Current status of rotavirus vaccines

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Background: **Rotaviruses remain the major cause of childhood diarrheal disease worldwide and of diarrheal deaths of infants and children in developing countries. The huge burden of childhood rotavirus-related diarrhea in the world continues to drive the remarkable pace of vaccine development.**

Data sources: **Research articles were searched using terms "rotavirus" and "rotavirus vaccine" in MEDLINE and PubMed. Articles not published in the English language, articles without abstracts, and opinion articles were excluded from the review. After preliminary screening, all articles were reviewed and synthesized to provide an overview of current vaccines and vaccination programs.**

Results: **In this review of the global rotavirus vaccines and vaccination programs, the principles of rotavirus vaccine development and the efficacy of the currently licensed vaccines from both developed and developing countries were summarized.**

Conclusions: **Rotavirus is a common cause of diarrhea in children in both developed and developing countries. Rotavirus vaccination is a cost-effective measure to prevent rotavirus diarrhea.**

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Introduction

Rotavirus is the major cause of severe diarrhea in infants and young children worldwide. Since 2008, the World Health Organization (WHO) has initiated the programs of the Global Rotavirus Surveillance Network.[1,2] During the period of 2011 and 2012, these programs have collected and analyzed data from 79 sites in 37 countries and areas (Fig.).[3] It was reported that approximately 453 000 younger children [95% confidence interval (CI): 420 000-494 000] die from severe dehydration and electrolyte and acid-base disturbances each year throughout the world.[4,5] The majority of rotavirus-related deaths (>80%) occur in resource-limited countries, for instance, in South Asia and sub-Saharan Africa.[6] Most children are infected with rotavirus before 5 years old.[7] However, the overall incidence of rotavirus infections would not change even if improvements have been made in housing, water supply, sanitation, personal hygiene, food quality, nutrition, and public education, suggesting that non-fecal routes may play a role in transmission.[8] Vaccines are an effective and available measure for combating rotavirus infection and for prevention of rotavirus diarrhea.[9]

Currently, the second-generation rotavirus vaccines, RotaTeq® (Merck and Co, Inc, Pennsylvania, USA) and Rotarix™ (GSK Biologicals, Rixensart, Belgium), have been licensed in over 100 countries. Both of them had high efficacy against severe rotavirus diarrhea in industrialized countries as well as in middle-income countries in Latin America.[10,11] After the introduction of the vaccines, hospitalizations of children with rotavirus infection and all-cause diarrhea were decreased in many regions.[12] Such decrease (35% in Mexico and 22% in Brazil) in diarrhea-related mortality was also seen in younger children after the introduction of rotavirus vaccine.[13,14] During the first few years of life, the efficacy of both vaccines was maintained.[15-17] Despite the high efficacy demonstrated by the vaccines in studies in developed countries and in Latin America, the WHO's Strategic Advisory Group of Experts (SAGE) on immunization, deferred making a recommendation for global use in 2006, pending the availability of efficacy data from developing countries, such as countries in Africa and Asia. This was based on the fact that the efficacy of other live oral vaccines has varied between different population groups, with efficacy being

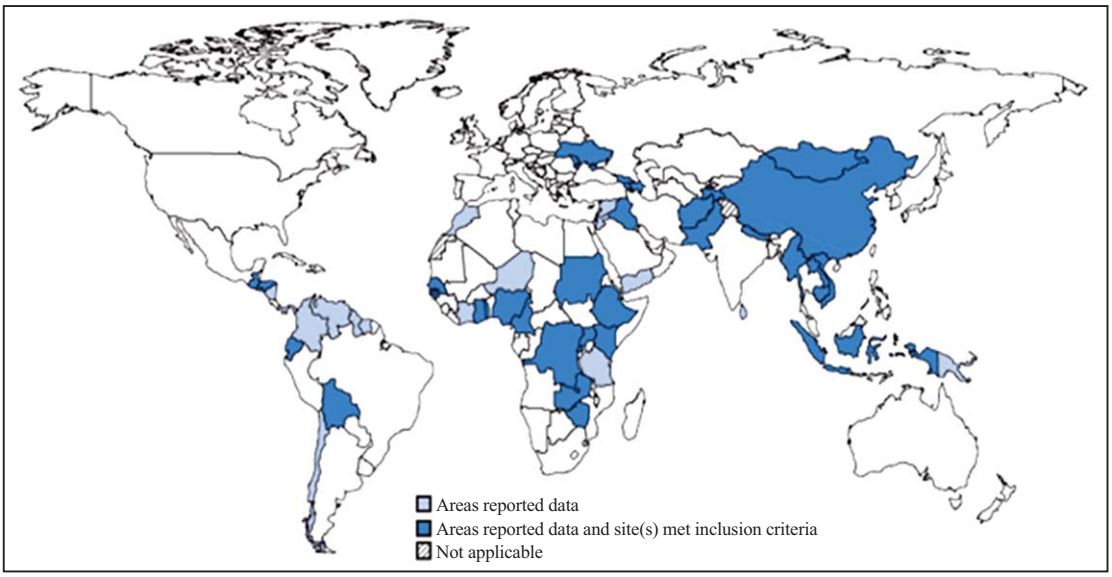

Fig. Global rotavirus surveillance network in the period of 2011-2012.[3]

lower in developing country populations with the highest burden of disease.[18] The efficacy of rotavirus vaccines in developing countries was initially published in 2010.[19-21] While the SAGE noted the inverse relationship between child mortality rates and rotavirus vaccine efficacy, and the recommendation for the use of the vaccines was extended to include all countries, especially those where diarrhea disease accounts for ≥10% of child deaths.[22] The aim of this review is to assess the development of the rotavirus vaccine and to summarize the current status and effectiveness of licensed rotavirus vaccines around the world.

Data collection

A literature review was undertaken to identify studies concerning childhood rotavirus. These studies were searched from MEDLINE (National Library of Medicine, Bethesda, Maryland, USA) using the key words "rotavirus" and "rotavirus vaccine". The search was limited to the English language literature published during the period from January 2002 through August 2014. Articles without an abstract and opinion articles were excluded from the review. From the enrolled articles, the relevant information was extracted and classified according to rotavirus vaccine, the effectiveness of rotavirus vaccine, the efficacy of rotavirus vaccine, the country of the study, the year of publication, and the study design.

The search was done in the period of May-June 2014. Using the search terms, we retrieved 523 articles from MEDLINE. Finally, 121 articles were verified to be relevant.

Rotavirus vaccines

Bishop et al[23] found that infants infected with rotavirus would have immunity to rotavirus infection. Oral delivery of live attenuated rotavirus strains has been a predominant idea on the development of rotavirus vaccine. With the "Jennerian" concept, researchers have considered that immunization with an animal rotavirus may result in naturally attenuated rotavirus in humans.[24] Attenuated human rotaviruses that have been produced by passage in cell culture have also been used in experimental studies.[25] Furthermore, rotaviruses isolated from asymptomatic infants might be naturally less virulent and can be a good candidate for the development of an oral vaccine.[26]

Vaccines based on animal rotaviruses

Both vaccine strain RIT4237 (P6[1]G6) and Wistar Calf 3 (WC3, serotype P7[5]G6) are bovine origin of rotavirus strains. The RIT4237 bovine strain was recovered from a calf and attenuated rotavirus by passage in cell culture. Vaccine strain MMU18006 (P5B[3]G3) is a simian (rhesus) rotavirus reassortant vaccine (RRV) strain.[27-31] The efficacy of the vaccines derived from these strains has been studied extensively. Initially, the efficacy trials in Finland showed satisfactory results; however, the follow-up studies were disappointing because there was little or no protection against rotavirus diarrhea.[29-31]

The WC3 bovine strain WC3 was obtained in 1981 when it was discovered from a calf. Field trials showed that vaccines generated from this strain had variable efficacy, even giving particularly disappointing results for protection against rotavirus infection in developing countries.[27,28]

Between 2000 and 2001, the Lanzhou lamb rotavirus (LLR) vaccine was approved in China as a childhood vaccine for protection against childhood rotavirus diarrhea.[32] This vaccine is a monovalent (P[12]G10) live attenuated oral rotavirus vaccine. The LLR vaccine strain was derived from a lamb rotavirus and was developed and produced by the Lanzhou Institute of Biological Products. The LLR vaccine efficacy trial was performed in Guangzhou province. A total of 838 children with rotavirus infections, aged 2 months to 5 years, were enrolled as study patients and 838 as controls.[32] The efficacy of LLR vaccine on hospitalized patients with rotavirus diarrhea was 73% (95% CI: 61%-82%). Another study consisting of 3130 children aged 2 to 35 months with laboratory-confirmed rotavirus gastroenteritis and 3607 controls was conducted from 2009 to 2011. The effective rate of one dose LLR vaccine for combating rotavirus infection was 44.3% (95% CI: 28.4%-56.7%) in children aged 9-11 months, 52.8% (95% CI: 40.8%-62.3%) in children aged 12-17 months, and 51.8% (95% CI: 11.6%-73.8%) in children aged 18-35 months.[33] Immunologic studies showed that the neutralizing antibody titer specific for all G serotypes of rotavirus among children aged 6-24 months was 40% and 70% respectively before and after use of LLR vaccine.[34] However, the actual efficacy of LLR vaccine remains undetermined because of the absence of randomized, placebo-controlled phase III clinical trials on the vaccine.[19] According to the reported trials, the majority of children vaccinated at older age would be typical for initial infection and acute rotavirus diarrhea. It was not determined whether the children who had been previously vaccinated were exposed to rotavirus, during which LLR could improve the status of the pre-existing antibody reaction.[34] In China, children aged 2 to 36 months are vaccinated with this vaccine.[34] Approximately 30 000 000 doses of LLR vaccine were administered in China during 2000 and 2012;[34] however this vaccine has not been recommended for use in national immunization programs in China or elsewhere at present.

Human-animal reassortant vaccines

Because the efficacy of monovalent animal rotavirus-based vaccines is inconsistent,[35] effort was made in the development of rotavirus vaccine focusing on either naturally attenuated human rotavirus strains or reassortant rotavirus strains. The second generation of vaccines included more than one rotavirus G serotype. These vaccines provided both heterotypic and homotypic immunity. With the concept of "modified Jennerian", the ability of rotaviruses to reassort during mixed infections *in vitro* allowed the production of reassortant vaccines.[24] To evoke an immune response to a G-type antigen from a human virus was the goal of this production. At the beginning, reassortants were studied by co-infecting a monkey with bovine and human rotavirus and allowing the reasssortment to occur by chance. In a study, reassortants were conducted in laboratories and propagated in Vero cells.[36]

Human-animal rotavirus reassortants include several genes. One gene encoding viral structural protein (VP) 7 , with or without VP4 was derived from the human rotavirus parent and the remaining genes were derived from the animal rotavirus parent. These reassortants were created as vaccine candidates; while maintaining the attenuated properties of the parent strain, they could induce immune responses to the human capsid proteins.[35] Based on either simian or bovine strains, several reassortant vaccines have been developed.

Quadrivalent human-rhesus reassortant vaccine

RotaShield was the first multivalent live oral reassortant vaccine. It belongs to a group that includes the rhesus rotavirus tetravalent vaccine, which is a combination of G1 to G4 virus strains. It includes three rhesus-human reassortant strains (G1, G2, and G4) including human serotype strain and rhesus RRV serotype (G3).[35] The trials of primary efficacy demonstrated that the vaccine-conferred protection against all cases of rotavirus-related diarrhea was 57%-76%, and protection against severe rotavirus gastroenteritis was 82%-96%.[36] An adverse reaction of fever was observed after the first vaccination of RotaShield; however, no other important complications have been found as a result of RotaShield vaccination at the time of licensing.[37]

This vaccine was approved by the Food and Drug Administration (FDA) of USA in 1981 and was then proposed for routine use in younger children. However, it was suspended from use and withdrawn from market in 1999 because of the risk of intussusception.[38] Investigators indicated that this vaccine was significantly associated with higher risk of intussusception, with an estimated incidence of 1 in 10 000 individuals vaccinated.[39] Within 3-14 days after the first dose of vaccination, the children who received the vaccination after 3 months had the highest risk of intussusception.[40] The cause of this association remains unclear; however, the side-effects indicate that large field trials should be conducted for candidates of rotavirus vaccines. The criteria of safety for rotavirus vaccines are required to be less than a 1/10 000 risk of intussusception in large field trials.[41,42] As a further precaution, strict vaccination schedules have been established, in which the first dose of vaccination is given to infants at age of 6-14 weeks and no "catch-up" programs are allowed. Post-marketing surveillance for intussusception has been established in several countries.[43]

Human-bovine rotavirus reassortant vaccine

A series of human-bovine reassortant vaccine strains, which were combined into a polyvalent vaccine, were developed from the WC3 vaccine strain.[44] In maintaining immunogenicity, fever was rarely found in children who had been vaccinated with bovine-human reassortants compared with rhesus reassortants.[45]

RotaTeq vaccine contains 4 human and 1 bovine live reassortant rotaviruses, including the G1-G4 common VP7 types from human rotavirus parent strain and the attachment protein (P7[5]) from WC3 bovine rotavirus parent strain.[44,45] The fifth reassortant virus expresses the attachment protein (P1A[8]) from the human rotavirus parent strain and the G6 outer capsid protein from the bovine rotavirus parent strain.[46,47] RotaTeq is an oral vaccine that is administered at 1- to 2-month intervals starting at 6 to 12 weeks of age and given in three doses.[47]

The efficacy of major human rotavirus vaccines in different settings is shown in the Table.[36,47-59] Trials[47,60,61] showed that the efficacy of RotaTeq on diarrheal diseases and severe gastroenteritis was 74% and 98%, respectively. RotaTeq was also effective in combating each of the common circulating serotypes. In addition, there was a large safety trial in 70 000 infants with various subgroup analyses of a large European cohort.[47,61] RotaTeq is highly effective to prevent rotavirus gastroenteritis-associated hospitalization and emergency department visits. Compared with risk of intussusceptions after treatment with placebo, there was no evidence of increased risk of intussusception after vaccination. Additionally, efficacy and safety trials conducted in developing countries showed that the vaccine reduced the use of healthcare resource in infants with rotavirus gastroenteritis, but no intussusception or other serious side-effects were observed.[62] However, post-licensure analyses in the USA showed that approximately 1.5 cases of intussusceptions per 100 000 recipients received the first dose of RotaTeq.[63] The effectiveness of RotaTeq vaccine against rotavirus-related hospitalizations and deaths was determined in Asian countries,[64] showing that the overall effectiveness against rotavirus-related hospitalizations and the substantial reduction in rotavirus-related deaths was 82% to 89%.

RotaTeq vaccine was approved by the FDA of the USA, and in 2006 it was recommended by the Advisory Committee on Immunization Practices (ACIP) for routine use in infants.[65] Moreover, no association was found between intussusceptions or Kawasaki disease and the safety of RotaTeq.[66]

UK-based bovine-human reassortant vaccine

The National Institute of Allergy and Infectious Diseases has developed another multivalent bovine-human reassortant vaccine. This bovine rotavirus tetravalent vaccine contains G1, G2, G3, and G4 human serotypes which incorporate 4 reassortant viruses with a single gene for *VP7* and *VP10* genes from the UK bovine rotavirus strain (P[7]G6). A study from the USA showed that the vaccine showed satisfactory attenuation, safety, infectivity and immunogenicity in infants.[67] In Brazil, the UK-derived reassortant tetravalent vaccine, added of fifth (G9) serotype, just completed a phase I clinical trial.[68] No difference was found in mild side-effects between experimental and control groups. The seroconversion rate was consistently higher in the vaccinated group than in the control group after the administration of vaccine of any doses.

Human rotavirus strain vaccines

Either human common attenuated rotavirus strains or uncommon strains isolated from asymptomatic neonates were developed as vaccines or vaccine candidates.

Monovalent human G1 rotavirus vaccine

Another live-attenuated human rotavirus vaccine (strain 89-12) was developed by tissue culture passage of a wild-type human rotavirus isolate.[48] This vaccine used the P1A[8]G1 strain as a parent strain which contains the most common human rotavirus VP7 and VP4 antigens. Originally, this vaccine was modified using avant immunotherapeutics. Then, it was further modified by using cloning and tissue culture passaging of the parent 89-12 vaccine strain by GlaxoSmithKline Biologicals (GlaxoSmithKline BiologicalsRixensart, Belgium). Finally, this vaccine was licensed by GlaxoSmithKline Biologicals. The vaccine is known as RIX4414 vaccine (Rotarix) (Table). The efficacy trials conducted in the United States and Finland showed that Rotarix had a high efficacy.[69,70] In addition, this vaccine was tested in Latin American countries. Overall, the efficacy rate of Rotarix against severe rotavirus disease was 85%.[50] Other clinical trials involving 63 000 children have been conducted. These studies showed that the efficacy rate of Rotarix against hospitalization was 85%, and that against non-G1 serotypes was 75%.[50] Another study involving 15 000 healthy infants, aged 6-13 weeks and living in Latin American countries, was conducted to determine the efficacy and safety of Rotarix. This study showed that the efficacy rate of vaccine against the G1 wild-type was 81%-82%, against the pooled non-G1 strain was 78%, against the non-G1P[8] strain was 81%, against hospitalization with severe diarrhea was 83%, and against hospitalization with any cause was 39%.[71] The vaccine has also been tested in China and Hong Kong,[54,55] with an efficacy rate of 87%-96% against hospitalization

Table. Efficacy of live-attenuated oral rotavirus in different settings worldwide

Vaccine	Years reported	Countries and areas	Efficacy on conditions	Efficacy, % (95% CI)
RotaShield[48]	1996	USA	Rotavirus episodes	49
			Very severe episodes	80
			Dehydrating illness	100
RotaShield[49]	1997	Finland	RVGE of any severity	68 (57-76)
			Severe RVGE	91 (82-96)
Rotarix[50]	2006	Argentina, Brazil, Chile, Colombia, the Dominican Republic, Honduras, Mexico, Nicaragua, Panama, Peru, Venezuela, Finland	Severe RVGE and rotavirus associated hospitalizations	85 (71-93)
Rotarix[51]	2009	Singapore	Severe RVGE	96 (85-100)
Rotarix[52]	2010	Malawi, South Africa	Severe RVGE	61 (44-73)
Rotarix[53]	2013	USA	RVGE of any severity	91 (80-95)
Rotarix[54]	2013	China	Seroconversion rate	87 (60-98)
Rotarix[55]	2013	Hong Kong, China	RVGE of any severity	96 (73-100)
RotaTeq[56]	2009	Europe	Severe RVGE	68 (60-74)
RotaTeq[57]	2010	Ghana, Kenya, Mali	RVGE of any severity	31 (17-42)
			Severe RVGE	39 (19-55)
RotaTeq[58]	2010	Bangladesh, Vietnam	RVGE of any severity	43 (21-58)
			Severe RVGE	48 (22-66)
RotaTeq[59]	2013	Japan	Severe RVGE	100 (55-100)
RotaTeq[53]	2013	USA	RVGE of any severity	92 (75-97)

RVGE: rotavirus gastroenteritis; CI: confidence interval.

with rotavirus gastroenteritis. There was no evidence of increasing adverse events or risk of intussusception in individuals after vaccinnation.[71] This vaccine was first licensed in Mexico and the Dominican Republic in 2004 and then in the USA in 2008. The ACIP immediately recommended it for inclusion in the routine immunization schedule for infants.[65] To date, Rotarix has been approved for use in more than 100 countries.

Serotype G3 (RV3) neonatal strain vaccines

RV3, a P2A[6]G3 strain, was isolated from newborns hospitalized at the Children's Hospital in Melbourne, Australia.[72] Since neonates infected with RV3 rotavirus strain in hospitals were usually asymptomatic and were later protected against severe rotavirus diarrhea in their childhood, RV3 vaccine was developed. Safety trials using a single dose of vaccine showed that no important side-effects were observed initially; however, the activities of immune response were low.[34] A clinical trial using three doses of vaccine was conducted, showing an immune response rate of of 54% in infants. Because of the promising results, BioPharma (Bandung, Indonesia) modified this vaccine by increasing its titer. Then the vaccine was again subjected to clinical trials. Followed by a double-blind, randomized placebo-controlled study, a phase I study was conducted to evaluate the safety and tolerability of a single oral dose of the second generation RV3-BB rotavirus vaccine. It was demonstrated that the RV3-BB rotavirus vaccine was well tolerated in adults, children and infants.[68]

Indian neonatal strain vaccines

In India, candidate rotavirus vaccines are being developed using two strains (116E strain and I321 strain) isolated from newborns. The 116E strain is a P8[121]G9 natural reassortant between a human parent strain and a *VP4* gene of bovine origin.[73,74] This strain was isolated in 1985 from an outbreak of asymptomatic rotavirus gastroenteritis in New Delhi.[73] The sequence of the *VP4* gene is homologous to that of P[11], a genotype commonly found in cattle. Additionally, the I321 strain was isolated from an outbreak of nosocomial infection at a maternity center in Bangalore and was identified to be a bovine-human reassortant strain.[75] The genome of the I321 strain is different from the genome of the 116E strain. The I321 strain includes nine bovine gene segments. Among them, only gene segments five and seven, which encoded nonstructural proteins 1 and 3, are of human origin. A new strain with the same G and P segments as I321 strain has emerged in Vellore, India as a cause of diarrhea in children.[76]

Recently published results from a phase III clinical trial of an oral, attenuated rotavirus vaccine (Bharat Biotech International Limited of India), manufactured in India and based on the natural human-bovine reassortant strain G10P, which causes asymptomatic infection in infants, showed that the effective rate of the vaccine for protection from severe rotavirus diarrhea was 56%.[77,78]

Other considerations to rotavirus vaccination

Rotavirus infection or rotavirus vaccination induces

innate and acquired virus-specific humoral and cellular immune antibody.[79,80] The mechanism of immune responses, by which protection from rotavirus infection occurs after natural infection or after immunization, is unknown.[81] Serum and intestinal antibodies produced after rotavirus infection protect from severe rotavirus gastroenteritis caused by subsequent infection.[81,82] The mechanism of protection is difficult to understand and has complicated the interpretation of various clinical trials. Taken together, most immunological studies have indicated that the presence of fecal immunoglobulin A or serum antibodies is served as an efficient surrogate marker for protection from re-infection[83] although other markers of the immune response are believed to be important. These markers such as cluster of determinant (CD) 4 and CD8 T cells are undefined in humans at present, although animal studies have indicated their importance for the mechanisms of protection from infection.[84]

Although orally administered live virus vaccines represent the primary approach to rotavirus vaccine development, other approaches and routes of administration are being evaluated and tested in animal models. Various studies, such as virus-like particles, cold-adapted strains, inactivated strains, and DNA vaccines have been undertaken.[85-87] These studies could improve the variable immune responses to oral vaccines in the future. They also could be combined with other parenterally administered vaccines or could avoid the risk of intussusception.

Vaccination program

RotaTeq and Rotarix have been involved in a national immunization program in over 50 countries since 2013.[88] The age restriction was given up in 2009 when the rotavirus vaccine was recommended for use in all countries; the administration of the first dose of vaccine was extended up to 15 weeks of age, and the administration of the last dose of vaccine was at age of 32 weeks.[3,22,89,90] In 2013, WHO recommended the wide use of vaccine to reduce the rotavirus mortality of children in high mortality settings.[91] In these settings, rotavirus vaccine is now given whenever children are present for their routine vaccinations. Although countries introducing the rotavirus vaccine as a national immunization program have their own age restrictions for administration, the cost-effectiveness of rotavirus vaccination still outweighs the risk of intussusception. The elimination of the age restrictions in universal use of rotavirus vaccine could prevent anually 47 000 additional deaths while potentially causing an additional 300 deaths due to intussusception in younger children.[92] In some countries, age restrictions appeared to prevent rotavirus vaccine from achieving the same coverage rates of other routine infant immunizations but in other countries this policy appeared to increase the timeliness of other routine immunizations.[93-95] Some clinical trials for identifying other administration schedules are still going on. A recent randomized clinical trial was conducted to evaluate the immunogenicity of two different 2-dose monovalent rotavirus vaccine programs (dose given at age of 6 and 10 weeks and at age of 10 and 14 weeks) as well as that of a 3-dose monovalent rotavirus vaccine program administrated at age of 6, 10, and 14 weeks.[53] There was no significant difference in immunogenicity of the different programs in this trial, however, additional trials are needed to further address this issue. Because most rotavirus disease occurs in younger children, particularly in developing countries, successful administration of rotavirus vaccine in infants would potentially offer a substantial benefit to the public health. However, if the greater levels of passively transferred maternal antibodies are seen in younger infants, the performance of rotavirus vaccine may be pending.

Conclusions

The burden of rotavirus gastroenteritis is a substantial, and it is an economic burden from infection in infants and children worldwide. Since rotavirus was discovered as an important enteric pathogen in children more than 40 years ago, researchers have made efforts in developing a rotavirus vaccine. The present studies on animal and human models revealed that rotavirus disease can be controlled by passive transfer of rotavirus-specific immune response antibodies or by vaccination. Rotavirus vaccination is a cost-effective strategy for controlling rotavirus infection. Significant effect on all-cause diarrhea and hospitalization with rotavirus infection has been noted in countries where rotavirus vaccine is included in the national immunization program.

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