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Rotavirus vaccines

Current status and future considerations

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Abbreviations: GACVS, Global Advisory Committee on Vaccine Safety; LLR, Lanzhou lamb rotavirus vaccine; SAGE, Strategic Advisory Group of Experts on Immunization; WHO, World Health Organization

Rotavirus is the leading cause of severe diarrhea among children <5 years worldwide. Currently licensed rotavirus vaccines have been efficacious and effective, with many countries reporting substantial declines in diarrheal and rotavirus-specific morbidity and mortality. However, the full public health impact of these vaccines has not been realized. Most countries, including those with the highest disease burden, have not yet introduced rotavirus vaccines into their national immunization programs. Research activities that may help inform vaccine introduction decisions include (1) establishing effectiveness, impact, and safety for rotavirus vaccines in low-income settings; (2) identifying potential strategies to improve performance of oral rotavirus vaccines in developing countries, such as zinc supplementation; and (3) pursuing alternate approaches to oral vaccines, such as parenteral immunization. Policy- and program-level barriers, such as financial implications of new vaccine introductions, should be addressed to ensure that countries are able to make informed decisions regarding rotavirus vaccine introduction.

Background

Diarrhea is a major cause of death among children <5 y of age globally.[1] Rotavirus is the leading cause of severe diarrhea, resulting in an estimated 453 000 deaths in 2008, most of which occurred in developing countries of sub-Saharan Africa and South-East Asia (**Fig. 1**).[2] Rotavirus also causes considerable morbidity, with global estimates of 2.3 million hospitalizations and 24 million outpatient visits annually among children aged <5 y.[2,3] Data from the Global Rotavirus Surveillance Network of the World Health Organization (WHO), a network of sentinel surveillance sites in over 50 countries, indicate that rotavirus is responsible for ~40% of acute gastroenteritis hospitalizations among children <5 y of age in regions without widespread rotavirus vaccine use.[4] Since improvements in water and sanitation do not prevent the majority of rotavirus disease, rotavirus vaccines are an essential part of an integrated approach to the control of diarrhea that also includes interventions, such as access to safe drinking water, sanitation, and handwashing facilities, breast feeding, vitamin A and zinc supplementation, and appropriate case management.[5] Since 2009, WHO, with support from its Strategic Advisory Group of Experts (SAGE) on Immunization, has recommended that rotavirus vaccines be included in all national immunization programs and considered a priority, particularly in countries with high diarrhea-related mortality.[6] By April 2014, 56 countries had introduced rotavirus vaccines into their national immunization programs, and ~50 more likely will follow within the next several years.[7,8]

This review will discuss the 2 globally licensed rotavirus vaccines and other vaccines locally available or in development, the current status of vaccine introduction, information on the impact of vaccine introduction on immunization systems and disease burden, vaccine safety issues, and future considerations for vaccine introduction.

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Rotavirus Vaccines

Since 2006, 2 rotavirus vaccines have been licensed and used globally—Rotarix (GlaxoSmithKline) and RotaTeq (Merck and Co., Inc.). Rotarix is a live, attenuated vaccine containing a single G1P[8] human rotavirus strain. RotaTeq is a live, attenuated vaccine containing 5 human-bovine reassortant rotavirus strains—G1P7[5], G2P7[5], G3P7[5], G4P7[5], and G6P1A[8] (**Table 1**). Both vaccines are administered orally to infants starting at a minimum age of 6 wk, with a minimum 4 wk interval between doses (2 doses per Rotarix course, 3 doses per RotaTeq course).[6] Previous WHO administration recommendations for upper age limits of 15 wk for the first dose of vaccine and 32 wk for the last dose of vaccine were removed in 2013.[6] For both vaccines, clinical trials conducted in high and upper-middle-income countries in the Americas, Asia, and Europe demonstrated vaccine efficacy of 72–100% in preventing severe rotavirus disease during 1- to 3-y follow-up periods, while trials conducted in lower income countries in Africa and Asia demonstrated vaccine efficacy of 49–72% (**Table 1**).[9-17] Although definite reasons for this lower efficacy are unknown, reasons proposed include

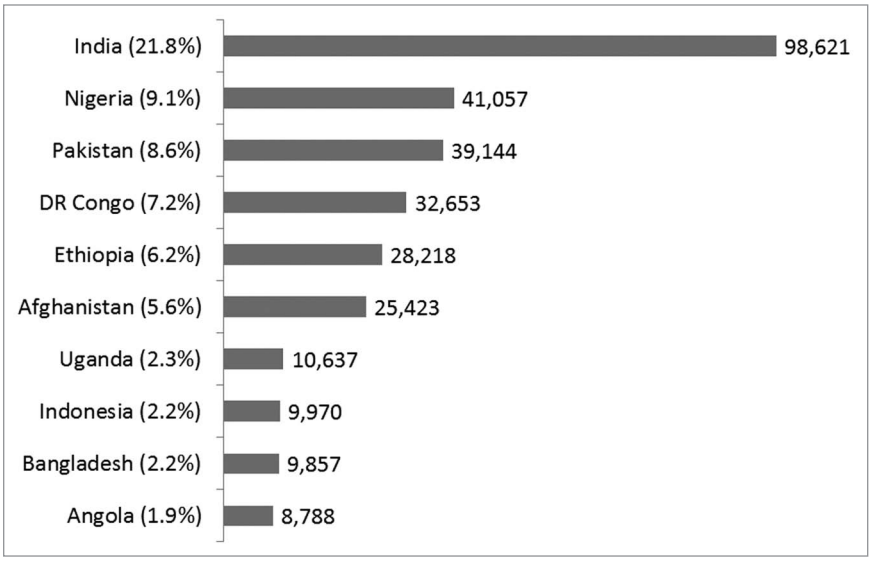

Figure 1. 10 countries with the greatest number of rotavirus deaths in 2008. Adapted from: Tate et al. 2008 estimate of worldwide rotavirus-associated mortality in children younger than 5 y before the introduction of universal rotavirus vaccination programmes: a systematic review and meta-analysis. Lancet Infect Dis 2012; 12(2):136–141.

factors that can result in interference of uptake of a live, oral vaccine, such as breast milk, stomach acid, maternal antibodies, and co-administration of oral poliovirus vaccine (OPV), and factors that may cause an impaired immune response to vaccine, such as malnutrition, and other infections (e.g., human immunodeficiency virus, malaria, and tuberculosis).[18,19]

China and Vietnam have locally manufactured oral vaccines that are licensed for use only within these countries (**Table 2**). Available in China, the Lanzhou lamb rotavirus vaccine (LLR; Lanzhou Institute of Biological Products) is a live, attenuated vaccine containing a single G10P[12] lamb rotavirus strain. The recommended schedule of administration is one dose annually for children 2 mo to 3 y of age and one dose at age 3–5 y.[20] Since 2000, over 30 million doses have been sold, but little is known about vaccine efficacy, safety, and vaccination coverage since LLR is available only through the private market.[20] Available in Vietnam, Rotavin-M1 (POLYVAC) is a live, attenuated vaccine containing a single G1P[8] human rotavirus strain similar to Rotarix. The recommended schedule of administration is 2 doses, starting at a minimum age of 6 wk, given at least 30 d apart.[21] Phase I and II studies demonstrated immunogenicity and safety profiles similar to Rotarix;[21] efficacy data currently are unavailable. Recently, India licensed its own locally manufactured oral vaccine, ROTAVAC (Bharat Biotech International, Ltd) (**Table 2**). ROTAVAC is a live, attenuated vaccine containing a single neonatal rotavirus G9P[11] strain, 116E. The recommended schedule of administration is 3 doses at 6, 10, and 14 wk. The phase III trial demonstrated vaccine efficacy of ~56% in preventing severe rotavirus diarrhea.[22] Bharat Biotech is pursuing WHO pre-qualification of the vaccine so that it may be available globally.[23]

Additional live oral and parenteral rotavirus vaccines are in development or clinical trial stages, but not yet licensed (**Table 2**). Five live, single to multi-strain vaccines, including 2 lamb-human reassortant vaccines from China (Lanzhou and NF-R7), the previously licensed rhesus-human reassortant vaccine RotaShield, a bovine-human reassortant vaccine (UK), and a neonatal human strain vaccine from Australia (RV3), currently are undergoing clinical trials. One subunit rotavirus vaccine currently is undergoing a phase I trial, while several other candidates, including an inactivated rotavirus vaccine (IRV), are in pre-clinical stages of development. Alternative schedules, such as administration of a neonatal dose (RotaShield, RV3) are also being explored.

Current Status of Rotavirus Vaccine Introduction

As of April 2014, 56 countries have introduced rotavirus vaccines into their national immunization programs; an additional 4 have introduced vaccines regionally, and 3 have widespread coverage through the private market (**Fig. 2**).[7] Although Australia and countries in the Americas and Europe were the earliest to introduce after vaccine licensure, countries in other regions have followed, many with support from the GAVI Alliance, a public-private global health partnership with a mission to save children's lives and protect people's health by increasing access to immunization in poor countries. As of March 2014, 16 countries have GAVI Alliance support to introduce rotavirus vaccines nationally, 4 countries have GAVI applications under review, and 11 countries are planning to submit GAVI applications.[7,8] In addition, 16 non-GAVI eligible countries are planning introductions, making a total of 47 more countries planning to introduce rotavirus vaccines within the next several years. However, despite this progress and a universal recommendation for inclusion of rotavirus vaccines in national immunization programs, 84 countries have no reported plans to introduce rotavirus vaccines. The majority (70%) of these countries are located in Europe, South-East Asia, and the Western Pacific.

Table 1. Currently licensed and globally recommended rotavirus vaccines

Characteristic	Rotavirus vaccine	
Trade name	Rotarix®	RotaTeq®
Manufacturer	GlaxoSmithKline	Merck and Co., Inc.
Country of manufacture	Belgium	USA
Composition	Live-attenuated G1P1A[8] human rotavirus strain	Live human-bovine reassortant rotavirus strains: G1P7[5], G2P7[5], G3P7[5], G4P7[5], G6P1A[8]
Pharmaceutical form	Liquid, lyophilized + diluent	Liquid
Presentation	1 dose plastic tube or 1 dose applicator or 1 dose vial	1 dose tube
Route of administration	Oral	Oral
Recommended schedule of administration	Minimum age of 1st dose: 6 wk 2 doses at least 4 wk apart *Previous WHO recommendations for upper age limits of 15 wk for the first dose and 32 wk for second dose have been removed*	Minimum age of 1st dose: 6 wk 3 doses at least 4 wk apart *Previous recommendations for upper age limits of 15 wk for first dose and 32 wk for third dose have been removed*
Contraindications per manufacturer	Hypersensitivity to the active substance or to any of the excipients; hypersensitivity after previous administration of rotavirus vaccines; history of intussusception; history of uncorrected congenital malformation of the gastrointestinal tract that would predispose for intussusception; history of severe combined immunodeficiency disease (SCID)	A demonstrated history of hypersensitivity to the vaccine or any component of the vaccine; history of severe combined immunodeficiency disease (SCID); history of intussusception
Volume per dose	1.5 mL (tube and applicator) 1 mL (lyophilized + diluent)	2 mL
Cost per dose	GAVI-eligible: $2.43 (2014 UNICEF pricing) Non-GAVI: variable	GAVI-eligible: $3.50–5.00 (2014 UNICEF pricing) Non-GAVI: variable
Date of WHO prequalification	Mar 2009 (tube and applicator) Jan 2007 (vial)	Oct 2008
Licensure status	Licensed in >100 countries	Licensed in >100 countries
Full series efficacy against severe rotavirus gastroenteritis (95% confidence interval)	3-y follow-up: 97% (88–100) (Hong Kong/Singapore/Taiwan) 2-y follow-up: 81% (71–87) (Latin America) 90% (85–94) (Europe) 72% (54–84) (China) 92% (62–99) (Japan) 1-y follow-up: 49% (11–72) (Malawi) 72% (40–88) (South Africa)	3-y follow-up: 94% (89–97) (Finland) 1-y follow-up: 98% (88–100) (US/Finland) 51% (13–73) (Bangladesh/Vietnam) 64% (40–79) (Kenya/Ghana/Mali) Up to 1-y follow-up: 100% (55–100) (Japan)

Vaccine Impact

While data from clinical trials provide important information on vaccine efficacy and safety in controlled settings, program and field conditions may differ with regards to vaccine management and administration and thus impact both vaccine effectiveness and the immunization system. Evaluation of the impact of vaccine introduction on immunization systems and disease burden is crucial for improving and sustaining immunization programs and stimulating introduction of additional vaccines.

To help evaluate the programmatic impact of new vaccine introduction on immunization systems, WHO recommends post introduction evaluations (PIEs) 6–12 mo after any new vaccine introduction.[24] Findings from these evaluations may provide countries with information regarding the impact of rotavirus vaccine introduction on various program topics (e.g., vaccination coverage recording and reporting, cold chain and vaccine management, monitoring and supervision, training and knowledge of health-care workers, waste management, adverse events following immunization, and advocacy and communication planning), which may be used to improve local immunization systems and inform subsequent vaccine introductions. From 2009–2013, rotavirus vaccine PIEs were conducted in 13 countries in Africa, Latin America, the Eastern Mediterranean region, and Europe.[25]

Table 2. Rotavirus vaccines that are regionally used, recently licensed, or in development

Name	Composition	Route of administration	Organization/Company	Stage of development
Lanzhou Lamb Rotavirus (LLR)	Live attenuated lamb rotavirus strain, G10P[12]	Oral	Lanzhou Institute of Biological Products, China	Licensed for use in China
Rotavin-M1	Live attenuated human rotavirus strain, G1P[8]	Oral	POLYVAC, Vietnam	Licensed for use in Vietnam
ROTAVAC	Live attenuated neonatal rotavirus strain, G9P[11] (aka 116E)	Oral	Bharat Biotech, India	Recently licensed for use in India; pursuing WHO pre-qualification
LLR reassortants	Live attenuated lamb-human reassortant rotavirus strains, G2, G3, G4	Oral	Lanzhou Institute of Biological Products, China	Phase III
RotaShield	Live attenuated rhesus-human reassortant rotavirus strains, tetravalent	Oral	International Medica Foundation, USA	Phase II complete, Phase III pending
RV3	Live attenuated neonatal rotavirus strain, G3P[6]	Oral	Biofarma, Indonesia	Phase II
UK reassortants	Live attenuated bovine-human reassortant strains, tetravalent to hexavalent	Oral	National Institutes of Health, USA; Instituto Butantan, Brazil; Serum Institute of India, India; Shantha Biotech, India; / Minghai Biotechnology Co., China; Wuhan Institute of Biological Products, China	Phase I and II, Research
NF-R7	Live attenuated lamb-human reassortant strain, G4	Oral	Shenzhen Kangtai Biological Products Company, China	Phase I
Subunit	Truncated VP8 of P4, P6, P8	Intramuscular	National Institutes of Health and PATH, USA	Phase I
IRV	Inactivated G1P[8], G2P[4]	Intramuscular or intradermal	US CDC; multiple (China, Europe, India)	Pre-clinical
Subunit	Virus-like particles: VP 2/6/7 and VP 2/4/6/7	To be determined	Baylor College of Medicine, USA	Research
Subunit	Truncated VP8 in norovirus P particles	To be determined	Cincinnati Children's Hospital Medical Center, USA	Research
Subunit	VP6 combined with norovirus G1 and GII VLPs	To be determined	University of Tampere School of Medicine, Finland	Research

Monitoring of disease trends and vaccine effectiveness studies can provide timely information necessary to evaluate the impact of vaccine introduction on disease burden. Findings generated from Rotarix and RotaTeq impact assessments, mostly in Australia and countries in Europe and the Americas, have demonstrated substantial declines of 22–50% in diarrhea-related mortality,[26-29] 17–55% in diarrhea-related hospitalizations,[27,30-45] and 49–91% in rotavirus-specific hospitalizations among children <5 y of age (**Table 3**).[30-34,36,37,42-59] Many of these studies also have reported potential indirect benefits for unvaccinated older children and young adults, with reductions of 6–51% in diarrhea-related hospitalizations[30-32,35,37,45,60-62] and 20–92% in rotavirus-specific hospitalizations(**Table 4**).[31,32,34,37,42-45,49,50,54,56,5,61-63] Additional studies have demonstrated vaccine effectiveness in preventing rotavirus hospitalizations similar to vaccine efficacy observed in clinical trials. High and upper-middle-income countries including Australia (certain regions), Taiwan, Austria, Belgium, France, Germany, Northern Israel, Spain, Mexico, Brazil (certain regions), and the US have reported vaccine effectiveness estimates of 79–100%,[37,38,53,60,64-83] while lower income countries including Bolivia, El Salvador, and Nicaragua have reported vaccine effectiveness estimates of 43–92% (**Table 5**).[84-89]

To date, both Rotarix and RotaTeq have provided protection against a range of rotavirus strains, as demonstrated by the Rotarix clinical trials conducted in Africa, for which vaccine efficacy was ~60–64% for both G1 (contained in Rotarix) and non-G1 (not contained in Rotarix) rotavirus types,[90] and by various vaccine effectiveness studies conducted in Australia, Europe, and the Americas, for which vaccine effectiveness estimates were 71–95% against rotavirus strains not contained in RotaTeq and/or Rotarix.[38,66,70,78,80,83,89,91] Monitoring of rotavirus strains continues in order to detect any global changes in strain prevalence and any emergence of unusual strains, and allow for strain-specific measures of vaccine effectiveness in the event that there is concern about vaccine effectiveness against an emergent or novel strain.

Vaccine Safety

In 1999, the first licensed rotavirus vaccine, RotaShield (Wyeth), was withdrawn from US market within a year after

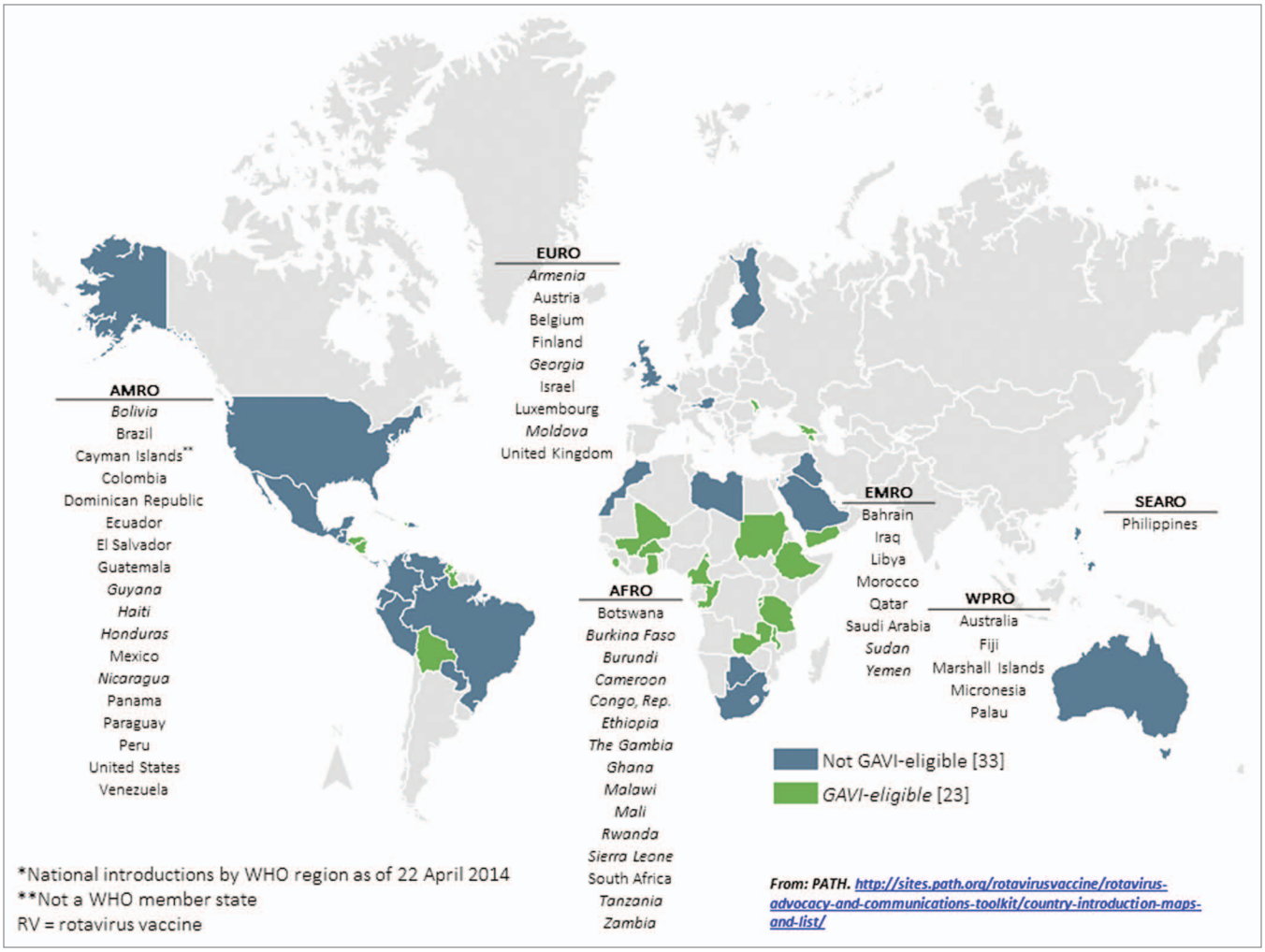

Figure 2. National rotavirus vaccine introductions, by geographic region—56 countries*

licensure due to an association with intussusception, an obstruction of the small intestine that can require radiological or surgical intervention. It was estimated that ~1 excess case of intussusception occurred per 10000 infants vaccinated with RotaShield.[92] Pre-licensure clinical trials for Rotarix and RotaTeq that included 60000–70000 infants each did not demonstrate an increased risk for intussusception,[14,16] However, post-licensure monitoring studies were recommended to detect a possible low risk that may not have been identified in the clinical trials. In 2011, findings from studies conducted in Mexico (Rotarix only) and Australia (Rotarix and RotaTeq) reported a low level risk of intussusception with both Rotarix and RotaTeq on the order of ~1–2 excess cases per 100000 vaccinated infants, mostly within the first week after the first dose of vaccine.[93-9] These risks were lower than the risk associated with RotaShield, and a subsequent review of available data and a risk-benefit analysis of rotavirus vaccination conducted by the WHO Global Advisory Committee on Vaccine Safety (GACVS) determined that the benefits of rotavirus vaccination of all infants greatly exceeded the risks of intussusception associated with vaccination (**Table 6**).[96] Additional analyses to examine the risk-benefit of rotavirus vaccination without upper age restrictions estimated that universal rotavirus vaccination in low- and low-middle-income countries could prevent an additional 47200 (range: 18000–63700) rotavirus deaths while potentially causing an additional 294 (range: 161–471) intussusception deaths among a cohort of children <5 y of age.[98] These analyses contributed to the 2013 WHO recommendation that upper age restrictions for rotavirus vaccination be removed to allow for greater vaccination coverage and potentially greater reductions in the number of rotavirus deaths as the benefits of vaccination continue to outweigh the risks of intussusception.[6]

Recently, new data from the US also have demonstrated a low risk of intussusception with both vaccines. In 2 studies conducted among separate managed care populations, an approximate risk of 1–5 excess cases of intussusception per 100000 infants vaccinated with rotavirus vaccine was reported.[98,99] While the risk-benefit of rotavirus vaccination with these 2 vaccines remains approximately the same as that seen when using the earlier risk estimates from Mexico and Australia, questions remain as to whether this risk may be higher in any particular subgroup of infants and whether the level of risk seen in high- and middle-income countries will occur in low-income countries where

Table 3. Summary of rotavirus vaccine impact studies among children <5 y – disease trends[a]

Location	Vaccine	% Reduction	References
Reduction in diarrheal death rates			
Brazil			
• Nationwide	Rotarix	22%	27
• Nationwide	Rotarix	33–39%	28
Mexico, Nationwide	Rotarix	46%	29
Panama, Nationwide	Rotarix	32–50%	26
Reduction in diarrhea hospitalizations			
Australia			
• National	Rotarix, RotaTeq	38%	36
• Queensland	RotaTeq	20–40%	37
• South Australia	RotaTeq	48% (0 to <6 y)	32
Belgium, Nationwide	Rotarix, RotaTeq	33% (0 to 2 y)	42
Brazil			
• Nationwide	Rotarix	26–48% (0 to 1 y)	39
• Nationwide	Rotarix	17%	27
• Sao Paolo	Rotarix	29%	43
• Sergipe	Rotarix	44–55%	38
El Salvador, Nationwide	Rotarix	28–37% (includes outpatient)	44
Mexico, Nationwide	Rotarix	40% (during rotavirus season)	41
Panama, Bocas del Toro, Chiriquí, Los Santos, San Miguelito, Metropolitan Region	Rotarix	37%	40
USA			
• Nationwide	RotaTeq	45% (during rotavirus season)	35
• Nationwide	RotaTeq	29–50%	45
• 3 regions (Northeast, Midwest, South)	RotaTeq	30–45%	34
• Privately insured children, 13 states[b]	RotaTeq	25–33%	33
• New Orleans, LA	RotaTeq	50%	30
• New York, NY	RotaTeq	40% (0 to <2 y)	31
South Africa, Gauteng and Mpmalange provinces	Rotarix	32–33%	51

[a]Estimated rotavirus vaccination coverage ranges of 37–94% mostly among children 0–1 y or 0–2 y, if reported. [b]Alaska, Idaho, Massachusetts, Maine, North Dakota, New Hampshire, New Mexico, Oregon, Rhode Island, Vermont, Washington, Wisconsin, Wyoming.

vaccine efficacy is lower.[100] Additional special studies and continued post-introduction intussusception monitoring, especially in low-income countries, may help answer these questions.

Future Considerations

Countries worldwide have established estimates of the considerable diarrheal disease burden of rotavirus.[4,6] Existing licensed rotavirus vaccines have proven to be efficacious in clinical trials and effective in post-introduction evaluations, with many countries demonstrating adequate capacity to introduce these vaccines into routine immunization programs and substantial declines in diarrheal and rotavirus-specific morbidity and mortality (**Tables 3–5**). Despite this, the full public health impact of these vaccines on rotavirus disease and child mortality has not been realized as most countries, including some with the highest disease burden, have not yet introduced rotavirus vaccines into their national immunization programs. Why is this the case? What are the remaining questions to be answered? What are the potential barriers to introduction?

Several key research activities may help to address remaining questions about rotavirus vaccine use under field conditions and inform vaccine introduction decisions, especially in low-income countries. These include: (1) establishing effectiveness, impact, and post-licensure safety of the current WHO-prequalified rotavirus vaccines in low-income settings; (2) identifying potential strategies to improve performance of oral rotavirus vaccines in developing countries, such as zinc supplementation to potentially strengthen the immune response to vaccination, withholding breast feeding just before and after vaccine administration to prevent interference of vaccine uptake by maternal antibodies, or a neonatal dosing schedule to help increase the amount of rotavirus disease prevented in settings where children may acquire disease at an earlier age; and (3) pursuing alternate approaches to oral vaccines, such as parenteral vaccines to bypass possible interference of vaccine uptake by gastric acid and breast milk to improve vaccine efficacy in developing countries.[18]

To identify potential barriers to introduction at a policy level, one may consider key issues in the decision-making process to introduce a new vaccine.[101] Once barriers are identified, solutions

Table 3. Summary of rotavirus vaccine impact studies among children <5 y – disease trends[a] (continued)

Location	Vaccine	% Reduction	References
Reduction in rotavirus hospitalizations			
Australia			
• National	Rotarix, RotaTeq	71%	36
• New South Wales, Queensland, Victoria	Rotarix, RotaTeq	87%	47
• Queensland	RotaTeq	53–57%	51
• Queensland	RotaTeq	50%	37
• South Australia	RotaTeq	83% (0–71 mo)	32
Austria			
• Nationwide	Rotarix, RotaTeq	70% (0 to 1 y)	55
• Nationwide	Rotarix, RotaTeq	76–79% (0 to 2 y)	54
• Nationwide	Rotarix, RotaTeq	73–74%	53
• Tyrol	Rotarix, RotaTeq	62–88%	59
Belgium			
• Nationwide	Rotarix, RotaTeq	58–77%	42
• Leuven	Rotarix, RotaTeq	49–66%	58
Finland, Tampere	Rotarix, RotaTeq	91% (<2 y; incl. ER visits)	50
Brazil, Sao Paolo	Rotarix	59%	43
El Salvador, San Salvador, Santa Ana, San Miguel, La Libertad, La Paz	Rotarix	69–81%	44
USA			
• Nationwide	RotaTeq	67–69%	57
• Nationwide	RotaTeq	66–83%	45
• 3 regions (Northeast, Midwest, South)	RotaTeq	69–81%	34
• Privately insured children, 13 states[b]	RotaTeq	60–75%	33
• Chicago	RotaTeq	62% (during viral season)	46
• Cincinnati, OH, Nashville, TN, Rochester, NY	RotaTeq	55–89% (0 to 35 mo)	56
• Jacksonville, FL	RotaTeq	72%	48
• New Orleans, LA	RotaTeq	67% (includes ED visits)	30
• New York, NY	RotaTeq	85% (0 to <2 y)	31
• US military dependents	RotaTeq	62%	49
South Africa, Gauteng and Mpmalange provinces	Rotarix	40–44%	52

[a]Estimated rotavirus vaccination coverage ranges of 37–94% mostly among children 0–1 y or 0–2 y, if reported. [b]Alaska, Idaho, Massachusetts, Maine, North Dakota, New Hampshire, New Mexico, Oregon, Rhode Island, Vermont, Washington, Wisconsin, Wyoming.

may be implemented (**Table 7**). While each country should have a mechanism for an evidence-based, informed-decision making process, which may include expert groups that provide technical advice to national immunization programs, such as National Immunization Technical Advisory Groups (NITAGs) (http://www.healthinternetwork.com/immunization/sage/national_advisory_committees/en/) or other advisory committees on immunization,[101] barriers and concerns may differ by country or even region. For example, one country may be concerned with vaccine introduction costs while another may be concerned with the programmatic impact of vaccine introduction or vaccine efficacy and safety. Given the potential diversity of opinion, it will be crucial to understand issues at the local policy making level to best inform decision makers.

During the past several years, significant progress has been made in the prevention and control of rotavirus diarrhea. The introduction of rotavirus vaccines into the national immunization programs of over 50 countries has resulted in substantial declines in rotavirus-related morbidity and mortality. However, questions remain that will need to be answered by additional research, and policy- and program-level barriers should be removed to ensure that countries are able to make informed decisions regarding rotavirus vaccine introduction and to help realize the full potential impact of these vaccines.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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Disclaimer

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

Table 4. Summary of rotavirus vaccine impact studies – indirect benefits for unvaccinated individuals[a]

Location	Vaccine	Age range	% Reduction	References
Reduction in diarrhea hospitalizations				
Australia				
• Queensland	RotaTeq	2 to 4 y	30–40%	37
• South Australia	RotaTeq	2 to <6 y	42–49%	32
USA				
• Nationwide	RotaTeq	2 to <5 y	35–41%	34
• Nationwide	RotaTeq		43–45%	35
• Nationwide	RotaTeq	2 to <5 y	17–48% (during rotavirus season)	45
• Nationwide	RotaTeq	5 to 24 y	8–29%	62
• Nationwide	Rotarix, RotaTeq	5 to 44 y	6–30%	61
• New Orleans, LA	RotaTeq	2 to <5 y	51%	30
• New York, NY	RotaTeq	2 to <3 y	31–36%	31
• New York, NY	RotaTeq	3 to <5 y	33–37%	31
• New York, NY	RotaTeq	5 to 18 y	9–12%	31
Reduction in rotavirus hospitalizations				
Australia				
• Queensland	RotaTeq	2 to 19 y	30–70%	37
• South Australia	RotaTeq	2 to <6 y	50–83%	32
Austria				
• Nationwide	Rotarix, RotaTeq	2 to 5 y	35%	54
• Tyrol	Rotarix, RotaTeq	2 to 18 y	62–89%	59
Belgium, Nationwide	Rotarix, RotaTeq	2 to 5 y	20–64%	42
Finland, Tampere	RotaTeq	2 to <16 y	72%	50
Brazil, Sao Paolo	Rotarix	2 to <5 y	24%	43
El Salvador, Nationwide	Rotarix	2 to <5 y	41–81%	44
USA				
• Nationwide	RotaTeq	2 to <5 y	69–78%	34
• Nationwide	RotaTeq	2 to <5 y	41–80%	45
• Nationwide	RotaTeq	5 to 24 y	65–71%	62
• Nationwide	Rotarix, RotaTeq	5 to 44 y	43–70%	61
• Chicago, IL	RotaTeq	[3]18 y	48%	63
• Cincinnati, OH, Nashville, TN, Rochester, NY	RotaTeq	2 to <3 y	92%	56
• New York, NY	RotaTeq	2 to <3 y	70–76%	31
• New York, NY	RotaTeq	3 to <5 y	79–88%	31
• New York, NY	RotaTeq	5 to 18 y	70%	31
• US military dependents	RotaTeq	0 to 4 y	57% (unvaccinated individuals)	49

[a]Estimated rotavirus vaccination coverage ranges of 37–94% mostly among children 0–1 y or 0–2 y, if reported.

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Table 5. Vaccine effectiveness (VE) against rotavirus hospitalizations

Location	Vaccine type	Vaccine effectiveness	Predominant strain	References
Australia				
• Queensland	RotaTeq	94%		37
• Central Australia	Rotarix	84%	G9P[8]	80
• Central Australia	Rotarix	51%	G2P[4]	79
Taiwan, Linkou, Changhua, Kaohsiung	Rotarix, RotaTeq	92%, 97%	G1P[8]	69
Austria, Nationwide	Rotarix, RotaTeq	79–96%	G1P[8], G2P[4]	53
Belgium, Nationwide	Rotarix	90%	G2P[4]	67
France, Nortwest Britanny	RotaTeq	98%		74
Germany, Mecklenberg-Western Pomerania	Rotarix, RotaTeq	80%	G1P[8], G9P[8]	64
Northern Israel	Rotarix, RotaTeq	89%		77
Spain				
• Nationwide	Rotarix, RotaTeq	97%, 95%	G9	76
• Navarre	Rotarix, RotaTeq	83%		68
Bolivia	Rotarix	69–77%	G9P[8], G2P[4], G3P[8], G9P[6]	89
Brazil				
• Northeast Brazil	Rotarix	89–95%	G2P[4]	38
• Recife	Rotarix	80–81%	G2P[4]	70
• Belem	Rotarix	40–76%	G2P[4]	75
El Salvador, Nationwide	Rotarix	76%	G1P[8]	85
Mexico, Chiapas	Rotarix	94%	G9P[4]	83
Nicaragua, Nationwide				
• Nationwide	RotaTeq	43–49%	G2P[4]	87
• Managua, Jinotepe, Masaya, Matagalpa	RotaTeq	45–70%		88
• Western Region	RotaTeq	64–87% (includes ED visits)	G1P[8], G2P[4]	86
• Western Region	RotaTeq	72–92% (includes ED visits)		84
USA				
• Nationwide	RotaTeq	100%		82
• Houston, TX	RotaTeq	100%	G3P[8]	65
• Houston, TX	RotaTeq	83–86% (includes ED visits)	G3P[8]	66
• Cincinnati, OH, Nashville, TN, Rochester, NY	RotaTeq	95%	G1-G3, G9, G12	81
• Cincinnati, OH, Nashville, TN, Rochester, NY	RotaTeq	92% (includes ED visits)	G1P[8]	73
• CA,MO,NY,OH,TN,TX,WA	RotaTeq	86%	G1P[8], G2P[4], G3P[8], G12P[8]	78
• New Haven, CT	RotaTeq	94–97%	G1-G4, G9	72
• CT, GA	Rotarix, RotaTeq	94–98%, 97%	G1P[8], G2P[4]	71
• CT, GA, MN	RotaTeq	90–92%		60

Table 6. Risk of intussusception and benefits of rotavirus vaccination in Mexico, Brazil, Australia, and the US[a]

Country	Diarrhea hospitalizations (deaths) prevented by vaccination	Intussusception cases (deaths) potentially caused by vaccination	Reference
Mexico	11 600 (663)	41 (2)	94
Brazil	69 600 (640)	55 (3)	94
Australia	7000 (0)	6 (0)	102
US	53 444 (14)	45–213 (0.1–0.5)	103

[a]Data are for one fully vaccinated birth cohort followed to age 5 y.

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Table 7. Key issues and potential barriers and related questions in the decision to introduce rotavirus vaccine

Key issues	Potential barriers/concerns	Related questions	Potential solutions
Policy-related			
Rotavirus/diarrheal disease as a public health priority	Competing priorities (e.g., other new vaccine introductions, other health interventions on the public health agenda)	Do policy makers have sufficient information to appropriately prioritize rotavirus vaccine?	Ensure that existing disease burden and vaccine information and impact data available to policy makers
Evidence of disease burden	• Lack of local disease burden data • Lack of regional disease burden data	• Is the local rotavirus disease burden similar to other countries? • What is the rotavirus disease burden in other countries in the region?	• Establish sentinel rotavirus surveillance • Communicate with regional partners to share available disease burden data
Vaccine efficacy, quality and safety	• Lack of local efficacy/effectiveness data • Concerns about intussusception	• Will the current vaccines be able to provide protection against the local rotavirus strains? • Why is vaccine efficacy worse in lower income countries? • Will vaccine use be associated with an increase in intussusception cases in my country?	• Provide existing rotavirus strain-specific effectiveness data • Investigate strategies to improve vaccine uptake • Develop vaccines with improved efficacy (e.g., parenteral vaccines) • Establish baseline intussusception rate and/or post-introduction intussusception surveillance if possible
Existing interventions to prevent rotavirus	Lack of awareness regarding the role of rotavirus vaccine as the main means of prevention	Won't improve access to clean water and sanitation prevent rotavirus disease?	Improve communication about the role of rotavirus vaccines as the current mainstay for rotavirus prevention
Economic and financial issues (e.g., cost-effectiveness, fiscal impact, financial sustainability)	• High cost of existing rotavirus vaccines • Lack of cost-related analyses	• Will rotavirus vaccines ever be sold at a lower price? • What is the potential cost-effectiveness of a rotavirus vaccination program? • What is the potential fiscal impact of rotavirus vaccine introduction on the immunization program?	• Ensure affordable vaccine prices • Conduct cost-effectiveness and fiscal impact evaluations in countries that have not introduced vaccine
Program-related			
Vaccine presentation	Vaccine packaging will take up too much cold chain space	Is there sufficient cold chain capacity for rotavirus vaccines? If not, how can we increase capacity?	Support cold chain assessments (i.e., Effective Vaccine Management) and expansion as needed
Vaccine supply availability	Available vaccine supply insufficient to accommodate national introduction	Will there be enough vaccine supply for the country's target population?	Work with vaccine manufacturers to ensure sufficient global vaccine supply
Strength of the existing immunization program	Current routine immunization program not ready to introduce a new vaccine (e.g., insufficient capacity to accommodate new vaccine, insufficient resources - funding and/or staff - to conduct training sessions and social mobilization)	How will we be able to acquire the resources and technical support required to introduce rotavirus vaccine?	Provide technical support for vaccine introduction planning and implementation, including potential means for acquiring necessary funding

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