



Published in final edited form as:

Clin Infect Dis. 2016 May 01; 62(Suppl 2): S91–S95. doi:10.1093/cid/civ1015.

Health Impact of Rotavirus Vaccination in Developing Countries: Progress and Way Forward

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Abstract

Two rotavirus vaccines have been licensed in >100 countries worldwide since 2006. As of October 2105, these vaccines have been implemented in the national immunization programs of 79 countries, including 36 low-income countries that are eligible for support for vaccine purchase from Gavi, the Vaccine Alliance. Rotavirus vaccines were initially introduced in Australia and countries of the Americas and Europe after completion of successful clinical trials in these regions, and the impact of routine vaccination in reducing the health burden of severe childhood gastroenteritis in these regions has been well documented. Because of concerns around the performance of orally administered rotavirus vaccines in developing countries, vaccine implementation in these settings only began after additional clinical trials were completed and the World Health Organization issued a global recommendation for use of rotavirus vaccines in 2009. This supplementary issue of *Clinical Infectious Diseases* includes a collection of articles describing the impact and effectiveness of routine rotavirus vaccination in developing countries that were among the early adopters of rotavirus vaccine. The data highlight the benefits of vaccination and should provide valuable evidence to sustain vaccine use in these countries and encourage other countries to adopt routine rotavirus vaccination to reduce the health burden of severe childhood gastroenteritis.

Keywords

rotavirus; rotavirus vaccines; impact; effectiveness; developing countries

In 2006, pivotal clinical trials of 2 live oral rotavirus vaccines—a pentavalent bovine-human reassortant vaccine (RV5) given in a 3-dose schedule (RotaTeq, Merck & Co), and a

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Potential conflicts of interest. All authors: No reported conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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monovalent human vaccine (RV1) given in a 2-dose schedule (Rotarix, GSK Biologicals) —demonstrated good efficacy (85%–98%) in preventing severe rotavirus gastroenteritis [1, 2]. In addition, these large trials of 60 000–70 000 infants each were specifically designed to evaluate the risk of intussusception, an uncommon adverse event that had led to the withdrawal of an earlier rotavirus vaccine (RotaShield, Wyeth Lederle) from the United States in 1999; reassuringly, no risk was found with either vaccine [1–6]. The World Health Organization’s (WHO) Strategic Advisory Group of Experts reviewed these data from trials conducted in Europe and the Americas and recommended that rotavirus vaccines be included in the national immunization programs of countries in these regions where vaccine efficacy had been demonstrated [7].

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Beginning with the United States in February 2006, many countries in the Americas and Europe, as well as Australia, soon adopted rotavirus vaccines as part of their routine childhood vaccination programs. In many of these countries, the remarkable impact of these vaccines in reducing the burden of severe childhood gastroenteritis has been unequivocally demonstrated. A systematic review of data from 8 countries reported a 49%–89% decline in laboratory-confirmed rotavirus hospitalizations and 17%–55% decline in all-cause gastroenteritis hospitalizations among children aged <5 years within 2 years of vaccine introduction [8]. As an unanticipated benefit, in some countries, rotavirus vaccination of young infants has also resulted in the declines in rotavirus disease among children who missed vaccination and among older children and even adults who were not vaccine eligible [9–19]. This phenomenon, known as herd protection, is likely related to reduction in community transmission of rotavirus because vaccination limits the number of children susceptible to rotavirus disease. Most notably, studies from Mexico, Brazil, and Panama showed a reduction in childhood deaths from all-cause diarrhea following vaccine implementation, a key outcome that was not evaluated in clinical trials [20–24].

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Despite this impressive success in developed countries, the full impact of rotavirus vaccines remained to be realized in developing countries of Asia and Africa where morbidity and mortality due to rotavirus are greatest. Because of concerns that the performance of orally administered rotavirus vaccines may be diminished in developing countries of Africa and Asia due to possible interference by concurrent enteric infections, greater levels of maternal antibodies, and higher rates of malnutrition and comorbidities, WHO recommended further efficacy testing in these settings prior to issuing a global recommendation for vaccine use [7]. As expected, efficacy trials of both RV5 and RV1 in developing countries showed lower vaccine efficacy (50%–64%) against severe rotavirus gastroenteritis compared with developed countries [25–27]. Notably, despite the diminished efficacy, the public health benefits of vaccination in terms of the numbers of severe rotavirus gastroenteritis episodes prevented for every 100 vaccinated infants were greater in developing compared with developed countries because of the substantially greater baseline rate of severe rotavirus gastroenteritis in developing countries [26]. These considerations led WHO to issue a recommendation for global use of rotavirus vaccines in 2009, particularly in developing countries with high mortality from childhood diarrhea [28–30].

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As of September 2015, 79 countries worldwide have implemented rotavirus vaccines in their national immunization programs, including 36 low-income, developing countries that are

eligible for support for vaccine purchase from Gavi, the Vaccine Alliance (Figure 1). The global rollout of rotavirus vaccines provides an opportunity to assess the real-world impact of rotavirus vaccination in preventing and reducing the health burden of severe childhood diarrhea in developing countries. Such post-vaccine introduction data are particularly important to generate as (1) vaccine performance in routine programmatic use could differ from the ideal conditions of a clinical trial; (2) widespread vaccine use may result in changes in rotavirus epidemiology (eg, changes in average age of infection and seasonality) that may not be detected in trials; and (3) vaccination may have effects on disease transmission in the community and, thus, may provide indirect benefits to unvaccinated individuals as well (ie, herd immunity). The articles in this supplement describe the effects of rotavirus vaccination in many developing countries in Africa, Eastern Europe/Central Asia, and Latin America that were early adopters of vaccination. The evidence and lessons learned, summarized in this report, will be valuable for these countries to sustain their vaccination programs and will also inform decision making in countries that are considering implementing rotavirus vaccination.

IMPACT OF ROTAVIRUS VACCINATION IN REDUCING MORBIDITY AND MORTALITY FROM SEVERE DIARRHEA

Perhaps the most convincing and readily interpretable evidence of vaccine impact is the documentation of a decline in the burden of the target disease following vaccine introduction. However, assessing trends in disease before and after vaccine introduction requires cautious interpretation to account for secular trends and other possible factors (eg, changes in surveillance practices or healthcare-seeking behavior) that might be associated with the decline. Several articles in this supplement from African (Botswana, South Africa, Ghana, Togo, Zambia) and East European/Central Asian (Armenia and Moldova) countries show evidence of rapid and substantial declines in severe diarrhea and/or rotavirus disease following vaccine introduction [31–37]. In these evaluations, a role for vaccine in disease reduction is supported by observations such as (1) sharp declines coinciding temporally with the timing of vaccine introduction; (2) greater declines during the months of the year with seasonal peaks of rotavirus disease; and (3) greater initial declines in younger age groups that receive vaccination in the initial years of the vaccination, followed by a progressive decline in older age groups in later years after introduction. Of note, data from Botswana and Zambia showed a decline in in-hospital mortality from diarrhea at sentinel hospitals conducting surveillance [31, 35]. Although some caution in interpretation is warranted given the relatively small number of deaths observed in these studies, these promising data on life-saving benefits of rotavirus vaccination were indicated by findings from Latin American countries that have convincingly shown a decline in diarrhea mortality after rotavirus vaccine implementation. In fact, a report in this supplement found that nationwide diarrhea mortality in Mexican children has been reduced by almost half following rotavirus vaccine implementation, and these declines have been sustained for 7 years after vaccine introduction [38].

VACCINE EFFECTIVENESS IN ROUTINE USE

Observational studies such as those using a case-control design can measure field effectiveness of vaccination in routine programmatic use, providing a measure of vaccine performance under “real world” conditions. These data expand the evidence from clinical trials, as they include groups that may have been excluded from clinical trials (eg, malnourished or immunocompromised children) and children with less rigidly adhered to vaccination schedules (eg, age at administration, interval between doses, the number of doses). Several reports in this supplement provide reassuring evidence that the real-world effectiveness of rotavirus vaccination in developing countries is similar to the vaccine efficacy in prelicensure trials, with a gradient of lower efficacy in countries with greater levels of child mortality [36, 37, 39–45]. Some observations are noteworthy. First, evidence of a decline in effectiveness in the second year of life compared with the first year was seen in some studies but not in others; furthermore, it was encouraging that effectiveness against the most severe rotavirus disease that is likely to be associated with the worst clinical outcomes was well sustained over the first 2 years of life when the vast majority of rotavirus cases occur. Second, evidence of some protection from a partial series of rotavirus vaccine was seen, which is particularly relevant regarding protection against severe rotavirus disease that occurs at a very young age before a child is fully immunized. Finally, both RV5 and RV1 provided protection against a range of circulating rotavirus strains, supporting observations from clinical trials and other postlicensure data that both rotavirus vaccines provide good cross-protection against non-vaccine-type strains.

INDIRECT PROTECTION FROM ROTAVIRUS VACCINATION

Indirect protection (ie, herd immunity) occurs as a result of decreased transmission of the infectious pathogen in the community because of vaccination of a proportion of the population, thereby amplifying the benefits of vaccination among both vaccinated and unvaccinated persons. Indirect protection from rotavirus vaccination has been well documented in developed countries in the Americas and Europe, and in Australia, evident from substantial reductions in disease in age groups who were too old to be vaccinated, including young adults in some settings. However, it was unclear if these observations would extend to developing countries, given differences in population age-group structure and intensity of viral transmission. The reports from Armenia and Moldova in this supplement both demonstrate a decline in severe rotavirus disease among older age groups that were not vaccinated and also greater declines in vaccinated age groups than that expected based on vaccine coverage and effectiveness, indicating evidence of indirect protection [36, 37]. However, data from Zambia and South Africa do not indicate any evidence of indirect protection, and thus further evidence is required to understand the extent of herd protection across a range of geographic and socioeconomically diverse settings [32, 35].

THE WAY FORWARD

The early evidence on the real-world impact and effectiveness of rotavirus vaccination in developing countries from the articles in this supplement is encouraging, and provides powerful information to encourage countries to sustain rotavirus vaccine use and to

help inform decision making regarding vaccine use in countries that have not yet recommended rotavirus vaccination. However, further monitoring and evidence generation are required to address several key issues (Table 1). First, given the observed variability in vaccine effectiveness across countries, additional evidence should be generated to improve the generalizability of the findings, particularly from challenging settings in the most impoverished countries with the weakest healthcare and immunization programs. Additionally, a better understanding of the extent of herd protection across a range of geographic settings will help to quantify the full impact of a rotavirus vaccination program. Data on the impact and effectiveness of rotavirus vaccines in developing countries can also help drive the research agenda to improve the performance of existing vaccines or develop new vaccines. Second, as the experiences described in these reports are limited to the first 2–3 years after vaccine implementation for most countries, continued monitoring is desirable to assess whether over the long term the observed disease reductions and vaccine effectiveness are sustained and to examine if any changes in disease epidemiology occur, such as shifts in the age distribution of rotavirus cases or the emergence of unusual rotavirus strains due to possible vaccine-driven selection pressure. Third, while changes in the proportion of severe diarrhea attributable to nonrotavirus pathogens are expected to occur with the decline in incidence of rotavirus disease following vaccine implementation, monitoring the incidence of severe diarrheal disease caused by nonrotavirus pathogens before and after rotavirus vaccine implementation would help to assess if vaccination leads to changes in the overall ecology of diarrheal disease. Fourth, to date, no developing country in Asia has implemented routine rotavirus vaccination with either RV5 or RV1; thus, generating evidence from Asian countries as they introduce vaccines is a high priority. Of note, India recently recommended inclusion of an indigenously manufactured rotavirus vaccine (Rotavac) in its national immunization program [46, 47], and Vietnam has also licensed its own rotavirus vaccine (Rotavin), providing initial opportunities to examine the effect of rotavirus vaccination in low-income Asian countries. Fifth, because only 6 of the 36 Gavi-eligible countries that have implemented rotavirus vaccination to date have selected RV5, generation of additional postlicensure data from developing countries for this vaccine in particular should be prioritized. Finally, postlicensure evaluations in developed countries have identified a low risk of intussusception with both RV5 and RV1; however, this risk is exceeded by the marked health benefits of vaccination seen in these countries and has not led to any change in vaccination recommendations from WHO and many national health authorities that have reviewed the evidence [48]. Although the benefits of vaccination are likely to be even more substantial in low-income countries given the greater health burden of rotavirus, efforts should be made to generate information on any intussusception risk associated with vaccination in these settings to allow informed risk-benefit assessments and provide additional confidence in the vaccination program.

Supplement sponsorship.

This article appears as part of the supplement “Health Benefits of Rotavirus Vaccination in Developing Countries,” sponsored by PATH and the CDC Foundation through grants from the Bill and Melinda Gates Foundation and GAVI, the Vaccine Alliance.

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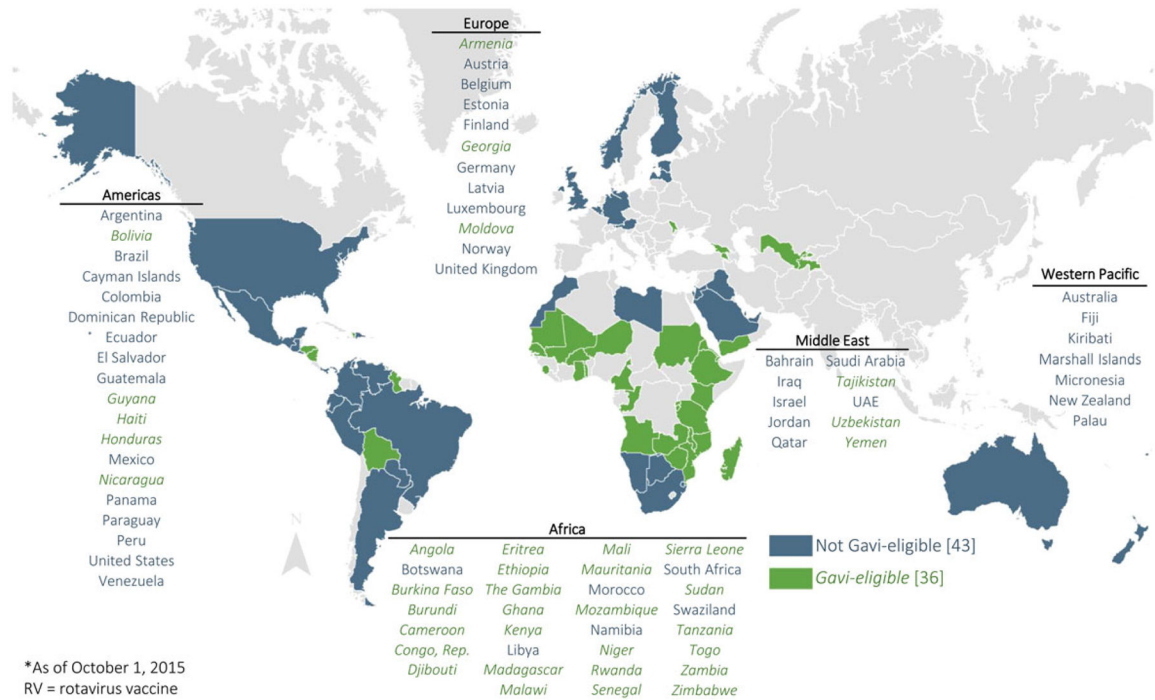


Figure 1. National rotavirus vaccine introduction, by geographic region, as of 1 October 2015. Source: PATH rotavirus vaccine country introduction maps available at <http://sites.path.org/rotavirusvaccine/country-introduction-maps-and-spreadsheet/>. Abbreviation: UAE, United Arab Emirates.

Table 1.**Key Priorities for Future Rotavirus Vaccine Monitoring Efforts**

- Additional data on impact and effectiveness of vaccination in the most impoverished countries with the weakest healthcare and immunization programs.
- Improve understanding of the extent of herd protection across a range of geographic settings.
- Continued monitoring to assess long-term impact of vaccination on rotavirus epidemiology, including effect on circulating strains.
- Monitor incidence of severe diarrheal disease caused by nonrotavirus pathogens before and after rotavirus vaccine implementation to assess if vaccination leads to changes in the overall ecology of diarrheal disease.
- Evidence of vaccine impact and effectiveness from Asian countries as they introduce vaccines.
- Additional postlicensure data on vaccine impact from developing countries for RV5 (RotaTeq).
- Generate information on any intussusception risk associated with vaccination in low-income settings to allow informed risk-benefit assessments.

Abbreviation: RV5, pentavalent bovine-human reassortant vaccine.