

# THE IMPACT OF ROTAVIRUS VACCINATION

## INTRODUCTION

Two oral, live attenuated rotavirus vaccines—the three-dose RotaTeq<sup>®</sup>, produced by Merck & Co., and the two-dose ROTARIX<sup>®</sup>, manufactured by GlaxoSmithKline (GSK)—have been on the global market since 2006. ROTARIX consists of a single strain of human rotavirus, and RotaTeq comprises five strains of human-bovine rotaviruses; both were found in clinical trials in the U.S., Western European, and Latin American countries to provide 80–90% protection against severe rotavirus diarrhea in infants and young children.<sup>(1,2)</sup>

Many of these countries became early adopters of rotavirus vaccines, and the real-world impact of their introduction in national immunization programs has been substantial—and often greater than expected. Both vaccines cut the number of hospitalizations caused by rotavirus in children under 5 years of age by 45–94% in high-income countries, such as the U.S., Australia, Belgium, and Austria, and all hospitalizations from diarrhea in this age group by 25–54%.<sup>(3–14)</sup> Latin American countries also saw declines in diarrheal hospitalizations ranging from 13% to as high as 48%, and several experienced a significant reduction in childhood deaths from diarrhea—from 16% in Honduras to 64% in Venezuela.<sup>(15–22)</sup>

Clinical trials of rotavirus vaccines in low- and middle-income countries in Africa and Asia also found both vaccines to be effective in preventing rotavirus gastroenteritis, but at a somewhat lower level of efficacy than in the trials in high-income

countries and Latin America. The efficacy against severe rotavirus diarrhea of ROTARIX was 49% in Malawi and 77% in South Africa,<sup>(23)</sup> while RotaTeq provided 55% protection in Ghana and 64% in Kenya.<sup>(24)</sup> Similarly, a trial of RotaTeq in Asia yielded a vaccine efficacy of 43% in Bangladesh and 64% in Vietnam.<sup>(25)</sup> Because of these results, there was some concern that the real-life impact of rotavirus vaccination may be less in low- and middle-income countries in Asia and Africa.

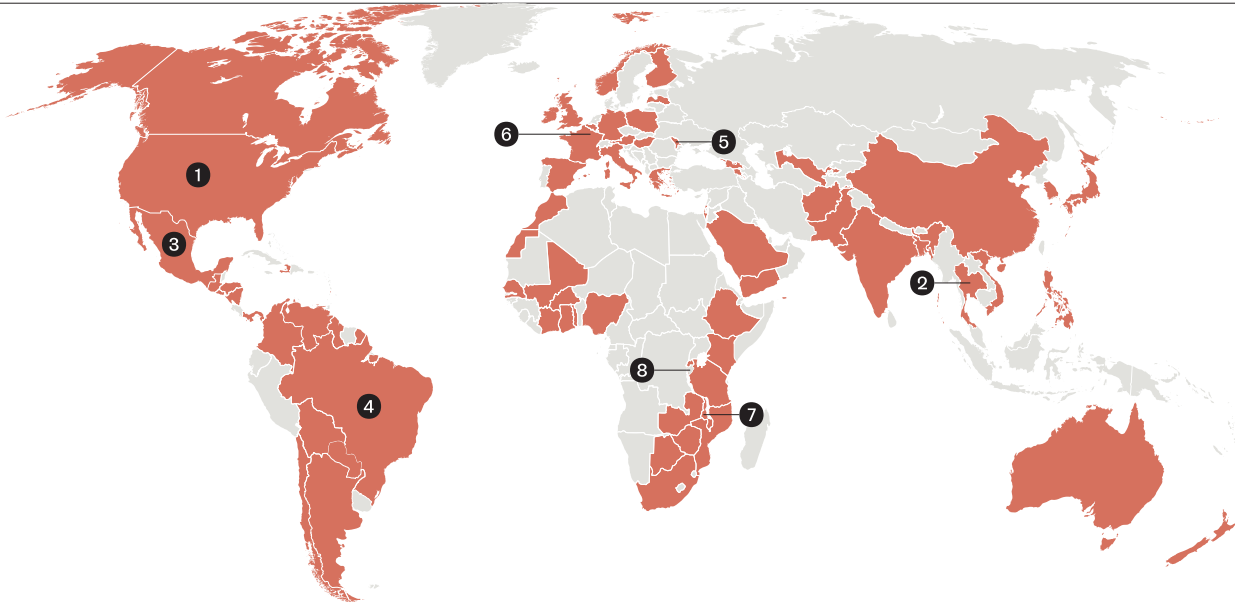
However, as more countries have introduced these vaccines into their national immunization schedule—including many low-income, high-burden countries in Africa and middle-income countries in Asia and Eastern Europe—a more complete picture of the impact of rotavirus vaccination in countries at different levels of development and with varying levels of disease burden and child mortality has emerged.

In this brief, we present data from countries in different regions and income levels demonstrating the real-world impact of introducing rotavirus vaccines on rotavirus and diarrhea-related hospitalizations and deaths; on herd immunity (the ability of vaccination to protect unvaccinated individuals); on the extent to which the vaccines provide protection against a variety of rotavirus strains, including those not included in the vaccines (“cross-protection”); and on how vaccination coverage can affect the impact of vaccination.

# REAL-WORLD IMPACT

FIG.1 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.<sup>(10, 12-14)</sup>

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

3) Mexico<sup>(27)</sup>

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

5) Moldova<sup>(29)</sup>

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

7) Malawi<sup>(30)</sup>

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

2) Thailand<sup>(26)</sup>

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

4) Brazil<sup>(28)</sup>

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

6) Belgium<sup>(8)</sup>

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.

8) Rwanda<sup>(31)</sup>

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

## The difference in the efficacy of rotavirus vaccines between high-income and low- and middle-income countries

Rotavirus vaccine is one of several oral, live vaccines—including oral polio vaccine (OPV), cholera, and typhoid vaccines—that have lower levels of efficacy in low-income, high-mortality countries than in wealthier countries. The reasons for this lower efficacy are not completely understood. Some factors that may reduce the immune response of oral vaccines in low-income settings include higher rates of malnutrition and micronu-

trient deficiencies; interference from other infections in the gut, as well as from infections such as HIV, tuberculosis, and malaria; and higher levels of maternal antibodies.<sup>(32-34)</sup>

Another reason that has been suggested is the administration of rotavirus vaccines at the same time as OPV, which is used mainly in low- and middle-income countries, whereas industrialized countries use the injectable IPV.<sup>(34-37)</sup> This may be due to the fact that both rotavirus and OPV contain live virus strains that replicate in the gut, and thus OPV could interfere with the immune response to rotavirus vaccine.

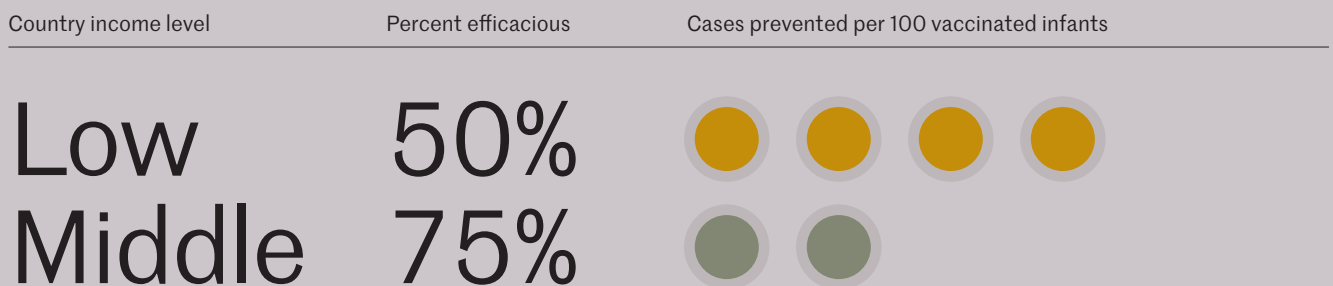
# ROTAVIRUS VACCINES HAVE A GREATER PUBLIC HEALTH IMPACT IN LOW-INCOME COUNTRIES DESPITE LOWER VACCINE EFFICACY RATES IN CLINICAL TRIALS

Efficacy rates in rotavirus vaccine clinical trials were found to be lower (43–65%) in low-income countries than in middle- and high-income countries (77–90%). However, because rates of severe rotavirus diarrhea tend to be higher in low-income countries and those with high levels of child mortality, and transmission of the disease is year-round, the vaccines prevent more hospitalizations and deaths per population in low-income countries than they do in middle- and high-income countries.

For example, in Malawi, the vaccine had an ef-

ficacy rate of 49% against severe rotavirus diarrhea in a clinical trial, compared to 77% in the same trial in South Africa.<sup>(23)</sup> However, the baseline incidence of severe rotavirus (as seen in the placebo group) was nearly 2.5 times higher in Malawi (13.1 per 100 infants) than in South Africa (5.4 per 100 infants). Consequently, the vaccine prevented nearly seven cases of severe rotavirus gastroenteritis for every 100 children vaccinated in Malawi, versus around four cases per 100 vaccinated children in South Africa. Similar results were seen comparing two countries in Asia.

## CASES OF SEVERE ROTAVIRUS PREVENTED PER 100 VACCINATED INFANTS IN COUNTRIES WITH DIFFERENT BASELINE RATES OF ROTAVIRUS<sup>\*(25)</sup>



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

### Rotavirus vaccines in real-life use: Spotlight on Malawi

Clinical trials in Africa found rotavirus vaccines to be 49–77% efficacious in preventing severe rotavirus gastroenteritis (depending on the country). Malawi introduced ROTARIX into their national immunization program in 2012. One study found ROTARIX to be 71% effective in preventing rotavirus-related hospitalizations in the first year of

life,<sup>(38)</sup> while another study found a vaccine effectiveness of 83% against severe disease in infants less than 12 months of age.<sup>(39)</sup> Vaccine effectiveness was substantially lower (32%) in the second year of life in both studies.

A recent, large population-based study found that ROTARIX reduced infant diarrheal deaths by one-third in Malawi.<sup>(30)</sup> These studies demonstrate a similar impact to that seen in middle-income countries, such as Mexico (see page 8).

# DECLINES IN ROTAVIRUS DIARRRHEA HOSPITALIZATIONS

Hospital-based studies in five African and two Eastern European countries showed that two years following the introduction of rotavirus vaccines (either ROTARIX or RotaTeq) into their national immunization programs, hospitalizations due to rotavirus had fallen by 63–80% in infants under 12 months of age (Figure 2).<sup>(14,29,40-45)</sup> In several countries, such as Armenia, Burkina Faso, and Moldova, these declines were on par with those seen, on average, in the U.S.<sup>(14)</sup> The reduction in rotavirus hospitalizations among children in their second year of life varied more widely (21–75%), but was still 50% or greater in several countries.

The immediate impact of rotavirus vaccine was apparent in Ghana, which achieved 95% vaccination coverage soon after ROTARIX was intro-

duced into the national immunization program. The number of hospital admissions due to rotavirus at six sentinel sites throughout the country fell sharply, and the usual high seasonal peaks, most notable in infants, did not reappear (Figure 3).<sup>(40)</sup>

The blunting or near disappearance of the typical seasonal peaks of rotavirus has been seen in many other countries, such as Armenia (Figure 4).<sup>(41)</sup> Prior to the national introduction of rotavirus vaccine in late 2012, rotavirus diarrhea made up 60% of acute gastroenteritis cases among children under 5 years of age that occurred during mid-winter months in the capital of Yerevan. Two years later, only 20% of acute diarrhea during these months was due to rotavirus.

FIG.2 REDUCTIONS IN ROTAVIRUS HOSPITALIZATIONS TWO YEARS FOLLOWING THE INTRODUCTION OF ROTAVIRUS VACCINE, BY COUNTRY INCOME LEVEL

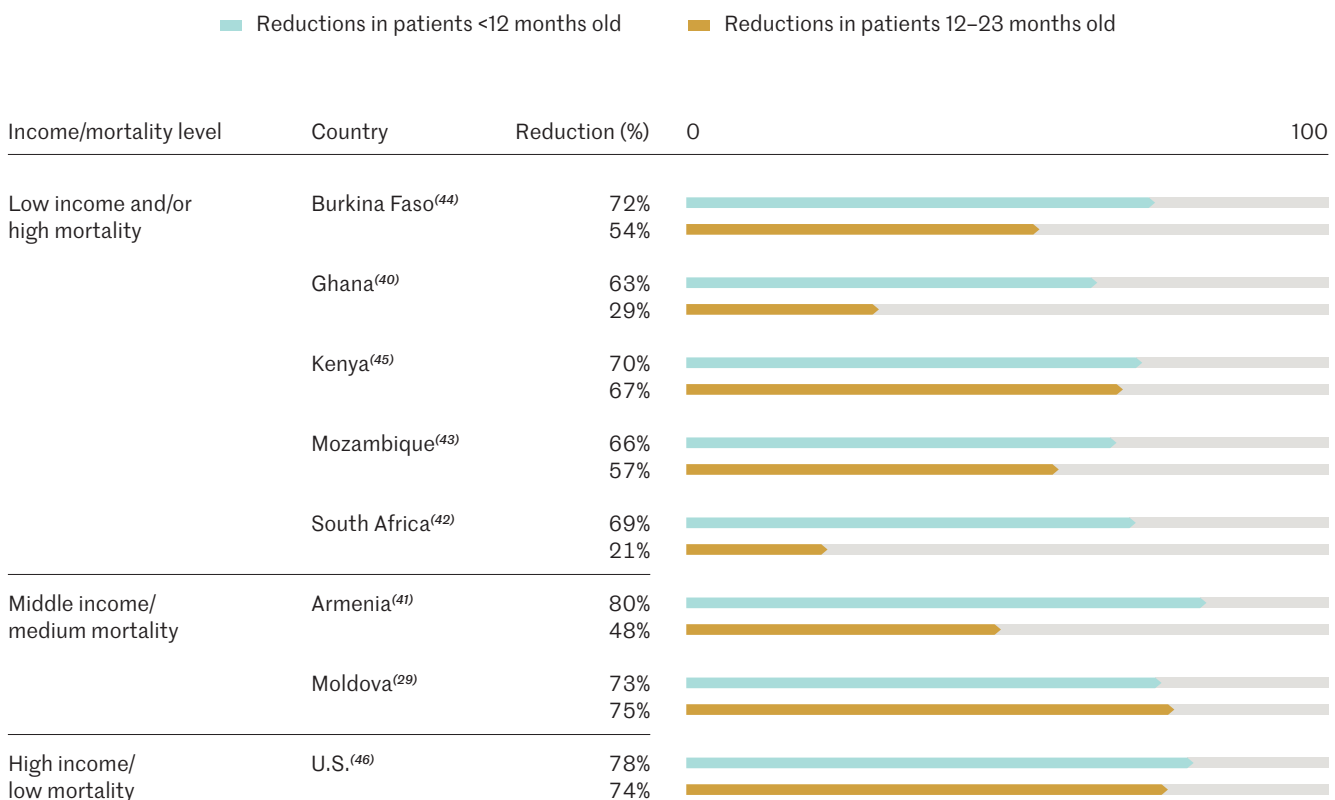


FIG.3 ROTAVIRUS-POSITIVE ADMISSIONS AT SIX SENTINEL SURVEILLANCE HOSPITALS IN GHANA BY AGE GROUP<sup>(40)</sup>

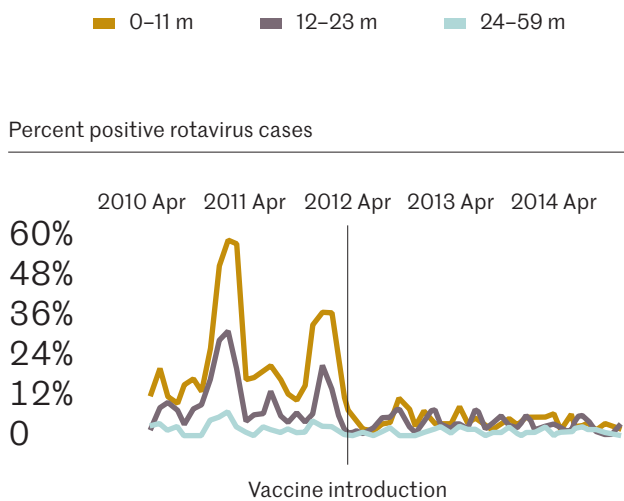
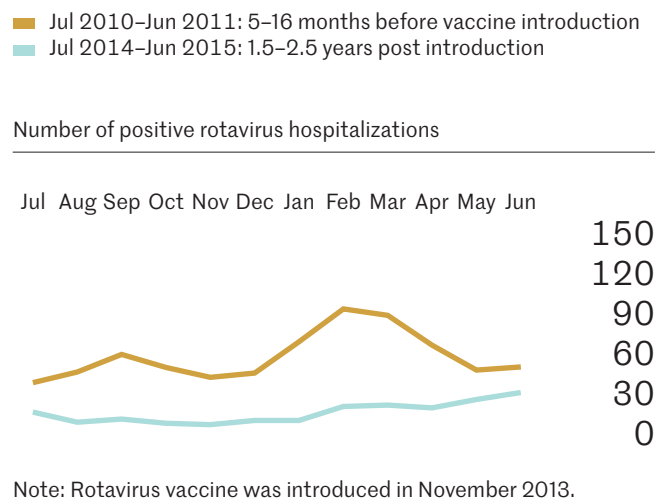


FIG.4 CHANGE IN HOSPITALIZATIONS AMONG CHILDREN <5 AT 2 HOSPITALS IN ARMENIA FOLLOWING VACCINE INTRODUCTION<sup>(41)</sup>

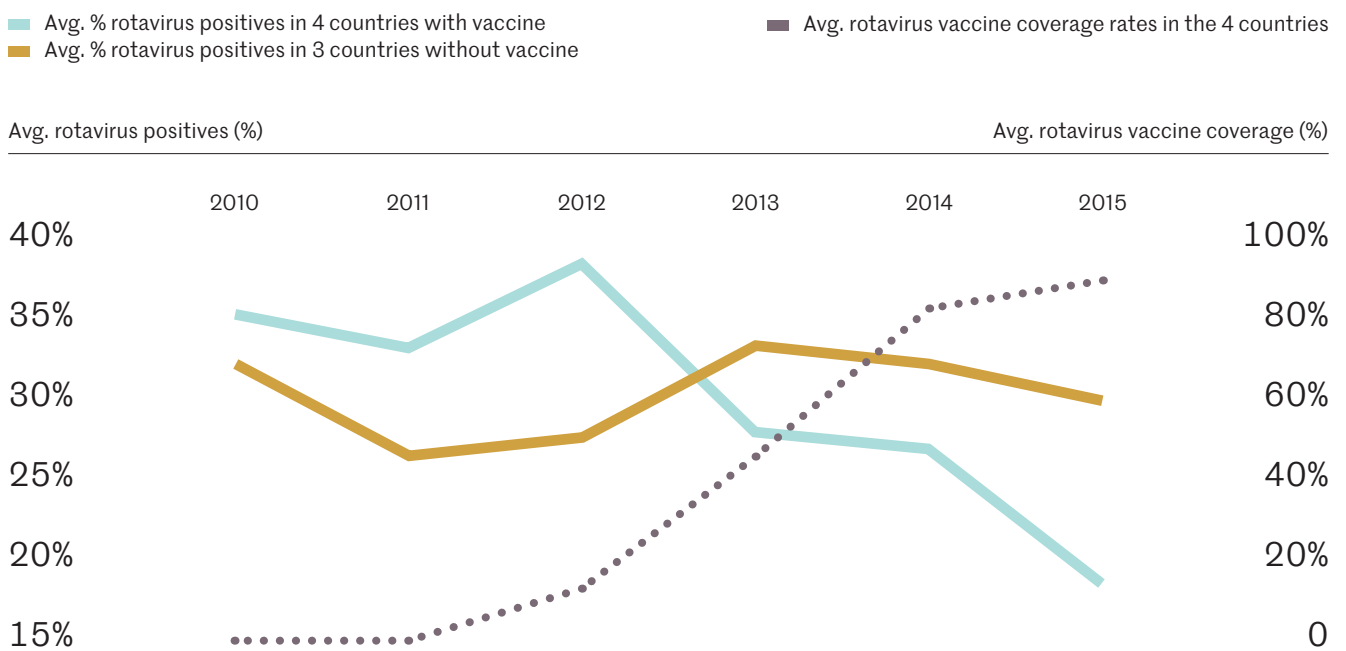


In countries where rotavirus occurs only during certain months, such as South Africa, the seasonality of the disease still occurs following vaccine introduction, but peaks have greatly declined and the seasons have considerably shortened, for instance, by four weeks in South Africa.<sup>(42)</sup>

Vaccine impact is heavily driven by immunization coverage. In four African countries—Ethiopia, Rwanda, Tanzania, and Zambia—that introduced the vaccine in 2012 or 2013, the average proportion of hospitalized diarrhea in children under

5 that tested positive for rotavirus in surveillance hospitals was 38% in 2013 when vaccine coverage averaged 13% in the four countries (Figure 5).<sup>(47)</sup> By 2015, once average vaccination coverage reached 90%, the percent positive for rotavirus had fallen to 19%. In contrast, the rotavirus positivity rate in three countries that hadn't introduced the vaccine by 2015 (Lesotho, Seychelles, and Uganda) remained about the same (about 30%) during this same period.<sup>(47)</sup>

FIG.5 ROTAVIRUS DIARRHEA HOSPITALIZATIONS DECLINED IN COUNTRIES WITH ROUTINE ROTAVIRUS VACCINE USE<sup>(47)</sup>



# DECLINES IN OVERALL DIARRRHEA HOSPITALIZATIONS

The impact of rotavirus vaccination on overall hospitalizations due to diarrhea in African countries that have introduced the vaccine in the past several years has been comparable to that seen in the U.S. and Latin America countries.

In three countries (Ghana, Rwanda, and South Africa), diarrheal hospitalizations from all causes fell by more than half in infants the year following the vaccine's introduction, as compared to pre-vaccination periods (Figure 6).<sup>(31, 40, 48)</sup> These reductions from the years before vaccination continued at a similar or higher level into the second year following vaccine introduction.

Data from a middle-income country in Asia also demonstrate the large effect that rotavirus vaccine introduction can have on diarrheal hospitalization rates.

A pilot introduction of ROTARIX in the Philippines also saw diarrhea admissions decline as immunization coverage increased.<sup>(49)</sup> By the third year, once the vaccine was provided throughout the province and coverage of both doses had reached 88%, hospitalizations due to diarrhea in children under 5 had declined by 63% from the average annual number of cases over three years prior to the vaccine introduction. Only when vaccine coverage declined in 2016, due to a six-month stockout of the vaccine, did diarrheal hospitalizations begin to rise again.

A review of the impact of rotavirus vaccination in 25 countries found that, on average, the decline in hospitalizations from all-cause diarrhea among children following vaccine introduction

FIG.6 MAJOR DECLINES IN DIARRRHEAL DISEASE HOSPITALIZATION AMONG CHILDREN <1 ACROSS COUNTRIES AFTER ROTAVIRUS VACCINE INTRODUCTION

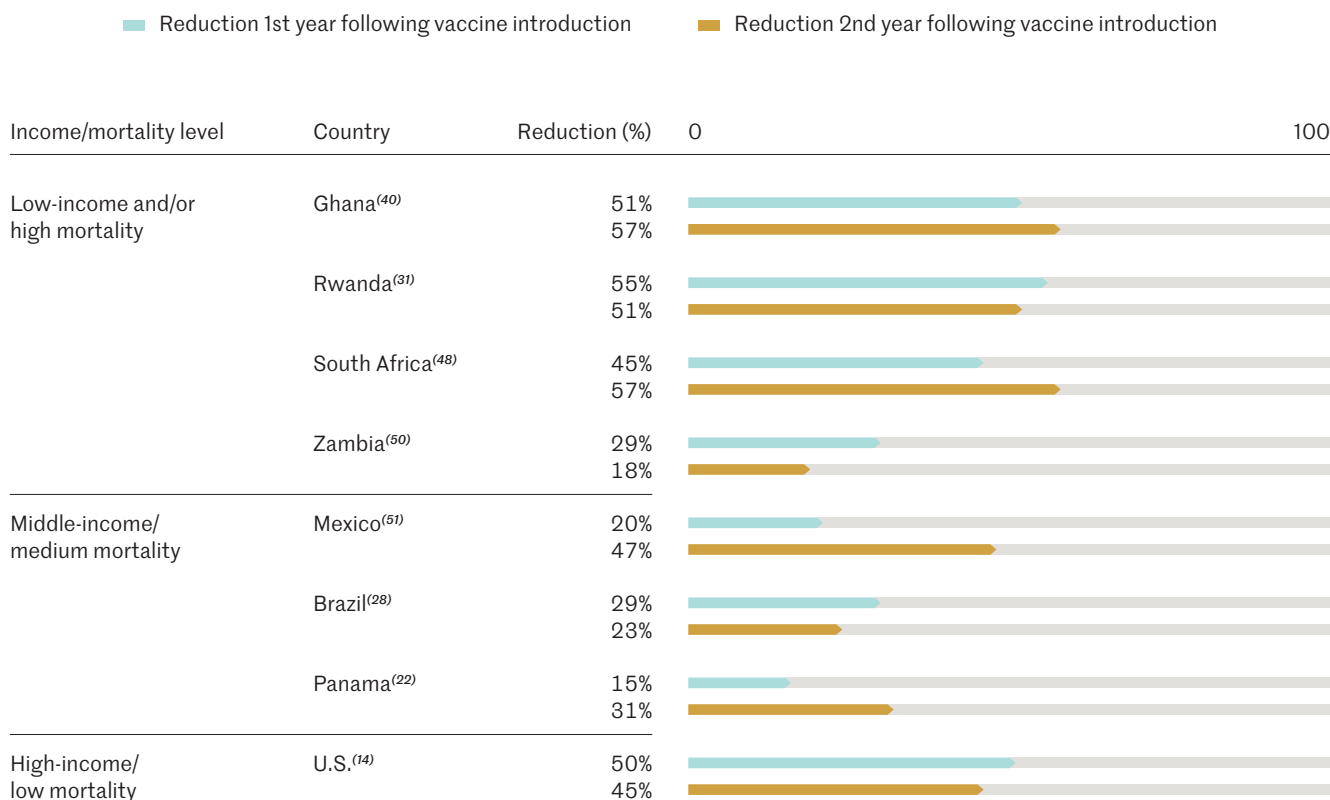


FIG.7 <5 DIARRHEA HOSPITALIZATIONS AND VACCINE COVERAGE AT REFERRAL HOSPITAL IN THE PHILIPPINES POST-PILOT INTRODUCTION<sup>(49)</sup>

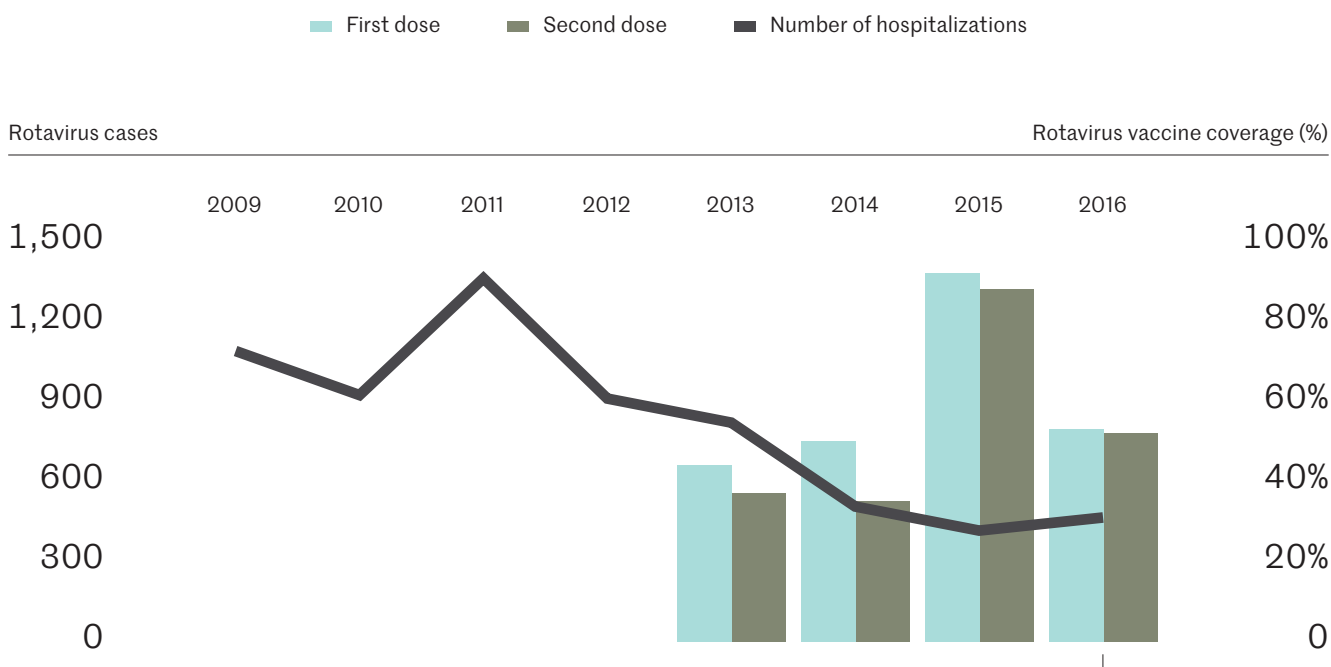


Chart: courtesy of Anna Lena Lopez.

\*There were vaccine stockouts in 2016.

did not differ that much across countries with differing child mortality levels (Table 1).<sup>(52)</sup> This is despite the lower vaccine efficacy found in clinical trials of rotavirus vaccines in low-income as com-

pared to middle- and high-income countries. In fact, high-mortality countries saw the largest reductions, on average, in diarrheal hospitalizations in children under 5 (see Table 1 for more details).

TABLE 1 MEDIAN REDUCTION IN ACUTE GASTROENTERITIS HOSPITALIZATIONS FOLLOWING ROTAVIRUS VACCINE INTRODUCTION IN 25 COUNTRIES<sup>(52)</sup>

Child mortality level of country	Number of countries	Reduction in infants <1 year	Reduction in children <5 years
Low (1.9–7 deaths per 1,000 live births)	8	36%	41%
Medium (8–17 deaths per 1,000 live births)	9	28%	30%
High (13–157 per 1,000 live births)	8	33%	46%

## POTENTIAL IMPACT IN ASIA

A 2018 analysis estimates that 1.4 million hospitalizations and 89,000 deaths from rotavirus occur each year in Asia.<sup>(53)</sup> Most countries in the region haven't introduced rotavirus vaccines yet. If all 43 countries in Asia were to introduce the vaccine nationally at the same coverage rates as pentavalent vaccine, rotavirus hospitalizations would be cut

in half and deaths would be reduced by 40%. National introductions in six countries alone—China, India\*, Bangladesh, Indonesia, Philippines, and Vietnam—would prevent about half a million rotavirus hospitalizations each year. Vaccine introduction in China alone would prevent about 212,000 hospitalizations per year.

\*India has since introduced nationally



## ROTAVAC AND ROTASIIL

Two vaccines, Rotavac and ROTASIIL, received WHO pre-qualification in 2018. India has been using Rotavac since April 2016, and ROTASIIL since April 2018. There are not many completed impact studies of these two vaccine products, but more data is anticipated.

One study in India evaluated the impact of Rotavac from 2016 to 2020 and found that the vaccine significantly decreased the prevalence of rotavirus in children hospitalized with gastroenteritis which indicated that the effectiveness is mirroring what was predicted by the clinical trials and modeling and similar to the initial impact seen for Rotateq and ROTARIX.<sup>(54)</sup>



# REDUCTION IN CHILDHOOD DIARRHEAL DEATHS

In several middle-income, medium-mortality countries in Latin America, rotavirus vaccine reduced diarrheal deaths in children by half or more.

8).<sup>(55,56)</sup> This decline continued over time—reaching 53%, on average, over a seven-year period compared to the pre-vaccination period.<sup>(27)</sup>

## Brazil

Following the introduction of rotavirus vaccine, the number of hospital deaths due to gastroenteritis in children under five was 60% lower, on average, over a four-year period than expected, based on the number of pre-vaccination hospital deaths and accounting for secular declines in diarrheal mortality due to improvements in water and sanitation and other factors.<sup>(28)</sup> The reduction grew each year—reaching 73% by the fourth year following vaccine introduction.

## Other countries

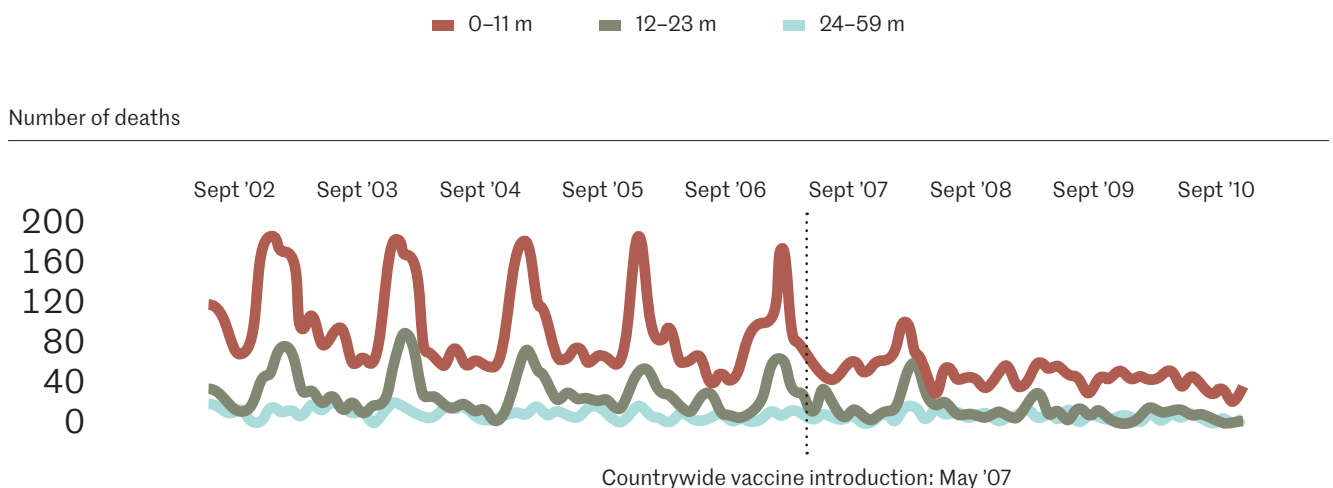
In other Latin American countries with higher child mortality rates, reductions in diarrheal deaths after rotavirus vaccine introduction were lower, but still substantial. The reductions among children under 5 were 35–43% in Bolivia, 16–20% in Honduras, and 0–36% in El Salvador, with the range due to different estimation methods.<sup>(15)</sup> Recent data from two high-mortality African countries (Zambia and Botswana) show similar declines—of around one-third—in hospital deaths from diarrhea in children under age 1.<sup>(50,57)</sup>

## Mexico

Mexico saw a 46% drop in all-diarrhea mortality in children less than 5 years old, on average, over three years following the introduction of rotavirus vaccines in the national immunization program, with a vaccine coverage rate of about 90% (Figure

A review of data from 14 countries found that, on average, the reduction in diarrheal deaths in children following rotavirus vaccine introduction was greater (45–55%) in countries with medium child mortality rates (generally middle-income countries) than in high-mortality, low-income countries (where it was 30–36%).<sup>(52)</sup>

FIG.8 DEATHS IN MEXICO AMONG CHILDREN <5 YEARS BEFORE AND 3 YEARS AFTER INTRODUCTION OF ROTAVIRUS VACCINE<sup>(56)</sup>



More Reading: There are a number of time-series analyses of national administrative datasets of mortality following rotavirus vaccine introduction from Bolivia, Brazil, Mexico, and other South American countries. See [preventrotavirus.org](http://preventrotavirus.org).

# CROSS-PROTECTION AND INDIRECT EFFECTS

## Rotavirus vaccines offer broad protection against different strains of the virus

There are more than 60 strains of rotavirus that are known to cause disease in humans. Each strain consists of a unique combination of two types of antigens—a G type and a P type. The most common strain currently circulating worldwide is G1P[8]. However, in some parts of the world, other strains are more common. In fact, predominant strains can differ from region to region, from country to country within a region, and even over time within the same country. The diversity of strains is greatest in Africa and Asia, and new strains have recently emerged in Africa.<sup>(38)</sup>

Therefore, it is essential that rotavirus vaccines provide protection across a broad range of strains. Otherwise, it would be necessary to have many different vaccine formulations for different regions or even countries, and to change them as the prevailing strains in an area change over time.

Fortunately, both ROTARIX, made up of the single G1P[8] strain, and RotaTeq, made up of five

different G and P genotypes (G1, G2, G3, G4, and P8), have been shown in clinical trials to cross-protect against a variety of rotavirus strains. In an integrated analysis of clinical trials that took place mainly in Latin America and Europe, ROTARIX provided protection against several circulating strains.<sup>(58,59)</sup> However, further study is needed in less developed settings to study cross-protection of non-vaccine strains.<sup>(38)</sup> This pattern was also seen in the first African trial of ROTARIX that took place in Malawi and South Africa.<sup>(60)</sup> The vaccine performed equally well or better against genotypes not included in the vaccine, such as G8 and P4, as it did against those in the vaccine (G1 and P8). RotaTeq has also been found to provide protection against a variety of strains, including those not in the vaccine.<sup>(46,61)</sup>

In addition, clinical efficacy trials in India showed that ROTAVAC (made up of the single G9P[11] strain) protected against multiple strains not included in the vaccine.<sup>(62)</sup>

TABLE 2 REDUCTIONS IN ROTAVIRUS-RELATED HOSPITALIZATIONS AMONG UNVACCINATED 2–5 YEAR-OLD CHILDREN FOLLOWING VACCINE INTRODUCTION

Country	Timeframe post-vaccine introduction	Percent reduction in rotavirus hospitalizations
Ghana <sup>(40)</sup>	2 years	29%
Mozambique <sup>(43)</sup>	1 year	55%
Thailand <sup>(26)</sup>	25 months	40–69%*
Armenia <sup>(41)</sup>	2 years	48%
Moldova <sup>(29)</sup>	2 years	55%
U.S. <sup>(14)</sup>	1 year	72%
Austria <sup>(9)</sup>	2 years	35%

\*69% reduction in 36–47-month-olds and 40% in 48–59-month-olds.

## Rotavirus vaccination can also protect people not vaccinated

Once rotavirus vaccines were introduced in several high-income countries and middle-income countries in Latin America, a number of countries noticed that rotavirus hospitalizations declined in children who were too old to have been vaccinated. This effect, called herd protection, is the result of there being fewer infected infants (as a result of vaccination) who can pass on the infection to those who haven't been vaccinated, thus reducing the exposure of unvaccinated individuals to the disease. Reductions in rotavirus hospitalizations in older children in the years following rotavirus vaccine introduction ranged from 20–92% in the U.S., Australia, Austria, Brazil, and El Salvador.<sup>(63)</sup>

In an analysis from the U.S. of the estimated 66,000 rotavirus hospitalizations that were prevented the year following full introduction of rotavirus vaccines for infants, 15% (about 10,200 cases) were in people 5–24 years of age.<sup>(64)</sup> This suggests a larger burden of rotavirus in older children and adults than had been previously recognized.

There was speculation that herd immunity would be less or non-existent in countries, such as those in Africa, with a greater force of infection.<sup>(39)</sup> However, new studies from different regions did find evidence of herd effects in several countries, including some in Africa.

Other studies have found no evidence of herd protection in older, unvaccinated children.<sup>(44,48,50,65)</sup> The reasons for different findings on herd immunity are unclear and require additional research. Vaccination coverage may be a possible factor, as the African countries that found herd protection tended to have higher coverage rates (such as over 90%) than those that did not. However, middle-income countries with relatively low vaccination coverage rates, such as Moldova (with 55% coverage for the first dose) still saw substantial herd effects.



A newborn baby sleeps in Kaolack, Senegal.

## A POTENTIAL ADDED BENEFIT ROTAVIRUS VACCINES: A REDUCTION IN CHILDHOOD SEIZURES

Recent studies have found reductions in seizures following rotavirus vaccination. These findings, while unexpected, make sense in view of the increasing evidence that the virus can leave the intestine and enter into the bloodstream and the central nervous system (CNS).<sup>(66)</sup> If the virus enters the CNS, it can trigger seizures. Seizures occur in 4–8% of patients infected with rotavirus.<sup>(66,67)</sup> Most seizures caused by rotavirus gastroenteritis do not cause permanent damage, but a portion—18% in one study in the U.S.—required a stay in the intensive care unit.<sup>(68)</sup>

Two studies in the U.S found that rotavirus vaccination reduced the risk of seizures requiring hospitalizations or a visit to the emergency room by about 20% in the year following vaccination, compared with unvaccinated children.<sup>(69,70)</sup> A study in Spain also found substantial reductions in childhood seizures following childhood rotavirus vaccination.<sup>(71)</sup> However, a separate study in Spain found no statistically significant link between rotavirus vaccination and seizures,<sup>(72)</sup> highlighting the need for further research into this area.

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# THE IMPACT OF ROTAVIRUS VACCINATION

## KEY FACTS

### Performance

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 lower-income countries due to their higher rates of severe rotavirus diarrhea. (See page 4)

### Illness

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 income levels. (See page 4)

### Deaths

Several low- and middle-income countries have also seen a sharp reduction in diarrheal-related deaths in infants and young children following vaccine introduction. (See page 9)

### Indirect

Many countries have found added benefits of rotavirus vaccination, including a decline in severe rotavirus diarrhea in older, unvaccinated children due to herd effects. (See page 11)