CURRENT AND UPCOMING ROTAVIRUS VACCINES

INTRODUCTION

The rotavirus vaccine landscape, or availability of products, has recently expanded considerably and is expected to continue to do so. With the prequalification by WHO of two new vaccines produced in India, there are now four globally available rotavirus vaccines. Additional vaccines are in advanced stages of development and thus the pipeline of rotavirus vaccines will continue to grow in the coming years (see Table 1). The increase in the number of rotavirus vaccines is beneficial for several reasons. It increases the choice countries have in selecting vaccine products and presentations and helps to improve the global supply of rotavirus vaccines to meet current and future demand. The expanded number of products could help lower vaccine costs, a major barrier to introducing rotavirus vaccines in some countries. In addition, some products in development have shown higher rates of efficacy in low-income countries. This brief focuses on the currently available rotavirus vaccines and those most likely to become available in the next several years.

TABLE 1 CURRENT ROTAVIRUS VACCINES AND CANDIDATES IN ADVANCED STAGES OF DEVELOPMENT (MANUFACTURER, COUNTRY)

WHO prequalified	Nationally-licensed	In advanced stages of development
ROTARIX® (GlaxoSmithKline Biologics, Belgium)	Lanzhou Lamb Rotavirus (Lanzhou Institute of Biological Products, China)	RV3-BB (PT Biofarma, Indonesia)
RotaTeq® (Merck & Co., Inc, U.S.A.)	ROTAVIN-M1 (POLYVAC, Vietnam)	LLR reassortants (Lanzhou Institute of Biological Products, China)
ROTAVAC® (Bharat Biotech, India)		Trivalent P2-VP8 (injectable subunit vaccine) (SK Chemicals, South Korea)
ROTASIIL® (Serum Institute of India Pvt. Ltd., India)		

ROTAVIRUS VACCINES PREQUALIFIED BY WHO

There are now four globally available rotavirus vaccines. Both ROTAVAC® and ROTASIIL® have formulations and presentations that differ from other globally available rotavirus vaccines, which may have an impact on costs. All four vaccines prequalified by WHO have shown similar efficacy rates in low-income settings.

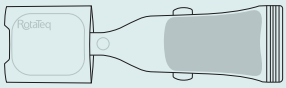
The four rotavirus vaccines prequalified by WHO are RotaTeq® (Merck & Co., Inc.); ROTARIX®, (GlaxoSmithKline Biologics); ROTAVAC® (Bharat Biotech); and ROTASIIL® (Serum Institute of India). All four vaccines are oral, live-attenuated vaccines given to infants starting at 6 to 8 weeks of age, along with other routine vaccines. ROTARIX is provided in two doses given one month apart, while RotaTeq, ROTAVAC, and ROTASIIL have three-dose regimens.

All four prequalified vaccines have been shown to offer protection against a broad range of common rotavirus genotypes—see Table 2 with vaccine efficacy rates.

Rotavirus vaccines currently available on the international market have been shown to be safe. The main safety concern has been a very small increased risk of a rare obstructed bowel syndrome called intussusception, which also occurs naturally in infants regardless of rotavirus vaccination status.

None of the four vaccines were found in clinical trials to increase the risk of intussusception. Post-marketing surveillance of ROTARIX and RotaTeq has found a slightly increased risk of intussusception in some high- and middle-income countries, while no increased risk was found following vaccination with ROTARIX in a pooled assessment of seven African countries.[1,2] Post-marketing safety data on ROTASIIL and ROTAVAC are not yet available (See brief on Rotavirus Vaccine Safety).

SukanyaTassa is administered a dose of ROTAVAC vaccine at Greenwood Tea Estate Hospital in Dibrugarh, Assam, India.



RotaTeq®

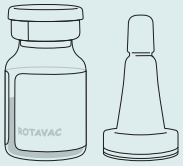
RotaTeq® (Merck & Co. Inc.) is made up of five human-bovine reassortant strains of rotavirus and administered to infants in the same three-dose schedule as DTP1, 2, and 3. RotaTeq was licensed by the U.S. Food and Drug Administration (FDA) in 2006 after clinical studies in high-income countries showed a range of efficacy from 98–100% against severe rotavirus gastroenteritis in children.[3,4] In studies in low- and middle-income countries, the vaccine was 43–64% protective against severe rotavirus gastroenteritis.[5,6] Studies show that RotaTeq protects children against a wide range of rotavirus strains, including those not included in the vaccine.

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

ROTARIX®

ROTARIX®, manufactured by GlaxoSmithKline (GSK), is made up of a single attenuated human strain of rotavirus. It is administered to infants in two doses on the same schedule as DTP1 and 2. ROTARIX was first licensed by the European Medicines Agency in 2006 and in the U.S. by the FDA in 2008 following efficacy studies that showed 85–96% protection against severe rotavirus gastroenteritis in high-income countries.[7,8] Studies found that the efficacy of ROTARIX in low- and middle-income countries was between 49–77% against severe rotavirus gastroenteritis.[9] ROTARIX protects children against a wide range of rotavirus strains, including those not included in the vaccine.

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

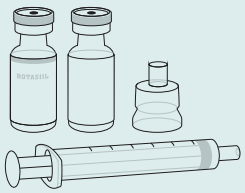


ROTAVAC®

ROTAVAC®, manufactured by Bharat Biotech, is made up of a single strain of human rotavirus that is naturally attenuated. After a phase 3 trial in India found that the vaccine provided 54% protection against severe rotavirus gastroenteritis in the first year of life and 49% in the second year of life, ROTAVAC was licensed by the Government of India in 2014.[10,11]

The vaccine is stored frozen (−20°C) and can be thawed out and kept in a refrigerator at 2-8°C for up to six months. Importantly, it can be refrozen and rethawed six times.[12]

ROTAVAC is administered on the same schedule as DTP1, 2, and 3, by attaching a dropper to the vial and placing five drops in the infant's mouth. Bharat has also developed a liquid (non-frozen) formulation (ROTAVAC 5CM); a trial comparing the immune response to this vaccine with that of the current formulation is being conducted in Zambia.[13]



ROTASIIL®

ROTASIIL® is made up of five bovine-human reassortant rotavirus strains, which Serum Institute of India licensed from the U.S. National Institutes of Health. Administered in three doses at the same time as DTP1, 2, and 3, ROTASIIL® was found in India to provide 36% protection against severe rotavirus diarrhea over a 10-month period and nearly 40% over two years.[14] In Niger, another trial that showed it provided 67% protection against severe rotavirus gastroenteritis during one year of follow-up.[15] ROTASIIL was licensed by the Government of India in 2017.

The vaccine is a freeze-dried powder that is reconstituted with an antacid diluent just before using. It has been found to be stable for three years at or below 25°C (77°F); WHO recommends refrigeration (see Table 2).[15,16] Serum Institute of India is also developing a fully liquid, ready-to-use presentation.

TABLE 2 MAIN CHARACTERISTICS OF THE ORAL, LIVE-ATTENUATED ROTAVIRUS VACCINES PREQUALIFIED BY WHO (APRIL 2019)

Vaccine name	RotaTeq®	ROTARIX®	ROTAVAC®	ROTASIIL®
Manufacturer	Merck & Co. Inc.	GlaxoSmithKine	Bharat Biotech	Serum Institute of India
Composition/ strains	5 human-bovine reassortant rotaviruses (G1, G2, G3 G4, P[8])	Single, attenuated human rotavirus strain (G1P[8])	Single, attenuated human rotavirus strain (G9P[11])	5 human-bovine (UK) reassortant rotaviruses (G1, G2, G3, G4, G9)
Dosing schedule	3-dose (same as DTP 1, 2, 3)	2-dose (same as DTP 1 and 2)	3-dose (same as DTP 1, 2, 3)	3-dose (same as DTP 1, 2, 3)
Efficacy against severe rotavirus gastroenteritis in:				
High- and upper-middle-income	98–100%[3, 4]	85–96%[7, 8]	No data	No data
Low- and lower-middle-income	43–64%[5, 6]	49–77%[9]	56% (in India)[10, 11]	– 36% (in India)[14] – 67% (in Niger)[15]
Presentation	Liquid vaccine suspended in a buffer (oral squeeze tube)	– Liquid vaccine (oral applicator) – Liquid vaccine (squeeze tube) – Freeze-dried vaccine reconstituted with buffer (oral applicator)	Liquid in glass vial (separate droppers)	Freeze-dried vaccine (lyophilized) in glass vial reconstituted with antacid diluent from separate vial (oral syringe)
Dosage volume	2.5 mL	– 1 mL (liquid) – 1.5mL (freeze-dried)	.5 mL	2.5 mL
Doses per container	1	1	5, 10 Single dose (cold chain storage volume: 45cm³ per dose) is available but not listed on WHO Prequalified vaccines database	1, 2
Storage and shelf life	– Refrigerated (2–8°C): 24 months – Cannot freeze	– Refrigerated (2–8°C): 36 months – Cannot freeze	– Refrigerated (2–8°C) at local level: 6 months – Frozen (–20°C) at central and district level: 5 years – Can be frozen-thawed up to 6 times without losing potency	– (Vaccine) Refrigerated (2–8°C): 30 months (per WHO prequalification) – (Diluent) Ambient temperature or refrigerated (2–8°C): 60 months – Once reconstituted, can be refrigerated (2–8°C) for up to 6 hours[16]
Cold storage volume per course[17, 19]	139 cm³ (in cartons of 25 doses)	34 cm³ (for single-dose squeeze tubes) (in cartons of 50 doses)	– 5-dose: 12.6 cm³ – 10-dose: 9.6 cm³	– 1-dose vials: 53 cm³ (excl. diluent) – 2-dose vials: 32 cm³ (excl. diluent)
Vaccine vial monitor	No	Yes (VVM14)	Yes (VVM2)	Yes (VVM30)
UNICEF price per course for Gavi-supported countries, 2020 (USD, not adjusted for wastage)[17, 18]	$9.60 (RotaTeq is no longer an option available to Gavi-supported countries)	$4.58	$2.55	$4.65 (1-dose vial) $2.85 (2-dose vial)

NATIONALLY-LICENSED ROTAVIRUS VACCINES

Two vaccines are licensed for domestic use and available through the private sector only. Uptake of these vaccines has been much lower than vaccines included in the countries' national immunization programs.

Lanzhou lamb rotavirus vaccine (China)

The Lanzhou lamb rotavirus (LLR) vaccine, available in China since 2000, is given to children between the ages of 2 and 35 months each year for 3 years. It is an oral live, attenuated vaccine made from a single strain of rotavirus found in lamb (G10P[12]). While efficacy data is not publicly available, various case-control studies have estimated its effectiveness. These estimates, each using different outcome measures, include 77% for one dose against hospitalized rotavirus gastroenteritis among children under 2 years of age and 81% among 2–11 month olds,[19] 39% against moderate or severe rotavirus illness for at least one dose in children under 5,[20] and 44% for one dose against rotavirus diarrhea of any severity presenting at a health center or hospital.[21]

The vaccine has not been integrated into the national immunization program, so parents must pay the full cost of the vaccine (about $72 for the three-dose series). A survey conducted in Guangzhou Province in 2013 found that 25% of 2–59 month olds had been vaccinated—90% with only one dose—while coverage among 2–5 month olds was around 1%.[22]

Additional animal-human reassortant vaccines are currently in development in China, including a new-generation trivalent human lamb reassortant vaccine at Lanzhou Institute. The Wuhan Institute of Biological Products is also developing human bovine reassortants derived from a strain obtained from the U.S. NIH, that was used to develop ROTASIIL.[23,24]

ROTAVIN-M1 (Vietnam)

This oral, live-attenuated vaccine, consisting of a single human rotavirus strain (G1P[8]) administered in two doses two months apart, was licensed in Vietnam in 2012.[25] An effectiveness study is currently underway.[23,26] The vaccine is available in the private sector at a price of approximately $17.60 per dose.[27]

An infant in Vietnam, where ROTAVIN-M1 has been licensed.

THE NEW FRONTIER

Several rotavirus vaccines are being developed using different approaches in the aim of increasing their effectiveness and impact in low-income countries and further improving their safety profile.

Neonatal vaccines

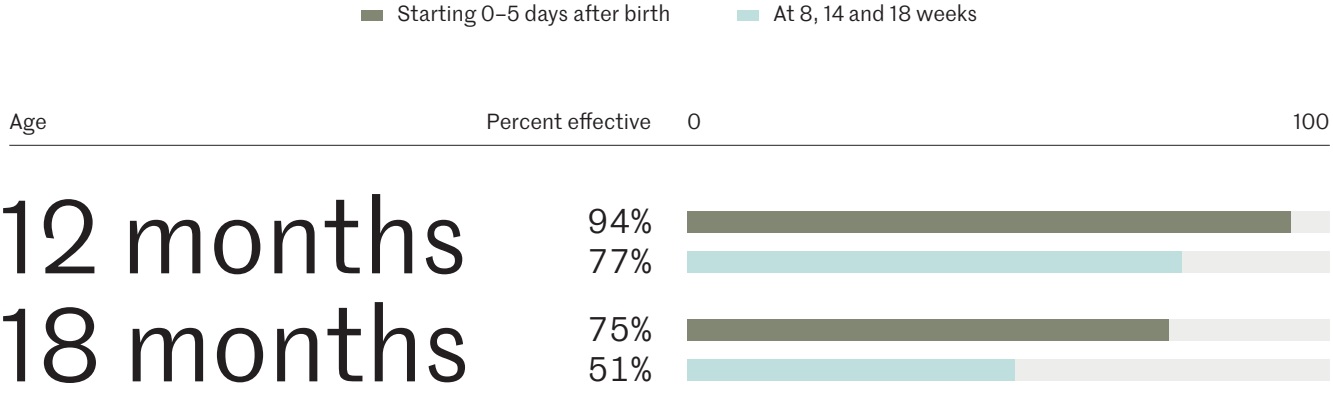
Vaccines given shortly after birth have several potential advantages over current rotavirus vaccines. They can potentially be more effective in impoverished settings because newborns do not yet produce much gastric acid and their intestines are not yet damaged by infections that can lead to malabsorption and reduced immune responses to the vaccine.[28] In addition, neonatal vaccines could provide early protection against the disease and improve vaccination coverage, since vaccines given shortly after birth (such as BCG) typically have higher coverage rates. They could also further reduce the risk of intussusception, since this condition is not known to occur in newborns.

An oral live vaccine candidate has been developed by Murdoch Children's Research Institute in Australia from a naturally-attenuated human strain found in newborns (G3P[6]) that doesn't cause disease and that replicates well in the newborn gut. This is true even in the presence of maternal antibodies and when an infant is breastfed—thus making it well adapted to newborns.[28] The vaccine, neonatal RV3-BB vaccine, has been licensed to PT Biofarma in Indonesia. When administered in three doses starting 0–5 days after birth, the vaccine was found in a Phase 2b clinical trial in Indonesia to be well-tolerated and to provide better efficacy rates than the same vaccine given in a typical schedule—see Figure 1. Efficacy rates also compare favorably with those of globally-available vaccines in low- and middle-income countries. Ongoing development of RV3-BB is underway in Indonesia by BioFarma with plans to have the vaccine available to infants in the Indonesian National Immunization Program, and prequalified by WHO.

Non-replicating, injectable vaccines

Non-replicating vaccines are either killed rotaviruses or just parts ("subunits") of the virus that, unlike current live, oral vaccines, do not require multiplying in the gut to induce immunity. These vaccines, inspired by the successes of the injectable inactivated polio vaccine, are given through injection, thereby bypassing the gut. They could potentially be more effective than oral vaccines in low-income settings by avoiding factors that may limit immune responses in the intestine, such as gut inflammation, malnutrition, or co-infections. By avoiding the gut, these vaccines should also reduce the increased risk of intussusception associated with rotavirus vaccination. However, there are questions as to whether they can protect against rotavirus disease as well as live, oral vaccines. Additional studies are being planned to evaluate the efficacy of the trivalent P2-VP8 non-replicating rotavirus vaccine candidate against severe rotavirus disease following positive safety and immunogenicity results from a Phase 2 clinical study in South Africa.[29]

FIG.1 EFFECTIVENESS OF NEONATAL RV3-BB VACCINE BY DOSAGE SCHEDULE AND AGE OF CHILD [28]



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CURRENT AND UPCOMING ROTAVIRUS VACCINES

KEY FACTS

Products

With the recent WHO prequalification of two rotavirus vaccines developed and produced in India, there are now four rotavirus vaccines available on the international market. (See page 1)

Expansion

This expansion of the choice of products, formulations, and presentations available to countries; improves the global supply of vaccines to meet demand; and may help to reduce their costs. (See page 3)

Profile

All four globally-available rotavirus vaccines are oral, live-attenuated, and given in two or three doses to infants. (See page 4)

Future

Several rotavirus vaccines using novel approaches aimed at increasing their impact in low-income settings are in advanced stages of development, including a neonatal vaccine, and a non-replicating rotavirus vaccine administered by intramuscular injection. (See page 6)

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