Outstanding challenges for rotavirus vaccine introduction in low-income countries – a systematic review

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ABSTRACT

Rotavirus infections are the most common cause of severe diarrhoea in children worldwide. Two internationally licensed rotavirus vaccines have proven to be efficacious in middle- and high-income countries and they could potentially be valuable tools for the prevention of rotavirus-associated diarrhoea in low-income countries where the disease burden is greatest. However, before the vaccines can be introduced into the national immunisation programmes in these countries, many challenges related to the financing of vaccine purchase, the cold chain capacity and vaccine efficacy must be overcome. There is also a need for political commitment to prevent rotavirus infections as well as a need for an overall strengthening of the health systems in low-income countries. If these challenges were met, rotavirus vaccination could substantially improve child health and survival from rotavirus-associated diarrhoea.

Diarrhoea remains one of the leading causes of child death worldwide and accounts for 15% of the estimated 8.8 million under-five deaths that occur annually [1]. Rotavirus is the principal agent of severe childhood diarrhoea. It has been estimated that rotavirus results in approximately 111 million episodes of diarrhoea and 527,000 child deaths annually. Eighty-five per cent of these deaths occur in low-income countries, particularly in Africa and Asia [2, 3].

The development of rotavirus vaccines was a major breakthrough in the global effort to prevent and control diarrhoea [4]. If the vaccines were introduced into all national immunisation programmes as recommended by the World Health Organization (WHO), they could potentially prevent 43% of all annual deaths due to rotavirus-associated diarrhoea [4, 5].

The aim of this review was to describe the existing rotavirus vaccines and discuss the challenges associated with their introduction into the national immunisation programmes in low-income countries. This will contribute to an understanding of how childhood diarrhoea can be prevented and thereby help achieve the United Nations' Millennium Development Goal of reducing the under-five mortality rate by two thirds in the period from 1990 to 2015.

MATERIALS AND METHODS

The PubMed database and Cochrane Library were searched to identify relevant literature on rotavirus vaccines and their introduction. Additional searches were carried out in online databases and libraries of major organisations such as the WHO, the United Nations Children's Fund, the GAVI Alliance and the World Bank. Scientific papers were retrieved using MeSH terms to consistently search by subject. The used MeSH terms were: "diarrhoea", "rotavirus infections", "rotavirus vaccines", "prevention and control", "clinical trials", "treatment outcome" and "patient acceptance of health care". The search terms were included either separately or in combination. The following inclusion criteria were applied: 1) literature published in the past ten years, i.e. 2001-2011; and 2) literature published in English. Additional searches were performed from the reference lists of the selected literature.

The literature identified included original research papers, reviews, reports, books, product information, clinical trial protocols, databases and press releases.

! FACTS

Rotavirus vaccines

Two rotavirus vaccines are licensed for international use: Rotarix and RotaTeq.

Large-scale trials have found the vaccines to be efficacious and safe.

The vaccines have only been implemented for routine use in a few low-income countries.

Outstanding challenges for vaccine introduction in low-income countries

The vaccines are expensive.

The vaccine volumes pose a significant strain on the cold chain capacity.

The vaccines are less efficacious in low-income countries.

There is a lack of knowledge about rotavirus infections among caretakers, health personnel and politicians in low-income countries.

There is a need for strengthening of the health systems and the access to these.

SYSTEMATIC REVIEW

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ROTAVIRUS VACCINES

Rationale for rotavirus vaccines

Reviews of the literature published in the period from 1975–to 2008 have shown that the global mortality of rotavirus-associated diarrhoea has remained high despite a significant reduction in total diarrhoea mortality over the past two decades [2, 3, 6]. Two factors may contribute to this trend: (1) Vomiting is a frequent symptom of rotavirus-associated diarrhoea and oral rehydration therapy is therefore less effective as a supportive treatment; and (2) rotavirus spreads efficiently because of a low infectious dose and because the virus tolerates a wide range of physical and chemical conditions [7]. The latter point indicates that environmental interventions such as improvements in water quality, sanitation and hygiene, are unlikely to significantly reduce the incidence of rotavirus-associated diarrhoea despite their success in reducing the incidence of diarrhoea due to other enteropathogens [2, 7]. Therefore, as identified by the WHO, prevention by means of vaccination is the best strategy to control the disease [4, 8].

Characteristics

The first rotavirus vaccine, RotaShield (Wyeth-Lederle, USA), was licensed in 1998. However, the product was removed from the market a year later due to an increased risk of intussusception [9, 10]. Subsequently, two rotavirus vaccines, Rotarix (GlaxoSmithKline Biologicals, Belgium) and RotaTeq (Merck & Co. Inc., USA), have been licensed for international use [11, 12].

Rotarix contains a monovalent, attenuated human rotavirus, while RotaTeq contains pentavalent, attenuated bovine-human reassortant vira. Both vaccines are administered orally; Rotarix in a two-dose schedule and RotaTeq in a three-dose schedule [13, 14]. The vaccine charactereristics are presented in **Table 1**.

TABLE 1

Characteristics of rotavirus vaccines. Sources: [13, 14, 28].

	Rotarix	RotaTeq
Origin	Human rotavirus strain, monovalent	Bovine-human reassortant strain, pentavalent
Strain	Human G_1, P(8)	Bovine-human G_1, G_2, G_3, G_4, P1A(8)
Dosage	2 doses	3 doses
Schedule	1st dose: from age 6 weeks	1st dose: age 6-12 weeks
	2nd dose: at least 4 weeks interval	2nd-3rd dose: 4-10 weeks interval
	Full course must be completed by age 24 weeks	Full course must be completed by age 32 weeks
Administration	Oral	Oral
Packed volume per dose	17.1 cm^3/dose	45.9 cm^3/dose
Storage and shelf life	+2-8° C for 3 years	+2-8° C for 2 years
Co-administration	DTP, HepB, Hib, IPV, PCV-7, MenC	DTP, HepB, Hib, IPV, PCV-7

DTP = diphtheria-tetanus-pertussis; HepB = hepatitis B; Hib = *Haemophilus influenzae* type b; IPV = inactivated polio vaccine; MenC = meningococcal C conjugate vaccine; PCV = pneumococcal conjugate vaccine.

Adverse events

Between 1% and 10% of infants vaccinated with Rotarix experience diarrhoea and irritability as adverse reactions to vaccination, whereas more than 10% of infants vaccinated with RotaTeq experience diarrhoea, vomiting, otitis media and nasopharyngitis as adverse reactions to vaccination [13, 14]. However, in a pooled analysis of 34 phase II and III clinical trials published up to 2010, no significant difference in the occurrence of adverse events was found between groups receiving placebos compared with groups receiving Rotarix or RotaTeq, respectively [15].

Neither of the vaccines has been associated with intussusception in clinical trials [15]. However, post-licensure safety monitoring has reported contradicting findings and an increased risk of intussusception following vaccination with Rotarix or RotaTeq cannot be excluded [16, 17].

Both vaccines are contraindicated for infants with severe combined immunodeficiency disease due to concern that vaccine-acquired rotavirus-associated diarrhoea may occur in these individuals [13, 14, 18]. Whether the vaccines are safe for infants with human immunodeficiency virus (HIV) remains unclear [19, 20].

Efficacy and effectiveness

A recently published meta-analysis of all phase III clinical trials of rotavirus vaccines found a pooled vaccine efficacy of 91% (95% confidence interval (CI): 86-94) against severe rotavirus-associated diarrhoea in high-income countries (Europe and USA). The corresponding efficacies in low- and middle-income countries were lower: 81% (95% CI: 71-87) in Latin America, 50% (95% CI: 23-67) in sub-Saharan Africa and 43% (95% CI: 10-64) in high-mortality Asia [21].

Post-licensure studies conducted after vaccine implementation to measure effectiveness have shown substantial decreases in mortality, number of outpatient cases and hospitalisations due to rotavirus-associated diarrhoea [8].

Countries using rotavirus vaccine

Rotarix and RotaTeq have been licensed in more than 100 countries, but in 2009 they were only in routine use in 22 countries worldwide [22]. The distribution of rotavirus vaccine introduction throughout the world is shown in **Figure 1**. As can be seen, the vaccines have not been introduced into the national immunisation programmes in Asia and only to a limited extent in Africa despite the higher burden of rotavirus-associated diarrhoea in these continents.

Other rotavirus vaccine candidates

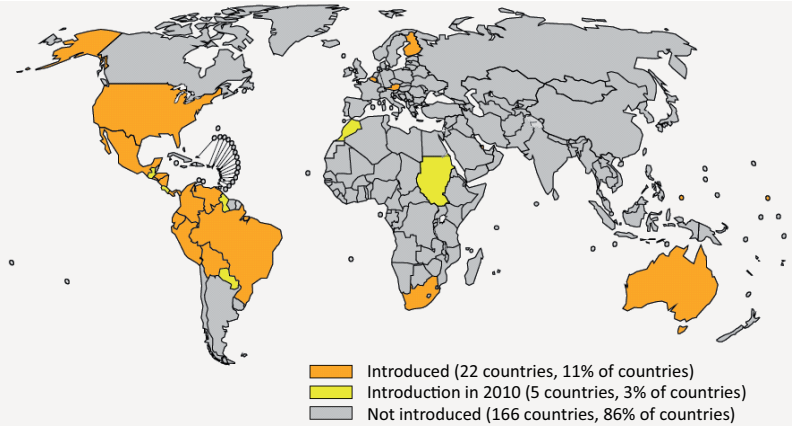
In 2000, China licensed a monovalent, attenuated ovine rotavirus vaccine, Lanzhou Lamb (Lanzhou Institute of Biological Products, China). However, the vaccine is not routinely used in the Chinese national immunisation programme. Furthermore, the vaccine has never been tested in a phase III clinical trial and, hence, its efficacy and safety remain undocumented [5].

Several other rotavirus vaccines are under development, most of which are in early trials. In India, however, a monovalent, attenuated human-bovine reassortant vaccine, ROTAVAC (Bharat Biotech, India), is currently undergoing phase III clinical trial with study completion in 2014 [23].

In addition, the safety profile of RotaShield is being re-evaluated by the International Medica Foundation (USA), which plans to manufacture the vaccine in collaboration with IDT Biologika GmbH (Germany) for use in low-income countries [24].

FIGURE 1

Countries using rotavirus vaccine in national immunisation schedule in 2009. Reproduced from the World Health Organization with permission. Copyright © WHO 2010. All rights reserved. Source: [22].



CHALLENGES FOR ROTAVIRUS VACCINE INTRODUCTION IN LOW-INCOME COUNTRIES

Even though Rotarix and RotaTeq have proven to be safe and efficacious in middle- and high-income countries, many challenges remain before the vaccines can be introduced into the national immunisation programmes in low-income countries.

Financial challenges

The current prices of the vaccines are between USD 5.15-7.50 per dose if they are procured through the Pan-American Health Organisation. These prices are far higher than the prices of other routine childhood vaccines such as the diphtheria-tetanus-pertussis (DTP) vaccine which can be purchased at USD 0.14 per dose [25]. Procurement of vaccines at such high prices exceeds the health budgets of most governments in low-income countries.

On average, these allocate USD 26.0 per capita per year to health care, which has to cover all health activities, including immunisation programmes [26]. Consequently, financial support is a prerequisite to the implementation of the rotavirus vaccines in the national immunisation programmes in low-income countries.

The GAVI Alliance is an example of such support as the organisation subsidises vaccine procurement in the world's poorest countries [27]. Another solution is to reduce the vaccine prices by creating more competition in the market, specifically by developing new rotavirus vaccines [27]. This can also be achieved by submitting vaccines that were marketed without phase III clinical trials, such as Lanzhou Lamb, to such trials to achieve approval for international use.

Logistical and capacity challenges

The rotavirus vaccines pose a significant strain on the cold chain capacity since they occupy more space than other routine childhood vaccines. Compared with the DTP vaccine, the packed volumes of Rotarix and RotaTeq are approximately seven times and 18 times greater, respectively [27, 28]. A consequence of this is an added financial burden to expand the cold chain capacity, which is needed prior to vaccine implementation [27]. In order to overcome this, vaccine manufacturers should reconsider the presentations of their products and initiate steps to further minimise the volume.

A global expansion of rotavirus vaccination programmes will also place a significant strain on the production capacity of the current vaccine manufacturers [27]. An inadequate supply of vaccines to meet the projected demand will threaten the long-term sustainability of vaccination programmes. Thus, it is critical that a functional market develops in which several manufacturers supply vaccines in sufficient quantities in a competitive environment.

Biological challenges

Phase III clinical trials have demonstrated that the two vaccines are less efficacious in low-income countries [21]. One reason for this could be the greater diversity of circulating rotavirus serotypes in Africa and Asia [29]. Further evaluations of vaccine efficacy in heterologous settings are required to better understand the vaccines' ability to provide cross-serotype protection. It is also important to establish surveillance systems to monitor the post-licensure impact of rotavirus vaccines on the disease burden as well as to monitor any changes in circulating serotypes. New serotype profiles can compromise

the vaccines' effectiveness, whereby the next generation of vaccines may have to protect against a broader spectrum of serotypes [8]. Finally, the incidence of intussusception in infants should be monitored to ensure that the vaccines do not increase the risk of this condition [17].

Other factors that may explain lower vaccine efficacies in low-income countries include high titres of maternally-derived neutralising antibodies transmitted to the infant in breast-milk, co-morbidities such as micronutrient malnutrition and HIV/AIDS, as well as co-infections with other enteropathogens [20, 30-33]. Additionally, children in low-income countries are exposed to higher faecal-oral pathogen loads in the environment and they are often infected with several rotavirus serotypes simultaneously, including unusual strains [33]. Further studies are needed to establish the relationship between these factors and vaccine efficacy. Subsequently, interventions to counteract inhibitory factors should be considered such as withholding breastfeeding at the time of vaccination, increasing vaccine titre or number of doses, supplementing micronutrients, and/or supplementing probiotics [33].

It has been demonstrated that rotavirus vaccines can be co-administered with the majority of routine childhood vaccines [13-15]. However, inconsistent data exist on the interference of the oral polio vaccine with the immunogenicity of rotavirus vaccines. It remains unclear whether these can be co-administered [15, 34].

Contextual challenges

Studies have shown that prevention of rotavirus-associated diarrhoea is not considered a priority among politicians and health personnel in low-income countries even though broader diarrhoea control interventions are given high priority. This may be due to the lack of knowledge of the local disease burden that could be prevented by vaccination [35]. Hence, it is necessary to inform decision-makers about rotavirus and to establish rotavirus surveillance systems. It is also important to inform caretakers about the disease and about the potential of the new vaccines. In this context, one challenge will be to explain that the vaccines only protect against rotavirus-associated diarrhoea and that a vaccinated child remains susceptible to diarrhoea due to other enteropathogens [13, 14, 36].

Another major barrier to the success of disease preventive interventions is the underlying weakness of health systems in many low-income countries. The function of health systems is often constrained by a lack of political and financial commitment, poor management as well as shortage of drugs, equipment and qualified staff [36]. In addition, studies have shown that multiple barriers exist in the access to health care in low-income countries, including socio-demographic (e.g. education and ethnicity), physical (e.g. distance to facilities), economic (e.g. socio-economic status and service costs) and cultural (e.g. low acceptance and low confidence in the quality of health care services) [36, 37]. These barriers may hinder or cause delays in vaccinations, which further compromise the effectiveness and safety of the vaccines.

A study of vaccination timing has estimated that more than 30% of children in low- and middle-income countries were past the recommended age for rotavirus vaccination when they were vaccinated with the DTP vaccine [38]. A possible solution to this is to broaden the age restrictions for rotavirus vaccination, since the additional mortality reduction would outnumber by far the hypothetical excess of intussusception deaths that would result from using a wider administration schedule. However, the ethical aspects of this approach are widely debated [39]. Alternatively, vaccination at birth could capitalise on the access of health personnel to newborns; a strategy that becomes available if two current neonatal vaccine candidates are proven efficacious and safe in clinical trials [40].

Finally, further research as well as political commitment is needed to develop strategies that ensure access to a functional and effective health system and increase public confidence in the services provided.

CONCLUSION

Despite a falling trend in total diarrhoea mortality worldwide, mortality due to rotavirus-associated diarrhoea has remained high. Two internationally licensed rotavirus vaccines have proven to be efficacious and safe in middle- and high-income countries. As such, they could potentially have a major impact on the high mortality of rotavirus-associated diarrhoea occurring in low-income countries. However, the vaccines are only in routine use in a few countries and many challenges remain before the vaccines can be introduced into the national immunisation programmes in low-income countries and thereby help achieve the Millennium Development Goal of reducing child mortality.

It should be emphasised that rotavirus vaccination is only one component in a comprehensive approach to prevent and control diarrhoea. In order to achieve a continuous reduction in diarrhoea mortality, it is important to ensure a high coverage of rotavirus vaccination and widespread use of oral rehydration therapy as well as to invest in preventive interventions such as improvement of environmental and nutritional factors and the promotion of breastfeeding.

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