

Review

Insights from global data for use of rotavirus vaccines in India[☆]

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A B S T R A C T

Rotavirus vaccines are being introduced in several low- and middle-income countries across the world with and without support from the GAVI Alliance. India has the highest disease burden of rotavirus based on morbidity and mortality estimates and several indigenous vaccine manufacturers are developing rotavirus vaccines. One candidate has undergone phase III testing and others have completed evaluation in phase II. Global data on licensed vaccine performance in terms of impact on disease, strain diversity, safety and cost-effectiveness has been reviewed to provide a framework for decision making in India.

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1. Introduction

Two live, attenuated, orally administered rotavirus vaccines – a monovalent human rotavirus vaccine (RV1; RotarixTM (GSK Biologicals, Rixensart, Belgium)) and a pentavalent bovine-human reassortant vaccine (RV5; RotaTeq[®] (Merck and Co, Inc, Pennsylvania)) – are licensed for use in more than 100 countries worldwide, including India [1,2]. Promising clinical trial data from the United States of America (USA), Latin America, and Europe showing that these newly developed rotavirus vaccines were highly efficacious and safe in preventing severe rotavirus gastroenteritis lead to the World Health Organization (WHO) recommendation in 2006 that vaccines against rotavirus be introduced into the national immunization programmes of countries in regions where clinical trial data are available.

In 2009, following additional clinical trials in low income countries and the availability of post-marketing data from early introducing countries in the Americas, Europe, and Australia, WHO extended its recommendation to include rotavirus vaccines in the routine immunization programs in all countries globally and particularly those countries with high child mortality due to diarrhea. Following further analysis, in 2013 the WHO recommended that all countries consider immunization along with the primary

immunization series at whatever age the series is administered [3]. Since 2006, over 50 countries have introduced rotavirus vaccine into their national immunization programs.

Of the estimated 453,000 annual deaths due to rotavirus diarrhea in children <5 years of age globally, approximately 99,000 (22%), occur in Indian children [4] (Fig. 1). In addition, rotavirus is a significant cause of childhood morbidity in India and is estimated to account for approximately 457,000–884,000 hospitalizations and 2 million outpatient clinic visits each year, incurring health care costs of Rs. 2.0–3.4 billion (US\$ 41–72 million) annually [5]. Thus, the potential health and economic impact of a national rotavirus vaccination programme in India is immense. In addition to having both internationally licensed vaccines in the market, Indian manufacturers are developing several candidate rotavirus vaccines. The most advanced of these vaccines is a candidate based on the indigenous 116E strain, a natural reassortant of the human rotavirus G9P[11] strain with the VP4 protein from a bovine rotavirus strain, that was isolated from a neonate with an asymptomatic infection in Delhi (Table 1). This vaccine has undergone a phase III clinical trial at three centres in India (Delhi, Pune, and Vellore) and results from this trial indicate efficacy at least equivalent to licensed vaccines in developing countries [6].

While rotavirus vaccines are not currently recommended or used in the national immunization programme in India, their use has been included in the Indian Academy of Paediatrics guidelines for immunization. Widespread experience with rotavirus vaccines under conditions of routine use in many countries worldwide coupled with clinical trial data provide much insight into the performance, impact, safety, and cost-effectiveness of rotavirus vaccines. The objective of this paper is to review data

[☆] The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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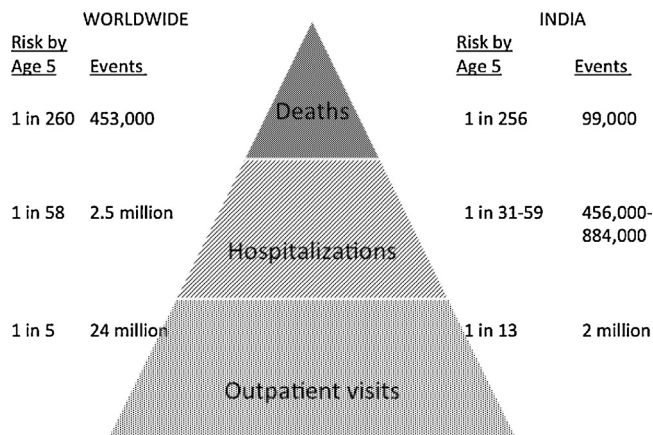


Fig. 1. Rotavirus disease burden globally and in India.

from international settings to help address key questions regarding anticipated rotavirus vaccine performance and impact in India.

2. Pre-licensure efficacy of rotavirus vaccines

Both internationally licensed rotavirus vaccines, RV1 and RV5, were found to be highly efficacious in clinical trials conducted in the USA, Latin America, Europe, and high income Asian countries (Table 2). RV1 was 85% (95% CI: 71–83%) efficacious in preventing severe rotavirus gastroenteritis (Vesikari score ≥ 11) among Latin American infants [1]. In subsequent trials examining efficacy during the first two years of life, RV1 was 81% (95% CI: 71–87%) efficacious against severe rotavirus gastroenteritis in Latin American children, 90% (95% CI: 85–94%) efficacious in European children, and 96% (95% CI: 85–100%) efficacious in children in high income Asian countries [7–9]. Similarly, in clinical trials conducted mainly in the USA and Finland, RV5 was 96% (95% CI: 91–98%) efficacious against hospitalizations due to rotavirus gastroenteritis caused by G1–G4 strains, 94% (95% CI: 89–97%) against emergency department visits, and 86% (95% CI: 74–93%) against office visits [2].

Because live oral vaccines, including earlier candidate rotavirus vaccines, have a history of performing less well in developing countries [10–17], WHO specifically recommended that efficacy trials of both RV1 and RV5 be conducted in low income countries of Africa and Asia before issuing a global recommendation for rotavirus vaccine use. Vaccine efficacy was modest in these trials. In Africa (South Africa and Malawi), two doses of RV1 administered at 10 and 14 weeks of age had 59% (95% CI: 36–74%) efficacy against severe rotavirus diarrhea during the first year of life and three doses at 6, 10, and 14 weeks of age had 64% (95% CI: 42–78%) efficacy [18]. Efficacy appeared to decline during the second year of life, particularly among 2 dose recipients.

In Malawi, efficacy was similar for two and three dose recipients during the first year of life (49% (95% CI: 11–72%) and 50% (95% CI: 11–72%), respectively) [18,19]. However, in the second year of life, efficacy disappeared in two dose recipients (3% (95% CI: –101 to 53%)) while declining to 33% (95% CI: –49 to 71%) among three dose recipients [18,19]. In South Africa, efficacy was similar in the three dose recipients during the first year of life (82% (95% CI: 55–94%)) and overall during the first two years of life (85% (95% CI: 35–98%)) [18,20]. However, among two dose recipients, the study observed a notable decline from 72% (95% CI: 40–88%) during the first year to 32% (95% CI: –71 to 75%) over the first two years of life [18,20].

For RV1, the two dose schedule was given at 10 and 14 weeks of age. No efficacy data for RV1 with the recommended 6 and 10 week schedule is available, and it is possible that the efficacy may be lower than that observed with the 10 and 14 week schedule due to higher maternal antibody and potential interference by first oral polio vaccine dose. The efficacy of three doses of RV5 administered at 6, 10, and 14 weeks of age in Africa (Ghana, Kenya, and Mali) was 64% (95% CI: 40–79%) and in Asia (Bangladesh and Vietnam) was 51% (95% CI: 13–73%) against severe rotavirus disease during the first year of life [21,22]. As seen for RV1, RV5 efficacy appeared to decline during the second year of life and was 20% (95% CI: –16 to 44%) in Africa and 46% (95% CI: 1–71%) in Asia [21,22].

Despite lower efficacy in low income countries, the significant disease burden in these settings results in a greater absolute number of rotavirus cases prevented per 100 vaccinated children compared with higher income countries with lower disease burden. In clinical trials, RV1 efficacy during the first year of life in South Africa (77%) was higher than in Malawi (49%) but the vaccine prevented seven episodes of severe rotavirus gastroenteritis per 100 vaccinated infants in Malawi compared with four episodes prevented per 100 vaccinated infants in South Africa due to the higher disease burden in Malawi compared with South Africa [18].

3. Post-licensure effectiveness and impact of rotavirus vaccines

Rotavirus vaccines have had a notable impact on mortality, hospitalizations and outpatient visits in countries that have introduced the vaccine into their national immunization programme, including some evidence suggesting that rotavirus vaccines may offer indirect protection to older, unvaccinated age groups. Perhaps the most exciting post-licensure data pertains to the effect of rotavirus vaccination in reducing deaths from childhood diarrhea in some countries in Latin America, as the mortality benefits of vaccination were not assessed in pre-licensure trials. In Mexico, following RV1 introduction into the national immunization programme in 2007, the diarrhea mortality rate declined to 35% (95% CI: 29–39%) in 2008 compared with the pre-vaccine baseline (2003–2006): the decline in mortality has been sustained for three years from 2008 to 2010 [23,24].

Table 1
Characteristics of rotavirus vaccines.

	RV1	RV5	116E
Manufacturer	GlaxoSmithKline; Rixensart, Belgium (Rotarix®)	Merck; Pennsylvania, USA (Rotateq®)	Bharat Biotech International Limited; Hyderabad, India
Parent Strain	Human rotavirus strain 89–12, type G1P1A[8]	Bovine rotavirus strain WC3, type G6P7 [5]	Human rotavirus virus G9P[11] strain of the Wa genogroup with a bovine rotavirus strain of genotype P[11]
Formulation	No reassortants	5 reassortants G1xWC3, G2xWC3, G3xWC3, G4xWC3, P1A[8]xWC3	Natural reassortant
Dosing Regimen	2 oral doses, given with DTP doses 1 and 2	3 oral doses, given with DTP	3 oral doses, given with DTP
Status	International Use	International Use	Licensed

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