

## Review

Insights from global data for use of rotavirus vaccines in India<sup>☆</sup>

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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; Rotarix<sup>TM</sup> (GSK Biologicals, Rixensart, Belgium)) and a pentavalent bovine-human reassortant vaccine (RV5; RotaTeq<sup>®</sup> (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

<sup>☆</sup> 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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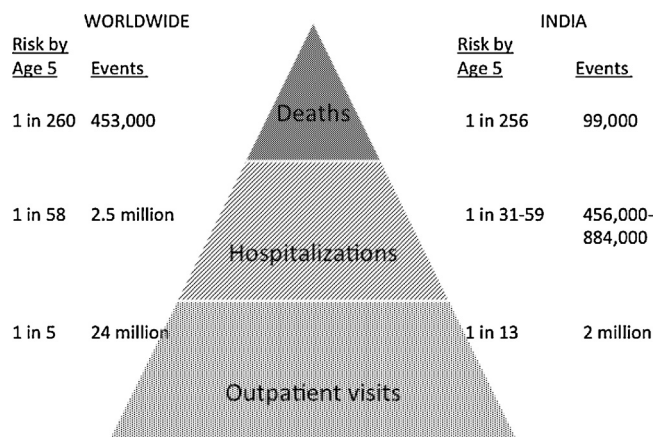


Fig. 1. Rotavirus disease burden globally and in India.

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  $\geq 11$ ) 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.

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

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].

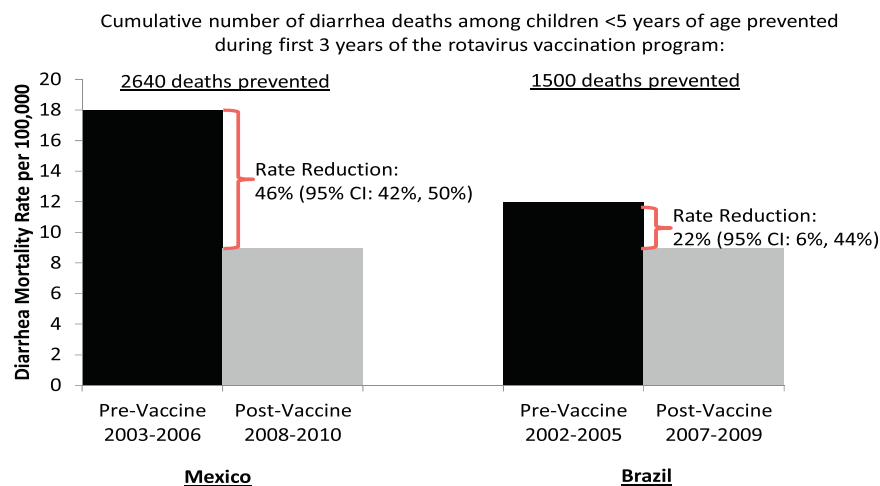
**Table 2**  
Efficacy of rotavirus vaccines against severe rotavirus disease by year of life and country.

	Vaccine	Schedule	Efficacy (95% CI)—1st year of life	Efficacy (95% CI)—2nd year of life	Overall Efficacy (95% CI)—1st two years of life	References
<b>High and Middle Income Settings</b>						
Latin America	RV1	2, 4 months	83% (67%, 92%)	79% (66%, 87%)	81% (71%, 87%)	[7]
Europe	RV1	3, 5 months	96% (90%, 99%)	86% (76%, 92%)	90% (85%, 94%)	[8]
Asia	RV1	3, 5 months	–	–	96% (85%, 100%)	[9]
US and Finland	RV5	2, 4, 6 months	98% (88%, 100%)	–	–	[2]
<b>Low Income Settings</b>						
South Africa	RV1	10, 14 weeks	72% (40%, 88%)	–	32% (–71%, 75%)	[18,20]
South Africa	RV1	6, 10, 14 weeks	82% (55%, 94%)	–	85% (35%, 98%)	[18,20]
Malawi	RV1	10, 14 weeks	49% (11%, 72%)	3% (–101%, 53%)	34% (–2%, 58%)	[18,19]
Malawi	RV1	6, 10, 14 weeks	50% (11%, 72%)	33% (–49%, 71%)	42% (9%, 64%)	[18,19]
Africa (Ghana, Kenya, Mali)	RV5	6, 10, 14 weeks	64% (40%, 79%)	20% (–16%, 44%)	39% (19%, 55%)	[21]
Ghana	RV5	6, 10, 14 weeks	65% (36%, 82%)	29% (–65%, 71%)	56% (28%, 73%)	[21]
Kenya	RV5	6, 10, 14 weeks	83% (26%, 98%)	–55% (–175%, 82%)	64% (–6%, 90%)	[21]
Mali	RV5	6, 10, 14 weeks	1% (–432%, 82%)	19% (–23%, 47%)	18% (–23%, 45%)	[21]
Asia (Vietnam, Bangladesh)	RV5	6, 10, 14 weeks	51% (13%, 73%)	46% (1%, 71%)	48% (22%, 66%)	[22]
Vietnam	RV5	6, 10, 14 weeks	72% (–45%, 97%)	65% (–48%, 94%)	64% (8%, 91%)	[22]
Bangladesh	RV5	6, 10, 14 weeks	46% (–1%, 72%)	39% (–18%, 70%)	43% (10%, 64%)	[22]

Brazil saw a similar decline of 22–41% in diarrhea mortality rates among children <5 years of age following the introduction of RV1 into the national immunization program in 2006 [25,26] (Fig. 2). While these were ecological analyses that could be affected by secular trends and failed to measure the specific reason for decline in rotavirus deaths (because the cause of diarrhea is rarely diagnosed for deaths), the dramatic decline in mortality seen after vaccine introduction, particularly during the winter seasonal months when rotavirus circulates, support the role of the vaccine.

Many middle and high income countries have observed substantial declines of 17–55% in all-cause gastroenteritis hospitalization and even larger declines of 49–89% in rotavirus gastroenteritis hospitalizations among children <5 years of age within the first two years following rotavirus vaccine introduction [25,27–42]. Due to the large rotavirus disease burden among hospitalized children, these declines translate into large numbers of hospitalizations prevented. For example, studies show that in the USA following the introduction of rotavirus vaccine in 2006 an estimated 40,000–60,000 acute gastroenteritis hospitalizations, or approximately 4–5% of all hospitalizations among US children <5 years of age, were prevented in 2008 [33] (Table 3).

In some settings, researchers have observed the indirect effects of rotavirus vaccines among children age-eligible but missed by the vaccination program, and among older children and adults. The USA observed declines of 6–46% in rotavirus gastroenteritis hospitalizations among age-eligible unvaccinated children although these declines were smaller than the 88–93% decline observed among age-eligible vaccinated children [42]. Many countries including the USA and Belgium have observed declines in rotavirus disease during the first few years of vaccine introduction that exceed the coverage levels of rotavirus vaccine in the population [43–46]. Furthermore, the declines in rotavirus hospitalizations among children <5 years of age that were age-ineligible during the first few years after vaccine introduction saw declines in rotavirus gastroenteritis hospitalizations (24–81%) that were similar to or slightly lower than those declines observed among vaccine-eligible age groups (50–96%) [27–29,31,32,34,35,38,40,43,47]. Additionally, studies in the USA observed declines in acute gastroenteritis hospitalizations of 8–29% among older children and adults 5–24 years of age during the rotavirus season following rotavirus vaccine introduction suggesting an unappreciated burden of rotavirus disease in these older populations [48].



**Fig. 2.** Reductions in all-cause diarrhea mortality rates among children <5 years of age pre- and post-rotavirus vaccine introduction in Mexico and Brazil.

**Table 3**  
Impact of national rotavirus vaccine introduction on all-cause and rotavirus diarrhea hospitalizations in children <5 years of age.

Country	Vaccine (Year Introduced)	Post-Vaccine Years Studied	Percent reduction in specified hospitalizations among children <5 years of age		Impact	Reference
			All-Cause Diarrhea Hospitalizations	Rotavirus Hospitalizations		
Brazil	RV1 (2006)	2007–2009	17%	–	40,000 diarrheal hospital admissions in children <5 years age averted annually Annual healthcare visits for diarrhea (inpatient and outpatient) among children <5 years of age decreased by 61,000 in 2008 and 46,000 in 2009	[25]
El Salvador	RV1 (2006)	2008–2009	28–37% <sup>a</sup>	69–81%		[28]‡
Mexico	RV1 (2006)	2008–2009	11–40% <sup>b</sup>	–	16,000 diarrheal hospitalizations in children <5 years of age averted annually; 1 hospitalization prevented per 125 vaccinated infants by 5 years of age	[80]
USA	RV5 (2006) RV1(2008)	2008–2009	31–33%	62–71% <sup>c</sup>		38,000 diarrheal hospitalizations in children <5 years age averted annually

‡ Study period July 2007–June 2009.

<sup>a</sup> Includes inpatient and outpatient visits for diarrhea.

<sup>b</sup> During peak rotavirus season.

<sup>c</sup> Rotavirus-coded hospitalizations.

#### 4. Strain diversity

Rotavirus strains are characterized by two surface proteins, VP7, the glycoprotein (G protein) and VP4, the protease-cleaved protein (P protein), that evoke antibody response. At least 10 G and 11 P antigen types have been identified among human rotavirus strains with five strains (G1P[8], G2P[4], G3P[8], G4P[8], and G9P[8]) found to be responsible for the majority of severe rotavirus infections worldwide [49–51]. However, there are extensive differences in the predominant circulating strains between geographic regions and change over time [51]. G1 strains predominated globally from 1996 to 2007 although the relative frequency decreased over time [51]. Conversely, in Southeast Asia, G2 strains were predominant during 1996–1999, G9 strains dramatically emerged in 2000–2003, and G1 and G2 strains predominated from 2004 to 2007 accompanied by the emergence of G12 strains [51].

Clinical trials of RV1 in Latin America found high efficacy (91%; 95% CI: 71–98%) against severe (Vesikari score  $\geq 11$ ) rotavirus gastroenteritis due to G1P[8] but lower, non-significant efficacy (45%; 95% CI: –82 to 86%) against G2P[4,1]. However, a subsequent trial in Europe with a larger sample size showed high levels of protection against severe rotavirus gastroenteritis due to G1 (96%; 95% CI: 90–99%) and G2 strains (86%; 95% CI: 24–99%) as well as G3 (94%; 95% CI: 53–100%), G4 (95%; 95% CI: 68–100%), and G9 strains (85%; 95% CI: 72–93%) [8]. The RV1 clinical trials in Africa showed similar efficacy against G1 strains (64%; 95% CI: 30–82%) and non-G1 strains (60%; 95% CI: 37–74%) [18]. The clinical trial of RV5 in the USA and Finland observed a 95% (95% CI: 92–97%) rate reduction in the number of hospitalizations and emergency department visits due to G1 strains and rate reductions of 93% (95% CI: 49–99%), 89% (95% CI: 52–98%), and 100% (95% CI: 67–100%) in the number of hospitalizations and emergency department visits due to G3, G4, and G9 strains, respectively [2]. The RV5 clinical trial in Africa provided significant protection against severe gastroenteritis due to G8 strains (88%; 95% CI: 7–100%), P1A[8] strains (36%; 95% CI: 4–58%), and P2A[6] strains (48%; 95% CI: 10–70%) [21]. In the RV5 clinical trial in Asia, strain-specific vaccine efficacy estimates were imprecise due to small numbers and the trial observed significant protection only against P1A[8] strains (50%; 95% CI: 19–69%) [22].

Strain-specific vaccine efficacy estimates from the clinical trials are limited to the predominately circulating strains at the time of the trials. However, post-licensure vaccine effectiveness data from countries that have introduced rotavirus vaccine into their routine immunization programs have enabled vaccine performance

against a variety of strains in a variety of settings to be evaluated. Of particular interest has been the apparent emergence of G2P[4] in Brazil and Australia following the introduction of RV1 in these countries [52,53]. G2P[4] is fully heterotypic compared to the RV1 strain and there was some concern that the selective pressure of the vaccine may have led to its predominance. However, vaccine effectiveness studies in Brazil found that RV1 was 39–89% effective against severe disease caused by G2P[4] strains although the effectiveness may wane in children >12 months of age [36,54,55]. RV1 was 83–85% effective against rotavirus gastroenteritis due to G2P[4] in children 6–11 months of age in Brazil but only 5–41% effective in children  $\geq 12$  months of age [54]. Similarly, a study among indigenous children <3 years of age in Australia noted waning vaccine effectiveness, where RV1 was 19% (95% CI: –105 to 68%) effective in preventing rotavirus hospitalizations among children <3 years of age during an outbreak of G2P[4] with higher vaccine effectiveness in children <1 year of age (51%; 95% CI: –92 to 88%) than in children 1–2 years of age (9%; 95% CI: –283 to 79%) [56]. An earlier study in the same indigenous population found that RV1 was 85% (95% CI: 23–97%) effective against rotavirus hospitalization when G9P[8] was the predominantly circulating strain [57]. RV1 has also been shown to be effective in El Salvador (76%; 95% CI: 64[8] was the predominantly circulating strain and in Mexico (94%; 95% CI: 16–100%) against G9P[4,58,59].

Post-licensure vaccine effectiveness studies have also shown RV5 to offer protection against several different strains. A study in the USA showed RV5 was 95% (95% CI: 57–99%) effective against hospitalizations and emergency department visits due to G3P[8,60] Another study in USA found that RV5 was 83–96% effective against G1, G3, G9, and G12 strains and 72–77% effective against G2 strains [61]. In Nicaragua, RV5 was 51% (95% CI: 23–69%) effective against G2P[4] rotavirus disease resulting in hospitalization or intravenous rehydration, 65% (95% CI: 39–80%) against severe (Vesikari score  $\geq 11$ ) G2P[4] rotavirus disease, and 82% (95% CI: 47–94%) against very severe (Vesikari score  $\geq 15$ ) G2P[4] rotavirus disease [62].

#### 5. Vaccine safety

A previous quadrivalent rhesus-reassortant rotavirus vaccine, RotaShield® manufactured by Wyeth and licensed in 1998, was withdrawn from use in the USA in 1999 after it was associated with an increased risk of intussusception, a rare adverse event in which one portion of the bowel telescopes into another [63–65]. Researchers in the USA observed an excess risk of one case of

**Table 4**  
Benefit-risk analyses for selected countries with national rotavirus vaccination programs.

	Rotavirus Hospitalizations (Deaths) Prevented	Intussusception (Deaths) Caused	Reference
Mexico	11,600 (663)	41 (2)	[67]
Brazil	69,600 (640)	55 (3)	[67]
Australia	6,500 (0)	14 (0)	[68,81]
United States	53,000 (14)	58 (0.2)	[76]

intussusception per 10,000 infants vaccinated with RotaShield [66]. Subsequently the USA conducted large clinical trials of for RV1 and RV5 among 60,000–70,000 infants to detect a risk of intussusception similar to that observed with RotaShield [1,2]. Trials failed to detect an increased risk of intussusception following rotavirus vaccination within 30 days of either dose of RV1 or 42 days after any of the RV5 doses [1,2]. However, post-marketing surveillance has detected a small increased risk of intussusception (1–2 excess cases per 100,000 infants vaccinated) in the first week following the first dose of vaccine in some populations but not in others [67–72].

Assessment analyses have found favorable benefit-risk ratios in countries with inconclusive rotavirus vaccine efficacy (Table 4). A self-controlled case series analysis observed a short term risk of intussusception of one excess case of intussusception per 51,000–68,000 infants vaccinated in the 1–7 days following rotavirus vaccination in Mexico and Brazil [67]. Both of these countries documented significant declines in all-cause diarrhea deaths in children following the introduction of rotavirus vaccine [23–26]. For example, each year in Mexico, the rotavirus vaccine will avert an estimated 663 deaths and 11,551 hospitalizations due to rotavirus among children <5 years of age and cause 2 excess deaths (approximately 1 for every 1 million vaccinated infants) and 41 excess hospitalizations (approximately 1 for every 51,000 vaccinated infants) for intussusception [67]. Similarly, in Brazil, the rotavirus vaccine will avert an estimated 640 deaths and 69,572 hospitalizations due to rotavirus among children <5 years of age annually and cause 3 excess deaths (approximately 1 for every 1.4 million vaccinated infants) and 55 excess hospitalizations (approximately 1 for every 68,000 vaccinated infants) for intussusception [67].

## 6. Cost-effectiveness of a rotavirus vaccination program

Global, regional, and country-specific studies have found rotavirus vaccine to be a cost effective intervention. Globally, rotavirus vaccine will prevent an estimated 180,000 rotavirus deaths in children <5 years of age annually when introduced into the national immunization programmes of all GAVI-eligible countries [73]. The estimated cost per disability adjusted life year (DALY) averted is US\$ 42 for all GAVI-eligible countries and US\$ 60 for GAVI-eligible countries located in Southeast Asia [73]. For every 1000 children vaccinated against rotavirus in GAVI-eligible countries in Southeast Asia, an estimated 52 DALYs will be averted, 87 health care visits due to rotavirus diarrhea will be prevented, and US\$ 1360 in medical costs will be saved [73]. Two independent analyses in India concluded that the introduction of rotavirus vaccines into the routine, national immunization program in India would be cost-effective [74,75]. At a price of US\$ 7.00 per dose, the initial price per dose of vaccine, these models estimated an incremental cost effectiveness ratio (ICER) of US\$ 174 per life years saved and US\$ 134–200 per DALY averted, which satisfies the WHO criterion for a cost effective intervention where the incremental cost-effectiveness ratio is less than the country's per capita gross domestic product [74,75]. At the more likely cost of US\$ 1.00 per dose in India, the ICER is US\$ 21 per DALY averted [74]. At current immunization levels a national rotavirus vaccination programme in

India would prevent 41,000–44,000 deaths and 203,000–293,000 hospitalizations due to rotavirus among children <5 years of age [74,75].

Studies have observed that following the introduction of rotavirus vaccine into national immunization programs, there are declines in annual costs to treat rotavirus disease associated with declines in medical visits. After rotavirus vaccine was introduced into the national immunization program in the USA in 2006, one study found that almost 65,000 hospitalizations due to rotavirus among children <5 years of age over the following two years from July 2007 to June 2009 were prevented which saved approximately US\$ 278 million in treatment costs [42]. Another USA study estimated that the vaccine could prevent 53,000 hospitalizations due to rotavirus among children <5 years of age [76]. Additionally, a study examining the indirect benefits of rotavirus vaccine in older children and young adults, a study in the USA estimated that approximately 8800 gastroenteritis hospitalizations were prevented among individuals 5–24 years of age in 2008 saving US\$ 42 million in treatment costs [48].

## 7. Lessons for India

The dramatic declines in rotavirus disease documented in middle and high income countries following vaccine introduction, coupled with the high disease burden in low income countries like India suggest that large declines in the number of deaths, hospitalizations, and outpatient visits due to rotavirus gastroenteritis may be observed following vaccine introduction into the national immunization programs despite modest vaccine efficacy. [5] Thus, with the high rotavirus disease burden in India, rotavirus vaccines have substantial potential to prevent a large number of deaths, hospitalizations, and outpatient visits due to rotavirus even with the modest efficacy. Data on rotavirus vaccine impact in developing countries are sparse due to limited use of rotavirus vaccines in these countries. This will change in the coming years with GAVI support and increased use of vaccines in developing countries. But it is important that Indian policy makers consider available data as early as possible.

The benefits of rotavirus vaccination may extend beyond those which are expected among children <5 years of age. Indirect benefits of rotavirus vaccination have been observed in the early years of the rotavirus vaccination program in early adopter countries suggesting that rotavirus vaccine may offer some protection to those populations not directly covered by the immunization program. Little information is available about the incidence of rotavirus disease among older children and adults in most countries, including in India, but even if a small unrecognized disease burden exists in these populations, the impact of rotavirus vaccines at the population level could be greater than anticipated. Further studies of disease burden among all ages and data from clinical trials or demonstration projects in India will help to determine the performance and project the impact of rotavirus vaccine introduction.

India, like other developing countries, has documented tremendous diversity in circulating rotavirus strains [77–79] (Fig. 3). Fortunately, substantial evidence suggests that rotavirus vaccines provide heterotypic protection against a wide range of genotypes.

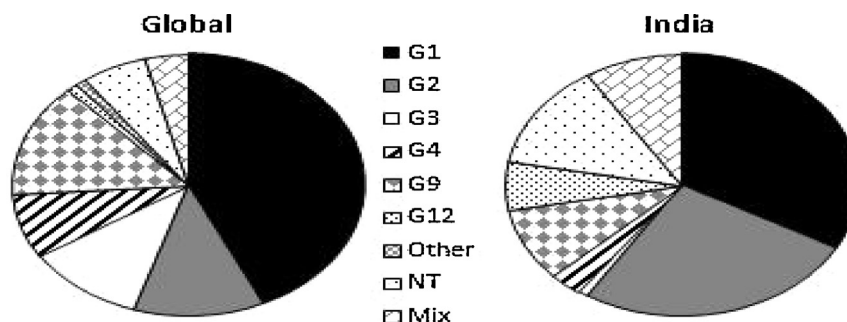


Fig. 3. Distribution of G Types Globally and in India. Adapted from refs. [51,79].

Note: NT indicates non-typable strains and Mix indicated mixed infections.

Secular trends in circulating strains continue to occur in countries that have introduced rotavirus vaccine. While it may be too soon to determine if vaccine pressure will result in the emergence of escape strains, both globally available vaccines have demonstrated effectiveness against multiple rotavirus strains. Countries that have introduced rotavirus vaccine, such as Brazil, Mexico, Australia, and the USA, have documented large declines in hospitalizations due to rotavirus disease further suggesting that these vaccines are having an impact on rotavirus disease burden due to a variety of strains. However, small differences in effectiveness against individual strains may lead to the emergence of escape strains over time making continued monitoring of circulating strains important following vaccine introduction.

Risk-benefit analyses in several countries that have introduced rotavirus vaccine into their national immunization programs have found that the benefits of rotavirus vaccination greatly outweigh the risk. While the analyses are country-specific and vaccine-specific, countries like India with high rotavirus mortality burden will likely benefit from the introduction of rotavirus vaccine even if there is a low level risk of intussusception. However, each country must weigh its own benefit-risk scenario prior to vaccine introduction.

## 8. Summary

India has its own rotavirus vaccines in the pipeline with phase 3 trials of the 116E vaccine completed and those of other candidates expected to start soon. Once this vaccine is available for use in India and as other vaccines become available, many issues including performance and impact under conditions of routine use, effectiveness against currently circulating strains, safety, and cost-effectiveness will need to be examined. However, the experience of the international community with the two currently available oral rotavirus vaccines does provide insight into the likely performance and impact of the Indian 116E vaccine. Due to the high rotavirus mortality burden, the introduction of a vaccine will likely have a notable impact on disease burden, protect against a wide variety of circulating strains, and result in a decrease in the economic burden of rotavirus in India. Studies to examine rotavirus vaccine impact and safety using many of the study designs employed by international researchers can help answer many of these questions and provide support for sustained use of rotavirus vaccine in India.

## Conflict of interest

None of the authors have a conflict of interest

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