Prevention of rotavirus gastroenteritis in infants and children: rotavirus vaccine safety, efficacy, and potential impact of vaccines

Aruna Chandran 1
Sean Fitzwater 1
Anjie Zhen 2
Mathuram Santosham 1
1Department of International Health, Division of Health Systems, 2Department of Molecular Microbiology and Immunology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA

Abstract: Rotavirus infection is the most common cause of severe gastroenteritis globally, with greater than 86% of deaths occurring in low-income and middle-income countries. There are two rotavirus vaccines currently licensed in the United States and prequalified by the World Health Organization. RV1 is a monovalent attenuated human rotavirus strain, given orally in two doses. RV5 is a pentavalent human-bovine reassortant rotavirus vaccine, given orally in three doses. A third rotavirus vaccine, LLV, is a lamb rotavirus strain given orally as a single dose, which is currently available only in China. RV1 and RV5 have been shown to be highly efficacious in developed countries, and initial results from trials in Africa and Asia are promising as well. At least three other vaccines are in development, which are being developed by manufacturers of developing countries. Further studies are needed to clarify issues including administration of oral rotavirus vaccines with breastfeeding and other oral vaccines, and alterations in dosing schedule. Using new data on global diarrheal burden, rotavirus is estimated to cause 390,000 deaths in children younger than 5 years. Should rotavirus vaccines be introduced in the routine immunization programs of all countries, a potential of 170,000 deaths could be prevented annually. The largest impact on mortality would be seen in low-income and middle-income countries, despite poor immunization coverage and lower efficacy. Therefore, international efforts are needed to ensure that rotavirus vaccines reach the populations with highest burden of rotavirus disease.

Keywords: vaccination, mortality, rotavirus, gastroenteritis

Introduction

Epidemiology

Rotavirus infection is the most common cause of severe diarrhea globally, resulting in an estimated 114 million episodes of gastroenteritis, 24 million outpatient visits, and 2.4 million hospitalizations each year.1 In total, there were over 500,000 deaths attributed to rotavirus in 2004, resulting in 5% of all deaths in children <5 years of age.2,3 The rate of rotavirus illness is similar in both developed and developing countries; in all settings, rotavirus is responsible for approximately 39% of hospitalizations due to diarrhea regardless of a country’s income status.4 However, the burden of mortality is almost entirely in developing countries where access to care is limited and risk factors for disease are high. Every year, greater than 86% of deaths occur in Asia and sub-Saharan Africa, whereas less than 1,000 rotavirus deaths occur in high-income countries.3

Rotavirus gastroenteritis occurs almost exclusively in infants and children, with nearly every child having been infected by the age of 5 years.5 The majority of serious infections occur between 4 and 24 months of age, although the peak age of serious
disease varies globally. In developing countries, the mean age of symptomatic rotavirus infection is between 6 and 9 months while industrialized countries have a median age between 9 and 15 months. Older children are protected from serious disease by previous exposure and apparent infection: if it occurs, it is usually mild. Similarly, disease can occur in neonates but is typically mild or asymptomatic due to protection from maternal antibodies. Rotavirus infection shows strong seasonal variation; in temperate high-income countries, rotavirus disease occurs most often during the winter, whereas seasonality is less pronounced in tropical and low-income countries.

**Biology**

Rotaviruses are nonenveloped viruses of the genus Reoviridae. The virus is characterized by a double-stranded RNA genome composed of 11 segments, which encode for six structural and six nonstructural proteins. Rotavirus particles are icosahedrons, 70–75 nm in diameter, composed of three concentric layers of structural proteins: the core, an inner capsid, and an outer capsid. The outer capsid is composed of a VP7 coating with VP4 spikes protruding from the viral surface. This layer is the most antigenically important portion of the virus, with the VP7 glycoprotein (G-type antigen) and VP4 protease-sensitive protein (P-type antigen) being the major immunological targets of the human immune system. The inner capsid is composed solely of VP6. Based on the antigenic properties of VP6, rotaviruses are broken into 7 serogroups, denoted A–G. Serogroup A is the only serogroup that commonly causes human disease. Conventionally, rotavirus strains are denoted by the P serotype name first, followed by its genotype in brackets, followed by the G-type.

**Serotype variation**

Evolutionary pressures have led to a diversity of VP4 and VP7, resulting in over 19 G types, 28 [P] types, and over 40 G and P antigen combinations observed in human disease (Table 1). Globally, six G + P combinations (P[8]G1, P[4] G2, P[8]G3, P[8]G4, P[8]G9, and P[6]G9) account for >80% of rotavirus disease in all regions with the exception of Africa. Prior to vaccine introduction, P[8]G1 was the most common strain globally, accounting for 72%–82% of all rotavirus disease in North America, Europe, and Oceania and for 23%–34% of strains isolated in South America, Asia, and Africa. Currently, P types 4, 6, 8, and 9 account for >95% of disease regardless of region. More diversity exists in G-type, with 1–4, 8, and 9 accounting for >95% of disease. Notably, genotype distribution is not constant in any region; substantial variation occurs over time and within countries.

**Transmission and pathogenesis**

Rotavirus is believed to be transmitted via the fecal oral route, close personal contact, and contact with contaminated environmental sources. However, the prevalence of rotavirus in high-income countries despite improved sanitation suggests that nonfecal routes play a role in transmission. Rotavirus has been identified being shed from the oropharynx of children with symptoms of upper respiratory track disease, both with and without apparent gastrointestinal disease; respiratory droplets may be an important source of transmission.

Upon ingestion, the rotavirus targets the epithelial lining of the intestine. During viral replication, the segments of the viral genome are disassociated from viral proteins and one another; this allows reassortment of genotypes in cells infected with more than one strain of rotavirus. Rotavirus disrupts the normal functioning of the gastrointestinal mucosa through a number of mechanisms; the most potent is the viral enterotoxin NSP4, which alters the permeability of the gut mucosa by weakening the tight junctions between cells, disrupting the cytoskeleton of the infected cells, increasing the secretion of chloride ions, and stimulating the gut motility through the enteric nervous system.

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**Table 1** Regional distribution of rotavirus serotypes

<table>
<thead>
<tr>
<th>Serotype</th>
<th>Africa, %</th>
<th>Asia, %</th>
<th>Europe, %</th>
<th>North America, %</th>
<th>Oceania, %</th>
<th>South America, %</th>
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<tr>
<td>P[8]G1</td>
<td>23</td>
<td>34</td>
<td>72</td>
<td>73</td>
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<td>34</td>
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<td>P[8]G3</td>
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<td>9</td>
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<tr>
<td>P[8]G9</td>
<td>5</td>
<td>5</td>
<td>3</td>
<td>1</td>
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<td>15</td>
</tr>
<tr>
<td>P[6]G9</td>
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<td>7</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Other</td>
<td>16</td>
<td>6</td>
<td>1</td>
<td>1</td>
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<td>27</td>
<td>14</td>
<td>1</td>
<td>5</td>
<td>0</td>
<td>11</td>
</tr>
</tbody>
</table>

causes in an uncontrolled outflux of water into the intestinal lumen, resulting in profuse diarrhea.

**Clinical disease**

Rotavirus disease is most commonly characterized by acute gastroenteritis. After an incubation period of 1–3 days, rotavirus infections present with symptoms common to many enteric pathogens: profuse watery diarrhea, vomiting, and fever. The severity of symptoms varies but on average is more severe than other viral enteric pathogens; although rotavirus only accounts for 6%–8% of community diarrhea cases, it accounts for 25%–40% of diarrheal cases requiring hospitalization. Rotavirus infections are not invasive and do not elicit a destructive inflammatory response; as a result, dysentery does not occur with rotavirus infections. Diarrhea typically lasts from 4 to 7 days. Virus-specific diagnostic tests and treatment are not necessary as symptoms typically resolve within a week of disease onset. However, supportive care, primarily rapid rehydration, is critical to preventing complications.

**Complications**

The most common complication associated with rotavirus infection is dehydration. The symptoms of mild and moderate dehydration, not specific to rotavirus, are restlessness, irritability, decreased skin turgor, sunken fontanelle (in infants), sunken eyes, and thirst. Severe dehydration is characterized by reduced or altered consciousness, lack of urine output, low blood pressure, weak quickened pulse, cool moist extremities, and peripheral cyanosis.

Malnutrition and diarrhea form a destructive cycle in children and as the most common diarrheal pathogen in infants, rotavirus plays an important role in this cycle. Malnutrition increases the susceptibility of children to future gastrointestinal infections, and diarrhea disrupts the gut’s ability to absorb nutrients, leading to an exacerbation of malnutrition. As a result, 61% of children who die of diarrhea have malnutrition as an underlying risk factor. Furthermore, malnutrition caused by diarrhea leads to significant physical and mental growth shortfalls that negatively affect children throughout their lives, including negative impacts on school performance. Nutritional support is a critical component of ameliorating the short-term and long-term consequences of rotaviral, as well as other diarrhea diseases.

**Treatment**

Dehydration is responsible for >90% of deaths from infectious diarrhea. Treatment for rotavirus gastroenteritis, as with the majority of infectious watery diarrhea, is supportive; children should receive appropriate hydration and nutritional support. Since the 1970s, the World Health Organization (WHO) has recommended the use of oral rehydration solution (ORS) for the treatment of dehydration; the worldwide extensive use of this solution saved millions of lives. In the early 1990s, multiple laboratory and clinical studies showed that reducing the osmolarity of ORS resulted in increased intestinal water absorption compared with standard ORS. A meta-analysis of trials of low-osmolarity ORS for acute diarrhea in children found that there was a 20% reduction in stool output, a 30% reduction in vomiting, and nearly a 40% reduction in the need for unscheduled intravenous treatment in patients receiving the low-osmolarity ORS compared with those receiving original ORS. The current WHO recommendation is for low-osmolarity ORS (245 mOsm/L) with 75 mmol/L each of sodium and glucose. In cases of severe dehydration in which the child is obtunded or unable to drink, intravenous or intraosseous fluids should be used for initial management.

Until the 1970s, the medical community endorsed the belief that feeding should be withheld during diarrhea in order to “rest the gut”. In the 1980s, a series of studies demonstrated that continued feeding during a diarrheal episode is safe and improves outcome. Based on these studies, the WHO incorporated early refeeding into their recommendations for diarrhea treatment.

Deficiency of zinc can result in diminished immune response and healing. Although the role of zinc supplementation in rotavirus diarrhea has not been evaluated separately, studies in developing countries have shown that zinc supplementation, when given in addition to ORS, is highly effective in decreasing the duration and severity of diarrheal episodes. Administration of zinc along with ORS led to a decrease in hospitalizations for diarrhea, as well as other illnesses, in two large-scale studies. In Bangladesh, Baqui et al reported a 24% reduction in the diarrhea hospitalization rate (95% confidence interval [CI]: 0.59–0.96) and resulted in an overall decrease in mortality (risk ratio = 0.49; 95% CI: 0.25–0.94). Therefore, in developing country settings, the WHO recommends the daily use of zinc supplementation for 10–14 days with every episode of acute diarrhea.

Antimicrobial therapy should be used only in specific cases of infectious diarrhea and in general do not have a role in the treatment of rotavirus gastroenteritis. Probiotics, microorganisms believed to restore microbial balance in the gastrointestinal tract, may have a role in the treatment of diarrhea by enhancing the immune response or providing...
a competitive blockade of pathogen receptor sites. In a meta-analysis of seven clinical trials, *Lactobacillus* GG (LGG) was shown to reduce the duration of rotavirus diarrhea by 2.1 days (95% CI: 3.6–0.6); however, a recent trial in rural India did not show any efficacy. Saccharomyces boulardii and *Lactobacillus reuteri* have also shown beneficial effects for rotavirus gastroenteritis. Additional studies are needed to further define the necessary dose and duration of treatment, particularly in developing country settings.

Several over-the-counter and prescription antimotility (eg, loperamide), antisecretory (eg, racecadotril), and toxin-binding agents (eg, cholestyramine) are available for symptomatic relief of diarrhea. Because of the limited evidence and uncertain side-effect profiles, most experts do not recommend the use of these agents, particularly for pediatric patients. Nitazoxanide, an antiprotazoal/antihelminthic drug, was shown to reduce the duration of rotavirus diarrhea from 75 hours in the placebo group to 31 hours in the intervention group (P = 0.0137) in an Egyptian trial of children hospitalized with severe rotavirus gastroenteritis. A more recent single-blind trial in Bolivia also showed that duration of diarrhea was reduced from 79 hours to 54 hours (P = 0.009) with nitazoxanide. Further studies will be needed to fully evaluate the safety and efficacy of nitazoxanide as a treatment for rotavirus gastroenteritis.

Although the morbidity and mortality from rotavirus gastroenteritis differ across socioeconomic strata, rates of illness are similar across developed and developing country settings. This indicates that hygiene and sanitation improvements, which have been credited with reducing incidence of most causes of infectious diarrhea in developed countries, are unlikely to prevent rotavirus disease significantly. Therefore, prevention in the form of vaccines is essential for the control of rotavirus disease.

**Rotavirus vaccines**

**Biological basis of vaccinology**

Protection against rotavirus infection has been associated with the presence of antirotavirus IgA antibodies in the gastrointestinal mucosal surface. Although the IgA response is often used to measure vaccine immune response, levels of serum rotavirus IgA antibody do not always correlate with levels of IgA antibody in the gut. Presence of virus-specific IgA in feces or serum was not predictive of protection against disease in studies of the simian–human reassortant vaccine. Therefore, it remains difficult to identify the best immune correlate of protection from a rotavirus vaccine.

It is also unclear how many serotypes a rotavirus vaccine should contain. Although initial infection does not confer complete immunity to rotavirus, clinical studies show that primary infection does seem to protect against severe disease upon reinfection. For example, one study in West Africa showed that primary infection conferred 70% (95% CI: 29–87) protection against subsequent rotavirus diarrhea. Similarly, although neonatal infection does not confer complete protection against disease in future, children who had rotavirus infection as neonates appear to have less-severe disease later in childhood. This protection does not appear to be strain specific, that is, children who were infected by one rotavirus strain as neonates had less-severe diarrhea later in childhood even when infected with a different strain. However, protection is stronger when a child is exposed to a G-type with which they have been previously infected. When measuring immunologic response to natural rotavirus infection, it appears that the antibody response is higher against the infecting G-type than against other G-types. The benefits of a multiseroype vaccine vs a single-serotype approach to vaccine development have not been established.

Several studies have evaluated animal strain vaccine candidates, with inconsistent results. The RIT4237 bovine strain was isolated from a calf and attenuated in cell culture, and found to be immunogenic by serum immunoglobulin response in human infants. Although initial efficacy trials in Finland appeared positive, subsequent studies showed little or no protection against rotavirus disease. The bovine strain WC3 was isolated from a calf in Pennsylvania in 1981. This strain alone as a vaccine was not consistently protective in all efficacy trials, with protection ranging from <10% to 76.1%. A third strain was the rhesus rotavirus vaccine (RRV), which was isolated from a monkey and also attenuated in cell culture. Similar to RIT4237, while initial efficacy studies showed a modest level of protection, subsequent studies showed little to no effect.

The poor results seen when using single-animal rotavirus strains as human vaccine candidates lead to the development of two major categories of rotavirus candidate vaccines: attenuated human rotavirus strains and recombinant (reassortant) rotaviruses containing human and animal rotavirus components. Attenuated human rotavirus strains are produced by serial passage of rotavirus strains isolated from humans in cell culture to reduce their pathogenicity. Reassortant rotavirus vaccines take advantage of the segmented rotavirus genome to create viruses that combine the RNA-encoding VP7 proteins from a human rotavirus with the remaining RNA segments of an animal rotavirus. The goal was to...
invoke the immune response to a G-type antigen from a human virus. Reassortants were initially created by coinfecting a monkey with bovine and human rotavirus and allowing the gene reassortant to occur by chance. Subsequent reassortants were created in laboratories and propagated in Vero cells.\textsuperscript{13}

RRV-TV

A quadrivalent human–animal reassortant vaccine (RRV-TV) containing serotypes G1, G2, G3, and G4 was developed by the National Institutes of Health and Wyeth Laboratories (Wyeth Laboratories, Monmouth Junction, NJ). The vaccine contained the RRV strain and three simian – human reassortant strains. Several different doses were tested for safety, immunogenicity, and efficacy. In the two trials done in the United States, the dose containing $10^7$ plaque-forming units per strain had an efficacy against all rotavirus disease of 49\% (95\% CI: 31–63) and 57\% (95\% CI: 26–67) and against severe rotavirus disease of 80\% (95\% CI: 56–91) and 82\% (95\% CI: 29–88).\textsuperscript{62,65} There was some concern about the efficacy of the vaccine in developing countries; the higher dose vaccine when tested in Venezuela had an efficacy of 48\% (95\% CI: 33–61) against all rotavirus disease and 88\% (95\% CI: 61–96) against severe rotavirus disease, which was similar to the results found in the United States.\textsuperscript{66} The vaccine was licensed in the United States in 1998 under the trade name Rotashield\textsuperscript{8} (Wyeth Lederle, Philadelphia, PA).

After several cases of intussusception were reported via the US Vaccine Adverse Event Reporting System (VAERS), a case–control investigation was conducted in 429 infants with intussusception and 1,763 matched controls. An increased risk of intussusception 3–14 days after the first dose was found (adjusted odds ratio [OR] = 21.7, 95\% CI: 9.6–48.9).\textsuperscript{67} Intussusception is not a known consequence of natural rotavirus infection. The possible explanations of why RRV-TV might cause intussusception include the following: (1) one strain in the vaccine may have been pathogenically unique from wild-type rotavirus, (2) the vaccine virus may be absorbed in the intestine in a different manner than wild type, and 3) the immune response induced by the vaccine strain might be different.\textsuperscript{13} Although the actual mechanism of the relationship between RRV-TV and intussusception is not clear, the simian strain RRV is considered the most likely causative vaccine strain. Following the results of this analysis, the use of the vaccine was discontinued. This vaccine was subsequently withdrawn from the market, and assessing the risk of intussusception has remained a key component of all subsequent rotavirus trials.

RV5

The oral human-bovine pentavalent reassortant rotavirus vaccine (Rotareq\textsuperscript{6}; Merck and Co., Whitehouse Station, NJ) consists of 5 human-bovine reassortants suspended in a fully liquid buffer-stabilized formulation (RV5). The vaccine is based on the creation of a new rotavirus strain that contains a single human virus coat protein on the viral surface, with the rest of the structural proteins from a bovine strain (WC3). Candidate reassortants were created in vitro by coinfecting cells with WC3 and a human rotavirus strain. The progeny containing the appropriate strain mixture is selected using molecular and immunologic selection. The human-bovine reassortants for this vaccine were initially cultured using the monkey cell line MA104, and then propagated in the commonly used monkey cell line Vero using standard cell-culture technique for production. The five human serotypes contained in the vaccine are G1, G2, G3, G4, and P1A[8].

Reassortant viruses with G1–G4 express the attachment protein P7[5] from the bovine strain. The reassortant virus expresses the attachment protein P1A[8] from the human strain and the outer capsid protein G6 from the bovine strain.\textsuperscript{68} A comparison of three different potencies of the RV5 vaccine for safety, immunogenicity, and efficacy was conducted in Finnish infants aged 2–8 months from 1998 to 2001.\textsuperscript{14} Efficacy estimates for gastroenteritis of any severity in the first year following vaccination were 68.0\% (95\% CI: 31.1–86.4), 74.3\% (95\% CI: 37.9–91.0), and 57.6\% (95\% CI: 11.8–80.9) in the high-potency, middle-potency, and low-potency groups, respectively; the middle-potency vaccine was chosen for the subsequent phase III efficacy trials.

Subsequently, clinical trials and postintroduction studies have demonstrated the efficacy of three doses of vaccine given with routine infant immunizations (Figure 1). From 2001 to 2004, the Rotavirus Efficacy and Safety Trial (REST), a double-blind, placebo-controlled, randomized trial, was conducted in over 68,000 infants in 11 countries.\textsuperscript{69} In an immunogenicity study in a small subset of the children, seroconversion rates for serum antirotavirus IgA were 95.2\% (95\% CI: 91.2–97.8) in 189 vaccine recipients and 14.3\% (95\% CI: 9.3–20.7) in 161 placebo recipients. In the per-protocol efficacy analysis, among 4,512 subjects, vaccine efficacy against G1–G4 gastroenteritis of any severity was 74\% (95\% CI: 66.8–79.9) and 98\% (95\% CI: 88.3–100) for severe disease in the first rotavirus season. Vaccine efficacy in the second season of RV gastroenteritis was 62.6\% (95\% CI: 44.3–75.4) against any disease and 88\% (95\% CI: 49.4–98.7) against severe disease. Efficacy has been shown across several regions. In fully vaccinated infants in the...
REST trial, reductions in RV-associated hospitalizations and emergency department visits up to 2 years after vaccination were 94.7% (95% CI: 90.9–96.9) in Europe, 94.9% (95% CI: 84.0–98.9) in the United States, and 90.0% (95% CI: 29.4–99.8) in Latin America/Caribbean. More recently, efficacy trials were implemented in Kenya, Ghana, Mali, Bangladesh, and Vietnam to determine the protection in lower income settings, with results now available for the first year of follow-up (Figure 1). Preliminary results from the efficacy trials in Africa (Kenya, Ghana, Mali) show a three-dose efficacy of 64% (95% CI, 40–79) against severe rotavirus gastroenteritis. In Asia (Bangladesh and Vietnam), a three-dose efficacy of 51% (95% CI, 13–73) has been shown against severe rotavirus gastroenteritis. Safety and immunogenicity have also been demonstrated in Taiwan.

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Since its introduction in the United States in 2006, RV5 has had a dramatic impact on rotaviral disease. Postintroduction surveillance data from the Centers for Disease Control and Prevention (CDC) in the United States for the 2007–2008 and 2008–2009 seasons compared with the prevaccination period showed that the rotavirus seasons were reduced from 26 weeks to 14–17 weeks, and the peak percentage of rotavirus positive tests reduced from 43% to 17%–25%. An evaluation of children in the United States vaccinated in the first two seasons after licensure compared with an unvaccinated cohort showed a vaccine efficacy of 100% (95% CI: 76–100) against rotavirus gastroenteritis hospitalizations and emergency department visits. A case–control study in Texas showed a three-dose vaccine efficacy of 100% (95% CI: 71–100) against severe rotavirus gastroenteritis requiring hospitalization. Vaccine effectiveness of one and two doses against hospitalization and emergency department visits was 69% (95% CI: 13–89) and 81% (95% CI: 13–96), respectively. In addition, RV5 has also shown promise in low-income settings. A postintroduction evaluation in Nicaragua showed a three-dose efficacy of 58% (95% CI: 30–74) against severe rotavirus diarrhoea. In the 2007 rotavirus season, despite a vaccination coverage of approximately 26%, hospitalizations and outpatient visits
for diarrheal illness declined by 11% and 23%, respectively, compared with prevaccination years.77

Due to the safety concerns associated with rotavirus vaccines, enhanced monitoring for possible vaccine-associated episodes of intussusceptions and other adverse effects is ongoing in many countries. The CDC published reports of postmarketing surveillance of intussusception after RV5 vaccination through September 25th, 2007. Under the assumptions that 100% of distributed doses were given and 100% of cases of intussusception were reported, the number of cases of intussusception reported through VAERS were lower than what would have been expected for the age-adjusted baseline rates at 1–7 days after vaccination (relative risk [RR] = 0.51; 95% CI: 0.32–0.81) or at 1–21 days after vaccination (RR = 0.30; 95% CI: 0.20–0.44). The Vaccine Safety Datalink (VSD), encompassing persons enrolled in 8 large health maintenance organizations, is also being used to monitor intussusception risk post vaccination. As of May 31st, 2008, 207, 621 doses of RV5 had been administered to infants in VSD-associated health management organizations; a total of five cases of intussusception were observed in children who had received all doses compared with an expected number of 6.75 episodes (RR = 0.74).78

RV1

The rotavirus vaccine RV1 (Rotarix®; GlaxoSmithKline, Genval, Belgium) is a monovalent vaccine composed of an attenuated human rotavirus strain G1P[8]. This parent strain was isolated during a clinical trial of an early rotavirus vaccine in 1988.2 Although the vaccine tested in this study was eventually found to be ineffective, observation over subsequent years showed that children infected with the naturally circulating strain during the clinical trial were protected against 81% of subsequent rotavirus infections and 100% protected against severe rotavirus disease. In addition, serum antibodies produced during infection were able to neutralize G types 1–4.79

An isolate of this strain, denoted 89–12, was serially passed in tissue culture, resulting in an attenuated viral strain that was subsequently used in clinical trials.2 Phase I and II clinical trials in Europe, the United States, and Latin America demonstrated excellent safety, immunogenicity, and efficacy.80 Early clinical trials showed an efficacy of 89% (95% CI: 65.4–94.5) after two doses of vaccine resulting in adoption of the two-dose schedule.81,82

Subsequent large randomized, double-blind, placebo-controlled phase three clinical trials have demonstrated the efficacy of the vaccine given with the first and second dose of routine infant vaccination (Figure 1). A study in Finland and 11 Latin American countries following 20,169 vaccine and placebo recipients for 9–10 months, following completion of the two-dose series, found an 85% reduction (95% CI: 71.7–92.4) in severe rotavirus gastroenteritis and a 42% (95% CI: 29–53) reduction in hospitalization for all-cause gastroenteritis.83 Subsequent follow-up in Finland showed no reduced protection during the second rotavirus season.84 A similar but smaller trial of 3,994 infants in six European countries demonstrated efficacy across two subsequent rotavirus seasons.85 During the first rotavirus season, the vaccine recipients had 87.1% (95% CI: 79.6–92.1) fewer rotavirus episodes and 95.8% (95% CI: 89.6–98.7) fewer severe rotavirus episodes. During the second season, the efficacy dropped slightly to 71.9% (95% CI: 61.2–79.8) against any rotavirus gastroenteritis and 85.6% (95% CI: 75.8–91.9) against severe rotavirus disease. A study in Hong Kong, Singapore, and Taiwan following 10,708 children until 24 months of age found higher efficacy, noting a 96.1% (95% CI: 85.1–99.5) reduction in severe rotavirus gastroenteritis and 30.3% (95% CI: 13.1–44.2) against reporting one or more episodes of severe all-cause gastroenteritis.86

To assess RV1 efficacy in low-income countries, a randomized trial was conducted in 3,166 South African and 1,773 Malawian infants.87 In South Africa, the overall efficacy was similar to what was seen in high-income country settings, with the vaccine recipients having 76.9% (95% CI: 56.0–88.4) fewer cases of severe rotavirus gastroenteritis and 44.1% (95% CI: 19.8–61.0) lower incidence of all-cause severe gastroenteritis. However, in Malawian children, the efficacy of the vaccine was reduced, preventing only 49.4% (95% CI: 19.2–68.3) of severe rotavirus gastroenteritis. This difference could not be explained by serotype differences, as both populations showed similar efficacy against G1 and non-G1 serotypes. Interestingly, despite the reduced efficacy, more disease was prevented per recipient in Malawi than in South Africa due to the higher burden of disease. In Malawi, vaccine prevented 3.9 episodes of severe rotavirus gastroenteritis per 100 vaccinated children compared with preventing 2.5 episodes per 100 vaccinated children in South Africa.88 In addition, the study compared two- and three-dose schedules of RV1, with vaccine given at 6, 10, and 14 weeks or 10 and 14 weeks. No statistical difference was found in the efficacy of the vaccine in children who received two versus three doses.

RV1 has demonstrated efficacy against vaccine serotype and nonvaccine serotype diseases. In Finland and Latin America, RV1 showed serotype-specific efficacy for G1P[8]
of 91.8% (95% CI: 74.1–98.4) and a combined efficacy against G3P[8], G4P[8], and G9P[8] of 87.3% (95% CI: 64.1–96.7).83 Too few cases of non-G1 or P[8] serotypes were isolated to determine efficacy against these groups. In Europe, the highest efficacy was seen against G1 serotypes, with the vaccine preventing 89.8% (95% CI: 82.9–94.2) of any severe gastroenteritis.83 In Asia, RV1 prevented 100% (95% CI: 80.8–100) of G1 serotypes and 93.6% (95% CI: 74.7–99.3) of non-G1 serotypes of severe gastroenteritis.86 Several Brazilian studies have shown efficacy against non-vaccine serotypes.89,90 Among these, a case control study comparing children hospitalized with G2P[4] rotavirus gastroenteritis to those hospitalized with acute respiratory infections demonstrated an efficacy of 77% (95% CI: 43–90) in infants aged 6–11 months.90 However, the efficacy dropped to 15% (95% CI: −101 to 64) in children older than 12 months. Further studies are needed to establish the efficacy of RV1 against serotypes that are neither G1 nor P[8]. 

Postintroduction impact of RV1 has been demonstrated in several countries.91–97 A retrospective case–control study in indigenous Australians during an outbreak of G9P[8] rotavirus found RV1 to be 84.5% (95% CI: 23.4–96.9) effective at preventing hospitalized rotavirus infections.92 RV1 was introduced to the national immunization system in Brazil in 2006, with a vaccination coverage of 46.5% in 2006 and 78.3% in 2007.91 In 2006, there were 26% fewer hospitalizations in children aged younger than 1 year due to gastroenteritis compared with the average number of yearly hospitalizations from 1998 to 2005. In 2007, the hospitalization reduction was 48% compared with prevaccination levels. In 2007, a decrease in all-cause diarrheal disease was seen in children aged 1–5 years, reversing an increasing trend in gastroenteritis in this age group that had been seen in the past 10 years. Mexico introduced RV1 in 2007. In 2008, the incidence of diarrhea-related deaths decreased to 11.8 per 100,000 children younger than 5 years compared with 2003–2006 with an average of 18.1 deaths per 100,000 children; a rate reduction of 35% (95% CI: 29–39). This reduction continued through the 2009 rotavirus season. Such a dramatic reduction in diarrhea mortality is very promising for reducing mortality due to rotavirus infections.

Due to the previous association of rotavirus vaccination with intussusception, an extended intensive follow-up phase to assess severe side effects was built into most clinical trials.83,85,86 Over 75,000 children were followed in these studies for 31–100 days but no increased risk of intussusception was found. In fact, across all studies, there were significantly fewer serious adverse events noted in the vaccine recipients compared with placebo recipients.83,86 In addition, a study in East Asia reported no difference in nongastrointestinal serious adverse events in vaccine vs placebo recipients.86

Lanzhou lamb

A live, attenuated oral rotavirus vaccine (LLV) was developed by the Lanzhou Institute of Biological Products. The vaccine was developed by passing a wild-type group A serotype G10P[12] lamb rotavirus through primary calf kidney cells. After 37 passages, the virus was subsequently tested in several clinical studies. In 2000, LLR vaccine was licensed by China Drug Inspection and Management Bureau using a one-dose oral schedule. It is currently licensed in China to be given to children aged 2 to 36 months, followed by yearly boosters.94 However, the vaccine is relatively expensive in China, costing $18.4 per dose; as a result, few children received more than one dose.95 Between 2001 and 2008, approximately 10,000,000 doses were administered in China.94 The vaccine is not routinely being used under China’s national immunization program.

The strongest evidence for efficacy of LLV comes from a case control study in Guangzhou province comparing 838 children aged 2 months to 5 years hospitalized with rotavirus infections to 838 matched community controls.95 This study demonstrated a 73.3% (95% CI: 61.2–81.6) efficacy of one dose of LLV against hospitalized rotavirus gastroenteritis. The efficacy was found to be higher in older children, with efficacy in 12–23 month olds found to be 80.9% (95% CI: 65.4–89.4) compared with 60.0% (95% CI: 28.6–77.6) in 2–11 month olds. This may be due in-part to older children receiving vaccine at a later date, resulting in booster effect on an already present wild-type rotavirus response. A larger efficacy trial done in 4,000 infants aged from 6 to 24 months showed an efficacy against all-cause rotavirus gastroenteritis of 78%.94 However, this study was not placebo controlled, and the results are not available in a peer-reviewed journal.

A nonrandomized cohort study in Guangzhou province in southern China following 102 vaccinated children and 145 unvaccinated children aged 6 months to 3 years for a total of 6 months found 53% fewer cases of rotavirus gastroenteritis in vaccinated children.96 In addition, disease was less severe; the average duration of disease was reduced by 24% (P < 0.001). A study comparing 225 children with rotavirus disease, 34 previously vaccinated and 191 unvaccinated, found a reduced duration (P < 0.001), severity (P = 0.041), and risk of hospitalization (P = 0.022) in the rotavirus vaccinated group.97 Immunologic studies among children aged 6–24 months before and after vaccination showed that LLR
induced neutralizing antibody against rotavirus of all the four G types ranging from 40% to 70%. However, these studies did not include non-vaccinated controls.

Available data suggests that there are no major safety concerns with LLR. Trials carried out in Beijing, Guangxi province, and Zhejiang province reported mild side effects, with 5.6%–8.2% of vaccinated children experiencing low-grade fever and 0%–2.1% reporting high-grade fever. There has been one case report of intussusception following vaccination with LLR. Appropriately powered studies to assess differences in intussusceptions rates in vaccinated vs unvaccinated children have yet to be reported.

LLR has never been tested in a randomized, placebo-controlled phase III clinical trial, so the true efficacy of the vaccine is unknown. In all of the reported trials, the majority of children were vaccinated during or after the peak age for rotavirus disease. In China, 50% of rotavirus infections occur between the ages of 6 and 11 months. It is unknown whether vaccinated children had prior natural rotavirus infection, in which case LLV could be boosting an already present immune response. The efficacy of LLR in rotavirus-naive populations is unknown. Controlled studies in which children are vaccinated prior to peak age of rotavirus incidence are necessary to demonstrate its true efficacy and potential impact on rotavirus gastroenteritis.

Vaccines under development

In India, two live, cell line-adapted human viruses obtained from asymptomatic neonatal strains (116E and I321) recently underwent early clinical evaluation. Candidates using both vaccines were shown to be safe, with adverse event rates not statistically different in the vaccinated vs placebo groups. 116E, a predominately human vaccine strain of serotype G9P[11], with the VP4 appearing to be a natural reassortant from a bovine strain of rotavirus, seems to be more promising. Immunologic evaluation showed a 73% serum IgA conversion rate compared with 20% in the placebo group. I321 was less immunogenic, resulting in 39% seroconversion. A subsequent immunogenicity study of 116E in 93 and 91 children receiving 10^4 and 10^5 focus-forming units of vaccine virus, respectively, were compared with 184 placebo recipients. There was a ≥4-fold increase in antirotavirus IgA titers in 66.7% of children receiving the lower dose and 62.1% of children receiving the higher dose after the first dose compared with 18% of placebo recipients. After 3 doses, 64.5% of infants receiving the lower dose and 89.7% of those receiving the higher dose had a ≥4-fold increase in IgA compared with 25% of placebo recipients. No increase in adverse events was found between vaccine and placebo recipients. This vaccine is scheduled to begin phase III efficacy trials in late 2010.

Early rotavirus vaccine development studies are underway in Vietnam in an effort to produce inexpensive rotavirus vaccine locally. Three human rotavirus strains (genotypes G1P[8], G1P[4], and G4P[6]) have been characterized for potential use in a live attenuated vaccine. The wild-type viruses for these strains have been passed more than 30 times, each through cell culture with the goal of developing an effective indigenously produced vaccine. The results of clinical trials are not yet available.

Additional considerations

Special populations

As a part of the RV5 REST trial, 2,070 preterm infants (gestational age, 25–36 weeks; median age, 34 weeks) were evaluated in a substudy. Vaccine efficacy was 73.0% (95% CI: −2.2 to 95.2) against all rotavirus gastroenteritis for the first season of follow-up, indicating that prematurity does not drastically reduce vaccine effectiveness.

There is some concern about vaccine-associated rotavirus disease occurring in immunocompromised individuals. There was a report of vaccine-acquired rotavirus disease following RV5 administration in three infants with severe combined immunodeficiency (SCID); RV5 is now contraindicated in children with SCID. Further studies are needed to determine the safety and efficacy of both RV1 and RV5 in severely immunocompromised individuals. The effect of vaccination in HIV infected infants was studied in the RV1 clinical trials. A substudy of the trial in South Africa showed that there was no increase in mortality in HIV-positive vaccine recipients and no difference in adverse events.

Viral shedding

For RV5, during REST and other phase III studies, potential fecal shedding between 4 and 6 days after each dose was monitored in nearly 250 children. In the 4- to 6-day period after the first dose, 8.9% of 360 RV5 recipients had detectable shedding by plaque assay of vaccine strains after the first dose. No shedding was detected after the second or third doses in vaccine recipients.

For RV1, viral shedding was evaluated in early clinical trials. In one study of 213 infants, vaccine-type virus was shed in 28% of vaccine recipients 3 weeks after first immunization. After the second dose of vaccine, the proportion of shedding after 3 weeks was only 5%. Studies of the concentration of vaccine virus in phase I and III trials have...
ranged from $10^4$ to $10^6$ plaque-forming units of vaccine virus to placebo. For both RV1 and RV5, the potential for disease transmission from viral shedding remains unclear.

**Breastfeeding**

Preliminary evidence suggests that the efficacy of RV5 does not appear to be adversely affected by breastfeeding. The efficacy, assessed retrospectively from a cohort from the REST trial, against all rotavirus gastroenteritis for infants never breastfed, sometimes breastfed, or exclusively breastfed was 68.3% (95% CI: 46.1–82.1), 82.2% (95% CI: 72.3–89.0), and 68.0% (95% CI: 53.8–78.3), respectively. Initial analysis of RV1 suggested that exclusive breastfeeding resulted in a 10%–12% decrease in vaccine take; however, response remained high in all groups. The clinical significance of the slight difference in immune response with exclusive breastfeeding remains unclear. Further trials are needed to establish the relationship between breastfeeding and vaccine efficacy in a variety of developing country settings.

**Concomitant administration with other vaccines**

Clinical trials have shown that oral rotavirus vaccine administration does not affect the immunogenicity of routine injected vaccines. There has been a fear of reduced immune response to rotavirus vaccine when given together with oral polio vaccine (OPV). In a study of 735 healthy infants in Latin America, children were randomized to receive RV5 concomitantly with OPV for 2 weeks prior to the OPV administration. Compared with staggered administration, the geometric mean titer of antirotavirus IgA was reduced by 46% with concomitant administration. However, the IgA titer in the concomitant-use group increased by ≥3-fold between doses 1 and 3 in 93% of subjects, meeting the definition of noninferiority of immune response. For RV1, studies in South Africa and Bangladesh found no statistically significant difference in rotavirus IgA seroconversion rates when RV1 was administered with and without OPV. Therefore, it appears that there is no contraindication to giving oral rotavirus vaccines simultaneously with OPV.

**Dosing schedules**

The rotavirus vaccine schedule is timed with other recommended routine infant immunizations. RV5 is given at the same time as the primary diphtheria-tetanus-pertussis series, whereas RV1 is given with the first DTP dose, and either the 2nd or 3rd dose, depending on the country. The CDC and WHO recommend that the first dose be given between the ages of 6 and 15 weeks and final dose be given by 32 weeks due to a lack of safety and efficacy data outside this age range. In developing countries, a significant number of children receive their primary DTP series outside these age ranges. Catch-up campaigns in older children are a common strategy for rapidly reducing disease burden in newly vaccinated populations and maintaining coverage in children missed during routine immunization. Due to lack of safety data in older children, no catch-up campaigns have been attempted with rotavirus vaccines. Additional research on safety is needed in children immunized outside of the recommended age range to inform scheduling.

The long-term immunogenicity of rotavirus vaccine is unknown or is the effect of reduced transmission on the maintenance of immunity in older children and adults. In this sense, it is not known if a booster dose is needed to maintain protective immunity, however observations of reduced efficacy in older infants suggest protection, may wane. Ongoing longitudinal surveillance in recently introduced countries is necessary to determine long-term control strategies once infant disease is controlled.

**Serotype shift/replacement**

Rotavirus shows considerable geographic and temporal variation in serotypes. In addition, wild-type reassortments continually occur and have the potential to affect clinical disease. Because of this natural variance and the relatively short time period in which rotavirus vaccines have been in routine use, it is not yet clear of the impact that routine vaccination will have on the serotype profile of disease-causing rotavirus strains, and whether serotype replacement will occur over time. Although some studies have suggested a change in serotype profile following vaccine introduction, it is not clear whether this change is due to vaccination or part of the normal serotype variation seen with rotavirus disease. Ongoing surveillance is needed in both developed and developing country settings to assess the affect of routine vaccination on the changing serotype profile and what serotypes are responsible for human disease.

**Relative effectiveness of RV1 and RV5**

The difference in efficacy and effectiveness between RV1 and RV5 has not been studied in a head-to-head clinical trial but appear to be similar based upon reported effect against severe rotavirus disease from single-vaccine clinical trials. In addition, the efficacies of both RV1 and RV5 against severe rotavirus disease vary depending on the income status of the countries that hosted the studies (Figure 1). Although overlap
exists between the efficacies estimated for each income group, and estimates likely vary based on the definition of severe gastroenteritis and length of follow-up, the overall trend is apparent; rotavirus vaccines are less effective in lower income settings. Lower efficacy in low-income settings is likely a combination of poor immunological response caused by malnutrition, other intestinal infections, and immunosuppression efficacy against other oral vaccines, as has been seen with the OPV. Across the listed studies, the average efficacy for high, upper middle, lower middle, and low income countries are 90%, 85%, 66%, and 55%, respectively.

Updated global estimations of rotavirus mortality

The most recent global estimations for rotavirus mortality were calculated based on child diarrheal mortality figures from 2004. However, the Child Health Epidemiology Reference Group at the WHO recently released data showing a substantial decline in global diarrheal morality. To update global rotavirus mortality estimates, we followed the methodology described by Parashar et al using 2008 country-level estimations of the number of deaths due to diarrhea in children aged younger than 5 years in 2008. The use of rotavirus vaccine was controlled in countries who introduced rotavirus vaccine prior to 2008 by reducing the proportion of diarrhea caused by rotavirus based on the rotavirus immunization coverage in 2008 or national estimates for coverage of three doses of diphtheria, pertussis, and tetanus vaccine (DTP-3) if rotavirus estimations were not available.

Rates of deaths based on national income status (Table 2), region (Table 3), and national levels (Figures 2 and 3) are provided. In 2008, rotavirus was responsible for nearly 400,000 deaths (Table 2) or the deaths of approximately 4% of all children aged younger than 5 years. Varying the regional proportion of diarrheal deaths caused by rotavirus to the extreme estimates provided by Parashar et al gives low and high estimates of 320,000 and 440,000 deaths. As with previous estimates, the vast majority of deaths occur in low and lower middle income countries (Tables 2 and 3). Nine countries in Africa and Asia had more than 10,000 childhood rotavirus deaths in 2008 (Figure 2) while 30 countries had an incidence of rotavirus death greater than 100 per 100,000 children aged younger than 5 years (Figure 3).

Potential impact of rotavirus vaccination on diarrheal mortality

By applying the average efficacies from national income status to the regional rotavirus mortality and hospitalization estimates calculated by Parashar et al and to the country-level DTP-3 coverage in 2008, we are able to estimate the potential impact of rotavirus vaccine. Country-level reductions were summed to predict the potential impact of the vaccines on rotavirus deaths and rates of deaths based on national income status (Table 4), region (Table 5), and national levels (Figures 4–6).

The potential impact of rotavirus vaccines is striking. If rotavirus vaccines were introduced at the current coverage of DTP-3, it would prevent approximately 166,000 deaths in children aged younger than 5 years each year globally (Table 4). Varying the regional proportion of diarrheal deaths caused by rotavirus to the extreme estimates provided by Parashar et al gives low and high estimates of 137,000 and 190,000 deaths prevented. Rotavirus vaccine is most effective in high-income countries, preventing approximately 71% of rotavirus deaths and 26% of diarrheal deaths. The two most populous upper middle income countries, Brazil and Mexico, already introduced rotavirus vaccines by 2008. However, in upper middle income countries that have not yet introduced the vaccine, it would prevent 64% and 21% of rotavirus and diarrheal deaths. Vaccination at current DTP-3 levels in low and lower middle income countries would prevent less than 45% and 12% of rotavirus and diarrheal deaths, respectively, due to low efficacy and poor vaccine coverage in many countries. However, due to the large burden of diarrhea deaths in regions.

Table 2 Deaths due to rotavirus in children aged younger than 5 years, stratified by national income stratum

<table>
<thead>
<tr>
<th>Income classification*</th>
<th>Total</th>
<th>Per 100,000 children younger than 5 y</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>413</td>
<td>0.6</td>
</tr>
<tr>
<td>Upper middle</td>
<td>5,330</td>
<td>6.9</td>
</tr>
<tr>
<td>Lower middle</td>
<td>191,264</td>
<td>53.4</td>
</tr>
<tr>
<td>Low</td>
<td>189,106</td>
<td>137.9</td>
</tr>
<tr>
<td>Total</td>
<td>386,113</td>
<td>209.7</td>
</tr>
</tbody>
</table>

Table 3 Deaths due to rotavirus in children aged younger than 5 years, stratified by region

<table>
<thead>
<tr>
<th>World bank Region</th>
<th>Rotavirus deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
</tr>
<tr>
<td>Africa</td>
<td>236,519</td>
</tr>
<tr>
<td>Asia</td>
<td>144,095</td>
</tr>
<tr>
<td>Europe</td>
<td>167</td>
</tr>
<tr>
<td>Latin America and Caribbean</td>
<td>5,000</td>
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<tr>
<td>North America</td>
<td>3</td>
</tr>
<tr>
<td>Oceania</td>
<td>328</td>
</tr>
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</table>
these countries and large birth cohorts, 98% of preventable rotavirus deaths occur in low and lower middle income countries. Similarly, the highest incidence of preventable deaths is also seen in lower income countries. The number of preventable rotavirus deaths per 100,000 children in low-income countries is over 100 times than that seen in high-income countries.

Regionally, the potential impact of rotavirus is highest in Africa and Asia, where 99% of preventable rotavirus deaths occur, which also have the higher incidence of preventable disease (Table 3). The highest absolute numbers of preventable deaths occur in the large, populous countries, such as India, Nigeria, the Democratic Republic of the Congo, Afghanistan, and Ethiopia (Figure 2), which account for 81,000 (49%) of preventable deaths, in which India alone accounts for 16% of preventable deaths. Globally, 26 countries would prevent >50 deaths per 100,000 children younger than 5 years if rotavirus vaccine was introduced (Figure 3), with the majority of high-incidence countries located in Sub-Saharan Africa. Such a substantial reduction in deaths would go a long way towards helping countries to reach the Millennium Development Goal 4 of reducing child mortality.
Although vaccine efficacy is lower in low-income settings, poor routine vaccination coverage reduces the potential impact of rotavirus vaccination substantially. If vaccination with rotavirus reached 100% of children, 237,000 deaths (children aged younger than 5 years, would be averted each year; an additional 71,000 deaths averted compared with those using current DTP-3 coverage. In some countries, poor vaccine coverage nearly negates the potential impact of rotavirus vaccines. In Chad, eg, the WHO estimates that only 20% of children received DTP-3 in 2008; combined with the efficacy seen in low-income countries, only 11% of rotavirus cases would be prevented. Similarly, many countries with high number of deaths due to rotavirus have poor vaccine coverage. India, which has a national DTP-3 coverage of 66%, could prevent an additional 14,000 rotavirus deaths. Clearly, strengthening routine immunization is critical to maximize the impact of any new vaccine and ensure protection with traditional childhood immunization.

There are several reasons to believe that the estimations provided here are not entirely accurate. Parashar et al³ noted that more recent studies show a higher proportion of severe diarrhea caused by rotavirus in low-income countries compared with older studies, suggesting an underestimate in the proportion of diarrheal deaths caused by rotavirus. RV1 is administered following a two-dose schedule, so DTP-3 coverage estimates would underestimate impact for any country using RV1. Both RV1 and RV5 provide some protection with incomplete vaccination and as a result, the proportion of disease prevented would be higher in developing countries where a substantial number of children are only partially immunized.¹¹ On the contrary, many developed countries have substantial delays in infant immunization,¹¹ nin which would miss early rotavirus cases and reduce impact. Efficacy estimations do not include herd effects of immunization, which have been suggested to increase efficacy by 13%–25%.¹²

**Conclusion**

Rotavirus is the leading cause of diarrheal morbidity and mortality globally, with nearly every child being infected in early childhood. Updated estimates indicate that over 380,000 rotavirus deaths occurred in 2008. Although treatment strategies exist, most deaths occur in settings where access to care is limited. Preventative strategies are limited, and sanitation-based strategies are not effective at preventing the spread of the virus. As a result, several rotavirus vaccines have been developed from animal, human, and hybrid strains. Two rotavirus vaccines have been licensed and used internationally, with several others being developed. Of the licensed vaccines, clinical trials have demonstrated excellent efficacy, although has generally been lower in low-income settings. Introductions with both the licensed vaccines have been promising and have shown an impact on rotavirus and all-cause diarrhea in both high-income and low-income settings. Using estimations of rotavirus and current immunization levels, rotavirus vaccine would prevent

<table>
<thead>
<tr>
<th>World Bank Region</th>
<th>Diarrheal deaths prevented Total</th>
<th>Per 100,000 children aged younger than 5y</th>
<th>Proportion prevented Rotavirus deaths, %</th>
<th>Diarrheal deaths, %</th>
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<tr>
<td>Africa</td>
<td>95,623</td>
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<td>67,803</td>
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<td>Europe</td>
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<td>0.4</td>
<td>80</td>
<td>31</td>
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<td>Latin America and Caribbean</td>
<td>2,145</td>
<td>3.8</td>
<td>31</td>
<td>11</td>
</tr>
<tr>
<td>Oceania</td>
<td>121</td>
<td>4.3</td>
<td>37</td>
<td>15</td>
</tr>
</tbody>
</table>

**Table 4** Impact of rotavirus vaccines on diarrheal deaths if introduced at level of DTP-3, stratified by national income stratum

**Table 5** Impact of rotavirus vaccines on diarrheal deaths if introduced at level of DTP-3, stratified by region

Note: ³³World Bank 2008 classification. GNP per capita estimations from the US Government¹³¹ were used to approximate GNI for the Cook Islands, Nauru, Niue, and Tuvalu.
Figure 4 Total deaths prevented by rotavirus vaccine in children aged under 5 years if introduced at level of DTP-3.

Figure 5 Total deaths prevented by rotavirus vaccine per 100,000 children aged younger than 5 years if introduced at level of DTP-3.

Figure 6 Global status of routine introduction of rotavirus vaccination.
over 160,000 deaths yearly if introduced on a global level. The largest impact on mortality would be seen in low-income and middle-income countries, despite poor immunization coverage and lower efficacy. Thanks to international efforts, vaccine introduction is progressing in both high-income and low-income settings. However, focused efforts are needed on large, highest burden countries if rotavirus mortality is to be reduced dramatically.

**Disclosure**

The authors report no conflicts of interest in this work.

**References**


