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Rotavirus vaccines: progress and new developments

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Abstract

Introduction: Rotavirus is the primary cause of severe acute gastroenteritis among children under the age of five globally, leading to 128,500 to 215,000 vaccine-preventable deaths annually. There are six licensed oral, live-attenuated rotavirus vaccines: four vaccines pre-qualified for global use by WHO, and two country-specific vaccines. Expansion of rotavirus vaccines into national immunization programs worldwide has led to a 59% decrease in rotavirus hospitalizations and 36% decrease in diarrhea deaths due to rotavirus in vaccine-introducing countries.

Areas covered: This review describes the current rotavirus vaccines in use, global coverage, vaccine efficacy from clinical trials, and vaccine effectiveness and impact from post-licensure evaluations. Vaccine safety, particularly as it relates to the risk of intussusception, is also summarized. Additionally, an overview of candidate vaccines in the pipeline is provided.

Expert opinion: Considerable evidence over the past decade has demonstrated high effectiveness (80–90%) of rotavirus vaccines at preventing severe rotavirus disease in high-income countries, although the effectiveness has been lower (40–70%) in low-to-middle-income countries. Surveillance and research should continue to explore modifiable factors that influence vaccine effectiveness, strengthen data to better evaluate newer rotavirus vaccines, and aid in the development of future vaccines that can overcome the limitations of current vaccines.

1. Introduction

Rotavirus infection causes severe diarrhea and vomiting, primarily among children <5 years of age [1]. These symptoms, which on average last for six days, can lead to dehydration, electrolyte imbalance, and even death [1, 2]. Prior to global introduction of rotavirus vaccines, rotavirus infections caused over 111 million cases of severe childhood diarrhea and >500,000 deaths in children <5 years of age annually [3].

In 2006, two rotavirus vaccines were licensed for the prevention of acute gastroenteritis (AGE) caused by rotavirus and the World Health Organization (WHO) subsequently recommended rotavirus vaccine use in regions where the initial clinical trials indicated

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vaccine efficacy (e.g. Europe, the Americas, Australia) [4]. Following the completion of additional rotavirus vaccine trials in low-income countries in Africa and Asia, in 2009, WHO expanded its recommendation for use of rotavirus vaccines in all countries, especially those with high diarrheal mortality [4]. After universal recommendation, it quickly became evident that rotavirus vaccination was leading to a paradigm shift in diarrhea morbidity and mortality among children <5 years of age. However, despite these successes, the burden of rotavirus disease remains high, particularly in low- and low-middle-income countries where rotavirus-associated mortality is also high and vaccine effectiveness is modest [5]. In 2018, the number of childhood deaths due to rotavirus was still high, at approximately 128,500, with the majority of deaths in countries that had yet to introduce rotavirus vaccination into their national immunization programs [6].

Currently, four rotavirus vaccines are pre-qualified for global use by WHO and two other vaccines are nationally licensed. Additionally, several other candidate vaccines are in the pipeline. This review will cover the progress in vaccine implementation, impact, effectiveness, and safety of the currently licensed vaccines, as well as summarize new developments in the rotavirus vaccine candidate pipeline.

2. Current rotavirus vaccines and vaccine implementation

Of the four rotavirus vaccine currently prequalified by WHO, two vaccines were first licensed in 2006 and prequalified by WHO for all countries in 2009 (Rotarix and RotTeq) and two Indian-manufactured vaccines were recently prequalified by WHO in 2018 (Rotavac and Rotasiil) [7]. Rotarix® (GlaxoSmithKline, Belgium) is a monovalent (G1P[8]) live-attenuated human rotavirus vaccine, RotaTeq® (Merck & Co., Inc., Kenilworth, NJ, USA) is a pentavalent (G1, G2, G3, G4, P[8]) live-attenuated human-bovine mono-reassortant vaccine, Rotavac® (Bharat Biotech, India) is a monovalent (G9P[11]) live, naturally-attenuated human-bovine mono-reassortant vaccine, and Rotasiil® (Serum Institute of India, India) is a pentavalent (G1, G2, G3, G4, G9) live-attenuated bovine-human rotavirus vaccine (Table 1). All four current prequalified vaccines are oral vaccines with a two dose (Rotarix) or three dose (RotaTeq, Rotavac, Rotasiil) series recommended within the first six months of life [7]. As of May 6, 2021, 110 (56%) countries have introduced rotavirus vaccine, 106 with introduction into national childhood immunization programs and four countries with subnational or regional introduction [8]. In addition to these four internationally available and WHO prequalified vaccines, two country-specific vaccines are available on the private market in Vietnam (Rotavin-M1) and China (Lanzhou Lamb Rotavirus [LLR]).

During the last decade alone, more than 70 countries have introduced rotavirus vaccine, indicating the tremendous global effort to expand rotavirus vaccination for the prevention of AGE hospitalizations and mortalities [8]. In October 2020, WHO's Strategic Advisory Group of Experts (SAGE) on Immunization updated their recommendations to include all four current oral rotavirus vaccines and reaffirmed their recommendation for use of rotavirus vaccine in all countries [10]. SAGE further recommended continued post-introduction evaluation of effectiveness and safety for rotavirus vaccines, particularly Rotavac and Rotasiil given their recent introduction into the global market. As of May 6, 2021, 77 countries were using Rotarix, 16 were using RotaTeq, 9 were using both Rotarix and

RotaTeq, two countries were using Rotavac, three countries were using Rotasiil, one country was using Rotavac and Rotasiil, and two countries have published press releases stating introduction of rotavirus vaccine but the specific vaccine is unspecified (Figure 1A) [8].

Vaccine coverage varies by country depending on the type of introduction (national, regional, private market) and the time since introduction (Figure 1B). Within countries that have introduced vaccine, studies assessing factors influencing rotavirus disease burden and vaccine coverage vary by country but generally identify geographic and socioeconomic disparities, such as household income, insurance status, maternal education and age, and accessibility and frequency of routine healthcare services [11–14].

3. Vaccine efficacy, effectiveness, and impact

3.1 Rotarix and RotaTeq

Rotarix and RotaTeq were both developed, evaluated in clinical trials, and licensed contemporaneously; thus, we will review the literature on their efficacy, effectiveness, and impact in tandem. A distinct gradient in vaccine efficacy and real-world vaccine effectiveness by country has been noted, with a higher effectiveness reported in low-mortality (or high-income) countries and reduced effectiveness in medium-to-high mortality (or low-to-middle-income) countries (Table 1). A recently updated Cochrane Review of Phase III clinical trials reported a Rotarix vaccine efficacy of 90%, 78%, and 54% against severe rotavirus within the first two years of life in low-, middle-, and high-mortality countries, respectively [15]. Vaccine efficacy estimates were similar for RotaTeq, at 94%, 81%, and 44% against severe rotavirus within the first two years of life in low-, middle-, and high-mortality countries, respectively [15]. Post-licensure evaluations of the real-world vaccine effectiveness have continued to report variable Rotarix and RotaTeq vaccine effectiveness by country mortality level. A 2020 meta-analysis of post-licensure studies reported a median Rotarix vaccine effectiveness against laboratory-confirmed rotavirus diarrhea of 83%, 67%, and 58% in low-, medium-, and high-mortality countries, respectively [16]. Additionally, a recent meta-analysis of 13 studies from 8 countries in Africa found a pooled Rotarix vaccine effectiveness of 58% against rotavirus-associated hospitalizations, aligning with clinical trial results (50–80% efficacy during clinical trials in Africa) and further highlighting the reduced effectiveness in less developed countries [17]. Similarly for RotaTeq, the median vaccine effectiveness was higher (85%) in low-mortality countries compared to high-mortality countries (45%), and results were consistent in another meta-analysis which categorized studies by high- vs low-income [16, 18].

The cause of this heterogeneity in vaccine effectiveness by country setting is likely multifactorial, with factors such as maternal antibodies, nutritional status, co-infections, concomitant administration with live oral polio vaccine, and the microbiome possibly playing a role in reducing vaccine effectiveness [19]. The role of maternal antibodies in rotavirus vaccine effectiveness remains uncertain [20, 21]. There is some evidence that transplacentally acquired maternal antibodies may influence immunogenicity of rotavirus vaccination [22–24], but studies that assessed transient abstention from breastfeeding during the time of rotavirus vaccination showed little to no impact on rotavirus vaccine efficacy [25, 26]. Investigations of the association between nutritional status of the infant and

vaccine effectiveness have indicated that zinc, vitamin A, and vitamin D deficiencies may play a role, possibly by causing dysfunctions of innate and acquired immune responses, but the confounding influences of environmental enteropathy and co-infection are challenging to disentangle [21, 27–29]. The gut microbiota is thought to affect the immune system through multiple pathways, and analyses have found correlation between the infant gut microbiome composition and response to rotavirus vaccination, although much remains to be explored in this area [30, 31]. While studies of Rotarix and RotaTeq have indicated similar immunogenicity when co-administered with live oral polio vaccine (OPV), a study in Bangladesh showed a reduction in rotavirus seroconversion following concomitant OPV administration when compared to staggered dosing [32, 33]. Genetic differences in expression of histo-blood group antigens, a receptor for cellular attachment, could also impact vaccine effectiveness, and could contribute to geographic differences in vaccine effectiveness due to variable prevalence of this genetic factor across racial and ethnic populations [34–36]. There has also been evidence of variation in Rotarix and RotaTeq vaccine effectiveness by age and genotype, with potential reduction in vaccine effectiveness in the second year of life and against non-vaccine strains, particularly for Rotarix. A recent meta-analysis found no evidence that the vaccine effectiveness was different between children <12 months and 12–23 months in low mortality countries, but did report slight, although sparse and non-conclusive, evidence of a decline in vaccine effectiveness between the first and second years of life in medium-to-high child mortality countries [16]. Hypotheses for this reduction in vaccine effectiveness within the second year of life include waning of vaccine-induced protective immunity or convergence of vaccine-induced immunity and immunity from natural infection in unvaccinated children [16]. As for variability by genotype, most clinical trials of Rotarix and RotaTeq showed evidence of cross protection against non-vaccine strains, although a lower vaccine effectiveness of Rotarix against non-vaccine strain G2P[4] was seen in one large Latin American trial [37, 38]. Additionally, a dominance of G2P[4] strains was observed initially after introduction of Rotarix in Latin American countries and Australia [39]. However, a meta-analysis of post-licensure data in 2014 found no evidence of different vaccine effectiveness by genotype [40].

Despite this multifactorial heterogeneity in vaccine effectiveness, implementation of these two vaccines has led to notable impact on the burden of rotavirus disease. Prior to Rotarix or RotaTeq introduction, the median percentage of hospitalized AGE cases positive for rotavirus across multiple countries was 40% (interquartile range [IQR], 28–45) across 47 countries from different child mortality strata; at four years after introduction this percent-positive had dropped to 20% (IQR, 20–20) leading to a reduction of 59% (IQR, 46–74) in rotavirus hospitalizations, 36% (IQR, 23–47) in AGE hospitalizations, and 36% (IQR, 28–46) AGE mortality [41]. Consistent with the gradient in vaccine effectiveness by country and age group, reductions in the percent-positive were larger in countries with low child mortality and among younger age groups. However, despite a smaller reduction in countries with high child mortality, the absolute number of cases averted and lives saved is substantial given the high burden of rotavirus in these settings [6]. In 2016 alone, estimates indicate that rotavirus vaccination averted the deaths of 24,200 children in sub-Saharan Africa [6].

Rotarix and RotaTeq vaccine impact is also highest in countries with higher vaccine coverage, and mathematical models predict that expanded use of rotavirus vaccine, both in terms of increased coverage and new introductions into national immunization programs, could prevent approximately 20% of all deaths attributable to diarrhea in children aged 5 and younger globally [6]. Additionally, estimates of vaccine effectiveness against rotavirus transmission are approximately 40%, and reductions in rotavirus disease in unvaccinated individuals has also been demonstrated across age groups, highlighting the public health impact of rotavirus vaccination beyond direct protection for the infant [42, 43]. A meta-analysis of studies published between 2008 and 2014 found evidence of herd immunity effects of approximately 22–25% against rotavirus-specific and all-cause gastroenteritis beyond the expected reduction direct vaccine efficacy[44]. However, these indirect benefits have primarily been documented in high- and middle-income settings, warranting continued evaluations of these findings in low-income, high-mortality settings.

3.2 Rotavac and Rotasiil

For Rotavac, clinical trial data from India estimated a vaccine efficacy against severe rotavirus AGE of 54% within the first two years of life [15, 45]. For Rotasiil, clinical trials in Niger and India reported a vaccine efficacy of 44% against severe rotavirus AGE in per protocol analyses ([15, 46, 47]). Despite modest efficacy estimates of these newer vaccines, Rotavac and Rotasiil offer several advantages, such as lower cost of production and, in the case of Rotasiiil, long-term stability for up to 18 months at 40°C, compared to a storage requirement of 2–8°C for 24 and 36 months for RotaTeq and Rotarix, respectively [48]. Rotasiil was originally formulated and licensed as a lyophilized presentation, but a liquid formulation was recently pre-qualified by the WHO in 2021 after a Phase 2/3 trial demonstrated non-inferiority to the lyophilized formulation [49]. Rotavac, which originally was formulated and licensed in a frozen liquid form stored as −20°C, also recently had an alternative formulation pre-qualified by WHO in 2021. This new form is a non-frozen liquid formulation, called Rotavac 5D, is stable at 2–8°C and was found to have non-inferior immunogenicity to Rotavac in a clinical trial in Zambia [50]. Studies to assess vaccine effectiveness and impact are ongoing for these two newer prequalified vaccines.

3.3 Rotavin-M1 (Vietnam) and Lanzhou lamb rotavirus (LLR) vaccine (China)

The two nationally licensed vaccines, Rotavin-M1 (Vietnam) and Lanzhou lamb rotavirus (LLR) vaccine (China) are also oral, live-attenuated vaccines with monovalent compositions (Rotavin-M1: G1P[8], LLR: G10P[15]) (Table 1) [51, 52]. Rotavin-M1 was licensed in Vietnam based on clinical trial data indicating a 73% IgA seroconversion rate, similar to Rotarix [53–55]. Of relevance, there is no established correlate of protection for rotavirus, thus clinical trials and effectiveness studies primarily rely on clinical endpoints; however, IgA seroconversion is considered a surrogate marker [56, 57]. A vaccine effectiveness evaluation in Vietnam of all three available private market vaccines (Rotavin-M1, Rotarix, RotaTeq) reported an overall vaccine effectiveness of 69.9%, although Rotavin-M1 only accounted for 5% of vaccinations in this study thus limiting extrapolation of these results to this vaccine [55]. Rotavin-M1 is a frozen formulation, but a liquid form, called Rotavin, was recently found to be safe and immunologically non-inferior to Rotavin-M1 [58].

The LLR vaccine has also exclusively been used in China since 2000, although coverage is relatively low because it is not part of the national immunization program [59]. Several post-licensure case-control studies have estimated LLR vaccine effectiveness against rotavirus AGE ranging from 35 to 77%, depending on the outcome definition [52, 60–62]. Results from a randomized placebo-controlled clinical trial in China were recently published for a trivalent human-lamb reassortant formulation of this vaccine (LLR3), reporting a LLR3 vaccine efficacy of 56.6% (95% CI: 50.7, 61.8), 70.3% (95% CI: 60.6, 77.6) and 74.0% (95% CI: 57.5, 84.1) against rotavirus AGE of any severity, severe rotavirus AGE, and inpatient rotavirus AGE caused by any serotype, respectively [63]. Chinese surveillance has reported a reduction in the rate of rotavirus AGE requiring hospitalization from 45% in 2001–2005 to 40% in 2006–2011 [64], and regions of China with higher rotavirus vaccine coverage have seen greater reductions in the incidence of rotavirus AGE compared to lower coverage regions [59].

4. Vaccine safety

Overall, rotavirus vaccines have an excellent safety record, as evidenced through clinical trials and through over 15 years of post-licensure evaluation [15]. However, in 1999, the first rotavirus vaccine, RotaShield, was withdrawn from the US market after just one year of routine use over concerns surrounding an increased risk of a rare complication, called intussusception, associated with the vaccine [65]. Intussusception occurs when one portion of the intestine invaginates into another more distal portion causing bowel obstruction. Intussusception, while rare, can be serious and potentially require surgery [66].

The clinical trials for Rotarix and RotaTeq, which had safety arms powered to evaluate the risk of intussusception, showed no increased risk of serious adverse events [67–69]. However, even with the encouraging safety data from the clinical trials, post-licensure studies of larger magnitude and alternative study design (e.g. self-controlled case series) have been necessary to further evaluate this rare event. Additionally, rates of intussusception vary by country, thus it has been, and continues to be, a priority to evaluate the relationship between current vaccines and intussusception globally.

For Rotarix and RotaTeq, surveillance post-licensure in high-and-middle-income countries have report a low-level increase in intussusception within the 1–7 days following vaccination, approximately 1 to 6 excess cases per 100,000 infants vaccinated [70, 71]. However, there has been no increased risk associated with rotavirus vaccination in a pooled analysis from 7 low-income countries in sub-Saharan Africa or in a recent study of Rotarix in South Africa [72]. Reviews conducted by the Global Advisory Committee on Vaccine Safety (GACVS) on Rotarix and RotaTeq have contended that the benefits of rotavirus vaccination outweigh the small risk of intussusception, re-affirming the position of the WHO and SAGE for recommendation for use of these vaccines worldwide [10, 73]. For Rotavac and Rotasiil, no increased risk of serious adverse events was identified during clinical trials, but these trials were not sufficiently powered to evaluate the risk of intussusception [45–47, 67]. However, for Rotavac, recently published results from multiple post-licensure studies in India have found no evidence of increased risk of intussusception following Rotavac

administration [74–76]. Safety monitoring of these newer vaccines is critical to inform risk-benefit policy recommendations.

5. Vaccines in development

Given the reduced vaccine effectiveness in low-to-middle income countries and potential limited duration of effectiveness after the first year of life, developing new and/or improved rotavirus vaccines remain a priority for addressing these current vaccine limitations. There are multiple rotavirus vaccine candidates in development (Table 2). This section with review recent developments for these candidate vaccines.

5.1 RV3-BB and RV3 rotavirus vaccine

One of the furthest candidates in the rotavirus vaccine pipeline is RV3-BB (PT BioFarma, Bandung, Indonesia), a 3-dose oral vaccine intended for neonatal administration shortly after birth (“birth dose”)[77]. This vaccine is based on a naturally attenuated neonatal strain G3P[6], which is able to replicate in the neonatal intestine even in the presence of maternal antibodies [77]. Early administration may have the added benefit of earlier protection against rotavirus disease if this vaccine is able to protect against infection during the first months of life [21]. Results from a phase 2b randomized placebo-controlled trial in Indonesia from 2013 through 2016 reported a per-protocol vaccine efficacy against severe rotavirus AGE up to 18 months of age of 75% (95% CI: 44, 91) in the neonatal-schedule (0–5 days, 8–10, and 14–16 weeks of age), 51% (95% CI: 7, 76) in the infant-schedule (8–10, 14–16, and 18–20 weeks of age), and 63% (95% CI: 34, 80) in the neonatal- and infant-schedule groups combined [77]. Furthermore, this trial found no evidence of interference by or with oral polio vaccine, which has been one hypothesis for reduced vaccine effectiveness of the oral rotavirus vaccines in low-to-middle-income countries [19]. Secondary analyses of the phase 2A clinical trial found that differential expression of histo-blood group antigens (HBGAs), known as secretor and Lewis status, did not impact the cumulative vaccine take after vaccination with RV3-BB [78]. A phase I trial of the RV3 vaccine developed using a process free of porcine material, which has >99% genetic homology with the RV3-BB vaccine, was found to be well-tolerated in adults children, and neonates and immunogenic in the neonatal cohort which received doses at 0–5 days, 8–10 weeks, and 12–14 weeks [79].

A clinical dose-ranging trial in Malawi was completed in 2020, although results have not yet been published (NCT03483116; clinical trials gov). Studies have already begun to determine optimal manufacturing and formulation processes for future RV3-BB vaccine production [80].

5.2 Parenteral vaccine VP8 subunit protein vaccine

Parenterally administered vaccines have the potential to overcome factors that may be reducing current vaccine effectiveness of the oral vaccines, including interference from breast milk antibodies, and could be combined with other infant immunizations.

The parenterally administered vaccine candidate furthest along in the vaccine pipeline is an injectable truncated VP8 subunit protein vaccine, with monovalent and trivalent formulations. Safety and immunogenicity studies of the monovalent formulation in the

United States and South Africa indicated this vaccine was safe and well tolerated, but a trivalent formulation was developed over concerns around low heterotypic protection against non-vaccine strains [81]. This trivalent P2-VP8 subunit rotavirus vaccine was recently evaluated in a phase II trial among adults, toddlers, and infants in South Africa and found to be well tolerated and immunogenic, with robust serum neutralising antibody and IgG responses across the three vaccine P types [81]. However, while the IgA seroresponses were higher in the vaccine group (20–34% 4-fold or higher antibody increase) compared to the placebo group (5%), these results were lower than seroresponse in trials of the monovalent formulation [82, 83]. A phase 3 clinical trial is underway (NCT04010448), which will better elucidate how these immunogenicity studies translate to vaccine efficacy.

5.3 Bovine-human reassortant RV (BRV) strain vaccines

Additional bovine-human reassortant (BRV) vaccines in development include the tetravalent UK-BRV (Shanta Biotechnics), pentavalent UK-BRV (Instituto Butantan, Brazil), and a hexavalent UK-BRV (Wuhan Institute of Biological Products, China)[84]. The tetravalent UK-BRV was found to be non-inferior to RotaTeq [85] but development of this vaccine appears to have been abandoned [84]. The pentavalent UK-BRV vaccine was shown to be safe and immunogenic in a phase 1 study, but further clinical trials have not been pursued for this candidate vaccine in Brazil, where use of Rotarix in the national immunization program has demonstrated a significant reduction on rotavirus disease burden [86, 87]. Results were recently reported from a phase I clinical trial of the hexavalent UK-BRV vaccine, indicating that this candidate is safe in adults, infants, and toddlers, and immunogenic in infants as indicated by higher IgA seroconversion rates in the vaccine groups compared to the placebo group [88]. A phase III is indicated to be underway for this hexavalent UK-BRV vaccine candidate [88].

5.4 Inactivated vaccine

Another non-replicating parenterally administered rotavirus vaccine under development is the inactivated G1P[8] vaccine under development by the Centers for Disease Control and Prevention (CDC), USA [89]. Pre-clinical animal studies indicated this vaccine induced high IgG antibody titers and heterotypic immunity [90–92]. This candidate has also been tested in combination with an inactivated polio vaccine (IPV-IRV), and no evidence of interference was found [93]. This combined IRV-IPV vaccine candidate is also being evaluated with administration using a novel microneedle patch, with studies currently underway for early-phase clinical trials [93].

5.5 Other early-stage candidate vaccines

Other early-stage parenterally administered rotavirus candidates include the inner capsid VP6 antigen subunit vaccine with norovirus viral-like particles (VLP) (University of Tampere), an expressed VP6 protein vaccine (Cincinnati Children’s Hospital Medical Center), VLP VP2/6(/7) vaccine (Baylor College of Medicine) [7]. These vaccine candidates have demonstrated good immunogenicity in pre-clinical animal models, but have not progressed to clinical trials in humans [94–99]. In addition to a development as a candidate vaccine against rotavirus, the rotavirus inner capsid protein VP6 is being explored as a potential adjuvant for candidate norovirus vaccine-like-particle vaccines, indicating

potential rotavirus-norovirus combination vaccines may be feasible in the future[100, 101]. Furthermore, research continues to elucidate the best correlates of protection to inform rotavirus vaccine trials [57]; for example, recent use of an intracellular neutralization assay has indicated a more significant role of VP6-specific IgG antibodies in rotavirus protection [102].

6. Conclusion

The introduction of rotavirus vaccines globally has resulted in substantial reductions in childhood morbidity and mortality due to severe rotavirus gastroenteritis, marking an extraordinary achievement in global public health over the past fifteen years. Continued efforts should be made to enable expansion of rotavirus vaccination to more countries and to increase coverage in countries which have already introduced. The reduced vaccine effectiveness of current vaccines in low-income countries remains a challenge, and further research is needed to continue evaluating what modifiable factors contribute to this heterogeneity. Vaccine candidates in the pipeline may help address some of these challenges and are promising prospects for the future of rotavirus disease prevention.

Expert opinion

The profound public health success of rotavirus vaccines is undeniable. With the expansion of rotavirus vaccines worldwide, an overall reduction of 59% in rotavirus hospitalizations, 36% in AGE hospitalizations, and 36% AGE mortality has been seen in countries that have introduced rotavirus vaccines into their national immunization programs. Mathematical models have helped to further quantify the extent of this impact, estimating that approximately 28,000 deaths were averted in 2016 alone. However, there remains an unmet need for rotavirus vaccines; despite the benefits of introduction of rotavirus vaccine in over 100 countries, many countries have yet to introduce and some countries have inequitable coverage, leading to a continued high burden of this vaccine-preventable disease. Now with the addition of Rotavac and Rotasiil to the global market, countries have more options when considering vaccine introduction. Countries that have already introduced rotavirus vaccines should consider conducting evaluations to identify barriers to vaccination to facilitate targeted public health efforts, such as enhanced healthcare accessibility to vaccination, to address these barriers and improve health equity. Additionally, global partnerships should continue to facilitate vaccine introduction for countries that have yet to introduce, with the goal of reducing rotavirus morbidity and mortality.

Research priorities should remain focused on identifying ways to improve the effectiveness of current vaccines in low- and middle-income countries, as well as continuing development of future vaccines that may overcome the limitations of these current oral vaccines. While current evidence regarding the safety of oral rotavirus vaccines is re-assuring, the concern of a slight increase in the risk of the rare, yet serious, condition of intussusception warrants continued vigilance. Candidate vaccines of alternative formulation may offer future options with lower concerns of intussusception.

With the continuous expansion of rotavirus vaccine worldwide, the future of rotavirus disease prevention remains promising. However, it remains crucial to implement and

maintain high quality surveillance for evaluation of post-licensure vaccine effectiveness and safety, particularly for the recently pre-qualified Indian-manufactured vaccines. Looking to the future, results from pre-clinical and early stage human trials for next generation rotavirus vaccines are encouraging, providing hope of even more effective and beneficial vaccines.

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Highlights

- Rotavirus is the primary cause of severe acute gastroenteritis among children under the age of five globally, causing 128,500 deaths annually.
- There are currently six licensed oral, live-attenuated rotavirus vaccines, including four vaccines pre-qualified for global use by the WHO (Rotarix, RotaTeq, Rotavac, and Rotasiil), and two country-specific vaccines (Lanzhou Lamb Rotavirus [LLR]-China and Rotavin-M1-Vietnam)
- As of May 2021, 110 countries have introduced rotavirus vaccine, 106 with introduction into national childhood immunization programs and four countries with subnational or regional introduction
- Vaccine effectiveness against severe rotavirus disease in high-income countries is approximately 80–90%, but this effectiveness is reduced in low-to-middle income countries to approximately 40–70%.
- Despite this multifactorial heterogeneity in vaccine effectiveness, implementation of rotavirus vaccines has led to a 59% decrease in rotavirus hospitalizations and 36% decrease in diarrhea deaths due to rotavirus in the burden of rotavirus-associated gastroenteritis in vaccine-introducing countries.
- Several other rotavirus vaccine candidates are in the pipeline which aim to overcome current limitations of rotavirus vaccines.

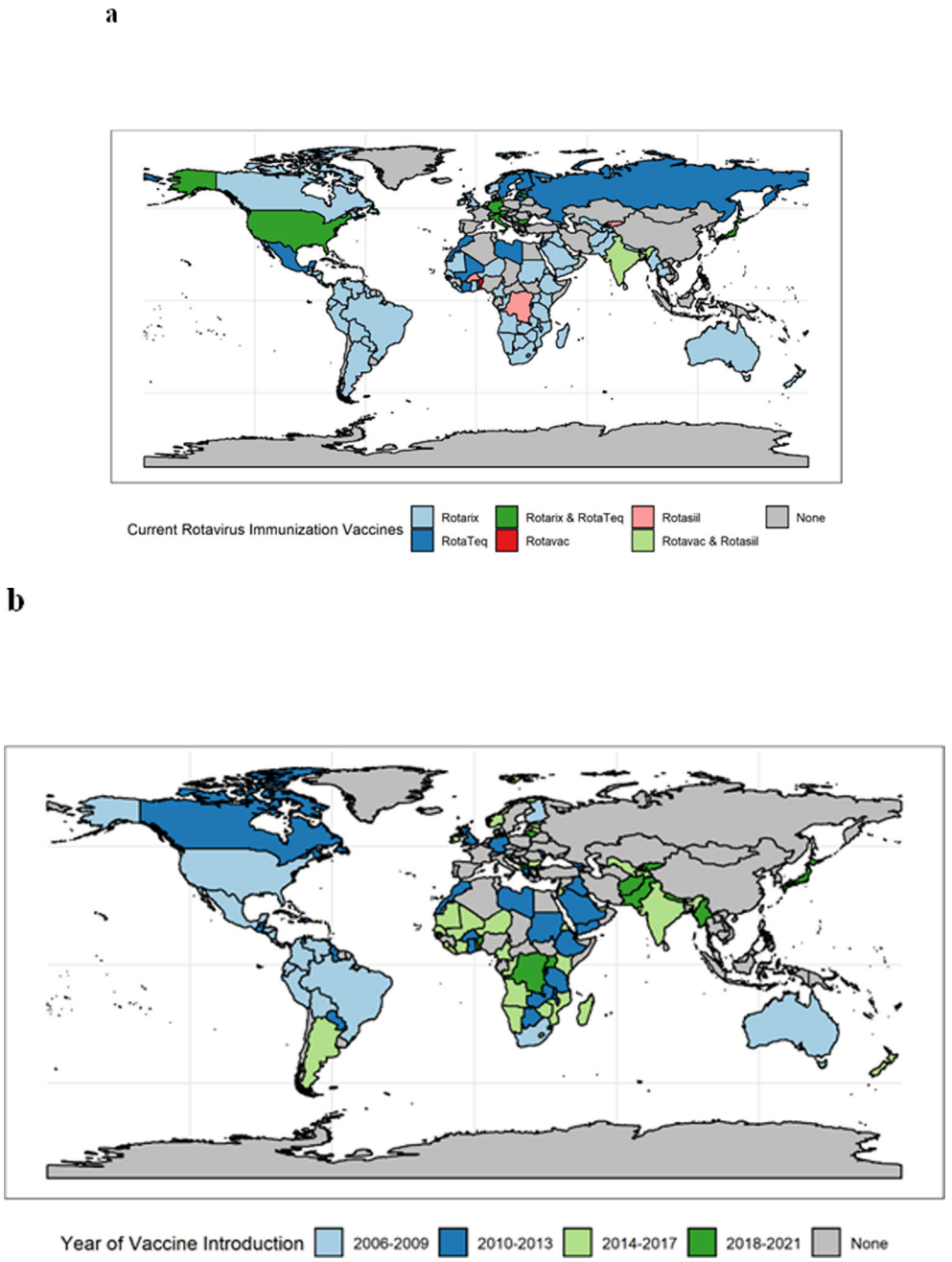

Figure 1.

Map of rotavirus vaccine introduction worldwide, by rotavirus vaccine used (A) and year of vaccine introduction (B) in national immunization programs. Source: Data accessed through International Vaccine Access Center (IVAC), Johns Hopkins Bloomberg School of Public Health. VIEW-hub. www.view-hub.org. Access date: 6/30/2021.

Table 1.

Characteristics of currently available rotavirus vaccines.

Trade name	Manufacturer	Year of WHO pre-qualification	Doses	Composition	Form	Vaccine efficacy*	Post-licensure vaccine effectiveness* (VE)
Globally licensed							
Rotarix	GSK	2009	3	G1P[8]	Liquid	LMC: 90% MMC: 78% HMC: 54%[15]	LMC: 83% MMC: 67% HMC: 58%[16]
RotaTeq	Merck	2008	2	G1, G2, G3, G4, P[8]	Liquid	LMC: 94% MMC: 81% HMC: 44%[15]	LMC: 85% HMC: 45%[16]
Rotavac	Bharat Biologicals	2018	3	G9P[11]	Liquid (frozen) and nonfrozen liquid (Rotavac 5D)	India: 54%[15]	VE studies are ongoing [9]
Rotasiil	Serum Institute of India	2018 (lyophilized) 2021 (liquid)	3	G1, G2, G3, G4, G9	Lyophilised and liquid forms available	India & Niger: 44%[15]	VE studies are ongoing
Nationally licensed							
Rotavin-M1	POLYVAC	N/A	3	G1P[8]	Liquid (frozen) and nonfrozen liquid (Rotavin)	None published; IgA seroconversion 73%[53]	VE studies are ongoing
Lanzhou Lamb Rotavirus Vaccine	Lanzhou Institute of Biological Products	N/A	1 annually age 2 months to 3 years	G10P[15]	Liquid	Any severity: 57% Severe RVGE: 70% Inpatient RVGe: 74%[63]	35%—73% [52, 60, 61]

LMC=low-mortality countries; MMC=medium-mortality countries; HMC=high mortality countries;

*against severe rotavirus gastroenteritis, per protocol analysis, unless otherwise noted

Table 2.

Characteristics of candidate rotavirus vaccines in development.

Product	Producer/Developer	Characteristics	Composition	Current stage of development
RV3-BB	PT BioFarma, Bandung, Indonesia	Based on human neonatal live-attenuated strain; neonatal (“birth dose”) and infant schedules being evaluated	G3P[6]	Phase 2/3; Phase 2b completed
VP8 subunit protein vaccine	PATH Rotavirus Vaccine Program, USA	Subunit vaccine based on recombinant proteins; Parenteral administration being evaluated	Trivalent truncated VP8: P[4],P[6], P[8]	Phase 3
Tetravalent UK-BRV	Shanta Biotechnics	Based on live-attenuated bovine-human reassortant strain	G1–4	Phase 3, development abandoned
Pentavalent UK-BRV	Instituto Butantan, Brazil	Based on live-attenuated bovine-human reassortant strain	G1–4, G9	Phase 1
Hexavalent UK-BRV	Wuhan Institute of Biological Products, China	Based on live-attenuated bovine-human reassortant strain	G1–4, G8, G9	Phase 2/3
Inactivated G1P[8] vaccine	CDC, USA	Heat inactivated human strain; Parenteral administration being evaluated	G1P[8]	Preclinical; Animal studies
VP6-norovirus VLP	University of Tampere	Subunit vaccine based on virus-like particles; Parenteral administration being evaluated	n/a; VP6 protein	Preclinical: Animal studies
expressed VP6 protein	Cincinnati Children’s Hospital Medical Center	Subunit vaccine based on recombinant proteins; Parenteral administration being evaluated	n/a; VP6 protein	Preclinical: Animal studies
VLP VP2/6(/7)	Baylor College of Medicine	Subunit vaccine based on virus-like particles; Parenteral administration being evaluated	n/a; VP2/6/7 proteins	Preclinical: Animal studies