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An overview of rotavirus vaccination programs in developing countries

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Abstract

Introduction: Rotavirus is the leading cause of acute diarrhea among children <5 years worldwide. As all children are equally susceptible to infection and disease development, rotavirus vaccination programs are the best upstream approach to preventing rotavirus disease, and the subsequent risk of hospitalization or death.

Areas covered: We provide an overview of global rotavirus vaccine policy, summarize the burden of rotavirus disease in developing countries, review data on the effectiveness, impact, safety, and the cost-effectiveness of rotavirus vaccination programs, and identify areas for further research and improvement.

Expert opinion: Rotavirus vaccines continue to be an effective, safe, and cost-effective solution to preventing rotavirus disease. As two new rotavirus vaccines enter the market (Rotasiil and Rotavac) and Asian countries continue to introduce rotavirus vaccines into their national immunization programs, documenting vaccine safety, effectiveness, and impact in these settings will be paramount.

Keywords

Rotavirus; rotavirus vaccine; vaccines; vaccine implementation; low and middle-income countries; developing countries; diarrhea

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Declaration of interest

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1. Introduction

In 2013, an estimated 215,000 deaths were attributed to rotavirus infection globally, with 99.8% occurring in developing countries [1]. In contrast to the prevention of all-cause diarrhea mortality, rotavirus is a unique cause of infectious diarrhea as all children are equally susceptible to infection and disease development, independent of location, socioeconomic status, or hygiene and sanitation level [2]. As such, rotavirus vaccination programs are the best upstream approach to preventing rotavirus disease, and the subsequent risk of hospitalization or death. To help encourage the continued use and adoption of rotavirus vaccines, the goal of this review is to provide an up-to-date overview of the global rotavirus vaccine policy, the burden of rotavirus disease in developing countries, the implementation, effectiveness, impact, safety, and cost-effectiveness of rotavirus vaccination programs, and to identify areas for further research and improvement.

2. Global rotavirus vaccine policy

In 2006, the World Health Organization's (WHO) Strategic Advisory Group of Experts (SAGE) first recommended the inclusion of rotavirus vaccine into national immunization programs in regions with data showing that the vaccine was effective. The recommendation followed two pre-licensure trials conducted in the Americas and Europe that enrolled >60,000 infants each; these trials found no increased risk of intussusception following rotavirus vaccination and exhibited high vaccine efficacy against severe rotavirus disease [3-5]. At the time, implementation of vaccination in developing countries in Africa and Asia was not recommended by WHO due to the lack of available data on rotavirus vaccine efficacy in these regions [3]. Because of a number of factors, including the greater prevalence of concurrent enteric infections, malnutrition, and gut enteropathy, concerns existed that live oral rotavirus vaccines may not perform well in these regions. Indeed, later trials performed in Africa and Asia showed a moderate vaccine efficacy, lower than the initial trials in developed countries [6-8]. However, given that even moderately effective rotavirus vaccines would have a substantial health impact in developing countries given the especially high burden of rotavirus disease, including mortality, SAGE recommended the integration of rotavirus vaccine into all immunization programs worldwide in 2009 [9,10].

Currently, four rotavirus vaccines have been pre-qualified by WHO for use internationally (Table 1). In developing countries, WHO recommends the use of Rotarix vaccine in a 2-dose schedule given at 6 and 10 weeks of age, and RotaTeq, Rotavac, and Rotasiil in a 3-dose schedule at 6, 10, and 14 weeks of age, with vaccine doses given concurrently with other childhood vaccines given at these ages. Because of safety concerns about the risk of intussusception particularly with the first dose of rotavirus vaccine, strict age restrictions were initially placed on the vaccination schedule to help minimize the risk of intussusception [11]. Baseline rates of naturally occurring intussusception are very low in the first two to 3 months of life, rapidly increase and peak at four to 7 months, and then decline, with few cases occurring after 12 months of age [12]. Thus, WHO recommended that the rotavirus vaccine series be started before the child was 15 weeks old [13]. They also recommended that the full vaccine series be completed by 32 weeks of age, as the vaccine had not been tested in children older than this age in the clinical trials. While

these recommendations were reasonable from a safety standpoint, they hampered rotavirus vaccine coverage in developing countries where children frequently present at later than recommended ages to receive immunizations, and could be disqualified based on the recommended age windows [11]. Indeed, a mathematical modeling analysis found that, by removing the age restrictions on rotavirus vaccination in developing countries and the consequent increase in vaccine coverage, an additional 47,200 rotavirus deaths could be prevented each year while potentially causing an additional 294 intussusception deaths [14,15]. These findings led WHO to revise its recommendation for rotavirus vaccine use in 2013; WHO currently recommends that the rotavirus vaccine series can be started at 6 weeks of age and subsequent vaccine doses can be given until 24 months of age [13,15]. However, on-time vaccination at 6 and 10 weeks, or 6, 10, and 14 weeks of age is strongly encouraged to achieve protection against rotavirus disease early in life [13].

In 2019, various rotavirus vaccine schedules were reevaluated to assess the risk-to-benefit ratio of allowing later vaccination in low- and middle-income countries. While a higher risk-to-benefit ratio was obtained utilizing the original WHO recommendation compared with the new recommendation to relax age restrictions (512:1 vs 148:1 rotavirus deaths averted per excess intussusception deaths), removing the upper age limit resulted in 12,000 fewer rotavirus deaths and 79 additional intussusception deaths per year, supporting the current WHO recommendation [16]. Due to a lack of data on the safety, effectiveness, and cost effectiveness of these relaxed age restrictions, however, some countries still utilize the original vaccine schedule.

3. High burden in developing countries

In 2013, an estimated 214,664 deaths were attributed to rotavirus infection in developing countries. By region, most deaths attributed to rotavirus occurred in Sub-Saharan Africa (121,000), Southern Asia (70,109), and Southeast Asia (10,765) with a lower burden among other regions [1]. Four countries accounted for nearly half of all rotavirus deaths globally, with 47,100 deaths in India, 30,800 in Nigeria, 14,700 in Pakistan, and 13,526 in the Democratic Republic of Congo [1].

In the absence of rotavirus vaccine introduction, 38% of all hospitalized diarrhea cases among <5 children globally are due to rotavirus infection [1,17]. This proportion remains fairly consistent by region, with 38.2%, 37.5%, 35.7%, 36.3%, 37.2%, and 42.3% of diarrhea hospitalizations attributed to rotavirus infection in the African, American, Eastern Mediterranean, European, Southeast Asian, and Western Pacific regions, respectively [17].

4. Vaccine implementation, efficacy, effectiveness, impact, and safety

4.1. Vaccine implementation

As of December 2019, 100 countries have introduced a rotavirus vaccine into their national immunization programs, with 48 countries having introduced rotavirus vaccine with support from Gavi, the Vaccine Alliance. An additional 6 low-income countries with a gross national income of <$1,580 USD per capita have been approved for funding support for vaccine introduction from Gavi and are awaiting a national introduction, and another 13 countries

are preparing to introduce independent of Gavi support (Figure 1). Given that only 47 countries had introduced rotavirus vaccine into their national immunization program by 2012, including only one country in Africa and Asia, remarkable progress has been made in vaccine implementation over the last few years, particularly in low-income countries eligible for Gavi support [18,19].

4.2. Vaccine efficacy and effectiveness

In the preliminary clinical trials in developed countries (US, Latin America, and Europe) RotaTeq and Rotarix had an efficacy of 85–98% at preventing severe rotavirus disease [2,4,5,20]. However, mirroring the findings from other oral vaccines (e.g. cholera, polio), initial efficacy studies in Africa and Asia found that rotavirus vaccines were less effective at preventing severe rotavirus disease (39–77%) when compared to developed countries, with wide variation by region [8,11,20-29]. Later systematic reviews using clinical trial data have found efficacies of 90.6% in developed countries, compared with 88.4% in East and Southeast Asia, 79.6% in Latin America and the Caribbean, 50.0% in Southern Asia, and 46.1% in Sub-Saharan Africa [30].

A systematic review of observational studies stratified by region aligned with these findings, with rotavirus vaccines 88.9% effective at preventing rotavirus hospitalizations in developed regions, compared to 67.6% in Latin America and the Caribbean and 57.0% in Sub-Saharan Africa [30]. When stratified by vaccine similar findings were observed. In a systematic review that analyzed post-licensure vaccine effectiveness data stratified by the countries' childhood mortality rates, Rotarix had a vaccine effectiveness of 84% (13 studies), 75% (8 studies), and 57% (9 studies) in countries with low, medium, and high childhood mortality rates, while RotaTeq had a vaccine effectiveness of 90% (20 studies) and 45% (7 studies) in countries with low and high child mortality rates, respectively, [31].

Currently, no data have been published on the effectiveness of Rotavac or Rotasiil in any developed or developing countries; however, efficacy data from three clinical trials are available. Rotavac's clinical trial conducted in India showed the vaccine to be 53.6% effective at preventing severe rotavirus gastroenteritis [32]. Rotasiil's trials, conducted in Niger and India, found the vaccine efficacy against severe rotavirus gastroenteritis to be 66.7% and 39.5%, respectively, [33,34].

Of note, in addition to lower vaccine efficacy and effectiveness, vaccine efficacy wanes more rapidly over time in developing countries [8,22,35-37]. A recent meta-analysis combined follow-up data from 50 studies in low (15 studies), medium (11 studies), and high (24 studies) childhood mortality strata to examine the efficacy of rotavirus vaccines by follow-up duration [38]. In low mortality settings, efficacy was 98% at 2 weeks, 94% at 12 months, and 91% at 60 months, in medium mortality settings efficacy was 82% at 2 weeks, 77% at 12 months, and 75% at 60 months, and in high mortality settings efficacy was 66% at 2 weeks, 44% at 12 months, and 30% at 60 months [38].

There are a number of possible explanations for why rotavirus vaccine effectiveness is lower and wanes more rapidly in developing countries, including: higher transmission rates of rotavirus, differences in gut microbiota, host mucosal factors, inhibitory effect of higher

maternal antibodies in serum or breast milk, higher rates of malnutrition, micronutrient deficiencies (specifically zinc, vitamin A, or vitamin D), interference from other concurrent enteric viruses or helminth infections, microbial overload of mucosal surfaces, presence of other comorbidities, and co-administration with oral polio vaccine [2,18,29,39-42].

While the exact effect that many of these factors have on vaccine effectiveness is still inconclusive, or have been shown to have a minimal effect (breastfeeding/maternal antibodies in breast milk [43], zinc or probiotic supplementation at the time of vaccination) [44], some interventions (alternative immunization schedules [11,45], staggered administration of oral rotavirus and poliovirus vaccines) [46-48] have been shown to improve seroconversion rates by 15–20%, but they are hard to translate into practical recommendations for programmatic use [49].

4.3. Vaccine impact

4.3.1. Global—Utilizing data from WHO's Global Rotavirus Surveillance Network (GRSN), including rotavirus test results from 305,789 children enrolled at 198 sites in 69 countries, rotavirus vaccine introduction has reduced the global proportion of hospitalized diarrhea cases attributed to rotavirus among children <5 years from 38.0% in the pre-vaccine period, to 23.0% in the post-vaccine period, a 39.6% relative decline [17]. While the magnitude of the decline varies by WHO region, due to varying vaccine effectiveness and vaccine coverage, overall reductions remain relatively consistent with a 34.5% relative decline in Africa, 39.6% in the Americas, 26.4% in Eastern Mediterranean, and 55.2% in the European Region [17].

A systematic review utilizing data from 57 studies and 27 countries globally found even greater declines after vaccine introduction, with a median 38% reduction in all-cause AGE hospitalizations and/or ED visits among children <5 years overall, and a 41%, 30%, and 46% reduction in countries with low, medium, and high child mortality strata, respectively, [50]. AGE mortality among children <5 years also declined 42% overall (medium and high mortality strata only), with a 50% decline in medium and 36% decline in high child mortality strata [50]. When looking at rotavirus-specific hospitalizations and/or ED visits among children <5 years, the impact was even greater with a 67% overall decline, and 71%, 59%, and 60% decline in countries with low, medium, and high child mortality strata, respectively, [50].

Of note, in these impact evaluations, and those discussed later in this article, the role of rotavirus vaccine is supported by the sharp declines observed after vaccine introduction, the greater declines that occurred during the months of the year corresponding to the rotavirus season, and the larger impact first observed among younger vaccine-eligible children before expanding to older age groups [40].

4.3.2. Latin America—When looking at specific regions, a recent systematic review utilizing data from 31 impact studies in Latin America and the Caribbean found that among countries that had implemented rotavirus vaccine, rotavirus hospitalizations declined 64%, AGE hospitalizations declined 32%, and AGE related mortality declined 54% among children <5 years [51]. As a result of this, in 2015, Chavers et al., estimated that 123,000

rotavirus hospitalizations and 660 rotavirus-related deaths were prevented among the 15 countries that had implemented rotavirus vaccine in Latin America. They additionally estimated that if all Latin American countries had introduced by 2015, an additional 18,000 rotavirus hospitalizations and 50 rotavirus-related deaths could have been prevented that year [51]. Another study using data from WHO's GRSN found similar results. Pooling rotavirus testing data from 60,433 individuals across 14 Latin American countries, rotavirus positivity among hospitalized AGE cases declined from 37.5% to 22.7% after vaccine introduction, and 39.6% reduction [17].

4.3.3. Africa—A review by Shah et al. estimated the impact of rotavirus vaccine introduction in Africa, and found that among the 29 African countries that had introduced rotavirus vaccine by 2015, there was a 47% reduction in the number of rotavirus hospitalizations and a 39% reduction in rotavirus-related deaths when compared to the burden estimates from 2013 [52]. As a result, among countries that had introduced the vaccine an estimated 130,000 rotavirus hospitalizations and 21,000 rotavirus-related deaths were prevented in 2016 among children <5 years [52]. If all countries in Africa had introduced rotavirus vaccine, an additional 139,000 hospitalizations and 27,000 deaths could have been prevented that year [52]. These findings align closely with those from WHO's GRSN, which using data from 24 countries in Africa and 56,301 individuals found that rotavirus positive declined after vaccine introduction, from 38.2% among hospitalized AGE cases to 25.0%, a 34.5% decline [17]. Of note, the declines in rotavirus hospitalizations vary from country to country, ranging from 23% to 76% among children <5, and 28–82% among children <1 year of age [53].

4.3.4. European region—In developed countries in Europe, a review found that rotavirus hospitalizations declined 65–84% among countries that introduced rotavirus vaccine, however, no developing countries were included in this review [54]. Of the four developing countries in Europe who have introduced the rotavirus vaccine, no impact data are available for two countries (Bulgaria – introduced 2017, Georgia – introduced 2013). Data are available for the Republic of Moldova and the Republic of Armenia, both of which introduced rotavirus vaccine in 2012. In Moldova, the percent of diarrhea hospital admissions positive for rotavirus among children <5 years fell 67% 2 years after vaccine introduction [27]. In Armenia, near identical declines were observed with rotavirus hospital admissions reduced 69% among children <5 years of age in the 3 years after vaccine introduction [55]. Additionally, in Armenia over 30% of the reduction was observed among children who were not age eligible to receive the vaccine, suggesting herd immunity [55].

4.3.5. Asia—Since countries in Asia have been delayed in implementing rotavirus vaccines into their national immunization programs, no data on vaccine impact currently exists for any Asian country [17,40]. To help encourage the implementation of rotavirus vaccine in Asian countries, Burnett et al. estimated the potential impact of rotavirus vaccine in Asia if all countries introduced. They estimated that 1,452,257 rotavirus hospitalizations and 88,889 rotavirus-related deaths occur annually in Asia. However, with universal rotavirus vaccine introduction, an estimated 710,580 rotavirus hospitalizations and 35,865 rotavirus-related deaths would be prevented annually [56].

4.4. Vaccine safety

Because the first commercial rotavirus vaccine (RotaShield) was introduced and subsequently withdrawn from the market due to an association with intussusception, this adverse event has been closely monitored with current vaccines through large safety studies and post-marketing surveillance [57]. The initial clinical trials for Rotarix and RotaTeq both enrolled 60,000–70,000 infants in the United States, Europe, and Latin America and did not identify any increased risk of intussusception in the 30–42 day window post vaccination [4,5,57]. However, later post-marketing evaluations conducted in Australia and the Americas have identified a slight increase in risk of intussusception 1–7 days following vaccination for both Rotarix and RotaTeq at a rate of 1 excess case per 20,000–100,000 vaccinated infants [57-60]. Given that the benefits greatly exceed the risk, these findings have not resulted in any vaccine policy change in these countries (Table 2).

To evaluate the risk of intussusception after Rotarix vaccination among children residing in Sub-Saharan Africa, two active surveillance systems were set up to enroll intussusception cases that occurred in Ethiopia, Ghana, Kenya, Malawi, Tanzania, Zambia, Zimbabwe, and South Africa [64,65]. In contrast to what has been observed in developed countries, both studies found no increased risk of intussusception associated with either dose of Rotarix [64,65].

While the exact cause for the lack of association between intussusception risk and rotavirus vaccination in developing countries is unknown, there are a few possible explanations. First, intussusception risk is linked to the high viral replication of the vaccine virus after vaccination. As rotavirus vaccine has lower effectiveness in these settings (and is commonly coadministered with oral poliovirus vaccine which further reduces its effectiveness), there may be lower viral replication occurring in the guts of children in developing countries and thus a subsequently lower intussusception risk [46,48,64]. Second, the first dose of rotavirus vaccine is given at an earlier age in these developing compared to developed countries (6 weeks vs 2 months) when children have a naturally lower baseline risk of intussusception when they are vaccinated, resulting in lower overall risk [12,64,65]. Finally, it could be due to other mechanisms for which lower intussusception risk is not known (e.g. differences in microbiome, maternal antibodies, diet, or breastfeeding practices) [64]. Because of the lag in adoption of rotavirus vaccines by Asian countries, no post-marketing data currently exists on the intussusception risk following vaccination for infants residing in Asia [40].

To date, there has been no increased intussusception risk associated with the administration of Rotavac or Rotasiil; however, with only 3,500–7,500 children enrolled in the clinical trials, these studies were not powered to detect the level of risk observed with Rotarix and RotaTeq [32-34]. As such, post-marketing surveillance data is needed to monitor intussusception risk as countries begin to introduce these vaccines.

The WHO Global Advisory Committee on Vaccine Safety has reviewed all of this data and reaffirmed the recommendation for continued rotavirus vaccine use. While there is a slight risk associated with intussusception in some settings, the benefits of vaccination far outweigh the observed risks [11,15,57].

5. Cost-effectiveness

Current Gavi prices for Rotarix, Rotavac, and Rotasiil range from 0.85 USD-$2.29 USD per dose (Table 1; Merck supplied RotaTeq to Gavi from 2012 to 2019). While vaccine prices decline when multidose vials are purchased, this can lead to higher wastage rates as a vaccine container must be fully used the day it is opened, or the remaining doses are discarded at the end of the day. Accounting for the wastage rates and the number of doses needed for each vaccine, prices to fully immunize a child against rotavirus range from 3.17 USD-$4.77 USD with Gavi prices (Table 1).

When looking at all countries, previous work has found that at 5 USD per dose, the cost-effectiveness of rotavirus vaccine per disability-adjusted life year (DALY) averted in low, low-middle, and upper-middle-income countries was 88, USD 291, USD, and 329 USD USD, respectively, [66]. Debellut et al. evaluated the potential impact and cost-effectiveness of rotavirus vaccination in 73 Gavi eligible or formerly eligible countries from 2018 to 2027 [67]. This work found that rotavirus vaccine would prevent 158.6 million cases of rotavirus gastroenteritis, 80.7 million outpatient visits, 7.9 million hospitalizations and 576,567 deaths over the 10-year period, and in turn, would avert 14.7 million DALYs [67]. For all countries included in the analysis the cost-effectiveness on average was 325 USD per DALY averted for the entire time period, ranging from a low of 195 USD for countries in the African region to a high of 1158 USD for countries in the Americas [67]. In this analysis, the cost per DALY averted was on average was 0.16 times a country's GDP per capita (GDP used as the threshold for DALY cost-effectiveness), four countries, however, did have costs exceeding 1.0 times GDP per capita, including; Armenia, Honduras, Moldova, and Ukraine. This is likely due to the fact that these countries are entirely self-financing their rotavirus vaccine purchases [67]. Of note, other studies have occasionally found rotavirus vaccine not to be cost effective, but this generally occurs when only direct medical costs are considered, and not those incurred by the family or society [18].

6. Expert Opinion

Rotavirus vaccines continue to be the most effective, safe, and cost-effective solution to preventing rotavirus disease in developing countries. To ensure the continued introduction and sustained use of rotavirus vaccines; however, work must continue in a number of areas.

6.1. Generating effectiveness and safety data in Asia

Although efficacy data exist for rotavirus vaccine's performance in low-income Asian countries, no data currently exists on rotavirus vaccine's effectiveness, safety, or impact in routine use in Asian countries. Given regional and socioeconomic variability in rotavirus vaccine performance, as Asian countries continue to introduce rotavirus vaccines, gathering, analyzing, and distributing these data will be paramount [17,40]. This will allow for better informed risk-to-benefit assessments, which in turn will aid countries in their decision to introduce and/or continue to use the rotavirus vaccine.

6.2. Generating effectiveness and safety data for Rotavac and Rotasiil

As the demand for rotavirus vaccines among Gavi eligible countries is projected to increase to 66 million doses per year, the addition of Rotavac and Rotasiil to the marketplace should help increase vaccine availability, limit stockouts, and help maintain affordable vaccine prices [49]. However, minimal data currently exists on their effectiveness and safety in routine use. With the introduction of both vaccines in India and recent and impending introduction of these Indian-manufactured vaccines in several low and middle-income countries globally, the first reports of their real-world effectiveness and safety should be available soon. These data will allow countries to be better informed when selecting a vaccine for introduction or advocating for its continued use.

6.3. Ensuring vaccine affordability

One emerging threat to the continued use and implementation of rotavirus vaccines is their cost. While 45 countries are currently purchasing rotavirus vaccine through Gavi, after their gross national income per capita surpasses 1,580 USD, they begin to enter a transition phase and after 5 years assume the full financial responsibility of their vaccination program [68]. Unfortunately, prices over 1 USD per dose in the absence of Gavi likely mean that once countries are no longer eligible for subsidized vaccine prices, the vaccination program may become unsustainable [29]. As the cost-effectiveness of a vaccine is almost entirely dictated by its price, additional reductions in market prices are essential to ensure that these countries will be able to maintain their vaccination programs [68,69]. To help ease this transition, some rotavirus vaccine manufacturers (e.g. GSK) have agreed to maintain the Gavi level discounted prices after countries graduate from Gavi assistance, locking prices at Gavi levels for 10 years. In addition, the recent introduction of Rotavac and Rotasiil into the market should help keep vaccine prices low by adding to market pressure and help ensure an adequate vaccine supply globally [47]. Despite these improvements, however, further reductions in vaccine prices are essential to ensure that countries will be able to maintain their vaccination programs after co-financing has ended [11].

Among non-Gavi eligible countries, or those who are transitioning from Gavi assistance, another barrier to vaccine introduction and use is transparency in vaccine pricing. While prices for Gavi eligible countries are easily accessible, many countries that have not introduced have assumed that prices would be the same as those paid by developed countries, or prices that were reflected in the private market. Based on this feedback, organizing ways for countries to join a pooled purchase group (similar to PAHO's revolving fund) or setting up a reliable source for vaccine pricing, procurement options, and suppliers (particularly in Asia and Africa) could aid additional countries in introducing rotavirus vaccine in the future [69].

6.4. Expanding cold-chain capacity

Even with favorable cost-effectiveness analyses and pricing, many countries who are planning to introduce a rotavirus vaccine may face challenges due to a lack of cold-chain storage capacity. Because of the large packaging volume of the vaccine, many countries do not have space to accommodate the vaccine once introduced [29]. Unfortunately, the highest burden of rotavirus disease is also in countries with the lowest ability to store and effectively

give the vaccine. To ensure vaccines are not wasted, understanding the cold-chain storage capacity and resources required prior to procuring the vaccine is essential [70]. Continued efforts should be directed toward the expansion of the cold-chain capacity in developing countries, and adequately evaluating a country's capacity prior to vaccine introduction. Of note, this issue could also be relieved by the further development and production of heat-stable vaccines, such as the one developed by Serum Institute of India (stable for 2 years at 37°C or 6 months at 40°C) [34].

6.5. Understanding indirect protection

In developed settings, large reductions in rotavirus disease have been documented among children who were unvaccinated and among age groups too old to be vaccinated (herd protection), implicating infants as the primary transmitters of rotavirus infection [18,20]. These benefits are of lesser importance in areas with high vaccine effectiveness and uptake (developed countries), but could help swing the pendulum further in favor of rotavirus vaccination in areas where vaccine effectiveness and coverage may be lower [20,40]. Data on indirect protection in developing countries is less clear, and additional work is needed to better understand the extent of herd protection in these settings [40,71,72].

6.6. Improving vaccine performance in developing countries

As previously discussed, rotavirus vaccine's effectiveness and the duration of immunity in developing countries are nearly half of that observed in developed countries. Fortunately, there are a number of potential interventions that can be explored (e.g. staggering poliovirus and rotavirus vaccine administration, providing catch-up doses, transitioning from oral to microneedle skin patch vaccinations, parenteral vaccination) that could improve vaccine performance [49,73,74]. Given that over 85% of the world's children live in developing countries, even interventions that offer small increases in vaccine performance could have a dramatic impact on alleviating the burden of rotavirus disease globally. Improvements in vaccine performance could also help ensure that rotavirus vaccine remains the most cost-effective solution to preventing rotavirus disease.

6.7. Conclusion

As two new rotavirus vaccines enter the market (Rotasiil and Rotavac) and Asian countries continue to introduce rotavirus vaccines into their national immunization programs, documenting vaccine safety, effectiveness, and impact in these settings will be paramount. As issues around vaccine effectiveness, cost, and indirect protection are addressed in the coming years, it is likely that the effectiveness and cost-effectiveness of rotavirus vaccines in developing countries will continue to improve. As rotavirus vaccine introductions continue, efforts toward evaluating and expanding their cold-chain capacity should continue. Until universal rotavirus vaccine introduction is achieved, the full benefits of the rotavirus vaccine have yet to be realized.

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Article highlights

- In 2006 the World Health Organization's (WHO) Strategic Advisory Group of Experts (SAGE) first recommended the inclusion of rotavirus vaccines into national immunization programs in Europe and the Americas, and in 2009 SAGE recommended the integration of rotavirus vaccine into all immunization programs worldwide.
- Currently, four rotavirus vaccines have been pre-qualified by WHO for use globally. In developing countries, WHO recommends the use of Rotarix vaccine in a 2-dose schedule given at 6 and 10 weeks of age, and RotaTeq, Rotavac, and Rotasiil in a 3-dose schedule at 6, 10, and 14 weeks of age, with vaccine doses given concurrently with other childhood vaccines given at these ages.
- WHO currently recommends that the rotavirus vaccine series can be started at 6 weeks of age and subsequent vaccine doses can be given until 24 months of age. However, on-time vaccination at as early of an age as possible is strongly encouraged to achieve protection against rotavirus disease early in life.
- In 2013, an estimated 214,664 deaths were attributed to rotavirus infection in developing countries, and in the absence of rotavirus vaccine introduction, 38% of all hospitalized diarrhea cases among children <5 years globally are due to rotavirus infection.
- As of December 2019, 100 countries have introduced a rotavirus vaccine into their national immunization programs; an additional 6 low-income countries with a gross national product of <US$1,580 per capita have been approved for funding support for vaccine introduction from Gavi, the Vaccine Alliance and are awaiting national introduction and another 13 countries are preparing to introduce independent of Gavi support.
- A systematic review that analyzed post-licensure vaccine effectiveness data stratified by a country's childhood mortality rates aligned with these findings, with Rotarix vaccine effectiveness at 84% (13 studies), 75% (8 studies), and 57% (9 studies) in countries with low, medium, and high childhood mortality rates, and RotaTeq vaccine effectiveness at 90% (20 studies) and 45% (7 studies) in countries with low and high child mortality rates, respectively.
- Rotavirus vaccine introduction has reduced the global proportion of hospitalized diarrhea cases attributed to rotavirus among children <5 years from 38% in the pre-vaccine period, to 23.0% in the post-vaccine period, a 39.6% relative decline. While the magnitude of the decline varies by WHO region, due to varying vaccine effectiveness and vaccine coverage, overall reductions remain relatively consistent.
- Post-marketing surveillance conducted in several high and middle-income countries has identified a slight increase in risk of intussusception 1-7 days following vaccination for both Rotarix and RotaTeq at a rate of 1 excess

case per 20,000 – 100,000 vaccinated infants. The WHO Global Advisory Committee on Vaccine Safety has reviewed all of these data and reaffirmed the recommendation for continued rotavirus vaccine use.

- Currently, minimal data have been published on the effectiveness or intussusception risk associated with Rotavac or Rotasiil in routine use.
- When looking at all countries, previous work has found that at $5 per dose, the cost effectiveness of rotavirus vaccine per DALY averted in low, low-middle, and upper-middle-income countries was $88, $291, and $329, respectively. While occasionally some countries have found rotavirus vaccine not to be cost effective, this generally occurred when only direct medical costs were considered, and not those incurred by the family or society.

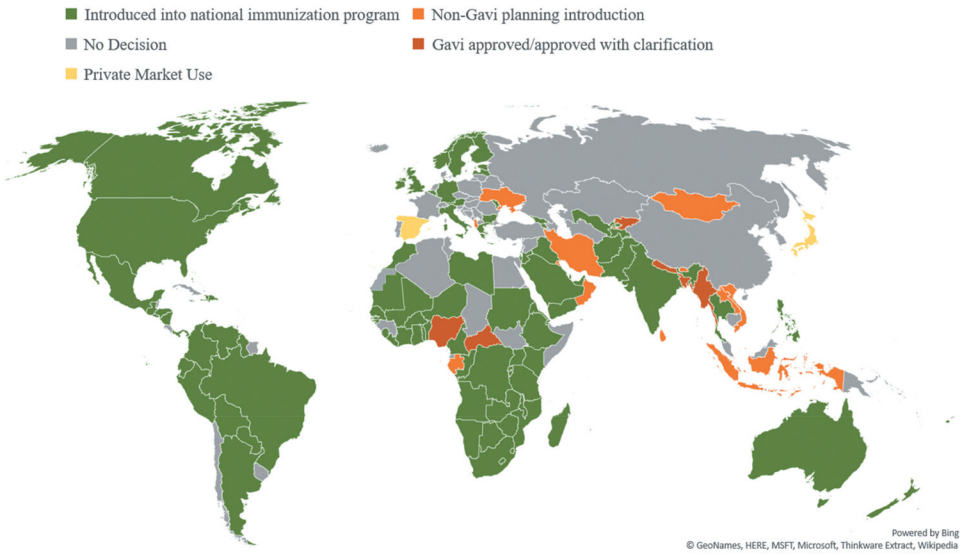

Figure 1.

National rotavirus vaccine introduction, by geographic region – as of December 2019. Underlying data source: http://view-hub.org/viz/.

Table 1.

Rotavirus vaccines currently pre-qualified by the World Health Organization.

Characteristic	Rotavirus Vaccine			
Trade name	Rotarix	RotaTeq	Rotavac	Rotasiil
Manufacturer	GlaxoSmithKline	Merck and Co., Inc.	Bharat Biotech International Limited	Serum Institute of India Pvt. Ltd.
Country of manufacture	Belgium	USA	India	India
Composition	Live-attenuated G1P1A [8] human rotavirus strain	Live human-bovine reassortant rotavirus strains: G1P7 [5], G2P7 [5], G3P7 [5], G4P7 [5], G6P1A [8]	Live-attenuated G9P [11] human rotavirus strain	Human-bovine reassortant rotavirus strains: G1, G2, G3, G4, G9
Pharmaceutical form	Liquid	Liquid	Liquid	Lyophilized + diluent
Presentation	a) 1 dose plastic tube b) 1 dose applicator c) 5 dose plastic tube	1 dose plastic tube	a) 5 dose vial b) 10 dose vial	a) 1 dose two vial set b) 2 dose two vial set
Route of Administration	Oral	Oral	Oral	Oral
Recommended schedule of administration	1st dose: 6 weeks 2nd dose: 10 weeks	1st dose: 6 weeks 2nd dose: 10 weeks 3rd dose: 14 weeks	1st dose: 6 weeks 2nd dose: 10 weeks 3rd dose: 14 weeks	1st dose: 6 weeks 2nd dose: 10 weeks 3rd dose: 14 weeks
Volume per dose	1.5 ml	2 ml	0.5 ml	2.5 ml
Storage temperature	2–8°C	2–8°C	−20°C	2–8°C
Shelf life	a) 24 months b) 36 months c) 24 months	24 months	60 months	30 months
Cold chain volume (cm3/dose)	a) 17.1–115.3 b) 85.3–134.0 c) 11.8	46.3–75.3	a) 4.2 b) 3.2	a) 17.6 b) 10.5
Date of WHO prequalification	2009, 2019	2008	2018	2018
GAVI 2019–2021 price per dose (USD)	a) 2.29 USD b) 2.29 USD c) -	*1* –	a) 0.85 USD b) 0.85 USD	a) 1.55 USD b) 0.95 USD
GAVI 2020 price per fully immunized person (USD)	a) 4.58 USD b) 4.58 USD c) -	*1* –	a) 2.55 USD b) 2.55 USD	a) 4.65 USD b) 2.85 USD
Indicative Wastage Rate	a) 4% b) 4%	*1* –	a) 23% b) 41%	a) 4% b) 10%
2020 waste-adjusted price per fully immunized person (USD)	a) 4.77 USD b) 4.77 USD c) -	*1* –	a) 3.31 USD b) 4.32 USD	a) 4.65 USD b) 3.17 USD

Underling data source: https://www.gavi.org/library/gavi-documents/supply-procurement/rotavirus-vaccine-profiles/.

[1] RotaTeq was withdrawn from the Gavi market at the end of 2019, therefore Gavi prices and wastage rates are no longer available.

Table 2.

Annual benefits and risks associated with rotavirus vaccination in Mexico, Brazil, Australia, the United States, and England.

Country	Diarrhea hospitalizations prevented by vaccination	Diarrhea deaths prevented by vaccination	Intussusception cases potentially caused by vaccination	Intussusception deaths potentially caused by vaccination	Reference
Mexico	11,600	663	41	2	[58]
Brazil	69,600	640	55	3	[58]
Australia	7,000	0	14	0	[61]
United States [1]	53,444	14	45–213	0.1–0.5	[62]
England	13,000	3	35	0	[63]

[1] data for one vaccinated birth cohort followed until age 5.