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COMMENTARY

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Improving rotavirus vaccine coverage: Can newer-generation and locally produced vaccines help?

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ABSTRACT

There are two internationally available WHO-prequalified oral rotavirus vaccines (Rotarix and RotaTeq), two rotavirus vaccines licensed in India (Rotavac and Rotasiil), one in China (Lanzhou lamb rotavirus vaccine) and one in Vietnam (Rotavin-M1), and several candidates in development. Rotavirus vaccination has been rolled out in Latin American countries and is beginning to be deployed in sub-Saharan African countries but middle- and low-income Asian countries have lagged behind in rotavirus vaccine introduction. We provide a mini-review of the leading newer-generation rotavirus vaccines and compare them with Rotarix and RotaTeq. We discuss how the development and future availability of newer-generation rotavirus vaccines that address the programmatic needs of poorer countries may help scale-up rotavirus vaccination where it is needed.

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Background

Globally, there were an estimated 215,000 rotavirus deaths in children under 5 years of age in 2013, of which 121,000 (56%) occurred in sub-Saharan Africa and 47 100 (22%) occurred in India.[1] Two WHO-prequalified and internationally licensed live-attenuated rotavirus vaccines are currently available: Rotarix (GlaxoSmithKline Biologicals, Belgium), a monovalent vaccine derived from an attenuated human strain and RotaTeq (Merck, USA), a pentavalent human–bovine reassortant vaccine. In addition, there are two rotavirus vaccines licensed in India, one in China and one in Vietnam and several rotavirus vaccine candidates in the pipeline. Since 2009, the WHO Strategic Advisory Group of Experts has recommended that infant rotavirus vaccination be included in national immunization programs, especially in high diarrheal disease burden settings and the first dose should be given at 6 to 12 weeks of age to reduce the rotavirus disease peak at 6 months of age.[2]

Pooled efficacy estimates of Rotarix and RotaTeq against severe rotavirus gastroenteritis in industrialized countries is 88% and 83% during the first and second year but much lower in countries with high under-five mortality rates[3] (Table 1). A systematic review of vaccine effectiveness confirms the differential protection in rich versus poor countries and the decline during the second year.[4] Despite the lower protection conferred by Rotarix and RotaTeq in high child mortality settings, the public health benefits of rotavirus vaccination is greater in these countries because of the larger absolute number of severe rotavirus gastroenteritis prevented per number of vaccine doses administered.[5] It is the protection during the first year of life that is particularly important because infants are especially vulnerable.[6]

Rotavirus vaccine introduction in low- and middle-income countries

Generally, new vaccines are introduced in low- and middle-income countries long after their availability in high-income countries. With the support of Gavi, the Vaccine Alliance, and other partners, this delay has shortened. The rotavirus vaccine was the first vaccine concomitantly introduced into the USA and a Gavi-eligible country (Nicaragua) during the same year; followed soon by other Latin American countries.[7] As of December 2, 2016, 82 countries have added rotavirus vaccination to their national infant immunization schedule and an additional six countries have introduced the vaccine sub-nationally.[4]

The impact of Rotarix and RotaTeq on childhood gastroenteritis following inclusion in national immunization programs in Latin American and sub-Saharan African countries is significant and unequivocal.[4] Despite these achievements, the full potential of rotavirus vaccination in low income countries is still to be realized.[8] Sub-Saharan African countries have started to include rotavirus vaccine in their national programs,

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Table 1. A comparison of rotavirus vaccines.

	Internationally-available		Licensed for national markets			
Name	Rotarix	RotaTeq	Rotavac	Rotasiil	LLR	Rotavin-M1
Manufacturer, country	GlaxoSmithKline Biologicals, Belgium	Merck, USA	Bharat Biotech International Limited, India	Serum Institute of India Limited, India	Lanzhou Institute of Biological Products, China	Center for Research and Production of Vaccines, Vietnam
Strain(s) present in vaccine	Attenuated human G1P[8] strain	Human-bovine reassortant strain with G1, G2, G3, G4, and P[8] proteins	Human G9, P[11] strain	Human-bovine reassortant pentavalent (G1-G4, G9) strain	Lamb G10P[12] strain	Human G1P[8] strain
Presentation	1. Liquid vaccine in oral, single-dose applicator 2. Liquid vaccine in squeezable, polyethylene single-dose tube 3. Lyophilized vaccine, reconstituted with calcium carbonate buffer and oral applicator	Liquid vaccine in oral, squeezable tube	Liquid vaccine in single- and multi-dose vial. Liquid antacid buffer given before the vaccine	Lyophilized vaccine, reconstituted with calcium carbonate buffer	Liquid vaccine with buffer	Liquid vaccine in single-dose vial.
Vaccine vial monitor (VVM) on label[15]	Yes, VVM 14	None	Yes, VVM 2	Yes, VVM 30	None	None
Storage requirements	2 to 8° C, not frozen and protected from light	2 to 8° C, not frozen and protected from light	Frozen at $-20°C \pm 5°C$	Stable at 37°C for two years and 40°C for six months	2 to 8°C	Frozen at $-20°C \pm 5°C$
Route of administration	Oral	Oral	Oral	Oral	Oral	Oral
Number of doses and schedule of administration	Two doses, given on same schedule as DPT vaccine	Three doses, given on same schedule as DPT vaccine	Three doses, four weeks apart, beginning at 6 weeks of age	Three doses, four weeks apart, beginning at 6–8 weeks of age	One dose every year for three years between 2 and 35 months of age	The first dose from 6 weeks of age. The second dose after 1–2 months. Should be given before 6 months of age.
Vaccine efficacy (95% CI) against severe rotavirus gastroenteritis during the first year, developing country study location	61% (44 to 73%), South Africa and Malawi[33]	59% (40 to 72%), Ghana, Kenya, Mali, Bangladesh and Vietnam[34]	56% (37 to 70%) Delhi, Pune and Vellore[16]	67% (50–78%), Niger[18]	Not available	Not available
Licensure and WHO prequalification[15]	Internationally licensed, Prequalified in 2007	Internationally licensed, Prequalified in 2008	Licensed in India	Licensed in India	Licensed in China	Licensed in Vietnam
Price per vaccination course	From approximately US$0.50 in GAVI-eligible countries up to US$185–$226 in the USA[1]		US$ 2.50[2]	US$ 6.00 maximim[3]	US$ 24.00[4]	US$ 17.60[5]

[1]Price varies depending on the country[12]
[2]Each dose of Rotavac will be available at about 54 Indian Rupees equivalent to US$0.84[35]
[3]Each dose of Rotasiil will be available at under US 2.0. A Gavi subsidized price will also be available.
[4]The cost for a single dose of LLR is US$24.00 as it is listed as a second-category vaccine and fully charged to users[36]
[5]Each dose of Rotavin-M1costs around VND200,000 equivalent to US$8.80[37]

although at varying degrees of coverage with many facing barriers to rollout. There is a notable lack of rotavirus vaccine introductions into national immunization programs in Asia despite the well-characterized burden of rotavirus disease.[9] Recent work in Matlab, Bangladesh demonstrated a one third reduction in rotavirus diarrhea presentations to treatment facilities among the entire population of age-eligible infants when 70% received at least one dose of Rotarix.[10] In the Philippines, where Rotarix was gradually provided through public health centers in Agusan del Sur starting in 2012, infant diarrhea hospitalizations and outpatient consultations decreased during the 3 years following vaccine introduction.[11]

Gavi provides funding for vaccine introduction in low-income countries but these countries must commit to continuing the vaccination program after Gavi support ends.[12] Countries with large birth cohorts will most likely be impacted by vaccine costs as they transition from Gavi support.[13] Non-Gavi eligible lower-middle- and middle-income countries face challenges in introducing new vaccines; they have to consider the costs of purchasing rotavirus vaccine against other public health interventions. Lack of knowledge about rotavirus or misconceptions about the burden of rotavirus diarrhea and vaccine cost-effectiveness among public health providers and policy makers; concerns about the sustainability of time-limited vaccine subsidies from Gavi; the need to increase existing EPI storage and transport capacity and competing priorities for introduction of other new vaccines have been cited as constraints to wider rotavirus vaccine introduction.[14]

In this forum, we discuss how the varying characteristics of rotavirus vaccines licensed for national markets and candidates in the pipeline may be able to meet the needs of different national programs to increase rotavirus vaccine introduction.

Rotavirus vaccines licensed for national markets

A comparison of Rotarix, RotaTeq and the rotavirus vaccines licensed in India, China and Vietnam is shown in Table 1. Although all six vaccines are given orally, there are differences in presentation, storage requirements, recommended number of doses and schedule of administration. All six vaccines are in liquid form except for one, which is lyophilized and reconstituted with buffer prior to administration. The storage requirements range from room temperature, to refrigeration, to freezing. Currently, vaccine vial monitors (VVM) have been validated for use with three vaccines.[15] The various rotavirus vaccine regimens include 2 to 3 doses in infancy versus one annual dose from 2 months to 35 months of age (Table 1).

Rotavac (Bharat Biotech International Limited) is a monovalent human-bovine rotavirus vaccine. The vaccine consists of the 116E rotavirus strain, which is a naturally occurring reassortant strain G9P[11], containing one bovine rotavirus gene P [11] and ten human rotavirus genes.[16] A large double-blind, randomized placebo-controlled, multicenter trial at three sites in Delhi, Pune and Vellore showed that the vaccine was well-tolerated with an efficacy against severe rotavirus gastroenteritis of 56% (37 to 70%) in the first year of life.[16] Following licensure in India in 2014, the country introduced routine vaccination using Rotavac in four states (Odisha, Andhra Pradesh, Haryana and Himachal Pradesh) with plans to scale-up nationwide.[17] Bharat Biotech is seeking WHO prequalification of the vaccine, which will make it eligible for purchase by United Nations procurement agencies and by Gavi.

The Serum Institute of India Limited, in collaboration with the USA National Institute of Allergy and Infectious Diseases and PATH developed a live attenuated human-bovine reassortant rotavirus pentavalent vaccine, containing serotypes G1, G2, G3, G4, and G9 (Rotasiil). Rotasiil is lyophilized and supplied with a citrate bicarbonate buffer that is added for reconstitution just before oral administration. The vaccine is stable at 37°C for two years and 40°C for six months.[18] A randomized double-blind, placebo-controlled trial in Niger, where the vaccine was given out of cold chain, showed a vaccine efficacy against severe rotavirus gastroenteritis of 67% (50–78%) during one year of follow-up.[18] A Phase III multi-center trial of Rotasiil has been completed in India and data will be published soon.[15] The vaccine recently received approval from the Drug Controller General of India and is undergoing assessment for WHO prequalification.

The Lanzhou Lamb rotavirus vaccine (LLR), a monovalent lamb vaccine strain, G10P[12], attenuated by cell passage, is manufactured by the Lanzhou Institute of Biological Products and was licensed in China in 2000.[19] From 2008 to 2014, 60 million doses of LLR were distributed to children in the country. The efficacy of LLR has not been confirmed in a placebo-controlled Phase III clinical trial but vaccine effectiveness in children under 5 years of age was recently estimated at 35% (13 to 52%) against rotavirus diarrhea and 53% (15 to 75%) against moderate to severe rotavirus diarrhea through a large case-control study.[20]

Rotavin-M1 rotavirus vaccine is manufactured by the Center for Research and Production of Vaccines and Biologicals and was licensed for use in Vietnam in 2012. The vaccine was derived from an attenuated strain, G1P[8], isolated from a Vietnamese child. A clinical trial found the vaccine to be safe and immunogenic in Vietnamese infants.[21] Currently the vaccine is only available in the private market. An effectiveness study will be starting soon.[15]

Rotavirus vaccines in the pipeline

There are several candidate rotavirus vaccines in the pipeline. RV3–BB, is being developed as a vaccine for administration at birth. RV3 is a human neonatal rotavirus strain that is associated with asymptomatic neonatal infection and replicates well in the infant gut.[22] A single-center, double-blind, randomized placebo-controlled Phase 1 study found that a single dose of RV3–BB rotavirus vaccine was well tolerated in adults, children and infants.[22] A Phase 2a trial in New Zealand of 95 neonates showed that the vaccine is safe and well tolerated.[23] A Phase 2B trial of safety, efficacy & immunogenicity is currently underway in Indonesia. The Instituto Butantan in Brazil is developing a second candidate, a live-attenuated bovine-human reassortant rotavirus vaccine, containing five viral antigens. A Phase 1 clinical trial in 79 adult volunteers showed that the vaccine is safe and immunogenic.[24] Third, a live attenuated bovine-human reassortant rotavirus tetravalent vaccine (BRV-TV) including antigens against four serotypes is being developed by the Sanofi affiliate, Shantha Biotechnics in India. The vaccine consists of three, ready-to-use liquid doses administered orally, starting

from six-to-eight weeks of age, with the subsequent doses administered at 4 week intervals. A Phase 1/ 2 study showed that the vaccine is safe, well tolerated and immunogenic.[25] The vaccine is currently in Phase 3 clinical trials. Fourth, PATH and China National Biotec Group/Wuhan Institute of Biological Products (WIBP) announced a partnership to manufacture a bovine-human reassortant hexavalent vaccine. The phase I study has been completed. Fifth, a parenteral rotavirus vaccine (P2-VP8 subunit rotavirus vaccine) was developed at the NIH, USA. A Phase 1 study will examine the safety and immunogenicity of this vaccine first in healthy South African toddlers. If the safety profile is deemed appropriate, the study will continue to explore the safety and immunogenicity of the vaccine in healthy South African infants.[26] Seventh, the Lanzhou Institute of Biological Products is developing a trivalent genetic reassortant rotavirus vaccine that includes G2, G3 and G4 with the lamb strain from the LLR as the backbone. The phase 3 trial was recently completed.

Rotavirus vaccine characteristics that may increase deployment in developing countries

Without Gavi support, the costs of the two internationally available rotavirus vaccines are unaffordable to poor countries. In addition, the global supply of rotavirus vaccines is constrained. Thus the recent licensure of rotavirus vaccines in India with pending applications for WHO pre-qualification could be a game changer for countries ineligible for or graduating out of Gavi. Aside from India, countries with large birth cohorts such as China, Vietnam and Indonesia traditionally wait to widely introduce a new vaccine until a locally manufactured product is ready and supplies are sufficient. The increased availability of several locally produced rotavirus vaccine may expand and sustain rotavirus vaccine coverage in these countries.

One rotavirus vaccine, Rotasiil can be delivered out of cold-chain,[27] which may be a huge advantage in many impoverished settings where there is a lack of refrigerators and dependable electrical supply. Cold chain issues have been repeatedly identified as barriers to vaccine delivery. Moreover, cold-chain demands are increasing with the introduction of new vaccines and the ability to forgo refrigeration may help improve access to remote and difficult to reach populations.

Another important characteristic of rotavirus vaccines is the age of administration and number of doses. The RV3–BB is being developed for administration at a younger age and with a decreased number of required doses. The impact of rotavirus vaccines is maximized when given early in life, before exposure to the first symptomatic natural infection, which is usually the most severe.[28] In cohort studies in India, Guinea-Bissau and Mexico 53, 26 and 34% of children were infected by 6 months of age.[29-31] In Niger, children less than 6 months of age accounted for 17% of all rotavirus-positive cases and those 6–11 months of age accounted for 62%.[32]

Conclusions

There are major opportunities for increasing the rollout of rotavirus vaccines. Whether the availability of newer-generation and locally produced vaccines will accelerate rotavirus vaccine implementation and coverage in low- and middle-income countries remains to be seen. Lower cost with comparable efficacy and thermostability are important characteristics that may enhance their use. National cost-effectiveness analyses are much needed to make the case for vaccine introduction. With the increasing availability of locally manufactured vaccines, the potential availability of a greater supply will extend the opportunity for national programs and other partners to procure vaccine.

Disclosure of potential conflicts of interest

ALL, SK, XW, DDA and RG were study investigators of rotavirus vaccine trials in the Philippines, India, China, Vietnam and Niger, respectively. MT is working on a research grant from Merck. There are no other conflicts of interest.

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