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Rotavirus vaccination in developing countries

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Although two oral rotavirus vaccines are licensed in many countries, multiple factors may affect decision-making regarding introduction into national immunization programs in developing countries. Financial and logistic challenges to introduction of rotavirus vaccines in countries with limited infrastructure and resources are accompanied by a perceived lack of need and evidence from recent vaccine trials, which demonstrated significantly lower efficacy in high burden countries. Nonetheless, even at a low efficacy, the use of existing vaccines in developing countries is predicted to alleviate considerable rotavirus disease burden and mortality. Potential alternate strategies for improving response to existing vaccines or the development of improved vaccines need to be considered to ensure that the remaining burden of mortality and morbidity can be addressed in the future.

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Introduction

Rotavirus is responsible for at least 36% of all diarrhea admissions and for an estimated 37% of diarrhea deaths, translating to 453 000 deaths in children <5 years of age across the world. Developing countries bear the major burden of mortality with 5 countries, India, Nigeria, Pakistan, Ethiopia and the Democratic Republic of the Congo contributing the majority of deaths [1••].

The development and deployment of rotavirus vaccines was a major breakthrough in the fight against diarrheal diseases. Two rotavirus vaccines are licensed and widely available in several countries, Rotarix™ and Rotateq®, and many countries have included rotavirus vaccination in their national immunization schedule. The use of these vaccines has now been shown to clearly translate to a large decrease in hospital admissions due to rotaviral and all-cause diarrhea in these settings [2]. In 2009, the Strategic Advisory Group of Experts (SAGE) on immunization at the World Health Organization (WHO) recommended that rotavirus vaccination be included in the national immunization schedule for all member states. This recommendation was based on the evidence from the rotavirus vaccine trials in developing countries of Asia and Africa, which though demonstrating a lower efficacy, comprehensively showed the decrease in absolute number of rotavirus-specific and all cause diarrheal episodes. The post licensure data from Latin-American countries on decrease in disease and mortality also strengthened this recommendation [3]. The WHO is actively involved in mobilizing resources to purchase rotavirus vaccines for low-income countries eligible for support through the GAVI Alliance [4]. Among the GAVI eligible countries, Sudan introduced the vaccine in 2011 and several other countries have been approved for support by GAVI during the next few years.

However, there are several barriers in developing countries that may result in a lower impact than has been seen in more industrialized nations, which may require a consideration of additional or alternative approaches.

Rotavirus vaccine efficacy

In pre-licensure vaccine trials, the two currently licensed vaccines, Rotarix™ and Rotateq®, had shown very high efficacy in the Americas and in Europe [5,6]. Efficacy trials with Rotarix™ were also conducted in Taiwan, Singapore and Hong Kong, which are high-income settings in Asia, and reported a vaccine efficacy of 96%, comparable to that seen in northern Europe and America [7].

In post-licensure efficacy trials that were carried out in resource-poor Africa and Asia as recommended by the WHO, vaccine efficacy was much lower (Table 1) [7,8••,9••,10••]. Although the studies were powered for combined efficacy across sites, there were remarkable differences in efficacy in different countries, only partially explained by the socio-economic status of the communities. Before the trials, poor efficacy of these vaccines in developing countries was considered a distinct possibility, given that previous rotavirus vaccines had failed in Africa after showing high efficacy levels when tested in industrialized countries [11,12•]. Similar findings with oral polio vaccines, where three doses result in near universal seroconversion to all three polioviruses in industrialized countries, but each dose results in a calculated efficacy of only 13% in some parts of India [13], also made it essential to carry out rotavirus vaccine efficacy studies in the areas where the vaccines are most needed.

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Table 1

Efficacy of rotavirus vaccines in the Asian and sub-Saharan Africa region

	Vaccine	No. of children enrolled	Percent efficacy (CI)	Reference
Asia				
Bangladesh	Rotateq®	1136	42.7 (10.4–63.9)	[8••]
Vietnam		900	63.9 (7.6–90.9)	
Taiwan	Rotarix™	1141	96.1 (85.1–99.5)	[7]
Singapore		6542	85.1–99.5	
Hong Kong		3025	96.1 (85.1–99.5)	
Africa				
South Africa	Rotarix™	1944	76.9 (56.0–88.4)	[9••]
Malawi		1030	49.4 (19.2–68.3)	
Ghana	Rotateq®	2162	55.5 (28.0–73.1)	[10••]
Kenya		1221	63.9 (−5.9–89.8)	
Mali		1842	17.6 (−22.9–45.0)	

However, despite the poor efficacy in low-income high mortality countries, it was clear that the vaccines had a greater public health impact in areas with a high disease burden. In the Rotarix™ study, although the vaccine showed 76.9% efficacy in South Africa and 49.4% efficacy in Malawi, vaccination prevented 4.2 episodes of severe rotavirus gastroenteritis per 100 child years in South Africa but 6.7 episodes per 100 child years in Malawi, because the background rate of severe rotavirus gastroenteritis is about 2.4 times greater in Malawi [9••].

Effectiveness of rotavirus vaccines in low-income and middle-income countries

Unlike vaccines given parenterally where the goal is eradication of disease by prevention of infection, the concept of vaccine effectiveness becomes important for orally delivered vaccines where sterilizing immunity or eradication of infection is not possible. An effective oral vaccine decreases the burden of severe disease but does not necessarily prevent infection.

Vaccine effectiveness studies done in Latin American countries, where the rotavirus vaccine has been introduced as part of the national immunization schedule have shown a significant decrease in the admission rates due to rotavirus diarrhea. A comprehensive review of publications from Latin America, has shown that in Mexico, Brazil, El Salvador and Panama, use of vaccine resulted in 22–41% reduction diarrhea-associated mortality, a 17–51% decrease in hospitalizations for diarrhea and a 59–81% decrease in rotavirus associated gastroenteritis hospitalizations in children less than five years of age [14•]. Case–control studies in Brazil and El Salvador showed 76–85% effectiveness in reducing rotavirus associated hospitalizations [15,16]. However, in Nicaragua, the only low-income country with published data, a similar case–control design showed a lower effectiveness of 46%. Even so, in Nicaragua, diarrhea related deaths came down from 1.03/100 000 child years in the pre vaccination period to 0.82/100 000 child years. The effect is more dramatic in the rotavirus season, where the incidence of diarrhea deaths decreased by 31% [17].

Projected impact with use of rotavirus vaccines in low-income and middle-income countries

Except Sudan, which introduced rotavirus vaccination in late 2011, none of the developing countries in the South–East Asian and sub-Saharan Africa region had implemented the vaccination in their national immunization program at the end of 2011. The impact of rotavirus vaccine introduction in the Latin American countries and its effects seen over the past two years has lead to several modeling exercises aimed at understanding the potential impact of national rotavirus vaccination in developing countries.

The introduction of rotavirus vaccines, even at lower efficacy, is predicted to have a tremendous impact in the developing countries, because of the high disease burden and mortality (Table 2). [18–25] For example India alone accounts for 98 621 deaths due to rotavirus, which translates to 22% of the global burden [1••]. Even a 30% decrease in mortality due to rotavirus gastroenteritis with vaccination would save more lives annually than are lost to the same cause in the richest 20 countries in the world in a decade. In addition to mortality, the economic burden of hospitalizations due to rotavirus diarrhea puts an enormous constraint on resources in an already resource poor setting [26,27].

Challenges to vaccine introduction in developing countries

Recently, after negotiations with the GAVI Alliance, the vaccine manufacturers have decreased the price of oral rotavirus vaccines for governments procuring vaccines for their national programs with GAVI support [http://www.gsk.com/media/pressreleases/2011/2011-pressrelease-462284.html]. Nonetheless, any price above 1 US$ a dose is likely to not be sustainable beyond the duration of GAVI support for several countries with large birth cohorts, leading to a reluctance on the part of some countries to introduce vaccine.

Surveys have shown that in some developing countries, both politicians and health personnel, including

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Table 2

Projected effectiveness of introduction of rotavirus vaccination in the developing world

	Vaccine	%Rotavirus deaths prevented	% Decrease in hospitalizations	DALYs averted	Reference
Asia					
Indonesia	ND	76.5%	84%	ND	[18]
India	ND	30%	33%	1 361 410	[19]
	Rotarix ™	41%	34.3%	ND	[20]
India	Rotateq®	70–81%	70–82%		[21]
China		83–89%	83–89%	ND	
Hong Kong		ND	93–94%	ND	
South Korea		ND	89–91%	ND	
Taiwan		ND	90–93%	ND	
Thailand		75–85%	75–86%	ND	
Africa					
Malawi	Rotarix ™	43%	ND	79 081	[22]
Ghana	Rotateq®	88%	ND	ND	[23]
Uganda	Rotarix ™	38%	42%	163 083	[24]
Kenya	Rotarix ™	55%	65%	58/1000 children	[25]

ND: not defined.

pediatricians, do not support the introduction of rotavirus vaccination for a range of reasons [28]. Partly this is due to the lack of knowledge of the local disease burden and a fear that cases of intussusception might result in a derailment of existing routine immunization programs. The first licensed vaccine was withdrawn in 1999 because of the increase in cases of intussusception [29]. Although the vaccine trials for licensure of Rotarix™ and Rotateq® were designed to capture a risk of intussusception similar to Rotashield®, no increase in cases was detected in studies that enrolled approximately 70 000 subjects each [30]. However, post-licensure studies in Australia and Mexico have shown an increased risk following the first dose of vaccine, although similar data from the US and Brazil do not show an association with increased risk [30–32].

The rotavirus disease burden is highest in countries where the capacity to deliver routine immunization is weak [12•]. The rotavirus vaccines require a cold chain and the large volume packaging of currently licensed vaccines results in a need for expansion of cold chain capacity [33]. In addition, given that the total volume of vaccine doses produced since licensure would be insufficient to meet the annual need for Asia alone, a significant expansion of production capacity will be needed.

In addition to the financial and logistic challenges for vaccine introduction, the data from the vaccine efficacy studies clearly demonstrate the biological challenges to having a safe and effective vaccine for use in national immunization programs of developing countries.

Understanding the factors related to decreased efficacy

Over the past five decades since oral vaccines were first introduced, experience with polio, cholera and now rotavirus vaccines, in developing countries has shown that immune responses may be lower and less consistent than in more industrialized countries [34,35]. There are several reasons that have been proposed for the differences in immune response, but no one factor has been unequivocally implicated. These include nutritional factors, both overt malnutrition and deficiency of zinc, vitamin A or vitamin D, the presence of competing enteric viruses or of helminths and the presence of maternal antibodies, either transplacental or through breast milk that may decrease vaccine take [36•]. In addition, the age of natural infection and the timing of vaccination require balancing of the exposure to pathogens with the maturity of the infant immune system [37].

Other factors to be considered are the high rates of tropical enteropathy in developing countries, where an abnormal intestinal mucosa, damaged by frequent or chronic infection may also diminish immune responses to oral vaccines [38]. The intestinal microbiota also play a major role in maintaining gut homeostasis and promoting resistance to infection, by preventing colonization with pathogens, modulating innate and adaptive immune responses, preserving intestinal integrity, controlling inflammation and contributing to nutritional status. Animal studies have shown a role for the intestinal microbiota in development of gut-associated lymphoid tissue, expression and secretion of cytokines and anti-microbial peptides including defensins, expression of MHC molecules and Toll-like receptors, regulation of the balance between T_H1/T_H2 and T_H17 responses and between T_H cell and T_{Reg} cell subsets and secretory IgA responses, all of which would be critical for mucosal vaccine response, but as yet no data are available from humans [39,40].

Vaccines in development

In Asia, manufacturers in China, India, Vietnam and Indonesia have initiated projects to develop either indigenous vaccine candidates or products developed

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elsewhere being taken forward for local manufacture under a license [41]. An oral rotavirus vaccine using 116E, a human neonatal, naturally reassorted and 'asymptomatic' strain of Indian origin, is under development by an Indian manufacturer. This strain has been evaluated in phase I and II studies, has high immunogenicity and is now in phase III studies [42,43]. Another neonatal candidate, RV3 is undergoing development in Indonesia [41]. Other manufacturers are developing bovine human reassortant vaccines based on the UK bovine strain, which has been licensed from the National Institutes of Health, and these candidate vaccines are in early phase trials [41].

Alternate approaches to rotavirus vaccination in developing countries

Strategies to improve oral vaccine take with variable success have included increasing the number of vaccine doses, increasing the dose of vaccine, and the addition of zinc [44,45]. Given the recent data emerging from Africa and Asia on the lower efficacy of oral rotavirus vaccines, there is increasing interest in attempting to identify more clearly the cause of such compromise in immunogenicity and protection. It is likely that although vaccine formulations and adjuvants can be redesigned to result in some increase in response, host factors will play the major role in determining the individual and the population response.

Natural infection with rotavirus occurs at a younger age in developing countries and protection conferred by infection from subsequent setting is lower than in more developed settings (79% after three infections in India vs 100% after two infections in Mexico) [46,47]. Therefore, it becomes important to consider alternate strategies to decrease the window of susceptibility. Maternal immunization during pregnancy, as is practiced to prevent neonatal tetanus may be one possible approach [48], which could provide protection in early life and be combined with immunization at a later age, when the infant immune system is more mature [49]. Since immunization during pregnancy with a live virus vaccine is inadvisable, a non-replicating vaccine would need to be developed.

The use of a non-replicating vaccine, such as either an inactivated formulation of currently available oral vaccines or virus-like particles, which have undergone pre-clinical development [50], merits consideration in children as well. In animal models, the development of protective immunity is induced both by inactivated and live attenuated vaccines given parenterally [51–53]. Although we do not completely understand the mechanism of protection in rotavirus immunization [51,52], it is possible that as with polio, a systemic response may be sufficient to protect the individual child. It is not known whether in humans viral replication is an absolute prerequisite for mounting a protective immune response [53], but it is likely that delivery of non-replicating antigens parenterally could induce a stronger and sustained immune response [54,55].

Conclusions

Rotavirus vaccination is a key part of a comprehensive approach to prevent and control diarrheal disease, which includes use of oral rehydration therapy, promotion of breastfeeding and improvement of environmental and nutritional factors. Rotavirus vaccination in the developing countries of Latin America has been shown comprehensively to decrease the burden of disease both in terms of numbers of deaths and disability adjusted life years. Based on data from vaccine trials in low-income countries in sub-Saharan Africa and south-east Asia, it is likely that vaccines will be less effective than in Latin America, but will still save a significant number of children's lives annually. Nonetheless, ongoing research on the development of new and better vaccines and strategies to improve the performance of current vaccines is needed to parallel efforts to use available vaccines where they are most needed.

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