



Rotavirus Disease Burden – Vaccine Uptake and Impact

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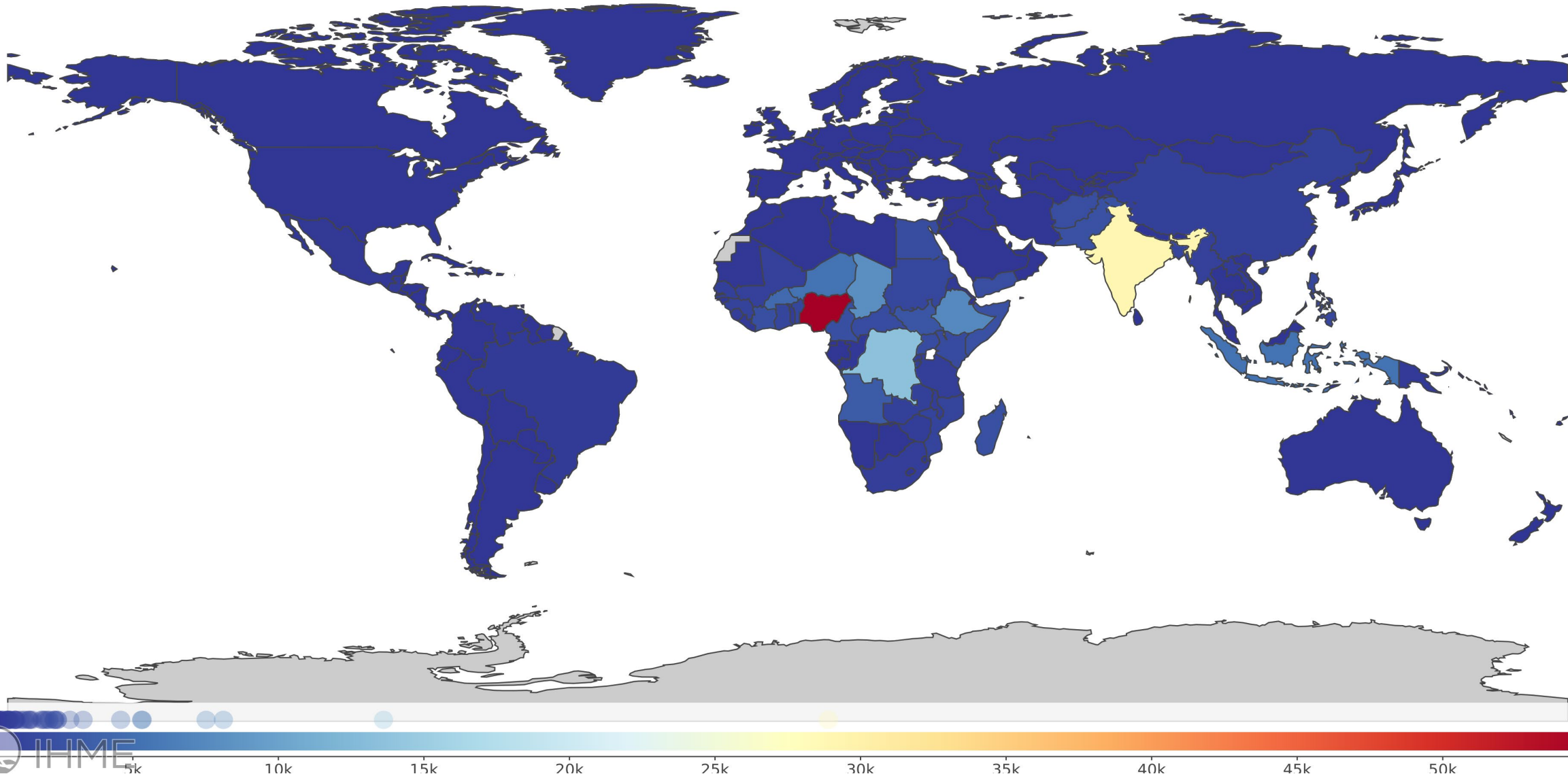


Diarrhea: A leading cause of child death

- Diarrhea is leading cause of child illness death^{1,2}
- More than 1.7 billion cases occur each year in children <5 years of age worldwide²
- In developing countries, children <3 years of age experience on average 3 episodes of diarrhea every year²
- If left untreated, diarrhea can cause severe dehydration and lead to hospitalizations or death²

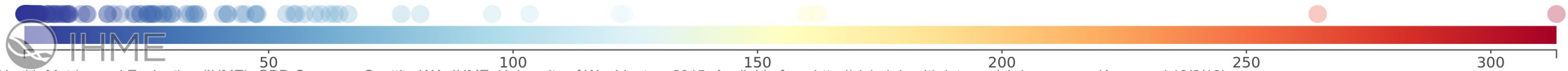
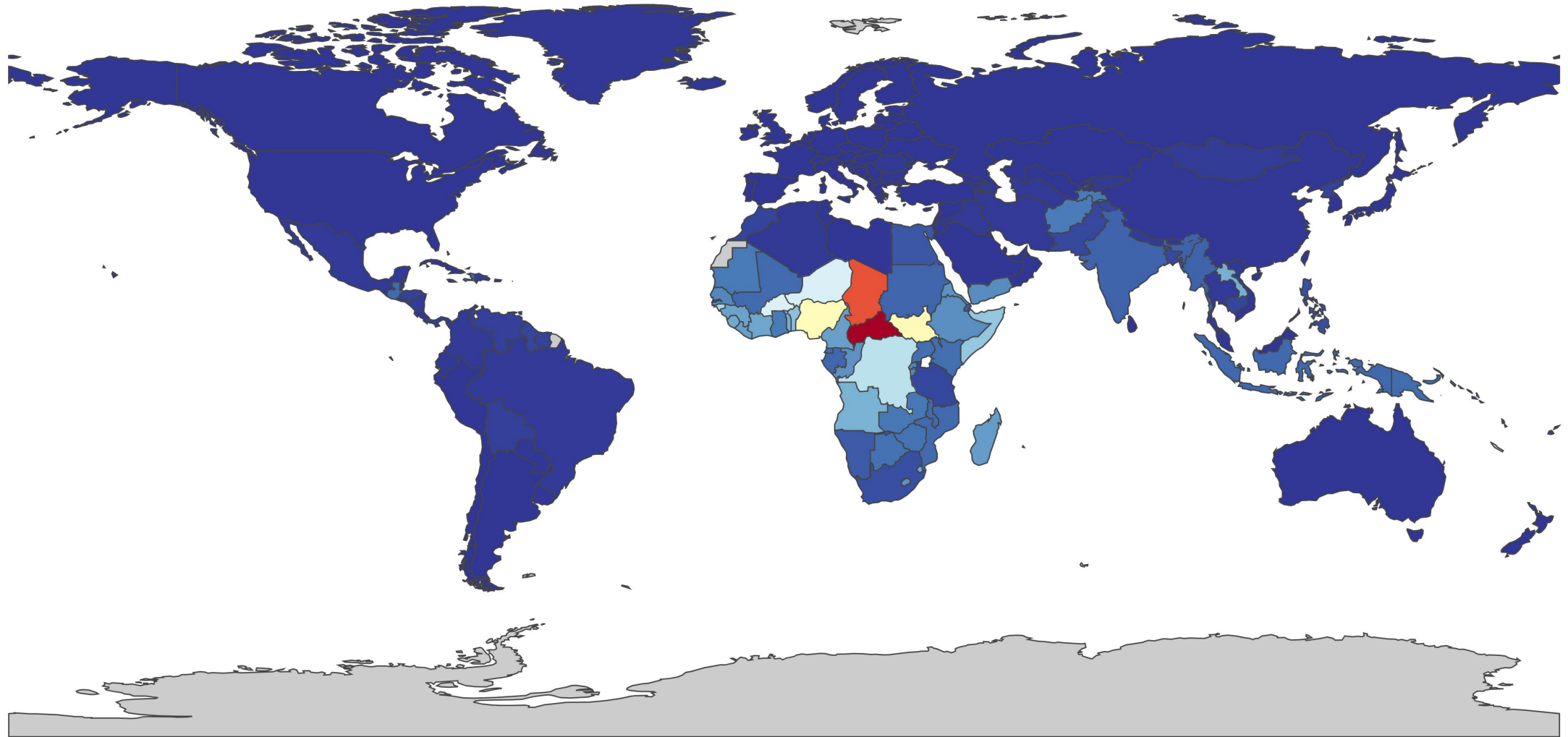


Rotavirus diarrhea deaths among children under 5 years of age, 2017





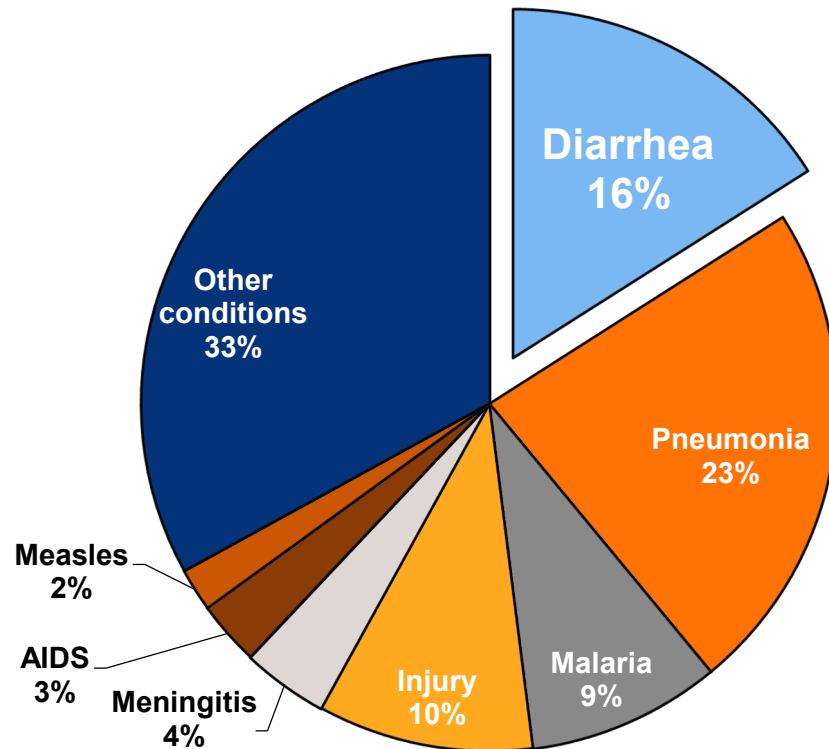
Rotavirus diarrhea mortality rate among children under 5 years of age, 2017





Diarrhea is a top cause of child death

Leading Causes of Death for Children Aged 1-59 Months*



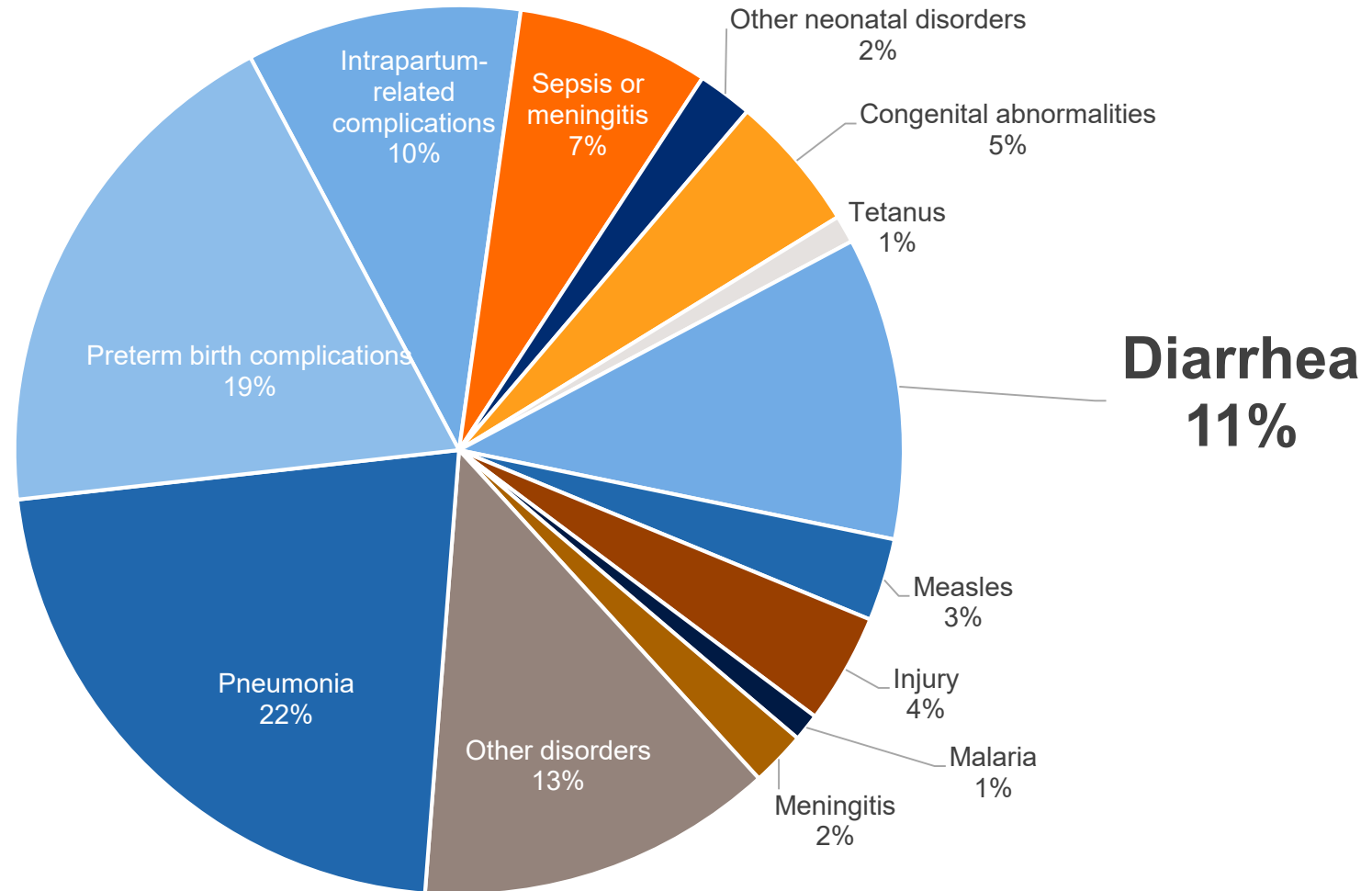
More than 509,000 deaths of children 1-59 months were attributed to diarrhea in 2015 globally¹

¹ Liu, Oza, Hogan et al., Global, regional, and national causes of under-5 mortality in 2000–15, Lancet 2016.

*Excludes neonatal deaths, which make up a significant burden of under-five deaths, but have unique causes that must be addressed separately.



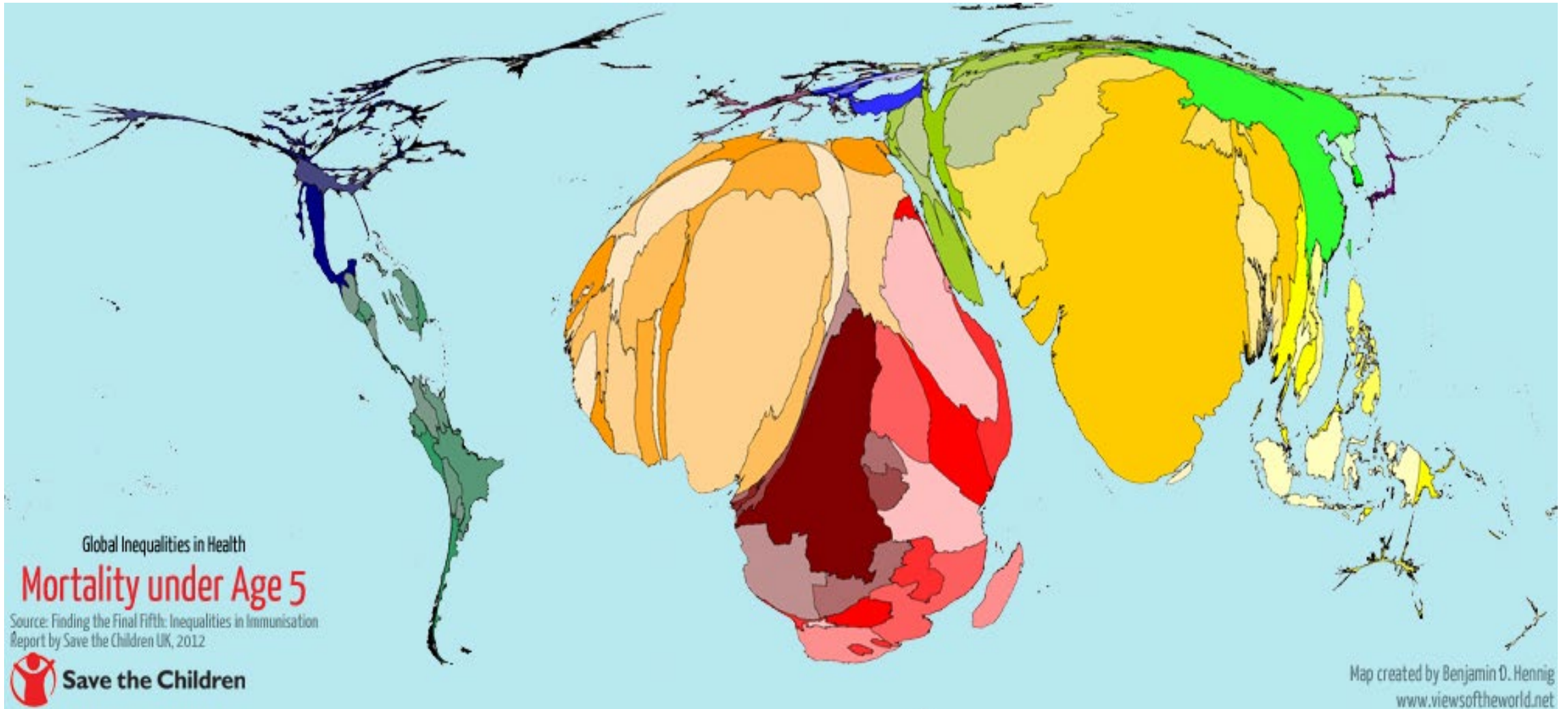
Causes of death in Asian children under 5 in WHO SEARO region, 2010



¹Liu L, Johnson HL, Cousens S, et al. Global, regional, and national causes of child mortality: An updated systematic analysis for 2010 with time trends since 2000. The Lancet. 2012;379(9832):2151–2161. [N.B. WHO's South-East Asia region does not include all countries on the Asian continent. For example, the Philippines is part of WHO's Western Pacific Region].



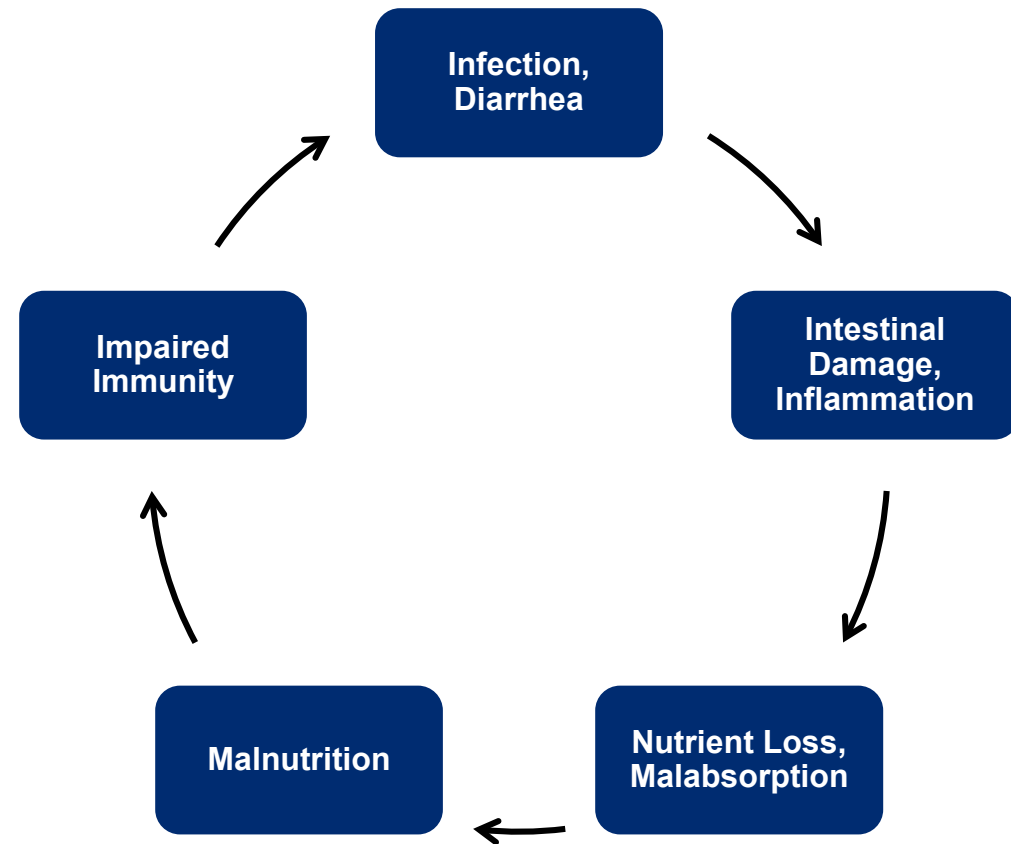
World map redrawn based on child deaths





Lasting effects of diarrhea

Diarrhea leaves children vulnerable, is a major contributor to malnutrition, and can lead to growth delays and cognitive impairment¹





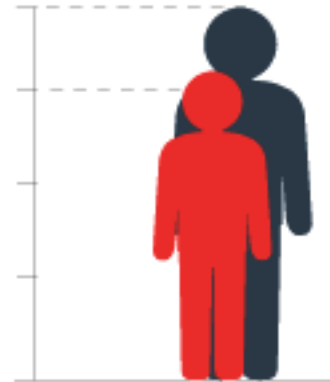
Diarrhea's devastating impact

APPROXIMATELY **1 IN 5** CHILDREN



UNDER THE AGE OF TWO **SUFFER FROM AN EPISODE OF MODERATE TO SEVERE DIARRHEA (MSD)** EACH YEAR.

THESE CHILDREN ARE **8.5 TIMES** MORE LIKELY **TO DIE** WITHIN TWO MONTHS OF HAVING DIARRHEAL DISEASE, USUALLY AFTER THEY LEAVE THE HOSPITAL.



IF THE CHILD SURVIVES, HIS/HER **GROWTH IS LIKELY TO BE STUNTED** COMPARED TO PEERS OVER THE SAME TWO-MONTH PERIOD.

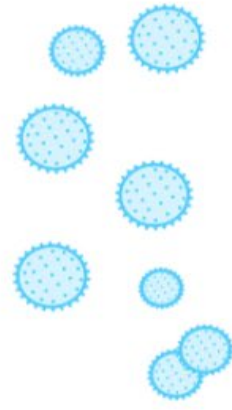
61% of deaths occurred **more than 1 week** after a child's initial acute episode – when he or she may no longer have been receiving care



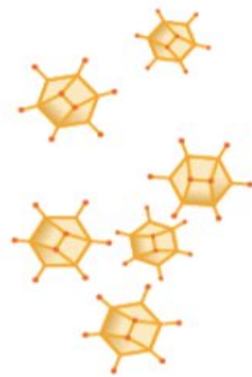
Rotavirus: The pathogen



Shigella



Rotavirus



Adenovirus



*Enterotoxigenic E.
Coli*



Cryptosporidium



Campylobacter

- **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)



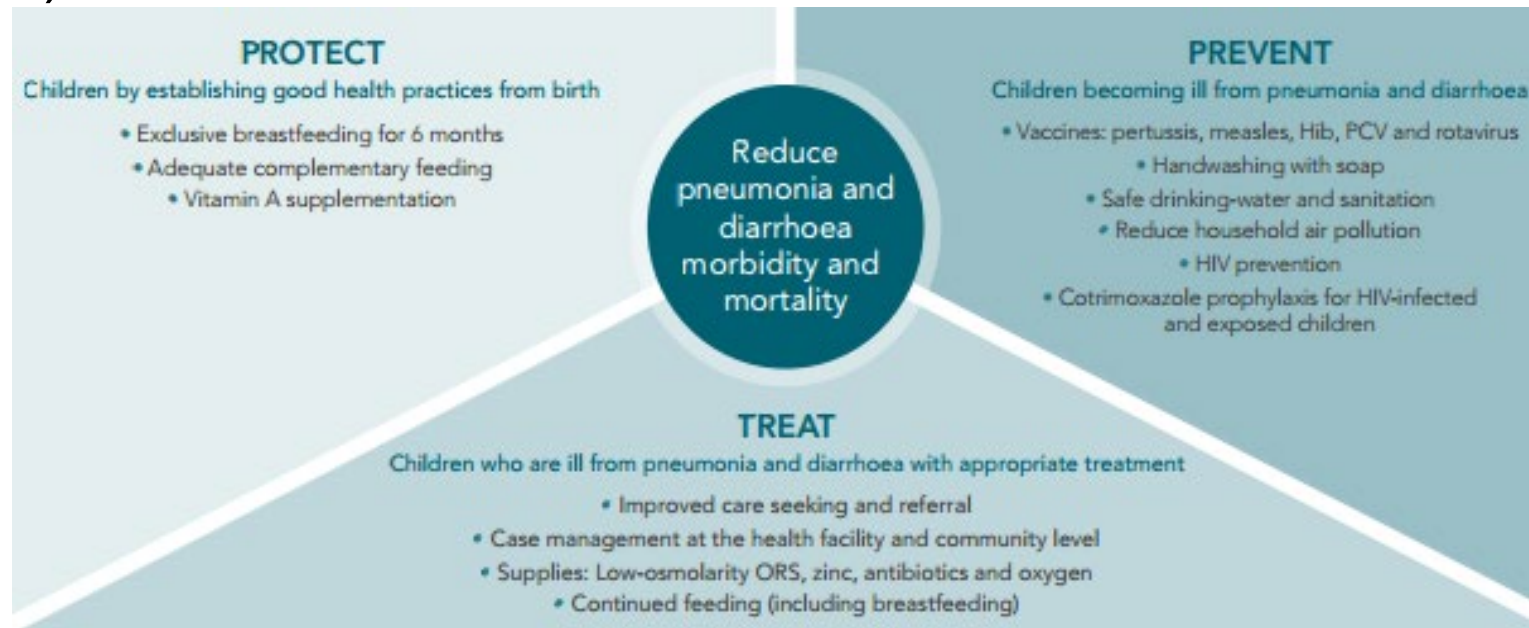
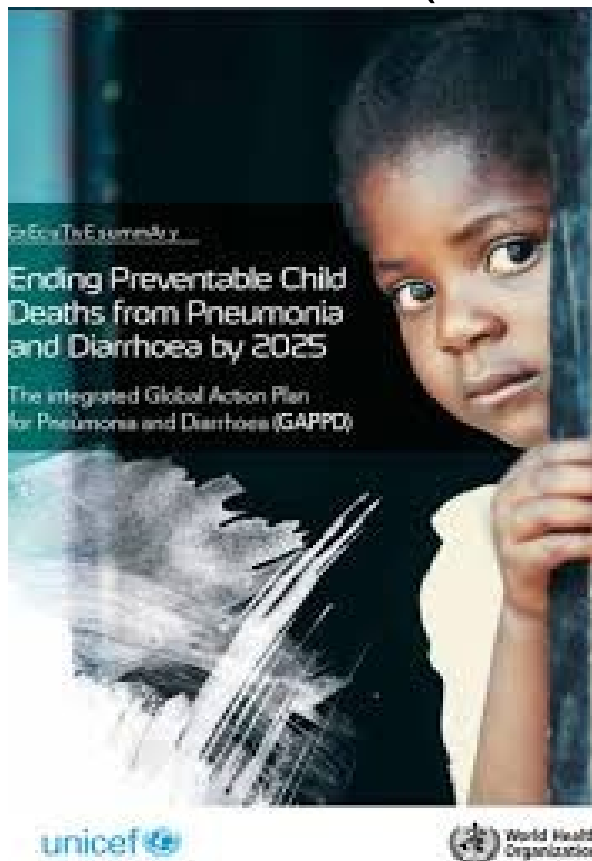
Rotavirus: Common and serious

- Rotavirus is the **most common cause** of severe diarrhea among children¹ and responsible for **over 200,000 under-5 deaths** in 2013²
- Rotavirus is **easily spread** from person-to-person and can survive on hands and surfaces for long periods of time²
- In the absence of vaccine use, **almost every child is infected by age 5**, rich or poor, regardless of where they live
- Improvements in hygiene, sanitation and drinking water **do not adequately prevent** rotavirus¹
- Most infections occur in **very young children**, who are most at-risk for dehydration



GAPPD: The comprehensive approach

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



Even when treatment is available, children still suffer from illness. Children with an episode of moderate to severe diarrhea have an 8.5-fold increased risk of death and grow significantly less in length during the two months following their illness compared to similar children who do not experience an episode of diarrhea.¹

¹Kotloff KL, Lancet, 2013



Strategies for preventing and treating pneumonia

- Protection
 - Breast feeding promotion
 - Hand washing promotion
 - Zinc supplementation
 - Adequate nutrition
 - Reduce indoor air pollution
- Prevention
 - Vaccination
 - New: Pn
 - Routine: Measles, pertussis
 - HIV prevention
- Treatment
 - Improve care seeking behavior
 - Community case management
 - Health facility case management
 - Antibiotics

Strategies for preventing and treating diarrhea

- Protection
 - Breast feeding promotion
 - Hand washing promotion
 - Vitamin A and Zinc supplementation
 - Adequate nutrition
 - Safe water and sanitation
- Treatment
 - Improve care seeking behavior
 - Community case management
 - Health facility case management
 - Low-osmolarity ORS
 - Zinc

Many interventions and treatment strategies are identical



Integrated Global Action Plan for Pneumonia and Diarrhea (GAPPD)

Many interventions and treatment strategies for pneumonia and diarrhea are identical



Adapted from PATH: Tackling the deadliest diseases for the world's poorest children. Source: WHO/UNICEF (2013). GAPPD.



Treatment and prevention

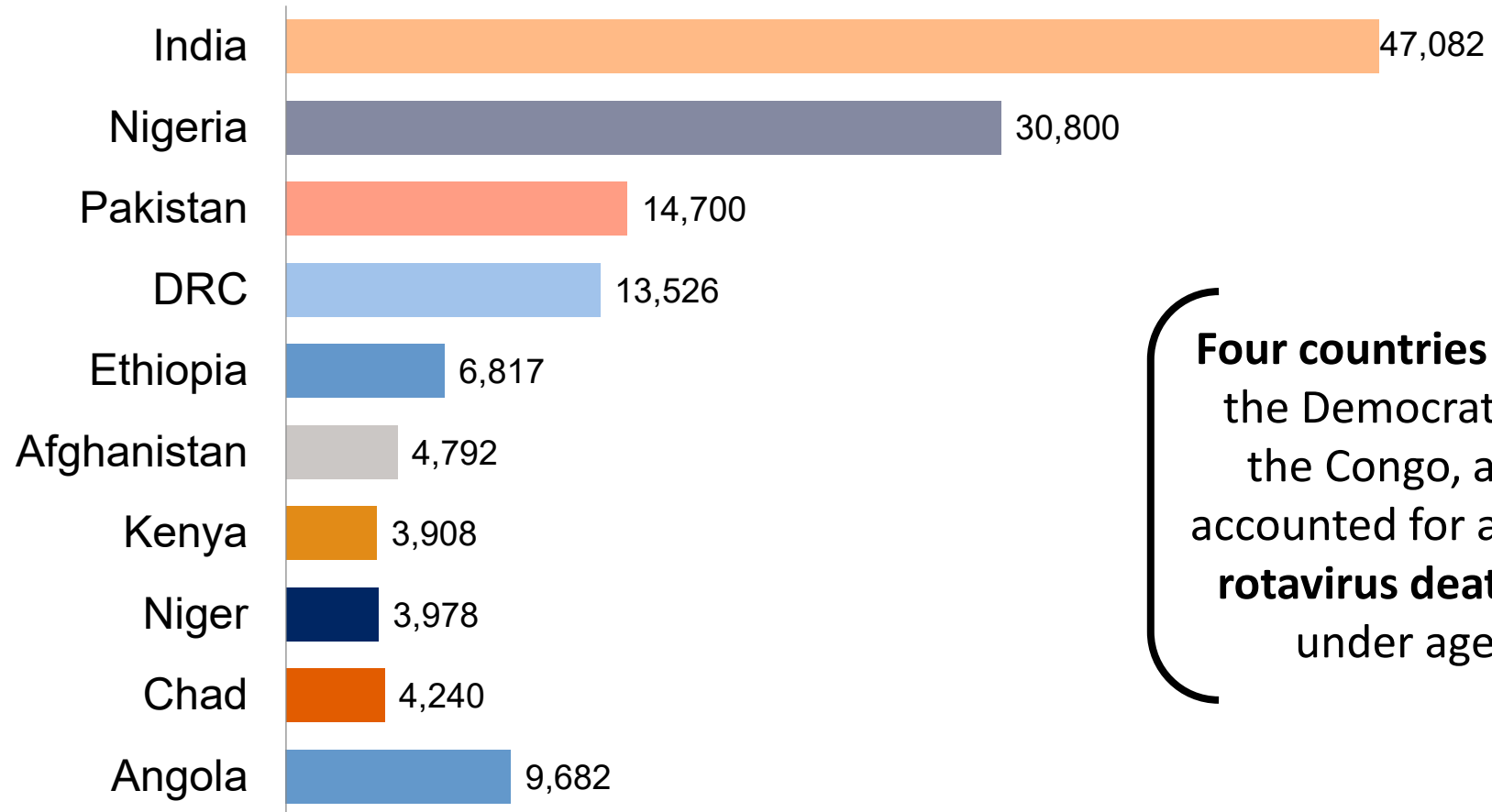
Without access to treatment for the severe dehydration it can cause, rotavirus can be a death sentence

- Rotavirus cannot be treated with antibiotics or other drugs
- Prompt treatment with oral rehydration therapy (ORT) can be effective in treating most mild-to-moderate cases
- 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 occur¹



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

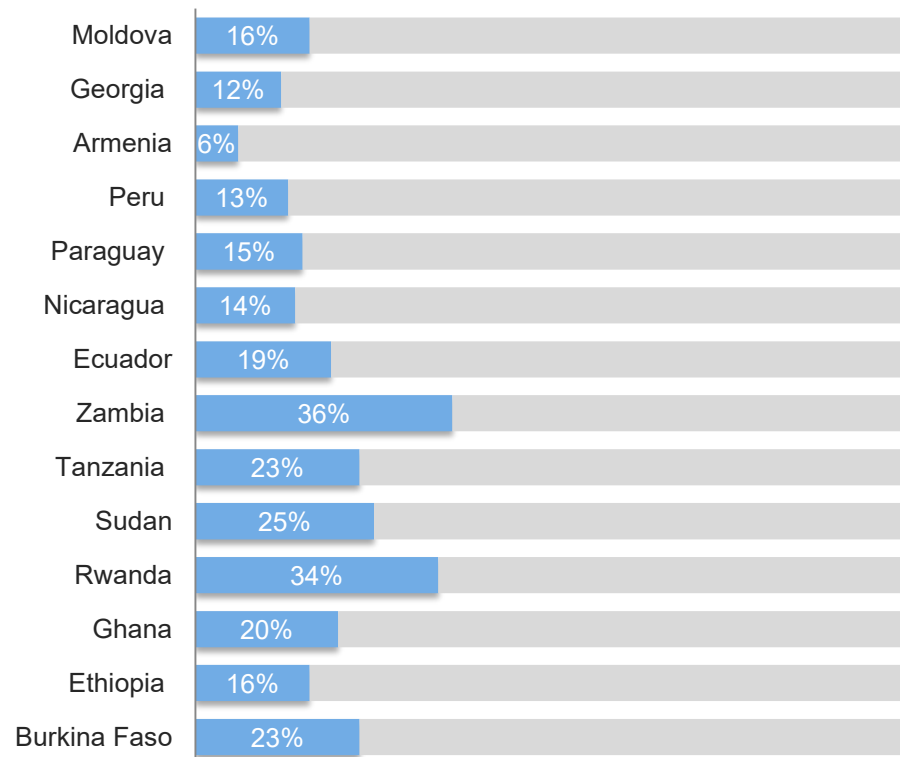
WHO. Estimated rotavirus deaths for children under 5 years of age in 2013. http://www.who.int/immunization/monitoring_surveillance/burden/estimates/rotavirus/en/



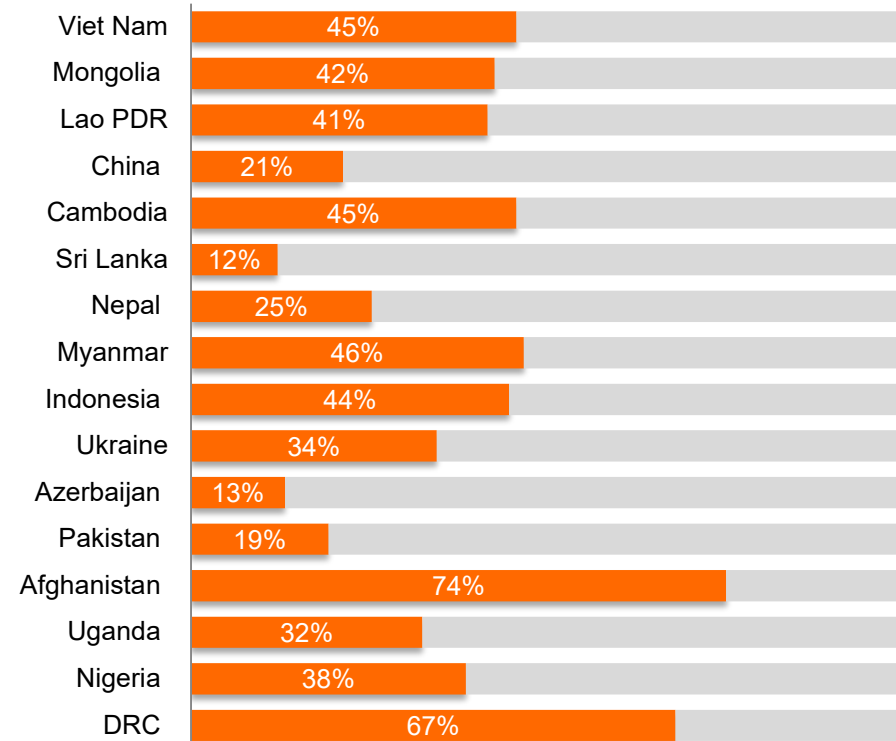
Disease burden: hospitalizations

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

Countries with rotavirus vaccine in national program
Median = 17.5%

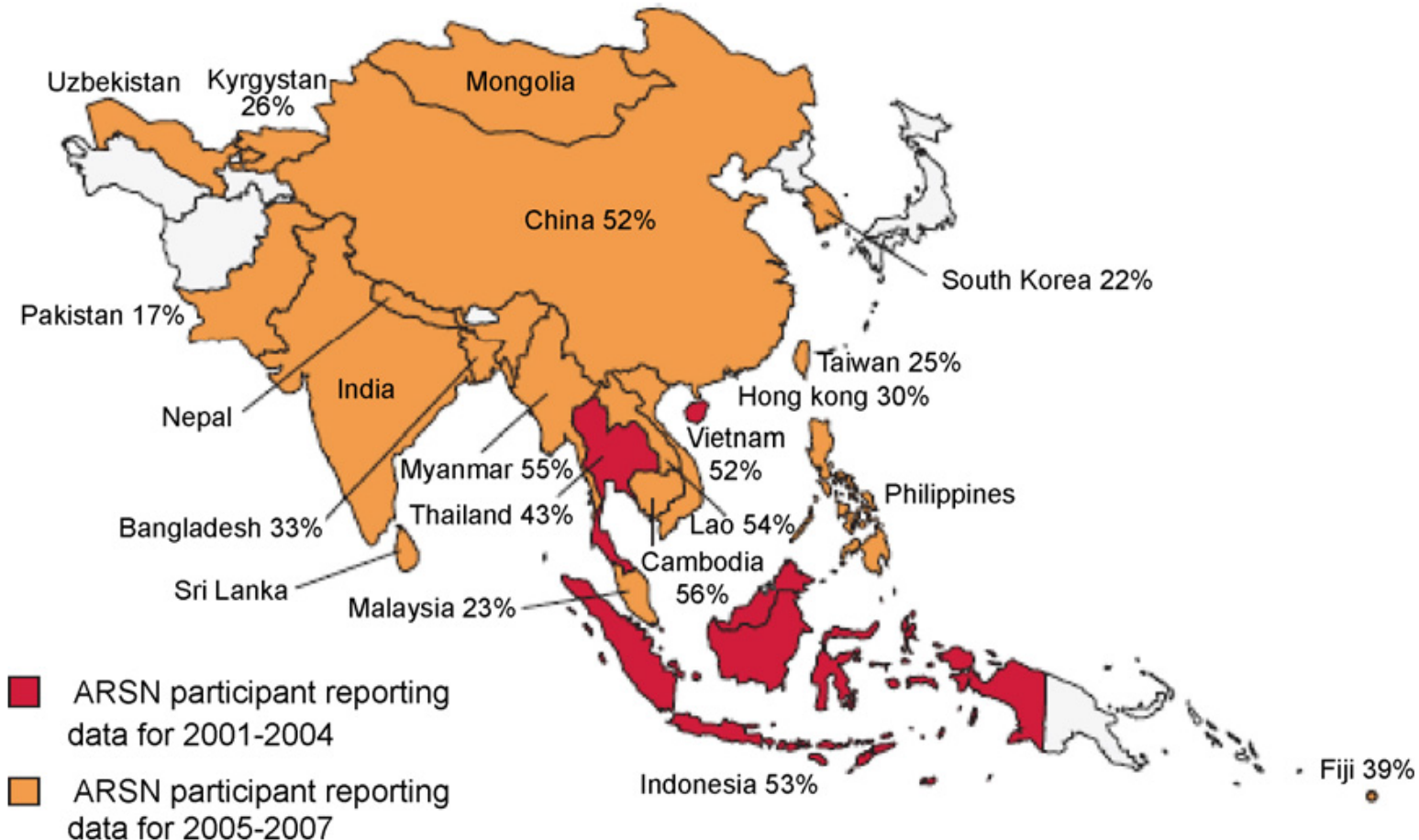


Countries without rotavirus vaccine in national program
Median = 40%





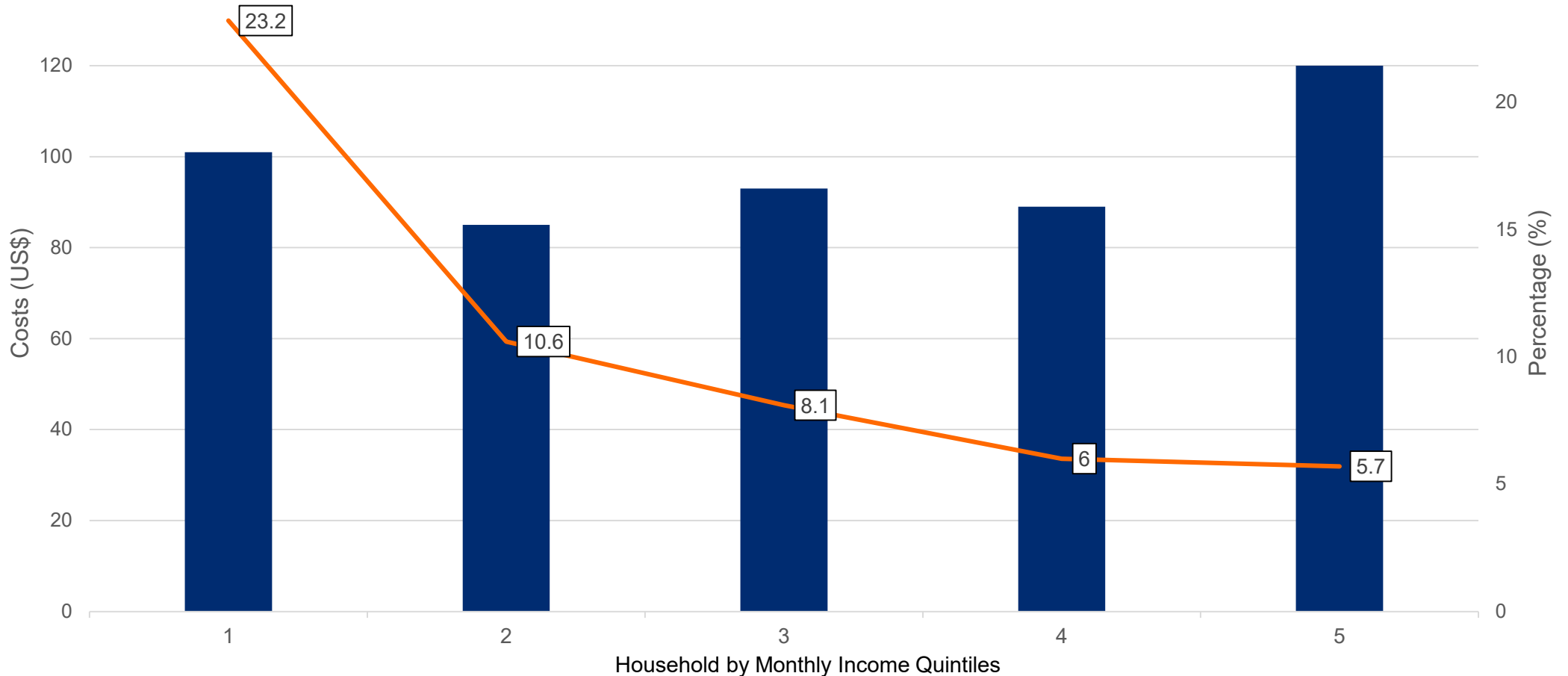
Proportion of diarrhea-related hospitalizations due to rotavirus under the age of 5 years





Mean out-of-pocket costs for RV hospitalization at University of Malaysia Medical Center, Kuala Lumpur, 2013

- Costs of more than 10% of household income are considered to be “catastrophic”
- In study, researchers found 33% of households experienced catastrophic expenditures in Kuala Lumpur





Rotavirus in developed and developing countries

| Parameter | Developed | Developing |
|--------------------------------------|------------------|-----------------------|
| Median age at first infection | 12–18 months | 6–9 months |
| Percent infected by 12 months of age | 40% | 80% |
| Mortality | Low | High |
| Presence of other enteric pathogens | Uncommon | Common (10–30%) |
| Circulating strains | 4–5 common types | More diverse types |

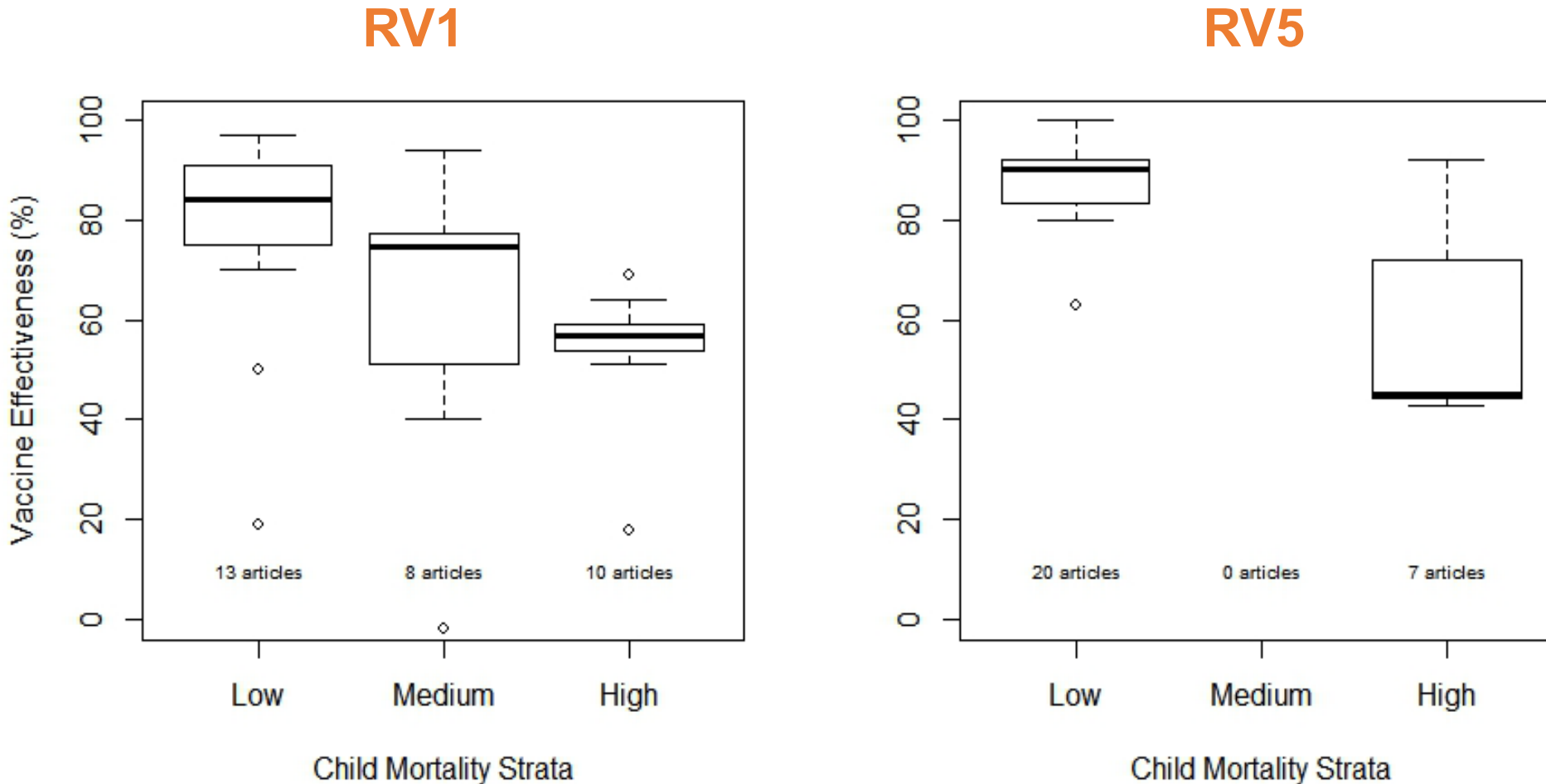


Efficacy of rotavirus vaccines in clinical trials

| Vaccine | Region | Efficacy (95%CI) |
|-----------------|-------------------------------|------------------|
| RotaTeq | Europe/US | 98% (88%-100%) |
| RotaTeq | Africa (Ghana, Kenya, Mali) | 64% (40%-79%) |
| RotaTeq | Asia (Bangladesh, Vietnam) | 51% (13%-73%) |
| ROTARIX | Europe | 96% (90%-99%) |
| ROTARIX | Latin America | 85% (72%-92%) |
| ROTARIX | Africa (South Africa, Malawi) | 62% (44%-73%) |
| ROTAVAC | Asia (India) | 54% (35%-67%) |
| ROTASIIL | Africa (Niger) | 67% (50%-78%) |
| ROTASIIL | Asia (India) | 34% (6%-54%) |

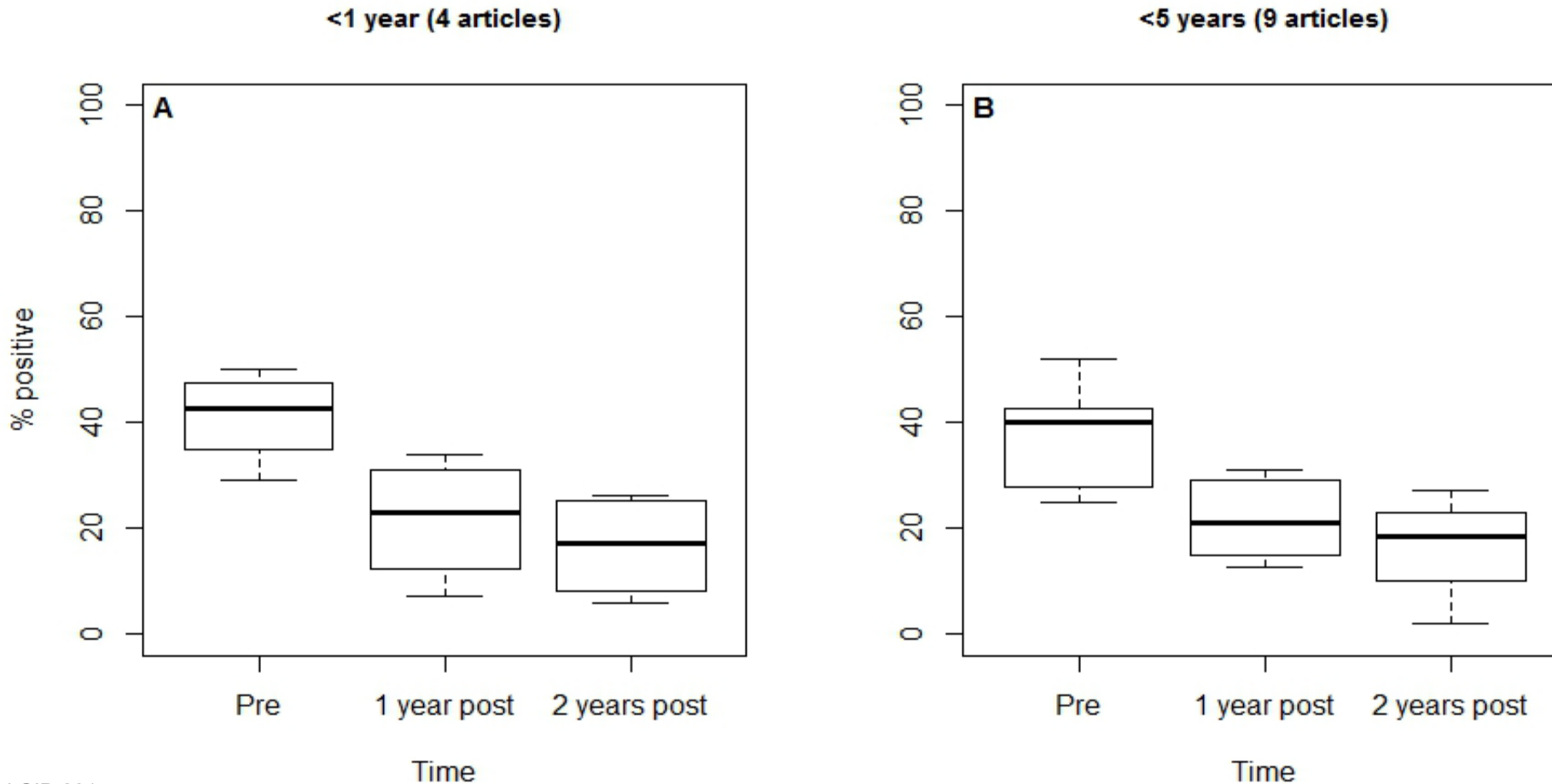


Median VE by child mortality strata and vaccine



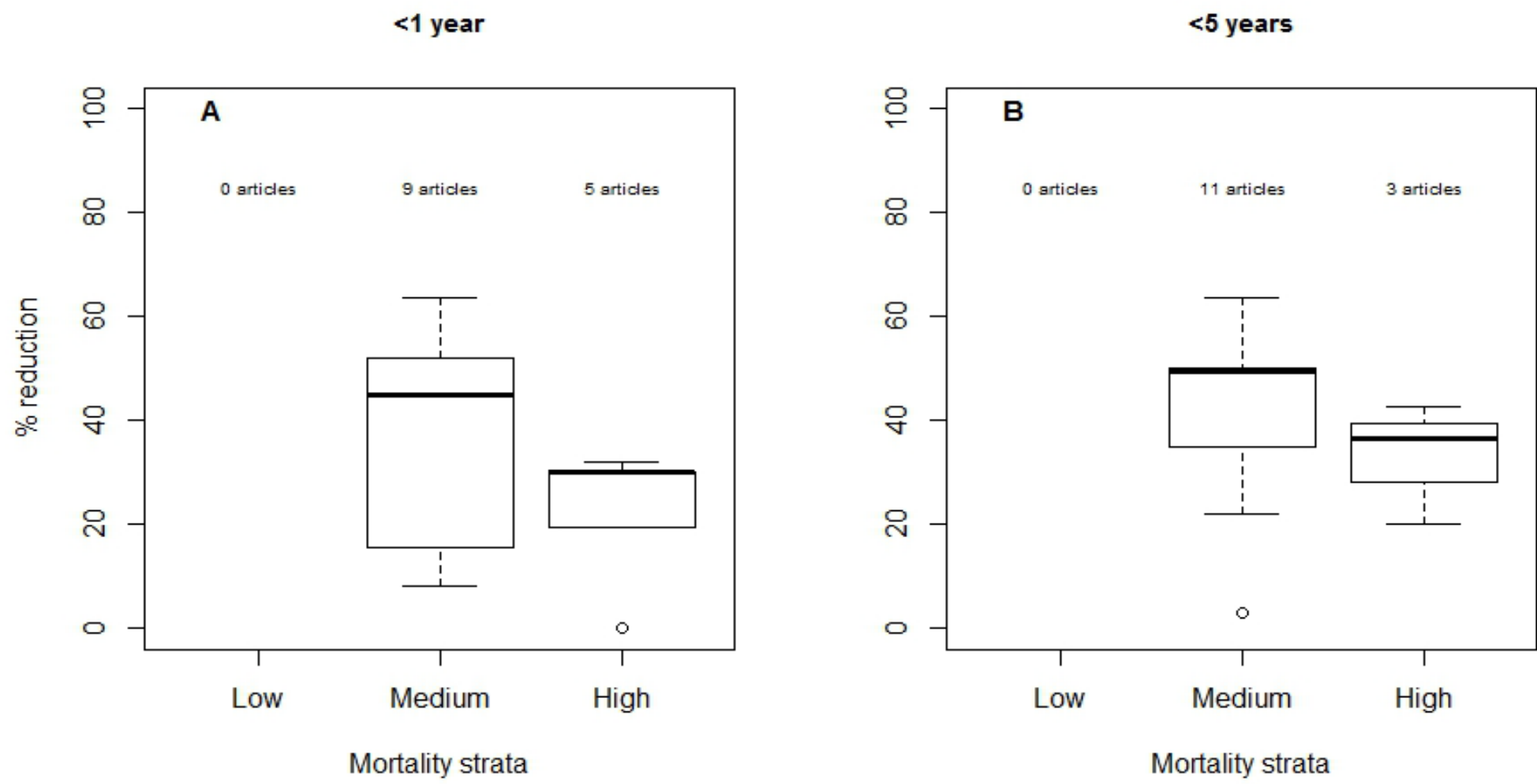


Percent of specimens positive for rotavirus by age group



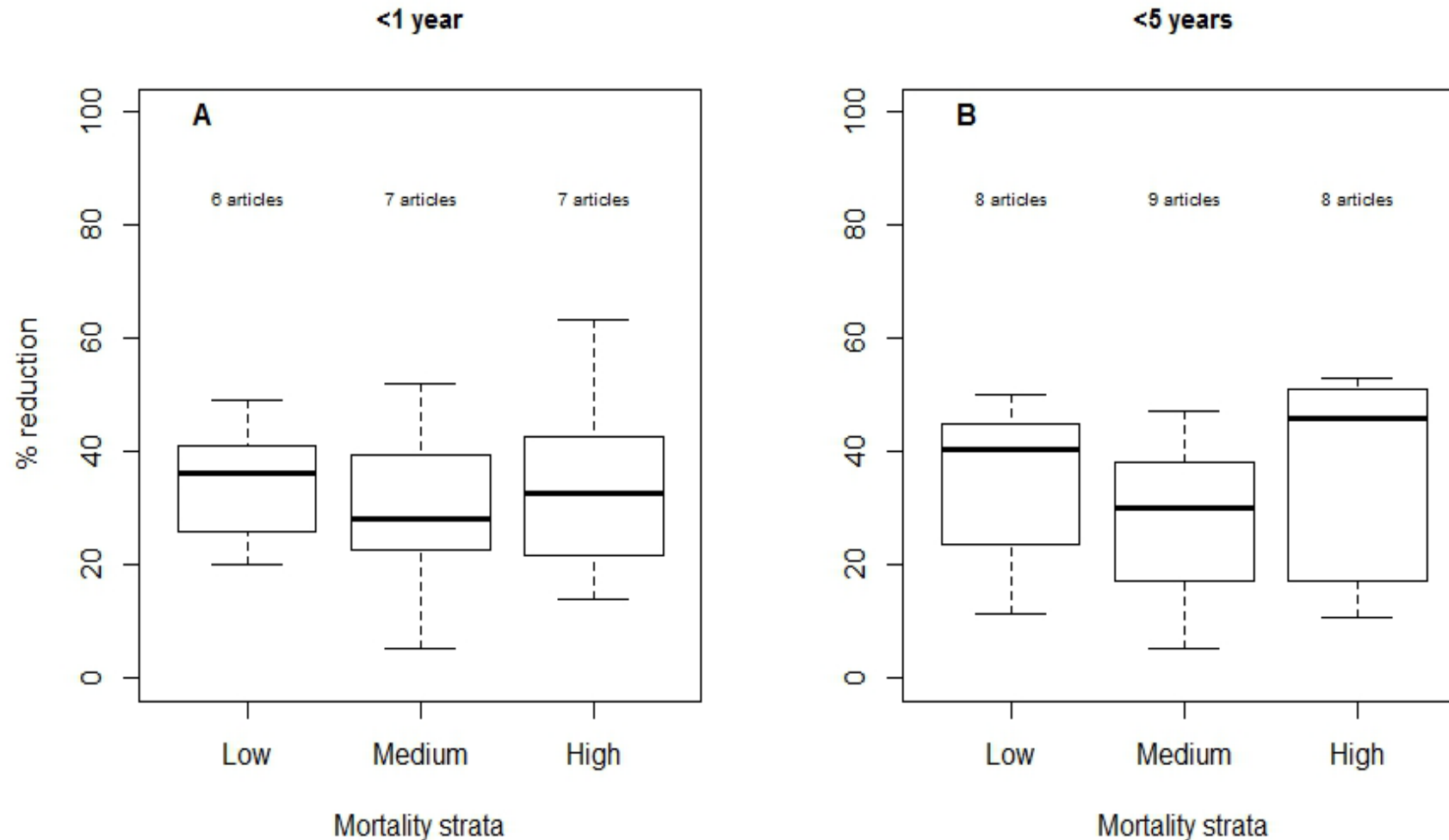


Real-world impact: Reductions in diarrhea deaths



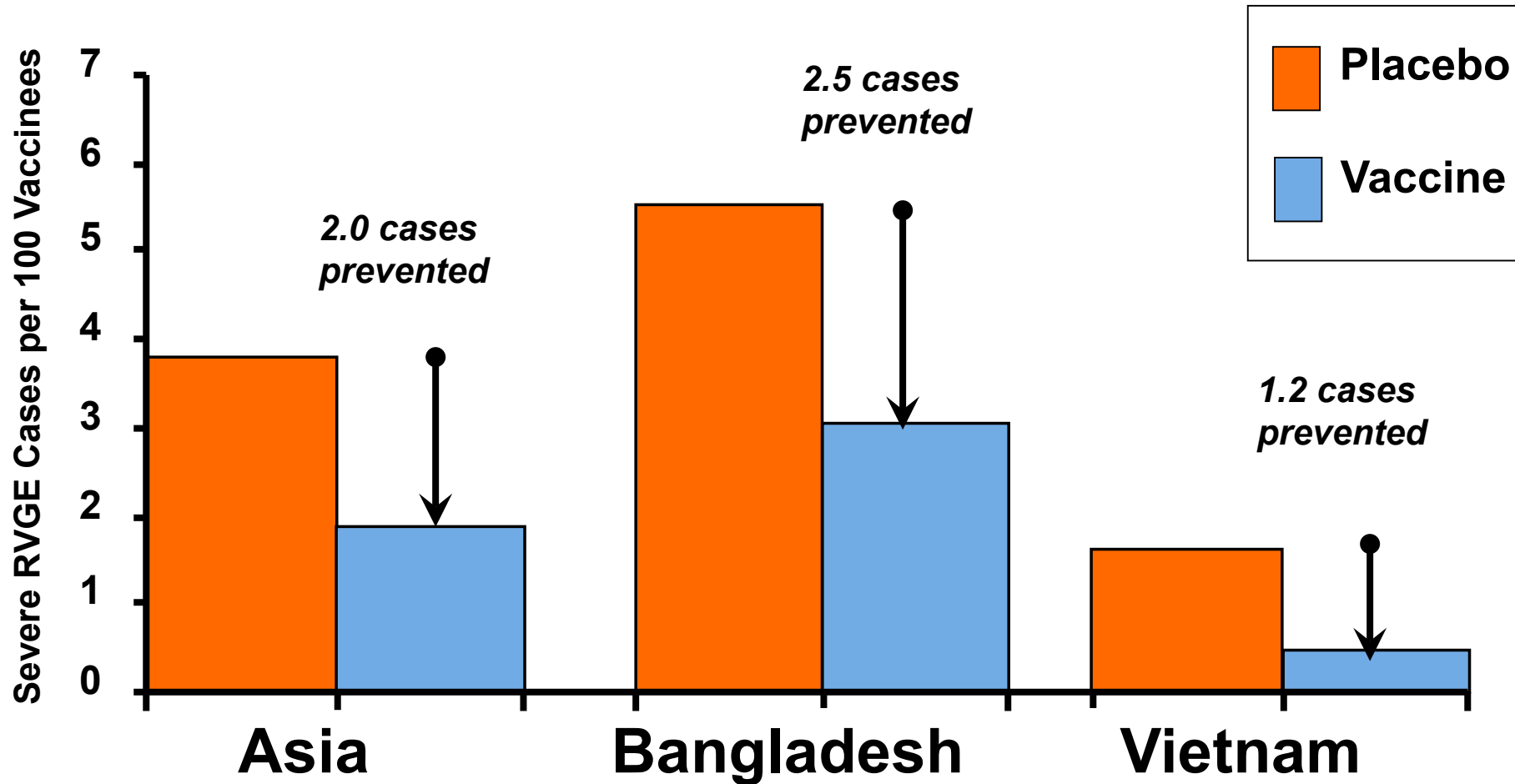


Real-world impact: Reductions in diarrhea hospitalizations





Efficacy and severe RVGE cases prevented through the first year of life





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.”

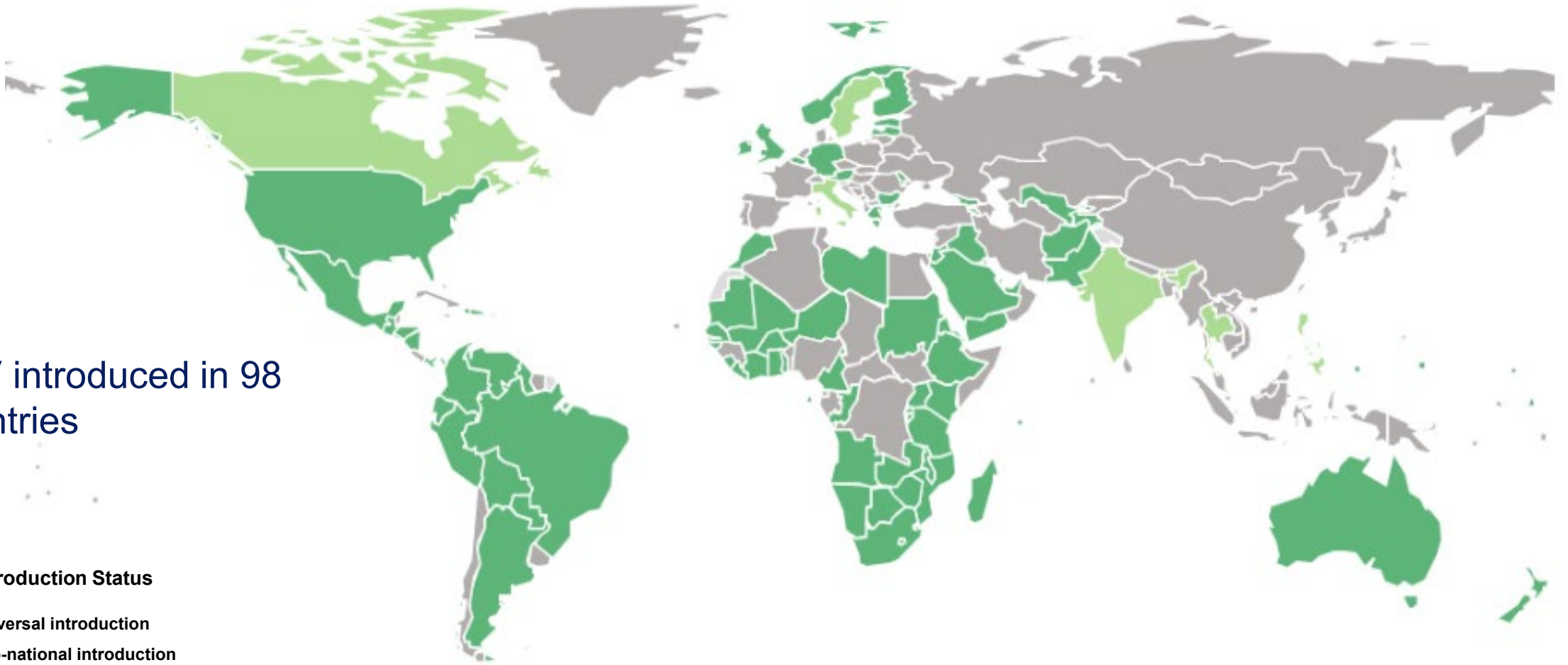
Rotavirus vaccines WHO Position Paper - January 2013

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.



Rotavirus vaccine introduction status

As of February 2019





WHO prequalified rotavirus vaccines

| NAME | DETAILS | MANUFACTURER | STRAIN(S) | SCHEDULE | EFFICACY IN LMIC |
|------------------|--|--------------------------|---|-------------------------------------|------------------|
| RotaTeq® | Pentavalent human-bovine reassortant rotavirus vaccine | Merck | G1, G2, G3, G4, P[8] | 3-dose (Same schedule as DTP1-3) | 51-64% |
| ROTARIX® | Monovalent human rotavirus vaccine | GSK | G1P[8] | 2-dose (Same schedule as DTP1-2) | 49-85% |
| ROTAVAC® 116E | Bovine-human reassortant rotavirus vaccine | Bharat Biotech | G9P[11] | 3-dose (Same schedule as DTP1-3) | 53.6% |
| ROTASIIL® | Pentavalent human-bovine reassortant rotavirus vaccine | Serum Institute of India | Bovine (G6P[7]) + G1, G2, G3, G4 reassortants | 3-dose (Same schedule as DTP1-3) | 36%-66.7% |



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
- ROTARIX and 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 and RotaTeq is comparable—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 holds the position that the benefits of rotavirus vaccines outweigh the small risk of intussusception.⁴



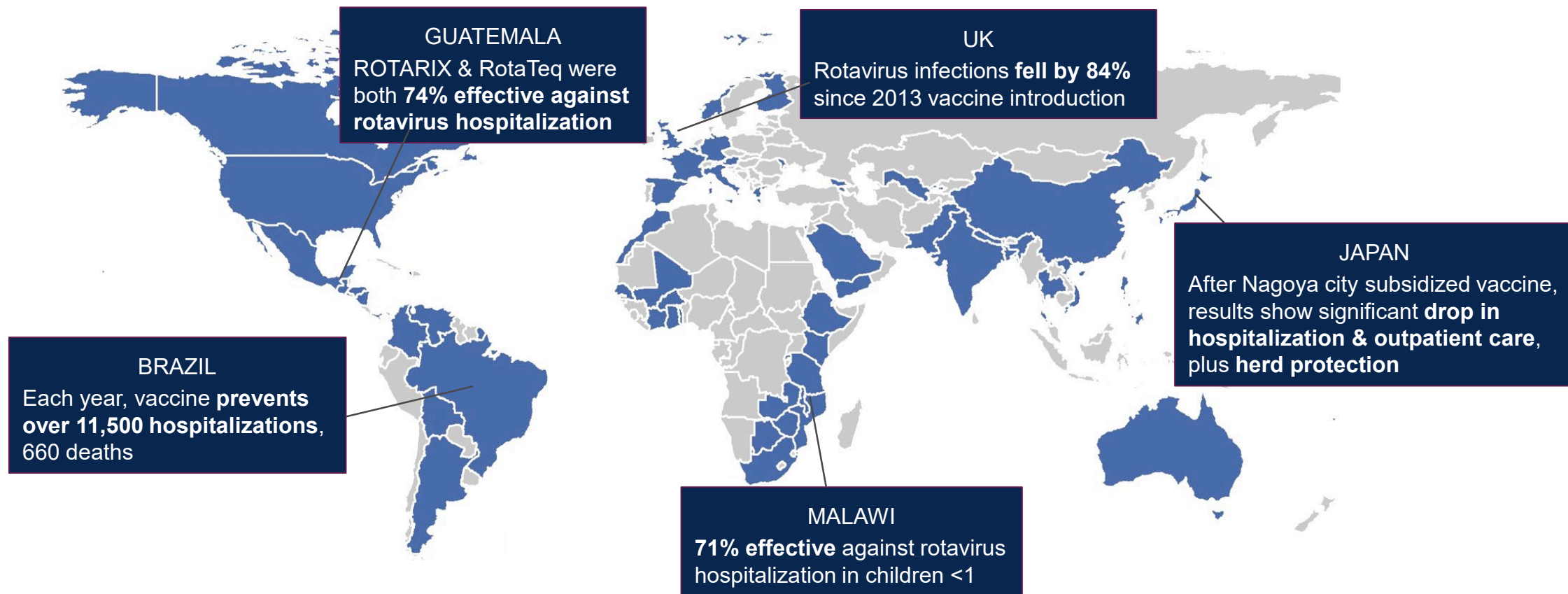
Brazil and Mexico: Vaccination benefit versus risk

| | Admissions per year | Deaths per year |
|---|---------------------|-----------------|
| Rotavirus events averted by vaccination | -81,123 | -1,303 |
| Intussusception events caused by vaccination* | +118 | +5 |
| Benefit to Risk comparison | 687 to 1 | 261 to 1 |

* Source of background IS rates: Patel et al. Exp Rev Vacc; 2009; 8(11); assumes ROTARIX coverage at current DTP3 rates; risk estimates from current study for week 1 after vaccination; with assumption of 5% case-fatality



Vaccine impact data available from all world regions and income groups





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*



Vaccine impact: Mexico and Brazil

Post-introduction Impact in Mexico and Brazil Comparable to phase 3 clinical trial efficacy data

Mexico

- Widespread introduction in 2007
- In 2008, diarrhea deaths declined by 35%¹
- In 2009, diarrhea deaths declined by more than 65%

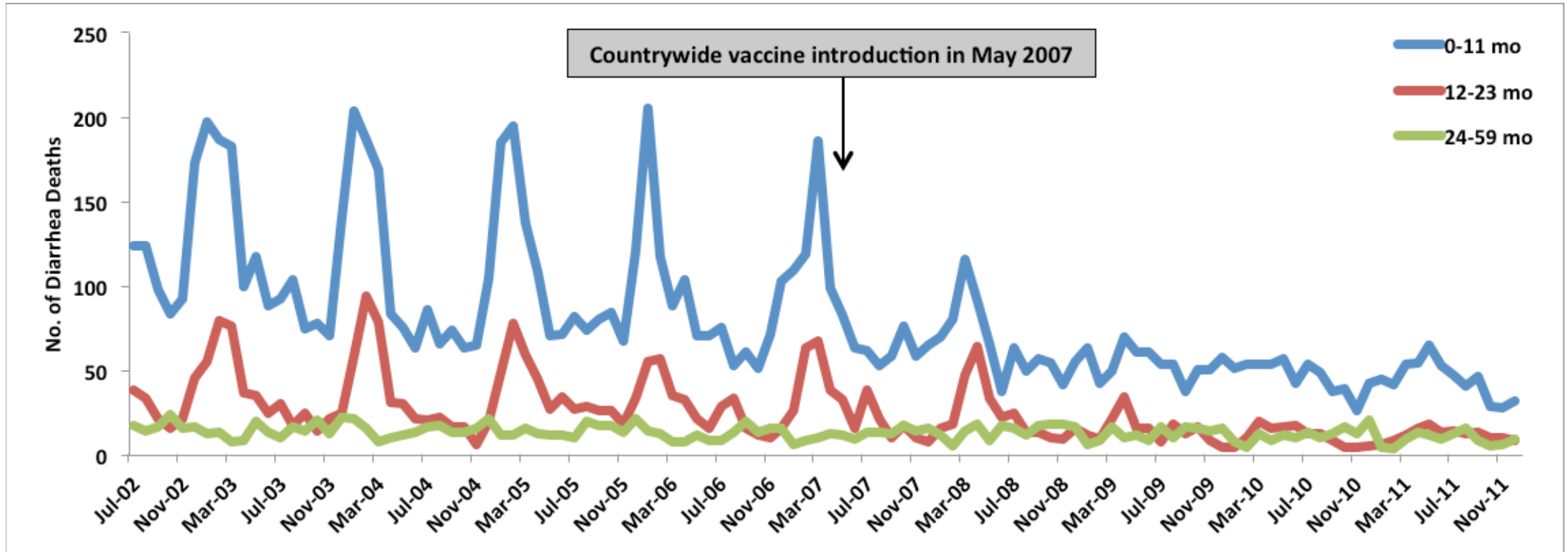
Brazil

- Widespread introduction in 2006
- In 2007, diarrhea deaths declined by 30%²
- In 2008, diarrhea deaths declined by 39%²
- Sustained reduction of 22% over 3 years (2007-2009)³

Hospitalizations for rotavirus and all causes of diarrhea also declined



Decline in diarrheal deaths in children <5 in Mexico following vaccine introduction



- Reductions in deaths by 35% seen in just the first year¹
- Reduction in deaths of >50% realized and sustained across all regions – even less economically developed regions²



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% |
| USA | ROTARIX, RotaTeq | 55-94% |

In the **first 4 years** of their use in the U.S., rotavirus vaccines prevented

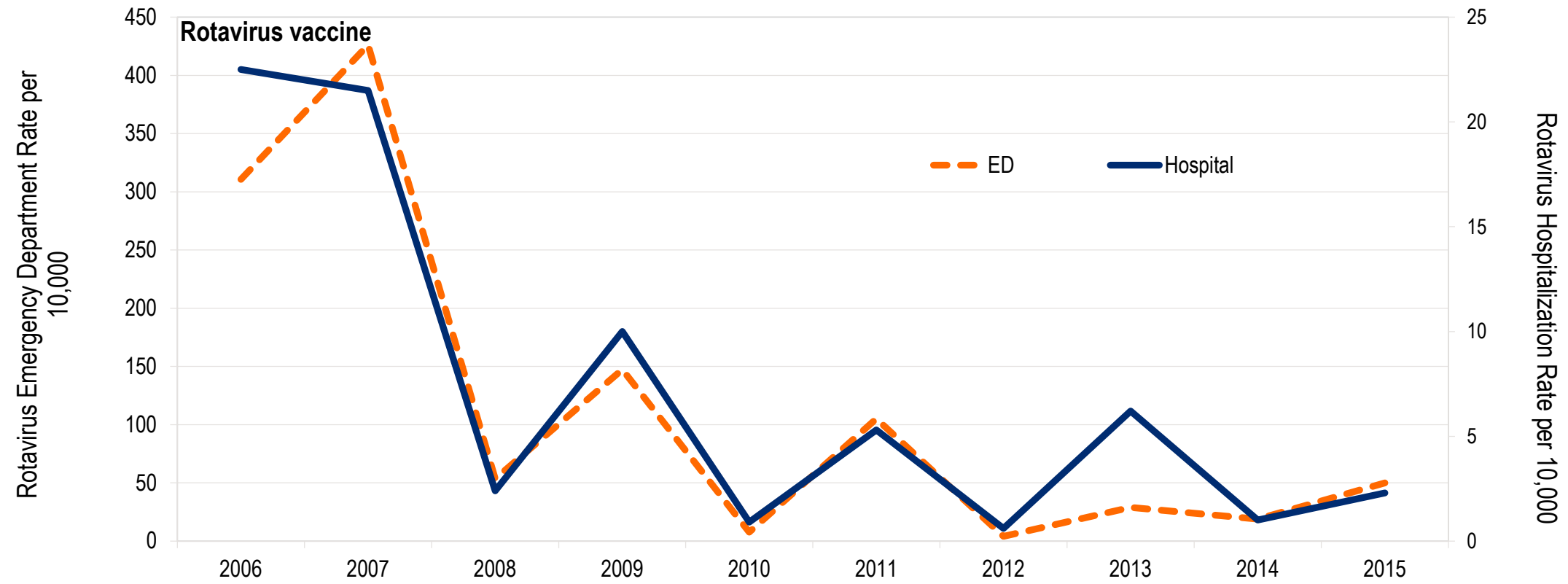
- 176,000 hospitalizations
- 242,000 emergency department visits
- 1.1 million doctor visits

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

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.



Population-based rates of rotavirus-attributable hospital and emergency department visits in the US, 2006-2015





Vaccine impact: Africa

| COUNTRY | YEAR OF NATIONAL ROTAVIRUS VACCINE INTRODUCTION | DATA TIME PERIOD | | REDUCTION IN ROTAVIRUS DIARRHEA HOSPITALIZATIONS AMONG CHILDREN <5 YEARS FOLLOWING INTRODUCTION |
|--------------|---|-------------------|-------------------------------|---|
| | | PRE-VACCINE | POST-VACCINE | |
| 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% |



Effects beyond the vaccinated: Herd Protection

- Rotavirus vaccines have been shown to have high levels of herd protection
- Reductions of rotavirus hospitalizations ranged from 20-92% in the U.S., Australia, Austria, Brazil, and El Salvador in older children in the years following rotavirus vaccine introduction¹

Reductions in rotavirus-related hospitalizations among unvaccinated 2-5 year old children following vaccine introduction

| Country | Timeframe post-introduction | Percent reduction in hospitalizations |
|-------------------------|-----------------------------|---------------------------------------|
| Ghana ² | 2 years | 29% |
| Mozambique ³ | 1 year | 55% |
| Thailand ⁴ | 25 months | 40-69% |
| Armenia ⁵ | 2 years | 48% |
| Moldova ⁶ | 2 years | 55% |
| U.S. ⁷ | 1 year | 72% |
| Austria ⁸ | 1 year | 35% |



Reduced risk of childhood seizures associated with rotavirus vaccination

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

Clinical Infectious Diseases 2014;58(2):173–7

MAJOR ARTICLE

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



Rotavirus vaccines offer broad protection

| | Protection against strains <u>NOT</u> 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 |

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.

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



Summary

- Rotavirus is the leading cause of severe childhood diarrhea
- Safe, effective rotavirus vaccines are in use around the world—four vaccines are WHO-prequalified
- Rotavirus vaccines are a powerful tool and should be used as part of a comprehensive approach to diarrheal disease prevention and control
- Yet, only about 98 countries have introduced rotavirus vaccines into their national immunization programs
- Asia in particular is lagging in rotavirus vaccine introduction



Thank you

ORS—the most important medical advancement of the 20th century



Water with Sugar and Salt

THE discovery that sodium transport and glucose transport are coupled in the small intestine, so that glucose accelerates absorption of solute and water, was potentially the most important medical advance this century.¹ It opened the way to oral hydration treatment for severe diarrhoea—the main cause of infant death in the developing world.

