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REVIEW

The performance of licensed rotavirus vaccines and the development of a new generation of rotavirus vaccines: a review

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ABSTRACT

Rotavirus, which causes acute gastroenteritis and severe diarrhea, has posed a great threat to children worldwide over the last 30 y. Since no specific drugs and therapies against rotavirus are available, vaccination is considered the most effective method of decreasing the morbidity and mortality related to rotavirus-associated gastroenteritis. To date, six rotavirus vaccines have been developed and licensed by local governments. Notably, Rotarix™ and RotaTeq™ have been recommended as universal agents against rotavirus infection by the World Health Organization; however, lower efficacies were found in less-developed and developing regions with medium and high child mortality than well-developed ones with low child mortality. For now, two promising novel vaccines, Rotavac™ and RotaSiil™ were pre-qualified by the World Health Organization in 2018. Other rotavirus vaccines in the pipeline including neonatal strain (RV3-BB) and several non-replicating rotavirus vaccines with a parenteral delivery strategy are currently undergoing investigation, with the potential to improve the performance of, and eliminate the safety concerns associated with, previous live oral rotavirus vaccines. This paper reviews the important developments in rotavirus vaccines in the last 20 y and discusses problems and challenges that require investigation in the future.

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Introduction

Rotavirus (RV), an RNA virus of the family, *Reoviridae*, is a ubiquitous pathogen that causes acute gastroenteritis, leading to severe diarrhea and vomiting, among infants and children worldwide, particularly in low-income countries.[1–6] RV was first discovered in stool specimens from children with gastroenteritis by Ruth Bishop and collaborators in 1973.[7,8] Five years later, the International Committee on Taxonomy of Viruses officially named the virus RV, because of its characteristic wheel-like appearance, observed through an electron microscope by Thomas Henry Flewet.[9–11]

RV is highly contagious and transmitted by the fecal-oral route. It spreads primarily through contaminated food, water, environmental contamination, aerosolized viral particles in vomitus, or direct person-to-person contact within closed communities and institutions, such as daycare centers, schools, restaurants, cruise ships, and resorts, as well as hospitals and military establishments.[12–15] RV disease is characterized by acute onset watery diarrhea, vomiting, fever, and abdominal pain. It generally lasts 3–8 d, usually beginning 2 d after a person has been exposed.[16] This disease also has a winter seasonal pattern, most frequently occurring from December through June in countries with temperate climates.[17] Latest annual RV mortality rates for RV disease in children <5 y of age, ranging from 122,322 to 215,757 worldwide were estimated by different organizations and methods in 2013.[1,3,18] For now, no specific therapies, antibiotics or other drugs against RV are currently available and good hygiene is insufficient to control the spread of the disease. Vaccination has become the most efficient solution to control and prevent RV infection.

Due to the wide application of RV vaccines in some developed countries, the rate of hospitalization from acute gastroenteritis has decreased significantly in last decade.[19,20] With the support of Gavi (the Vaccine Alliance) and other partners, RV vaccines were introduced to more than 110 countries like Ghana and resulted in substantial declines in hospitalizations due to RV.[21,22] The global impact of RV vaccines from 2006 to 2019 showed the similar reductions in RV and acute gastroenteritis hospitalizations, with the largest decreases in countries with low child mortality and higher coverage, and among younger age groups.[23] However, there are some low- or middle-income countries in south-eastern Asia or sub-Saharan Africa still suffered a large number of cases and deaths from RV every year, which have yet to launch RV vaccine campaigns.[16] Besides, compared with developed regions, a significantly lower efficacy of RV vaccines has been reported in less-developed countries, which may be attributable to the high disease burden, differences in prevalent serotypes, preexisting antibodies, malnutrition, microbiome or intestinal enteropathy, the concomitant use of oral poliovirus vaccine (OPV) and other factors.[13,24-32] Moreover, since intussusception (a bowel obstruction, in which one segment of bowel becomes enfolded within another), a serious adverse reaction, was associated with vaccination

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using the first licensed RV vaccine (RotaShield™), the much stricter safety evaluation was progressed in the following RV vaccines.[33–41] Previous reviews compared the licensed RV vaccine introductions with vaccine coverage and introduced the possible methods of raising the coverage of RV vaccines to improve the efficacy between high and low-income countries.[42,43] In order to achieve the full immunization goal and solve the above deviation of efficacy between different countries and other issues on the safety of RV vaccines, our review will not only provide an overview of current research and development of licensed RV vaccines, including their efficacy, immunogenicity, and safety profiles, but also add the novel prequalified RV vaccines and other candidates in the pipeline. Besides, this review will assess the health impact of vaccination in countries where RV vaccines had been introduced for universal use and discuss hot topics in research and future directions.

RV structure and overview of RV vaccines

The mature RV virion is a non-enveloped double-stranded RNA virus with a segmented genome comprising a triple-layered protein capsid. There are six viral proteins (VPs) form the virus particle (virion) and six nonstructural proteins (NSPs) produced in cells infected by RV, which were called as VP1, VP2, VP3, VP4, VP6, VP7, and NSP1, NSP2, NSP3, NSP4, NSP5, NSP6, respectively.[44,45] Of them, VP4 (P protein) and VP7 (G protein) in the outer layer are responsible for determining the genotype of the strain and also inducing specific neutralizing antibodies.[46,47] The VP6 which is highly antigenic can be used to identify RV species and the NSP4 is a viral enterotoxin that induces diarrhea.[48,49] The role of these proteins makes them key antigenic targets for designing novel RV vaccine candidates and immunotherapies.

RV vaccines can be roughly divided into four categories according to origins or compositions: non-human, animal-human reassortant, human, and non-replicating vaccines (Figure 1 near here).

Non-human RV vaccines are those based on animal RV strains, which are heterotypic to human RV and need high titers to produce a moderate efficacy profile.[50–63] Further, the efficacies of the pioneering RIT 4237,[50–63] bovine strain WC3,[64–72] and simian strain RRV[73-82] vaccines varied significantly in different regions. In particular, lower protection of the non-human RV vaccines was found in developing countries with high natural infection burdens, and in areas with prevalent serotypes differing from the vaccine. These evidences have led to suspension of the most non-human RV vaccines.

Animal-human reassortant RV vaccines are constructed by containing the VP7 (or VP4) gene from human strains alongside the remaining animal RV genes (to attenuate RV virulence in infants). These RV vaccines were generally found to have high efficacy and immunogenicity profiles, and to provide heterotypic protection.

Human RV vaccines are derived from human RV and capable of exhibiting great immune response. This might be associated with the homotypic human strains included in the vaccines.

Non-replicating vaccines with a parenteral delivery strategy have safety advantages of potentially reducing the risk of intussusception and other side effects that has been associated with some oral vaccines, since the vaccine viruses could not replicate in the gut.[13]

Current licensed RV vaccines

Bovine (strain WC3)-human reassortant RV (RotaTeq™)

RotaTeq™ (Merck & Co., Inc., Whitehouse Station, New Jersey, USA) is a live, oral three-dose vaccine that contains five reassortant RVs (G1, G2, G3, G4, and P1A[8]) derived from human and bovine parent strains. It was approved by the US Food and drug Administration (FDA) in February 2006 and is recommended to be given to infants at 2, 4, and 6 months of age[83] (Table 1 near here).

In view of the previous association of the RotaShield™ vaccine with intussusception, substantial clinical trials were conducted to evaluate the safety of RotaTeq™ with respect to intussusception. Notably, in a large RV efficacy and safety trial (REST), conducted from 2001 to 2004 in 11 countries, involving almost 70,000 infants between 6 and 12 weeks, six vaccines and five placebo recipients developed intussusception within 42 d after any dose, which did not represent a significant difference between the groups[84–85] (Table 2 near here). Besides, the efficacy profile of RotaTeq™ was encouraging; efficacy after three doses was estimated at up to 74% against G1–4 RV gastroenteritis (RVGE) and 98% against severe RVGE, compared with placebo during the first RV season. Further, an overall 95% reduction in hospitalizations and emergency department visits was found, which was consistent among regions (94.7%, 94.9%, and 90.0% in Europe, USA, and the Latin American/Caribbean regions, respectively).[97] Similar results were found in American Indian infants from REST, indicating no difference between types of population in the same developed region.[86] Furthermore, 98.3% and 68.0% protection against severe RVGE and RVGE, respectively, were obtained in Europe for two RV seasons postvaccination, regardless of serotype.[87] Extended Finnish research proved that the protection prolonged up to 3.1 y, following the last vaccine dose.[88] Another sub-study demonstrated that RotaTeq™, at the end of its shelf life, remained generally well tolerated, immunogenic, and efficacious.[89] Moreover, delayed vaccination, with an interval between previous and subsequent doses greater than 10 weeks, had no significant effect on efficacy or immunogenicity, supporting the use of various dosing intervals.[90] In another developed country, Japan, RotaTeq™ showed strong potency in preventing RVGE, moderate-to-severe RVGE, and severe RVGE (74.5%, 80.2%, and 100%, respectively), consistent with prior studies.[91]

However, there are significantly lower vaccine efficacies of RotaTeq™ were found in developing countries or regions with high mortality rates of RV, which was significantly different from the protective levels achieved in developed regions. In two field trials of RotaTeq™ performed in sub-Saharan Africa (Ghana, Kenya, and Mali) and Asia (Bangladesh and Vietnam), the efficacy against severe RVGE of 39.3% and 48.3% for the first 2 y of life, respectively.[24,27] Combining data from the five

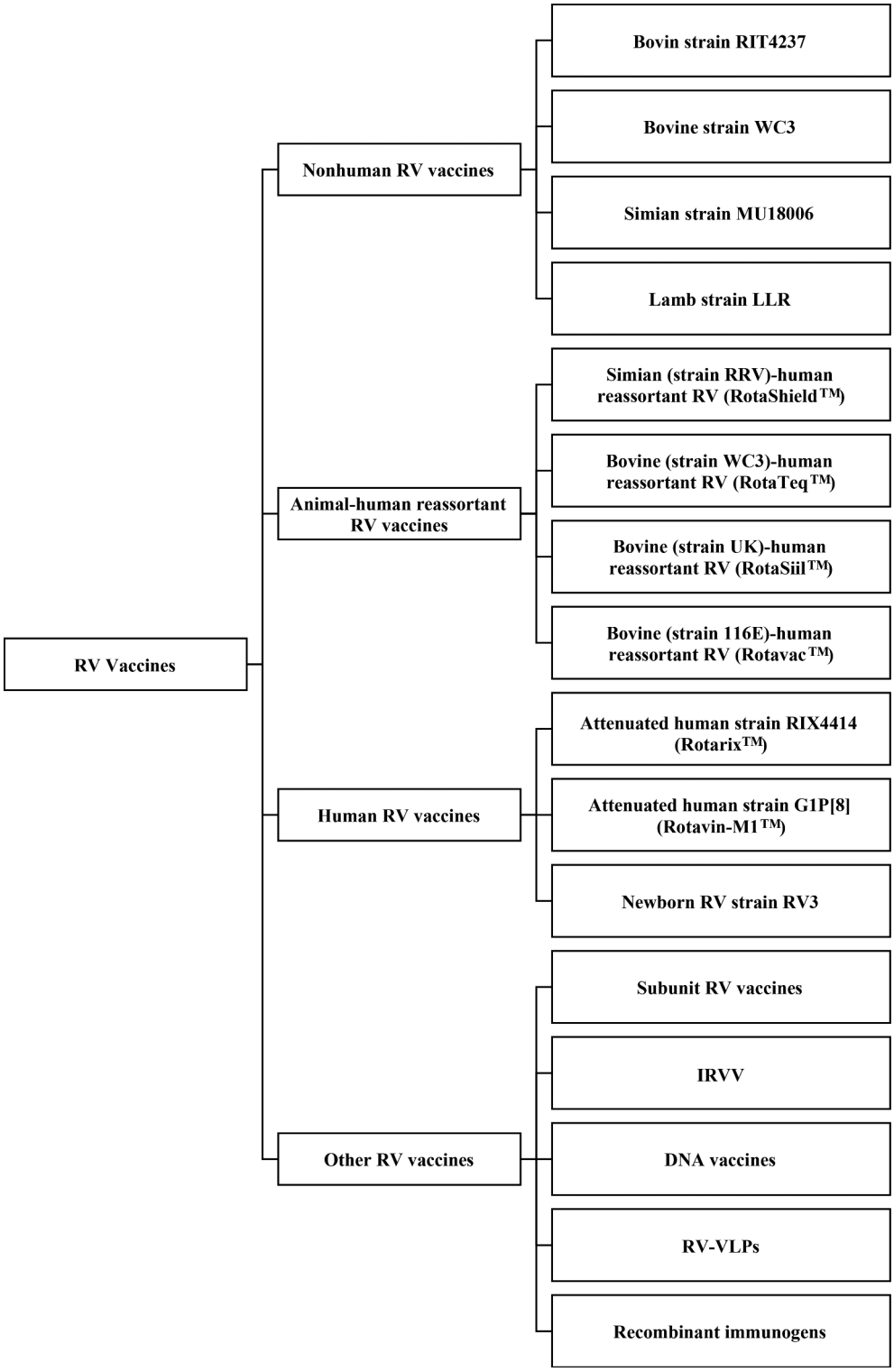

Figure 1. The classification of rotavirus vaccines Rotavirus vaccines can be roughly divided into four categories according to origins or compositions: non-human, animal-human reassortant, human, and other rotavirus vaccines.

sites in developing countries, the efficacy against RVGE for any severity, severe, and very severe was 33.9%, 42.5% and 51.2%, respectively, which strengthened the precision of efficacy estimates and revealed rising efficacy with increased RVGE severity.[92–94] Further, RotaTeq™ vaccine provided 69.3% efficacy against RVGE by any serotype and was generally well tolerated in healthy Chinese infants.[95]

After the licensure of RotaTeq™ for global use in 2006, abundant effectiveness studies and real-world impact of introducing into national vaccination programs were conducted.[96–102] Recent systematic review suggested that the effectiveness (VE) was 90% and 45% in countries with low and high child mortality, respectively.[103] Pooled VE of full series RotaTeq™ against RV-associated hospitalizations and emergency department (ED)

Table 1. The table of the characteristics of licensed RV vaccines.

Vaccine Name	Rotarix™	RotaTeq™	RotaShield™	Rotavac™	RotaSiil™	LLR	Rotavin-M1™
Status	Worldwide license	Worldwide license	Withdrawn	Worldwide license	Worldwide license	Restricted license	Restricted license
Category	Human RV	Animal-human reassortant RV	Animal-human reassortant RV	Animal-human reassortant RV	Animal-human reassortant RV	Nohuman RV	Human RV
Valent	1	5	4	1	5	1	1
Origin of antigen	Attenuated human G1P [8] strain	Human-bovine reassortant strain with G1, G2, G3, G4, P1[8] proteins	Human-simian reassortant strain with G1, G2, G4, G3P[5] proteins	Human G9P[11] strain	Human-bovine reassortant strain with G1-G4, G9 proteins	Lamb G10P[12] strain	Attenuated human G1P[8] strain
Storage Conditions	2 to 8°C, not frozen; avoid light	2 to 8°C, not frozen; avoid light	2 to 8°C	Frozen at −20±°C5°C	Stable at 37°C for 2 y and 40°C for six months	2 to 8°C	Frozen at −20±°C5°C
Intervention Route	Oral	Oral	Oral	Oral	Oral	Oral	Oral
schedule of administration	2 doses, given on same schedule as DPT vaccine	3 doses, given on same schedule as DPT vaccine	N/A	3 doses, four weeks apart, beginning at 6 weeks of age	3 doses, four weeks apart, beginning at 6–8 weeks of age	1 dose every year for 3 y between 2–35 months of age	The 1st dose from 6 weeks of age. The 2nd dose after 1–2 months before 6 months of age
Country	Belgium	USA	USA	India	India	China	Vietnam
Licensure Date	2008	2006	1998	2014	2016	2000	2014
WHO prequalification/ Date	2009	2008	N/A	2018	2018	N/A	N/A
Manufacturer or sponsor	GlaxoSmithKline Biologicals	Merck	Wyeth-Ayerst Research, W-AR	Bharat Biotech International Limited	Serum Institute of India Limited	Lanzhou Institute of Biological Products	Center for Research and Production of Vaccines
Efficacy against severe RVGE	39.3%-96.9%	39.3%-100%	N/A	55.1%	66.7%	N/A	N/A
Price per vaccination course	From approximately US$0.50 in GAVI-eligible countries up to US$185–$226 in the USA		NA	US$ 2.50	US$ 6.00 maximim	US$ 24.00	US$ 17.60

Abbreviations: RV, rotavirus; N/A, not applicable; WHO, World Health Organization; DPT, diphtheria, pertussis and tetanus.

Table 2. Selected efficacy clinical trials* of four WHO prequalified live oral RV vaccines.

Vaccines	Study Time/ Reporting Time	Countries or Regions	Enrollments	Observation Duration (Year)	Doses	Efficacy on Conditions	Efficacy, %(95%CI)	Reference
Rotarix™	2001–2003	Singapore	2464	1	2	RVGE	82.0% (N/A)	231
	2003–2004	Latin American, Finland	63,225	1	2	severe RVGE	84.7% (71.7%-92.4%)	110
	2004–2005	Europe countries	3994	1	2	RVGE	78.9% (72.7%-83.8%)	106
						severe RVGE	90.4% (85.1%-94.1%)	
	2003–2008	Hong Kong, Singapore, Taiwan	10,708	2	2	severe RVGE	96.1% (85.1%-99.5%)	113
				3	2	severe RVGE	96.9% (88.3%-99.6%)	114
	2003–2005	Singapore	6542	3	2	severe RVGE	95.2% (70.5%-99.9%)	232
	2003–2005	Hong Kong	3025	3	2	severe RVGE	96.1% (76.5%-99.9%)	233
	2005	South Africa, Malawi	4939	1	2/3	severe RVGE	61.2% (44.0%-73.2%)	25
	2006–2007	Malawi	1773	3	2/3	severe RVGE	38.1% (9.8%-57.3%)	118
RotaTeq™	2001–2004	Belgium, Costa Rica, Finland, Germany, Guatemala, Italy, Jamaica, Mexico, Puerto Rico, Sweden, Taiwan, United States	70,301	First RV season	3	RVGE	74% (66.8%-79.9%)	84
						severe RVGE	98% (88.3%-100%)	
				second RV season		RVGE	62.6% (44.3%-75.4%)	
						severe RVGE	88% (49.4%-98.7%)	
	2001–2004	Finland	23,422	3.1	3	RVGE hospitalizations and ED visits	93.8% (90.8%-95.9%)	88
	2007–2009	Ghana, Kenya, Mali	5560	2	3	severe RVGE	39.3% (19.1%-54.7%)	24
	2007–2009	Bangladesh, Vietnam	2119	2	3	severe RVGE	48.3% (22.3%-66.1%)	27
	2014–2015	China	4173	At least 14 d after the third dose	3	RVGE	69.3% (54.5%-79.7%)	95
						severe RVGE	78.9% (59.1%-90.1%)	
Rotavac™	2011–2013	India	6799	1	3	severe RVGE	53.6% (35.0%-66.9%)	133
				2	3	severe RVGE	55.1% (39.9%-66.4%)	132
RotaSiil™	2014–2015	Niger	4137	28 d after the third dose	3	severe RVGE	66.7% (49.9%-77.9%)	144

Abbreviations: RV, rotavirus; RVGE, RV gastroenteritis; CI, confidence interval; ED, emergency department; N/A, not applicable.
*These selected clinical trials were chosen in terms of the representative researches and the number of participants more than 1500.

visits were 84% (95% CI: 80–87%) in the USA.[104] Since post-licensure data demonstrated that RotaTeq™ was effective against RV disease under routine use, adoption of RV vaccines into expanded national programs would support the World Health Organization's (WHO) recommendation to promote their global use, especially in regions with high RV disease burden and child mortality.

Attenuated human strain RIX4414 (Rotarix™)

Rotarix™, which is based on an attenuated human RV strain, RIX4414, genotype G1P[8], developed by GlaxoSmithKline. This monovalent human-derived RV vaccine was officially recommended for infants, with a two-dose oral regimen at 2 and 4 months of age in the USA in October 2008. Since then, more than 100 countries worldwide have introduced this vaccine (Table 1 near here).

An early efficacy trial demonstrated 72% protection against RVGE and 85% against severe RVGE during the entire follow-up period.[105] Besides, significant protection for 2 y was demonstrated in six European countries, with efficacies of 89.8%, 84.8%, 83.1%, 72.9%, and 58.3% against RVGE caused by circulating G1, G2, G3, G4, and G9 RV types, respectively.[106] Similar to observations in Europe, 63.5% heterotypic protection against severe RVGE caused by the G9 strain was found in Brazil.[106–108] In Latin America, a two-dose regimen of Rotarix™ achieved excellent efficacy rates against any RVGE, severe RVGE, and hospitalizations, as high as 70%, 86%, and 93%, respectively.[109] Moreover, a large phase III trial enrolling 63,225 healthy infants inoculated with two doses of Rotarix™ demonstrated 84.7% and 100% efficacy against severe RVGE and more severe RVGE in 11 Latin American countries and Finland[110] (Table 2 near here). In addition, the following efficacy study reported an overall 80.5% efficacy against RVGE during the entire 2 y.[111] Moreover, a high heterotypic protection against wild-type G9 RV strains (81.8%) was also shown in Brazil.[112] Rotarix™ was deemed not to be associated with an increased risk of intussusception in these studies.

In Singapore, Hong Kong, and Taiwan, vaccine efficacy of Rotarix™ was 96.1% against severe RVGE, 100% against G1, and 93.6% against circulating non-G1 RV types during the first 2 y of life;[113] 100% efficacy against severe RVGE was sustained until the third year.[114] Similar vaccine efficacy against severe RVGE was obtained in other developed countries in Asia, such as Japan[115] and Korea,[116] indicating that Rotarix™ offered high protection among affluent Asian urban populations.

On the contrary, Rotarix™ provided moderate protection (72%) against severe RVGE in Chinese children over two consecutive RV seasons.[117] Yet, one study adopting two or three dose regimens of Rotarix™ among African infants declared an overall efficacy against severe RVGE of 61.2%. Besides, a much lower efficacy was also found in Malawi than in South Africa (49.4% vs. 76.9%) for the first year,[25] indicating the different efficacies between Africa countries. The efficacy of Rotarix™ later reached nadir as low as 38.1% in Malawi and 59% in South Africa during two entire consecutive RV seasons.[118,119] In India, two doses of Rotarix™ induced a moderate seroconversion rate of 58.3% and the seroconversion rate did not interfere by increasing the number of doses.[120,121]

After the licensure of Rotarix™ in 2006, abundant effectiveness studies showed the VE against RVGE hospitalization were 83%, 65–96%, 76–77% in the high-income USA,[104] upper-middle-income Brazil,[122] lower-middle-income Bolivia and El Salvador, respectively.[123,124] Though the majority of real-world data has been generated in high- or middle-income settings, the VE in an African setting with a high prevalence of HIV infection was 57% for two doses and 40% for one dose which was lower than prior studies in middle- or high-income countries.[125] Recent meta-analysis concluded the previous VE studies and suggested that the overall VE was 69%[126] and the VE was 84%, 75%, and 57% in countries with low, medium, and high child mortality, respectively.[103] The analysis of real-world studies showed that Rotarix™ is effective against hospitalizations and/or ED visits due to RV infection. Though the vaccine efficacy and VE in low-income countries with high children mortality due to diarrhea was lower than in well-developed regions, Rotarix™ still saved many lives regardless of theoretic risk of intussusception.[127]

Bovine (strain 116E)-human reassortant RV (Rotavac™)

In the 1990s, two natural bovine-human reassortant RV strains were isolated from two sites in New Delhi and Bangalore, the 116E strain and the I321 strain, respectively.[128,129] As infants infected with either strain were found to be protected against severe disease when re-infected,[130] the two strains were later developed as RV vaccines. The two vaccines, administered orally as single doses of 10^5 fluorescence-forming units (FFU), induced 73% and 39% serum IgA seroconversion rates in the 116E and I321 groups, respectively, in 2005.[131] As the 116E strain was proven to be safe and robustly immunogenic than those for strain I321, clinical trials of strain 116E are further advanced. This vaccine was officially named as Rotavac™ (strain 116E, genotype G9P[11]) manufactured by Bharat Biotech International Limited in India. It was licensed in India in 2014 and launched in the public health system 2 y later (Table 1 near here). This vaccine is given in three doses to infants on the same schedule of diphtheria-tetanus-pertussis vaccine (DTP) 1, 2, and 3.

Vaccine efficacy of Rotavac™ against severe RVGE was 56.3% reported in the first year of life, and 48.9% in the second year of life in a multi-center phase III trial,[132,133] which is comparable to the results for Rotarix™ and RotaTeq™ in developing countries (Table 2 near here). However, the incidence of confirmed intussusception was 94/100,000 child-years among vaccinees and 71/100,000 child-years among the placebo group.[134] Although there was no statistical difference between the treatments, further investigation of the association between vaccination and intussusception is ongoing, using a surveillance system to monitor the safety profile.[135,136] Further, since there is no evidence of potential interference of co-administration with other childhood vaccines, a field trial assessed and confirmed the hypothesis that co-inoculation avoided interference with the immune response to the antigens contained in childhood vaccines.[137,138] In order to examine the role of buffer on the performance of RV vaccines, a phase Ⅳ study assessed whether Rotavac™ without buffer is as effective as the version with buffer added. The results suggested Rotavac™ was well tolerated and immunogenic, in terms of highest geometric mean titer and the proportion of seroconversion, in the absence of citrate-bicarbonate buffer.[139] Overall, Rotavac™ was successfully prequalified by the WHO in January 2018, and these favorable clinical trial results warrant further global marketing and development, expanded the choice of products, improved the global supply of vaccines, and helped to reduce costs.

Bovine (strain UK)-human reassortant RV (RotaSiil™)

The development of Rotarix™ can be traced to an earlier bovine-human RV reassortant tetravalent (BRV-TV) vaccine, incorporating 10 genes from the UK bovine strain and the human RV G1, 2, 3, or 4.[140] The efficacy of BRV-TV was approximately 69% against any RVGE, 79% against moderately RVGE, and 88% against severe RVGE during the first RV epidemic season;[141] Though the vaccine showed no protective efficacy against any RVGE during the second RV epidemic season, the efficacy against severe RVGE was sustained and the number of cases was very small. Subsequently, given the emergence of the novel, epidemiologically important serotype G9, the Serum Institute of India Ltd. (SIIL) collaborated with the national institute of allergy and infectious diseases (NIAID) to develop the lyophilized RotaSiil™ vaccine, containing RV serotypes G1, G2, G3, G4, and G9, which is the only heat-stable RV vaccine available worldwide (storage for 2 y at 37°C; 6 months at 40°C)[142](Table 1 near here). This vaccine is also given in three doses to infants on the same schedule of DTP 1, 2, and 3. RotaSiil™ was found to be safe, immunogenic, and well tolerated in phase Ⅰ & Ⅱ clinical trials.[143] In contrast, RotaSiil™ vaccine efficacies of 34.5%, 66.7%, and 78.8%, against all RVGE, severe RVGE, and very severe RVGE, respectively, were found among infants in a phase Ⅲ trial in Niger[144] (Table 2 near here). Only one confirmed case of intussusception (1/2042) occurred in vaccine group, 542 d after receiving the third dose of RotaSiil™, and was deemed unrelated to vaccination.[145] Similarly, efficacy of RotaSiil™ against severe RVGE and very severe RVGE was 39.5% and 54.7%, respectively, over the entire follow-up period of 2 y in India.[146] In 2016, RotaSiil™ became the second local RV vaccine licensed in India, and the fourth WHO prequalified RV vaccine in September 2018. This novel vaccine shared the same favorable advantages with Rotavac™.

Lamb strain LLR

As the only developed and licensed live RV vaccine in China, the live monovalent oral Lanzhou lamb RV vaccine (LLR) was derived from an ovine RV (G10P[12]) in 1985, which was passaged 37 times in calf kidney cells by the Lanzhou Institute of Biological Products[147] (Table 1). The vaccine, licensed early in 2000 in China, is a liquid formulation, with buffer containing $10^{5.5}$ infectious particles per dose, and recommended for children on the following schedule: one dose annually for those 2 months to 3 y old, then one dose for those 3–5 y old.[147] At the end of 2014, a total of 60 million doses of LLR had been distributed to children in China;[148] However, little data were reported about the safety, immunogenicity, and efficacy of LLR as it has not been confirmed

by designed clinical trials. In 2002–2004, a post-licensure case–control study demonstrated that one dose of LLR vaccine was moderately effective (73.3% protection) in preventing RV disease requiring hospitalization.[147] However, the following study proved that one or two doses of the LLR vaccine conferred partial protection against RV disease, with 43.8% or 44.6% efficacy, respectively, during 2009–2011.[149] Similarly, the overall protection of 35.0% was subsequently identified from October 2011 to March 2012.[148] This may be attributed to the current used regimen of LLR was too complicated to follow, which leads to insufficient coverage of the LLR vaccine in this study. Besides, since the LLR vaccine has not been included into the National Immunization Program and the price is relatively expensive (about 18.4 USD per dose, 74 USD for four doses) in China and people are lack of the awareness of RV, lots of parents are not willing to complete the recommended immunization regimen.[147] According to the report, only 25.3% of children aged 2–59 months received at least one dose of LLR vaccine in Guangzhou (a highly developed urban region in China).[150]

Attenuated human strain G1P[8] (Rotavin-M1™)

The licensed live, oral, RV vaccine (Rotavin-M1™), manufactured by POLYVAC-Vietnam, is derived from an attenuated G1P[8] strain recovered in 2003 from a child hospitalized for acute gastroenteritis[151,152](Table 1 near here). Before the licensure of Rotavin-M1™ in 2014, because the prices of the two available international RV vaccines were unaffordable for Vietnamese children, the government of Vietnam pursued a policy to encourage local bio-companies to address this need. The safety of Rotavin-M1™ was established with no serious adverse events or intussusception were recorded in infants, relative to Rotarix™.[152] Infants aged 6–12 weeks received either two- or three-dose schedules of low titer ($10^{6.0}$ FFU/dose) or high titer ($10^{6.3}$ FFU/dose) vaccines, separately from the OPV. The highest IgA seroconversion rate (73%, 95%CI 58–88%) was achieved in the two-dose schedule with high-dose RV vaccine administrated 2 months apart. Since no more data are available for this vaccine, further post-marketing studies should focus on exploring effectiveness, and the possible association of interference between Rotavin-M1™ and other vaccines administered concomitantly.

RV vaccines in the pipeline

Newborn RV strain RV3-BB

The Australian RV3-BB strain as a potential vaccine is isolated from infants in the first month of life and has completed Phase Ⅰ&Ⅱ clinical trials.[153–157] In the phase Ⅰ trial, one dose of RV3-BB (serotype G3P[6]) was safe and well tolerated. However, low-level immune responses were observed in infants.[158] The phase Ⅱ clinical trial adopted a three-dose regimen (6.5×10^5 FFU/mL), but immune response was still unsatisfactory (46% infants), partially because of limited replication of RV3 in the small intestine, which may be solved by increasing the dose of vaccine. Among the responders, RV3 provided partially heterotypic protection (54%) against challenge by the predominant G1P [8] community strain during the subsequent winter epidemic.[154] In order to increase the infectivity of RV3, a single, higher titer (8.3×10^6 FFU/mL) dose of second-generation RV3-BB vaccine was developed and well tolerated in vaccinees, without any associated adverse reactions in 2013.[155] The immune response to this advanced vaccine was not effected by maternal antibodies and this second-generation vaccine was highly immunogenic, with a positive cumulative response of up to 90% in a phase Ⅱ trial in New Zealand.[156,159] These favorable data support progression of RV3-BB into efficacy trials. Recently, an overall heterotypic protection of 63% in the neonatal-schedule and infant-schedule groups combined was observed in Indonesia.[157,160] Although RV3-BB is efficacious in preventing severe RVGE, further development and assessment are required to determine whether or not RV3-BB can offer protection against a range of circulating RV strains.[161]

Subunit RV vaccines

Since subunit RV vaccines induced specific neutralizing antibodies in preclinical studies,[162–165] the P2-VP8-P[8] protein, consisting of a truncated VP8 subunit from the Wa strain (G1P[8]) of human RV, fused with the P2 epitope from tetanus toxin expressed in *Escherichia coli*, was finally produced at the Walter Reed Army Institute of Research, Pilot Bioproduction Facility (Silver Spring, MD, USA). This subunit RV was found to be well tolerated, with promising immunogenicity, when administered intramuscularly to adults in a clinical trial.[166] All vaccine recipients demonstrated significant IgA responses, and all but one demonstrated IgG responses. Later, this parenteral RV vaccine was also found to be immunogenic in infants, providing an alternative approach for RV disease prevention. Infants also received three doses of the Rotarix™ vaccine at 4, 8, and 12 weeks after the third study injection. The results suggested that P2-VP8-P[8] did not negatively affect the subsequent immune response to Rotarix™, indicating a possibility for concomitant use of parenteral and oral vaccines to achieve optimal protection against severe RV disease.[167] Based on these trial data, a trivalent P2-VP8 (P[4], P[6], and P[8]) subunit vaccine is undergoing testing at three sites in South Africa.[167] A liquid formulation of P2-VP8 is currently undergoing human clinical trials.[168] Additionally, another non-live subunit vaccine candidate consisting of human RV inner-capsid rVP6 protein and norovirus virus-like particles (VLPs) showed 65% protection against heterologous RV challenge regardless of delivery route in preclinical mouse model, which indicating the use of highly conserved VP6 protein could induce non-serotype-specific antibody responses.[169] Based on these results, subunit RV vaccine was considered as alternatives for RV immunization.

Other candidate vaccines

Inactivated RV vaccines (IRVV) are origin from weakened or killed RV strains like human RV strain CDC-9, G2P[8], G3P [8], G9P[8] and G1P[8] and ZTR-68 by stimulating antibodies against RV infection.[170–178] IRVV protected animal models through different challenging routes like oral or intramuscular, microneedle delivery for skin vaccination in preclinical trials. According to several studies, intramuscular inoculation with three doses of IRVV could elicit high serum IgG antibody and neutralizing antibody responses in gnotobiotic piglets,[171] which is similar to the results of mice model.[170,172,175]

The DNA vaccines, RV virus-like particles (RV-VLPs) and recombinant proteins in vitro and in vivo models were found to induce homologous and cross-reactive immune responses.[179–188] Of them, RV-VLPs, which was first reported in the 1980s, are superior to the conventional vaccines because they are conformationally similar to the parent virus and thus able to stimulate both the cellular and humoral immune responses to a greater extent.[189,190] These promising data offer a great experimental basis and research direction for the development of RV-VLPs to reach a reasonable protective immunization level against RV in the future.

Except the above candidates, there are several other RV vaccines in the development with little published data. Firstly, the Instituto Butantan in Brazil developed a live-attenuated bovine-human reassortant RV vaccine containing five viral antigens (G1, G2, G3, G4 and G9). This vaccine showed a good profile of safety and immunogenicity in a phase I study.[191] Second, a live-attenuated bovine-human reassortant RV tetravalent vaccine including antigens against four serotypes was developed by the Sanofi affiliate, Shantha Biotechnics in India. A phase I/II study showed three doses of vaccine were safe, tolerated and immunogenicity in healthy Indian infants.[192] Third, PATH and China National Biotec Group/Wuhan Institute of Biological Products co-manufacture a novel bovine and human hexavalent reassortant RV vaccine candidate.[193] Fourth, a new version of the LLR vaccine, based on the original monovalent vaccine (a tervalent human-lamb reassortant vaccine, combining human RV serotypes G2, G3, G4 with lamb RV genes[194]) was developed and is undergoing clinical trials, whose results are yet to be published. Moreover, a novel liquid formulation of bovine RV pentavalent vaccine (LBRV-PV), stored at 2–8°C, like traditional vaccines, was well tolerated in adults, without safety concerns, indicating the possibility that it could become an alternative RV candidate vaccine, providing end-users with a convenient choice of a ready to use vaccine.[195]

Conclusions and future perspectives

In the last 30 y, we have seen significant progress in the development of RV vaccines. There are six licensed RV vaccines available and a number of RV vaccine candidates undergoing development. Generally, data from current clinical trials and surveillance systems indicate that Rotarix™ and RotaTeq™ are effective against RVGE, and significantly reduced acute hospitalization associated with RV. Also, a cost-effectiveness study in Kenya predicted that cumulatively, over the first 5 y of life, the estimated vaccination costs of US 1,782,761, USD using Rotarix™ or RotaTeq™, would lead to savings of 48,585 disability adjusted life years.[196] Besides, another modeling study estimated that, RV vaccination would prevent nearly 600,000 deaths in Gavi countries and save approximately 484.1 USD million from the government perspective and 878.0 USD million from the societal perspective over the period 2018–27.[197] The high cost-effectiveness of RV vaccines provides a strong argument for their widespread use, particularly in low-income, high-burden settings.[62,198-200] Moreover, the Rotavac™ and RotaSiil™ RV vaccines may provide additional choice in low-income regions, with several great advantages, including heat stability, low cost, and cold-chain footprint.

There are several issues that remain to be addressed for these licensed RV vaccines. First, although licensed RV vaccines are generally tolerated and safe in clinical trials, the occurrence of intussusception caused by RotaShield™ decreased the acceptability of RV vaccines for parents and impeded RV research progress.[201] Since safety is considered the principal parameter for developing any new vaccine, the unexpected intussusception postvaccination with RV vaccines should be monitored closely. For now, abundant post-marketing surveillance data for RotaTeq™ had been reported from Australia and the United States.[202–205] Australian investigators suggested that the risk of intussusception remained low and occurred primarily in the first week after the first immunization. In the United States, researchers suggested that RotaTeq™ is not associated with intussusception. Besides, another study confirmed that the risk of intussusception after administration of Rotarix™ vaccine was not higher than the background risk of intussusception in seven lower-income sub-Saharan African countries.[206] Though data available with Rotarix™ and RotaTeq™ in these regions are insufficient to exclude any risk associated with RV vaccines, but this is outweighed by the large benefits of vaccination. Hence, further active surveillance studies still need to be progressed to determine whether RV vaccines are causally with intussusception or not. Though there are no post-marketing surveillance data available for other licensed RV vaccines at present, the performance during clinical trials indicated that there is no significant increase of risk associated with intussusception. To date, the cause of intussusception post-vaccination remains unknown, necessitating further investigation and surveillance. Apart from the above intussusception, another possible safety issue was the virus shedding which was common post-vaccination with live RV vaccines and may occasionally generate new or unusual RV strains by reassorting. It also can lead to passive transmission in healthy children. The duration of shedding and amounts of virus affect the risk of infection within the unvaccinated infants, which deserves research attention. Hence, strains infecting humans should be closely monitored, using modern sequencing technologies and phylogenetic analyses.

Second, the licensed RV vaccines exhibit great efficacy worldwide; Nevertheless, efficacies in resource-limiting settings were lower than those observed in industrialized settings potentially due to higher disease burden and mortality. Although the reason for this difference has not been thoroughly elucidated, it is possibly associated with preexisting antibodies and differences between circulating RV strains and those used for RV vaccine development. Additionally, other factors such as OPV, concomitant infections, and gut microbiome/intestinal enteropathy might also have a role in the discrepancy. To date, most RV infections globally were attributed to G1P[8], G2P[4], G3P[8], and G4P[8] in the past 30 y;[207] however, rare strains like G2P[6], G9P[4], G12P[6], G12 P[8] recently contributed to a larger proportion of RV infections as the results of circulating genotypes varied by years and regions.[208–210] Strain diversity, resulting from point mutations, genetic reassortment, genome rearrangement, and interspecies transmission, increases the difficulty in developing corresponding RV vaccines as backup.[211–213] Though mass RV vaccine introduction in the future may lead to gradual replacement of circulating genotypes detected in the pre-vaccine period by another in the post-vaccine period, several

pre – and post-licensure studies have shown that Rotarix™, RotaTeq™, and Rotavac™ provide significant protection against severe RV disease caused by a variety of strains in high – and middle-income countries, suggesting that their efficacy/effectiveness may not be serotype-specific.[97,98,106,139]

Third, the simultaneous administration of current RV vaccines with most other vaccines in a routine immunization program showed no significant interference with the protective immune responses or safety profiles of the respective vaccines.[214–220] Nonetheless, potential interference was recorded on co-administration of Rotarix™ with monovalent, bivalent, or trivalent OPV, compared with inactivated polio vaccine. This interference highlights the need for separating RV vaccines and OPV in the EPI schedule and requires further investigation to explore the mechanism and emerging risk.[29,221] Therefore, once a novel RV vaccine is introduced, we should not only consider its safety and efficacy profiles, but also the potential risk of interference with co-administrated vaccines.

Fourth, RV vaccines are recommended for healthy infants, but they are forbidden to infants with human immunodeficiency virus (HIV) infection in the United States at present. RV vaccines are particularly important to specific groups, such as malnourished children, premature infants and infants with acquired immunodeficiency syndrome, who are especially vulnerable to RV. However, clinical trials targeting malnourished children, premature infants and children with acute diarrhea, intussusception, cancer, or HIV infection are exceedingly rare. According to several studies, RotaTeq™ can prevent 73.0% of RVGE and reduce hospitalizations and ED visits in premature infants by 100%.[83,222] Moreover, one study suggested that breastfed and non-breastfed infants were equally protected from the severe consequences of RVGE.[223] However, other studies found that the immune response was not enhanced by withholding breastfeeding and IgA seroconversion in infants immediately breastfed tended to be higher than in those withheld from a feeding.[224,225] Since whether breastfeeding plays a protective role in RV infection is controversial, a meta-review systematically found that there may be no direct correlation between RV diarrhea and breastfeeding.[226,227] In addition, satisfactory immune responses were mounted post-vaccination with Rotarix™ or RotaTeq™ in HIV-positive infants, without aggravating their immunologic or HIV-related parameters; however, the small number of vaccinees did not provide sufficient power to fully assess safety in HIV-infected infants, which therefore requires further evaluation.[228,229]

Fifth, an additional challenge toward increasing the impact of RV vaccination is the need for improving coverage, which still lags behind coverage of DTP and other routine vaccines.[42,230–231] Though the estimated national RV vaccine coverage increased since vaccine introduction in USA in 2013–2015,[104] lower than that of other routine childhood vaccines. Even though RV vaccines have been routinely implemented in major developed countries for a decade, poor medical infrastructure, a lack of refrigerators or dependable electrical supply, and related economic issues in impoverished settings interfere with the implementation of RV vaccines. Since heat stability of the RV vaccine is important for its successful application in areas with less developed cold-chains, development of stable RV vaccines, such as the bovine-human RV reassortant vaccine, RotaSiil™, are necessary for their use in varying local conditions. Besides, as the people most at risk for RV are usually those least able to pay for vaccines, some local vaccine manufacturers in China and India have launched domestic programs for RV vaccine development. Considering the high RV disease burden in low-income settings where have not launched the RV vaccine program yet, great efforts are needed and necessary for improving coverage and encourage the development of suitable vaccines for native populations at an affordable cost.

In conclusion, the current licensed RV vaccines were safe and effective in settings with low child mortality due to diarrhea, but less effective was found in settings with medium and high child mortality. How to improve protection and expand coverage requires further investigation. The ideal RV vaccine should be an efficacious and heat-stable RV vaccine at an affordable price. The future development and introduction of RV vaccines will still require substantial investment in human resources and materials, given the extraordinary performance of introducing RV in developed regions. Hopefully, the introduction of an effective RV vaccine worldwide is promising to reduce the morbidity and mortality of RV-associated gastroenteritis, the disease impact and severe diseases among children <5 y old in the next few years.

Abbreviations

RV	Rotavirus
OPV	Oral poliovirus vaccine
VPs	Viral proteins
NSPs	Nonstructural proteins
P	VP4
G	VP7
RotaTeq™	Bovine (strain WC3)-human reassortant RV vaccine
FDA	Food and Drug Administration
RVGE	RV gastroenteritis
ED	Emergency department
WHO	World Health Organization
Rotarix™	Attenuated human strain RIX4414 vaccine
Rotavac™	Bovine (strain 116E)-human reassortant RV vaccine
FFU	Fluorescence-forming units
RotaSiil™	Bovine (strain UK)-human reassortant RV vaccine
BRV-TV	Bovine-human RV reassortant tetravalent vaccine
SIIL	Serum Institute of India Ltd.
NIAID	National institute of allergy and infectious diseases
LLR	Lanzhou lamb RV vaccine
Rotavin-M1™	Attenuated human strain G1P[8] RV vaccine
RV3-BB	Newborn RV strain G3P[6] RV vaccine
IRVV	Inactivated RV vaccine
RV-VLPs	RV virus-like particles
LBRV-PV	Liquid formulation of bovine RV pentavalent vaccine
HIV	Human immunodeficiency virus

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