

ROTAVIRUS DISEASE AND IMMUNIZATION: AN OVERVIEW

This summary highlights select themes and evidence covered in a seven-brief series tailored to support immunization programs and policies.

THE EPIDEMIOLOGY AND BURDEN OF ROTAVIRUS

Common cause

Rotavirus remains among the most common causes of severe and fatal diarrhea in children under 5 worldwide and is the leading cause of severe and fatal diarrhea in infants under 1.⁽¹⁾

Rotavirus accounted for the highest proportion of cases of moderate to severe diarrhea in children under the age of one presenting at hospitals and health centers across sites participating in a seven-country prospective study.^(2, 3)

Vulnerability

Children under 1 year of age suffer the highest rates of rotavirus diarrhea, and in high-incidence

settings, a substantial proportion of cases occur in children less than 6 months of age.^(4, 5)

The morbidity caused by rotavirus—in terms of hospitalizations, outpatient visits and diarrheal episodes—is often underappreciated by policymakers.⁽⁶⁾

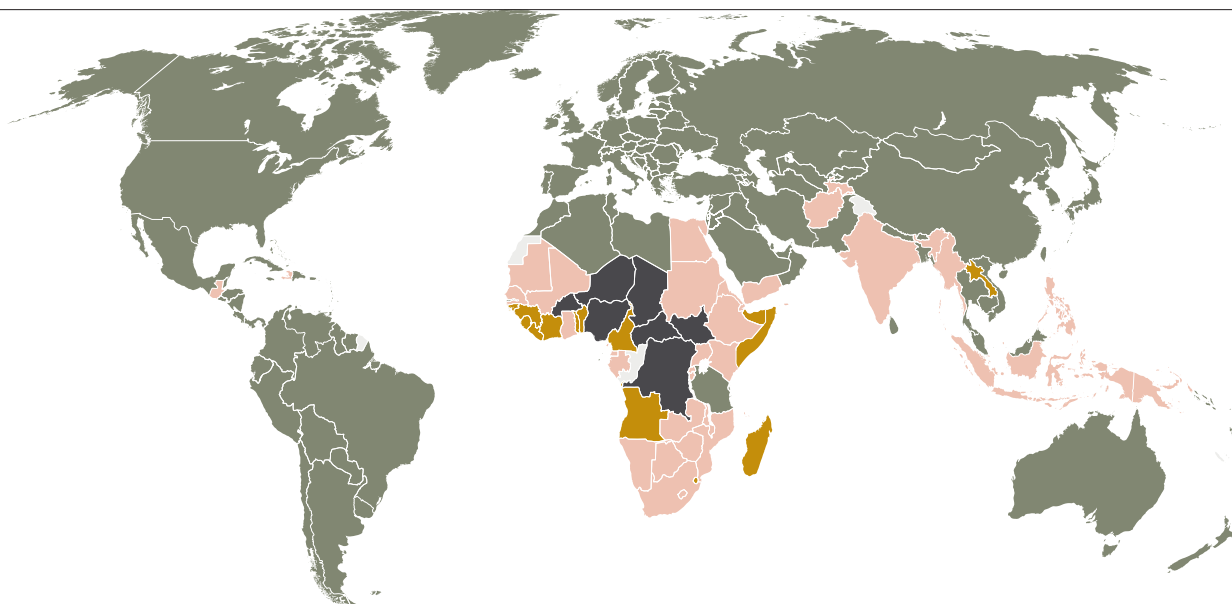
Where are children dying of rotavirus?

An estimated 185,300 children died from rotavirus in 2017 worldwide—nearly all in low- and middle-income countries.^(6, 7)

In 2019, four countries—Nigeria, Chad, Niger, and Pakistan—were estimated to account for half of all rotavirus deaths, and about three-quarters (70%) of all global deaths occurred in only ten countries.⁽⁶⁾

FIG.1 RATES OF ROTAVIRUS MORTALITY PER 100,000 CHILDREN UNDER AGE 5 IN 2019 , BY COUNTRY⁽⁶⁾

■ >100 ■ 50–99 ■ 49–10 ■ <10



CURRENT AND UPCOMING ROTAVIRUS VACCINES

Products

With the most recent prequalification by WHO of two rotavirus vaccines developed and produced in India (ROTAVAC® and ROTASIIL® and their respective fully liquid formulations ROTAVAC5D® and ROTASIIL-Liquid®), there are now four rotavirus vaccines available on the international market. These include two vaccines (ROTARIX® and RotaTeq®) that have been available internationally since 2008 or 2009.^(8, 9)

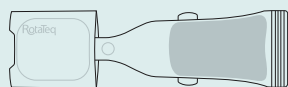
The availability of four rotavirus vaccines on the international market expands the choice of products, formulations and presentations available to countries; improves the global supply of vaccines to meet demand; and may help to reduce their costs (See page 5).

All four rotavirus vaccines are oral, live-attenuated vaccines given in two or three doses to infants.^(8, 9)

The new frontier

The efficacy of the four vaccines against severe rotavirus gastroenteritis has been found in clinical trials to be similar (36%–77%) across low-income settings, though the first two licensed vaccines have demonstrated higher efficacy (86% or greater) in high- and upper-middle-income countries.^(10–20)

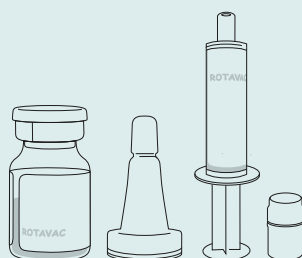
Several rotavirus vaccines using novel approaches aimed at increasing their effectiveness in low-income settings are in advanced stages of development, including a neonatal vaccine, and killed or subunit (non-replicating) vaccines administered by injection.^(21, 22)



RotaTeq®

RotaTeq® (Merck & Co. Inc.) is made up of five human-bovine reassortant strains of rotavirus and administered to infants in the same three-dose schedule as DTP1, 2, and 3. RotaTeq was licensed by the U.S. Food and Drug Administration (FDA) in 2006 after clinical studies in high-income countries showed a range of efficacy from 98–100% against severe rotavirus gastroenteritis in children.^(17,18) In studies in low- and middle-income countries, the vaccine was 43–64% protective against severe rotavirus gastroenteritis.^(10,11) Studies show that RotaTeq protects children against a wide range of rotavirus strains, including those not included in the vaccine.

One dose of RotaTeq consists of 2.5 ml of liquid vaccine suspended in a buffer in an oral squeeze tube, which is administered by drops into an infant's mouth. The product can be stored up to two years in refrigeration and cannot be frozen.

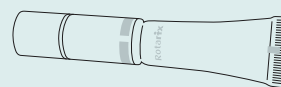


ROTAVAC® and ROTAVAC5D®

ROTAVAC®, manufactured by Bharat Biotech, is made up of a single strain of human rotavirus that is naturally attenuated. After a phase 3 trial in India found that the vaccine provided 54% protection against severe rotavirus gastroenteritis in the first year of life and 49% in the second year of life, ROTAVAC was licensed by the Government of India in 2014.^(13,14)

The vaccine is stored frozen (–20°C) and can be thawed out and kept in a refrigerator at 2–8°C for up to six months. Importantly, it can be refrozen and rethawed six times.⁽²³⁾

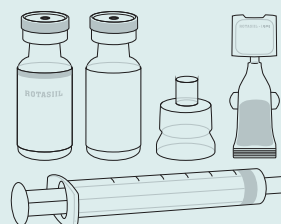
ROTAVAC is administered on the same schedule as DTP1, 2, and 3, by attaching a dropper to the vial and placing five drops in the infant's mouth. Bharat has also developed a liquid (non-frozen) formulation, ROTAVAC 5D, which was prequalified by the WHO in 2021. A trial among infants in Zambia found ROTAVAC5D to be safe and elicit just as strong of an immune response as ROTAVAC.⁽²⁴⁾



ROTARIX®

ROTARIX®, manufactured by GlaxoSmithKline (GSK), is made up of a single attenuated human strain of rotavirus. It is administered to infants in two doses on the same schedule as DTP1 and 2. ROTARIX was first licensed by the European Medicines Agency in 2006 and in the U.S. by the FDA in 2008 following efficacy studies that showed 85–96% protection against severe rotavirus gastroenteritis in high-income countries.^(19,20) Studies found that the efficacy of ROTARIX in low- and middle-income countries was between 49–77% against severe rotavirus gastroenteritis.⁽¹²⁾ ROTARIX protects children against a wide range of rotavirus strains, including those not included in the vaccine.

One dose of ROTARIX consists of 1 ml of liquid vaccine in a single-dose vial or a single-dose squeeze tube, given by drops in an infant's mouth. The product can be stored up to three years in refrigeration and cannot be frozen.



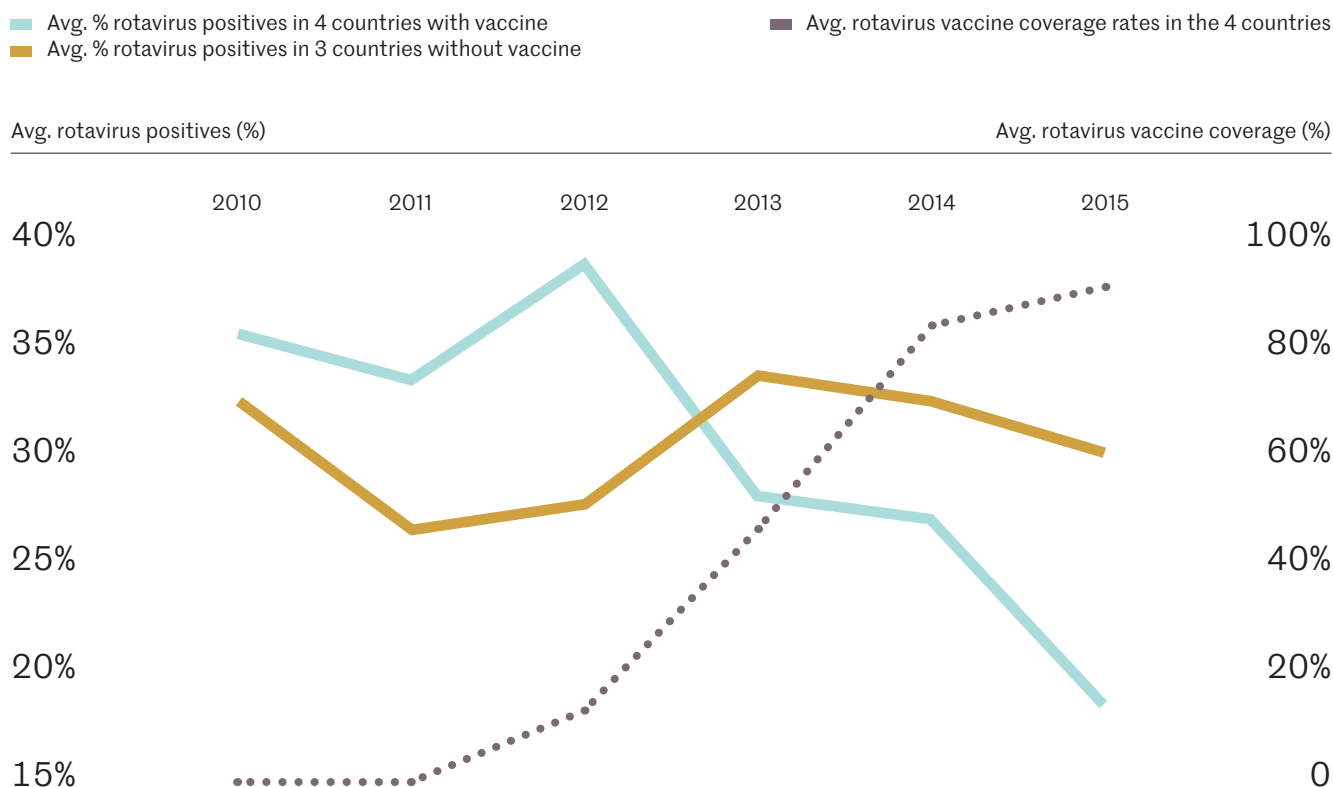
ROTASIIL® and ROTASIIL-Liquid®

ROTASIIL® is made up of five bovine-human reassortant rotavirus strains, which Serum Institute of India licensed from the U.S. National Institutes of Health. Administered in three doses at the same time as DTP1, 2, and 3, ROTASIIL® was found in India to provide 36% protection against severe rotavirus diarrhea over a 10-month period and nearly 40% over two years.⁽¹⁵⁾ In Niger, another trial that showed it provided 67% protection against severe rotavirus gastroenteritis during one year of follow-up.⁽¹⁶⁾ ROTASIIL was licensed by the Government of India in 2017.

The vaccine is a freeze-dried powder that is reconstituted with an antacid diluent just before using. It has been found to be stable for three years at or below 25°C (77°F); WHO recommends refrigeration (see Table 2).^(16,25) Serum Institute of India also developed ROTASIIL-Liquid—a fully liquid, ready-to-use presentation—that was prequalified by the WHO in 2021.

THE IMPACT OF ROTAVIRUS VACCINATION

FIG.2 ROTAVIRUS DIARRHEA HOSPITALIZATIONS DECLINED IN COUNTRIES WITH ROUTINE ROTAVIRUS VACCINE USE⁽²⁶⁾



Declines in rotavirus diarrhea

Rotavirus vaccination has substantially reduced the number of hospitalizations due to rotavirus diarrhea and diarrhea in general in young children in all regions of the world and in countries at different wealth levels.^(27–34)

Several low- and middle-income countries have also seen a sharp reduction in diarrheal-related deaths in infants and young children following vaccine introduction.^(35–42)

While efficacy rates of rotavirus vaccines have been found to be lower in low-income countries in Africa and Asia than in higher-income countries, the impact of the vaccines—in the number

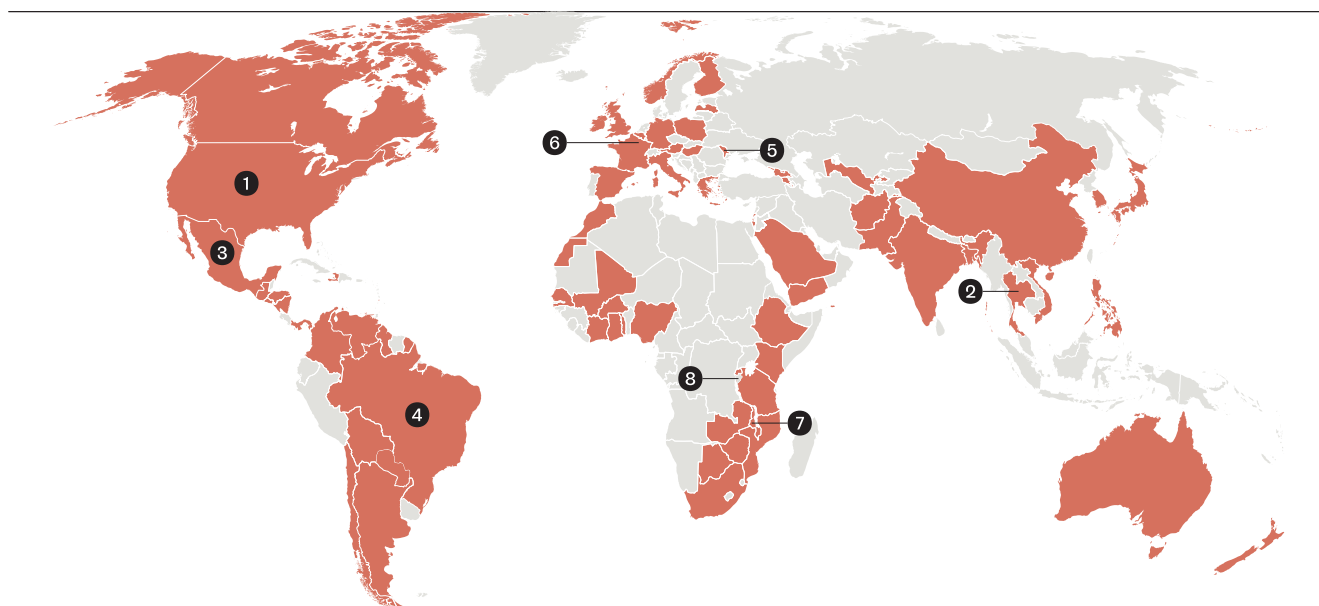
of hospitalizations prevented and lives saved—is greatest in less developed countries due to their higher rates of severe rotavirus diarrhea.⁽⁴²⁾ Rotavirus vaccines offer broad protection against different strains of the virus.

Rotavirus vaccination can also protect people not vaccinated

Many countries have found added benefits of rotavirus vaccination, including a decline in severe rotavirus diarrhea in older, unvaccinated children, due to herd immunization, and a reduction in childhood seizures associated with severe gastroenteritis.^(43–47)

FIG.3 REAL-WORLD IMPACT OF INTRODUCING ROTAVIRUS VACCINES IN NATIONAL IMMUNIZATION PROGRAMS, IN ALL REGIONS AND INCOME LEVELS

■ Countries with ≥ 1 rotavirus vaccine impact study



1) U.S.^(28, 47–49)

The lab diagnosis of rotavirus declined 58–90% since rotavirus vaccines were introduced in 2006.

2) Thailand⁽⁵⁰⁾

In a pilot introduction of rotavirus vaccine in one province, hospitalizations from rotavirus declined 88% over 2 years.

3) Mexico⁽³⁸⁾

Deaths due to diarrhea in <5s fell 53% on average in post-vaccination years, preventing nearly 1,000 deaths/year.

4) Brazil⁽³⁵⁾

Diarrheal deaths in children <5 were cut by more than half (55%) following vaccine introduction.

5) Moldova⁽²⁸⁾

Rotavirus hospitalizations in two national hospitals fell 73% in infants by the second year following vaccine introduction.

6) Belgium⁽⁵¹⁾

A study of 12 hospitals found an 80% decline in the percent of hospitalized diarrhea due to rotavirus in children 2–24 months of age by the second year following vaccine introduction.

7) Malawi⁽⁵²⁾

In Malawi, impact against diarrhea-associated mortality in infants was 31%.

8) Rwanda⁽⁵³⁾

With 99% vaccination coverage, hospital admissions due to rotavirus fell by 61–70% in <5s in two years post vaccine introduction.

FIG.4 CASES OF SEVERE ROTAVIRUS PREVENTED PER 100 VACCINATED INFANTS IN COUNTRIES WITH DIFFERENT BASELINE RATES OF ROTAVIRUS^{*(10)}

Country income level

Percent efficacious

Cases prevented per 100 vaccinated infants

Low

50%



Middle

75%



*Baseline incidence rates are the rates found in the placebo group in each clinical trial.

THE ECONOMIC COSTS OF ROTAVIRUS DISEASE AND VALUE OF ROTAVIRUS VACCINES

Rotavirus costs

Health care systems and governments across the globe incur substantial costs from rotavirus illness each year.^(54–60)

Low income families, particularly in urban areas, often experience catastrophic expenditures due to a rotavirus hospitalization in developing countries.^(61–63) Lost wages from a caregiver missing work can increase the economic burden of the illness significantly in countries across income levels, including for home-treated and outpatient cases.^(55, 58, 61, 62, 64, 65)

Benefits

Several studies in high-income countries following rotavirus vaccine introduction have found a greater than expected economic benefit from the vaccine—leading in some cases to cost savings after taking the vaccination program costs into account.^(66–69) The availability of new, lower-cost vaccines may help improve affordability of rotavirus vaccines for countries.

FIG.5 COST SAVINGS OVER SIX YEARS FOLLOWING INTRODUCTION OF ROTAVIRUS VACCINATION IN AUSTRALIA⁽⁶⁶⁾

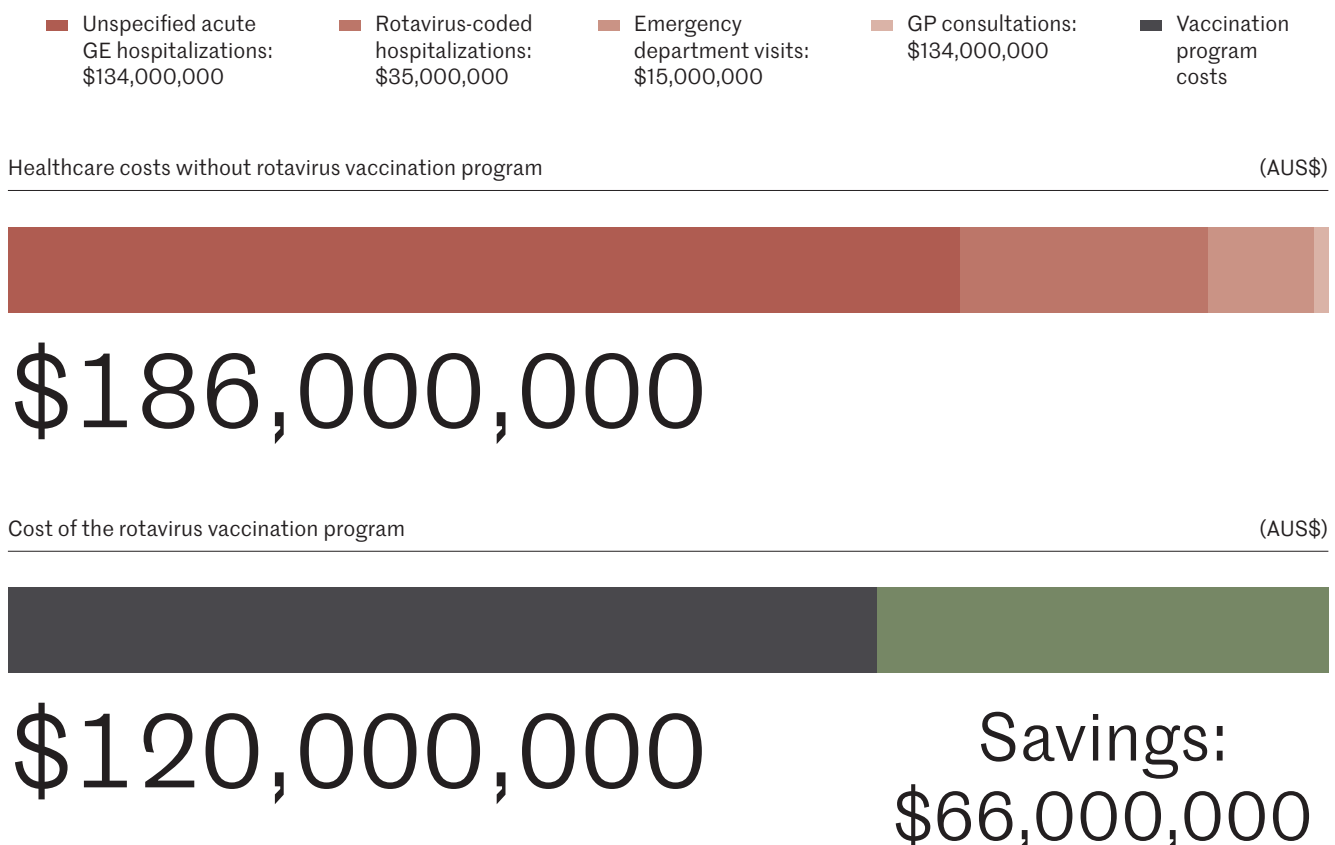
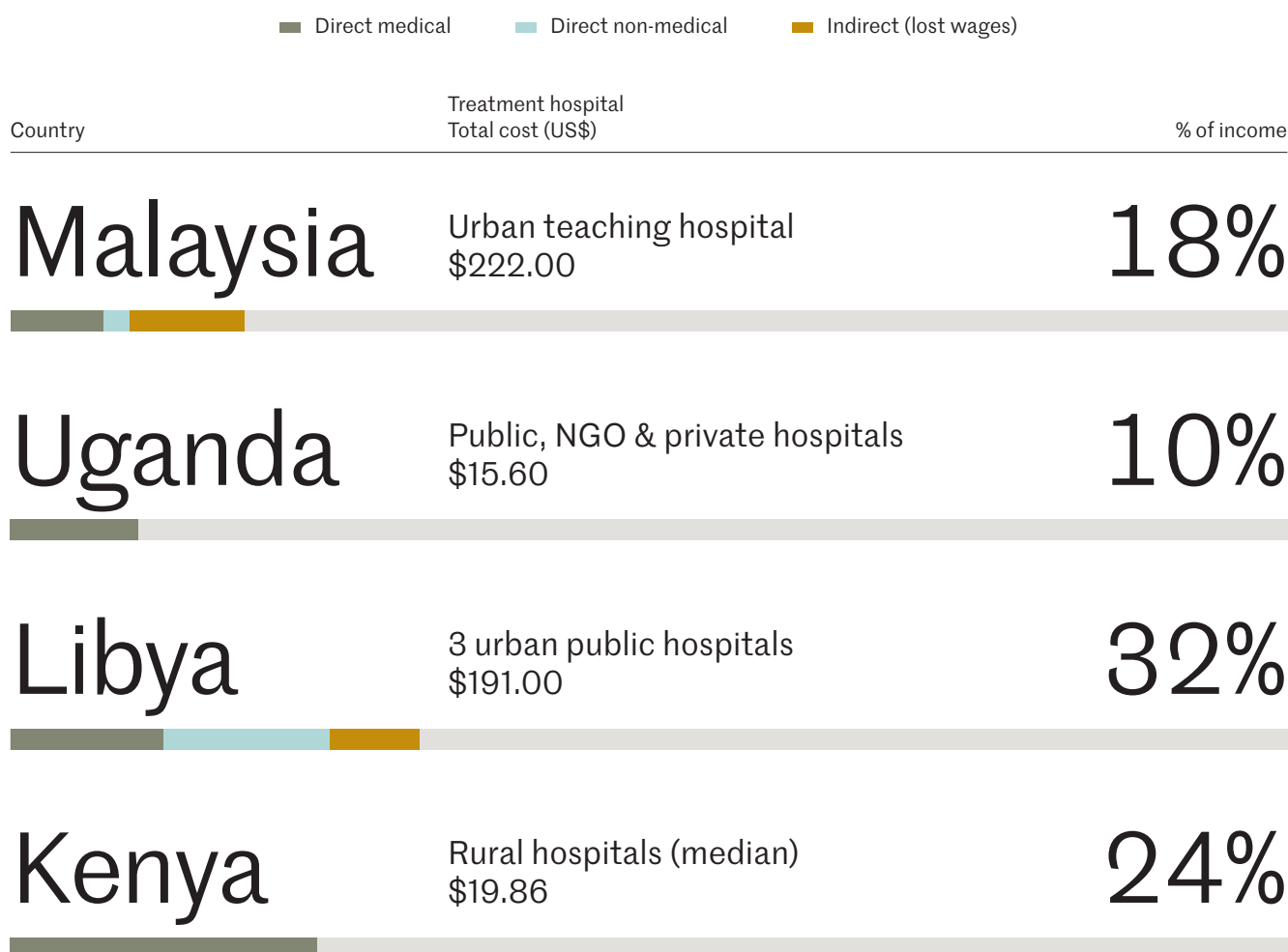


FIG.6 AVERAGE COSTS OF ROTAVIRUS HOSPITALIZATION TO FAMILIES AS A PERCENTAGE OF NATIONAL MONTHLY HOUSEHOLD INCOME^{*(56, 61, 62, 70)}



*Mean costs unless otherwise indicated.

TABLE 1 CURRENT PRICES OF ROTAVIRUS VACCINES

Country/region	Vaccine	Price per course (US\$)
Full GAVI prices ⁽²¹⁾	RotaTeq	No longer available for Gavi countries
	ROTARIX	\$5.08
	ROTAVAC	\$2.55–4.05
	ROTASIIL	\$4.65–5.55
Lower-middle-income countries in Eastern Mediterranean Region ^{*(22)}	RotaTeq	\$3.32–12.30
	ROTARIX	\$13.00
PAHO ⁽²³⁾	ROTARIX	\$2.50–7.11
Upper-middle-income countries in Western Pacific Region ^{*(22)}	ROTARIX	(estimated) \$7.35
	Rotateq	\$67.63
Australia ⁽²⁴⁾	ROTARIX/RotaTeq	(estimated) \$45.50
U.S. ⁽²⁵⁾	ROTARIX/RotaTeq	(CDC price) \$189.38–211.47 (private market) \$241.90–248.67

*V3P database does not identify countries

THE STATUS OF ROTAVIRUS VACCINE INTRODUCTION AND COVERAGE

The number of countries that have introduced rotavirus vaccines in their national immunization program has more than doubled in the past nine years, including countries with large birth cohorts, such as India and the Democratic Republic of the Congo.⁽⁷⁶⁾ Other high-burden countries including

Nigeria have been approved by Gavi, the Vaccine Alliance to introduce the vaccine with its support.

Despite recent progress, the majority of infants worldwide still live in countries or states that have yet to introduce the vaccine.⁽⁷⁶⁾

FIG.7 NUMBER OF COUNTRIES THAT HAVE INTRODUCED
ROTAVIRUS VACCINE (BY JANUARY 2022)⁽⁷⁶⁾

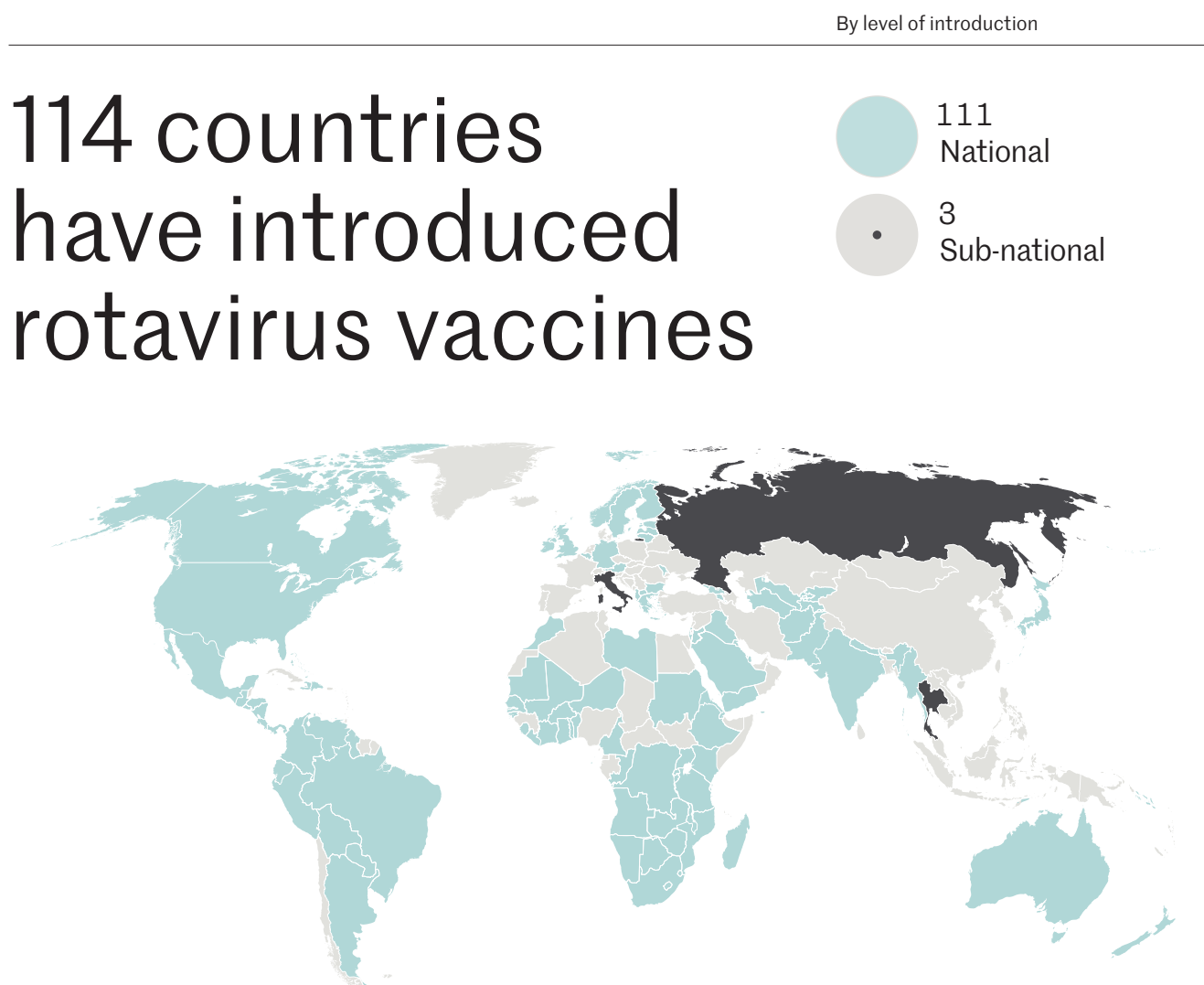
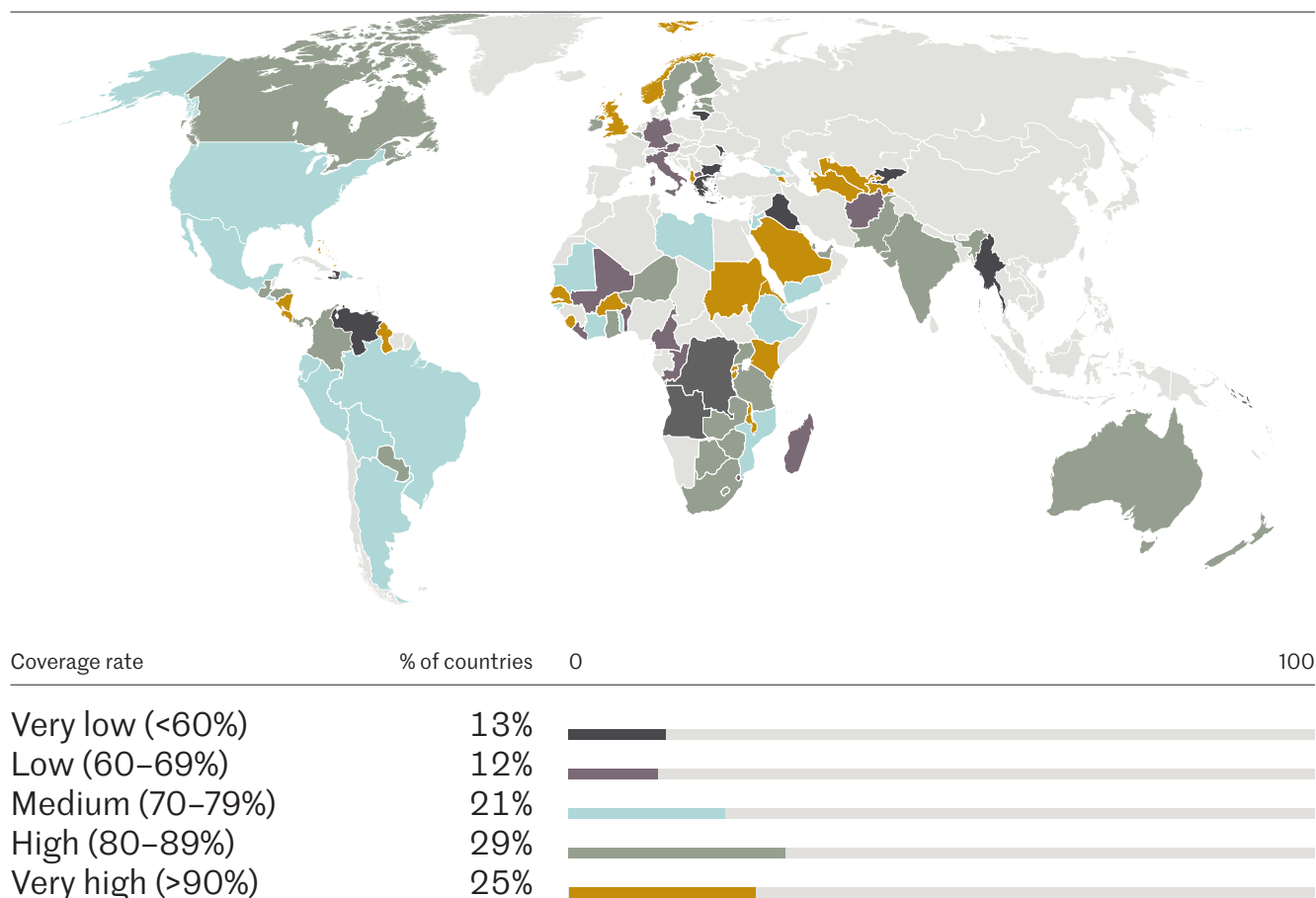


FIG.8 ROTAVIRUS VACCINE COVERAGE RATES IN COUNTRIES THAT HAVE INTRODUCED THE VACCINE (2020 WHO-UNICEF ESTIMATES)^{(77)*}



*Map shows some countries that have recently introduced and have not fully scaled up coverage.

Successes

With recent introductions, an estimated 77 million infants—or 57% of the world’s infants—now live in countries or subnational regions that have introduced rotavirus vaccines.

The greatest uptake of rotavirus vaccines is in lower-income countries that receive support from Gavi, the Vaccine Alliance, especially in Africa, while many high and middle-income countries have yet to introduce the vaccines.⁽⁷⁾

Barriers

Barriers to rotavirus vaccine introduction include cost and financial constraints, a lack of data on or questions among policymakers about the burden and severity of the disease, and safety concerns.^(9, 50, 78–82)

Rotavirus vaccination coverage lags behind coverage of diphtheria-tetanus-pertussis (DTP) and other routine vaccines in countries at all levels of development, due largely to the continued adherence to age restrictions in some regions, and questions about the importance of the vaccine among health providers and parents.^(83–86)

The COVID-19 pandemic has significantly impacted routine immunization globally—halting new rotavirus vaccine introductions and disrupting access.

THE SAFETY OF ROTAVIRUS VACCINES

Intussusception & rotavirus vaccination

Some post-marketing surveillance studies have shown a small increased risk of intussusception—a naturally-occurring bowel obstruction in infants—following rotavirus vaccination in several high and upper-middle income countries.⁽⁸⁷⁾

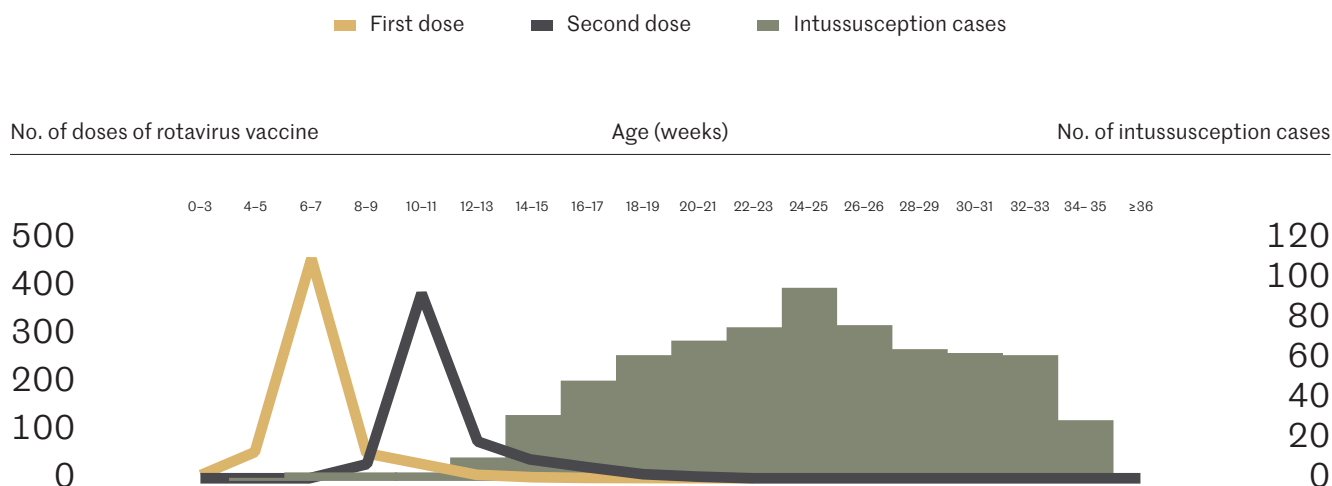
No increased risk of intussusception following rotavirus vaccination has been shown in a seven-country surveillance study in Africa.⁽⁸⁾

Studies show that the benefits of the vaccine, in preventing many rotavirus hospitalizations and deaths, greatly outweigh the small increased risk of intussusception following vaccination.^(88, 89)

The World Health Organization recommends that countries introducing rotavirus vaccine conduct intussusception surveillance at sentinel hospitals and raise awareness among both health workers and the public about the danger signs of both dehydration and intussusception.⁽⁹⁰⁾

No increased risk of intussusception has been found in Africa.

FIG.9 AGES AT IMMUNIZATION AND THE ONSET OF INTUSSUSCEPTION AT SENTINEL SITES IN 7 AFRICAN COUNTRIES, 2012–2016



The African Intussusception Surveillance Network conducted a study from 2012 to 2016 in seven African countries that have introduced ROTARIX—Ethiopia, Ghana, Kenya, Malawi, Tanzania, Zambia and Zimbabwe—to determine if the vaccine increases the risk of intussusception.⁽⁸⁾ The study

identified 717 intussusception cases in infants through active surveillance in 29 major pediatric hospitals in large urban areas in the seven countries.

The study found that few cases occurred shortly after vaccination with either dose, and most occurred well after the 21-day post-vaccination

period considered to be high risk. The incidence of intussusception was, in fact, no higher during these 21 days following vaccination than the usual incidence rates in these countries.

Read more about the benefit-risk ratio in other regions in “Rotavirus vaccination and intussusception—Science,

surveillance, and safety: A review of evidence and recommendations for future research priorities in low and middle income countries,” from Human Vaccines & Immunotherapeutics (October 2016).⁽⁹⁾

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