XI International Symposium for Latin American experts

Enteric vaccines
Progress and challenges

VACCINOLOGY 2018

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Disclosures

- Speaker at sponsored training sessions/meetings for healthcare workers
  - MSD
- Sponsored attendance to scientific conferences
  - Pfizer

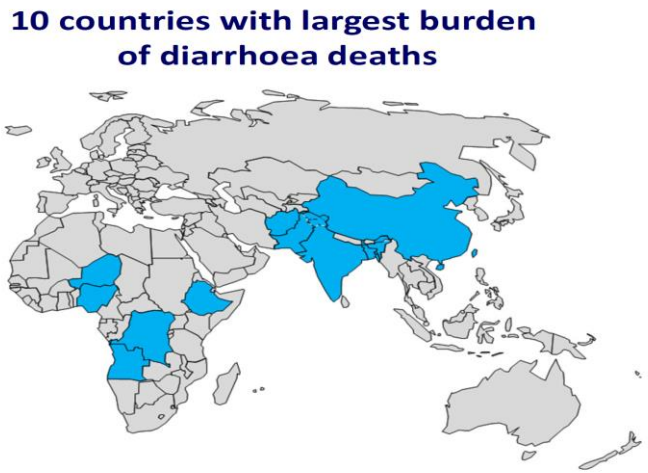
Outline

- Epidemiology of enteric pathogens
- Vaccine research and development
- Lessons learned from real experiences with enteric vaccines
- Challenges and gaps for enteropathogen vaccines
- Conclusions

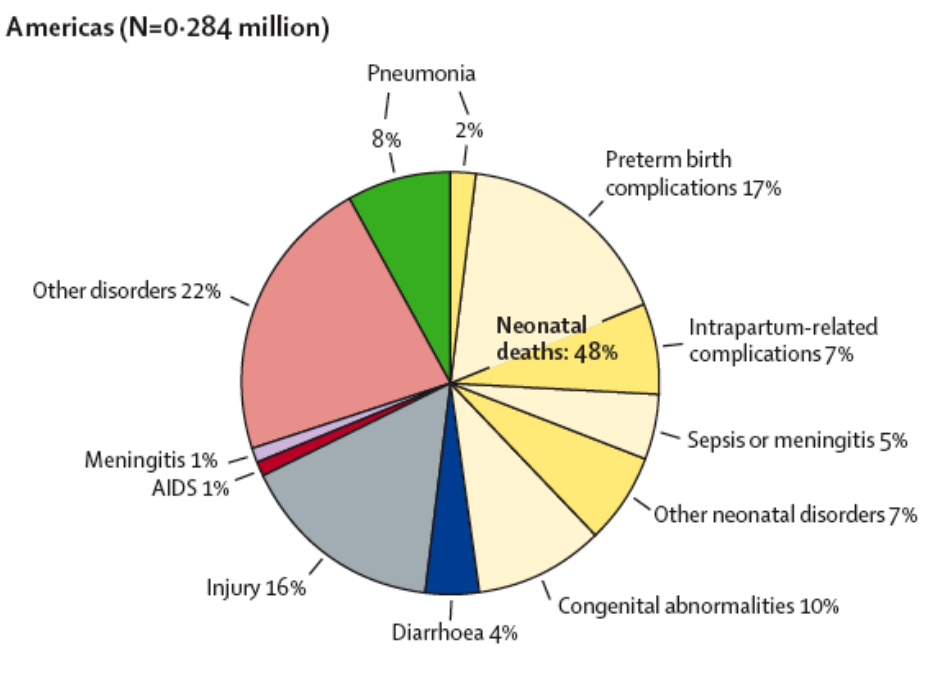
Global threat of AGE

Enteric pathogens: a threat to public health

- >1 million deaths per year to diarrhea across all age groups
- 760,000 diarrhoea deaths annually in children <5 yoa
- Focus in less developed countries
- 4% of total global DALYS



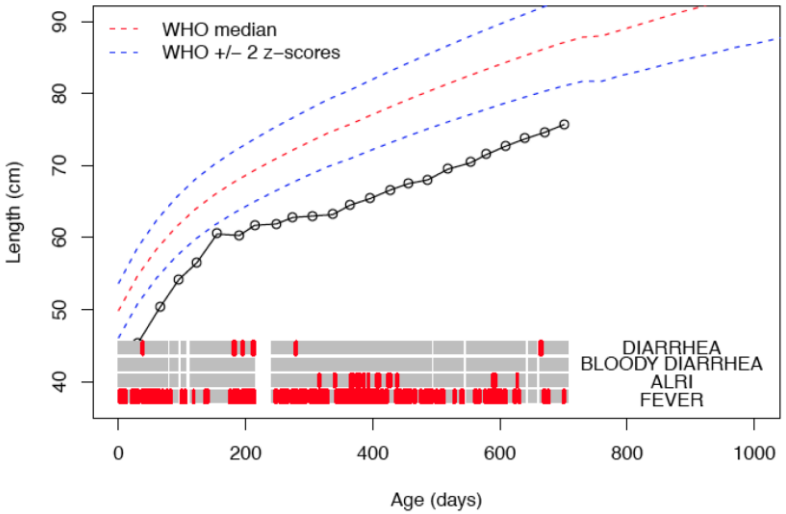
- 64% of global diarrheal deaths

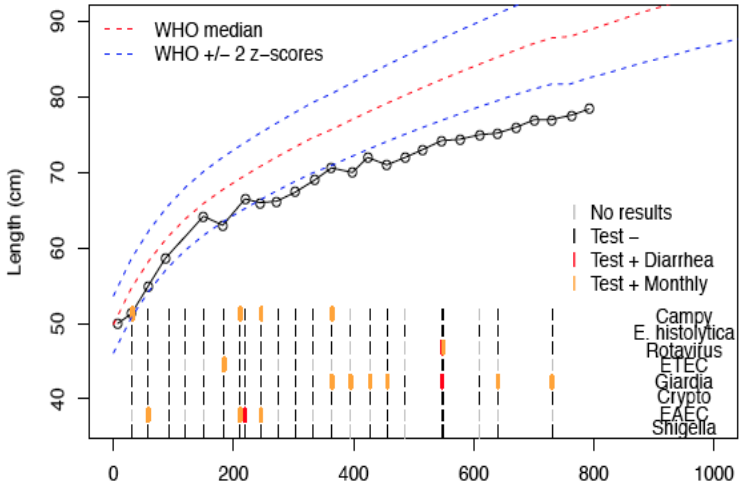


Despite reductions in mortality, diarrhoeal morbidity remains high, and the condition remains a major burden in LMICs

Liu L et al, Lancet. 2012 Jun 9;379(9832):2151-61, Hosangadi D, et al Vaccine. 2017 Oct 11

Non-severe diarrhoeal episodes are of public health importance



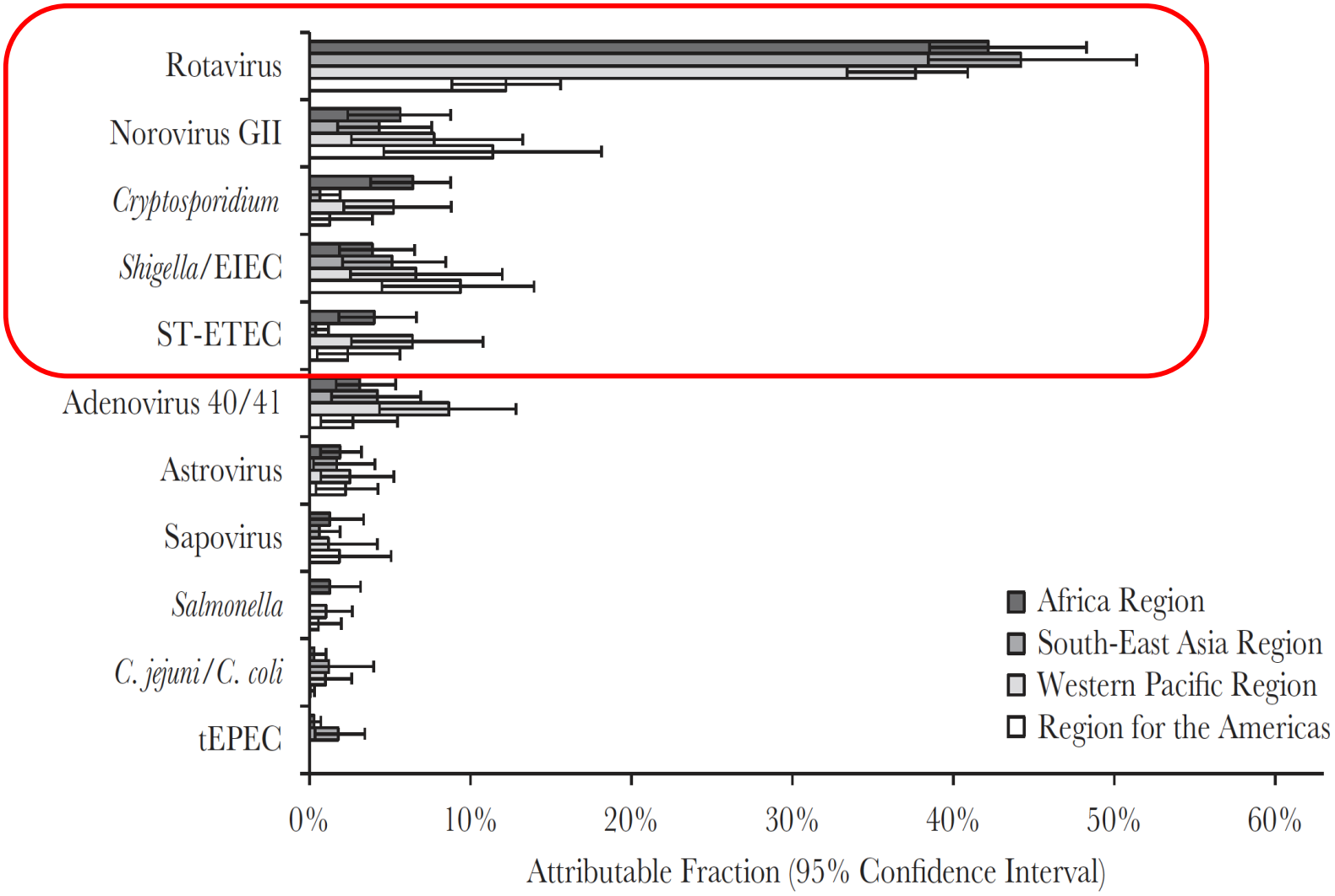


- Repeated enteric infections ➔ long term sequelae and diseases
  - poor growth, impaired cognitive development, enteropathy
- Antibiotic resistance development
- Post-acute illness mortality and growth impairment

- Brazilian cohorts in 4–10y FU
  - Correlation among burden of diarrhoea and impairment of:
    - Visual-motor coordination
    - Hearing short-term memory and information processing
    - Lower scores on the Test of Non-Verbal Intelligence-III and the Wechsler Intelligence Scale for Children

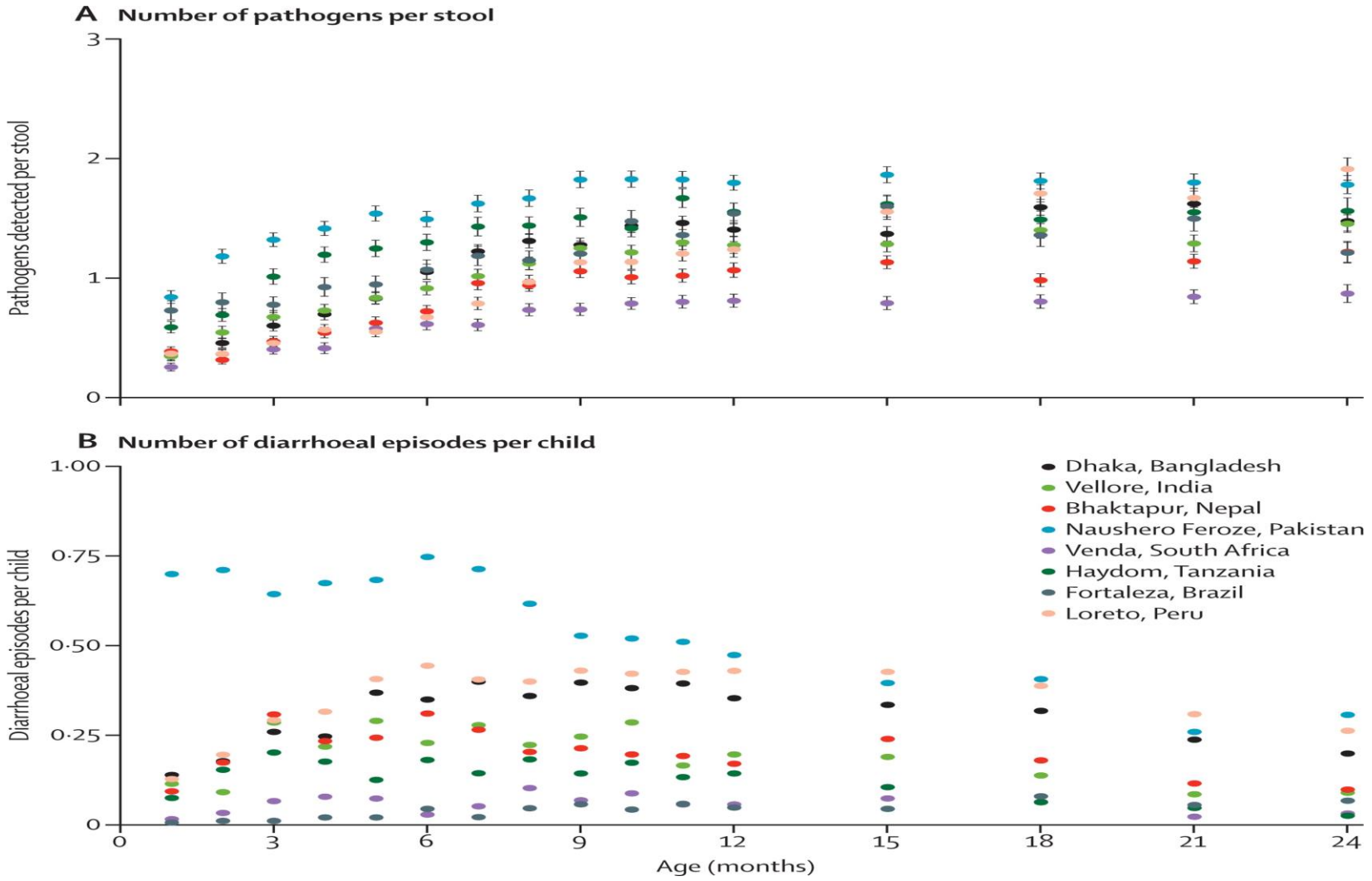
Checkley W, et al. Int J Epidemiol 2008; 37: 816–830; Hosangadi D, et al Vaccine. 2017 Oct 11; Platts-Mills J, et al Lancet Glob Health 2015; 3: e564–75

Etiology of acute watery diarrhea remains poorly characterized



Operario D., et al JID 2017;216:220–7

Incidence of diarrhoea and number of pathogens per stool increase during the first year of life



Platts-Mills J., et al The Lancet Global Health, Vol 3, Issue 9, 2015 Pages e564-e575

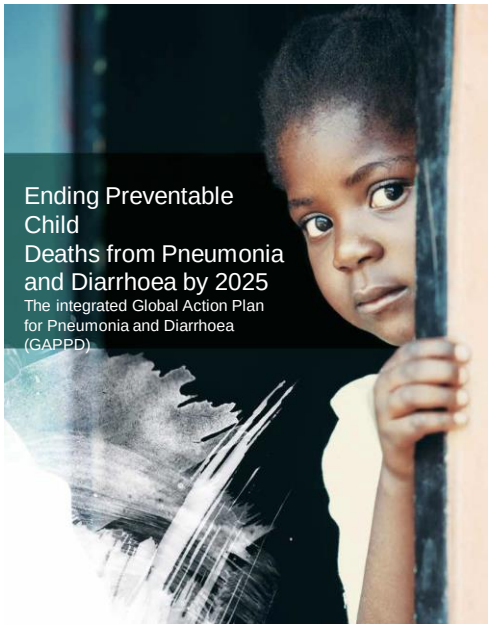
Prevention strategies: progress on enteric vaccines

Goals for 2025

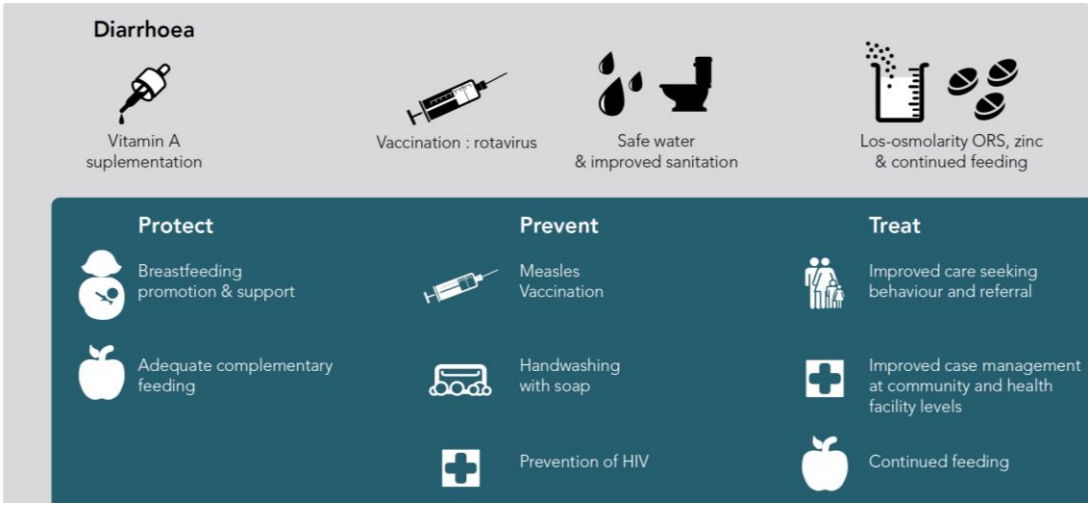
Integrated Global Action Plan for Pneumonia and Diarrhoea

For children under 5 years of age

- Reduce mortality from diarrhoea to <1/1,000 LB
- Reduce the incidence of severe diarrhoea by 75% compared to 2010 levels
- Reduce by 40% the global number who are stunted compared to 2010 levels



unicef World Health Organization



Main policies to address

(a) improved water and sanitation

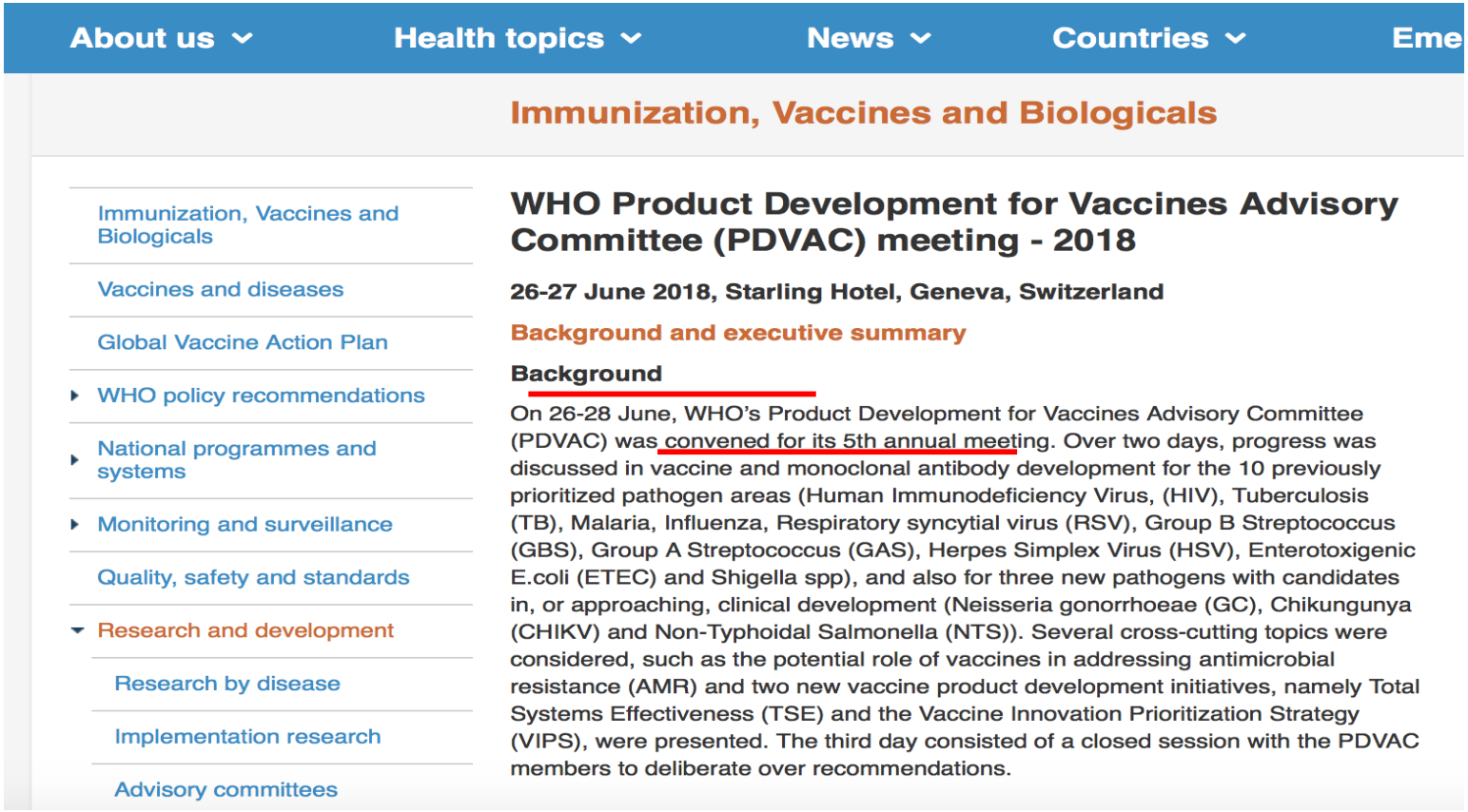
(b) vaccination

http://apps.who.int/iris/bitstream/handle/10665/79200/9789241505239_eng.pdf;jsessionid=BA1E573E6443973399B2337164A40F65?sequence=1

WHO Product Development for Vaccines Advisory Committee (PDVAC)

5th version

Vaccines for enteric pathogens



http://www.who.int/immunization/research/meetings_workshops/PDVAC_executive_summary_june_2018.pdf?ua=1

Shigella vaccine

- Pipeline: oral and parenteral
- Advanced candidates elicit responses to the Shigella O-antigen and have data from phase II in CHIM
- In May 2018, WHO convened a workshop to evaluate the role of CHIMs in the pathway to licensure and policy recommendation
  - Travelers' vaccine approach
  - Pathway for policy recommendation LMICs will require demonstration of safety and efficacy in young children

http://www.who.int/immunization/research/meetings_workshops/PDVAC_executive_summary_june_2018.pdf?ua=1

Enterotoxigenic E. coli vaccine

- ETVAX: oral, whole cell formalin- inactivated
  - 5 to 10 years from licensure
  - Phase 2b efficacy study in adult travellers
  - Safety and immunogenicity in cohorts aged 6–11 months
  - Focus expecting to reduce severe diarrhoea ➔ ETEC, severity scores

- TSWC: trivalent vaccine
  - Includes formalin-killed *Shigella flexneri* 2a and 3a and *Shigella sonnei*

Hosangadi D, et al Vaccine. 2017 Oct 11, Fleckenstein FM, JID 2017:216, July
http://www.who.int/immunization/research/meetings_workshops/PDVAC_executive_summary_june_2018.pdf?ua=1,

Typhoid/NTS vaccine

Table 1 **Characteristics of different typhoid vaccines**[15, 36]
Tableau 1 **Caractéristiques des différents vaccins antityphoïdiques**[15, 36]

	Typhoid conjugate vaccine (Typbar-TCV®) – Vaccin antityphoïdique conjugué (Typbar-TCV®)	**Unconjugated Vi polysaccharide vaccine – Vaccin polyosidique Vi non conjugué**	**Live attenuated Ty21a vaccine – Vaccin vivant atténué Ty21a**
Composition	25 µg of purified Vi capsular polysaccharide conjugated to TT – 25 µg de polyoside capsulaire Vi purifié, conjugué à l'anatoxine tétanique	25 µg of purified Vi capsular polysaccharide – 25 µg de polyoside capsulaire Vi purifié	2 to 6 × 109 CFU of Ty21a (attenuated Ty2 strain of *S.* Typhi) – 2 à 6 × 109 UFC de Ty21a (souche Ty2 atténuée de *S.* Typhi)
Route, dose – Voie d'administration, posologie	IM, 1 dose – Intramusculaire, 1 dose	IM/SC, 1 dose – Intramusculaire/sous-cutanée, 1 dose	Oral, 3 (4 in USA and Canada) doses every second (alternate) day – Orale, 3 doses (4 aux États-Unis d'Amérique et au Canada) administrées 1 jour sur 2
Presentation – Présentation	Liquid – Liquide	Liquid – Liquide	Enteric- coated capsules – Gélules gastrorésistantes
Recommended target age for vaccination – Âge cible recommandé pour la vaccination	Adults and children ≥6 months to ≤45 years of age – Adultes et enfants âgés de ≥6 mois à ≤45 ans	Adults and children ≥2 years of age – Adultes et enfants âgés de ≥2 ans	Adults and children older than 6 years – Adultes et enfants de plus de 6 ans

- **NTS Vaccines**: trivalent vaccine will be needed
- 2 candidates are expected to enter phase 1 studies
- Combination with the licensed typhoid vaccine ?

http://www.who.int/immunization/research/meetings_workshops/PDVAC_executive_summary_june_2018.pdf?ua=1

Cholera vaccine

Generic name – Dénomination commune	WC-rBS – WC-rBS	Modified bivalent WC – WC bivalent modifié
Trade name – Nom commercial	Dukoral® (first licensed in Sweden) – Dukoral® (première homologation en Suède)	mORCVAX™ (licensed in Viet Nam), Shanchol™ (licensed in India), Euvichol® (licensed in the Republic of Korea) – mORCVAX™ (homologué au Viet Nam), Shanchol™ (homologué en Inde), Euvichol® (homologué en République de Corée)
Target – Cible	O1 (Classical, El Tor – Ogawa and Inaba) Cholera toxin B subunit – O1 (classique, El Tor – Ogawa et Inaba) Sous-unité B de la toxine cholérique	O1 (Classical, El Tor – Ogawa and Inaba), and O139 No cholera toxin subunit – O1 (classique, El Tor – Ogawa et Inaba) et O139 Pas de sous-unité de la toxine cholérique
Regimen – Schéma vaccinal	2 doses given 1–6 weeks apart – 2 doses espacées de 1 à 6 semaines 3 doses for children aged 2–5 years – 3 doses pour les enfants âgés de 2 à 5 ans	2 doses given 14 days apart – 2 doses espacées de 14 jours
Age recommended for vaccination – Âge recommandé pour la vaccination	≥2 years – ≥2 ans	mORCVAX™: ≥1 year – mORCVAX™: ≥1 an Others: ≥1 year – Autres: ≥1 an

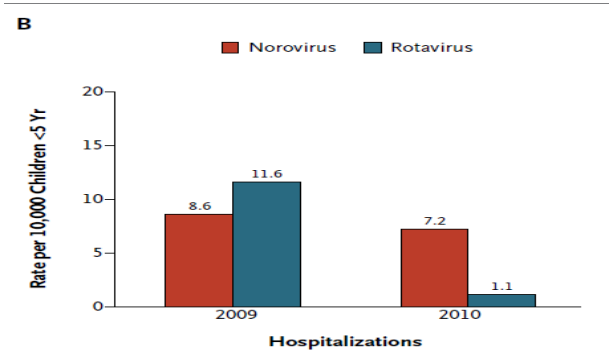
- Vaccines should be used in areas with endemic cholera, in humanitarian crises with high risk of cholera, and during cholera outbreaks
- Encouraging development of improved new generation OCVs
  - higher efficacy in children, longer duration of protection, easy-to-deliver presentations

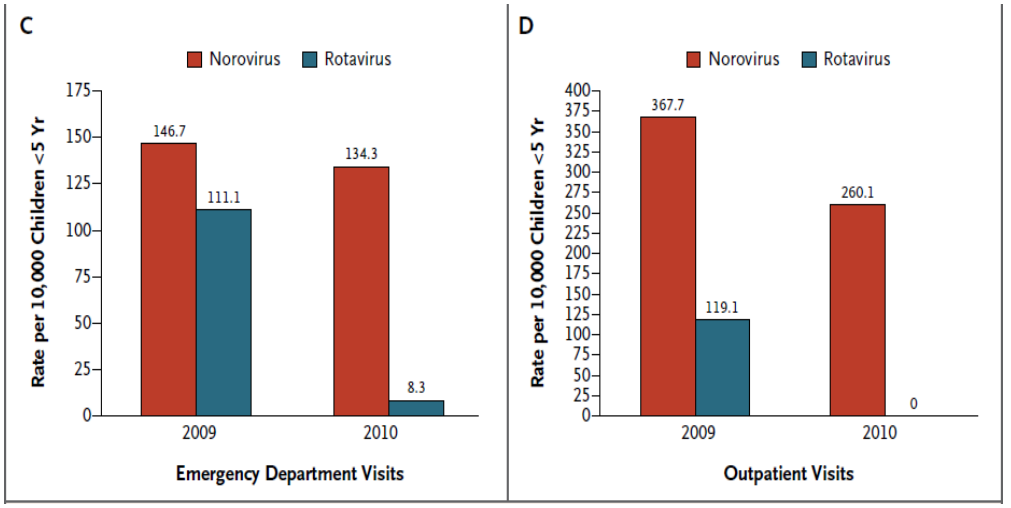
Weekly epidemiological record, no 34, 92, 477–500, 25 august 2017

Norovirus

Rotavirus vaccine deployment implication: an emergent new leader– *Norovirus*

United States





ORIGINAL STUDIES

Norovirus in Latin America

Systematic Review and Meta-analysis

Miguel O'Ryan, MD, Margarita Riera-Montes, MD, MSc,† and Benjamin Lopman, PhD‡*

Location	Number of Studies: Total	Pre-RV Vaccine	Post-RV Vaccine	Mean Prevalence (95% CI): All	Pre-RV Vaccine	Post-RV Vaccine
Overall	29	21	8	15% (13–18)	15% (12–19)	16% (12–22)
Community	8	3	5	15% (11–21)	11% (4–21)	18% (14–23)
Outpatient	7	6	1	14% (10–19)	13% (9–17)	21% (15–27)
Hospital	19	16	3	16% (12–21)	17% (12–22)	13% (4–26)

- Epidemiology of NoV is similar to rotavirus
- Prior infection plays a protective role against later infections

Payne D. N Eng J Med 2013; 368:1121-30; O'Ryan M., Pediatr Infect Dis J. 2017 Feb;36(2):127-134

Norovirus vaccine development process

- Phase IIb/III clinical studies in adults and paediatrics
  - Clinical proof of concept demonstrated in a human challenge model
  - Infants: similar to the rotavirus vaccine
    - Primarily protect against more severe infections
  - Adults specific target groups
    - Military personnel, individuals in confinement, general travelers and the elderly
- Bivalent candidate vaccine: GI.1 + GII.4
- Candidate should be able to protect against any emerging genotypes
- VLPs designed approach ➔ cross-protection
  - 25 human genotypes

B.K. Giersing et al. Vaccine 34 (2016) 2865–2869; Lucero Y., et al. Vaccine 36 (2018) 5435–5441

Pathway to norovirus vaccine

Human vaccine candidates against norovirus.

Antigens in the vaccine	Stage of development	Comments
Norovirus VLPs GI.1 and GII.4	Clinical: Phase I and II in adults completed, advancing to phase III trials in adults and children	Baculovirus expression system of VLPs. First delivered by intranasal route, and currently developed for intramuscular administration
Norovirus VLPs GI.1, GI.3, GII.4 and GII.12	Pre-clinical: *in vitro* and BALB/c mouse model	Baculovirus expression system, intramuscular administration. Triggers serum HBGA blocking antibodies
Norovirus VLPs GI.3 and GII.4 and Rotavirus rVP6	Pre-clinical: Immunogenic in BALB/c mouse model	Baculovirus expression system, intramuscular administration. Norovirus VLPs associated with rVP6 rotavirus nanotubes elicited higher titers of anti-Norovirus antibodies with higher blocking activity against binding to HBGAs than free VLPs alone
Norovirus VLPs GII.4 and Enterovirus 71	Pre-clinical: Immunogenic in BALB/c mouse model	Baculovirus expression system, intraperitoneal administration. Elicits production of HBGA blocking antibodies against GII.4 Norovirus and neutralizing antibodies against Enterovirus 71
Norovirus P-particles	Pre-clinical: Immunogenic in BALB/c mouse model and gnotobiotic pigs	High expression yield in *E. coli* system. Intranasal administration
Norovirus GII.4 P-particle enhanced by adjuvant FlaB	Pre-clinical: Immunogenic in BALB/c mice model	Expression in *E. coli* system. Administered by intranasal and sublingual route. Higher levels of response by intranasal administration. FlaB induces systemic and mucosal Th1 and Th2 responses
Norovirus, Hepatitis E and Astrovirus P-particles	Pre-clinical: Immunogenic in a BALB/c mouse model	Expression of recombinant fusion protein including P domain of the 3 viruses. Intranasal administration. Elicits a significant increase in titers of antibodies against the 3 viruses. High blocking activity against Norovirus binding to HBGAs
Virus replicon particles including Norovirus P domain	Pre-clinical: Replication *in vitro* model and immunogenic in BALB/c mouse model	Replication in eukaryotic cell lines and inoculation in mice by intranasal administration. Elicits a Th1 predominant response. Higher levels of seric IgG than Baculovirus expressed VLPs

Lucero Y., et al. Vaccine 36 (2018) 5435–5441

Rotavirus

Rotavirus vaccines

	Internationally-available	
Name	Rotarix	RotaTeq
Manufacturer, country	GlaxoSmithKline Biologicals, Belgium	Merck, USA
Strain(s) present in vaccine	Attenuated human G1P[8] strain	Human-bovine reassortant strain with G1, G2, G3, G4, and P[8] proteins
Presentation	1. Liquid vaccine in oral, single-dose applicator 2. Liquid vaccine in squeezable, polyethylene single-dose tube 3. Lyophilized vaccine, reconstituted with calcium carbonate buffer and oral applicator	Liquid vaccine in oral, squeezable tube
Vaccine vial monitor (VVM) on label[15]	Yes, VVM 14	None
Storage requirements	2 to 8° C, not frozen and protected from light	2 to 8° C, not frozen and protected from light
Route of administration	Oral	Oral
Number of doses and schedule of administration	Two doses, given on same schedule as DPT vaccine	Three doses, given on same schedule as DPT vaccine
Vaccine efficacy (95% CI) against severe rotavirus gastroenteritis during the first year, developing country study location	61% (44 to 73%), South Africa and Malawi[33]	59% (40 to 72%), Ghana, Kenya, Mali, Bangladesh and Vietnam[34]
Licensure and WHO prequalification[15]	Internationally licensed, Prequalified in 2007	Internationally licensed, Prequalified in 2008
Price per vaccination course	From approximately US$0.50 in GAVI-eligible countries up to US$185–$226 in the USA[1]	

Deen J., et al Human vaccines & immunotherapeutics 2018, Vol. 14, No. 2, 495–499

Rotavirus vaccines

	Licensed for national markets			
Name	Rotavac	Rotasiil	LLR	Rotavin-M1
Manufacturer, country	Bharat Biotech International Limited, India	Serum Institute of India Limited, India	Lanzhou Institute of Biological Products, China	Center for Research and Production of Vaccines, Vietnam
Strain(s) present in vaccine	Human G9, P[11] strain	Human-bovine reassortant pentavalent (G1-G4, G9) strain	Lamb G10P[12] strain	Human G1P[8] strain
Presentation	Liquid vaccine in single- and multi-dose vial. Liquid antacid buffer given before the vaccine	Lyophilized vaccine, reconstituted with calcium carbonate buffer	Liquid vaccine with buffer	Liquid vaccine in single-dose vial.
Vaccine vial monitor (VVM) on label[15]	Yes, VVM 2	Yes, VVM 30	None	None
Storage requirements	Frozen at $-20^{\circ}C \pm 5^{\circ}C$	Stable at $37^{\circ}C$ for two years and $40^{\circ}C$ for six months	2 to $8^{\circ}C$	Frozen at $-20^{\circ}C \pm 5^{\circ}C$
Route of administration	Oral	Oral	Oral	Oral
Number of doses and schedule of administration	Three doses, four weeks apart, beginning at 6 weeks of age	Three doses, four weeks apart, beginning at 6–8 weeks of age	One dose every year for three years between 2 and 35 months of age	The first dose from 6 weeks of age. The second dose after 1–2 months. Should be given before 6 months of age.
Vaccine efficacy (95% CI) against severe rotavirus gastroenteritis during the first year, developing country study location	56% (37 to 70%) Delhi, Pune and Vellore[16]	67% (50–78%), Niger[18]	Not available	Not available
Licensure and WHO prequalification[15]	Licensed in India	Licensed in India	Licensed in China	Licensed in Vietnam
Price per vaccination course	US$ 2.50[2]	US$ 6.00 maximim[3]	US$ 24.00[4]	US$ 17.60[5]

Deen J., et al Human vaccines & immunotherapeutics 2018, Vol. 14, No. 2, 495–499

RV1 and RV5 post marketing studies

Table 2. Risk–benefit estimates of rotavirus disease and intussusception outcomes by country†.

Country	Outcome	Rotavirus outcomes averted	Intussusception outcomes caused	Rotavirus outcome averted: intussusception outcome caused	Ref.
Mexico	Hospitalizations	11,551	41	282:1	[24]
RV1	Deaths	663	2	331:1	
Brazil	Hospitalizations	69,572	55	1265:1	[24]
RV1	Deaths	640	3	213:1	
Australia	Hospitalizations	6528	14	466:1	[27]
RV1 & RV5	Deaths	NR	NR	NR	
USA	Hospitalizations	53,444	35–166	322–1530:1	[52]
RV1 & RV5	Deaths	14	0.1–0.5	28–134:1	

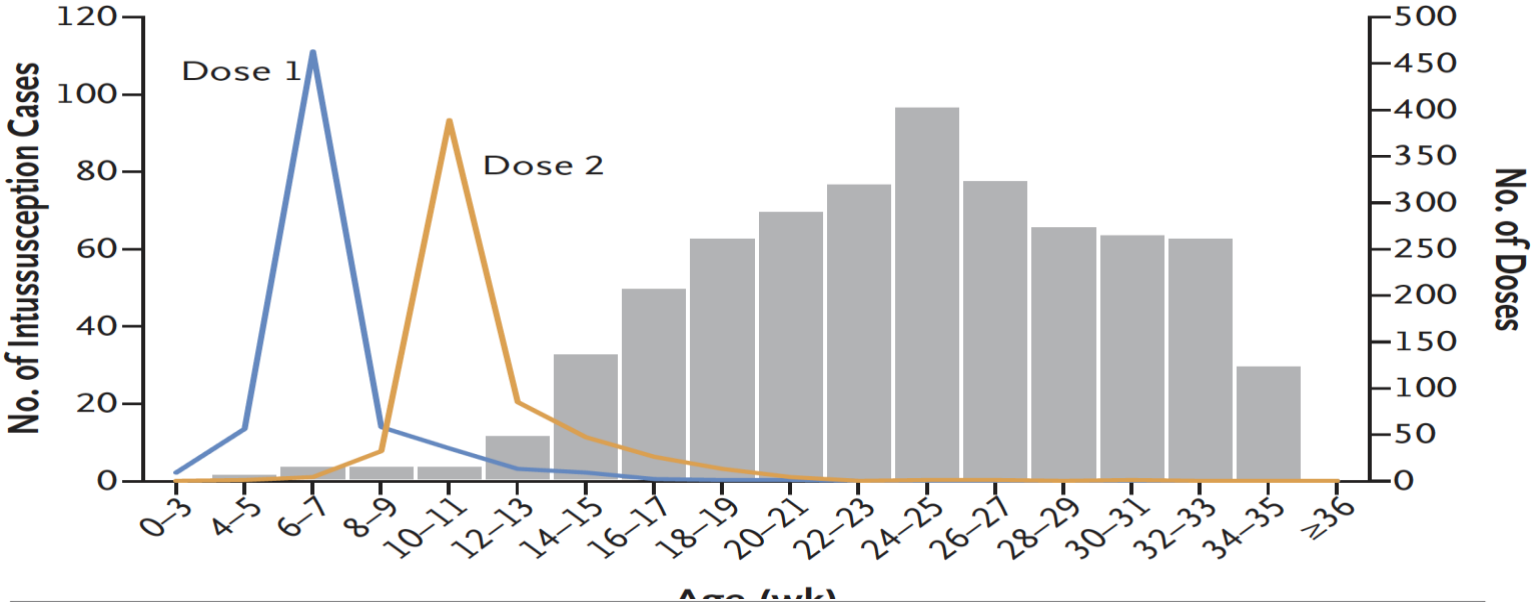
†Estimates based on one vaccinated birth cohort to age 5 years.
NR: Not reported.

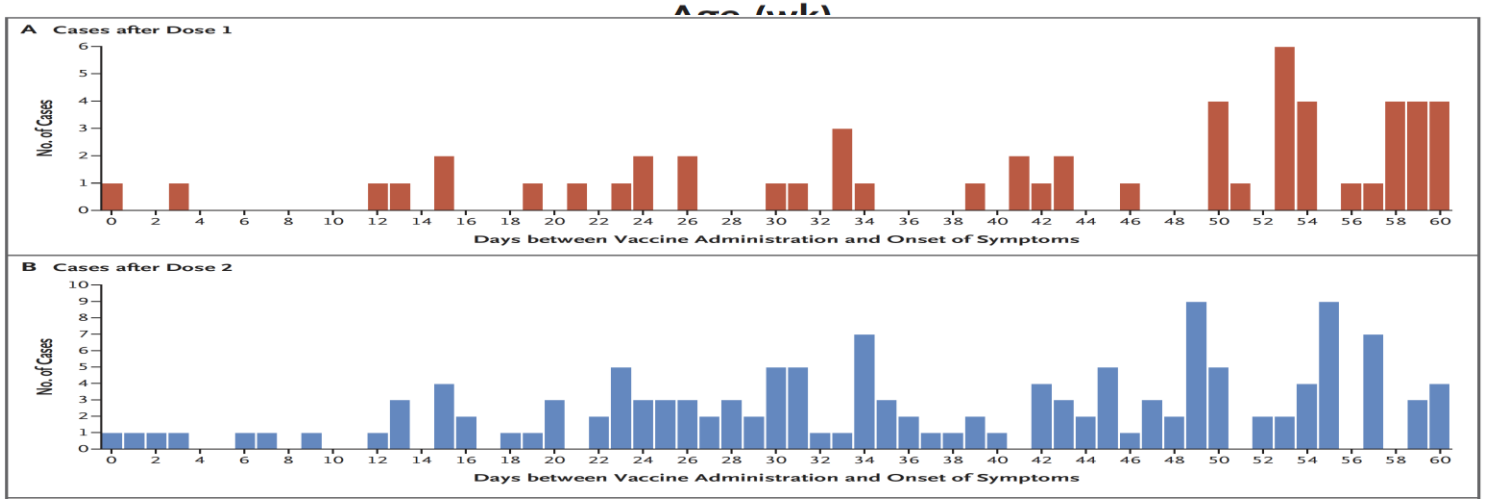
Vaccines are safe (9 years experience)

1- 6 additional cases per 100,000 doses of vaccines

Expert Rev. Vaccines 13(11), 1339–1348 (2014)

African Intussusception Surveillance Network





Tate JE, et al N Engl J Med 2018;378:1521-8

Risk of intussusception after RV1 not higher than background risk in LIC

Table 2. Relative Incidence of Intussusception in the Risk Periods after the First and Second Doses of Monovalent Rotavirus Vaccine, February 2012 through December 2016.

Dose and Risk Period	No. of Cases	Relative Incidence (95% CI)*
Dose 1		
Days 1–7	1	0.25 (<0.001–1.16)
Days 8–21	6	1.01 (0.26–2.24)
Days 1–21	7	0.85 (0.35–1.73)
Dose 2		
Days 1–7	5	0.76 (0.16–1.87)
Days 8–21	16	0.74 (0.39–1.20)
Days 1–21	21	0.81 (0.49–1.22)

- 29 African countries had introduced RV by 2014,
- Preventing in 2017
  - 135,000 hospitalizations
  - 21,000 deaths

- Large health benefits in the absence of increased risk of intussusception after RV1 administration

Tate JE, et al N Engl J Med 2018;378:1521-8

Vaccine impact in the US

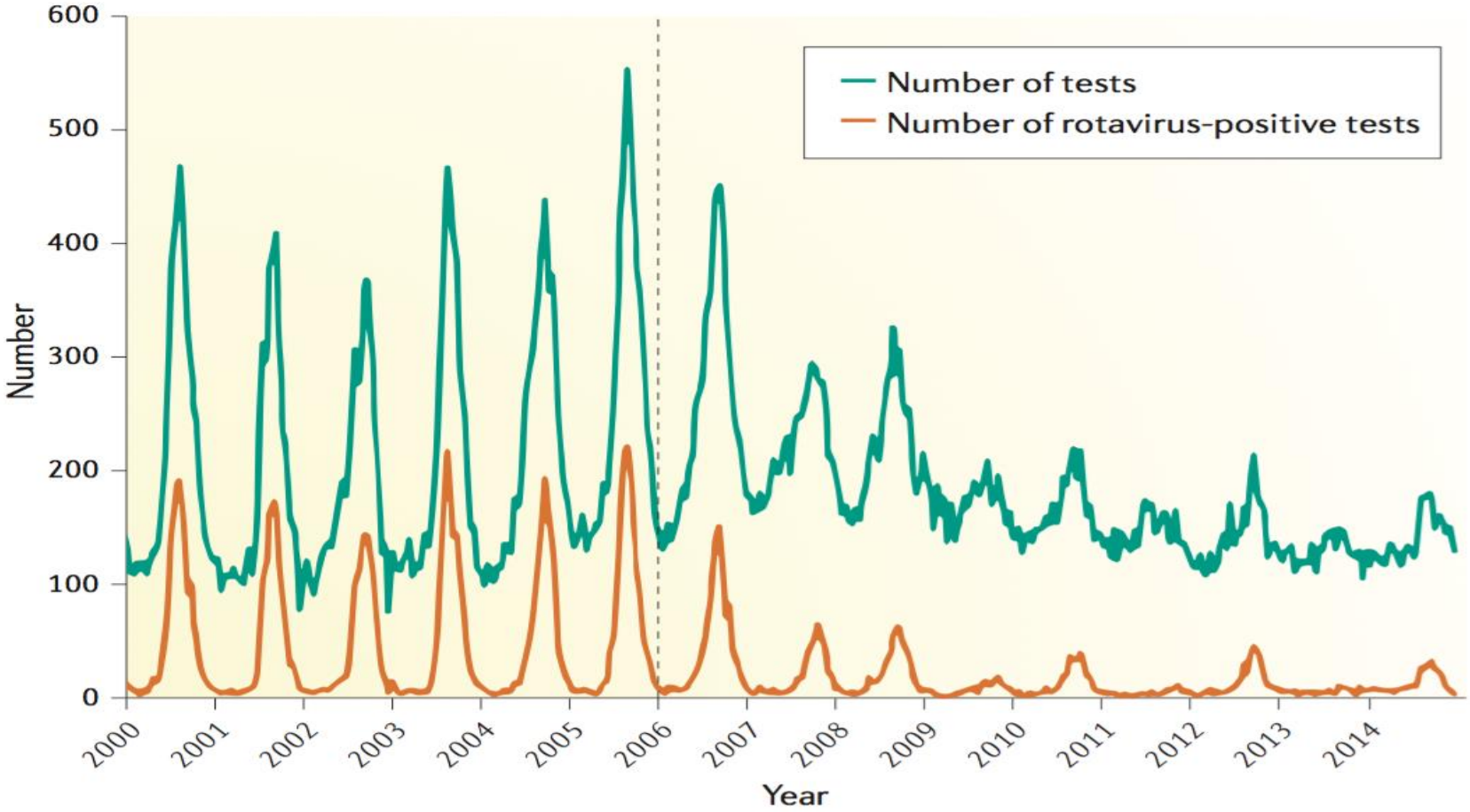
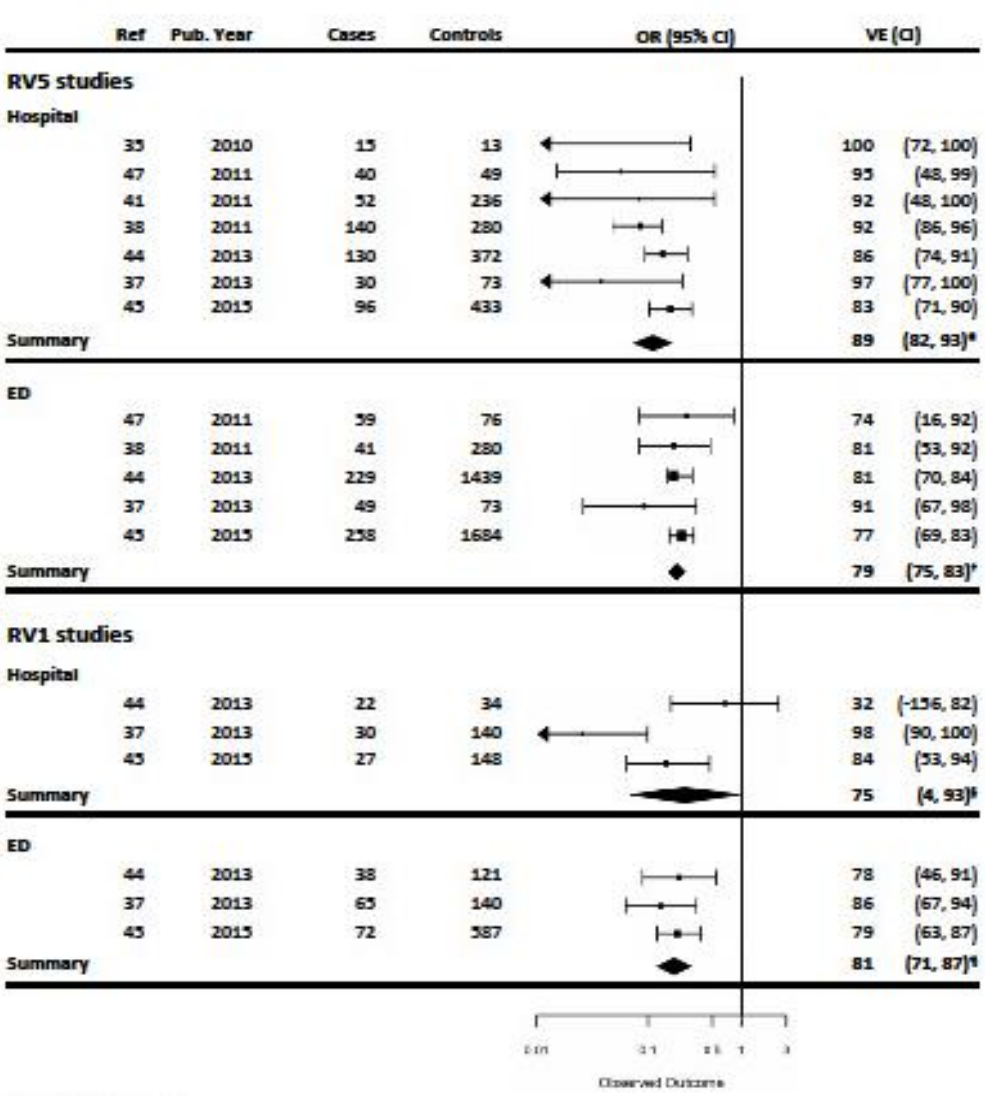


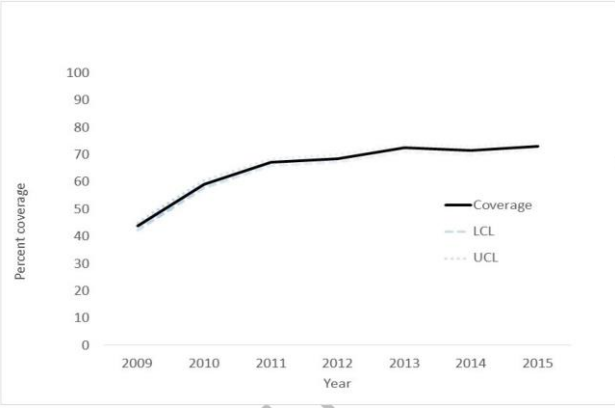
Figure 3 | **The number of rotavirus-positive tests in the United States before and after vaccine introduction.** These data are from 21 continuously reporting National Respiratory and Enteric Viruses Surveillance System laboratories, collected by

Nat Rev Dis Primers. ; 3: 17083. 2018

VE of RV5 and RV1 by clinical setting, USA

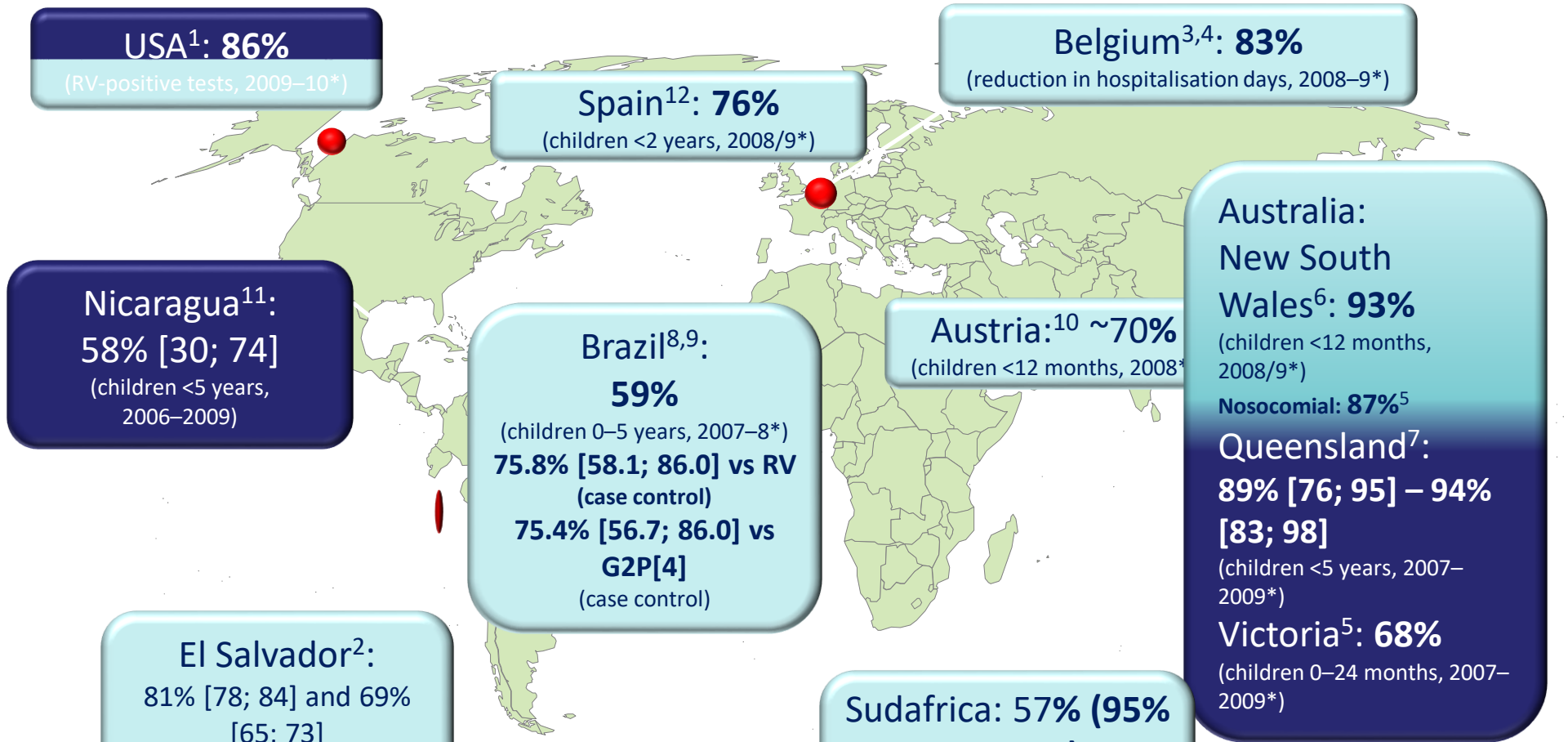


- Overall VE against hospitalization and ED visits
  - RV5: 84%
  - RV1: 83%
- Coverage 73,2%
  - Under optimal 80%



Pindyck T., et al Expert Review of Vaccines, DOI: 10.1080/14760584.2018.1489724

Global impact on AGE hospitalizations



USA[1]: **86%**
(RV-positive tests, 2009–10*)

Belgium[3,4]: **83%**
(reduction in hospitalisation days, 2008–9*)

Spain[12]: **76%**
(children <2 years, 2008/9*)

Nicaragua[11]:
58% [30; 74]
(children <5 years, 2006–2009)

Brazil[8,9]:
59%
(children 0–5 years, 2007–8*)
75.8% [58.1; 86.0] vs RV (case control)
75.4% [56.7; 86.0] vs G2P[4]
(case control)

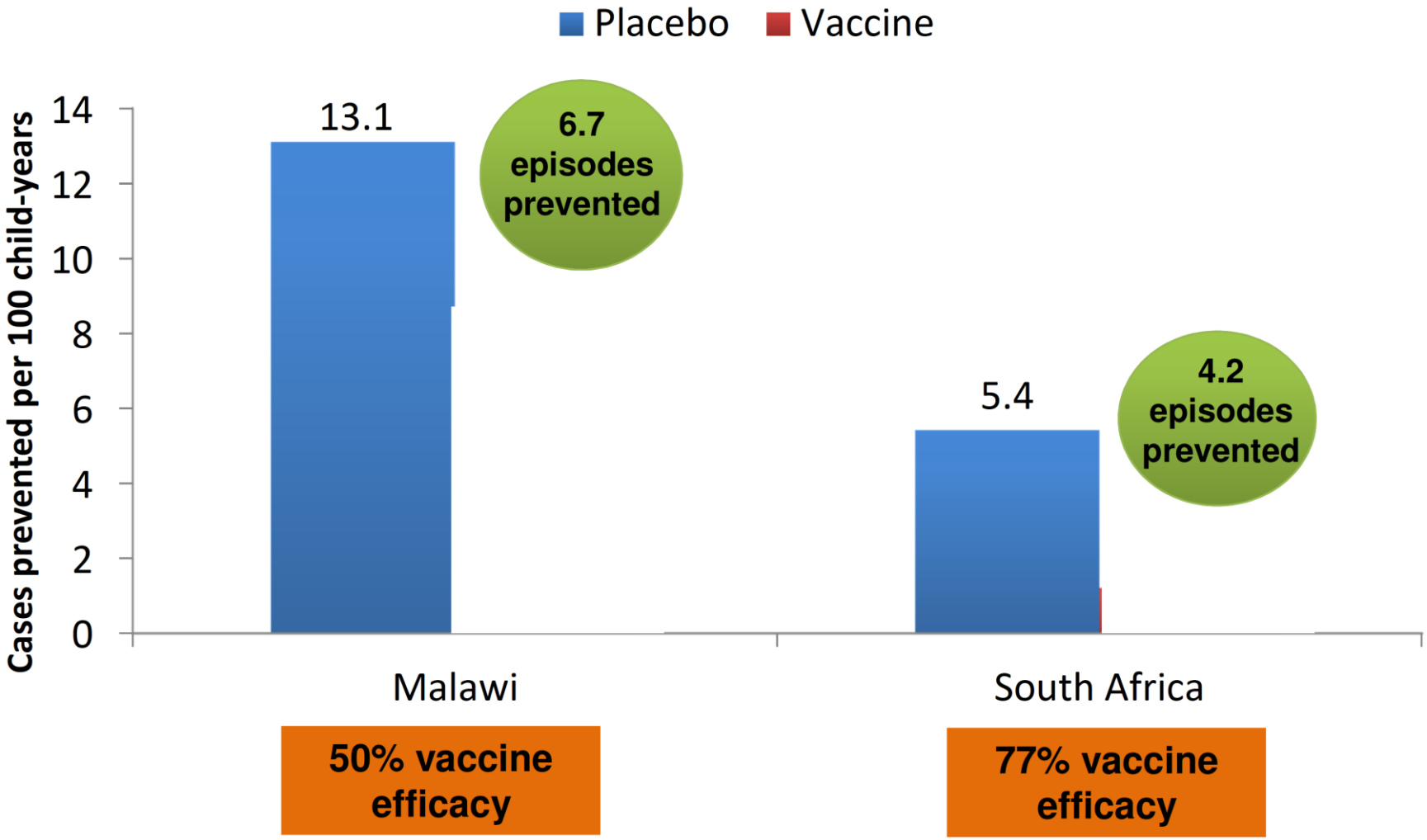
Austria:[10] ~70%
(children <12 months, 2008*

Australia:
New South Wales[6]: **93%**
(children <12 months, 2008/9*)
Nosocomial: 87%[5]
Queensland[7]:
89% [76; 95] – 94% [83; 98]
(children <5 years, 2007–2009*)
Victoria[5]: **68%**
(children 0–24 months, 2007–2009*)

El Salvador[2]:
81% [78; 84] and 69% [65; 73]
(children <5 years, 2008 and 2009*)

Sudafrica: 57% **(95% CI 40-68)**
Malawi: 64% (95% CI 24-83)

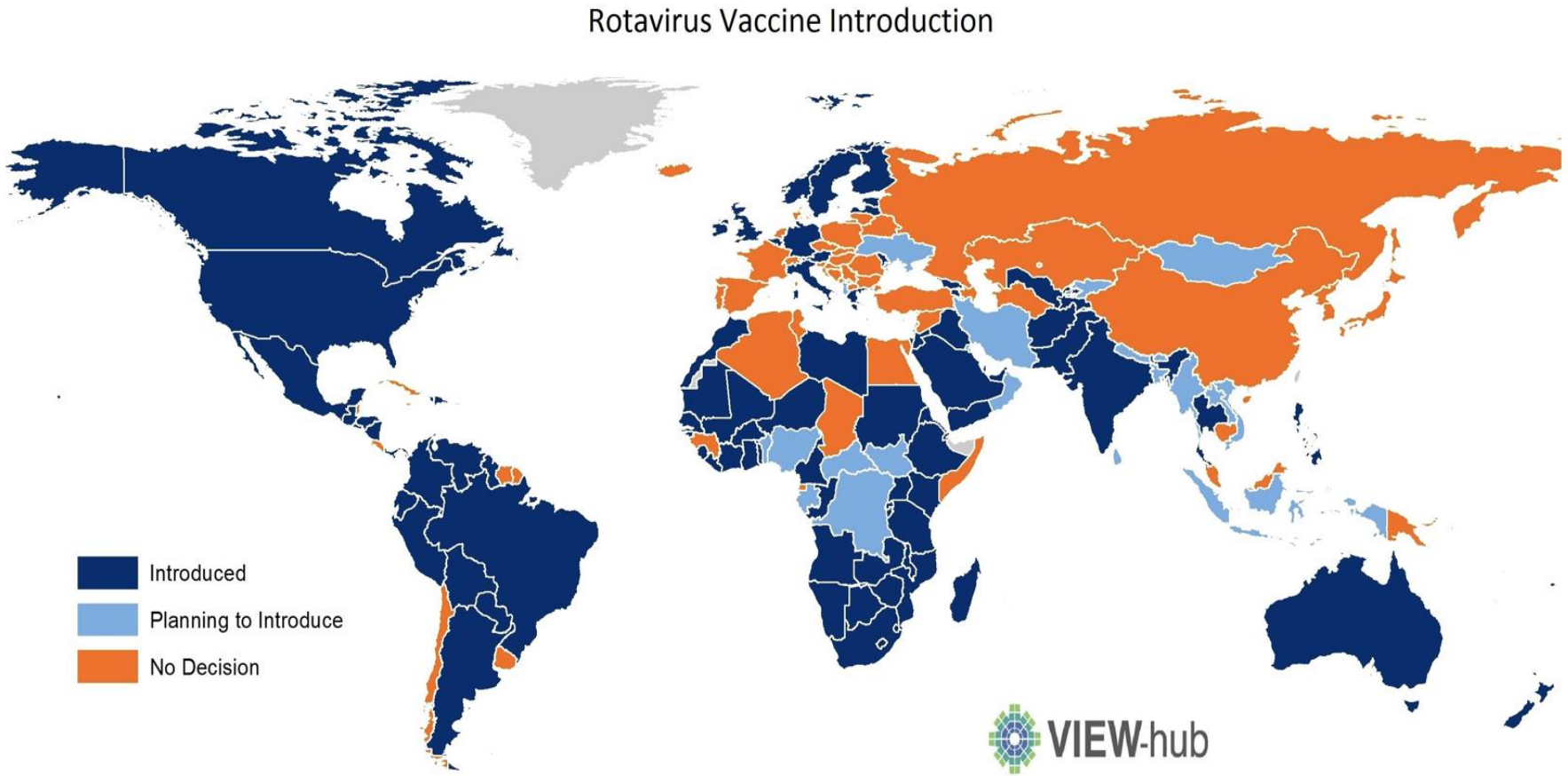
High burden settings: greater disease prevention



Madhi, NEJM 2010

Worldwide rotavirus vaccine introduction status

August 2018



Source: International Vaccine Access Center (IVAC), Johns Hopkins Bloomberg School of Public Health. VIEW-hub. www.view-hub.org.

https://www.defeatdd.org/blog/lifesaving-power-rotavirus-vaccines-malawi-behind-numbers

RV5 and RV1 reduction in hospital admissions and emergency department visits, the frequency of diarrheal disease of any cause and rotavirus-related gastroenteritis

Velázquez et al. BMC Pediatrics (2017) 17:14
DOI 10.1186/s12887-016-0771-y

BMC Pediatrics

RESEARCH ARTICLE Open Access

Efficacy, safety and effectiveness of licensed rotavirus vaccines: a systematic review and meta-analysis for Latin America and the Caribbean

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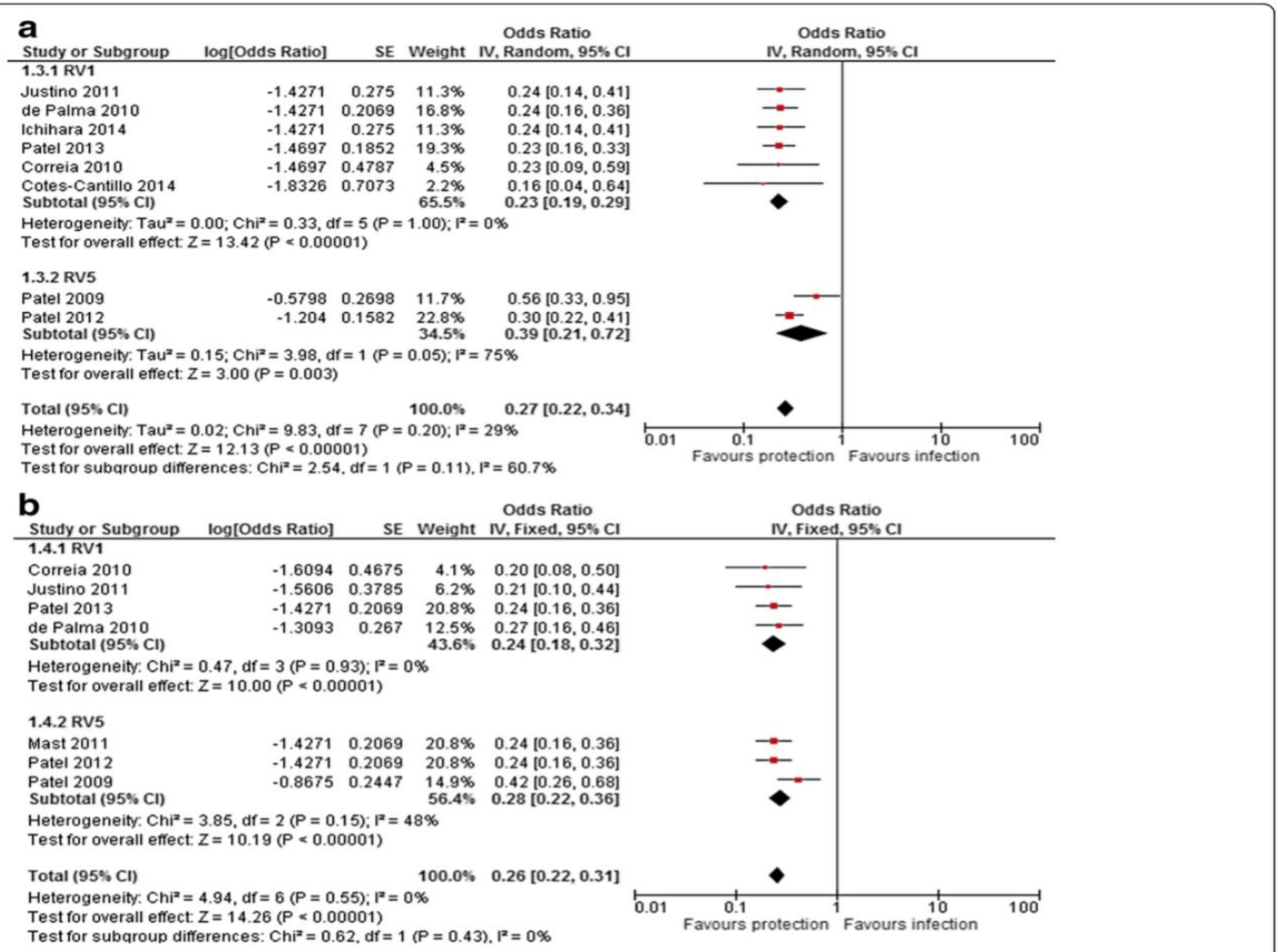


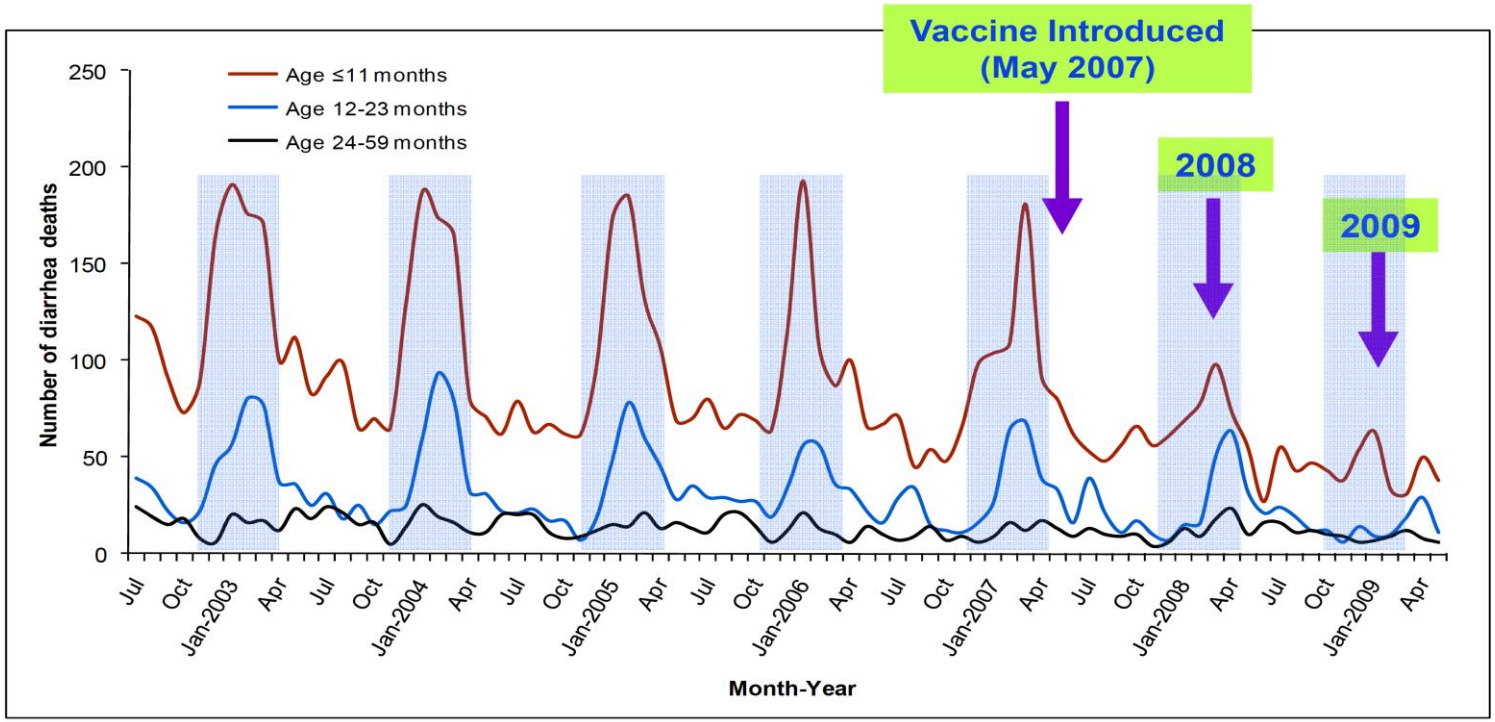
Fig. 4 Effectiveness of rotavirus vaccines against rotavirus hospitalisation (**a**) and severe rotavirus-diarrhoea (**b**)

Decrease in deaths cases in Mexico, after rotavirus vaccination

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Effect of Rotavirus Vaccination on Death from Childhood Diarrhea in Mexico



Richardson et al, NEJM 2010

Impact of RV vaccine in LATAM

National estimates of reduction in all-cause diarrhoea and species A rotavirus (RVA) disease burden after RVA vaccine introduction

Reference	Country	Per capita national income ($)	Pre-vaccine year(s)	Post-vaccine year(s)	RVA vaccine coverage (%)	Decline in disease	
						Vaccinated age groups[b] (%)	Children under five years of age (%)
Gastroenteritis mortality							
Richardson et al. (2010)	Mexico	8,960	2003-2006	2008	74	41	35
Lanzieri et al. (2010)	Brazil	8,070	2004-2005	2008	90	30-39	41
do Carmo et al. (2011)	Brazil	8,070	2002-2005	2007-2009	82[c,d]	22-28	22
Gastroenteritis hospitalization							
do Carmo et al. (2011)	Brazil	8,070	2002-2005	2007-2009	82[c,d]	21-25	17
Lanzieri et al. (2010)	Brazil	8,070	1998-2005	2007	78[d]	26-48	31
Molto et al. (2011)	Panama	6,570	2003-2005	2008	94	15-31	37
Quintanar-Solares et al. (2011)	Mexico	8,960	2003-2006	2009	89	43-52	40
de Palma et al. (2010)[a]	El Salvador	3,370	2006	2009	-	Not available	51
RVA hospitalization							
Yen et al. (2011a)	El Salvador	3,370	2006	2008-2009	77[c]	79-86	69-81
Sáfadi et al. (2010)	Brazil	8,070	2004-2005	2007-2008	82[c]	73-82	59

a: Jan-June estimates; *b*: children under one or two years of age depending on year of vaccine introduction; *c*: annual average over the post-vaccine; *d*: RVA dose 2 coverage years.

Rishi D., et al *Mem Inst Oswaldo Cruz*, Rio de Janeiro, Vol. *106*(8): 907-911, Dec 2011

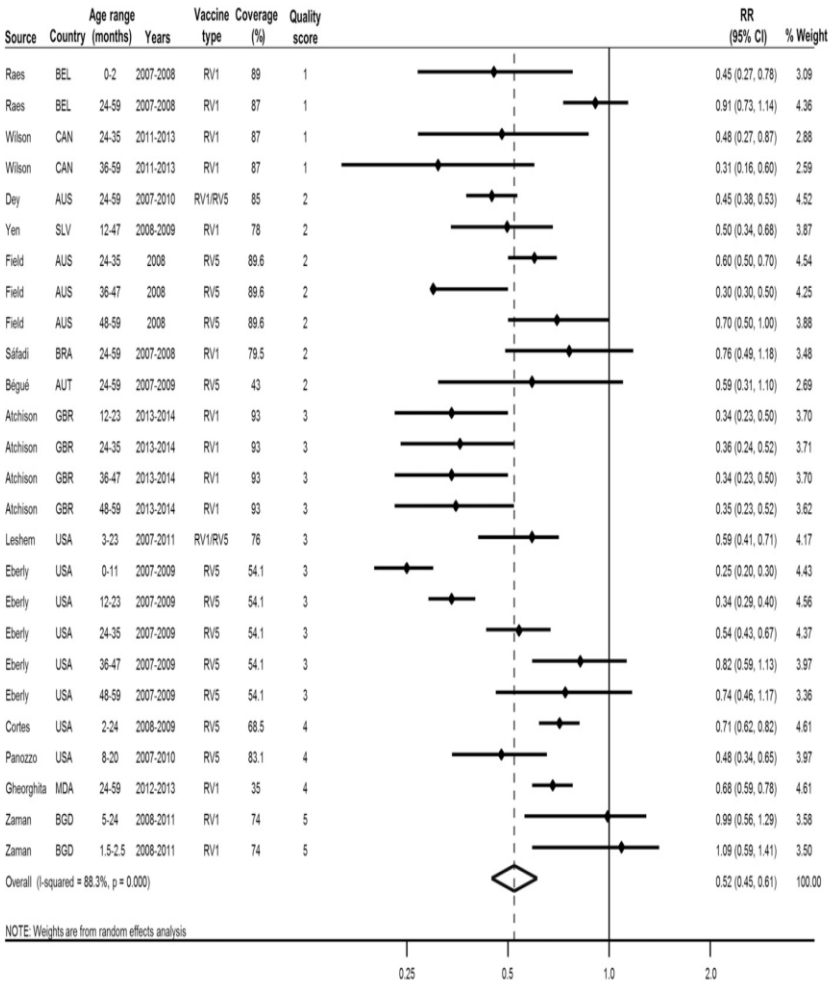
Herd Protection: reduction in rotavirus among unvaccinated age groups in El Salvador

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

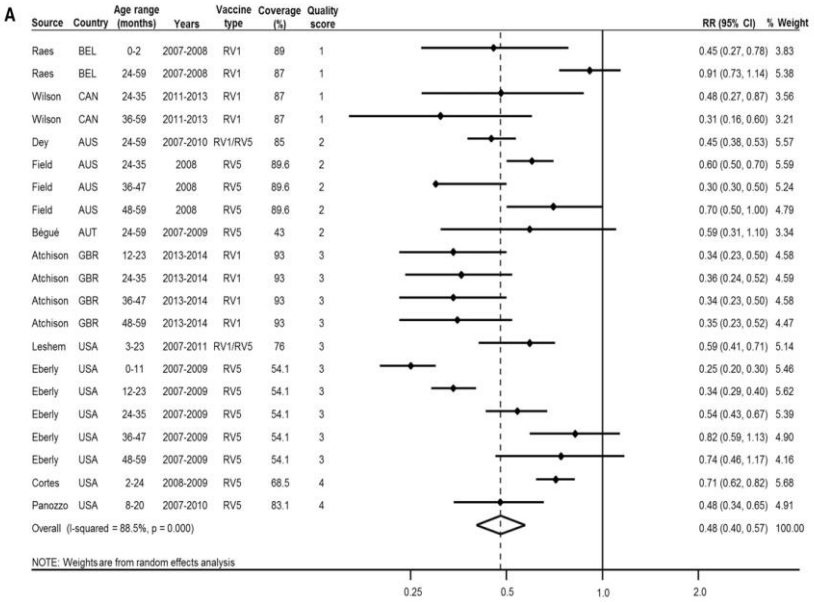
These age cohorts were ineligible to receive rotavirus vaccine

Yen et al, PIDJ 2011

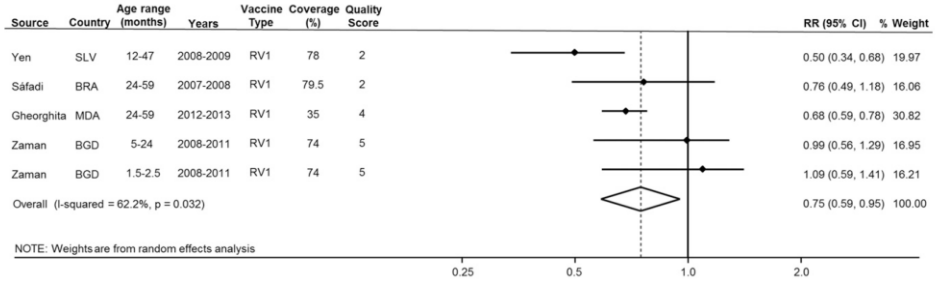
Potential benefits for unvaccinated through indirect effects: 48% in HIC and 25% in LMIC



A



B



Rosettie K., et al Am. J. Trop. Med. Hyg., 98(4), 2018, pp. 1197–1201

Lower antirotavirus IgA seroconversion after concomitant bOPV administration

Rotavirus Serum IgA Immune Response in Children Receiving Rotarix Coadministered With bOPV or IPV

Sasirekha Ramani, PhD, Nora Mamani, Med Tech,† Rodolfo Villena, MD,‡ Ananda S. Bandyopadhyay, MBBS,§ Chris Gast, PhD,¶ Alicia Sato, MS,¶ Daniel Laucirica, BS,† Ralf Clemens, MD,‖ Mary K. Estes, MD,* and Miguel L. O'Ryan, MD†*

A

IPV+rota/bOPV+rota | IPV+rota/IPV+rota

	Group 1			Group 2, 3			
Endpoint	**%**	**95% CI**	**n/N**	**%**	**95% CI**	**n/N**	***p-value***
Week 8 Seropositivity	6%	(3.3%, 11.4%)	(9/145)	6%	(3.7%, 9.2%)	(17/289)	*1.000*
Week 28 Seroconversion	50%	(42.3%, 58.4%)	(73/145)	65%	(59.7%, 70.6%)	(189/289)	*0.004*
Week 28 median Log_{10} IgA Titer units (IQR) overall	1.8 (1.2)			2.1 (1.3)			*0.007*
Week 28 median Log_{10} IgA Titer units (UIQR) among those seropositive at Week 28	2.4 (0.7)			2.4 (0.6)			*0.680*

B

	Group 2			Group 3			
Endpoint	**%**	**95% CI**	**n/N**	**%**	**95% CI**	**n/N**	***p-value***
Week 8 Seropositivity	4%	(1.6%, 8.2%)	(5/138)	8%	(4.6%, 13.4%)	(12/151)	*0.139*
Week 28 Seroconversion	63%	(54.7%, 70.6%)	(87/138)	68%	(59.7%, 74.5%)	(102/151)	*0.459*
Week 28 median Log_{10} IgA Titer units (IQR) overall	2.0 (1.3)			2.2 (1.3)			*0.156*
Week 28 median Log10 IgA Titer units (UIQR) in among those seropositive at Week 28	2.3 (0.7)			2.4 (0.5)			*0.797*

Group 1 receiving Rotarix™ and bOPV concomitantly
Groups 2 and 3 receiving Rotarix™ and IPV concomitantly

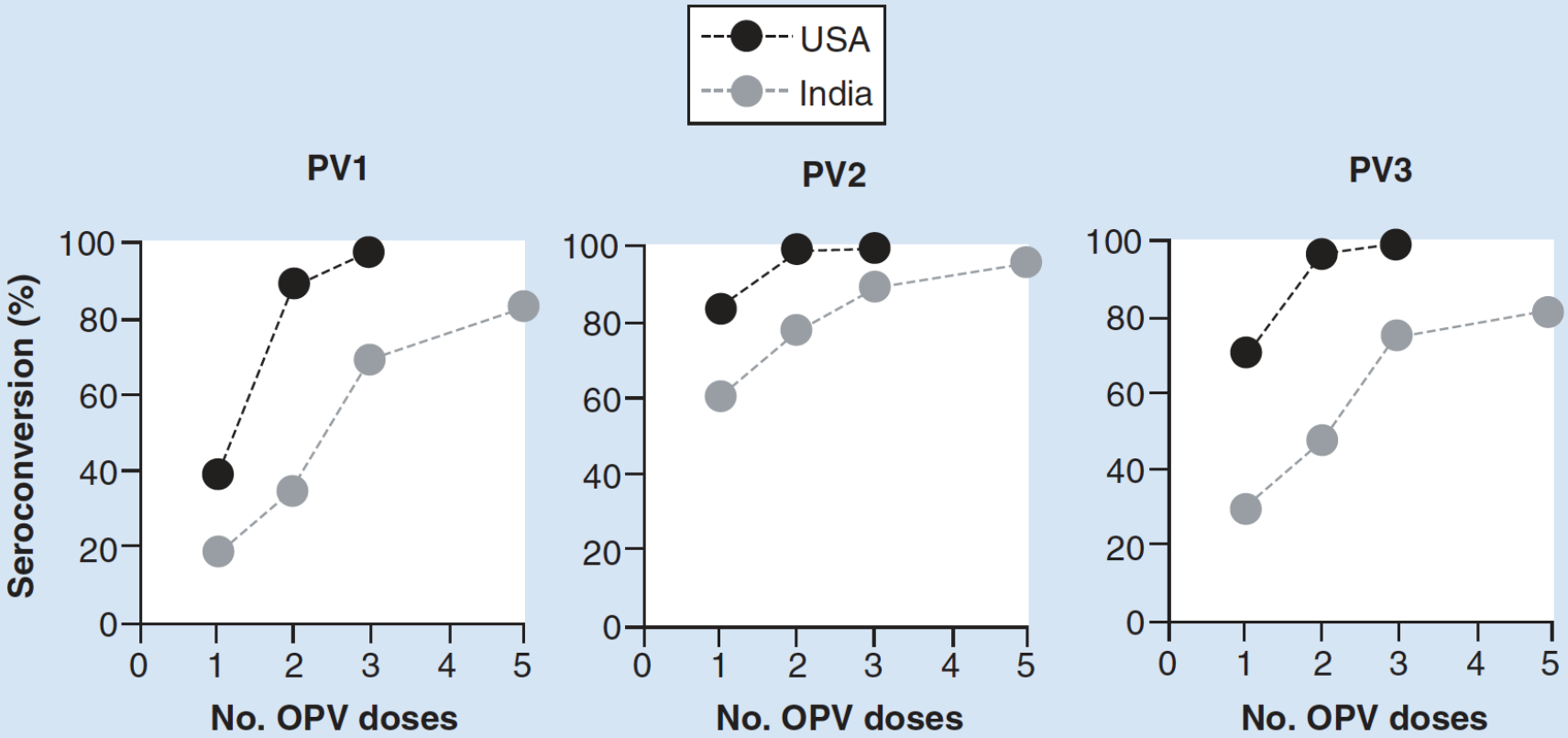
Ramani Pediatr Infect Dis J 2016;35:1137–1139

Where are we now?

Vaccine	Status	Comments	Selected references
RotaTeq ®/Rotarix ®	Worldwide License	Eleven years post-licensure; worldwide distribution; demonstrated effectiveness	Giaquinto et al., 2011[68]; O'Ryan et al., 2011[20]
Rotashield®	First licensed rotavirus vaccine in 1998 (USA); was withdrawn due to association with intestinal intussusception	Currently in clinical trials. Two-dose regimen beginning within the first 30 days of life; 64% efficacy for the first 12 months of life	Armah et al., 2013[42]
LLR®/Rotavin-M1®/Rotavac®	Restricted license	Only used in China/Vietnam/India (respectively); lack of robust effectiveness data	Fu et al., 2012[32]; Dang et al., 2012[69]; Bhandari et al., 2014[70]
UK reassortant (Rotasil®)	Restricted license	Phase III study	Isanaka el al[36]
RV3BB	Early clinical development	Phase I or early Phase II studies	Danchin et al., 2013[71]; Luna et al., 2013[72]; Bines et al[38]; Naik et al[35]
Truncated VP8 subunit and a tetanus toxoid P2 protein	Early clinical development	Phase I/II study	Groome et al [39]

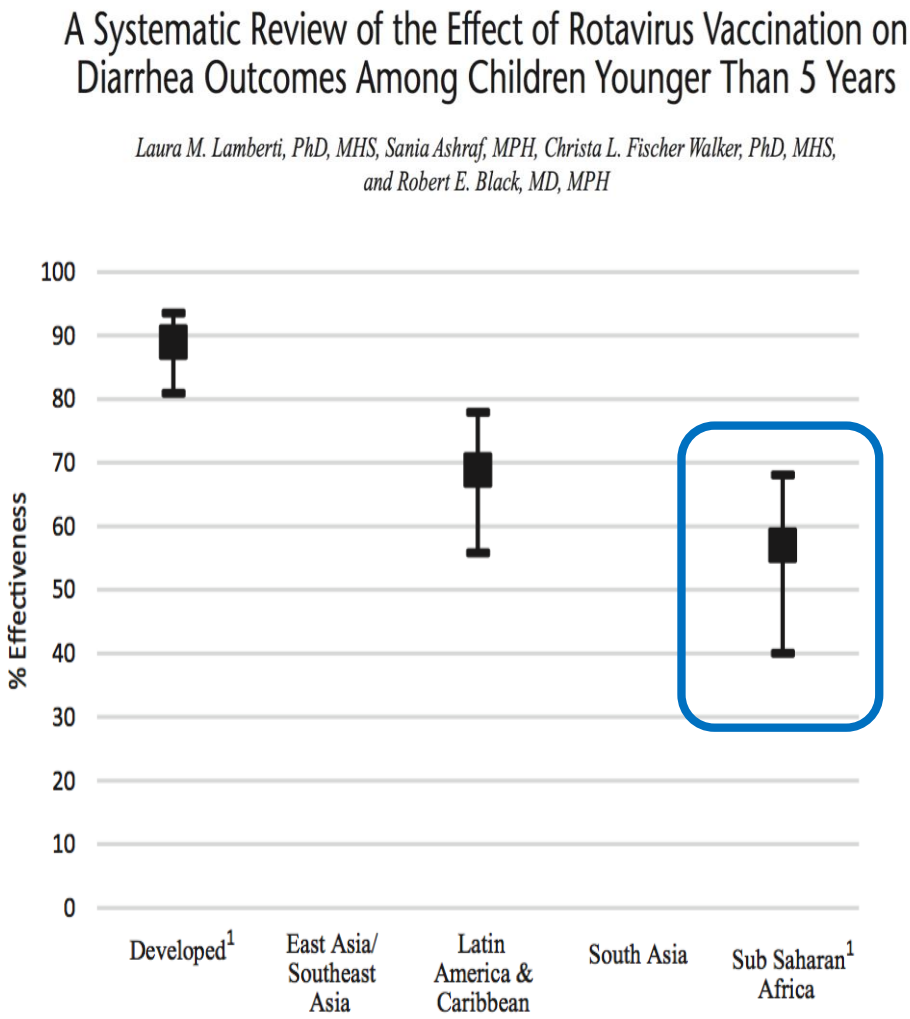
Lessons learned from real world experiences with enteric vaccines

Impaired immunogenicity of oral poliovirus vaccine in India



Parker E., et al FutureMicrobiol. (2018) 13(1), 97–118

Effectiveness comparison regarding GDP



Potential explanations

– Missed vaccination opportunity

Narrow range of vaccination

– First infection occurs at earlier ages

Previous to vaccination

– Environmental enteropathy:

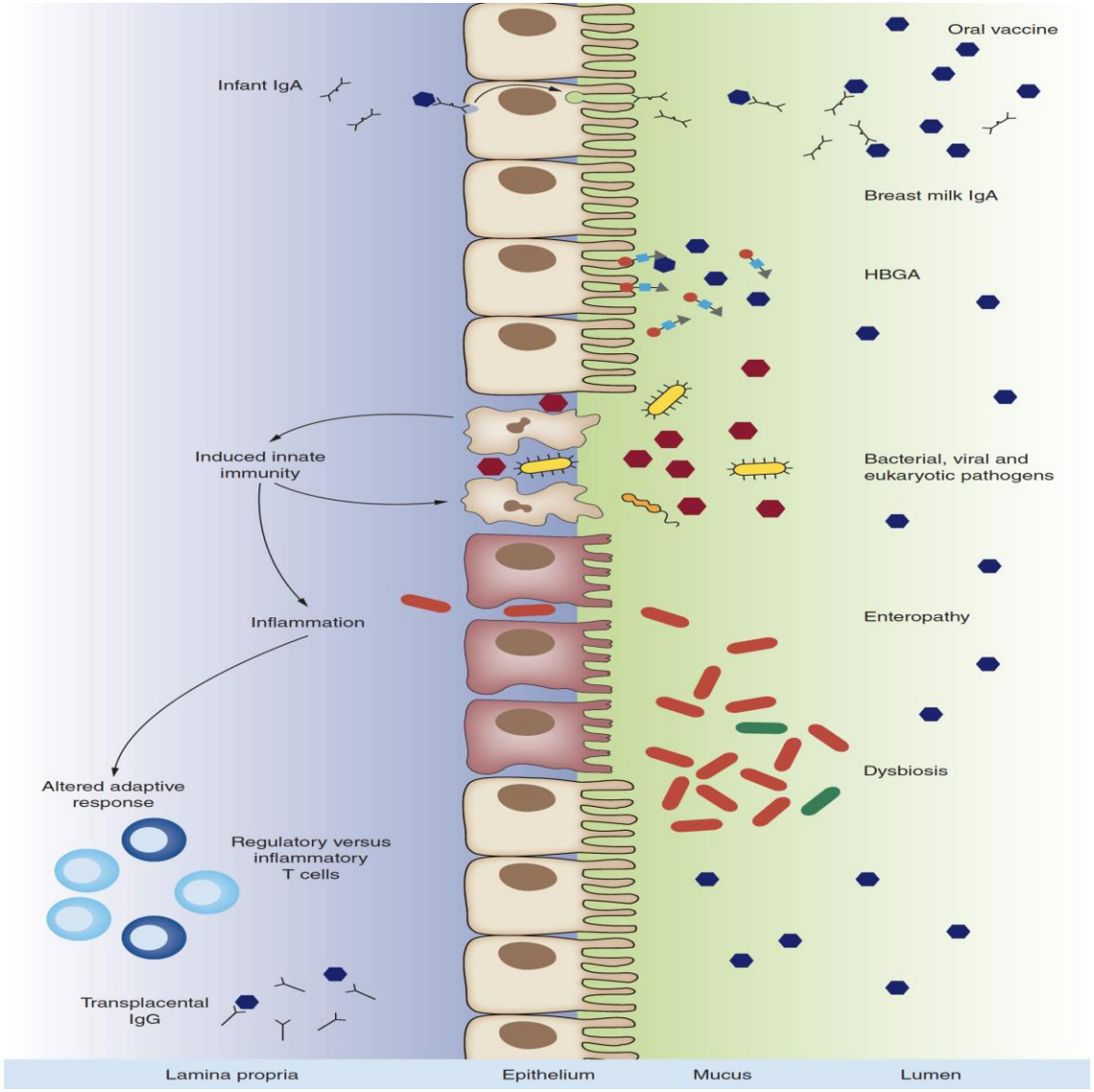
Malnutrition

Chronic intestinal inflammation due to exposure to other enteropathogens

– Microbiome

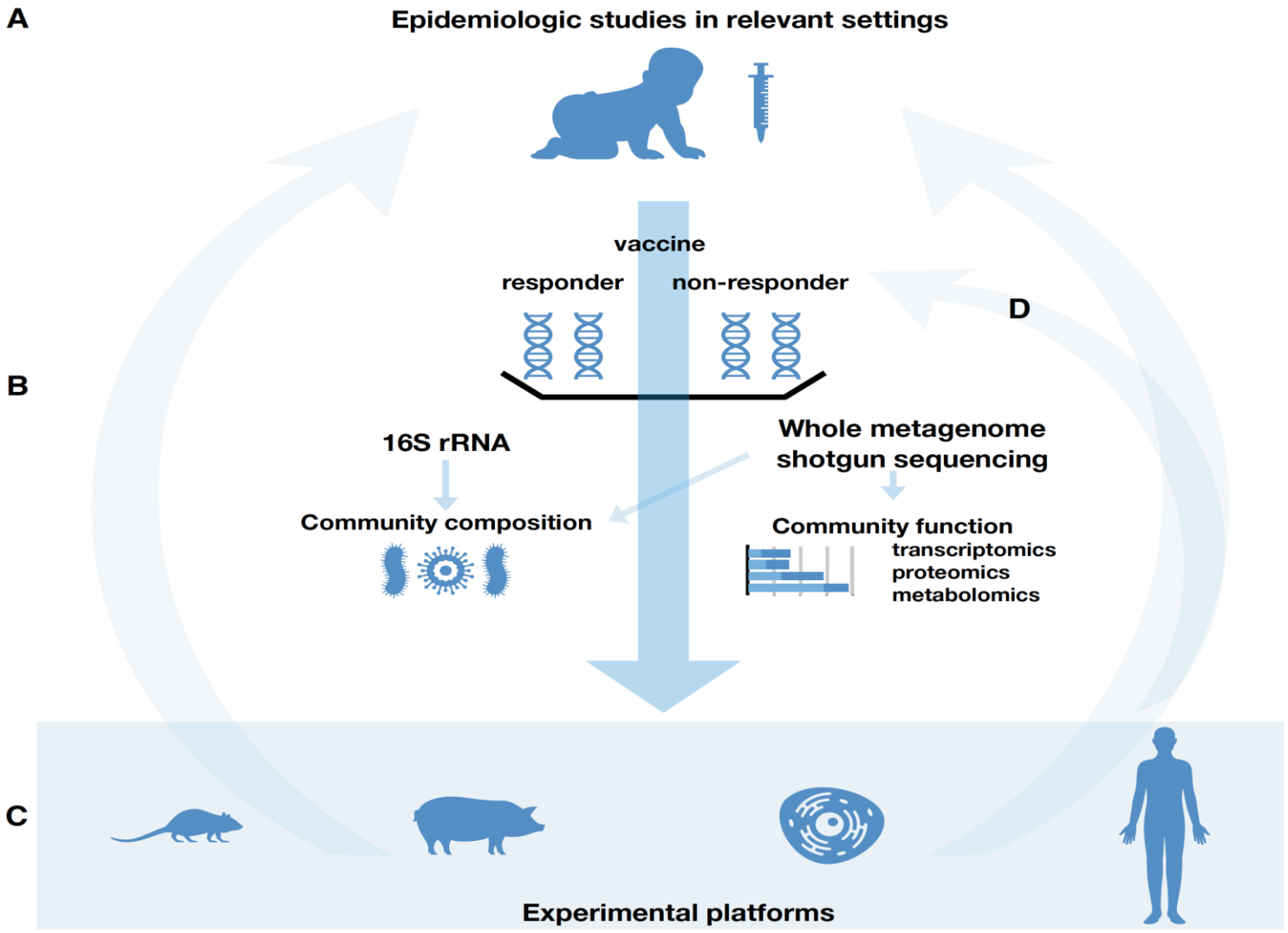
Lamberti L., et al Pediatr Infect Dis J 2016;35:992–998 ; O'Ryan M. F1000Research 2017, 6(F1000 Faculty Rev):1517

Potential mechanisms underlying oral vaccine efficacy variability



Parker E., et al FutureMicrobiol. (2018) 13(1), 97–118

Microbiome and immune response to enteric vaccines



Harris V., Drugs (2018) 78:1063–1072

Microbiome and immune response to enteric vaccines

Table 1 Known correlations between rotavirus and oral polio vaccine immunogenicity and microbiome composition

Vaccine	Population	Vaccine response outcome	Commensal microbiota correlation with response, FDR < 0.15, (Phylum)	Commensal microbiota correlation with nonresponse, FDR < 0.15, (Phylum)	Methods	References
Rotavirus (Rotarix)	India, pre-vaccination 6 weeks[a]	Seroconversion (anti-RV IgA > 20 IU/mL)	No commensal microbiota correlations		16S rRNA	[68]
Rotavirus (Rotarix)	India, pre-vaccination 6 weeks[a]	Shedding (RT-PCR)	Higher diversity (#OTU) Higher Proteobacteria diversity (#OTU) No taxonomic correlations		16S rRNA	[68] [98]
Rotavirus (Rotarix)	Pakistan, pre-vaccination 6 weeks	Seroconversion (anti-RV IgA > 20 IU/mL)	Higher diversity (Shannon index) *Eshcerichia coli et rel*[b] (Proteobacteria) *Bacteroides fragilis et rel* (Bacteroidetes) *Parabacteroides distasonis et rel* (Bacteroidetes) *Clostridium difficile et rel* (Firmicutes)	Uncultured *Selenomonadaceae*[b] (Firmicutes) *Megasphaera elsdenii et rel*[b] (Firmicutes)	HitChip	[69]
Rotavirus (Rotarix)	Ghana, pre-vaccination 6 weeks	Seroconversion (anti-RV IgA > 20 IU/mL)	No difference in diversity *Streptococcus bovis et rel*[b] (Bacilli)	*Allistepes et rel*[b] (Bacteroidetes) *Bacteroidetes ovatus et rel*[b] (Bacteroidetes) *Bacteroides uniformis et rel*[b] (Bacteroidetes) *Parabacteroides distasonis et rel*[b] (Bacteroidetes) *Prevotella melaninogenica et rel*[b] (Bacteroidetes) *Prevotella oralis et rel*[b] (Bacteroidetes) *Tannerella et rel*[b] (Bacteroidetes) *Coprococcus eutactus et rel*[b] (Firmicutes) *Eubacterium hallii et rel*[b] (Firmicutes) *Ruminococcus obeum et rel*[b] (Firmicutes)	HitChip	[70]

‘adjuvanting’ capacity of the endogenous microbiota in LMIC infants to effect vaccine immune response?

Harris V., Drugs (2018) 78:1063–1072

Microbiome and immune response to enteric vaccines

Table 1 Known correlations between rotavirus and oral polio vaccine immunogenicity and microbiome composition

Vaccine	Population	Vaccine response outcome	Commensal microbiota correlation with response, FDR < 0.15, (Phylum)	Commensal microbiota correlation with nonresponse, FDR < 0.15, (Phylum)	Methods	References
Polio	India pre-vaccination, 6 weeks[a]	Type 3 OPV seroconversion		Higher diversity (#OTU) Epsilonproteobacteria class (Proteobacteria) Betaproteobacteria class (Proteobacteria) Verrucomicrobiae class	16S rRNA	[98]
Polio	India pre-vaccination, 6 weeks[a]	Shedding (RT-PCR, ≥ 1 Sabin strain)	No taxonomic correlations	Higher diversity (#OTU)	16S rRNA	[98]
Polio	Bangladesh Composite of 6, 11, 15 week stool	Height of anti-OPV IgG		*Acinetobacter* genus (Proteobacteria) [$p < 0.05$, not corrected]	16S rRNA	[99]

Harris V., Drugs (2018) 78:1063–1072

Challenges and gaps in enteric vaccines

Latam NIPs

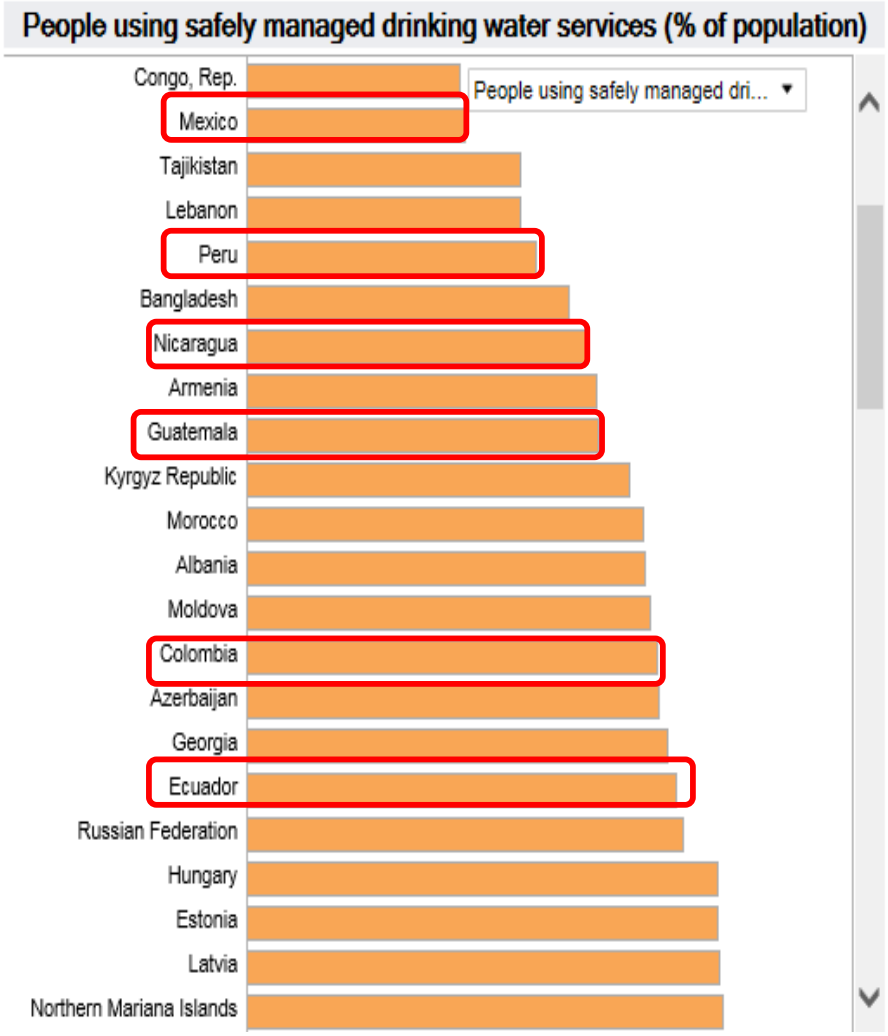
- International initiatives to improve childhood immunization rates in LIC/MIC in the last four decades
- Significant increase in child vaccination coverage → reduction of infant morbidity and mortality due to infectious diseases
- Crucial intervention in the reduction of inequities and in the extension of a universal coverage system for the entire population
- Inequalities between countries and socioeconomic in childhood vaccination in LIC/MIC

Hajizadeh M. J Epidemiol Community Health 2018;72:719–725; Bascolo E., et al *Rev Panam Salud Publica* 41, 2017

Challenges in enteric vaccines

- Consistent epidemiological surveillance
- Optimize coverages
- Analysis / Impact studies
  - Direct and indirect effects
- New vaccines
  - Efficacy models
  - Safety
  - Co administration
- Innovative technologies
  - Tolerate high temperatures
  - Decrease packaging volume
- Maintaining immunization as a high political priority

Drinking water supply



Uganda: 6,4%

México 42,6%
Peru: 50,2%
Guatemala 60,8
Colombia 71,1

Costa Rica 89,8%
Chile 98,2%
Argentina 98,5%

http://datatopics.worldbank.org/health/health

Conclusions

Take home messages

- Enteric pathogens are a substantial threat to public health
  - Severe malnutrition, stunting, cognitive dysfunction and decreased adult accomplishment and productivity
- Progress
  - Vaccines in development for enteric pathogens: Shiguella, ETEC, NoV
  - Rotavirus: Increasing data about safety and effectiveness
    - Indirect benefits to unvaccinated groups
- Challenges
  - Rotavirus vaccines:
    - Safe, effectives … Immunity impairment ….
  - Susteinables NIPs
  - Drinking water supply
- Vaccines are public health benefit and a right

XI International Symposium for Latin American experts

Enteric vaccines
Progress and challenges

GRACIAS!!

OBRIGADO!!

THANK YOU!!

MERCI!!