



ROTAVIRUS

COMMON, SEVERE, DEVASTATING, PREVENTABLE

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

ROTA COUNCIL
Rotavirus Organization of Technical Allies

ROTACOUNCIL.ORG

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Introduction

Diarrhea is one of the world's leading killers of children, and rotavirus is the most common cause of severe diarrhea. Every child is vulnerable. Each year, rotavirus kills about 200,000 children (1, 2) and hospitalizes hundreds of thousands more, despite the fact that safe, effective vaccines exist that can protect children from this disease.

There are currently two rotavirus vaccines licensed for global use (3, 4). These vaccines are being used in the national immunization programs of at least 80 countries—but nearly 100 million children worldwide lack access (5). Asia, for example, is home to about one-third of the world's rotavirus-related deaths (1). Despite this, to date, very few Asian countries have introduced the rotavirus vaccine into their national immunization programs.

Rotavirus deaths, hospitalizations and illnesses suffered by children and their families—and the associated economic burden—are unnecessary and preventable. We can stop this. Rotavirus vaccines are the most powerful tool available today to protect children from rotavirus, yet children in many parts of the world do not have access to them.

The paper that follows outlines the latest research on rotavirus and rotavirus vaccines, and provides specific recommendations on what governments, donor agencies, researchers, pharmaceutical companies and frontline health workers can do to reduce the burden of this preventable disease and accelerate the introduction and use of rotavirus vaccines.

- **The World Health Organization (WHO) recommends that rotavirus vaccines be introduced into every country's national immunization program, particularly those where diarrhea is a leading cause of child death (6).**
- While at least 80 countries have introduced rotavirus vaccines into their national immunization programs, more than 100 have not. Very few countries in Asia have introduced the vaccine despite high mortality and high morbidity. Over 94 million infants—70% of all worldwide—lack access to rotavirus vaccines (5).
- More must be done to reach children living in the places where diarrheal diseases, such as rotavirus, are a major public health issue.
- Millions of illnesses and tens of thousands of deaths could be prevented through rotavirus vaccination.

What is rotavirus?

Rotavirus is a virus that causes gastroenteritis, an inflammation of the stomach and intestines. Rotavirus primarily infects the small intestine, destroying the surface tissue and preventing the absorption of nutrients, causing diarrhea (7). Typical symptoms can range from mild, watery diarrhea to severe diarrhea with vomiting and fever. WHO-recommended treatment such as medical care, zinc supplements, oral rehydration therapy (ORT) and treatment with intravenous (IV) fluids, when needed, can help rehydrate children until the intestine repairs and recovers. In low-income countries, particularly in hard-to-reach areas where children do not have timely access to such medical care, severe disease can result in rapid dehydration, leading to shock, electrolyte imbalance and death.

Yet many of the world's poorest children do not have access to ORT, despite it being inexpensive and effective. ORT coverage is only about 30% in many of the places where the most diarrhea deaths occur (8). While efforts to increase ORT use should continue, providing ORT to treat each episode of rotavirus diarrhea in resource-poor settings is challenging. Vaccination protects children by preventing disease in the first place.

Rotavirus is commonly spread from person-to-person. It is highly contagious and passes easily through the fecal-oral route by way of contact with contaminated hands or objects, such as toys and surfaces, or through tainted food or water (9-14). The virus is incredibly resilient and can live on hands for hours and surfaces for days. Unfortunately, interventions that prevent bacterial and parasitic causes of diarrhea—such as improvements in hygiene, sanitation and drinking water—do not adequately prevent the spread of rotavirus.

Diarrhea is one of the world's leading killers of children, and rotavirus is the most common cause of severe diarrhea among infants and young children. Children under age 2 are most vulnerable to infection.

FIGURE 1: Rotavirus: a devastating burden

Reference: 15

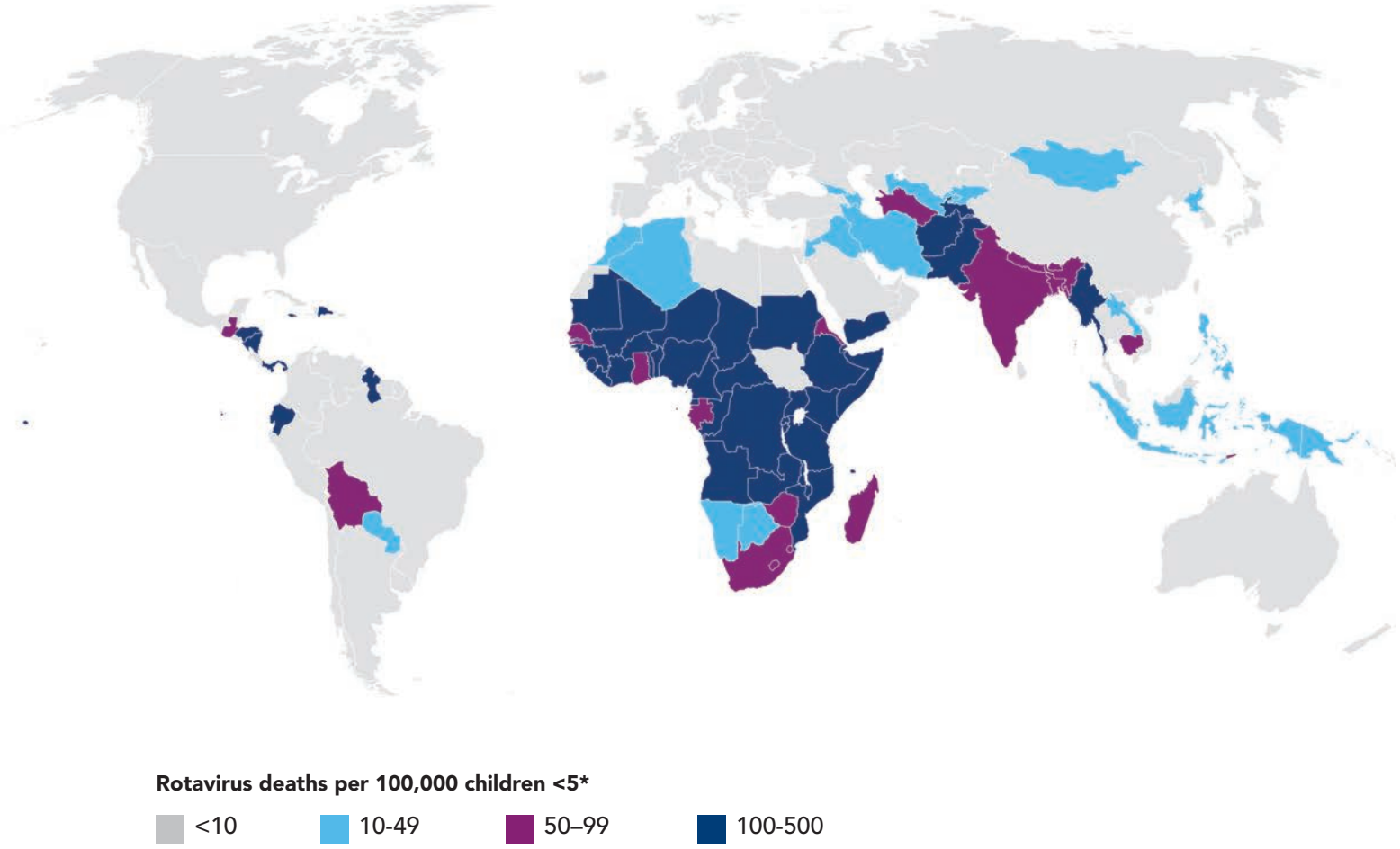
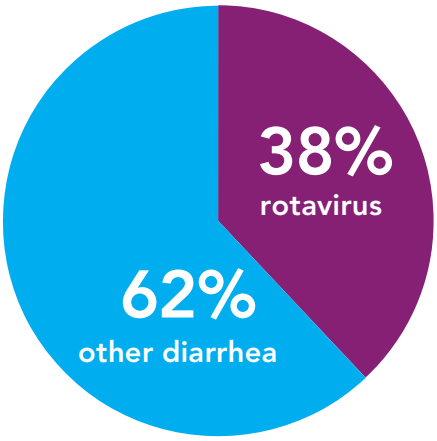


FIGURE 2: Global diarrhea hospitalizations

References: 2, 16



Rotavirus is found everywhere. Almost all children will be infected before age 5, regardless of where they live. While every child is vulnerable to rotavirus infection, survival depends on whether or not he or she has timely access to care.

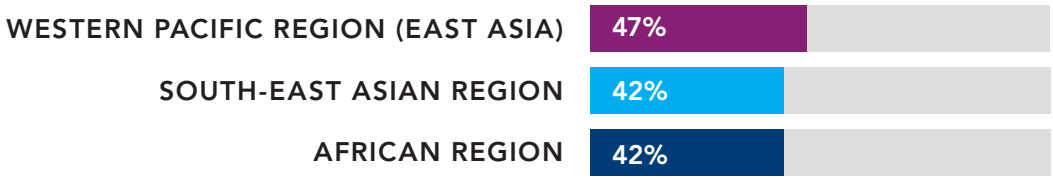
Today, nearly a quarter of a million children under age 5 die from rotavirus each year (1). That's over 500 children each day.

Rotavirus is not only a threat to child survival, but also a major cause of childhood illness. Rotavirus continues to be the leading cause of moderate-to-severe diarrhea in young children around the world in countries not using the vaccine. It is responsible for 38% of all diarrhea-related hospitalizations globally in children under 5 years of age (2, 16).

Of the tens of millions of children stricken with severe diarrheal disease in 2010, nearly 50,000 were included in WHO's rotavirus surveillance network (17). The bars below illustrate the varying proportion of hospitalizations caused by rotavirus in countries participating in the network.[1]

FIGURE 3: Proportion of hospitalizations caused by rotavirus in countries participating in the WHO Global Surveillance Network for Rotavirus

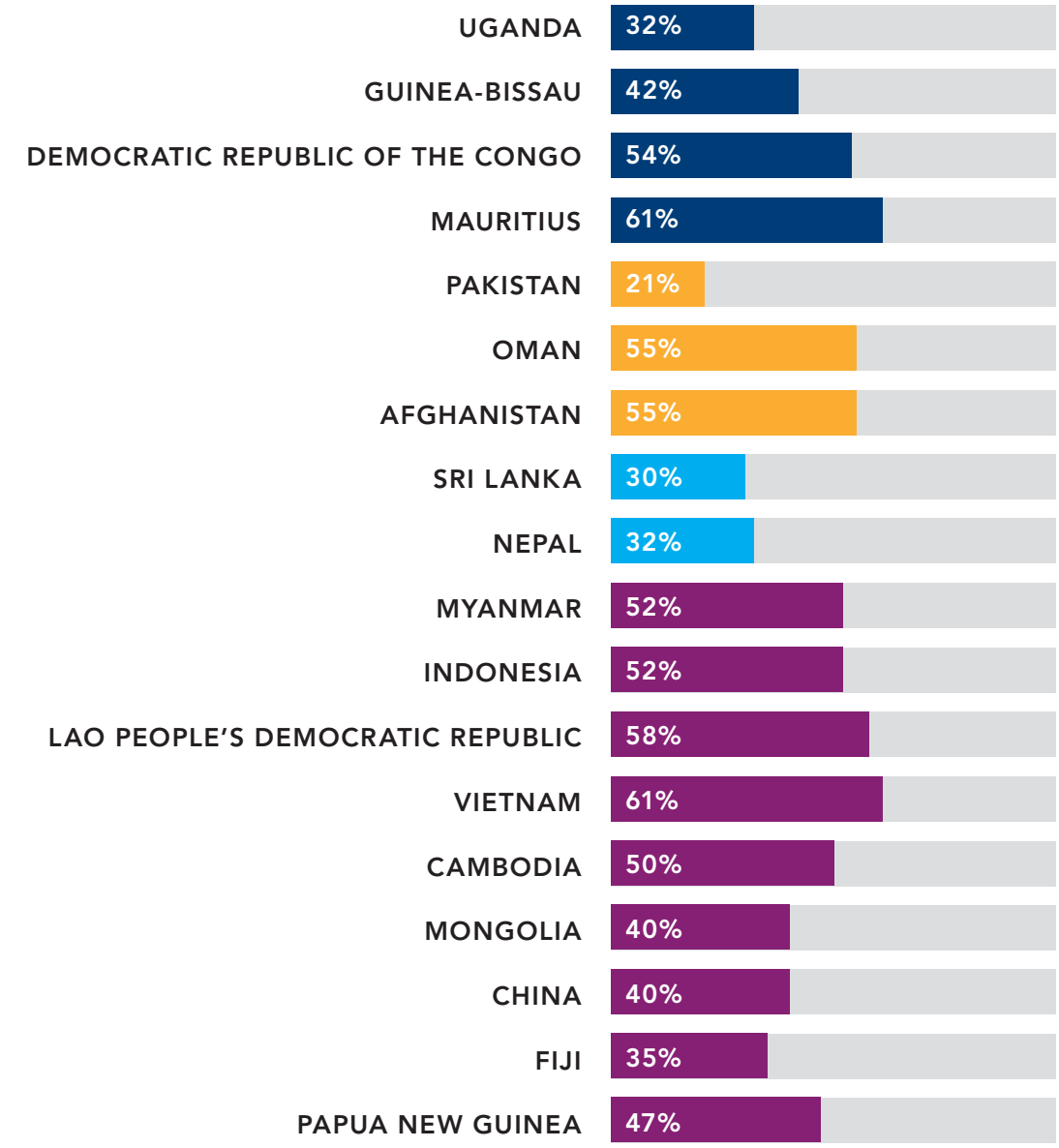
Reference: 17



[1] *48 of 57 countries participating in the WHO Global Surveillance Network for Rotavirus tested at least 100 specimens and reported each month of the year.*

FIGURE 4: Percentage of diarrheal disease hospitalizations caused by rotavirus in WHO surveillance countries

Reference: 17



Legend:

- African Region (AFRO)
- Eastern Mediterranean Region (EMRO)
- South-East Asia Region (SEARO)
- Western Pacific Region (WPRO)

ROTAVIRUS IS THE LEADING CAUSE OF DIARRHEAL DEATHS AND HOSPITALIZATIONS IN CHILDREN UNDER 5 WORLDWIDE (1, 15, 17)

As countries improve economically, the overall number of diarrheal disease deaths and hospital admissions goes down. As hygiene and sanitation-related causes of diarrhea decrease, the proportion of rotavirus diarrhea disease hospitalizations may increase.

AFRICA

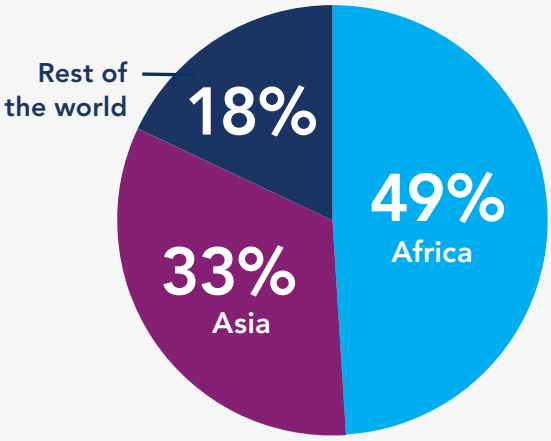
Rotavirus kills **about 95,000** African children under 5 each year—more than **260 each day** (1). The vast majority of countries worldwide with the highest child death rates from rotavirus are in sub-Saharan Africa. In sub-Saharan Africa, rotavirus accounted for about 42% of all diarrheal disease hospitalizations in 2010 (17). On top of that, treating rotavirus is expensive both for families and countries. For example, in Uganda, inpatient admission for one episode of severe rotavirus diarrhea costs 10% of the average family's monthly income (18).

ASIA

Rotavirus kills **about 63,000** Asian children under 5 each year—more than **170 each day** (1).[2] In 2010, rotavirus accounted for about 42% of all diarrheal hospitalizations in South Asia and 47% of diarrheal hospitalizations in East Asia (17). In Bangladesh, treating just one episode of rotavirus diarrhea can amount to nearly 85% of the average family's monthly income (19). In Malaysia, rotavirus hospitalization costs more than one-quarter of the average monthly income (20).

FIGURE 5: Worldwide rotavirus diarrheal deaths by region

Reference: 1



[2] *Total listed for WHO regions SEARO and WPRO (does not include Near East portion of Asia).*

Vaccines: the best protection against rotavirus

Rotavirus can be best prevented through vaccination. Research has shown that children naturally infected with rotavirus were protected against subsequent infections—with greatest protection against moderate-to-severe disease—and that the level of protection increased with each new infection (21, 22). These findings suggested than an attenuated (weakened) rotavirus vaccine simulating natural infection could provide protection against the disease, but that multiple doses would likely be required. Vaccine development has focused on orally administered vaccines because early animal studies suggested that the creation of local intestinal immunity fulfilled an important role in protection from disease (23).

Today, two vaccines are available on the global market, several other vaccines have been licensed for national use and new vaccines are in development.

Vaccines in global use

Since 2006, two orally-administered, multi-dose, live attenuated rotavirus vaccines have been available on the global market: Rotarix™, manufactured by GlaxoSmithKline (GSK), and RotaTeq®, manufactured by Merck & Co. Inc. RotaTeq, administered on a three-dose schedule, is a pentavalent vaccine, made up of five strains of human-bovine reassortant rotaviruses. Rotarix, administered in two doses, is a monovalent vaccine, made up of a single attenuated strain of human rotavirus. Both vaccines provide protection against a wide variety of rotavirus strains, even strains that are not included in the vaccines.

Rotarix and RotaTeq have been shown to be safe and effective in multiple pre-licensure, clinical studies involving tens of thousands of infants across Africa, Asia, Europe, Latin America and the United States. Vaccination against rotavirus has been shown to significantly reduce the risk of disease among children across the world.

In clinical trials in low-income countries in Africa and Asia, vaccination reduced a child's risk of getting severe rotavirus diarrhea by more than half (51-64%) during the first year of life, when the threat of severe disease is greatest (24-26). In middle- and high-income countries, including in Latin America, rotavirus vaccines reduced the risk of moderate or severe rotavirus diarrhea by at least 85% (85-98%) in the first year of life (27, 28). Based on these efficacy studies, WHO prequalified both vaccines and recommended them for use in all countries.

FIGURE 6: Two vaccines licensed for global use
Shown to be safe and effective in large-scale clinical studies and real-world use

References: 24–39

VACCINE NAME	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]
PROTECTS AGAINST OTHER STRAINS?	Yes, broad protection demonstrated	Yes, broad protection demonstrated
EFFICACY AGAINST SEVERE ROTAVIRUS DIARRHEA IN CHILDREN < 1 YEAR (high-income countries)	95.8–100%	85–96%
EFFICACY AGAINST SEVERE ROTAVIRUS DIARRHEA IN CHILDREN < 1 YEAR (low- and middle-income countries)	49–85%	51–64%
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 Given on same schedule as DPT1 and 2 vaccine doses	3-dose Given on same schedule as DPT1, 2 and 3 vaccine doses
PRESENTATION	1. Liquid vaccine in oral, single-dose applicator 2. Liquid vaccine in squeezable, polyethylene single-dose tube 3. Lyophilized vaccine, reconstituted with $CaCO_3$ buffer, oral applicator	Liquid vaccine in oral, squeezable tube
SHELF LIFE	36 months	24 months
VACCINE VIAL MONITOR ON LABEL?	Yes	No
STORAGE REQUIREMENTS	2–8° C, not frozen and protected from light	2–8° C, not frozen and protected from light
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

WHO recommendations and key guidance on vaccine administration

In 2006, WHO's Strategic Advisory Group of Experts (SAGE) reviewed all of the available evidence from clinical studies involving the two globally available vaccines conducted in Europe and the Americas and recommended that rotavirus vaccines be included in the national immunization programs of countries in those regions (40). SAGE's initial recommendation also stated that the vaccine should be given to children at no later than 15 weeks and completed before 32 weeks, in compliance with the package label of each manufacturer, to minimize the risk of potential adverse events (41).

In 2009, SAGE reviewed additional data from clinical studies in Africa and Asia, as well as post-licensure data from the Americas, and expanded their recommendation to state that all countries should include rotavirus vaccines in their national immunization programs, particularly in those countries with high child mortality due to diarrhea (6, 42, 43).

In high-mortality regions, vaccinating children on a strict schedule is often more difficult. To allow for greater vaccine coverage and thereby greater reductions in rotavirus-related deaths, in 2013, WHO recommended that age restrictions on rotavirus vaccination be removed, based on benefit-risk considerations (3). Vaccination is now recommended to be administered when children receive their other routine immunizations.

To obtain the maximum benefit from vaccination, all efforts should be made 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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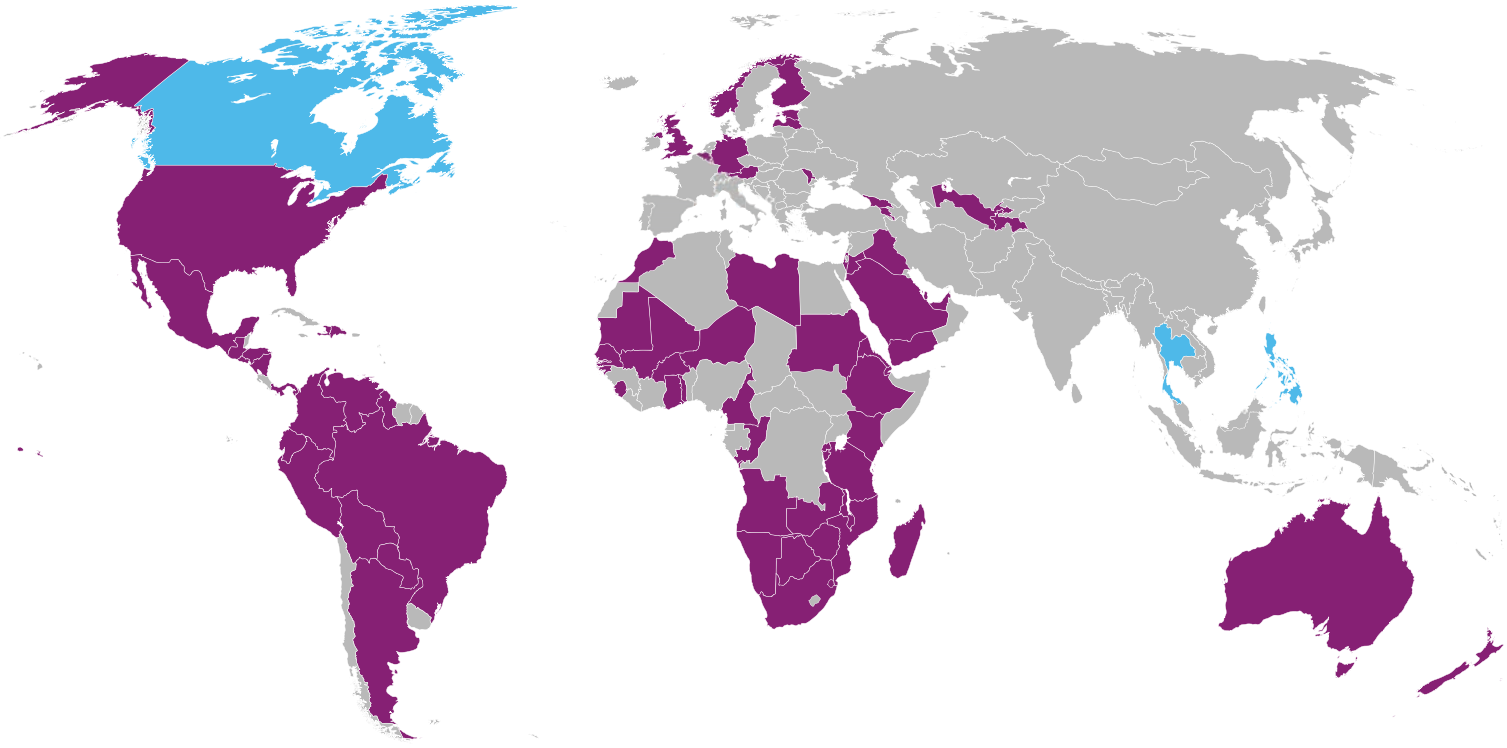
Rotavirus vaccines in use: introduction status

At least 80 countries have introduced rotavirus vaccines into their national immunization programs, and three countries—Canada, Philippines and Thailand—have introduced rotavirus vaccines regionally (44, 45). Most of the countries that have introduced the vaccines are either upper-middle and high-income countries in the Americas, or Gavi-eligible countries in Africa. To date, very few Asian countries have introduced rotavirus vaccines into their national immunization programs.

FIGURE 7: Rotavirus vaccine introduction status map (as of December 2015)

References: 44, 45



Of the 10 countries with the greatest number of rotavirus-related deaths, only two—Angola and Ethiopia—have introduced rotavirus vaccines. Progress is still needed in Afghanistan, Bangladesh, Democratic Republic of the Congo, India, Indonesia, Nigeria, Pakistan and Uganda (15). India has developed an indigenous vaccine and announced plans to introduce the vaccine into the country's national immunization program. Of the five countries with rotavirus-related mortality greater than 300 deaths per 100,000 children under 5—Afghanistan, Burundi, Chad, Mali and Somalia—only Burundi and Mali have introduced rotavirus vaccines (15). In total, 70% of the world's infants lack access to rotavirus vaccines (5).

Already, about 60% of countries in sub-Saharan Africa have introduced rotavirus vaccines. But because rotavirus disease burden is so high in this region, it is critical that the remaining countries introduce vaccines to protect their children from rotavirus. With nearly half of all rotavirus deaths occurring in Asia, there is also an urgent need for action in that region.

To date, 37 countries eligible for vaccine introduction support from Gavi, the Vaccine Alliance, have introduced the vaccines. The vast majority of these countries were in sub-Saharan Africa (24 countries), followed by the Americas (5 countries), Europe (5 countries) and the Eastern Mediterranean/Middle East (3 countries).

Real world impact: rotavirus vaccines are saving lives and improving health in countries where they are in use

As countries introduce rotavirus vaccines, rotavirus infection rates, illnesses and deaths are dropping.

Moreover, a number of countries have also observed declines in all diarrhea-related hospitalizations and deaths. Research from countries that have included rotavirus vaccines in their national immunization programs has found that vaccination reduced rotavirus-related hospitalizations by up to 92% (49-92%) and hospitalizations related to all causes of diarrhea by up to 55% (17-55%) (46). Furthermore, in some countries, deaths from all causes of diarrhea declined by up to 50% (20-50%) following rotavirus vaccine introduction (46).

There is a large and growing body of evidence demonstrating the impact of rotavirus vaccines following introduction into countries' national immunization programs. Swift and significant declines in hospitalizations due to rotavirus and all-cause diarrhea have been observed across high-, middle- and low-income countries. Early studies took place in high- and middle-income countries, and as more low-income countries have introduced, studies are underway in those settings as well. The findings from studies examining the real-world impact of rotavirus vaccines are critical, not only to informing decisions related to rotavirus vaccine use and programs in those countries, but also to countries considering vaccine introduction and the funding agencies that support them.

The impact of the two currently licensed vaccines on severe rotavirus and all-cause diarrhea has been dramatic in countries that have introduced the vaccine.

High-income countries

Rotavirus vaccines have been shown to be highly effective (79-100%) in preventing rotavirus-related hospitalizations in high- and middle-income countries. Effectiveness levels observed in high- and middle-income countries are similar to efficacy levels seen during clinical studies (47-66). The subsequent impact on severe rotavirus and all-cause diarrhea following rotavirus vaccine introduction has been dramatic, as evidenced by substantial decreases in diarrhea-related hospitalizations in multiple countries.

Before rotavirus vaccines became available in the United States, rotavirus was the top cause of severe diarrhea in infants and young children—responsible each year for more than 400,000 visits to doctors' offices, 200,000 visits to emergency departments and up to 70,000 hospitalizations and 60 deaths (67). In 2006, the United States became the first country to include one of the currently available rotavirus vaccines in its national immunization program. Since then, millions of American children have been vaccinated, and dramatic reductions in hospitalizations and illnesses have been achieved.

In the first four years of their use in the United States, rotavirus vaccines prevented more than 176,000 hospitalizations, 242,000 emergency department visits and 1.1 million doctors' visits among children under age 5, resulting in nearly US$1 billion in savings (68). Rotavirus hospitalizations also declined by up to 83% (60-83%) and all-cause diarrhea hospitalizations declined by up to 50% (29-50%) in children under 5 (32, 38, 69-72). The typical United States rotavirus season, peaking in the winter and spring months, became shorter and less consistent following vaccine introduction (73).

Major declines in rotavirus and diarrhea-related hospitalizations were observed in other early vaccine-introducing countries, including high-income countries such as Australia, Austria, Belgium and Finland. Additionally, regions in Australia showed reductions in rotavirus hospitalizations as high as 88% after the vaccine was introduced, while Austria, Belgium and Finland observed decreases of up to 80% in the annual rate of rotavirus hospitalizations following vaccine introduction (34, 74-81).

FIGURE 8: Real-world impact: rotavirus hospitalizations reduced by half or more

Reference: 82

COUNTRY	VACCINE USED	VACCINE IMPACT: REDUCTION IN HOSPITALIZATIONS
Australia	Rotarix, RotaTeq	45-88%
Austria	Rotarix, RotaTeq	74-79%
Belgium	Rotarix, RotaTeq	50-80%
Finland	RotaTeq	78%
USA	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.

Middle-income countries

Middle-income countries including Brazil, El Salvador, Mexico, Panama and South Africa showed great declines in both rotavirus and all-cause diarrhea-related hospitalizations following rotavirus vaccine introduction (83-94). In Brazil, reductions in annual hospitalizations for all causes of diarrhea decreased by more than one-quarter each year (26% and 48%) in the two years following vaccine introduction (84, 93). In Panama, hospitalizations for all causes of diarrhea declined by up to 31% (15-31%) among children under 1 year of age (94).

In Mexico, sharp declines in diarrheal deaths among children were observed following rotavirus vaccine introduction in 2007. During the 2009 rotavirus season, all-cause diarrhea deaths dropped by more than 65% among children age 2 and younger (90). The drastic reduction of child deaths and diarrhea-related hospitalizations in Mexico demonstrated the public health value of nationwide rotavirus vaccination and provided other countries with evidence of real-world impact (88). In the four years following vaccine introduction, Mexico observed sustained reductions in diarrhea deaths among children under 5 years old—by half (50%) (90-92).

South Africa also experienced a dramatic drop in diarrhea-related hospitalizations in the two years following rotavirus vaccine introduction in 2009. Among infants, rotavirus hospitalizations fell by roughly two-thirds (61-69%); for children under 5, they fell by more than half (54-58%). This translated into 13,000-20,000 fewer rotavirus-related hospitalizations for children under age 2. Additionally, all-cause diarrhea hospitalizations declined by one-third for children under 5 (89).

Low-income countries

Data on rotavirus vaccine experience in low-income countries are just beginning to emerge. Research from Latin America and Africa provides the first results from rotavirus vaccine use in impoverished, high child-mortality countries.

In Nicaragua, the first low-income country to introduce Merck's RotaTeq, vaccination prevented nearly 60% of severe rotavirus cases and cut hospitalizations and emergency room visits in half (95).

In Bolivia, the first low-income country to introduce GSK's Rotarix, vaccination was demonstrated to be as effective after introduction as it was during clinical studies. Vaccinated children were 70% less likely to be hospitalized for rotavirus-related diarrhea than unvaccinated children. The vaccine was also shown to maintain effectiveness over time, protecting children across the first two years of life, when the risk of infection is highest. Furthermore, the vaccine provided broad protection, even against strains of rotavirus not included in the vaccine (96).

In Malawi, which introduced Rotarix in 2012, vaccination was 64% effective in preventing rotavirus diarrhea hospitalizations among vaccinated infants and children. Moreover, nearly two years after introduction, both the proportion of under-5 rotavirus-related hospitalizations that occurred among infants and the absolute rate of rotavirus hospitalizations among infants had fallen significantly, indicating that the vaccination program is likely having a measureable impact on disease burden in the country (97).

Further research to better understand the real-world impact of rotavirus vaccines in low-income countries is ongoing.

Potential for powerful public health impact in low-income countries

FIGURE 9: Reductions in deaths in early adopter countries

References: 84, 92, 94, 98

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

Rotavirus vaccines have been studied throughout the world. Because of high disease burden in low-income countries, the absolute number of severe rotavirus cases prevented by vaccination is also greater in low-income countries, despite the lower efficacy as compared to high- and middle-income countries (24-26, 99).

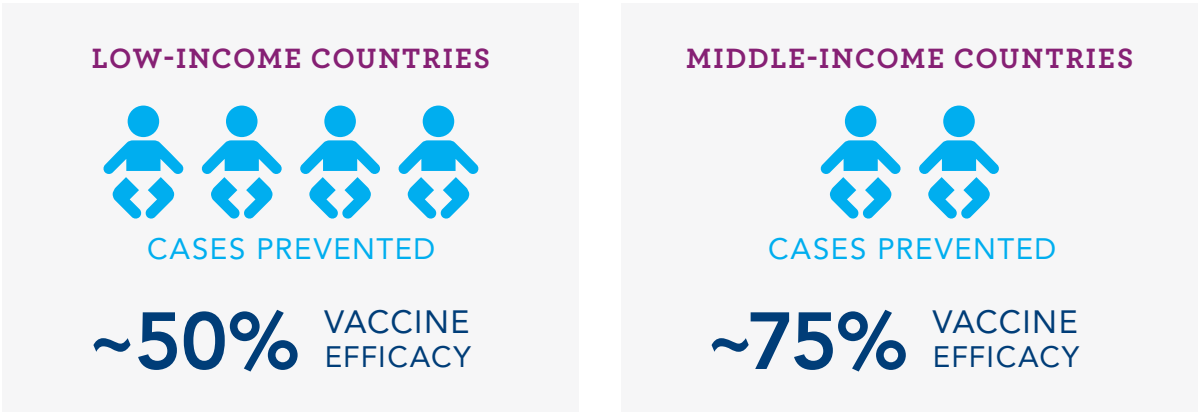
Pre-licensure, clinical studies found that during the first years of life, when the rotavirus threat is greatest, vaccination against rotavirus reduced the risk of severe disease by half in Malawi, a low-income country (26). In South Africa, a middle-income country, vaccination reduced the risk of severe disease by more than three-quarters

Efficacy is the measure of how a vaccine performs under ideal conditions, such as a clinical study. This is different from **effectiveness**, which measures how a vaccine performs in real-world conditions, and **impact**, which measures the number of lives saved or hospitalizations averted.

(77%) (26). Despite lower efficacy being observed in Malawi, the vaccine had a greater impact, preventing seven cases of severe rotavirus diarrhea for every 100 vaccinated Malawian children, compared with four cases per 100 vaccinated South African children (26). Because Malawi has higher baseline rates of rotavirus and the disease is transmitted year-round, the public health benefit in terms of number of cases prevented was demonstrated to be greater when compared with South Africa (100).

FIGURE 10: Cases of severe rotavirus diarrhea prevented per 100 vaccinated children

References: 25, 26



Similar findings were observed in Asia. In Bangladesh, a low-income country, rotavirus vaccination reduced the risk of severe disease by nearly half (46%) during the first year of life. In Vietnam, a middle-income country, vaccine efficacy was 72%. The vaccine was, however, shown to have a greater public health impact in Bangladesh, where four cases of severe rotavirus diarrhea per 100 vaccinated children were prevented, than in Vietnam, where two cases of severe rotavirus diarrhea per 100 vaccinated children were prevented (25).

More research is needed to better understand why lower efficacy is typical of orally administered vaccines—including cholera, typhoid and polio vaccines—in impoverished, high-mortality settings such as those found in low-income countries (101-111). Some scientists think that higher levels of maternal antibody, prevalence of other intestinal infections and incidence of other causes of death and diseases like HIV, malaria, tuberculosis and malnutrition may influence the vaccine's efficacy (39). Additionally, when the oral polio vaccine is given at the same time as the rotavirus vaccine, it may affect rotavirus vaccine performance in low-income countries.

While vaccine efficacy is an important factor, it is not the only factor decision makers should consider when determining whether or not to include a vaccine in their country's national immunization program. The local burden of disease should be another key factor. In countries where rotavirus is a leading cause of child death or

illness, rotavirus vaccines can have a major impact by helping to reduce the burden of disease and severe illness (2, 24-28, 35, 36, 39, 111-115). The economic burden of rotavirus diarrhea treatment should also be considered—not only direct medical costs, but also lost wages and productivity when parents must miss work to care for a sick child.

Indirect benefits: vaccination against rotavirus also protects the unvaccinated

Rotavirus vaccination has been shown, in some high- and middle-income countries, to reduce hospitalizations among children and adults who are too old to be vaccinated. This is an effect known as herd immunity, where vaccination of a significant portion of the population provides protection for individuals who were not vaccinated or have not developed immunity.

FIGURE 11: Reductions in rotavirus-related hospitalizations among vaccinated and unvaccinated

Reference: 82

COUNTRY (NATIONWIDE)	AGE-ELIGIBLE	NOT AGE-ELIGIBLE*
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%

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

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

Studies in Australia, Austria, Belgium, Brazil, El Salvador and Finland found that following rotavirus vaccine introduction in infants, rotavirus hospitalizations decreased by up to 89% (24-89%) among children too old to receive the vaccine (74, 76, 78, 80, 83, 85). Regional studies in Australia observed an impressive reduction in rotavirus hospital admissions of up to 70% in Queensland, 73% in New South Wales and 74-100% in the Australian Capital Territory (80, 116).

In the United States, rotavirus hospitalizations among children 2 to 4 years of age, who were too old to be vaccinated when the vaccines were first introduced, declined by up to 80% (41-80%), and all-cause diarrhea hospitalizations declined by more than one-third (35-41%) (32, 69). Among children over 5 and young adults up to age 25, diarrhea hospitalizations fell by up to 30% (8-30%), and rotavirus-specific hospitalizations declined by more than half (53-71%) (117, 118).

Studies are underway to assess the indirect benefits of rotavirus vaccines in low-income countries.

Broad protection: rotavirus vaccines protect against strains not included in the vaccine

Much like influenza, circulating rotavirus strains change from year to year and region to region. While rotavirus strain diversity and distribution varies around the world, clinical studies and post-licensure research have found that, unlike influenza vaccines, the two rotavirus vaccines available on the global market provide protection against a variety of circulating strains, including strains not included in the vaccines (24, 96, 119-121).

In Africa and Asia, the diversity of circulating strains is markedly different from that in the Americas and Europe. G1P[8] is the most common strain of rotavirus globally, accounting for over 70% of rotavirus infections in North America, Europe and

Australia but only 30% of rotavirus infections in South America and Asia, and 23% in Africa (122). High vaccine efficacy was observed against predominant rotavirus strains (G1-G4, G9) that were present at the time of the clinical studies, but protection against less common circulating strains could not be evaluated (27, 113, 120, 123).

Since then, post-licensure studies have enabled researchers to better evaluate rotavirus vaccine effectiveness against a wider variety of strains. For example, GSK's Rotarix—containing strain G1P[8]—was shown to be 94% effective against G9P[4] in Mexico, while in the United States, it was 88-94% effective against G2P[4] and 74% effective against G3P[8]. It was also 75-77% effective against G2P[4] in Brazil, and 72%, 84%, 87% and 92% effective against G2P[4], G9P[8], G9P[6] and G3P[8], respectively, in Bolivia (49, 50, 54, 59, 63). An integrated assessment with data from several countries in Europe and Latin America, as well as Singapore, showed that Rotarix induced high clinical protection from the G2P[4] strain, with 71% efficacy against severe rotavirus diarrhea and 81% efficacy against rotavirus diarrhea of any severity (124). In Malawi and South Africa, Rotarix also offered significant protection against severe rotavirus diarrhea due to strains that were not included in the vaccine: 79%, 64%, and 71% efficacy against G2, G8 and P[4], respectively (120). Similarly, Merck's RotaTeq—containing strains G1, G2, G3, G4 and P[8]—was 83% effective against G12P[8] and 87-98% effective against G2P[4] in the United States (59, 62).

Research to better understand strain diversity and vaccine effectiveness is ongoing.

Benefits of rotavirus vaccines outweigh potential risks

GSK's Rotarix and Merck's RotaTeq, the two rotavirus vaccines currently available on the global market, have strong safety records and have been studied in every region of the world.

While most children do not experience any side effects following vaccination, there is a slight chance of minor symptoms including diarrhea, vomiting and irritability. In extremely rare cases, intussusception, a bowel blockage where the intestine folds in on itself, can occur. Intussusception occurs naturally in infants, in the absence of vaccination, between 2 and 9 months of age, and the rates at which it occurs vary from region to region. The number of naturally occurring cases of intussusception ranges from 9 to 328 per 100,000 children under age 1, with an average of 74 cases per 100,000 (125). If left untreated, it can lead to bowel perforation and death (126).

Intussusception was associated with RotaShield®, a tetravalent rotavirus vaccine (RRV-TV; Wyeth Lederle Vaccines) licensed and used in the United States from 1998-1999. RotaShield is no longer on the market. It was withdrawn less than a year after licensure, when post-marketing surveillance detected an association with intussusception of approximately one additional case (i.e., one case that would not have occurred naturally, in the absence of vaccination) per 10,000 vaccinated infants (127-130).

Large-scale clinical safety and efficacy studies of Rotarix and RotaTeq have found that both are safe. Serious adverse events, like intussusception, are extremely rare. In these clinical trials, no increased risk of intussusception was observed when comparing vaccination with a placebo (27, 28). Post-marketing surveillance studies from Australia, Brazil, Mexico and the United States have found that the risk of intussusception for Rotarix and RotaTeq is comparable, and that for every 100,000 children vaccinated, there are an estimated one to six additional cases of intussusception (131, 132).

Because the number of rotavirus-related hospitalizations and deaths preventable by vaccination is high, and the number of intussusception cases attributable to rotavirus vaccination is very low, public health experts around the world agree that the benefits of vaccination substantially outweigh the risk of intussusception.

Country-level data support this conclusion. A study in Mexico estimated that rotavirus vaccination prevents 11,551 rotavirus-related hospitalizations and 663 deaths annually, compared to an estimated 41 excess intussusception cases and two deaths attributable to the implementation of rotavirus vaccination. In Brazil, the figures are an estimated 69,572 hospitalizations and 640 deaths prevented, compared to a predicted 55 excess intussusception cases and three deaths (29). In Australia, more than 6,500 rotavirus-attributable gastroenteritis hospitalizations in young children would be prevented each year post-vaccine introduction, which outweighs the 14 excess cases of intussusception that would occur in young children each year after implementing routine rotavirus vaccination (131).

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 (133).

Rotavirus vaccines are cost-effective

Economic evaluations of rotavirus vaccines have found them to be cost-effective across low-, middle- and high-income countries and across a range of vaccine prices. The WHO-CHOICE (Choosing Interventions that are Cost-Effective) initiative provides country-level information to help policy makers decide on health interventions. WHO-CHOICE uses gross domestic product (GDP) as an indicator to develop the following widely referenced categories of cost-effectiveness: highly cost-effective (<1 times GDP per capita), cost-effective (1 to <3 times GDP per capita) and not cost-effective (≥3 times GDP per capita) (134). Using these WHO-CHOICE thresholds as a benchmark, rotavirus vaccines are projected to be highly cost-effective, particularly in regions suffering from the highest levels of rotavirus mortality (135).

Key drivers of rotavirus vaccine cost-effectiveness include vaccine price, relative coverage (adjusted for the likelihood that those more likely to get sick or die from rotavirus diarrhea are less likely to be vaccinated), herd immunity, number of deaths from severe infection, effectiveness of the vaccine against severe disease and the rate at which vaccine protection wanes (135). Reduced hospitalizations and emergency department visits also play an important role in adding to the overall healthcare costs averted through vaccination.

In lower-income, higher-mortality countries, rotavirus mortality and waning vaccine protection rates are more influential in the economic evaluation. In higher-income, lower-mortality countries, inpatient admission rates have a greater influence on cost-effectiveness (135).

A cost-effectiveness analysis focusing on countries supported by Gavi found rotavirus vaccines to be cost-effective in the entire cohort of countries eligible for Gavi support, even when herd immunity is not taken into consideration. Rotavirus vaccines were also found to be cost-effective in each Gavi-eligible country individually (136).

For low-income countries in Asia, introducing rotavirus vaccines would halve rotavirus-related deaths and medical visits, leading to significant reductions in costs (137). In African and Eastern Mediterranean countries, lower vaccine coverage and

INCREMENTAL COST-EFFECTIVENESS RATIOS (ICERS)

$$\frac{\text{cost of the vaccination program} - \text{healthcare costs saved}}{\text{DALYs without vaccine} - \text{DALYs with vaccine}} = \frac{\text{incremental net cost of vaccination program}}{\text{DALYs averted}}$$

delays in vaccination would result in relatively lower reductions in death and illness (137). Despite this, implementing rotavirus vaccines would still be cost-effective due to the high rotavirus-related mortality in these regions (137).

The results of cost-effectiveness analyses come in the form of incremental cost-effectiveness ratios (ICERs), which can be interpreted as the net cost per health outcome measure (typically measured by the disability-adjusted life-years (DALYs) averted in low- and middle-income settings) considered in the study.

At US$5 for each dose of rotavirus vaccine, the cost-effectiveness in the low-, lower-middle- and upper-middle-income groups was US$88, US$291 and US$329, respectively, for each DALY averted (137). For the low-income groups in Africa and the Eastern Mediterranean, at the same price per dose, the cost per DALY averted was US$61 and US$104, respectively – leading to a 35% reduction in rotavirus-associated deaths and medical visits averted for this income group in both regions (137).

Recent studies show that national rotavirus vaccination programs will be highly cost-effective and will substantially reduce child illness and deaths due to rotavirus diarrhea, as well as reducing healthcare costs due to rotavirus-related illness.

COUNTRY	NUMBER OF CASES	DEATHS AVERTED	HEALTHCARE COSTS AVERTED	DATE RANGE
Iran	35.1 million	266	US$470 million	2014-2023
Kenya	1.2 million	61,000	US$30 million	2014-2033
Senegal	2 million	8,500	US$17.6 million	2014-2033
Uganda	4 million	70,000	US$10 million	2016-2035

References: 18, 138, 139

In the United States, in just four years, rotavirus vaccination saved nearly US$1 billion by preventing hospitalizations, emergency visits and doctors' visits among children under age 5 (68).

Vaccine affordability and financing assistance

Newer vaccines, like those used to prevent rotavirus, typically command higher market prices compared to other routine immunizations. Price is a key driver in the economic evaluations that inform the decision of whether to introduce. However, the precise price of the vaccine is often not available during these economic evaluations, so the private sector list price—often substantially higher than the eventual tender price or discounted price that can be negotiated by the country—is used in the analysis. Some countries may decide that the vaccine is not cost-effective at this higher price (140).

For low-income countries, Gavi provides support for vaccine introduction, including subsidizing the price of the vaccine. After Gavi support ends, countries must commit to taking on financial responsibility for sustaining the vaccination program. This may be challenging and can result in countries deciding not to seek Gavi support. Countries that may be deterred from seeking Gavi support could use insight from cost-benefit analyses to redefine competing priorities to develop a strategy that would allow them to sustain their vaccination program after graduating from Gavi support.

Lower-middle- and middle-income countries that are not eligible for Gavi support also face challenges for funding new vaccines, including rotavirus vaccines. Several options for assistance are available for some of these countries. Some vaccine manufacturers have committed to offering tiered pricing agreements with individual countries or to providing their vaccine at an affordable price (141, 142). In the Americas, the Pan American Health Organization (PAHO) created the Revolving Fund to facilitate bulk purchase of vaccines, cold chain equipment and related supplies for member states.

For countries that are not eligible for Gavi support for vaccine introduction and that are not part of the PAHO Revolving Fund, alternate funding strategies beyond direct negotiations with vaccine manufacturers may be needed. UNICEF recently proposed a strategy for vaccine procurement that would establish reference prices and also provide pooled procurement similar to the PAHO Revolving Fund (142). Negotiations for tiered prices may also benefit countries that are able to conduct one-on-one negotiations with vaccine manufacturers.

Availability of information on the public sector prices negotiated by countries currently using rotavirus vaccines in their national immunization programs would aid countries considering vaccine introduction in conducting more accurate economic evaluations and may assist in price negotiations with manufacturers. WHO's Vaccine Product Price and Procurement Project (V3P) was launched at the request of countries to increase price transparency by sharing their vaccine price information. As of September 2015, 17 countries reported their prices for rotavirus vaccines.[3] These data will help countries identify realistic prices to use in economic evaluations and facilitate tiered pricing and related discussions.

Finally, country-level economic evaluations can be conducted, and these assessments can help calculate a "break-even" price that can be used as a basis for negotiations with manufacturers or purchasing agencies. The "break-even" price can be calculated from both the healthcare system and societal perspectives, and this is the price per dose of rotavirus vaccine where the healthcare costs saved as a result of averting rotavirus disease exactly offsets the cost of vaccination (137). An economic evaluation of rotavirus disease and rotavirus vaccines in developing countries found that from the healthcare system perspective, the "break-even" prices for rotavirus vaccines would be <$US0.53 for lower-middle-income countries and <$US2.00 for upper-middle-income countries (137).

FIGURE 12: Prices of rotavirus vaccines

References: 140, 143–145

COUNTRY/REGION	VACCINE	PRICE (US$/COURSE)
Australia	Rotarix / RotaTeq	Not in public domain
Gavi	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)

[3] *More information is available through the WHO's Vaccine Product, Price and Procurement (V3P) web platform at http://www.who.int/immunization/v3p.*

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 average over the previous three years. Phase I and II represent updated Gavi Graduation Policies as of June 2015 (146).

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

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

III. **Phase II: Accelerated transition** (formerly called graduating countries, >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.

POTENTIAL MECHANISMS TO SECURE AN AFFORDABLE VACCINE

A BULK PURCHASING FUND

Driven by: Global Health Community, Global Health Agencies

Taking advantage of economies of scale, the PAHO Revolving Fund secures vaccines and related supplies—prequalified under WHO standards of safety and effectiveness—for its member states in bulk at affordable prices. By purchasing through the Revolving Fund instead of directly from producers, Latin American countries can make significant savings on the purchase price. Founded on the principle of equity, PAHO's Revolving Fund enables all participating member states to have access to the same products, offered at the lowest price, which is the same regardless of the country's size or economic situation. The Revolving Fund also handles key processes like planning, demand estimates, price negotiations, purchase orders, supply coordination, shipment monitoring and billing. As a result, Latin American countries have had continuous access to safe and effective vaccines at low, stable prices for over 30 years. This assists national governments with budget planning and fosters sustainable immunization programs. While this system requires significant work to establish, it is a model other regions—such as Asia—could consider.

UNICEF HYBRID PROCUREMENT STRATEGY

Driven by: Global Health Agencies

Recently, UNICEF presented a strategy for vaccine procurement for middle-income countries that would provide industry with demand forecasts, provide countries with information on products and availability, pool procurement and establish reference pricing. Exploring this strategy further may benefit middle-income countries.

MANUFACTURER TIERED PRICING

Driven by: Manufacturers

Vaccine manufacturers have indicated that they are willing to enter into tiered pricing agreements with individual governments. Unfortunately, the prices agreed to by companies and individual countries are generally not in the public domain to guide decision makers in other countries. Further, one-on-one negotiations may violate legal requirements in some countries.

POTENTIAL MECHANISMS TO SECURE AN AFFORDABLE VACCINE (continued)

SEPARATING TECHNICAL DECISIONS FROM ECONOMIC EVALUATIONS

Driven by: Country Governments

In this scenario, one technical advisory committee in a country would evaluate disease burden and vaccine efficacy and determine whether there is strong evidence in support of implementing the vaccine in this setting. Another advisory group would evaluate cost-effectiveness, determine whether the vaccine can be made available through the national immunization program or if a co-payment will be required and then provide the government with its recommendation regarding the implementation of the vaccine. Australia uses this mechanism, and it enables the country to work with industry to establish the vaccine price. However, in contrast with PAHO's Revolving Fund, the vaccine price is not made public. This mechanism may also be too cumbersome for smaller countries to manage.

COUNTRY-LEVEL ECONOMIC EVALUATIONS

Driven by: Country Governments

To help determine a suitable vaccine price, country-level economic evaluations can be conducted prior to the decision to introduce a new vaccine. Typically, the main drivers of these assessments are the price of the vaccine and the number of deaths and hospitalizations averted. Ideally, the vaccine would cost less and be more effective than the present intervention(s). Importantly, this mechanism requires accurate input of vaccine price. Often, because this information is not publicly available, the more expensive private market price is utilized, and decision makers are led to erroneously conclude that a national vaccination program is not cost-effective.

Reference: 140

Nationally available rotavirus vaccines

Several rotavirus vaccines are available in national markets only. These vaccines include ROTAVAC®, manufactured by Bharat Biotech International Limited and licensed for use in India; Rotavin-M1, manufactured by the Center for Research and Production of Vaccines and licensed for use in Vietnam; and Lanzhou Lamb Rotavirus Vaccine (LLR), manufactured by Lanzhou Institute of Biological Products and licensed for use in China. The Indian vaccine contains a G9P[11] human strain, the Chinese vaccine contains a single G10P[12] lamb rotavirus strain and the Vietnamese vaccine contains a single G1P[8] human rotavirus strain (112, 147, 148).

In March 2014, results were published from the phase III efficacy study of ROTAVAC (111, 112). This oral vaccine originated from an attenuated strain of rotavirus that was isolated from an Indian child, and is delivered on a three-dose schedule. This study, conducted in Delhi, Pune and Vellore, three geographically and culturally diverse Indian cities, found that ROTAVAC was 56% efficacious against severe rotavirus during the first year of life. The results were comparable to that of RotaTeq and Rotarix in low-income countries (24-26, 111). In a follow-up analysis, the vaccine was shown to have an efficacy of 56% in the first year of life and 49% during the second year of life (112, 149). ROTAVAC is licensed in India but is not yet WHO prequalified. Clinical trial data are not available for the Rotavin-M1 or LLR vaccines, but immunogenicity and effectiveness studies have been published.

New vaccines on the horizon

Manufacturers in Brazil, China, India and Indonesia are also developing new rotavirus vaccine products that could soon be available.

Companies in Brazil, China and India are developing a rotavirus vaccine based on a UK bovine-human reassortant vaccine developed by the U.S. National Institutes of Health (150, 151). In India, Shantha Biotechnics and the Serum Institute of India have candidate vaccines that are in or entering phase III studies. A quadrivalent formulation of the UK vaccine strain was shown to be safe and effective with three doses given to infants (152). In a preliminary study in Finland, efficacy rates against severe rotavirus disease of vaccines from the UK strain were 88-100% (153).

Two human-lamb reassortant vaccines are also in development in China. RotaShield (RRV-TV), the tetravalent rhesus rotavirus vaccine that was previously available but withdrawn in the United States, has recently completed a limited phase III study in Ghana. In this study, the vaccine was administered to children on a neonatal dosing schedule, when the risk of natural intussusception is low. In a small sample size, two doses of the vaccine were found to be 61% efficacious against severe rotavirus when administered at 0-29 days of age and 30-59 days of age with 21 days between doses

(154). International Medica Foundation has recently sublicensed RRV-TV to BravoVax Co., Ltd in China (155).

Another potential rotavirus vaccine, RV3-BB, was developed from a neonatal strain G3P[6] identified in Australia, with ongoing early clinical studies conducted in New Zealand and now underway in Indonesia.

Neonatal strains have several potential advantages over the strains used in the currently available vaccines. They replicate well in the intestines of newborn infants despite the presence of maternal antibodies; and, if given at birth, these vaccines could protect children from rotavirus within the first five days of life. This approach may also limit the risk of intussusception by avoiding administration at the age when the natural incidence of intussusception is high. Clinical studies of the RV3-BB vaccine suggest that RV3-BB could be given using a birth dose strategy (first dose at 0-5 days of life) or an infant schedule (first dose at 8 weeks) (156).

In addition to live, oral vaccines, other approaches for rotavirus vaccines, such as direct injection of rotavirus antigens and inactivated vaccines, are being explored (157). Some of these vaccines have shown promise but are still in the very early phases of development. Continued research and development are still needed to determine whether the inactivated vaccines are subject to the same efficacy challenges as oral rotavirus vaccines in low- and middle-income countries and whether there is an association with intussusception.

In addition to making rotavirus vaccines more available, efficacious and safer, these new vaccines will also potentially help make rotavirus vaccines more affordable.

Emerging data and areas for further research

Continuing to build the evidence base is critical to informing and encouraging the uptake of rotavirus vaccines. Research is underway to monitor the impact and safety of rotavirus vaccines in resource-limited settings, identify ways to improve vaccine performance in low- and middle-income countries and further examine the association between rotavirus vaccines and intussusception.

Impact. At least 36 low-income countries have introduced rotavirus vaccines with Gavi support, and additional data on vaccine impact and effectiveness from early introducing countries will be available over the next several years.

Safety. Several African countries have initiated surveillance for intussusception to better understand its occurrence in the region, track causes of intussusception and

monitor treatment patterns, rates of surgery and outcomes. Efforts are ongoing to initiate similar studies in Asia. Additionally, countries that have introduced rotavirus vaccines in Africa established an intussusception surveillance network to collect data. This will help determine if there is a short-term increased risk of intussusception following rotavirus vaccination in low-income African settings, and to assess this risk in the context of the benefits of reduced hospitalizations and deaths.

Vaccine performance. Results are also anticipated from several studies that examined potential strategies to improve oral vaccine performance. Results from studies assessing the role of zinc and probiotic supplementation at the time of vaccination are also expected soon.

Vaccine schedules. A recent randomized study evaluated GSK's Rotarix on different two-dose schedules: doses given on the WHO-recommended schedule of 6 and 10 weeks, and given at 10 and 14 weeks—as well as that of a three-dose schedule where doses were given at 6, 10 and 14 weeks of age (158). No significant differences in terms of vaccine performance were observed when comparing the two- and three-dose schedules. A study in Ghana, however, did find a difference in vaccine performance and affirmed the findings from studies in Malawi and South Africa (26, 154). Researchers are also examining if a booster dose might provide greater protection.

FUTURE AREAS OF RESEARCH

Areas where future research is needed include:

- Exploring alternative approaches such as parental delivery of rotavirus antigens and/or inactivated vaccines, which may have improved efficacy and could potentially lower the risk of intussusception
- Examining how the gut microbiome influences vaccine effectiveness
- Using new data from early adopting African countries to analyze risks and benefits to help countries evaluate vaccine programs and make decisions regarding sustained use
- Examining barriers to rotavirus vaccine introduction and ways to overcome them
- Continuing to research and develop new vaccine candidates to ensure sufficient supply and affordable prices

A comprehensive approach to controlling diarrheal disease

Prevention, protection and treatment make up the framework of the Integrated Global Action Plan for the Prevention and Control of Pneumonia and Diarrhea (GAPPD), a 2013 global plan from UNICEF and WHO and endorsed by the ROTA Council. The GAPPD represents the first-ever effort to protect children simultaneously from pneumonia and diarrhea, diseases that have overlapping interventions for protection, prevention and treatment.

Rotavirus vaccines are essential to a comprehensive approach to fighting diarrhea, which consists of (159):

- **Treatment.** When children do become sick with rotavirus, mild cases can be treated with oral rehydration solution (ORS)—a form of ORT and a simple mixture of sugar, salt and safe water—and with zinc supplements and appropriate case management. However, severely dehydrating diarrhea may require IV fluids and urgent medical care. Unlike diarrhea caused by some bacteria, rotavirus cannot be treated with antibiotics or other drugs.
- **Prevention.** Rotavirus vaccines are the best tool available today to prevent rotavirus. Rotavirus vaccines are a critical tool in fighting rotavirus, because hygiene and sanitation improvements—which can prevent other forms of diarrhea—do not adequately prevent the spread of rotavirus.
- **Protection.** Good health practices can help protect children from diarrhea. These practices include exclusive breastfeeding for the first six months of a baby's life and providing appropriate complementary feeding after six months.

Treatment of rotavirus diarrhea alone is not sufficient in many settings. Lack of access to medical care and hydration therapy for many children in low- and lower-middle-income countries limits the success of treatment programs. 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 did not experience an episode of diarrhea (160). Plus, families incur the financial burden for care of a sick child, including the caregiver's lost wages.

Recommendations

This paper has summarized the latest evidence on rotavirus: it is the most common cause of severe diarrhea, and every child is vulnerable. Vaccines are safe, effective and the most powerful tool to protect children from rotavirus. In countries where they are in use, vaccines are already saving lives and improving health. Despite the WHO recommendation that rotavirus vaccines be introduced into every country's national immunization program, children in many parts of the world still do not have access to this critical intervention. These countries should prioritize the vaccines now—millions of illnesses and tens of thousands of deaths can be prevented through rotavirus vaccination.

The ROTA Council strongly endorses the recommendation by WHO that all countries introduce rotavirus vaccines. In addition, to accelerate the introduction of lifesaving, health-improving rotavirus vaccines, the ROTA Council recommends key stakeholders in countries where these vaccines have not yet been introduced undertake actions in the areas that follow.

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ROTA COUNCIL RECOMMENDATIONS

In conjunction with the introduction of rotavirus vaccines, we urge countries to work with WHO, UNICEF and other partners (global, regional and/or in-country) working on diarrheal disease to plan and implement a comprehensive set of interventions to reduce illness and death from diarrheal disease, consistent with the GAPPD.

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

1. **Gavi-eligible countries** that have not yet introduced rotavirus vaccines into their childhood immunization schedules should strongly consider applying to Gavi for new vaccine support for rotavirus vaccines as soon as possible.

2. To optimize the rollout of vaccines and maximize the number of eligible infants immunized, **WHO, UNICEF, Gavi** and other partners should continue to support countries that plan to introduce the vaccine. Special emphasis should be placed on assessments of cold chain and other system requirements, plans for timing of vaccine introduction based on available supply and plans to ensure sustainable financing and support of rotavirus vaccination.

3. If the rotavirus vaccine of choice is not available due to supply constraints, **countries** should strongly consider introducing any prequalified rotavirus vaccine that is available in the short-term, and working with **Gavi** on longer-term options for the vaccine of choice.

4. **Low- and lower-middle-income countries that have introduced vaccines** should share lessons learned with **countries that have not yet introduced**. Focused regional meetings should be supported to facilitate these shared experiences among diverse stakeholders.

5. **Countries planning to introduce rotavirus vaccines** are encouraged to establish a strong surveillance system to monitor disease burden to evaluate the impact of vaccination on disease and rare adverse events before and after introduction of the vaccine.

6. **Countries that have introduced rotavirus vaccines or plan to introduce** are encouraged to collect high-quality data on rotavirus disease burden and rotavirus-related hospitalizations to evaluate vaccine impact. Particular emphasis should be placed on districts with high mortality rates.

7. **Funding agencies** should continue to support the evaluation of rotavirus vaccine programs in Gavi-eligible countries, as well as countries that have recently graduated from Gavi support, including the evaluation of: operational aspects, safety, public health impact, economic impact and effectiveness.

ROTA COUNCIL RECOMMENDATIONS

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

1. Noting the broad economic and social benefits of vaccination, it is recommended that **national and local governments** enact legislation that addresses issues of the rights of populations to receive recommended vaccines, and provisions to ensure a supply of quality, affordable vaccines.

2. **Governments and funding agencies** should continue to support the research and development of new, low-cost rotavirus vaccines using public, social business and public-private models. Emerging market manufacturers have demonstrated the ability to develop and license low-cost rotavirus vaccines (Rotavin and ROTAVAC) with technology transfer and public funding support.

3. To enable countries of all income groups to include rotavirus vaccines into their national immunization programs, transparent and flexible pricing mechanisms are required. It is recommended that **global health agencies** (i.e. UNICEF, WHO, Gavi), and **non-governmental organizations influential in vaccine programs** (e.g., Médecins Sans Frontières and Save the Children) expedite initiatives to ensure prices paid for rotavirus vaccines reflect true manufacturing costs, provide reasonable returns on manufacturers' investments and take into account an individual country's ability to pay. All countries using rotavirus vaccines in the national immunization program should be encouraged to report the price of their vaccine to WHO's V3P Project. Additional mechanisms may be required to provide innovative funding options for low-middle income, non-GAVI eligible countries.

4. To ensure integration with existing interventions outlined by the GAPPD, it is recommended that training courses be provided by **national governments** to update **frontline health workers** (physicians, nurses, public health professionals and community health workers), and that data be collected by **educational authorities and academia** to determine the extent to which this information is incorporated within medical, nursing and other healthcare worker curricula.

5. **National governments, funding agencies, and global health entities (WHO, UNICEF and NGOs)** should support **media and advocacy groups** to ensure that the benefits of rotavirus and other vaccines are successfully conveyed to the public.

6. Given the consistent, high public health impact and cost-effectiveness of rotavirus vaccines in high-income countries, **WHO, UNICEF** and **NGOs** should collect data to better understand the reasons why a number of high-income countries have not yet included rotavirus vaccines in their national immunization programs.

ROTA COUNCIL RECOMMENDATIONS

To influence the research agenda and gain a better understanding of:

1. Impact, effectiveness and safety of rotavirus vaccination in diverse geographic and socioeconomic settings, particularly in low-income countries of Africa and Asia, **researchers** should:
   - quantify changes in morbidity and mortality from severe diarrheal disease in countries using rotavirus vaccine;
   - examine the effect of vaccination on epidemiology (e.g., seasonality, age distribution) of rotavirus;
   - assess evidence of indirect benefits (i.e. herd immunity) among unvaccinated children;
   - perform long-term monitoring to assess possible changes in the ecology of circulating rotavirus strains after vaccine implementation;
   - assess effectiveness of vaccination beyond 1 year of age and against a range of circulating rotavirus strains; and
   - examine safety of vaccination with respect to intussusception in targeted settings and assess any identified risk in the context of vaccine benefits.

2. Reasons for the 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 (e.g., Lewis blood group) and specific immunological characteristics of circulating strains; and
   - examine the effect of different vaccine schedules (e.g., birth dose, two-dose versus three-dose schedules of monovalent vaccine, timing and spacing of vaccine doses, booster dose of vaccine later in the first year of life) on vaccine performance.

3. Different options for formulations aimed at increasing vaccine uptake and/or addressing diarrheal disease simultaneously (e.g., higher vaccine titer, or co-administration with probiotics, vitamin A and/or zinc), **researchers and manufacturers** should:
   - pursue development of non-live oral vaccines and birth dose of live oral vaccines that may overcome some of the interference observed in low-income countries;

- explore the mechanism of immunologic protection for rotavirus infection/disease to help identify correlates of protection that would facilitate vaccine testing;
- develop formulations and packaging that require less cold chain space or can even be outside the cold chain; and
- explore the impact of live oral rotavirus vaccines on the non-specific effects of vaccination.

ROTA COUNCIL RECOMMENDATIONS

To encourage the development of new rotavirus vaccines:

National governments, funding agencies, international health organizations, manufacturers and other stakeholders should:

1. Facilitate the development of new live oral vaccines that address barriers to global supply for Gavi and low- and middle- income countries; implementation challenges (cold chain, volume of administration and storage, delivery systems and safety concerns) and cultural sensitivity; and that are also safe, efficacious and available at low cost. The research agenda should address:
   i. The implications of a lack of a correlate of protection to avoid the ethical concerns of placebo-controlled trials;
   ii. The formulations to enhance programmatic suitability and vaccine stability; and
   iii. The improvements to manufacturing process efficiency.
2. Facilitate the development of alternative rotavirus vaccines. This research agenda should address the clinical development (safety, efficacy, co-administration with other Expanded Program on Immunization vaccines and implementation strategy) and vaccine development (volume, storage, delivery systems and cost), as well as determine the mechanism of action of injectable, non-replicating vaccines against rotavirus disease.
3. Pursue options for immunization schedules aimed at improving protection provided by rotavirus vaccines including neonatal schedules, booster dose or even prime-boost strategies.
4. Explore combination vaccine and non-vaccine strategies aimed at reducing diarrheal disease and/or improving vaccine uptake (for example probiotics, zinc and vitamin A).
5. Explore options for combination viral and bacterial enteric vaccines to provide protection against diarrhea caused by a range of potential pathogens.

Appendix: case studies

1. GHANA

Monumental dual vaccine introduction combats leading causes of child death

Pneumonia and diarrhea are a deadly duo, particularly for children. In Ghana, they were responsible for about 20% of deaths among children under the age of 5. Rotavirus alone killed more than 2,000 children annually (161, 162). But in April 2012, Ghana became the first Gavi-eligible country to simultaneously introduce pneumococcal and rotavirus vaccines into its national immunization program. To prepare for the dual introduction, the government built new vaccine storage rooms, issued millions of updated immunization cards and dispelled immunization myths through community campaigns (163, 164). In the two years following the dual introduction, rotavirus diarrhea hospitalizations fell from nearly 50% to 28% of severe diarrhea hospitalizations (165). Ghana serves as a model for other African nations capable of dual introduction. Dual introduction can potentially minimize strain on a country's limited resources, as the vaccines have similar cold chain requirement upgrades and training needs, and vaccine schedules.

2. INDIA

Innovative partnerships lead to development of an indigenous vaccine

India bears the greatest burden of rotavirus under-5 deaths in the world (15). More than 870,000 inpatient hospitalizations and 3 million outpatient visits are due to rotavirus, which incur more than Rs. 10 billion each year (166). The development and planned implementation of the indigenous Indian

vaccine, ROTAVAC, offers remarkable promise for curbing rotavirus disease and death in India and around the world.

Manufactured by Bharat Biotech International Limited, ROTAVAC was developed through a public-private partnership that included the Indian government, international donors, global rotavirus experts and the private sector, all sharing the risk and cost of its development (167, 168). Faced with new evidence from clinical trials and about the high rotavirus burden in India, the government announced it would introduce rotavirus vaccines into the country's national immunization program (169). If ROTAVAC is prequalified by WHO, the vaccine may also become available to other countries. Bharat Biotech announced ROTAVAC would be made available at US$1 per dose, making it an attractive option for countries seeking a more affordable vaccine (167, 168).

3. ZAMBIA

A pilot program in Lusaka deploys an integrated, comprehensive approach to diarrheal disease prevention and control

Before rotavirus vaccine introduction, Zambia faced a devastating diarrhea burden. Diarrhea killed more than 5,700 children under age 5 annually, and rotavirus alone was responsible for 3,600 of those deaths (17, 162). In 2012, Zambia launched the Programme for Awareness and Elimination of Diarrhoea (PAED) in Lusaka (170). This pilot program improved cold chain capacity, trained more than 500 health workers and informed communities of treatment options and the availability of the rotavirus vaccine. In just over one year, more than 100,000 children were immunized (170, 171).

PAED's success can be attributed to strong stakeholder partnerships, its integration with existing child health programs and its comprehensive approach to diarrheal disease control, as well as continued advocacy and support networks (170, 171). In November 2013, thanks to the foundation built with PAED, Zambia expanded its vaccination efforts and introduced rotavirus vaccines into its national immunization program (171). PAED was a winning model for future vaccine introductions and the implementation of a framework like the GAPPD in high-burden settings (170).

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