ROTAVIRUS

COMMON, SEVERE, DEVASTATING, PREVENTABLE

THE LATEST EVIDENCE &
WHAT'S NEEDED TO STOP
ILLNESSES AND DEATHS

ROTA COUNCIL
Rotavirus Organization of Technical Allies

Contents

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Executive summary

- Diarrhea is a **leading cause of child illness and death**, and rotavirus is the most common cause of severe diarrhea.
- **Each year, rotavirus kills over 200,000 children** in countries around the world, and hospitalizes hundreds of thousands more.
- **2 out of every 5 diarrhea-related hospitalizations** among children under 5 are caused by rotavirus. It is NOT your typical “stomach bug” or “flu”—**preventing illness** in the first place is critical.
- **The WHO recommends that all countries introduce rotavirus vaccines** into their national immunization programs.
- **Three WHO-prequalified, orally administered rotavirus vaccines are available today**: Rotarix (GSK), RotaTeq (Merck & Co., Inc.), and ROTAVAC (Bharat Biotech).
- Rotavirus vaccines are **already saving lives and improving health** in countries where they are in use, and are essential to a comprehensive approach to preventing and treating diarrhea.
- Rotavirus vaccines have been shown to **provide broad protection**, even against strains not included in the vaccine, and are projected to be **highly cost-effective**, particularly in regions suffering from the highest levels of rotavirus mortality.
- Despite the WHO recommendation, **over 90 million infants still do not have access** to this critical intervention.

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ROTAVIRUS: BACKGROUND, ILLNESSES, AND DEATHS

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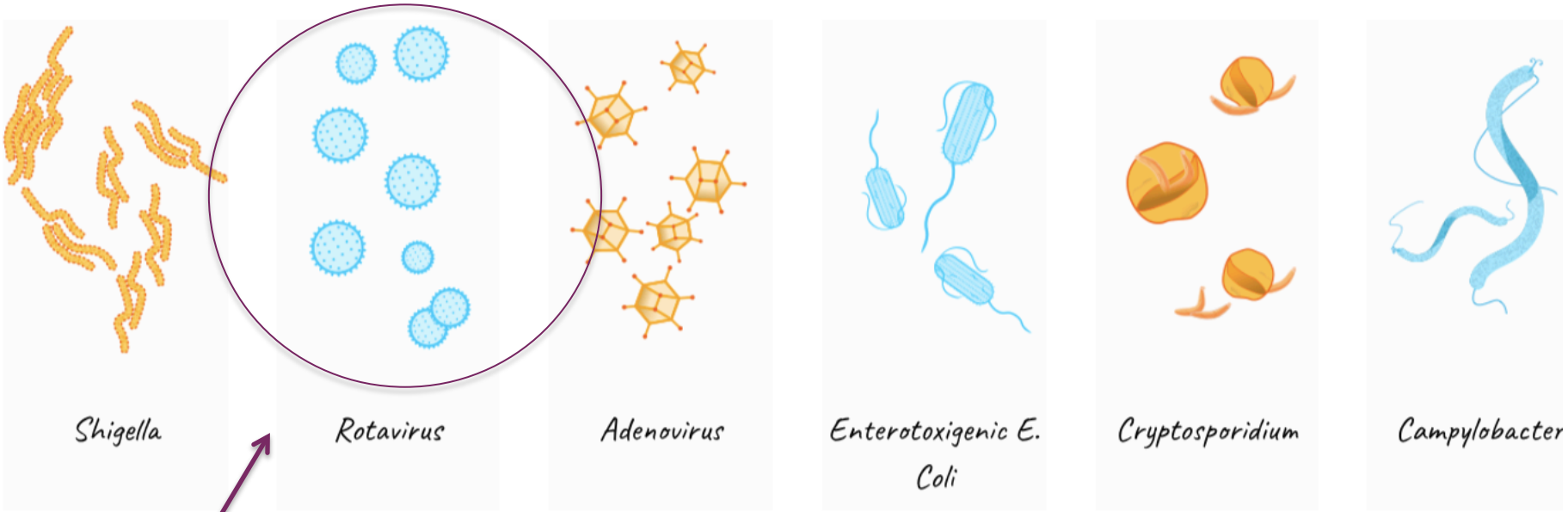
Rotavirus: The pathogen



Rotavirus is 1 of 6 pathogens causing the majority of moderate-to-severe diarrhea in children under age 5

Rotavirus is the #1 cause of diarrhea in infants (0-11 months)

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Illustration – PATH: Stop the Cycle of Diarrheal Disease: A State of the Field Report

Treatment and prevention

Without access to treatment for the severe dehydration it can cause, **rotavirus can be a death sentence**

- 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**

ORT coverage is only in ~30% of places where the most diarrhea deaths occur[1]

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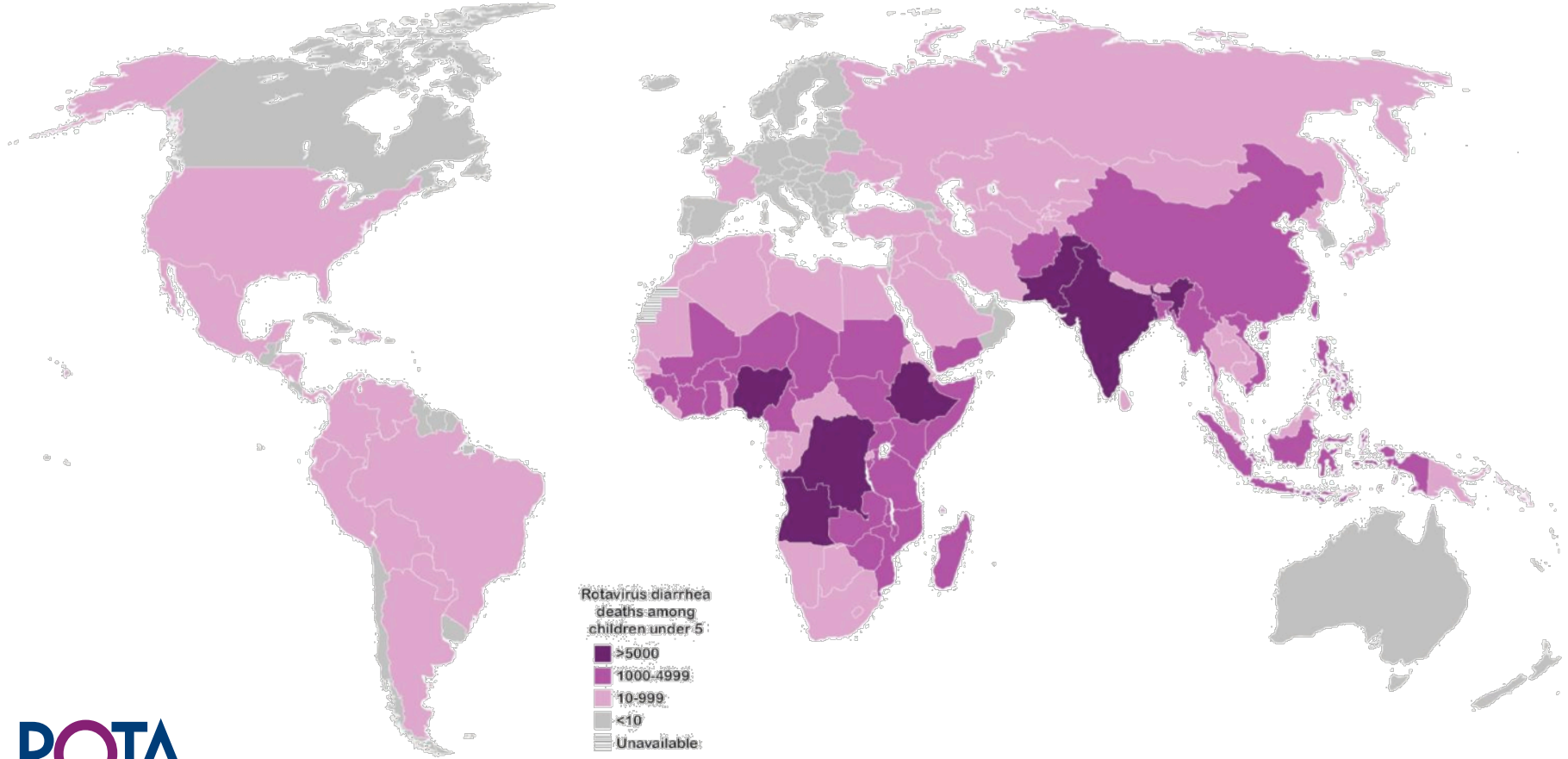
[1] *Santosham, Lancet, 2010*

Estimated global rotavirus deaths, 2013



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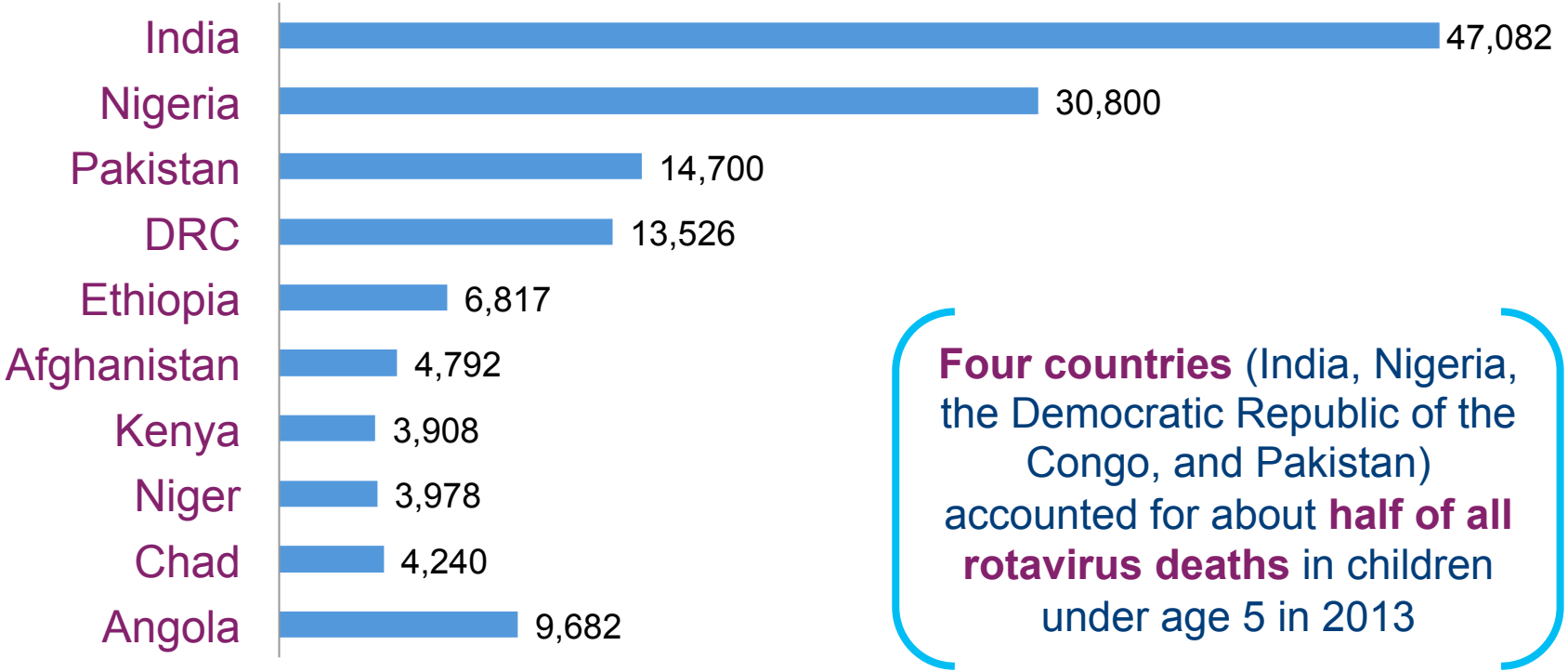
Tate, J.E., et al. (2016). "Global, Regional, and National Estimates of Rotavirus Mortaliiy in Children <5 Years of Age, 2000-2013." Clin Infect Dis. 62 Suppl 2: S96-S105

Rotavirus deaths: Top 10 countries in 2013



Four countries (India, Nigeria, the Democratic Republic of the Congo, and Pakistan) accounted for about **half of all rotavirus deaths** in children under age 5 in 2013

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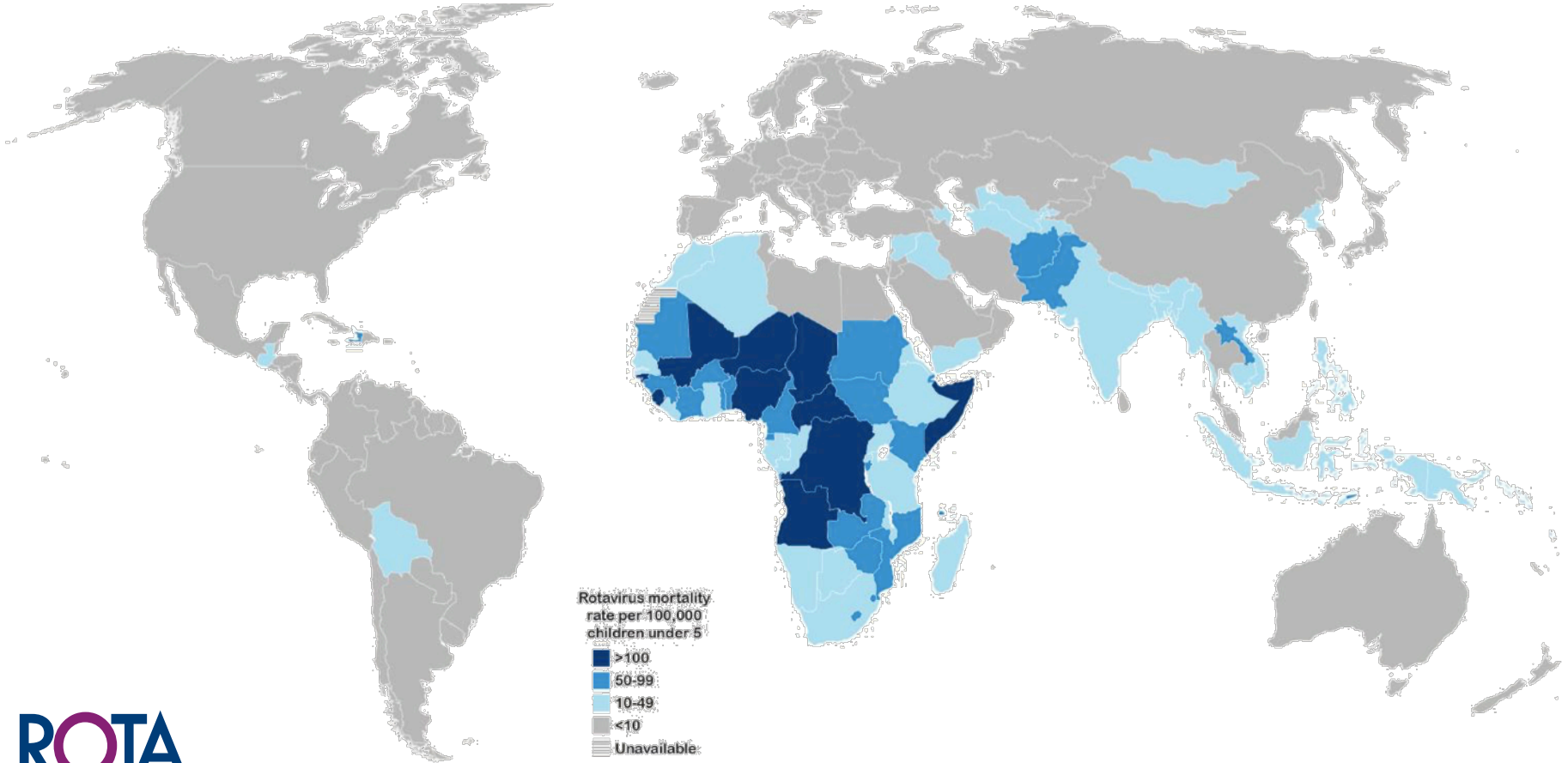
WHO. Estimated rotavirus deaths for children under 5 years of age in 2008
Tate JE, Clin Infect Dis, 2016

Rotavirus diarrhea mortality rate, 2013



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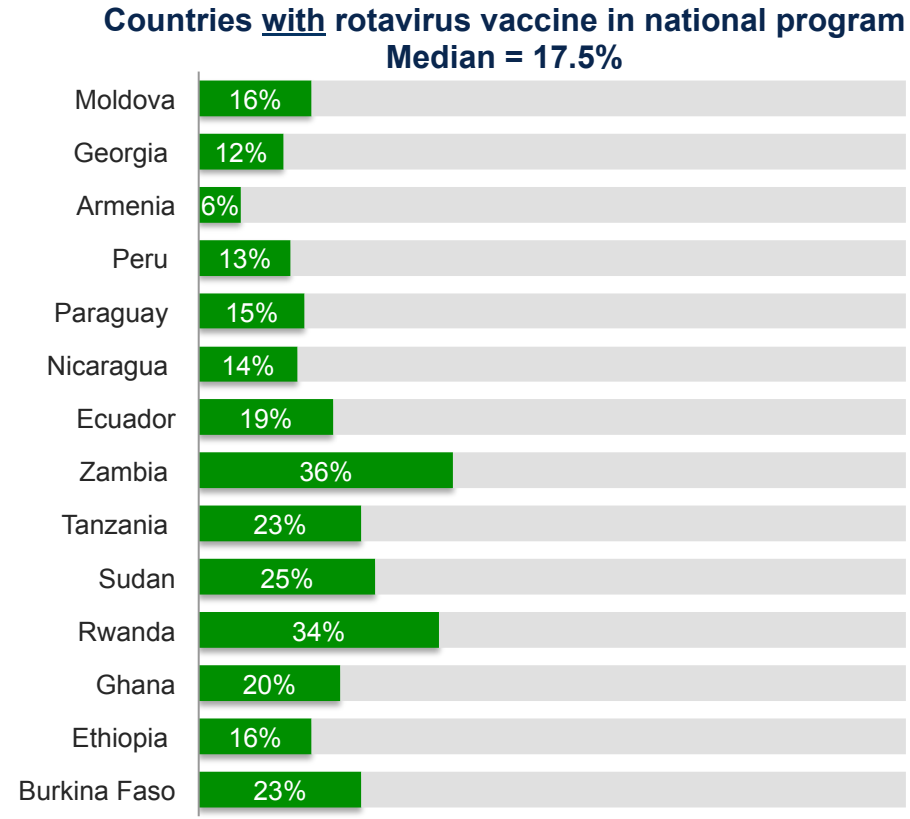
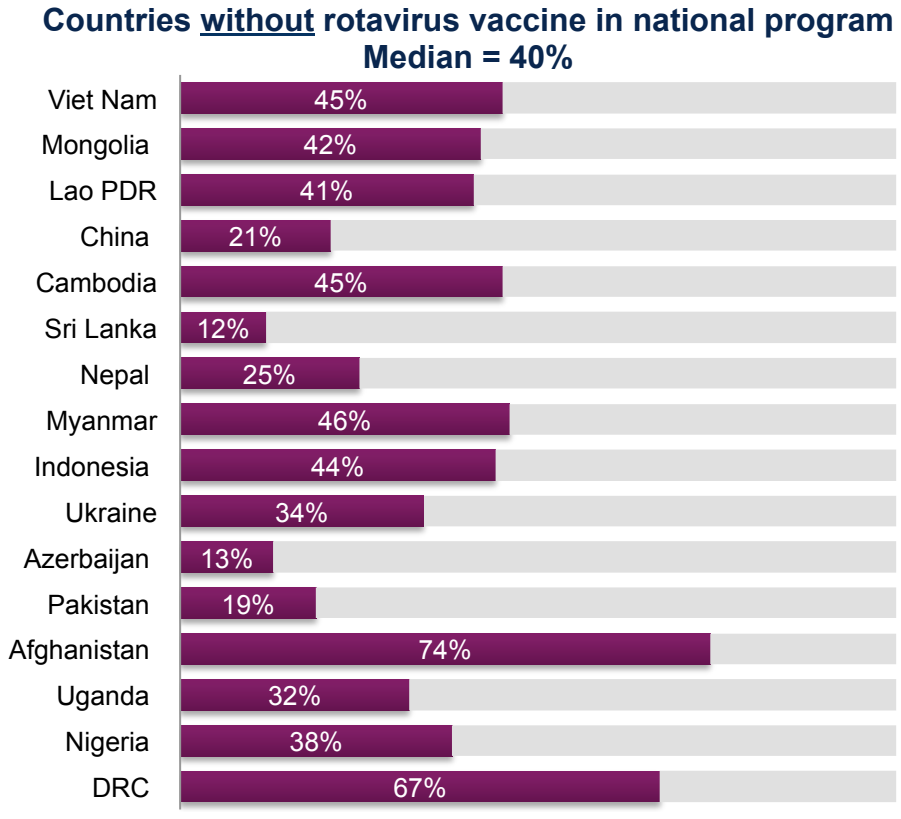
Tate, J.E., et al. (2016). "Global, Regional, and National Estimates of Rotavirus Mortaliiy in Children <5 Years of Age, 2000-2013." Clin Infect Dis. 62 Suppl 2: S96-S105

Disease burden: hospitalizations

Percentage of diarrheal disease hospitalizations caused by rotavirus in WHO surveillance countries - 2016





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VACCINES IN GLOBAL USE

WHO recommendation, GAPPD's comprehensive approach, current products, and benefits vs. risk

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WHO recommendation

"Rotavirus vaccines should be included in all national immunization programmes and considered a priority, particularly in countries with high rotavirus gastroenteritis-associated fatality rates, such as in south and south-eastern Asia and sub-Saharan Africa."

(Rotavirus Vaccines WHO Position Paper January 2013)

To obtain the **maximum benefit from vaccination,** all efforts should be more to provide **timely rotavirus vaccination** on the recommended schedule, particularly in **low-income countries** where rotavirus infection early in life is more likely.

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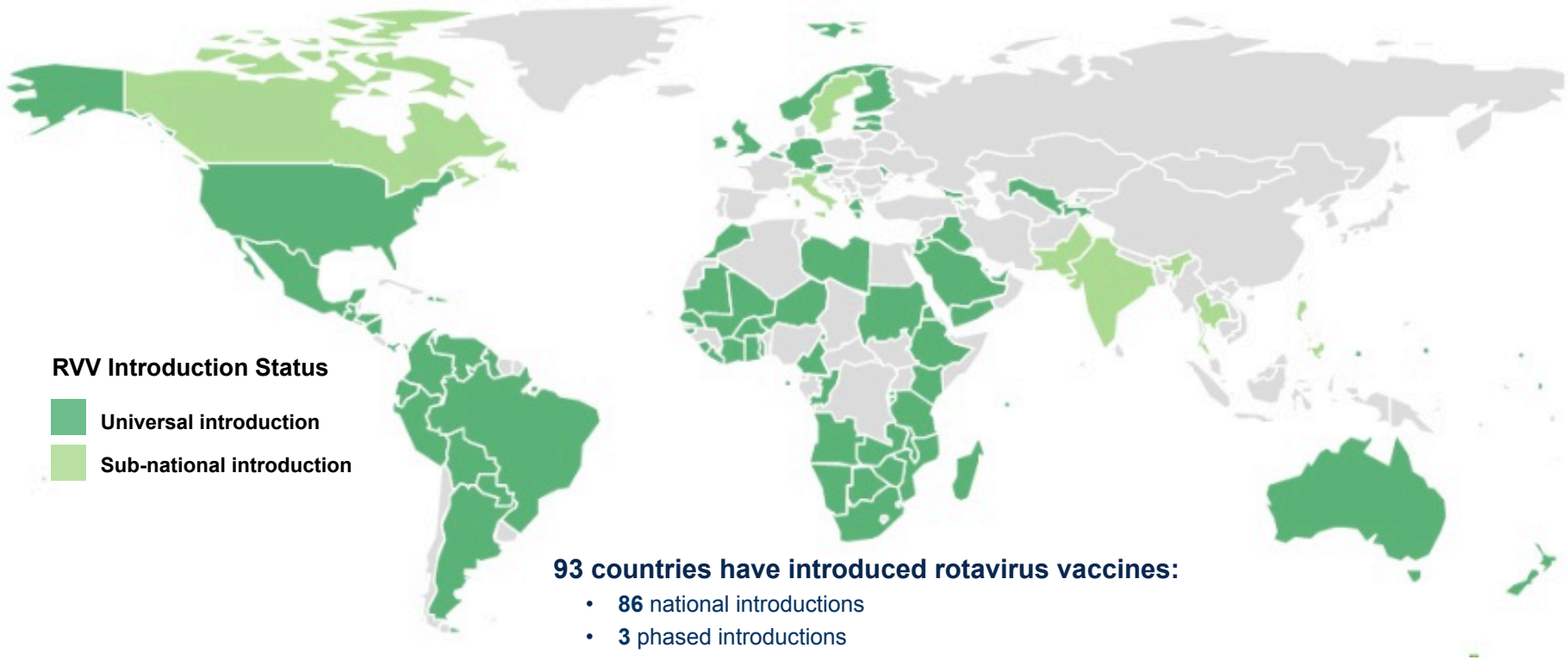
Global rotavirus vaccine introduction status, 2017



93 countries have introduced rotavirus vaccines:

- **86** national introductions
- **3** phased introductions
- **4** sub-national introductions

But more than 90 million children lack access to these life-saving vaccines

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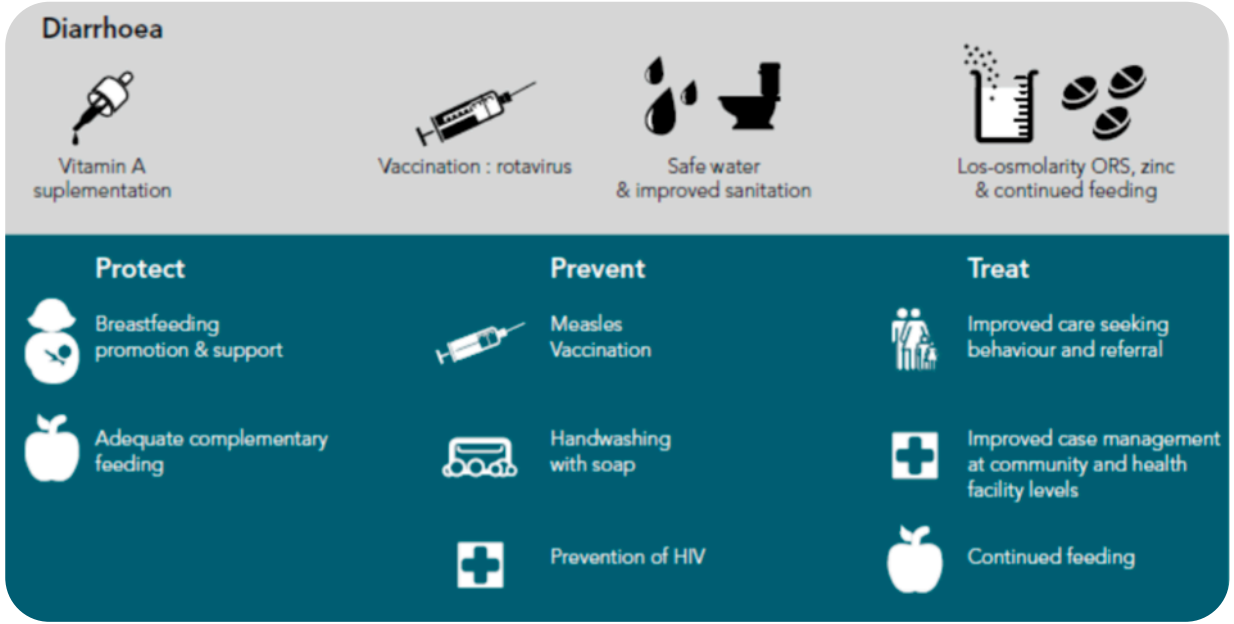
VIEW-hub

Source: IVAC, accessed January 4, 2018 Exported from www.VIEW-hub.org.

GAPPD: The comprehensive approach

Integrated Global Action Plan for the Prevention & Control of Pneumonia and Diarrhea (GAPPD)



Even with treatment, children still suffer.

Children with moderate to severe diarrhea have an 8.5x increased risk of death, grow significantly less in length during the two months following their illness, compared to similar children who do not have an episode of diarrhea.[1]

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[1]*Kotloff KL, Lancet, 2013; image from UNICEF / GAPPD*

Globally-used products: Rotarix™ & RotaTeq®

VACCINE	Rotarix™	RotaTeq®
MANUFACTURER	GlaxoSmithKline	Merck & Co., Inc.
FORMULATION	Monovalent attenuated human rotavirus strain	Pentavalent, human-bovine reassortant vaccine
STRAINS PRESENT IN VACCINE	G1P[8]	G1, G2, G3, G4, and P[8]
PROTECTION AGAINST OTHER STRAINS	Yes, broad protection demonstrated	Yes, broad protection demonstrated
EFFICACY AGAINST SEVERE ROTAVIRUS DIARRHEA IN CHILDREN <1 YR (HIGH-INCOME COUNTRIES)	95.8-100%	85-96%
EFFICACY AGAINST SEVERE ROTAVIRUS DIARRHEA IN CHILDREN <1 YR (LOW- AND MIDDLE-INCOME COUNTRIES)	49-85%	51-64%

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[1]Armah GE, Lancet, 2010; Zaman K, Lancet, 2010; Madhi SA, NEJM, 2010; Vesikari T, NEJM, 2006; Ruiz-Palacios, NEJM, 2006; Patel MM, NEJM, 2011; Soares-Weiser, Cochrane Database Syst Rev. 2012; Shui IM, JAMA, 2012; Cortese, PIDJ, 2010; Haber P, Pediatrics, 2008; Buttery JP, PIDJ, 2011; Vesikari T, Lancet, 2007; Chandran A, Biologics, 2010; Phua KB, Vaccine, 2009; Eberly MD, Vaccine, 2011; Patel M, J Infect Dis, 2009.

Globally-used products: Rotarix™ & RotaTeq® (cont)

VACCINE	Rotarix™	RotaTeq®
DOSAGE	At least 10^6 of live attenuated human G1P[8] particles per dose	A minimum titer of approximately 2.0 to 2.8 x 10^6 infectious units per reassortant and not greater than 116 x 10^6 infectious units per aggregate dose
SCHEDULE	2-dose (same schedule as DTP1 and 2)	3-dose (same schedule as DPT1, 2, and 3)
PRESENTATION	1. Liquid; oral, single-dose applicator 2. Liquid; squeezable, polyethylene single-dose tube 3. Lyophilized; reconstituted with $CaCO_3$ buffer, oral applicator	1. Liquid; oral squeezable tube
SHELF-LIFE	36 months at 2-8ºC	24 months at 2-8ºC

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[1]Armah GE, Lancet, 2010; Zaman K, Lancet, 2010; Madhi SA, NEJM, 2010; Vesikari T, NEJM, 2006; Ruiz-Palacios, NEJM, 2006; Patel MM, NEJM, 2011; Soares-Weiser, Cochrane Database Syst Rev. 2012; Shui IM, JAMA, 2012; Cortese, PIDJ, 2010; Haber P, Pediatrics, 2008; Buttery JP, PIDJ, 2011; Vesikari T, Lancet, 2007; Chandran A, Biologics, 2010; Phua KB, Vaccine, 2009; Eberly MD, Vaccine, 2011; Patel M, J Infect Dis, 2009.

Globally-used products: Rotarix™ & RotaTeq® (cont.)

VACCINE	Rotarix™	RotaTeq®
VACCINE VIAL MONITOR	Yes – VVM 14	No
SAFETY: CLINICAL STUDIES (intussusception risk)	No increased risk detected	No increased risk detected
SAFETY: POST-INTRODUCTION (intussusception risk)	Low-level risk in some countries, not in others	Low-level risk in some countries, not in others

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[1]*Armah GE, Lancet, 2010; Zaman K, Lancet, 2010; Madhi SA, NEJM, 2010; Vesikari T, NEJM, 2006; Ruiz-Palacios, NEJM, 2006; Patel MM, NEJM, 2011; Soares-Weiser, Cochrane Database Syst Rev. 2012; Shui IM, JAMA, 2012; Cortese, PIDJ, 2010; Haber P, Pediatrics, 2008; Buttery JP, PIDJ, 2011; Vesikari T, Lancet, 2007; Chandran A, Biologics, 2010; Phua KB, Vaccine, 2009; Eberly MD, Vaccine, 2011; Patel M, J Infect Dis, 2009.*

New products: ROTAVAC® & ROTASIIL®

VACCINE	ROTAVAC®	ROTASIIL®
MANUFACTURER	Bharat Biotech Int. Ltd.	Serum Institute of India
FORMULATION	Monovalent live attenuated strain	Pentavalent, human-bovine reassortant vaccine
STRAINS PRESENT IN VACCINE	G9P(11)	G1, G2, G3, G4, and G9
EFFICACY AGAINST SEVERE ROTAVIRUS DIARRHEA IN CHILDREN <1YR (LOW- AND MIDDLE-INCOME COUNTRIES)	53.6%	36%-66.7%

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[1]*Bhandari, Nita, Lancet, 2014; Isanaka, Sheila, NEJM, 2017; Kulkarni, Prasad, Vaccine, 2017*

New products: ROTAVAC® & ROTASIIL® (cont.)

VACCINE	ROTAVAC®	ROTASIIL®
DOSAGE	Not less than 10^5 fluorescent focus units	>5.6 log10 fluorescent focus units per serotype per dose
SCHEDULE	3-dose (same schedule as DPT1, 2, and 3)	3-dose (same schedule as DPT1,2, and 3)
PRESENTATION	Liquid; oral; 1, 5, and 10 dose vials	Lyophilized + 2.5ml antacid diluent
SHELF-LIFE	5 years at -20ºC 6 months at 2-8ºC	24 months at 37ºC 18 months at 40ºC

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[1]*Bhandari, Nita, Lancet, 2014; Isanaka, Sheila, NEJM, 2017; Kulkarni, Prasad, Vaccine, 2017; Kirkwood, Carl, Vaccine, 2017; Naik, Sameer, Vaccine, 2017.*

New products: ROTAVAC® & ROTASIIL® (cont)

VACCINE	ROTAVAC®	ROTASIIL®
VACCINE VIAL MONITOR	Yes – VVM 2	Yes – VVM 30
SAFETY: CLINICAL STUDIES (intussusception risk)	No increased risk detected	No increased risk detected
SAFETY: POST-INTRODUCTION (intussusception risk)	NA	NA

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[1]Bhandari, Nita, Lancet, 2014; Isanaka, Sheila, NEJM, 2017; Kulkarni, Prasad, Vaccine, 2017

Prices of rotavirus vaccines

COUNTRY/REGION	VACCINE	PRICE (US$/COURSE)
Australia	Rotarix / RotaTeq	Not in public domain
Gavi/UNICEF	Rotarix / RotaTeq	US$2.13-3.56/dose
Gavi-eligible countries	Rotarix / RotaTeq	US$0.30-0.60 (Subsidized co-pay price)
PAHO	Rotarix / RotaTeq	US$13-15.45
United Kingdom	Rotarix	US$45 (estimated)
United States of America	Rotarix / RotaTeq	US$184-192 (CDC) US$213-226 (private market)

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Nelson EA, Hum Vaccin Imunother, 2013; UNICEF, 2015; CDC, 2013; PAHO, 2013.

Gavi price for rotavirus vaccines

For Gavi-eligible countries, price per dose will depend on the country's gross national income (GNI) per capita on overage over the previous three years. Phase I and II represent updated Gavi Graduation Policies as of June 2015.

I. **Initial self-financing** (≤$1,045 GNI per capita)
   - US$0.20/dose with no annual increase

II. **Preparatory transition** (US$1,045-1,580 GNI per capita)
   - Starts at current Gavi co-financing price for one years.
   - Following this, co-financed share of price increases by 15% each year.

III. **Accelerated transition** (>US$1,580 GNI per capita)
   - One year of 15% increase (as in Preparatory Transition)

Following this, countries gradually ramp up over five years to reach the price paid by Gavi after co-financing ends.

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Gavi. Gavi Board minutes. Review of Gavi's co-financing policy. 2015. Available from: http://www.gavi.org/library/minutes/gavi-alliance-board/

Benefits vs. risks

- Intussusception (IS) **occurs naturally** in infants, in the absence of vaccination, between 2 and 9 months of age, and the rates at which it occurs varies from region to region.
- The number of naturally occurring cases of IS ranges from 9 to 328 per 100,000 children under age 1, with an average of 74 cases per 100,000.[1]
- GSK's Rotarix and Merck's RotaTeq have **strong safety records** and have been **studied in every region** of the world. Post-marketing surveillance studies from Australia, Brazil, Mexico, and the US have found the risk of IS for Rotarix & RotaTeq is comparable, and that for every 100,000 children vaccinated, there are an estimated 1 to 6 additional cases of IS.[2,3]

Based on all of the available evidence, WHO, whose Global Advisory Committee on Vaccine Safety most recently reviewed global intussusception data in February 2014, holds the position that the benefits of rotavirus vaccines outweigh the small risk of intussusception.[4]

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[1]*Jiang J, PLoS One, 2013*
[2]*Carlin JB, Clin Infect Dis, 2013*
[3]*Cortese M, CDC ACIP, 2013*
[4]*WHO, 2014*

REAL-WORLD RESULTS

Impact, cost-effectiveness, and indirect benefits

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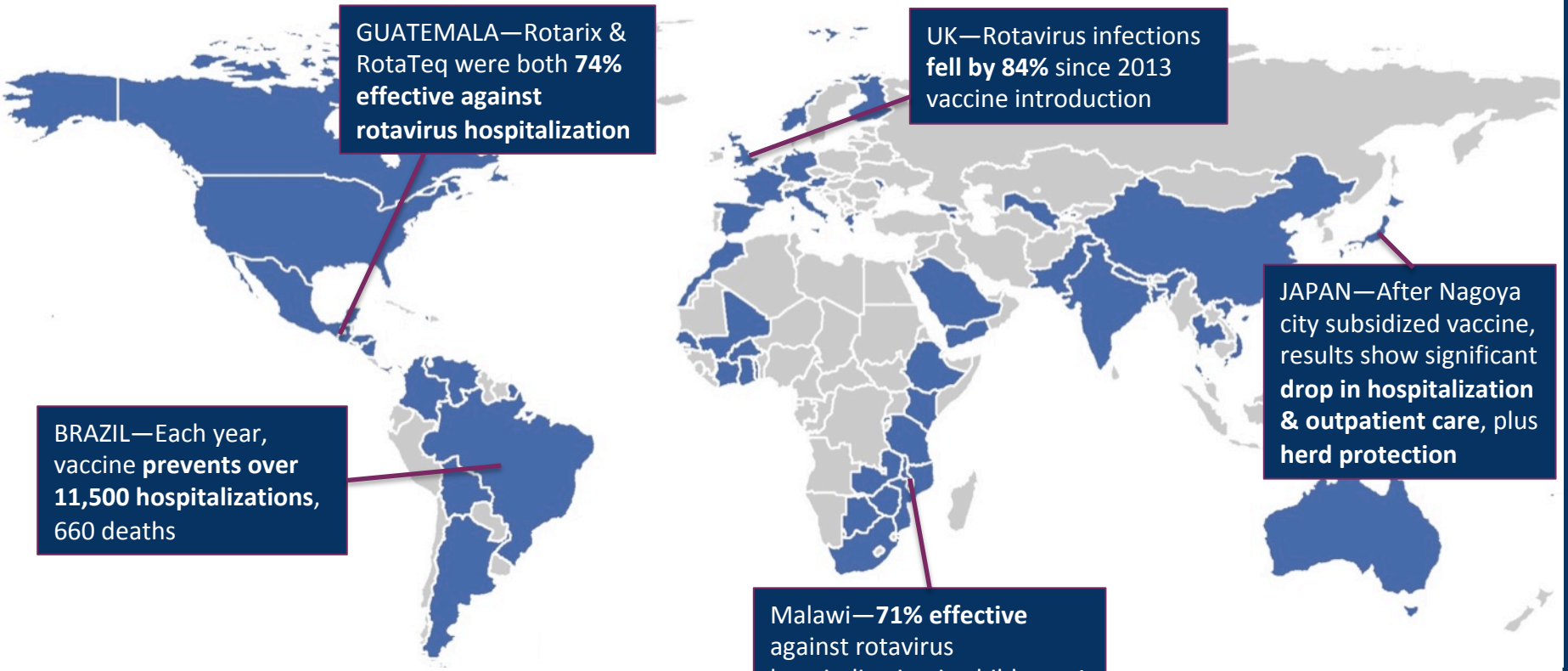
Vaccine impact data available from all world regions and income groups



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Guatemala: Gastanaduy 2016; Brazil: Patel MM 2011; UK: Public Health England 2016; Malawi: Bar-Zeev et al CID 2016; Japan: Yoshikawa

Vaccine impact: Early adopter countries

COUNTRY	ROTAVIRUS VACCINE INTRODUCTION YEAR	REDUCTION IN ALL-CAUSE GASTROENTERITIS DEATHS AMONG CHILDREN UNDER AGE 5 FOLLOWING INTRODUCTION
Bolivia	2008	36-43%
Brazil	2006	22%
El Salvador	2006	0-36%
Honduras	2009	16-20%
Mexico	2007	43-55%*
Panama	2006	50%**
Venezuela	2006	57-64%

**Measured from 2009-2011. While methodologies differ, and some studies aren't directly comparable, it is clear the vaccine has had a significant impact.*
***Among children age 0-4 years*

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[1] do Carmo GM, PLoS Med, 2011; [2]Gastanaduy PA, Pediatrics, 2013; [3]Bayard V, Int J Infect Dis. 2012;[4] De Oliveira LH, Vaccine, 2013

Vaccine impact: High-income countries

COUNTRY	VACCINE USED	VACCINE IMPACT: REDUCTION IN HOSPITALIZATIONS
Australia	Rotarix, RotaTeq	45-88%
Austria	Rotarix, RotaTeq	74-79%
Belgium	Rotarix, RotaTeq	50-80%
Finland	Rotarix, RotaTeq	78%
United States of America	Rotarix, RotaTeq	55-94%

Studies vary in time period and age group, and therefore are not directly comparable. However, when taken together, they demonstrate the significant impact of the vaccine.

In the **first four years** of their use in the U.S., rotavirus vaccines prevented

- **176,000 hospitalizations**
- **242,000 emergency department visits**
- **1.1 million doctor visits**

among children under age 5, resulting in nearly **US$1 billion** in savings.

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PATH. 2015; Gurgel RG, Gastroenterology, 2009

Vaccine impact: Africa

COUNTRY	YEARS OF NATIONAL ROTAVIRUS VACCINE INTRODUCTION	DATA TIME PERIOD: PRE-VACCINE	DATA TIME PERIOD: POST-VACCINE	REDUCTION IN ROTAVIRUS DIARRHEA HOSPITALIZATIONS AMONG CHILDREN <5 YEARS FOLLOWING INTRODUCTION
Ghana	2012	Jan 09 – Mar 12	Apr 12 – Dec 14	49%
Rwanda	2012	Jan 09 – Dec 11	Jan 12 – Dec 14	61-70%
South Africa	2009	May – Dec 09	May – Dec 10; May – Dec 11	54-58%
Togo	2014	July 08 – June 14	July 14 – June 15	32%

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[1]Armah G, Clin Infect Dis. 2016; [2]Ngabo F, Lancet Glob Health, 2016; [3]Msimang VM, Pediatr Infect Dis, 2013; [4]Tsolenyanu E, Clin Infect Dis, 2016

Vaccine impact: Africa

COUNTRY	YEARS OF NATIONAL ROTAVIRUS VACCINE INTRODUCTION	PRE-VACCINE	POST-VACCINE	REDUCTION IN ALL-CAUSE DIARRHEA HOSPITALIZATIONS AMONG CHILDREN <12 MONTHS FOLLOWING INTRODUCTION
Botswana	2012	Jan 09 – Dec 12	Jan 13 – Dec 14	43%*
Ghana	2012	Jan 09 – Mar 12	Apr 12 – Dec 14	52%
Malawi	2012	Jan 12 – June 12	Jan 13 – June 15**	48.2%
Rwanda	2012	Jan 09 – Dec 11	Jan 12 – Dec 14	51-55%
South Africa	2009	Jan 06 – 2008	Jan 10 – Dec 14	44.9-65.4%
Zambia	2013	Jan 09 – Dec 11	Jan 13 – Dec 14***	18-29%

Study methodologies differ, so the studies are not directly comparable. RotaTeq used in Rwanda; all others used Rotarix.
**During rotavirus season; **Pre/post periods not directly comparable because of enhanced surveillance; ***2012 excluded as transition year*

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[1]Enane LA, Clin Infect Dis. 2016; [2]Armah G, Clin Infect Dis. 2016 ; [3]Bar-Zeev N, Clin Infect Dis. 2016 ; [4]Tate JE, Clin Infect Dis. 2016; [5]Groome MJ, Clin Infect Dis. 2016; [6]Mpalbalwani, Clin Infect Dis. 2016

Rotavirus vaccines are cost-effective

Recent studies show that national rotavirus vaccination programs will be highly cost-effective and also reduce healthcare costs due to rotavirus-related illness.[1-7]

COUNTRY	NUMBER OF CASES AVERTED	DEATHS AVERTED	HEALTHCARE COSTS AVERTED	DATE RANGE
Iran	35.1 million	266	US$280 million	2014-2023
Kenya	1.2 million	61,000	US$30 million	2014-2033
Senegal	2 million	8,500	US$8 million	2014-2033
Uganda	4 million	70,000	US$10 million	2016-2035
Malawi	1 million	4,313	US$8 million	2014-2033
Afghanistan	1 million	12,000	US$1.35 million	2017-2027
Bangladesh	3.9 million	3900	US$7 million	2017-2027

In the US, in just four years, rotavirus vaccination saved nearly US$1 billion by preventing hospitalizations, emergency visits and doctors' visits among children under age 5.[5]

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[1]Sigei C, Vaccine, 2015; [2]Javanbakht M, Vaccine, 2015 ; [3]Diop A, Vaccine, 2015 ; [4]Bar-Zeev N, Clin Infect Dis. 2016; [5] Leshem E, Pediatrics, 2014; [6]Palwasha A., Vaccine, 2017; [7]Pecenka C, Vaccine, 2017

Rotavirus vaccines offer broad protection

	Protection against strains NOT included in vaccine	Vaccine effectiveness	Country
ROTARIX	G2P[4]	71-94%	United States, Brazil, Bolivia
	G9P[4]	94%	Mexico
	G9P[8]	84%	Bolivia
	G9P[6]	87%	Bolivia
	G3P[8]	74-92%	United States, Bolivia
ROTATEQ	G12P[8]	83%	United States
	G2P[4]	87-98%	United States

While study methodologies differ and studies may not be directly comparable, it is clear the vaccine has demonstrated effectiveness.

The two rotavirus vaccines available on the global market of circulating provide **protection against a variety of strains**, including those not included in the vaccines.

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Correia JB, J Infect Dis, 2010
Yen C, Hum Vaccin, 2010
Cortese MM, Pediatrics, 2013
Justino MC, PIDJ, 2011
Payne DC, Clin Infect Dis, 2013
Cortese MM, Pediatrics, 2011

Indirect benefits of rotavirus vaccination

	Rotavirus related hospitalizations reduced in:	
	Children age-eligible for vaccine	Children NOT age-eligible for vaccine*
Country (nationwide)		
El Salvador	79-86%	41-81%
Austria	76-79%	35%
USA**	74-96%	41-92%
Belgium	65-80%	20-64%
Country (regional)		
Australia***	50-89%	30-100%
Sao Paulo, Brazil	56-69%	24%

Significant reductions in rotavirus hospital admissions observed among vaccinated and unvaccinated children

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Note: table derived from Table 4 from: Patel MM, Glass R, Desai R, Tate JE, Parashar UD. Fulfilling the Promise of Rotavirus Vaccines: How Far Have We Come Since Licensure? The Lancet Infectious Diseases. 2012;12(7):561-570.

**Typically 2-5 years old, but varies by country; **Combines three national studies ; ***Combines three regional studies*

THE FUTURE OF ROTAVIRUS VACCINES

Product pipeline and research gaps

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Nationally available vaccines and upcoming products

VACCINE	NAME	COMPANY	STATUS	STRAIN(S)
Australian neonatal	RV3-BB	Biofarma (Indonesia) and MCRI (Australia)	Early clinical trials ongoing in New Zealand and Indonesia	G3, P[6]
NIH (bovine-human reassortant)	UK	Licensed to various manufacturers: Wuhan & Chengdu (China); Serum Institute, Shantha, Biologicals E, Bharat Biotech (India); Butantan (Brazil)	Serum Institute of India and Shantha vaccines undergoing Phase 3 clinical trials	Bovine (G6P[7]) + G1, G2, G3, G4 reassortants
Vietnamese	Rotavin M1	POLYVAC	Licensed in Vietnam	G1P[8]
Lamb rotavirus (lamb-human reassortant)	LLR LLR+	Lanzhou Biologicals / Xinkexian Biological Technology (China)	Licensed in China	G10, P[12] + G1, G2, G3, G4

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Emerging data

Impact:
- Additional data on impact and effectiveness from ongoing introductions will be available soon

Safety:
- Better understand intussusception occurrence, track causes, monitor treatment patterns, rates of surgery, and outcomes
- Maintain surveillance networks
- Assess intussusception risks in the context of benefits (reduced hospitalizations & deaths)

Vaccine performance:
- Examine strategies to improve oral vaccines
- Assess role of zinc & probiotic supplementation

Vaccine schedules:
- Evaluating various 2- and 3-dose regimens
- Examine booster dose

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Research gaps

- Introduction
  - Alternative approaches for vaccine delivery
  - Barriers to introduction and scale-up
- Products
  - Potential for new vaccines to ensure stable, sufficient supply and impact prices
  - Drivers of product choice
  - Dosing schedule
  - Potential interchangeability of products
- Biology
  - Influence of gut microbiome on vaccine effectiveness

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ROTA COUNCIL RECOMMENDATIONS

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Despite the WHO recommendation that rotavirus vaccines be introduced into every country's national immunization program, over **90 million children** throughout the world still do not have access to this critical intervention.

The ROTA Council **strongly endorses** the WHO recommendation.

To accelerate the introduction of life-saving, health-improving rotavirus vaccines, the ROTA Council recommends **key stakeholders** – in countries **where these vaccines have not yet been introduced** – undertake **actions** in the following areas…

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Key Stakeholders

- Global health organizations: WHO, UNICEF, Gavi
- Gavi-eligible (low-income) country decision makers
- Funding agencies
- National & local governments in LMICs & HICs
- Researchers
- Non-governmental organizations
- Manufacturers
- Educational authorities & academics
- Media & advocacy groups
- Frontline health workers

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To encourage rotavirus vaccine introduction in Gavi-eligible (low-income) countries:

- Gavi-eligible countries that have not yet introduced rotavirus vaccines should strongly consider applying to Gavi for new vaccine support as soon as possible
- To optimize vaccine rollout & maximize number of eligible infants immunized, WHO, UNICEF, Gavi, and other partners should continue to support countries planning to introduce the vaccine (especially cold chain, available supply, and sustainable financing)
- If rotavirus vaccine of choice is not available, countries should strongly consider introducing any prequalified rotavirus vaccine available in the short-term and work with Gavi for longer-term options.
- Low- and lower-middle-income countries that have introduced should share lessons with countries that have not yet introduced through focused regional meetings.
- Countries planning to introduce rotavirus vaccines should establish a strong surveillance system.
- Countries that have introduced OR plan to introduce should collect high-quality data to evaluate vaccine impact (esp. on districts with high mortality rates).
- Funding agencies should continue to support evaluation of rotavirus vaccine programs (operation, safety, impact).

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To encourage rotavirus vaccine introduction in non-Gavi-eligible (lower-middle-, upper-middle-, and high-income) countries:

- National & local governments enact legislation that addresses issues of the rights of populations to receive recommended vaccines & provisions to ensure supply of quality, affordable vaccines.
- Governments & funding agencies should continue to support research & development of new, low-cost rotavirus vaccines using public, social business, & public-private models.
- Global health agencies & NGOs influential in vaccine programs expedite initiatives to ensure prices paid for rotavirus vaccines reflect true manufacturing costs, provide reasonable returns on manufacturers' investments, and take into account a country's ability to pay. All countries should report the price of their vaccine to WHO's V3P Project.
- To ensure integration with existing interventions by GAPPD, national governments should provide training courses to update frontline health workers; and, data should be collected by educational authorities & academia to determine the information being incorporated into health worker curricula.
- National governments, funding agencies, and global health entities should support media & advocacy groups to ensure benefits of rotavirus & other vaccines are conveyed to the public.
- WHO, UNIFEC, and NGOs should collect data to better understand reasons why a number of high-income countries have not yet included rotavirus vaccines in their NIP.

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To influence the research agenda & gain better understanding of impact, effectiveness and safety of rotavirus vaccines – particularly in low-income countries of Africa and Asia – researchers should:

- Quantify changes in morbidity & mortality from severe diarrheal disease in countries using rotavirus vaccine
- Examine effect of vaccination on epidemiology of rotavirus
- Assess evidence of indirect benefits among unvaccinated children
- Perform long-term monitoring to assess possible changes in ecology of circulating strains after vaccine implementation
- Assess effectiveness of vaccination beyond one year of age & against circulating strains
- Examine vaccine safety with respect to intussusception in targeted settings & assess identified risks in the context of vaccine benefits

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To influence the research agenda & gain better understanding of reasons for moderate efficacy of live, oral rotavirus vaccines in low-income countries and to identify strategies to improve vaccine performance, researchers should:

- Assess possible interference of oral polio vaccine, breastfeeding, and gut microbiome and/or intestinal enteropathy on vaccine effectiveness
- Investigate regional differences in vaccine impact related to genetic differences and specific immunological characteristics of circulating strains
- Examine effect of different vaccine schedules on vaccine performance

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To influence the research agenda & gain better understanding of different options for formulations aimed at increasing vaccine uptake and/or addressing diarrheal disease simultaneously, researchers and manufacturers should:

- Pursue development of non-live oral vaccines and birth dose of live oral vaccine that may overcome come interference observed in low-income countries
- Explore the mechanism of immunologic protection for rotavirus infection/disease to help identify correlates of protection to facilitate vaccine testing
- Develop formulations and packaging that requires less cold chain space or can even be outside the cold chain
- Explore impact of live oral rotavirus vaccines on non-specific effects of vaccination

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To encourage the development of new rotavirus vaccines, national governments, funding agencies, international health organizations, manufacturers and other stakeholders should:

- Facilitate development of new live oral vaccines to address barriers to global supply for Gavi & low- and middle-income countries; implementation challenges & cultural sensitivity; and that are also safe, efficacious and available at low cost. This research agenda should address: implications of lack of correlate of protection, formulations to enhance programmatic suitability & vaccine stability, and improvements to manufacturing process efficiency.
- Facilitate development of alternative rotavirus vaccines. This research agenda should address: clinical development, vaccine development and mechanism of action of injectable, non-replicating vaccines against rotavirus disease.
- Pursue options for immunization schedules aimed at improving protection, including: neonatal schedules, booster dose or even prime-boost strategies.
- Explore combination vaccine & non-vaccine strategies aimed at reducing diarrheal disease and/or improving vaccine uptake.
- Explore options for combination viral & bacterial enteric vaccines to provide protection against diarrhea caused by a range of potential pathogens.

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CASE STUDIES

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GHANA

Monumental dual vaccine introduction combats leading causes of child death

- Rotavirus killed **>2,000 children annually.**[1,2]
- In April 2012, Ghana became the **first Gavi-eligible country** to introduce pneumococcal and rotavirus vaccines into its NIP simultaneously.
- The government built **new vaccine storage** room, issued millions of **updated immunization cards,** and **dispelled immunization myths** through community campaigns.[3,4]

✓ **Two years** following dual introduction, rotavirus hospitalizations **fell from 50% to 28%** of severe diarrhea hospitalizations

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[1]Black RE, Lancet, 2010
[2]WHO, 2008
[3]Gavi, YouTube, 2012
[4]PATH, RotaFLASH, 2012

INDIA

Innovative partnerships lead to development of indigenous vaccine

- **Greatest burden** of rotavirus under-five deaths in the world: over 870,000 hospitalizations and 3 million outpatient visits, costing over Rs. 10 billion annually.[1]
- **ROTAVAC®** is the indigenous vaccine manufactured by Bharat Biotech International Limited.
- ROTAVAC® was developed through **public-private partnership**: Indian government, international donors, global rotavirus experts, and private sector.

- ✓ ROTAVAC® is an attractive option – at **US$1 per dose.**
- ✓ As of 2017, **nine states** have introduced ROTAVAC®.

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[1]*Tate JE, Lancet Infect Dis. 2012*

ZAMBIA

Pilot program deploys integrated and comprehensive approach

- Rotavirus killed **3,600 children under five each year**.
- In 2012, **Programme for Awareness & Elimination of Diarrhoea** (PAED) launched in Lusaka.
- PAED improved **cold chain**, trained > 500 **health workers**, and informed **communities**; and had strong **partnerships**, **integration** with existing child health program, and a **comprehensive approach** to diarrheal disease control.

- ✓ PAED helped to implement **GAPPD framework.**
- ✓ In just over one year **>10,000 children** received rotavirus vaccine.

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Additional resources

ROTA Council resources

http://rotacouncil.org/resources/

Executive summary & full white paper

http://rotacouncil.org/resources/rota-council-white-paper/

VIEW-hub (Vaccine Information and Epidemiology Window)

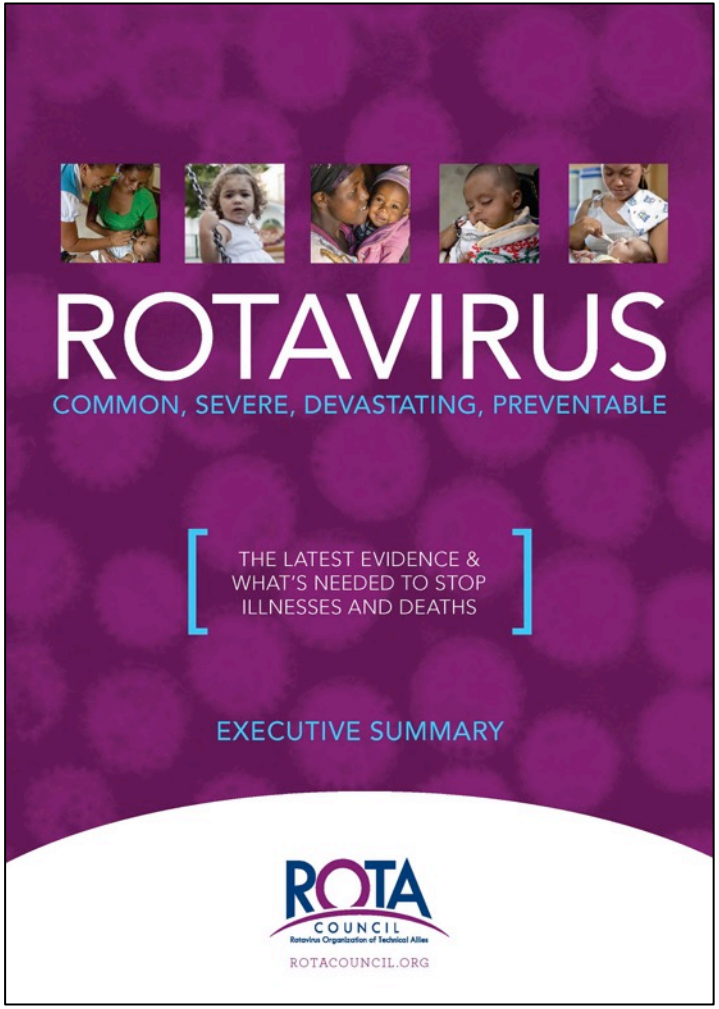
http://view-hub.org

VoICE (Value of Immunization Compendium of Evidence)

http://view-hub.org/voice/

PATH's State of the Field Report

http://report.defeatdd.org/



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