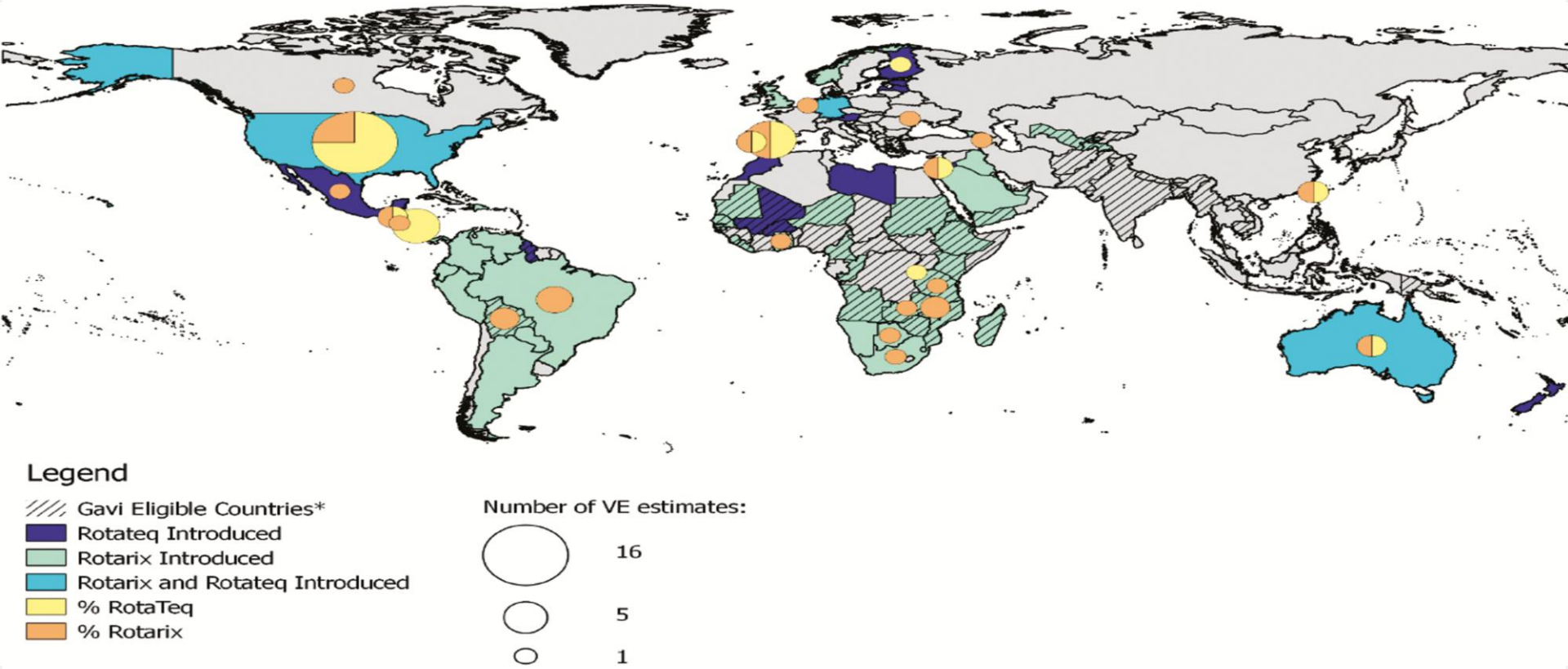


De Palma et al, BMJ, 2010

Herd immunity

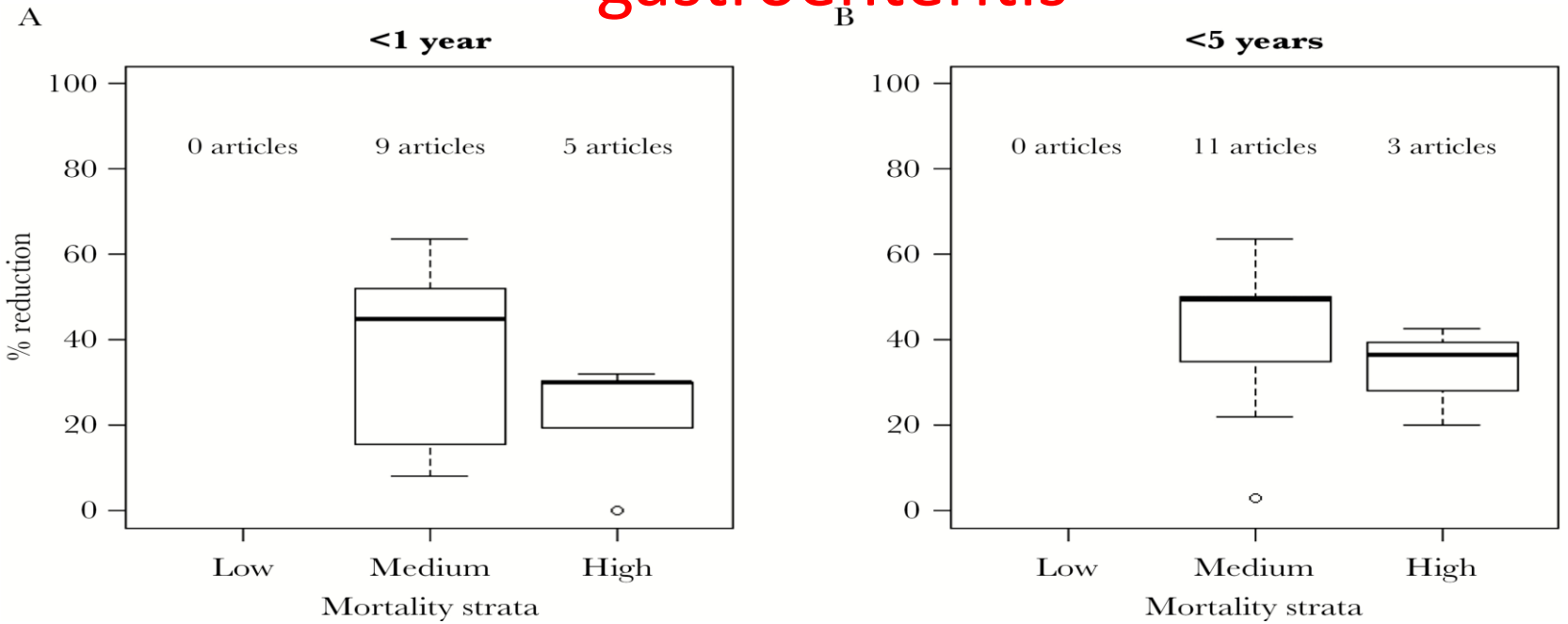
Significant reductions in hospitalization observed for non-vaccinated children in developed and some developing countries

	Rotavirus related hospitalizations reduced	
Country (nationwide)	Children age-eligible for vaccine	Children NOT age-eligible for vaccine
El Salvador	79-86%	41-81%
Austria	76-79%	35%
USA	74-85%	41-80%
Belgium	65-80%	20-64%
Country (regional)		
Sao Paulo, Brazil	56-69%	24%
Queensland, Australia	50-70%	30-70%



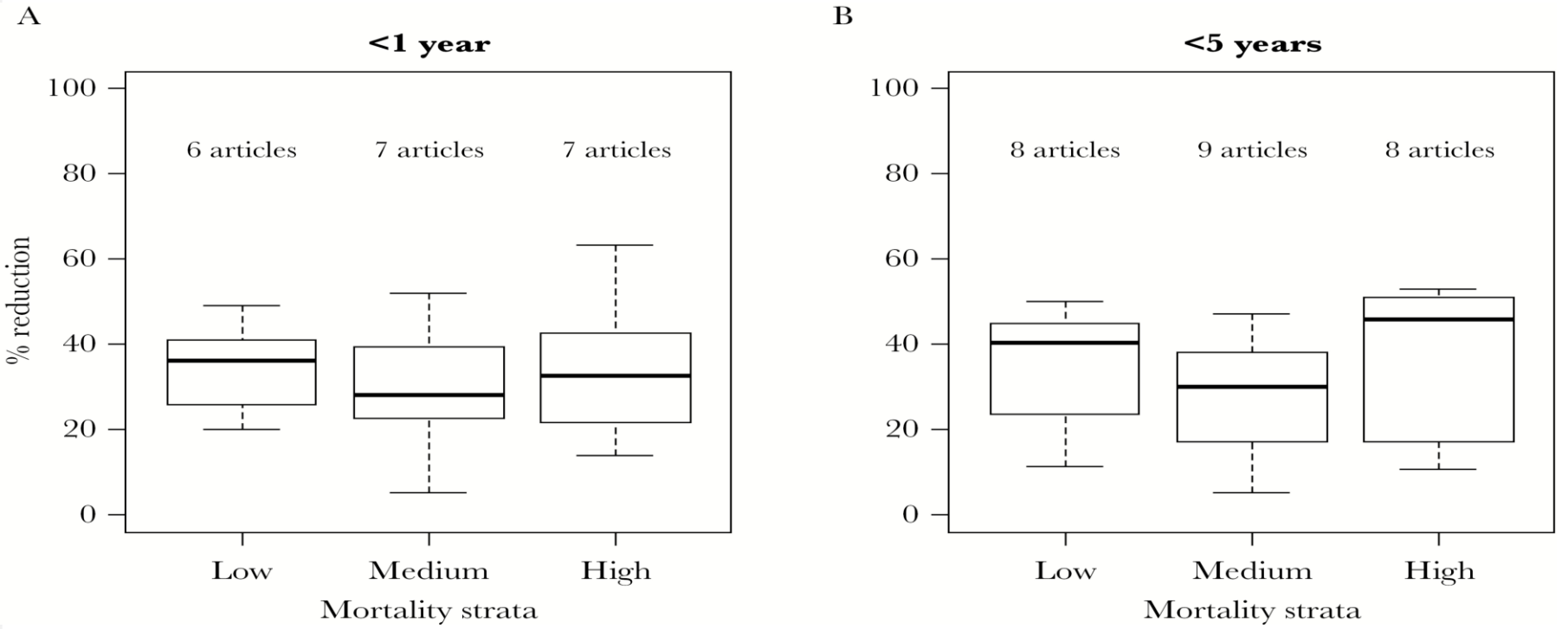
Jonesteller et al, Clin Infect Dis 2017

Reduction in mortality due to acute gastroenteritis



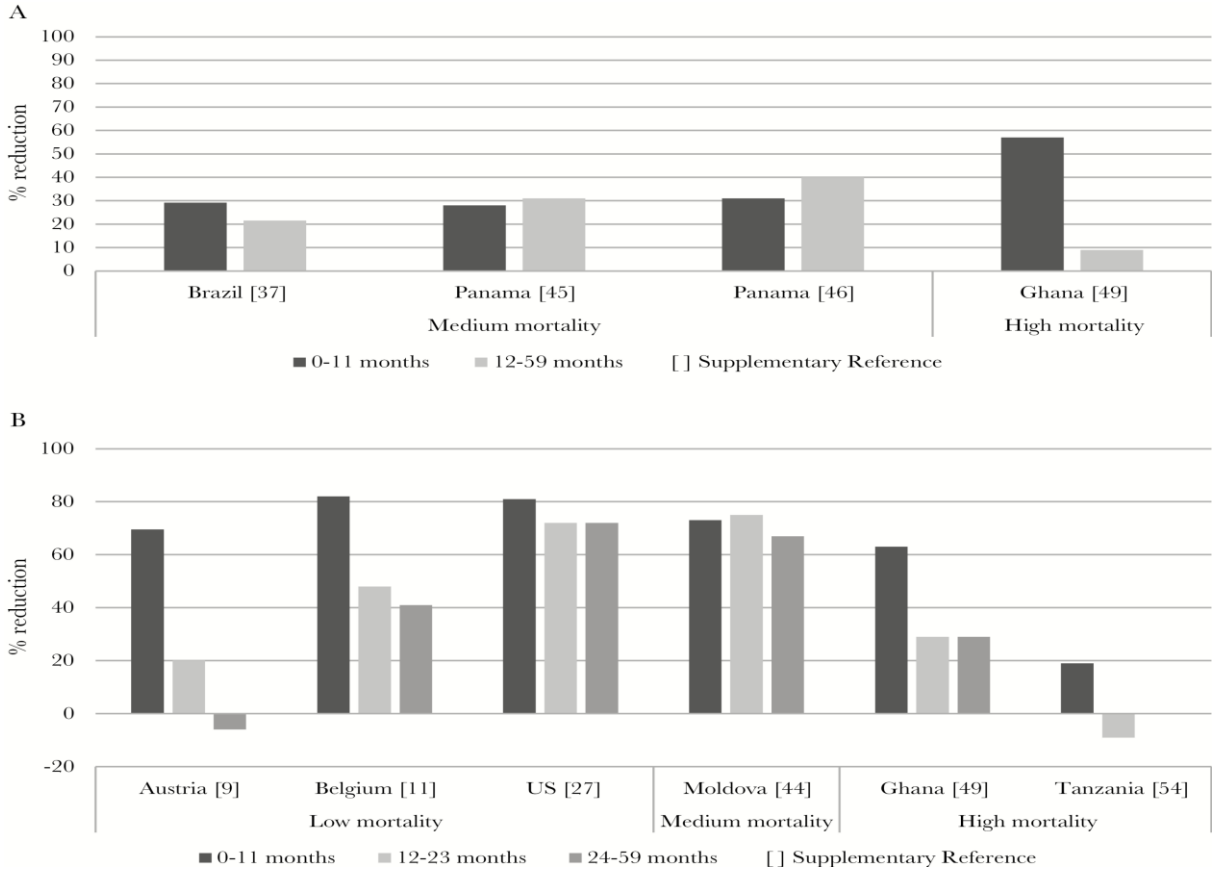
Burnett et al, J Infect Dis. 2017

Reduction in acute gastroenteritis hospitalizations



Burnett et al, J Infect Dis. 2017

Herd effects? Age specific reduction in disease in the first year after vaccine introduction



Burnett et al, J Infect Dis. 2017

Rotavirus vaccine effectiveness in Malawi

	Rotavirus positive	Test negative controls		Community controls	
Children with Vesikari ≥11	N=90	N=197	Vaccine effectiveness (95% CI)	N=288	Vaccine effectiveness (95% CI)
Median age in months	8 (0-16)	9 (0-17)			
0 doses	13 (14%)	10 (5%)	reference	19 (7%)	reference
2 doses	69 (77%)	195 (89%)	68% (22-87%)	239 (83%)	68% (23-86%)
At least 1 dose	77 (89%)	208 (95%)	69% (25-87%)	269 (91%)	68% (37-83%)

Bar-Zeev et al. Lancet Infect Dis 2015

Follow-up of rotavirus vaccine effectiveness in Malawi

Subgroup	Cases/Controls	2-dose vaccine effectiveness % (95% CI)	P value
All	241/692	58.3 (20.2, 78.2)	0.008
<12 mo	167/467	70.6 (33.6, 87.0)	0.003
12-23 mo	71/201	31.7 (-140.6, 80.6)	0.552
>23 mo	73/225	28.8 (-147.5, 79.5)	0.594
HIV unexposed	191/554	60.5 (13.3, 82.0)	0.021
HIV exposed, uninfected	48/126	42.2 (-106.9, 83.8)	0.400
Well nourished	74/183	78.1 (5.6, 94.9)	0.042
Stunted	53/152	27.8 (-99.5, 73.9)	0.320

Bar-Zeev et al. Clin Infect Dis 2016

Effectiveness in non-high income Asian countries

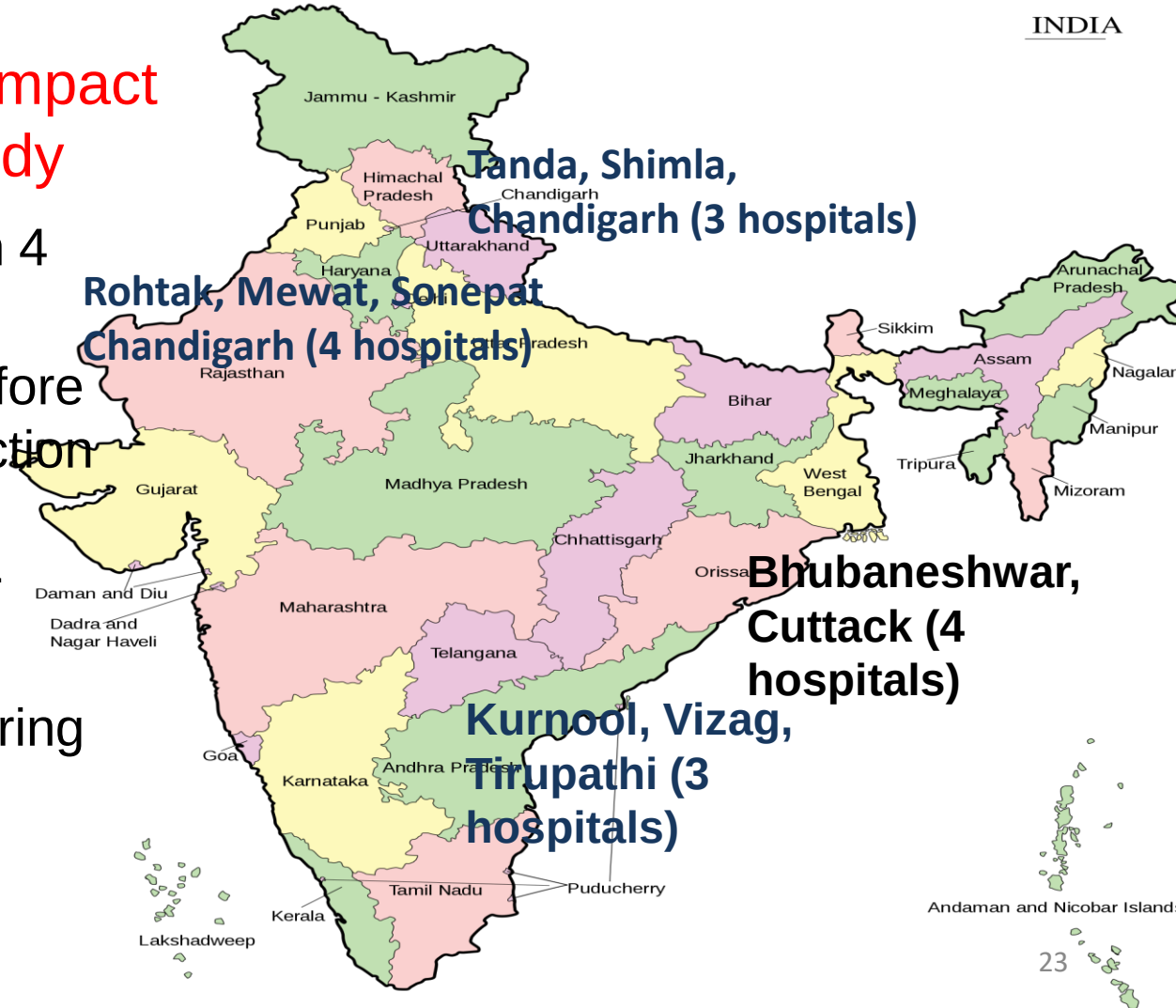
Location/design	Duration/vaccine	Effectiveness	Herd protection	Reference
Thailand, 2 provinces	2 years, Rotarix	IP: 88% (76-94) OP:24% (15-32)	Yes	Tharmaphornpilas et, Vaccine 2017
Bangladesh, Matlab CRT	2 years, Rotarix	Facility: 41% (23 to 55)	No	Zaman et al, PLosMed 2017
There are also studies from Taiwan, Israel and Korea that demonstrate effectiveness comparable to HICs in Europe, Australia and the Americas				

Summary of rotavirus vaccine effectiveness studies

- 57 articles from 27 countries
- Among children <5 years of age, the median percentage reduction in
  - AGE hospitalizations 38% overall and 41%, 30%, and 46% in countries with low, medium, and high child mortality, respectively
  - Hospitalizations and emergency department visits due to rotavirus AGE were reduced by a median of 67% overall and 71%, 59%, and 60% in countries with low, medium, and high child mortality, respectively

Rotavirus vaccine impact assessment study

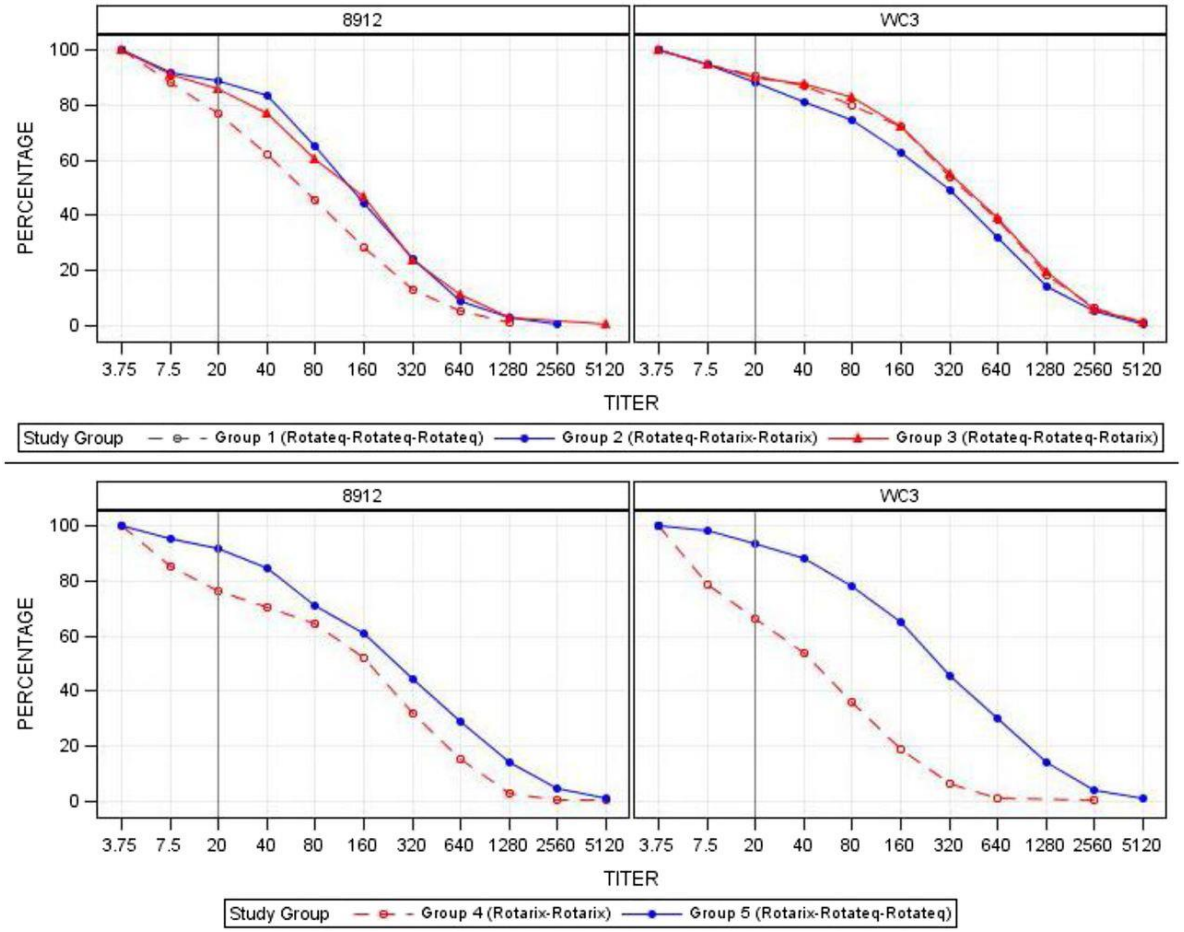
- Phase 1-14 hospitals in 4 states and 1 UT
- Surveillance started before or with vaccine introduction in April 2016
- Case-control design for vaccine effectiveness
- Intussusception monitoring in 9 hospitals



Outline

- Introduction
- Licensed vaccines and how they work
- Impact of vaccines in LMICs
- Interchangeability of currently licensed vaccines
- Correlates of protection
- Determinants of response
  - EED and the role of the microbiota
- Non-living vaccine candidates in development

Mixed schedules of Rotateq and Rotarix have been evaluated for immunogenicity



Libster et al, Pediatrics 2016

Outline

- Introduction
- Licensed vaccines and how they work
- Impact of vaccines in LMICs
- Interchangeability of currently licensed vaccines
- Correlates of protection
- Determinants of response
  - EED and the role of the microbiota
- Non-living vaccine candidates in development

A correlate of protection is an immune response correlated with protection (from disease or infection)

Antibodies

- Serum
  - Neutralizing
  - Non-neutralizing (e.g. cytotoxic)
  - Functional (e.g. OPA)
  - Avidity
- Mucosal
  - IgA (local)
  - IgG (diffusion from serum)

Cell-mediated

- CD4+
  - B cell help
  - T cell help
  - Help to inflammation (TH17)
  - Lysis
  - Tregs
- CD8+
  - Lysis
  - Avidity

Rotarix and Rotateq immune response by IgA in developed/developing countries

Stratification on <5y mortality	Number of children	IgA seroconversion % with Rotarix	GMT
Low	2287	87 (78, 92)	236 (174, 329)
Medium	1247	74 (61, 84)	101 (66, 157)
High	448	53 (41, 68)	47 (31, 74)

Stratification on <5y mortality	Number of children	IgA seroconversion % with Rotateq	GMT
Low	253	95 (87, 98)	322 (225, 467)
Medium	449	95 (90, 100)	157 (117, 212)
High	358	79 (66, 88)	39 (29, 60)

Patel et al, JID, 2013

Vaccine efficacy based on IgA of 90

Location	u5MR	Vac.	IgA Titer (95% CL)	Vaccine Efficacy over 2 y (95% CL)
IgA titer > 90				
US and Europe	Low	RV5	338 (266–429)	98 (88–100)
Singapore, Taiwan, Hong Kong	Low	RV1	239 (183–310)	97 (88–100)
Japan	Low	RV1	217 (110–122)	92 (62–99)
Europe	Low	RV1	197 (175–222)	90 (85–94)
Vietnam	Med.	RV5	159 (107–235)	64 (8–91)
Latin America	Med.	RV1	103 (86–122)	80 (71–87)
South Africa (3-dose)	High	RV1	94 (56–157)	85 (35–98)
POOLED[a]			**192 (140–228)**	**85 (80–90)**
IgA titer <90				
Malawi (3-dose)	High	RV1	63 (36–109)	42 (9–64)
South Africa (2-dose)	High	RV1	59 (38–94)	32 (–71 to 75)
Malawi (2-dose)	High	RV1	52 (26–102)	34 (– to 58)
Kenya	High	RV5	31 (18–51)	64 (– to 89)
Bangladesh	High	RV5	29 (19–46)	43 (10–64)
Ghana	High	RV5	24 (16–37)	56 (28–73)
POOLED[a]			**41 (25–70)**	**44 (30–55)**

Patel et al, JID 2013

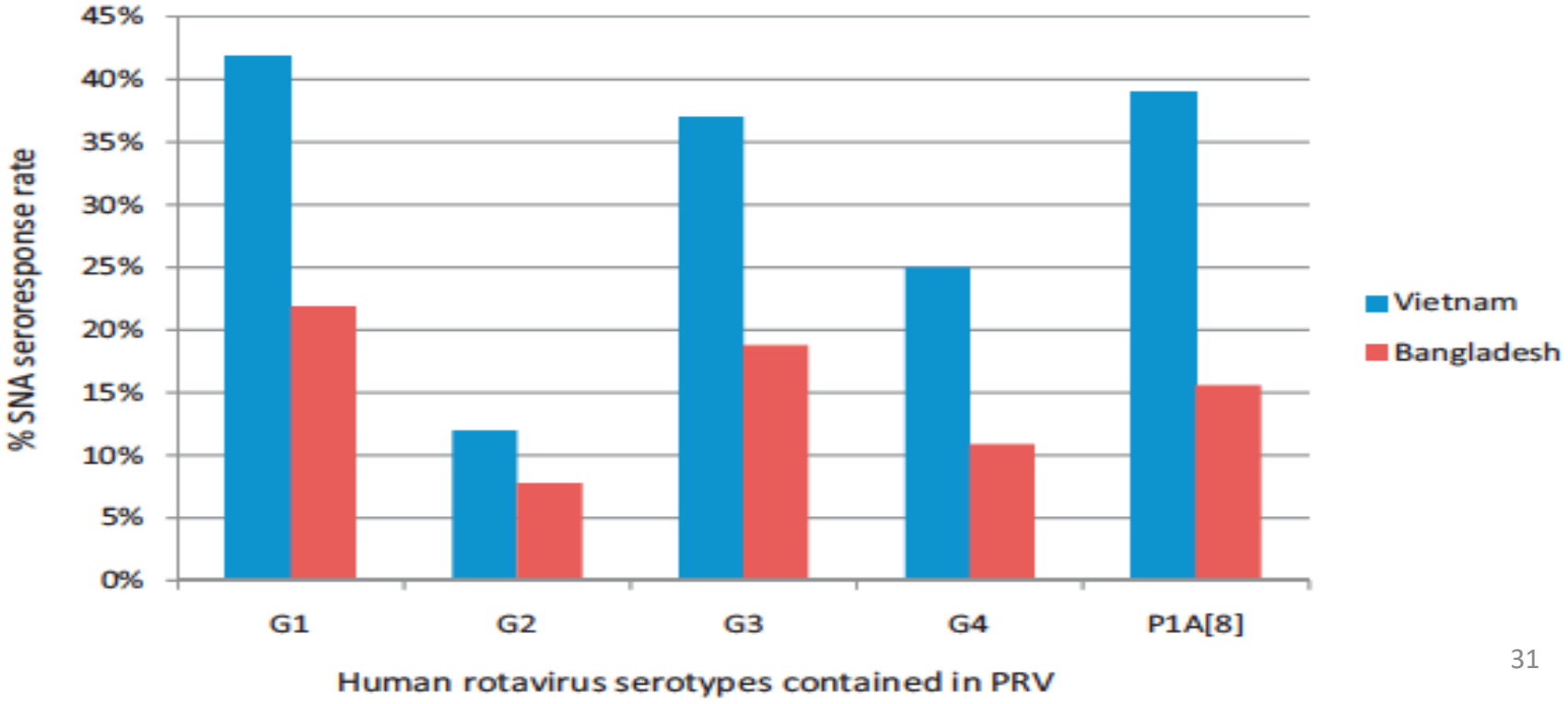
Serum neutralizing antibodies with Rotateq in Asia

Serum neutralizing antibody to	Vaccinee %	Placebo %	Vaccinee GMT	Placebo GMT
G1	32.1	2.3	99.5	19.9
G2	9.9	0.8	23.0	12.5
G3	28.2	3.0	30.8	10.1
G4	18.3	0	51.4	15.1
P8	27.5	5.3	78.9	18.0

Serum IgA responses were seen in 87.8% of vaccinees and 18.2% of controls

Zaman et al, Lancet, 2010

Neutralizing antibodies by country
>3 fold 14 days after 3rd dose



Summary of results of IgA and SNA in infection and vaccination

- No clear evidence that either is a correlate of protection

But the data have not been available for individual level analysis

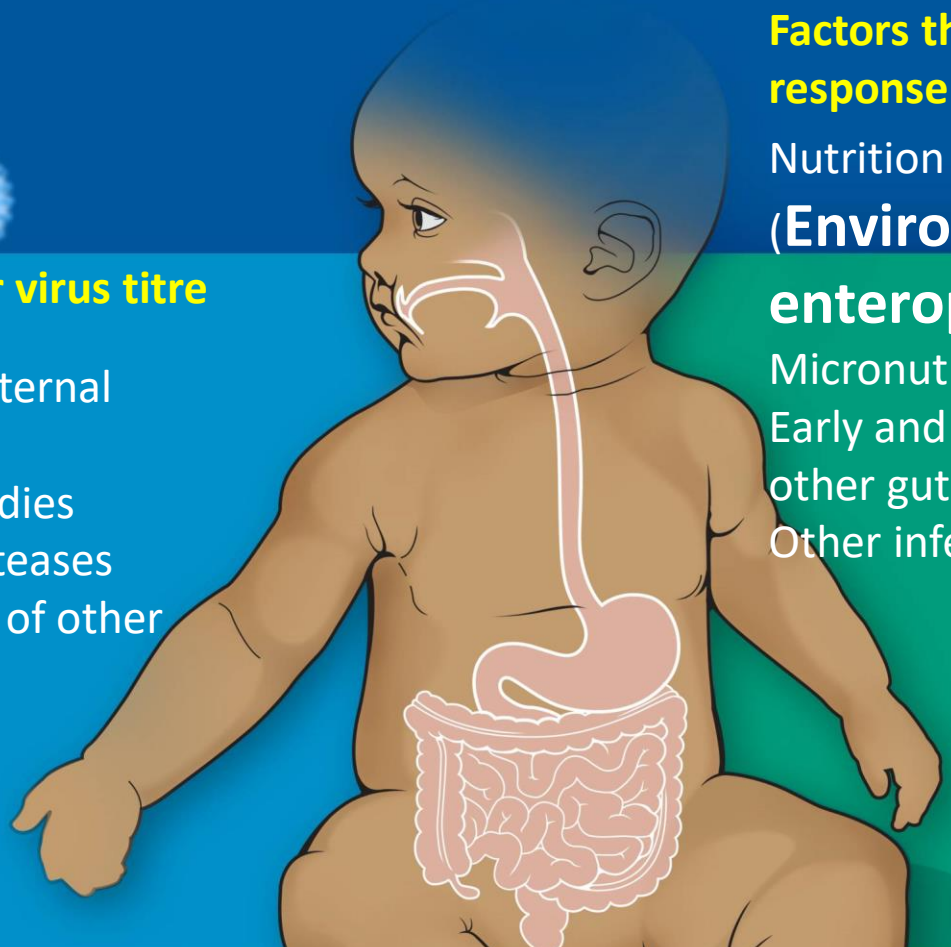
- Other efforts-antibodies to NSP4, VP7, VP5*, VP8*

Outline

- Introduction
- Licensed vaccines and how they work
- Impact of vaccines in LMICs - India and Africa
- Interchangeability of currently licensed vaccines
- Correlates of protection
- Determinants of response
  - EED and the role of the microbiota
- Non-living vaccine candidates in development

Factors that lower virus titre

Transplacental maternal antibodies
Breast milk antibodies
Stomach acid/proteases
Co-administration of other vaccines



Factors that affect antibody response

Nutrition
(**Environmental enteropathy/microbiota)**
Micronutrient deficiency
Early and constant exposure to other gut pathogens
Other infections

Microbiota in Ghana showed differences in responders and non-responders

- Nested, case-control study comparing prevaccination, fecal microbiome compositions between 6-week old, matched 39 RVV responders and 39 nonresponders in rural Ghana and normal Dutch children
- Fecal microbiome analysis using the Human Intestinal Tract Chip showed significant difference between RVV responders and nonresponders (FDR, 0.12)
- RVV response correlated with an increased abundance of *Streptococcus bovis* and a decreased abundance of the Bacteroidetes phylum

Genus-like groups	Correlation with IgA	p.adj
Prevotella oralis et rel.	-0.435	0.007
Prevotella melaninogenica et rel.	-0.425	0.007
Bacteroides splachnicus et rel.	-0.398	0.011
Bacteroides ovatus et rel.	-0.394	0.011
Bacteroides stercoris et rel.	-0.387	0.011
Oscillospira guillermondii et rel.	-0.378	0.012
Prevotella ruminicola et rel.	-0.371	0.013
Bacteroides uniformis et rel.	-0.369	0.013
Bilophila et rel.	-0.365	0.013
Allistipes et rel.	-0.360	0.014
Methylobacterium	-0.344	0.022
Leminorella	-0.335	0.027
Tannerella et rel.	-0.332	0.028
Bacteroides fragilis et rel.	-0.327	0.028
Uncultured Clostridiales I	-0.327	0.028
Bacteroides intestinalis et rel.	-0.325	0.028
Aeromonas	-0.324	0.028
Peptostreptococcus micros et rel.	-0.317	0.032
Megasphaera elsdenii et rel.	-0.316	0.032
Uncultured Mollicutes	-0.311	0.032
Brachyspira	-0.310	0.032
Ruminococcus obeum et rel.	-0.310	0.032
Clostridium symbiosum et rel.	-0.309	0.032
Bacteroides plebeius et rel.	-0.308	0.032
Dialister	-0.302	0.036
Prevotella tannerae et rel.	-0.300	0.036
Asteroleplasma et rel.	-0.297	0.037
Mitsuokella multiacida et rel.	-0.296	0.037
Campylobacter	-0.296	0.037
Lactobacillus catenaformis et rel.	-0.295	0.037
Helicobacter	-0.292	0.039
Clostridium orbiscindens et rel.	-0.288	0.040
Coprobacillus catenaformis et rel.	-0.287	0.040
Desulfovibrio et rel.	-0.286	0.040
Uncultured Selenomonadaceae	-0.284	0.040
Phascolarctobacterium faecium et rel	-0.284	0.040
Gemella	-0.283	0.040
Outgrouping clostridium cluster XIVa	-0.282	0.041
Uncultured Bacteroidetes	-0.277	0.045
Bacteroides vulgatus et rel.	-0.275	0.046
Megamonas hypermegale et rel.	-0.274	0.046
Eubacterium ventriosum et rel.	-0.270	0.049
Bryantella formatexigens et rel.	0.291	0.039
Streptococcus bovis et rel.	0.385	0.011

Harris et al, JID, 2017

Microbiota in Pakistan

- 10 responders and 10 non-responders
- RV1 response correlated with a higher relative abundance of bacteria belonging to *Clostridium* cluster XI and Proteobacteria, including bacteria related to *Serratia* and *Escherichia coli*.

Harris et al, Gut Microbe 2017

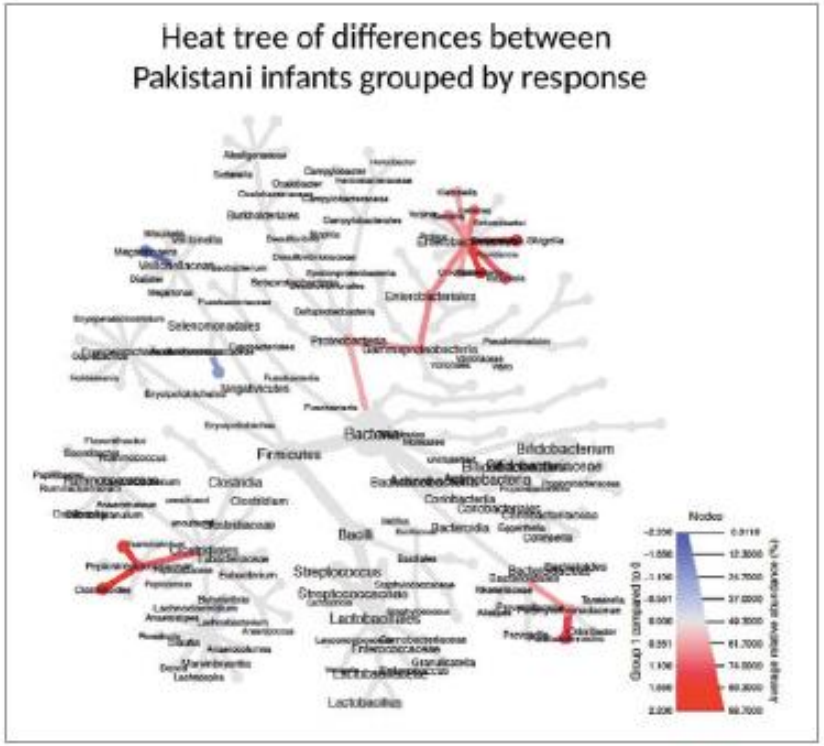
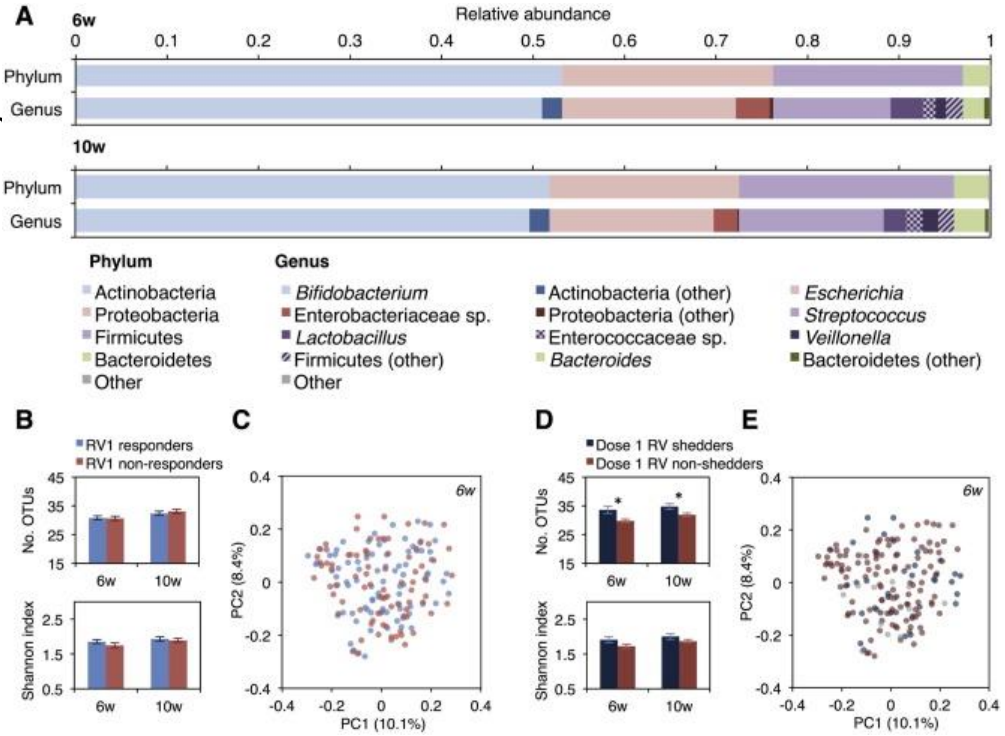


Figure 2. Phylogenetic Heat Tree illustrates the differences in relative bacterial abundance between Pakistani non-responders and responder infants. Colored blue are bacteria where a lower abundance associates with RVV response and colored red are bacterial groups where a higher abundance correlates with RW response.

But not seen in India

- No significant differences in microbiota diversity or stability or taxon relative abundance according to seroconversion status
- Infants who shed rotavirus after the 6-week RV1 dose had more OTUs before vaccination (P=0.007) but this explained a small proportion of the variance
- Random Forest models based on OTU abundance data did not accurately predict rotavirus seroconversion but showed modest predictive accuracy for shedding after dose 1 (mean accuracy 60.3% and 60.8% based on OTUs measured at 6 and 10 weeks, respectively; baseline accuracy, 50.0%; *P* = .038 and .040)



Parker et al, Vaccine 2018

Outline

- Introduction
- Licensed vaccines and how they work
- Impact of vaccines in LMICs - India and Africa
- Interchangeability of currently licensed vaccines
- Correlates of protection
- Determinants of response
  - EED and the role of the microbiota
- Non-living vaccine candidates in development

New non-replicating vaccines

- Triple- and double- layered virus-like particles (VLPs)-Baylor and others
- Inactivated rotavirus particles-CDC (with SII)
- Recombinant subunit proteins
  - PATH using VP8 subunit expressed in *E. coli* as a chimeric protein vaccine in which the VP8 is fused to the tetanus toxin P2 epitope
  - Phase 1 trial in adults and toddlers demonstrated to be safe and well tolerated and elicited significant neutralizing antibody responses
  - Phase 1/2 trial of a trivalent P2-VP8 (P[4], P[6], and P[8]) subunit vaccine is completed at three sites in South Africa

Summary

- Rotavirus vaccines are in use in about half the countries in the world
- Where they are introduced, impact is measurable
- The vaccines are interchangeable based on immunogenicity and this is likely to translate to efficacy
- A correlate of protection is as yet not defined, but new vaccine studies offer opportunities for exploration
- The gut environment influences response to oral rotavirus vaccines
- Once we know what to do we might be able to design interventions to improve oral vaccine performance
- Or we might have new non-living vaccines that have better performance in all settings
- Plenty done, and plenty to do!