Rotavirus Vaccines in Routine Use

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Vaccines are now available to combat rotavirus, the most common cause of severe diarrhea among children worldwide. We review clinical trial data for available rotavirus vaccines and summarize postlicensure data on effectiveness, impact, and safety from countries routinely using these vaccines in national programs. In these countries, rotavirus vaccines have reduced all-cause diarrhea and rotavirus hospitalizations by 17%–55% and 49%–92%, respectively, and all-cause diarrhea deaths by 22%–50% in some settings. Indirect protection of children who are age-ineligible for rotavirus vaccine has also been observed in some high and upper middle income countries. Experience with routine use of rotavirus vaccines in lower middle income countries has been limited to date, but vaccine introductions in such countries have been increasing in recent years. The risk-benefit analysis of rotavirus vaccines is extremely favorable but other strategies to improve the effectiveness of the vaccine, particularly in lower middle income settings, should be considered.

Keywords. rotavirus; rotavirus vaccine.

Despite declining child mortality due to diarrhea, rotavirus persists as the most common cause of severe dehydrating diarrhea among children <5 years of age worldwide. In 2008, rotavirus caused an estimated 453,000 deaths in children <5 years of age globally and it has consistently been shown to be a major cause of diarrhea hospitalizations in countries of all income levels [1–3] (Table 1). To combat this tremendous disease burden, several vaccines against rotavirus have been developed. In 1998, a rhesus–human reassortant rotavirus vaccine, RotaShield (Wyeth), was introduced in the US national immunization program. However, this vaccine was withdrawn within a year because it was associated with intussusception, a condition in which one portion of the bowel telescopes into another, resulting in a blockage [4, 5]. RotaShield caused approximately 1 excess case of intussusception among every 10,000 vaccinated children [6]. Two new live attenuated oral rotavirus vaccines, RotaTeq (RV5, Merck and Co) and Rotarix (RV1, GSK Biologicals), were licensed in 2006 and, by the end of 2013, were being used in the national immunization programs in >50 countries globally [7, 8] (Figure 1). In this article, we review clinical trial data for RV5 and RV1 as well as postlicensure data on effectiveness, impact, and safety from countries routinely using these vaccines in national programs.

CLINICAL TRIALS OF ROTAVIRUS VACCINES

RV5 is a pentavalent bovine–human reassortant vaccine (G1–G4 and P[8]) given as 3 oral doses, whereas RV1 is a monovalent human rotavirus vaccine (G1P[8]) given as 2 oral doses. Initial clinical trials for these vaccines performed in Europe and the Americas showed high vaccine efficacy against the predominant strains that were circulating at the time of the trials. RV1 was 85% efficacious in Latin America and 96% efficacious in Europe against severe rotavirus disease [7, 11]. In the United States and Finland, efficacy of RV5 was 98% against severe rotavirus disease [8, 12]. Efficacy of both vaccines was maintained over the first few years of life [11–15]. Furthermore, these trials enrolled 60,000–70,000 infants each to specifically assess any association with intussusception. No increased risk of
intussusception was identified within 42 days of the 3 RV5 doses or within 31 days of the 2 RV1 doses. Following availability of these data, in 2006 the World Health Organization (WHO) recommended use of the vaccine in high and upper middle income settings, where efficacy had been demonstrated [16].

WHO also recommended additional clinical trials for rotavirus vaccine to be performed in lower middle income settings, as other live oral vaccines have performed less well in lower middle income compared with high income settings [17–26]. Although the reasons for this gradient in efficacy are not fully understood, possibilities include differences in host factors such as higher levels of maternal antibody, persistent exposure to pathogens in the environment, higher prevalence of malnutrition, frequent comorbidities, and concurrent administration of oral polio vaccine, which adversely affects rotavirus vaccine performance [27].

Additional clinical trials of both vaccines performed in Africa and Asia showed modest efficacy against a range of strains that were circulating during the time of these trials. RV1 was 59%–64% efficacious against severe rotavirus diarrhea during the first year of life in South Africa and Malawi [28]. RV5 efficacy against severe rotavirus gastroenteritis was 64% during the first year of life in Africa (Ghana, Kenya, and Mali) and 51% in Asia (Vietnam and Bangladesh) [29, 30]. In trials, efficacy of these vaccines appeared to be lower in the second year of life [29, 31]. However, even with lower efficacy, rotavirus vaccine has great potential for substantial impact in lower middle income settings given the high vaccine-preventable disease burden [32]. For example, vaccine efficacy was 49% in Malawi compared with 77% in South Africa [28]. However, because Malawi had a higher background rate of rotavirus disease than South Africa, the vaccine prevented 7 episodes of severe rotavirus gastroenteritis per 100 vaccinated children in Malawi compared with 4 episodes per 100 vaccinated children in South Africa [28]. In 2009, following availability of these data, WHO recommended rotavirus vaccines use in all countries globally and especially those countries with high child mortality due to diarrhea [33–35].

**IMPACT OF ROUTINE ROTAVIRUS VACCINATION ON MORBIDITY AND MORTALITY FROM DIARRHEA**

The impact of rotavirus vaccine on all-cause and rotavirus diarrhea has been rapid and dramatic in early vaccine-introducing countries (Figure 2). In the United States, which was the first country to introduce rotavirus vaccine (in February 2006), rotavirus hospitalizations have declined 60%–83% in children <5 years of age, and all-cause diarrhea hospitalizations decreased by 29%–50% in this same age group following vaccine introduction [36–41]. Additionally, rotavirus vaccine was shown to offer indirect protection to children too old to have received the vaccine and to young adults. Rotavirus hospitalizations among children 2–4 years of age who were age-eligible to receive the vaccine declined by 41%–80%, and all-cause diarrhea hospitalizations declined by 35%–41% [36, 37]. Significant reductions of 8%–30% in unspecified gastroenteritis hospitalizations and 53%–71% in rotavirus-coded hospitalizations have also been observed among older children and young adults 5–24 years of age [42, 43]. Additionally, compared to the pre-vaccine era, rotavirus seasons were diminished in magnitude and shorter in duration following vaccine introduction [44]. A biennial pattern of relative increases in activity has also emerged, but activity remains well below prevaccine levels [44]. Over 2 seasons from 2008 to 2009, an estimated total of 60 000–80 000 diarrhoeal hospitalizations were prevented, resulting in a medical cost savings of $240–$280 million [45].

Similar declines in rotavirus and all-cause diarrhea hospitalizations have been noted in other early vaccine-introducing countries. Following vaccine introduction in 2006, Austria observed a 70%–79% reduction in rotavirus hospitalizations [46–48]. Belgium, which introduced rotavirus vaccine in 2007, experienced a 33% reduction in all-cause diarrhea hospitalizations among children <2 years of age and 49%–77% reduction in rotavirus hospitalizations [49, 50]. Rotavirus hospitalizations and emergency department visits among children <2 years of age declined by 92% following vaccine introduction in Finland in 2009 [51]. Australia, which introduced rotavirus vaccine in 2008, documented declines of 50%–87% in rotavirus hospitalizations and 20%–40% in diarrhea hospitalizations in children <5 years of age [52–55]. Additionally, rotavirus hospitalizations among children who were age-eligible to receive rotavirus vaccine in Belgium, Austria, Finland, and Australia also decreased by 20%–89% [47, 49, 51, 53, 56, 57]. Australia also documented a decline of 30%–49% in all-cause diarrhea hospitalizations among age-eligible children [53, 56].

Early-introducing upper and lower middle income countries in Latin America had similar experiences with decreases in all-cause diarrhea and rotavirus hospitalizations following vaccine introduction. Following rotavirus vaccine introduction in 2006

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<th>Table 1. Proportion of Diarrhea Hospitalizations Due to Rotavirus Among Children &lt;5 Years of Age</th>
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Adapted from Tate et al [1].
Figure 1. Countries that have introduced rotavirus vaccine into their national immunization program through 31 March 2014, by income level, based on World Bank classification [9]. Figure created from data in [10].
in El Salvador, all-cause diarrhea healthcare encounters (hospitalizations and outpatient visits) declined by 28%–37%, and rotavirus hospitalizations in children <5 years of age declined by 69%–81% [58]. In Brazil, which also introduced rotavirus vaccination in 2006, all-cause diarrhea hospitalizations in children <5 years of age decreased by 17%–55% and rotavirus hospitalizations by 59% [59–61]. Panama observed a 37% decrease in diarrhea hospitalizations in children <5 years of age following vaccine introduction in 2006 [62]. All-cause diarrhea hospitalizations in Mexico declined by 40% during the rotavirus season following vaccine introduction in 2007 [63]. Indirect protection of children age-ineligible to receive rotavirus vaccine was also observed in Brazil and El Salvador, with a 24% reduction in rotavirus hospitalizations among children 2–4 years of age in Brazil and a 41%–81% reduction in the same age group in El Salvador [58, 60].

In addition to documenting decreases in hospitalizations, Mexico, Brazil, and Panama also observed declines in diarrhea mortality following vaccine introduction [59, 64–68]. In Mexico, 74% of children <1 year of age had received at least 1 dose of rotavirus vaccine by December 2007 [64]. The all-cause diarrhea mortality rate in children <5 years of age subsequently declined by 35% in 2008, resulting in almost 700 fewer diarrheal deaths in this age group in 2008 alone [64]. A larger decrease was observed in the mortality rate of children <1 year of age where the all-cause diarrheal mortality rate fell by 41% compared with the prevaccine baseline from 2003 to 2006 [64]. These reductions in rotavirus mortality have been sustained over 4 postvaccine introduction years in all regions of Mexico with the largest decline of 56% observed during the rotavirus season [65, 66]. Brazil documented a 22%–39% decline in the all-cause diarrhea mortality rate in children <5 years of age following rotavirus vaccine introduction in 2006, and Panama similarly documented a decrease of 32%–50% in all-cause diarrhea mortality in children <5 years of age following vaccine introduction in 2006 [59, 67, 68].

In 2009, South Africa, an upper middle income country, became the first country in sub-Saharan Africa to introduce rotavirus vaccine into its national immunization program. During the first 2 May to December rotavirus seasons after vaccine introduction, all-cause diarrhea hospitalizations in children <5 years of age decreased by 32%–33% and rotavirus hospitalizations decreased by 54%–58% [69]. Even larger decreases in all-cause diarrhea and rotavirus hospitalizations of 38%–43% and 61%–69%, respectively, were seen in children <1 year of age, among whom 2-dose coverage increased from 40%–45% to 56%–78% during the study period.

![Figure 2](image-url). Percentage of reduction in the number of diarrhea deaths (A), diarrhea hospitalizations (B), and rotavirus hospitalizations (C) in children <5 years of age following rotavirus vaccine introduction by country income level. For articles that reported percentage reduction separately by year, individual bars were included for each data point.
Figure 2 continued.
Experience with rotavirus vaccine is sparse in lower-income settings (Figure 1). By the end of 2013, rotavirus vaccine had been introduced into 19 lower middle income countries with assistance from the GAVI Alliance [10]. Fourteen of these introductions occurred during 2012 and 2013 and data on impact are not yet available. In 2006, Nicaragua became the first GAVI-eligible country to introduce rotavirus vaccine through a public–private donation project. GAVI-assisted rotavirus vaccine introductions followed in Bolivia in 2008, Honduras and Guyana in 2009, and Sudan in 2011. Published data on rotavirus vaccine impact in these countries are limited. In Nicaragua, all-cause diarrhea hospitalizations declined by 29% during the rotavirus season among children <1 year of age following vaccine introduction but remained unchanged during the non–rotavirus seasons and among children 1–4 years of age [70]. In a community-based cohort study in Nicaragua, a 40% decrease in the incidence of watery diarrhea among children <5 years of age was observed following vaccine introduction [71]. The number of all-cause diarrhea deaths among children 0–5 years of age was estimated to decline by 36%–43% in Bolivia and by 16%–20% in Honduras following vaccine introduction and the number of all-cause diarrhea hospitalizations were similarly estimated to decline by 9%–11% in Bolivia and by 12%–18% in Honduras [72]. Additional studies are ongoing to document the impact of rotavirus vaccines in lower middle income settings.

FIELD EFFECTIVENESS OF ROTAVIRUS VACCINATION

Field effectiveness of the vaccine, most often measured through case-control evaluations, against rotavirus hospitalizations in high and upper middle income countries, including in Australia, Belgium, Brazil, France, Germany, Israel, Mexico, Spain, Taiwan, and the United States, has been shown to be high (79%–100%) and similar to the efficacy of both vaccines in the phase 3 clinical trials [73–92] (Figure 3). Additionally, rotavirus vaccines have been shown to provide good protection against a variety of strains in high and upper middle income countries, including strains not
included in the vaccine. For example, RV1 was 94% effective against G9P[4] in Mexico, 88%–94% effective against G2P[4] and 74% effective against G3P[8] in the United States, and 75%–77% effective against G2P[4] in Brazil [75, 76, 80, 86, 88]. Similarly, RV5 was 83% effective against G12P[8] and 87%–98% effective against G2P[4] in the United States [86, 88].

Due to the 2-phase recommendation by WHO for use of rotavirus vaccines in high and lower middle income settings, post–vaccine introduction effectiveness data are limited in lower middle income settings. However, several lower-middle income countries in Latin America introduced rotavirus vaccine following the initial 2006 recommendation, and these countries have provided some of the first post–vaccine introduction effectiveness estimates for rotavirus vaccine use in these settings [70, 93–95]. Rotavirus vaccine effectiveness in these countries is comparable to the efficacy observed in clinical trials in lower middle income settings. In Nicaragua, rotavirus vaccine was 43%–49% effective against rotavirus disease requiring hospitalization or intravenous rehydration but appeared to wane in children ≥1 year of age [70, 93]. In Bolivia, rotavirus vaccine was 69%–77% effective against rotavirus hospitalizations, with high effectiveness demonstrated against a variety of circulating strains including G9P[8], G3P[8], G2P[4], and G9P[6] [96]. Effectiveness studies are ongoing in some early-introducing lower middle income countries in Africa, but the results from these studies are not yet available.

POSTLICENSURE VACCINE SAFETY

Although large prelicensure trials of both vaccines did not show an increased risk of intussusception, postlicensure monitoring was specifically recommended to further examine this issue, including examining risks in smaller time windows. Studies conducted in Mexico and Australia identified a low-level risk of approximately 1–2 excess cases of intussusception per 100 000 vaccinated children, mostly in the first week after the first dose of vaccine [97–99]. No increased risk was observed after the first dose of rotavirus vaccine in a similar analysis in Brazil, but a low risk was observed following the second vaccine dose [98]. Following the availability of these data, WHO conducted a risk-benefit analysis and concluded that the benefits of rotavirus vaccine outweighed the low-level risk of intussusception and reaffirmed its recommendation for use of rotavirus vaccines in all countries globally [100]. Recent studies in the United States also found a risk of 1–5 excess cases of intussusception per 100 000 vaccinated infants [101, 102]. Again, policy bodies concluded that the benefits of vaccination in the United States greatly exceed the low risk. Studies to examine the risk of intussusception following rotavirus vaccine introduction in Africa are currently being conducted.

In 2010, DNA from porcine circovirus type 1 (PCV1) was detected in 2 commercial lots of RV1 vaccine [103]. Use of this vaccine was temporarily suspended by the US Food and Drug Administration (FDA) in March 2010, but global bodies including WHO continued to recommend use of rotavirus vaccine [104–107]. In May 2010, DNA from PCV1 and a related porcine circovirus type 2 (PCV2) was identified in RV5. Porcine circoviruses commonly infect pigs but are not known to cause infection or illness in humans, and there was no evidence that they posed a safety risk. After weighing the benefits of rotavirus vaccine against a theoretical risk from PCV1 or PCV2 contamination, the FDA’s Vaccine and Related Biological Products Advisory Committee recommended resumed use of RV1 and continued use of RV5 in the United States in May 2010 [108]. WHO and regulatory authorities in other countries also concluded that the benefits of rotavirus vaccine outweighed any theoretical risk [107, 109, 110]. Vaccine manufacturers are working to remove porcine circovirus from these vaccines.

Rotavirus vaccine strains replicate in the intestinal tract and can be shed in stool following vaccine administration. Thus, transmission of vaccine or vaccine-reassortant strains is a possibility. The transmission of an RV5 vaccine–derived strain from a recent vaccine recipient to an unvaccinated sibling was first documented in 2009 [111]. Additional patients with acute gastroenteritis and vaccine-reassortant rotavirus strains have been identified through active surveillance, although it has often been difficult to determine the extent to which the rotavirus detected contributed to the patients’ symptoms [112–114]. Although data are sparse, one study estimated that such vaccine-derived reassortant–associated disease occurs at a rate of about 1 per 140 000 vaccinated infants [111].

VACCINATION SCHEDULE

Due to concerns of an age-dependent risk of intussusception with rotavirus vaccines, WHO initially recommended that the vaccine be administered by 12 weeks of age, when the risk of natural intussusception was low [16]. However, in 2009, when rotavirus vaccine was recommended for use in all countries globally, the age restriction was relaxed; the administration window for the first dose of vaccine was extended up to 15 weeks of age, and the last dose of vaccine was to be administered by 32 weeks of age [33–35]. In 2013, WHO again evaluated the age restrictions and recommended that they be removed to allow for greater vaccine coverage and greater reductions in rotavirus mortality, as children in high-mortality settings often presented late for vaccination [100]. In these settings, rotavirus vaccine is now recommended to be given whenever children present for their routine immunizations. The benefits of rotavirus vaccination still outweigh the risk of intussusception, as universal use of rotavirus vaccine with the removal of the age restrictions could prevent an additional 47 000 deaths annually while potentially causing an additional 300 deaths due to intussusception in
children <5 years of age [115]. However, each country that introduces rotavirus vaccine into its national immunization program sets its own policy regarding age restrictions for administration. In some countries, the age restrictions appeared to prevent rotavirus vaccine from achieving the same coverage levels of other routine infant immunizations but in other countries appeared to increase the timeliness of other immunizations [116–118].

Clinical trials are under way to identify other administration schedules. A recent randomized clinical trial evaluated the immunogenicity of 2 different 2-dose RV1 schedules (dose given at 6 and 10 weeks [the WHO recommended schedule] and 10 and 14 weeks of age) as well as that of a 3-dose RV1 schedule given at 6, 10, and 14 weeks of age [119]. No significant difference in immunogenicity of the different schedules was observed in this trial; additional trials are ongoing to further address this issue.

Because rotavirus disease occurs early in life, particularly in developing countries, successful administration of vaccine in the neonatal period would potentially offer additional public health benefit. However, because of greater levels of passively transferred maternal antibody in younger infants, the performance of vaccine may be hampered and trials will be required to assess the benefits of such schedules.

VACCINES IN THE PIPELINE

Recently published results from a phase 3 clinical trial for an Indian-manufactured live, oral, attenuated rotavirus vaccine (Rotavac, Bharat Biotech) based on the natural human–bovine reassortant strain, G9P[11], which causes asymptomatic infection in neonates, was 56% effective against severe rotavirus gastroenteritis during the first year of life [120]. The efficacy of this vaccine from the multicenter trial in India was comparable to that of the 2 internationally licensed rotavirus vaccines in lower middle income settings. Several other live, oral rotavirus vaccines, as well as inactivated vaccines, are in development [121]. Alternate dosing schedules, including a neonatal dosing schedule, are also being evaluated [122, 123].

CONCLUSIONS

In countries where rotavirus vaccine has been introduced into the national immunization program, a significant impact has been noted on all-cause diarrhea and rotavirus hospitalizations and, in some settings, on all-cause diarrhea mortality rates. Indirect protection of children age-ineligible for rotavirus vaccine has also been observed. Experience with rotavirus vaccines in lower middle income countries has been limited to date. However, given that 14 lower middle income countries introduced rotavirus vaccination with assistance from the GAVI Alliance in 2012 and 2013, data on vaccine impact and effectiveness in these settings will be available over the next several years. Additional data on strain-specific effectiveness and waning immunity will also become available. Although a low risk of intussusception associated with rotavirus vaccine has been documented, the risk-benefit analysis of vaccination remains highly favorable.

Notes

Disclaimer. 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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References

42. Lopman BA, Curns AT, Yen C, Parashar UD. Infant rotavirus vaccination may provide indirect protection to older children and adults in the United States. J Infect Dis 2011; 204:980–6.
56. Clarke MF, Davidson GP, Gold MS, Marshall HS. Direct and indirect impact on rotavirus positive and all-cause gastroenteritis.


