CLINICAL MICROBIOLOGY REVIEWS, Jan. 2008, p. 198–208 Vol. 21, No. 1
0893-8512/08/$08.00+0 doi:10.1128/CMR.00029-07

Rotavirus Vaccines: an Overview

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INTRODUCTION 198
Disease Burden and Epidemiology 198
VIROLOGY 199
NATURAL PROTECTION 200
GOALS FOR A ROTAVIRUS VACCINE 201
VACCINE STRATEGIES 201
VACCINES BASED ON ANIMAL ROTAVIRUSES 201
Previous Strategies 201
Monovalent animal rotavirus vaccines 201
Human-rhesus RRV (RotaShield) 201
Currently Licensed Vaccine: Human-Bovine Rotavirus Reassortant Vaccine (RotaTeq) 202
Derivation 202
Safety, immunogenicity, and efficacy 202
Vaccine Candidates 204
Human-bovine rotavirus reassortants 204
Naturally occurring human-bovine reassortants 204
VACCINES BASED ON HUMAN ROTAVIRUS 204
Currently Licensed Vaccine: Live-Attenuated Human Rotavirus Vaccine (Rotarix) 204
Derivation 204
Safety, immunogenicity, and efficacy 204
Vaccine Candidates: Neonatal Rotavirus Strains 205
OTHER VACCINE APPROACHES 206
FUTURE CHALLENGES 206
REFERENCES 206

INTRODUCTION

Rotavirus is the leading cause of severe diarrhea disease in infants and young children worldwide. About 600,000 children die every year from rotavirus, with more than 80% of all rotavirus-related deaths occurring in resource-poor countries in south Asia and sub-Saharan Africa (66). Rotavirus-related deaths represent approximately 5% of all deaths in children younger than 5 years of age worldwide.

The virus infects the mature villus epithelial cells of the small intestine, and infection often leads to fever, vomiting, and diarrhea in children. Dehydration and electrolyte disturbances are the major sequelae of rotavirus infection and occur most often in the youngest children. Rotavirus infection is usually localized to the intestine; however, recent studies reported antigenemia or viremia in children with rotavirus diarrhea (11, 12, 17, 18, 90). Rarely, involvement of extraintestinal sites, including the respiratory tract, liver, kidney, lymph nodes, and central nervous system, has been reported (54, 55, 64, 70).

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Disease Burden and Epidemiology

Each year, rotavirus causes approximately 114 million episodes of gastroenteritis requiring home care only, 24 million clinic visits, and 2.4 million hospitalizations in children <5 years of age worldwide. By age 5, nearly every child will have an episode of rotavirus gastroenteritis, 1 in 5 will visit a clinic, 1 in 50 will be hospitalized, and approximately 1 in 205 will die (35). Recent studies indicate that rotavirus causes approximately 39% of childhood diarrhea hospitalizations worldwide (66).

In temperate climates, rotavirus disease occurs during the cooler months. Seasonal patterns in tropical climates are less pronounced, but disease is more common during the drier, cooler months. In the United States, rotavirus causes yearly epidemics of disease from late fall to early spring (Fig. 1). The peak of disease varies by region. In the southwest, the peak rotavirus season is November to December. The peak of the epidemic then travels sequentially across the United States from west to east, concluding in April to May in the northeast (41, 51, 78, 79).

Rotavirus gastroenteritis results in only 20 to 70 childhood deaths per year in the United States (30, 47). However, nearly every child in the United States is infected with rotavirus by 5 years of age, and most will develop gastroenteritis. One child in 7 will require a clinic or emergency room visit, and 1 in 70 will be hospitalized (36, 56). Each year, rotavirus causes more than

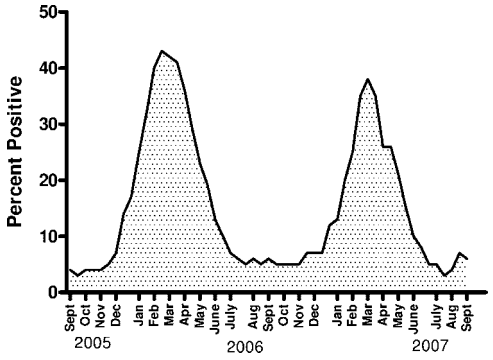

FIG. 1. Seasonal trends in rotavirus activity in the United States from September 2005 through September 2007. These data are from the National Respiratory and Enteric Virus Surveillance System, a voluntary, laboratory-based system organized by the CDC, Atlanta, GA. The National Respiratory and Enteric Virus Surveillance System prospectively monitors seasonal trends in viral activity on a weekly basis.

400,000 physician visits, more than 200,000 emergency room visits, and 55,000 to 70,000 hospitalizations (30). Rotavirus infection is responsible for only 5 to 10% of all gastroenteritis episodes among children <5 years of age in the United States. However, rotavirus causes more severe disease than other pathogens causing gastroenteritis and thus accounts for 30 to 50% of all hospitalizations for gastroenteritis among children aged <5 years and more than 70% of hospitalizations for gastroenteritis during the seasonal peaks of rotavirus disease in the United States (13, 48, 57, 72).

Although severity of disease may differ, rates of rotavirus illness among children in industrialized and resource-poor countries are similar, indicating that clean water supplies and good hygiene have little effect on virus transmission, and further improvements in water or hygiene are unlikely to prevent the disease. In view of the high burden of rotavirus disease, safe and effective rotavirus vaccines are urgently needed, particularly in the resource-poor countries of the world. Such vaccines would have universal application in childhood vaccination programs.

VIROLOGY

Rotaviruses were discovered in the 1960s in animals. The virus was first described in humans when it was found by electron microscopy in duodenal biopsies from children with acute gastroenteritis (9).

Rotaviruses are 70-nm icosahedral viruses that belong to the family *Reoviridae*. Seven rotavirus serogroups (serogroups A to G) are described. Most human pathogens belong to groups A, B, and C. Group A rotaviruses are the most important from a public health standpoint.

The virus is composed of three protein shells, an outer capsid, an inner capsid, and an internal core, that surround the 11 segments of double-stranded RNA (Fig. 2). For the most part, each gene segment codes for a single protein. When mixed infection with more than one rotavirus strain occurs, the gene segments from the parental viruses may reassort independently, producing reassortants of mixed parentage, a source of viral diversity.

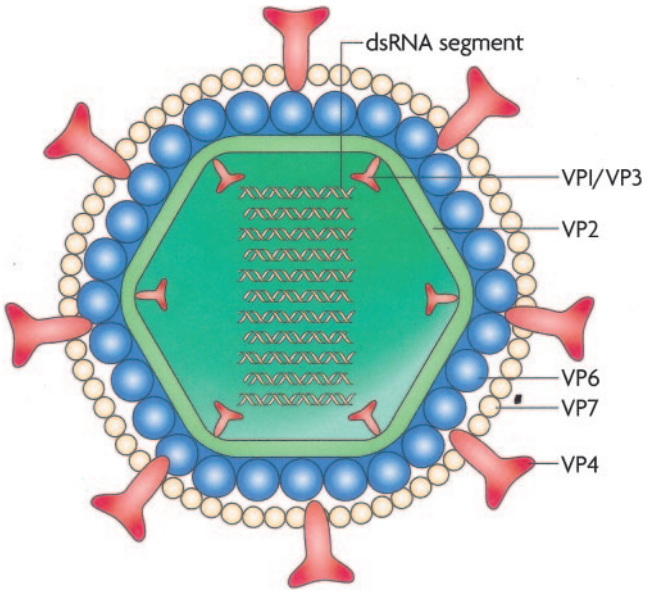

FIG. 2. Schematic representation of a rotavirus virion. The virus is composed of three protein shells, an outer capsid, an inner capsid, and an internal core, that surround the 11 segments of double-stranded RNA. The outer capsid proteins VP4 and VP7 are neutralization antigens and define the P and G serotypes, respectively. VP6, the inner capsid structural protein, is the subgroup antigen. (Reprinted from reference 1 by permission from Macmillan Publishers.)

Four major structural and nonstructural proteins are of interest in vaccine development: VP6, NSP4, VP7, and VP4. VP6, the most abundant viral structural protein, is found in the inner capsid (43). VP6 bears group-specific antigenic determinants. NSP4 is a nonstructural protein and has been shown to be an enterotoxin (2).

VP7 and VP4 are structural proteins found in the outer capsid. These two proteins define the serotype of the virus and are considered to be critical for vaccine development because they are targets for neutralizing antibodies that may provide both serotype-specific and, in some instances, cross-reactive protection (38). The VP7 protein is glycosylated, and serotypes determined by this protein are termed G serotypes. Fourteen G serotypes have been identified.

VP4 is a protease-cleaved protein, and serotypes determined by this protein are termed P serotypes. P types have been difficult to characterize by traditional methods of virus neutralization; therefore, molecular methods have been used to define a genotype based on sequence analysis. These genotypes correlate well with known serotypes, so the genotypes are tentatively designated in brackets (e.g., P1A[8]). Strains are generally designated by their G serotype specificities (e.g., serotypes G1 to G4 and G9).

Human rotaviruses exhibit enormous diversity. The gene segments that encode the G and P proteins can segregate independently, giving rise to strains with at least 42 different P-G serotype combinations (33). However, a small number of rotavirus strains bearing VP7 G serotypes G1 to G4 and G9 and VP4 P genotypes P1B[4], P2A[6], and P1A[8] are predominant worldwide. In a recent study, four G types (G1, G2, G3, and G4) in conjunction with P1A[8] or P1B[4] represented

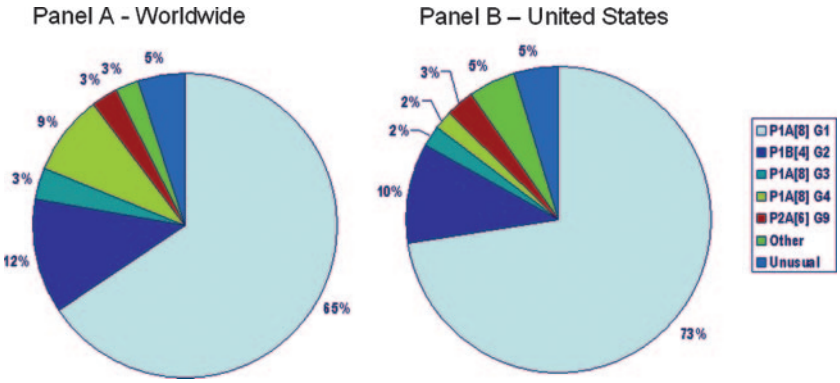

FIG. 3. Distribution of rotavirus serotypes worldwide and in the United States. (A) Global distribution from 1989 to 2004. The G serotypes of >88% of rotavirus strains worldwide are G1, G2, G3, and G4. The P serotype of >80% of rotavirus strains worldwide is P1A[8]. (B) U.S. distribution from 1973 to 2003. The G serotypes of >97% of rotavirus strains in the United States are G1, G2, G3, and G4. The P serotype of >80% of rotavirus strains is P1A[8]. This figure is based on data from reference 74.

over 88% of the strains analyzed worldwide. Serotype G9 viruses associated with P1A[8] or P2A[6] have been emerging since the late 1990s and now represent approximately 4% of global isolates (Fig. 3) (74).

G and P serotype distributions differ geographically. P1A[8]G1 is the globally predominant strain, representing over 70% of rotavirus infections in North America (Fig. 3), Europe, and Australia but only about 30% of the infections in South America and Asia and 23% of those in Africa (74). G9 strains now constitute the predominant strains in some parts of Asia and Africa, and G8 strains are proportionally more frequently isolated in Africa. In South America, G5 strains have emerged in children with diarrhea, and G9 is associated with more severe disease in Latin America (53). Similarly, the distribution of the VP4 P2A[6] antigen differs according to region. P2A[6] strains now constitute over 50% of the strains circulating in Africa, whereas P1A[8] is associated with most rotavirus strains from the rest of the world (76).

Implementation of an effective rotavirus vaccine program will need to take into account the geographical variation of prevalent strains. The continued identification of the most common G and P serotypes for inclusion in vaccines is an important priority. After the introduction of a vaccine candidate, monitoring of circulating strains may be necessary, as vaccine pressure may lead to the selection of novel rotavirus strains.

NATURAL PROTECTION

Most symptomatic rotavirus infections occur between 3 months and 2 years of age, with a peak incidence between 7 and 15 months. Rotavirus infections are more likely to be severe in children 3 to 24 months of age than in younger infants or older children and adults (21, 67, 88) Longitudinal studies demonstrated that naturally acquired rotavirus infections provide protection against rotavirus disease upon reinfection and that protection is greatest against the most severe disease outcomes (29, 80) Although children can be infected with rotavirus several times during their lives, initial infection after 3 months of age is most likely to cause severe diarrhea and dehydration.

Most mothers have rotavirus antibody from previous infection that is passed transplacentally, protecting the neonate. As a result, most infected neonates will have asymptomatic or mild disease (8) An exception is the preterm infant, who is at greater risk of severe illness than the term infant because of the lack of transplacental maternal antibodies (62). Exposure of neonates (asymptomatically) to rotavirus is associated with a reduced likelihood of their developing severe rotavirus diarrhea later in infancy (6, 8).

After a first natural infection, infants and young children are protected against subsequent symptomatic disease regardless of whether the first infection was symptomatic or asymptomatic. In a study in Mexico, 40% of children were protected against a subsequent infection with rotavirus after a single natural infection, 75% were protected against diarrhea caused by a subsequent rotavirus infection, and 88% were protected against severe rotavirus diarrhea (80). Second, third, and fourth infections conferred progressively greater protection. No child with two previous infections subsequently developed severe rotavirus diarrhea.

Despite three decades of research, the immune correlates of protection from rotavirus infection and disease are not completely understood. The mouse model has been extensively used to investigate the contribution of different components of the immune system in protection (87). These studies have suggested that both humoral and cell-mediated immunity are important in the resolution of ongoing rotavirus infection and in protection against subsequent infection.

Humoral immunity is believed to play an important role in protection. Studies of monkeys have demonstrated that the passive transfer of serum antibodies can provide protection against infection (89). Studies have also demonstrated that the first infection with rotavirus elicits a predominantly homotypic, serum-neutralizing antibody response to the virus, and subsequent infections elicit a broader, heterotypic response (19, 23, 58, 63) Controversy exists as to whether serum antibodies are directly involved in protection or merely reflect recent infection. Review of data from a variety of studies of humans, including challenge experiments with adult volunteers, longitudinal studies of rotavirus infection in young children, and clinical trials of animal and animal-human reassortant rotavi-

rus vaccines in infants, suggests that serum antibodies, if present at critical levels, are either protective themselves or an important and powerful correlate of protection against rotavirus disease, even though other host effectors may play an important role as well (40).

VP6 is the immunodominant antigen in the antibody response to human rotavirus infection (77). Serum immunoglobulin A (IgA) or IgG antibodies against VP6 antigen tested by enzyme immunoassay are regarded as an indicator of rotavirus immunity after infection and vaccination. Serum IgA appears to act intracellularly in rotavirus-infected cells (32). A high level of serum IgA antibody correlates with clinical protection against rotavirus gastroenteritis (81).

Neutralizing antibodies against VP7 and VP4 antigens clearly play a role in protection after natural rotavirus infection (19), but their role in rotavirus vaccine-induced immunity is less clear. The current live oral rotavirus vaccines rely on the concept that immunity to the rotavirus surface antigens is essential or important for vaccine-induced protection. However, vaccines that elicit low levels of serum antibodies have been effective in field trials.

Local immunity in the gut also seems to be important for protection against subsequent infection. The total serum antirotavirus IgA level, measured shortly after infection, generally reflects intestinal IgA levels and appears to be the best marker of protection (31). However, gut immunity appears to be of short duration and has been hard to measure.

Since a reliable immune correlate of protection has not been forthcoming from studies of humans, each new vaccine candidate must be tested in large field trials for efficacy.

GOALS FOR A ROTAVIRUS VACCINE

A realistic goal for a rotavirus vaccine is to duplicate the degree of protection against disease that follows natural infection. Therefore, vaccine program objectives include the prevention of moderate to severe disease but not necessarily of mild disease associated with rotavirus. An effective rotavirus vaccine will clearly decrease the number of children admitted to the hospital with dehydration or seen in emergency departments but should also decrease the burden on the practicing primary care practitioner by reducing the number of office visits or telephone calls due to rotavirus gastroenteritis. Finally, effective rotavirus vaccines are most needed in resource-poor countries, where mortality associated with rotavirus is high.

VACCINE STRATEGIES

Attenuation of rotaviruses for use as oral vaccines may be achieved in several ways. The most extensively evaluated approach is based on the "Jennerian" concept, involving immunization of infants with animal rotaviruses that are considered to be naturally attenuated for humans (39). More recently, human rotaviruses attenuated by passage in cell culture have been developed and tested (5). Finally, rotaviruses recovered from asymptomatic human neonates, which may be naturally less virulent, are being developed as oral vaccine candidates (4, 34).

VACCINES BASED ON ANIMAL ROTAVIRUSES

Previous Strategies

Monovalent animal rotavirus vaccines. Research to develop a safe, effective rotavirus vaccine began in the mid-1970s, when investigators demonstrated that previous infection with animal rotavirus strains protected laboratory animals from experimental infection with human rotaviruses (91). Researchers thought that live animal strains that were naturally attenuated for humans, when given orally, might mimic the immune response to natural infection and protect children against disease. Three nonhuman rotavirus vaccines, two bovine rotavirus strains, RIT 4237 (P6[1]G6) and WC3 (P7[5]G6), and a simian (rhesus) rotavirus reassortant vaccine (RRV) strain (P[3]G3), were studied (20, 22, 82). These vaccines demonstrated variable efficacy in field trials and gave particularly disappointing results in developing countries (37, 50). In 2000 and 2001, China introduced a rotavirus vaccine for childhood immunization (52). The LLR vaccine is a monovalent (P[12]G10) live-attenuated oral vaccine that was derived from a lamb strain of rotavirus developed and produced by the Lanzhou Institute of Biological Products. The efficacy of this vaccine is not known, as it was not tested against placebo in a controlled phase III trial.

In view of the inconsistency of protection from monovalent animal rotavirus-based vaccines, vaccine development efforts began to use either naturally attenuated human rotavirus strains or reassortant rotavirus strains bearing a human rotavirus gene for the VP7 protein together with the other 10 genes from an animal rotavirus strain (59). The next generation of vaccines was formulated to include more than one rotavirus G serotype to provide heterotypic as well as homotypic immunity. The ability of rotaviruses to reassort during mixed infections in vitro allowed the production of reassortant vaccines, termed the "modified Jennerian" approach (45). Reassortant viruses contain some genes from the animal rotavirus parent and some genes from the human rotavirus parent. VP7 was thought to be important for protection; therefore, human-animal reassortant rotaviruses for use as vaccines included human VP7 genes to provide protective immune responses.

Human-rhesus RRV (RotaShield). The first multivalent live oral reassortant vaccine developed was RotaShield (a rhesus rotavirus tetravalent [RRV-TV] vaccine). This tetravalent vaccine contained a mixture of four virus strains representing the most commonly seen G types, G1 to G4: three rhesus-human reassortant strains containing the VP7 genes of human serotypes G1, G2, and G4 strains were substituted for the VP7 gene of the parent RRV, and the fourth strain comprised serotype G3 of rhesus RRV (44). RRV-TV was extensively evaluated in field trials in the United States, Finland, and Venezuela and proved highly effective (80 to 100%) in preventing severe diarrhea due to rotavirus in each of these settings (42, 68, 71, 75). Due to the proven efficacy, the RRV-TV vaccine was licensed in August 1998 for routine use in children in the United States at 2, 4, and 6 months of age (16).

After inclusion of this vaccine in the immunization schedule in the United States and immunization of over 600,000 infants in the first 9 months of the program, several cases of vaccine-associated intussusception were reported (14). The period of

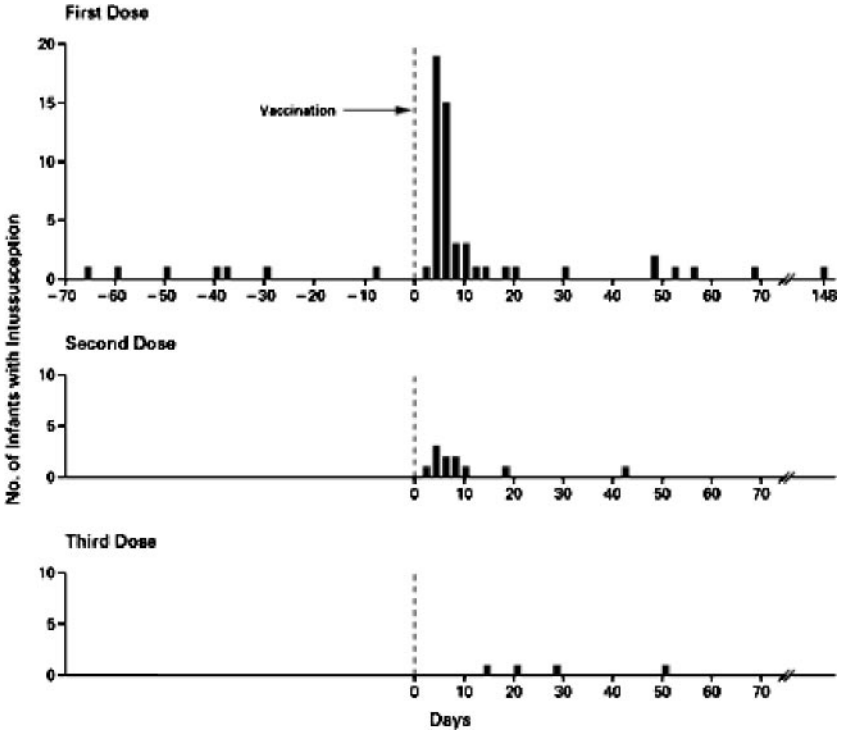

FIG. 4. Interval between vaccination with RRV-TV and the development of intussusception. (Reprinted from reference 60 with permission, copyright ©2007 Massachusetts Medical Society.)

greatest risk of intussusception was shown to be 3 to 10 days after the first of three oral doses (Fig. 4) (49, 60, 61). Although the true overall incidence of this adverse event proved to be difficult to assess, a group of international experts suggested a consensus rate of 1 per 10,000 vaccinated infants (69). The pathogenic mechanisms involved in intussusception following vaccination are currently unknown.

As a consequence of this rare but potentially dangerous adverse effect, Wyeth, the manufacturer, withdrew RotaShield from the market in the United States 14 months after its introduction. Unfortunately, the vaccine was not evaluated in terms of risk-benefit for children in resource-poor countries, as the ongoing trials in Asia (Bangladesh and India) and Africa (Ghana and South Africa) were stopped at that time. Although still licensed, the vaccine has not been tested since then or licensed in other parts of the world.

Currently Licensed Vaccine: Human-Bovine Rotavirus Reassortant Vaccine (RotaTeq)

Current human-animal reassortant rotaviruses for use as vaccines include either human VP7 or VP4 genes. Initially, VP7 was thought to be the most important antigen in inducing protection; therefore, human-animal reassortant rotaviruses for use in vaccines such as RRV-TV included only human VP7 genes to provide protective immune responses. More recently, VP4 has also been considered to be important for protection. Human-animal reassortant rotaviruses now include either human VP7 or VP4 genes to provide protective immune responses.

Derivation. A pentavalent human-bovine (WC3) reassortant live-attenuated, oral vaccine (RotaTeq) (see Table 1) has been developed by Merck Research Co. This vaccine contains five live reassortant rotaviruses (Fig. 5). Four reassortant rotaviruses express the VP7 protein (G1, G2, G3, or G4) from the human rotavirus parent strain and the attachment protein (P7[5]) from bovine rotavirus parent strain WC3. The fifth reassortant virus expresses the attachment protein (P1A[8]) from the human rotavirus parent strain and the outer capsid protein G6 from the bovine rotavirus parent strain. RotaTeq is administered in three oral doses at 1- to 2-month intervals beginning at 6 to 12 weeks of age.

Safety, immunogenicity, and efficacy. RotaTeq was tested in a large phase III trial in 11 countries, with subjects from the United States and Finland accounting for more than 80% of all enrolled subjects (85). The trial included more than 70,000 children and was designed primarily to evaluate vaccine safety with respect to intussusception but also to evaluate the immunogenicity and efficacy of the vaccine with respect to the severity of illness and the number of hospitalizations or emergency department visits for rotavirus gastroenteritis.

The risk of intussusception was evaluated for 42 days after each vaccine dose in the phase III trial. Six cases of intussusception were observed in the RotaTeq group, compared to five cases of intussusception in the placebo group (multiplicity-adjusted relative risk, 1.6). The data did not suggest an increased risk of intussusception in vaccine recipients relative to that for placebo. Among vaccine recipients, there were no confirmed cases of intussusception within the 42-day period

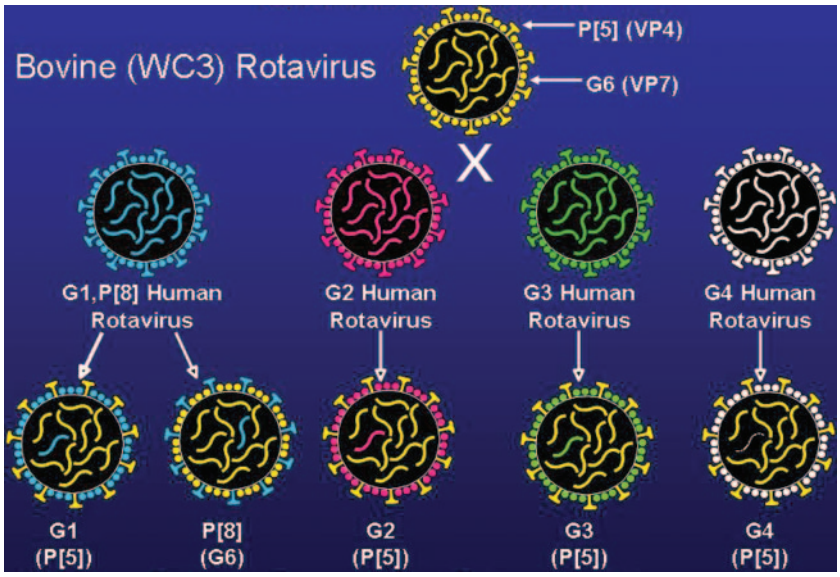

FIG. 5. Human-bovine rotavirus reassortant vaccine (RotaTeq). This vaccine contains five reassortant rotaviruses. Four reassortant rotaviruses express the VP7 protein (G1, G2, G3, or G4) from the human rotavirus parent strain and the VP4 protein (P7[5]) from the bovine rotavirus parent strain. The fifth reassortant virus expresses the VP4 protein (P1A[8]) from the human rotavirus parent strain and the outer capsid protein G6 from the bovine rotavirus parent strain. (Adapted with permission from SLACK Inc. [62a].)

after the first dose, which was the period of highest risk for the previously licensed RRV-TV vaccine. In addition, no evidence of clustering of cases of intussusception was observed within a 7- or 14-day window after immunization for any dose. The overall rate of intussusception is consistent with the expected background rate of intussusception.

Pooled data from the large phase III and two smaller phase III trials showed that in the week following the first dose of RotaTeq, the incidence of fever and irritability did not differ between vaccine and placebo recipients. Diarrhea and vomiting occurred more frequently among vaccine recipients than among placebo recipients (10.4% versus 9.1% and 6.7% versus 5.4%, respectively).

An increase in titer of rotavirus group-specific serum IgA antibodies was used as one of the measures of the immunogenicity of the pentavalent rotavirus vaccine. Serum samples were obtained from a subset of study participants before immunization and approximately 2 weeks after the third dose, and seroconversion was defined as a threefold or greater increase in antibody titer from baseline. Seroconversion rates for IgA antibody to rotavirus were 95% among 189 vaccine recipients, compared to 14% in 161 recipients of the placebo (85).

The efficacy of RotaTeq was evaluated in two phase III trials (10, 85). In these trials, the efficacy of RotaTeq against rotavirus gastroenteritis of any severity after completion of a three-dose regimen was 74%, and that against severe rotavirus gastroenteritis was 98%. RotaTeq also proved to be strongly efficacious in preventing rotavirus gastroenteritis of any severity caused by the predominant G1 serotype (75% efficacy) and the G2 serotype (63% efficacy). There was a trend toward efficacy for the remaining serotypes, but patient numbers were too small to show statistical significance (83% efficacy for G3, 48% efficacy for G4, and 65% efficacy for G9).

The efficacy of RotaTeq in reducing the number of office visits for rotavirus gastroenteritis and in reducing the number of emergency department visits and hospitalizations for rotavirus gastroenteritis was evaluated in a large study. (85). The efficacy of RotaTeq in reducing the number of office visits for rotavirus gastroenteritis among 5,673 subjects and in reducing the number of emergency department visits and hospitalizations for rotavirus gastroenteritis among 68,038 subjects over the first 2 years of life was evaluated. RotaTeq reduced the incidence of office visits by 86%, emergency department visits by 94%, and hospitalizations for rotavirus gastroenteritis by 96%. Efficacy against all gastroenteritis hospitalizations of any etiology was 59%.

The efficacy of RotaTeq in the second rotavirus season after immunization was 63% against rotavirus gastroenteritis of any severity and 88% against severe rotavirus gastroenteritis (85).

Data on the efficacy of fewer than three doses of RotaTeq are limited. In the large study, the efficacy of RotaTeq in reducing the number of emergency department visits and hospitalizations for rotavirus gastroenteritis was evaluated in children receiving fewer than three doses of vaccine (85). Although the study included more than 68,000 children, the number receiving fewer than three doses of vaccine or placebo was less than 8,600. The estimated rates of reduction in hospitalizations and emergency department visits of one, two, and three doses of vaccine in this study were 29%, 81%, and 95%, respectively (T. Vesikari, D. Matson, P. Dennehy, M. Dallas, R. Itzler, M. Dinubile, and P. Heaton, presented at the 44th Annual Meeting of the Infectious Disease Society of America, Toronto, Canada, October 2006).

RotaTeq was licensed in February 2006 by the Food and Drug Administration (FDA) for use among infants in the United States and is routinely recommended as a three-dose schedule at 2, 4, and 6 months of age (65). The first dose should be administered between 6 and 12 weeks of age, with

subsequent doses administered at 4- to 10-week intervals and all three doses of vaccine administered by 32 weeks of age. Immunization should not be initiated for infants older than 12 weeks because of insufficient data on the safety of the first dose of pentavalent rotavirus vaccine in older infants. The vaccine should also not be administered after 32 weeks of age because of insufficient data on the safety and efficacy of pentavalent vaccine in infants after this age.

In the United States, the postmarketing safety of RotaTeq is being monitored jointly by the Centers for Disease Control and Prevention (CDC) and the FDA through both evaluation of reports to Vaccine Adverse Event Reporting System and active surveillance using data from the Vaccine Safety Datalink. Merck and Co. is also conducting a postmarketing observational study, which will monitor patients for occurrences of intussusception within 30 days of vaccination of 44,000 infants in the United States. Data available to date do not suggest that RotaTeq is associated with intussusception (15). The number of intussusception cases among infants vaccinated with RotaTeq reported to the Vaccine Adverse Event Reporting System does not exceed the number of expected background cases for either the 1- to 7-day period or the 1- to 21-day period after vaccination. In addition, no cases of intussusception were detected within 30 days of vaccination in more than 28,000 infants reported to have received RotaTeq according to the Vaccine Safety Datalink.

As of May 2007, applications for licensure of RotaTeq have been filed in more than 100 countries, including Australia, Canada, the European Union, Asia, and Latin America. Through its partnership with the Rotavirus Vaccine Program at the Program for Appropriate Technology in Health (PATH), Merck plans to conduct clinical trials in Africa and Asia.

Vaccine Candidates

Human-bovine rotavirus reassortants. Another multivalent bovine-human reassortant vaccine has been independently developed by the National Institute of Allergy and Infectious Diseases (NIAID). This bovine rotavirus tetravalent (BRV-TV) vaccine incorporates four reassortant viruses with a single gene for VP7 of either a G1, G2, G3, or G4 human serotype and 10 genes from the bovine rotavirus UK strain (P[7]G6). Phase II data from a study with the BRV-TV vaccine showed a good immune response and no adverse interference with concomitantly administered childhood vaccines (24). Before the withdrawal of the RRV-TV vaccine, placebo-controlled trials of BRV-TV vaccine versus RRV-TV vaccine were conducted in Finland with a total of 510 infants. Two doses of study vaccine or placebo were administered at 3 and 5 months of age. The first dose of RRV-TV vaccine was followed by a significant excess rate of febrile reactions (36%), whereas the rate of fever after the administration of the BRV-TV vaccine did not differ significantly from that in the placebo group. A seroresponse was detected in 97% of BRV-TV vaccine recipients and 94% of RRV-TV vaccine recipients. Both vaccines were equally effective, with 68% to 69% efficacy against any and 88% to 100% efficacy against severe rotavirus gastroenteritis during the first epidemic season (84).

With the emergence of the G9 serotype as an epidemiologically important serotype and the importance of the G8 serotype in focal areas, the vaccine developers at NIAID are planning to add human-bovine (UK) reassortants with G8 and G9 specificities to the tetravalent vaccine, thereby formulating a hexavalent vaccine for use in developing countries (46). A nonexclusive license for the production of the human-bovine (UK) vaccine is being negotiated with vaccine producers in Brazil, China, and India.

Naturally occurring human-bovine reassortants. Various observational studies suggested that neonatal rotavirus infection confers protection against diarrhea due to subsequent rotavirus infection. Two strains obtained from asymptomatically infected newborns in Delhi (116E) and Bangalore (I321) have been assessed as vaccine candidates. These strains have P[10]G9 and P[11]G10 antigenic makeups, respectively. Each strain is a naturally occurring human-bovine reassortant; 116E is a human rotavirus with a single gene segment encoding VP4 derived from a bovine rotavirus, and I321 is a bovine strain with two nonstructural gene segments derived from a human strain (25, 27). These vaccine candidates are under development in India in a consortium with partners from the United States including the CDC and the Children's Vaccine Program at PATH (34). A phase I trial of a single dose of either vaccine candidate or placebo in 8-week-old infants was conducted in Delhi (7). That study demonstrated that while both vaccines were safe and well tolerated, strain 116E was superior in its ability to induce an immune response with strain I321 or placebo. In a recent study in three urban slums in Vellore, South India, neonatal G10P[11] infection with a strain resembling the I321 vaccine candidate did not confer protection against subsequent rotavirus infection or diarrhea of any severity in this setting (3). These findings suggest that strain 116E should be further evaluated as a vaccine candidate.

VACCINES BASED ON HUMAN ROTAVIRUS

Currently Licensed Vaccine: Live-Attenuated Human Rotavirus Vaccine (Rotarix)

Derivation. A live-attenuated human rotavirus vaccine (strain 89-12) was originally developed in Cincinnati, OH, by tissue culture passage of a wild-type human rotavirus isolate (5). This vaccine is a P1A[8]G1 strain and thus represents the most common of the human rotavirus VP7 and VP4 antigens. The vaccine was further developed by Avant Immunotherapeutics and licensed to GlaxoSmithKline Biologicals, who further modified the vaccine by cloning and tissue culture passaging of the parent 89-12 vaccine strain. The resulting vaccine, RIX4414 (Rotarix) (Table 1), underwent initial trials in Finland, which showed safety, immunogenicity, and efficacy. The assessments revealed that Rotarix was clinically more attenuated than the parent strain 89-12.

Safety, immunogenicity, and efficacy. A large-scale, double-blind, placebo-controlled trial of more than 63,000 infants enrolled in 11 Latin American countries and Finland was done to confirm that the vaccine did not cause intussusception (73). The vaccine was administered in two oral doses at 2 and 4 months of age and was well tolerated, with a reactogenicity profile similar to that of the placebo in terms of fever, diarrhea, and vomiting. During a 31-day period after each dose, there

TABLE 1. Comparison of currently licensed rotavirus vaccines

Vaccine[a]	Parent strain and genotype	Formulation	Dose regimen	% Protection against severe rotavirus infection[b]	% Reduction in hospitalization	Association with intussusception	% Vaccine virus shedding
RotaTeq	Bovine rotavirus strain WC3, P7[5]G6	5 reassortants; 4 reassortants with the VP7gene from G1, G2, G3, or G4 and 1 reassortant with the VP4 P1A[8] gene from the human rotavirus parent strain with the remainder of the genes from the WC3 bovine rotavirus parent	3 oral doses at 2, 4, and 6 mo of age	98	63	No	9
Rotarix	Human rotavirus strain 89-12, P1A[8]G1	No reassortants; RIX4414, a further-passaged human rotavirus 89-12 strain	2 oral doses at 2 and 4 mo of age	85	42	No	<50

[a] RotaTeq, a pentavalent vaccine, is manufactured by Merck. Rotarix, a monovalent vaccine, is manufactured by GlaxoSmithKline.
[b] Different scoring systems were used; therefore, these results are not comparable.

was no increase in intussusception among recipients of vaccine compared with that for placebo. Six vaccinated patients and seven placebo recipients developed intussusception in this period, confirming the lack of a causal association.

A subset of 20,000 infants in this large trial was monitored for efficacy (73). The results demonstrated a protection rate of 85% against severe rotaviral gastroenteritis and 100% protection against the most severe dehydrating rotaviral gastroenteritis episodes. The vaccine also proved to be strongly efficacious in preventing rotavirus gastroenteritis of any severity caused by the predominant G1 serotype (92% efficacy) and serotypes G3, G4, or G9 (88% efficacy). Efficacy against the G2 serotype (41%) was not significant in this large trial.

Although Rotarix was not efficacious against the G2 serotype in the large phase III trial, significant cross-protection against non-G1 and non-P[8] strains was shown using the meta-analysis of efficacy trials, where protection was 81% against the P[4]G2 strain. This finding was confirmed by the recent results of a European trial with two seasons of follow-up. In that study, efficacy against rotavirus gastroenteritis of any severity was 79%, that against severe rotavirus disease was 90%, and that against hospitalization due to rotavirus was 96%. For severe rotavirus gastroenteritis, the vaccine had efficacies of 96% against G1P[8] and 88% against non-G1P[8] RV strains (83).

Rotarix was first licensed in Mexico and the Dominican Republic in 2004. As of May 2007, Rotarix has been approved in 90 countries worldwide. Fifty countries in Latin America, Europe, Asia, and Africa are already using the vaccine, with more than 11 million doses distributed. Brazil, El Salvador, Mexico, Panama, and Venezuela included the rotavirus vaccine in their national vaccination programs. The vaccine is recommended in a two-dose schedule beginning at 6 weeks of age. Rotarix is not yet approved in the United States; however, the manufacturer is in late-stage development discussions with the FDA regarding licensure of the vaccine for the U.S. market.

Clinical data from efficacy and safety trials of Rotarix in Asia and Africa are expected to become available during the next months and years. A large phase III trial (>9,000 infants) currently ongoing in Singapore, Hong Kong, and Taiwan is expected provide efficacy results by the end of 2007. The phase III trial in Africa (South Africa and Malawi) is under way and has already enrolled more than 50% of the expected subjects. Smaller studies of human immunodeficiency virus-positive infants, preterm infants, and twins have been initiated.

The postmarketing safety of Rotarix will be monitored by the manufacturer according to recently established guidelines issued by the European Union addressing risk management for medical products with the aim to detect and identify risks and to implement strategies that minimize those risks. Rotavirus vaccines will be the first vaccines to follow these new guidelines. The number of reported intussusception cases will be monitored versus the number expected to occur by coincidence following vaccination based on the natural background rate. The manufacturer has also planned a safety study in Mexico in collaboration with the Mexican government. The manufacturer plans to continue monitoring vaccine effectiveness and impact on serotype distribution in Europe and elsewhere along with partners such as the European Rotavirus Network, the CDC, and the World Health Organization (WHO).

Vaccine Candidates: Neonatal Rotavirus Strains

Neonatal strains were initially explored as vaccine candidates because they appeared to be naturally attenuated, and a natural history study had shown that asymptomatically infected neonates subsequently had reduced frequency and severity of rotavirus diarrhea. However, a neonatal strain failed to provide protection in a small efficacy study, and this approach was temporarily abandoned (86).

A human neonatal P[6]G3 strain, RV3, developed by Bishop and colleagues in Australia, was evaluated as an oral vaccine in 3-month-old infants and was found to be safe and well tolerated. A small phase II study with three doses of 10^5 PFU of the vaccine indicated relatively low immunogenicity as measured by serum IgA levels. However, the vaccine recipients who developed an immune response were protected against clinical disease in the following year (4). Furthermore, phase II immunogenicity studies with a higher dose of the vaccine (10^7 PFU per dose) are planned.

OTHER VACCINE APPROACHES

Other approaches to the development of rotavirus vaccines are also being pursued. Rotavirus antigens for parenteral delivery have received some attention as virus-like particles prepared in baculovirus, expressed antigens, DNA vaccines, and killed virus. These novel approaches are being pursued using animal models.

FUTURE CHALLENGES

Postmarketing surveillance studies to monitor the impact of vaccine on circulating viral strains recovered from stool samples will be important to screen for possible vaccine selection pressure and strain replacement. Studies to measure the extent of cross-protection against different rotavirus serotypes, including serotype G9, which is becoming increasingly important across Asia and Africa, and G8, which is gaining prevalence in parts of Africa, will also need to be carried out to ensure that the vaccine protects children in the developing world, where those strains are prevalent.

The implementation of rotavirus immunization programs will require scientists and health officials to work effectively with the media to ensure that the public is informed about both the risks and benefits of the new rotavirus vaccines, particularly since the media may be the public's principal source of such information (Table 1). A balanced portrayal of these risks and benefits can help avert abrupt shifts in media and public reactions that can undermine the success of vaccination programs (26). Accurate information on vaccine risks and benefits will form the foundation of the dialogue that must take place between clinicians, health authorities, legislators, and the public to maintain public trust in rotavirus immunization (28).

The development and introduction of rotavirus vaccines for children in the resource-poor countries of the world have been given high priority by the WHO. Vaccine efficacy, which has already been demonstrated in children in industrialized and middle-income countries, needs to be proven in resource-poor countries in Africa and Asia. The availability of these vaccines will depend on distribution, including the need for a cold chain. The WHO's Initiative for Vaccine Research intends to provide funding for the development of liquid or dry powder formulations of rotavirus vaccines to facilitate the development of rotavirus vaccines that are logistically simple to administer in resource-poor countries, occupy minimal space in the cold chain, can be stored outside of the cold chain for reasonable time periods without a loss of activity, and are compatible with multidose vial formats.

In 2003, the Global Alliance for Vaccines and Immunizations sponsored a new public-private organization, the Rotavirus Vaccine Program, at PATH, whose role is to accelerate the development and introduction of rotavirus vaccines in developing countries. Despite this support, the implementation of rotavirus immunization programs in the developing world will require substantial input from the international donor community. Novel financing strategies will be needed to ensure that new vaccines are affordable and available in the developing world. Decision makers and parents in developing countries need to know about rotavirus disease since, currently, few have heard of the virus, and rotavirus infection is rarely diagnosed. Finally, for the global effort toward the prevention of rotavirus disease to be successful, special efforts will be required in India, China, and Indonesia, because one-third of all deaths due to rotavirus disease occur in these countries and because these countries depend almost entirely on vaccines manufactured domestically.

REFERENCES

1. **Angel, J., M. A. Franco, and H. B. Greenberg.** 2007. Rotavirus vaccines: recent developments and future considerations. Nat. Rev. Microbiol. **5:**529–539.
2. **Ball, J. M., P. Tian, C. Q. Zeng, A. P. Morris, and M. K. Estes.** 1996. Age-dependent diarrhea induced by a rotaviral nonstructural glycoprotein. Science **272:**101–104.
3. **Banerjee, I., B. P. Gladstone, A. M. Le Fevre, S. Ramani, M. Iturriza-Gomara, J. J. Gray, D. W. Brown, M. K. Estes, J. P. Muliyil, S. Jaffar, and G. Kang.** 2007. Neonatal infection with G10P[11] rotavirus did not confer protection against subsequent rotavirus infection in a community cohort in Vellore, South India. J. Infect. Dis. **195:**625–632.
4. **Barnes, G. L., J. S. Lund, S. V. Mitchell, L. De Bruyn, L. Piggford, A. L. Smith, J. Furmedge, P. J. Masendycz, H. C. Bugg, N. Bogdanovic-Sakran, J. B. Carlin, and R. F. Bishop.** 2002. Early phase II trial of human rotavirus vaccine candidate RV3. Vaccine **20:**2950–2956.
5. **Bernstein, D. I., D. A. Sack, E. Rothstein, K. Reisinger, V. E. Smith, D. O'Sullivan, D. R. Spriggs, and R. L. Ward.** 1999. Efficacy of live, attenuated, human rotavirus vaccine 89-12 in infants: a randomised placebo-controlled trial. Lancet **354:**287–290.
6. **Bhan, M. K., J. F. Lew, S. Sazawal, B. K. Das, J. R. Gentsch, and R. I. Glass.** 1993. Protection conferred by neonatal rotavirus infection against subsequent rotavirus diarrhea. J. Infect. Dis. **168:**282–287.
7. **Bhandari, N., P. Sharma, R. I. Glass, P. Ray, H. Greenberg, S. Taneja, M. Saksena, C. D. Rao, J. R. Gentsch, U. Parashar, Y. Maldonado, R. L. Ward, and M. K. Bhan.** 2006. Safety and immunogenicity of two live attenuated human rotavirus vaccine candidates, 116E and I321, in infants: results of a randomised controlled trial. Vaccine **24:**5817–5823.
8. **Bishop, R. F., G. L. Barnes, E. Cipriani, and J. S. Lund.** 1983. Clinical immunity after neonatal rotavirus infection. A prospective longitudinal study in young children. N. Engl. J. Med. **309:**72–76.
9. **Bishop, R. F., G. P. Davidson, I. H. Holmes, and B. J. Ruck.** 1973. Virus particles in epithelial cells of duodenal mucosa from children with acute non-bacterial gastroenteritis. Lancet **ii:**1281–1283.
10. **Block, S. L., T. Vesikari, M. G. Goveia, S. B. Rivers, B. A. Adeyi, M. J. Dallas, J. Bauder, J. W. Boslego, and P. M. Heaton.** 2007. Efficacy, immunogenicity, and safety of a pentavalent human-bovine (WC3) reassortant rotavirus vaccine at the end of shelf life. Pediatrics **119:**11–18.
11. **Blutt, S. E., C. D. Kirkwood, V. Parreno, K. L. Warfield, M. Ciarlet, M. K. Estes, K. Bok, R. F. Bishop, and M. E. Conner.** 2003. Rotavirus antigenaemia and viraemia: a common event? Lancet **362:**1445–1449.
12. **Blutt, S. E., D. O. Matson, S. E. Crawford, M. A. Staat, P. Azimi, B. L. Bennett, P. A. Piedra, and M. E. Conner.** 2007. Rotavirus antigenemia in children is associated with viremia. PLoS Med. **4:**e121.
13. **Brandt, C. D., H. W. Kim, W. J. Rodriguez, J. O. Arrobio, B. C. Jeffries, E. P. Stallings, C. Lewis, A. J. Miles, R. M. Chanock, A. Z. Kapikian, and R. H. Parrott.** 1983. Pediatric viral gastroenteritis during eight years of study. J. Clin. Microbiol. **18:**71–78.
14. **Centers for Disease Control and Prevention.** 1999. Intussusception among recipients of rotavirus vaccine—United States, 1998–1999. MMWR Morb. Mortal. Wkly. Rep. **48:**577–581.
15. **Centers for Disease Control and Prevention.** 2007. Postmarketing monitoring of intussusception after RotaTeq vaccination—United States, February 1, 2006–February 15, 2007. MMWR Morb. Mortal. Wkly. Rep. **56:**218–222.
16. **Centers for Disease Control and Prevention.** 1999. Rotavirus vaccine for the prevention of rotavirus gastroenteritis among children. Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Morb. Mortal. Wkly. Rep. **48:**1–20.
17. **Chiappini, E., C. Azzari, M. Moriondo, L. Galli, and M. de Martino.** 2005. Viraemia is a common finding in immunocompetent children with rotavirus infection. J. Med. Virol. **76:**265–267.
18. **Chiappini, E., L. Galli, and M. de Martino.** 2006. Viremia and clinical manifestations in children with rotavirus infection. J. Infect. Dis. **193:**1333.
19. **Chiba, S., T. Yokoyama, S. Nakata, Y. Morita, T. Urasawa, K. Taniguchi, S. Urasawa, and T. Nakao.** 1986. Protective effect of naturally acquired homotypic and heterotypic rotavirus antibodies. Lancet **ii:**417–421.
20. **Christy, C., H. P. Madore, M. E. Pichichero, C. Gala, P. Pincus, D. Vosefski, Y. Hoshino, A. Kapikian, and R. Dolin.** 1988. Field trial of rhesus rotavirus vaccine in infants. Pediatr. Infect. Dis. J. **7:**645–650.
21. **Chrystie, I. L., B. M. Totterdell, and J. E. Banatvala.** 1978. Asymptomatic endemic rotavirus infections in the newborn. Lancet **i:**1176–1178.
22. **Clark, H. F., F. E. Borian, L. M. Bell, K. Modesto, V. Gouvea, and S. A. Plotkin.** 1988. Protective effect of WC3 vaccine against rotavirus diarrhea in

infants during a predominantly serotype 1 rotavirus season. J. Infect. Dis. **158:**570–587.
23. **Clark, H. F., K. T. Dolan, P. Horton-Slight, J. Palmer, and S. A. Plotkin.** 1985. Diverse serologic response to rotavirus infection of infants in a single epidemic. Pediatr. Infect. Dis. **4:**626–631.
24. **Clements-Mann, M. L., R. Dudas, Y. Hoshino, P. Nehring, E. Sperber, M. Wagner, I. Stephens, R. Karron, A. Deforest, and A. Z. Kapikian.** 2001. Safety and immunogenicity of live attenuated quadrivalent human-bovine (UK) reassortant rotavirus vaccine administered with childhood vaccines to infants. Vaccine **19:**4676–4684.
25. **Cunliffe, N. A., B. K. Das, M. Ramachandran, M. K. Bhan, R. I. Glass, and J. R. Gentsch.** 1997. Sequence analysis demonstrates that VP6, NSP1 and NSP4 genes of Indian neonatal rotavirus strain 116E are of human origin. Virus Genes **15:**39–44.
26. **Danovaro-Holliday, M. C., A. L. Wood, and C. W. LeBaron.** 2002. Rotavirus vaccine and the news media, 1987–2001. JAMA **287:**1455–1462.
27. **Dunn, S. J., H. B. Greenberg, R. L. Ward, O. Nakagomi, J. W. Burns, P. T. Vo, K. A. Pax, M. Das, K. Gowda, and C. D. Rao.** 1993. Serotypic and genotypic characterization of human serotype 10 rotaviruses from asymptomatic neonates. J. Clin. Microbiol. **31:**165–169.
28. **Feudtner, C., and E. K. Marcuse.** 2001. Ethics and immunization policy: promoting dialogue to sustain consensus. Pediatrics **107:**1158–1164.
29. **Fischer, T. K., P. Valentiner-Branth, H. Steinsland, M. Perch, G. Santos, P. Aaby, K. Molbak, and H. Sommerfelt.** 2002. Protective immunity after natural rotavirus infection: a community cohort study of newborn children in Guinea-Bissau, west Africa. J. Infect. Dis. **186:**593–597.
30. **Fischer, T. K., C. Viboud, U. Parashar, M. Malek, C. Steiner, R. Glass, and L. Simonsen.** 2007. Hospitalizations and deaths from diarrhea and rotavirus among children <5 years of age in the United States, 1993–2003. J. Infect. Dis. **195:**1117–1125.
31. **Franco, M. A., J. Angel, and H. B. Greenberg.** 2006. Immunity and correlates of protection for rotavirus vaccines. Vaccine **24:**2718–2731.
32. **Franco, M. A., N. Feng, and H. B. Greenberg.** 1996. Molecular determinants of immunity and pathogenicity of rotavirus infection in the mouse model. J. Infect. Dis. **174**(Suppl. 1)**:**S47–S50.
33. **Gentsch, J. R., A. R. Laird, B. Bielfelt, D. D. Griffin, K. Banyai, M. Ramachandran, V. Jain, N. A. Cunliffe, O. Nakagomi, C. D. Kirkwood, T. K. Fischer, U. D. Parashar, J. S. Bresee, B. Jiang, and R. I. Glass.** 2005. Serotype diversity and reassortment between human and animal rotavirus strains: implications for rotavirus vaccine programs. J. Infect. Dis. **192**(Suppl. 1)**:** S146–S159.
34. **Glass, R. I., M. K. Bhan, P. Ray, R. Bahl, U. D. Parashar, H. Greenberg, C. D. Rao, N. Bhandari, Y. Maldonado, R. L. Ward, D. I. Bernstein, and J. R. Gentsch.** 2005. Development of candidate rotavirus vaccines derived from neonatal strains in India. J. Infect. Dis. **192**(Suppl. 1)**:**S30–S35.
35. **Glass, R. I., J. Bresee, B. Jiang, U. Parashar, E. Yee, and J. Gentsch.** 2006. Rotavirus and rotavirus vaccines. Adv. Exp. Med. Biol. **582:**45–54.
36. **Glass, R. I., P. E. Kilgore, R. C. Holman, S. Jin, J. C. Smith, P. A. Woods, M. J. Clarke, M. S. Ho, and J. R. Gentsch.** 1996. The epidemiology of rotavirus diarrhea in the United States: surveillance and estimates of disease burden. J. Infect. Dis. **174**(Suppl. 1)**:**S5–S11.
37. **Hanlon, P., L. Hanlon, V. Marsh, P. Byass, F. Shenton, M. Hassan-King, O. Jobe, H. Sillah, R. Hayes, B. H. M'Boge, et al.** 1987. Trial of an attenuated bovine rotavirus vaccine (RIT 4237) in Gambian infants. Lancet **i:**1342–1345.
38. **Hoshino, Y., and A. Z. Kapikian.** 2000. Rotavirus serotypes: classification and importance in epidemiology, immunity, and vaccine development. J. Health Popul. Nutr. **18:**5–14.
39. **Hoshino, Y., and A. Z. Kapikian.** 1994. Rotavirus vaccine development for the prevention of severe diarrhea in infants and young children. Trends Microbiol. **2:**242–249.
40. **Jiang, B., J. R. Gentsch, and R. I. Glass.** 2002. The role of serum antibodies in the protection against rotavirus disease: an overview. Clin. Infect. Dis. **34:**1351–1361.
41. **Jin, S., P. E. Kilgore, R. C. Holman, M. J. Clarke, E. J. Gangarosa, and R. I. Glass.** 1996. Trends in hospitalizations for diarrhea in United States children from 1979 through 1992: estimates of the morbidity associated with rotavirus. Pediatr. Infect. Dis. J. **15:**397–404.
42. **Joensuu, J., E. Koskenniemi, X. L. Pang, and T. Vesikari.** 1997. Randomised placebo-controlled trial of rhesus-human reassortant rotavirus vaccine for prevention of severe rotavirus gastroenteritis. Lancet **350:**1205–1209.
43. **Kalica, A. R., H. B. Greenberg, R. G. Wyatt, J. Flores, M. M. Sereno, A. Z. Kapikian, and R. M. Chanock.** 1981. Genes of human (strain Wa) and bovine (strain UK) rotaviruses that code for neutralization and subgroup antigens. Virology **112:**385–390.
44. **Kapikian, A. Z., Y. Hoshino, R. M. Chanock, and I. Perez-Schael.** 1996. Efficacy of a quadrivalent rhesus rotavirus-based human rotavirus vaccine aimed at preventing severe rotavirus diarrhea in infants and young children. J. Infect. Dis. **174**(Suppl. 1)**:**S65–S72.
45. **Kapikian, A. Z., Y. Hoshino, R. M. Chanock, and I. Perez-Schael.** 1996. Jennerian and modified Jennerian approach to vaccination against rotavirus diarrhea using a quadrivalent rhesus rotavirus (RRV) and human-RRV reassortant vaccine. Arch. Virol. Suppl. **12:**163–175.
46. **Kapikian, A. Z., L. Simonsen, T. Vesikari, Y. Hoshino, D. M. Morens, R. M. Chanock, J. R. La Montagne, and B. R. Murphy.** 2005. A hexavalent human rotavirus-bovine rotavirus (UK) reassortant vaccine designed for use in developing countries and delivered in a schedule with the potential to eliminate the risk of intussusception. J. Infect. Dis. **192**(Suppl. 1)**:**S22–S29.
47. **Kilgore, P. E., R. C. Holman, M. J. Clarke, and R. I. Glass.** 1995. Trends of diarrheal disease-associated mortality in US children, 1968 through 1991. JAMA **274:**1143–1148.
48. **Koopman, J. S., V. J. Turkish, A. S. Monto, V. Gouvea, S. Srivastava, and R. E. Isaacson.** 1984. Patterns and etiology of diarrhea in three clinical settings. Am. J. Epidemiol. **119:**114–123.
49. **Kramarz, P., E. K. France, F. Destefano, S. B. Black, H. Shinefield, J. I. Ward, E. J. Chang, R. T. Chen, D. Shatin, J. Hill, T. Lieu, and J. M. Ogren.** 2001. Population-based study of rotavirus vaccination and intussusception. Pediatr. Infect. Dis. J. **20:**410–416.
50. **Lanata, C. F., R. E. Black, R. del Aguila, A. Gil, H. Verastegui, G. Gerna, J. Flores, A. Z. Kapikian, and F. E. Andre.** 1989. Protection of Peruvian children against rotavirus diarrhea of specific serotypes by one, two, or three doses of the RIT 4237 attenuated bovine rotavirus vaccine. J. Infect. Dis. **159:**452–459.
51. **LeBaron, C. W., J. Lew, R. I. Glass, J. M. Weber, G. M. Ruiz-Palacios, et al.** 1990. Annual rotavirus epidemic patterns in North America. Results of a 5-year retrospective survey of 88 centers in Canada, Mexico, and the United States. JAMA **264:**983–988.
52. **Ling-Qiao, Z.** 2001. A rotavirus vaccine licensed in China. Health News **31:**1.
53. **Linhares, A. C., T. Verstraeten, J. Wolleswinkel-van den Bosch, R. Clemens, and T. Breuer.** 2006. Rotavirus serotype G9 is associated with more-severe disease in Latin America. Clin. Infect. Dis. **43:**312–314.
54. **Lynch, M., B. Lee, P. Azimi, J. Gentsch, C. Glaser, S. Gilliam, H. G. Chang, R. Ward, and R. I. Glass.** 2001. Rotavirus and central nervous system symptoms: cause or contaminant? Case reports and review. Clin. Infect. Dis. **33:**932–938.
55. **Lynch, M., W. J. Shieh, K. Tatti, J. R. Gentsch, T. Ferebee-Harris, B. Jiang, J. Guarner, J. S. Bresee, M. Greenwald, S. Cullen, H. D. Davies, C. Trevenen, S. R. Zaki, and R. I. Glass.** 2003. The pathology of rotavirus-associated deaths, using new molecular diagnostics. Clin. Infect. Dis. **37:** 1327–1333.
56. **Malek, M. A., A. T. Curns, R. C. Holman, T. K. Fischer, J. S. Bresee, R. I. Glass, C. A. Steiner, and U. D. Parashar.** 2006. Diarrhea- and rotavirus-associated hospitalizations among children less than 5 years of age: United States, 1997 and 2000. Pediatrics **117:**1887–1892.
57. **Matson, D. O., and M. K. Estes.** 1990. Impact of rotavirus infection at a large pediatric hospital. J. Infect. Dis. **162:**598–604.
58. **Matson, D. O., M. L. O'Ryan, L. K. Pickering, S. Chiba, S. Nakata, P. Raj, and M. K. Estes.** 1992. Characterization of serum antibody responses to natural rotavirus infections in children by VP7-specific epitope-blocking assays. J. Clin. Microbiol. **30:**1056–1061.
59. **Midthun, K., and A. Z. Kapikian.** 1996. Rotavirus vaccines: an overview. Clin. Microbiol. Rev. **9:**423–434.
60. **Murphy, T. V., P. M. Gargiullo, M. S. Massoudi, D. B. Nelson, A. O. Jumaan, C. A. Okoro, L. R. Zanardi, S. Setia, E. Fair, C. W. LeBaron, M. Wharton, and J. R. Livengood.** 2001. Intussusception among infants given an oral rotavirus vaccine. N. Engl. J. Med. **344:**564–572.
61. **Murphy, T. V., P. M. Gargiullo, and M. Wharton.** 2002. More on rotavirus vaccination and intussusception. N. Engl. J. Med. **346:**211–212.
62. **Newman, R. D., J. Grupp-Phelan, D. K. Shay, and R. L. Davis.** 1999. Perinatal risk factors for infant hospitalization with viral gastroenteritis. Pediatrics **103:**E3.
62a. **Offit, P. A., and H. F. Clark.** 2006. RotaTeq: a pentavalent bovine-human reassortment rotavirus vaccine. Pediatr. Ann. **35:**29–34.
63. **O'Ryan, M. L., D. O. Matson, M. K. Estes, and L. K. Pickering.** 1994. Anti-rotavirus G type-specific and isotype-specific antibodies in children with natural rotavirus infections. J. Infect. Dis. **169:**504–511.
64. **Pang, X. L., J. Joensuu, and T. Vesikari.** 1996. Detection of rotavirus RNA in cerebrospinal fluid in a case of rotavirus gastroenteritis with febrile seizures. Pediatr. Infect. Dis. J. **15:**543–545.
65. **Parashar, U. D., J. P. Alexander, and R. I. Glass.** 2006. Prevention of rotavirus gastroenteritis among infants and children. Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recommend. Rep. **55:**1–13.
66. **Parashar, U. D., C. J. Gibson, J. S. Bresse, and R. I. Glass.** 2006. Rotavirus and severe childhood diarrhea. Emerg. Infect. Dis. **12:**304–306.
67. **Perez-Schael, I., G. Daoud, L. White, G. Urbina, N. Daoud, M. Perez, and J. Flores.** 1984. Rotavirus shedding by newborn children. J. Med. Virol. **14:** 127–136.
68. **Perez-Schael, I., M. J. Guntinas, M. Perez, V. Pagone, A. M. Rojas, R. Gonzalez, W. Cunto, Y. Hoshino, and A. Z. Kapikian.** 1997. Efficacy of the rhesus rotavirus-based quadrivalent vaccine in infants and young children in Venezuela. N. Engl. J. Med. **337:**1181–1187.
69. **Peter, G., and M. G. Myers.** 2002. Intussusception, rotavirus, and oral vaccines: summary of a workshop. Pediatrics **110:**e67.

70. **Ramig, R. F.** 2007. Systemic rotavirus infection. Expert Rev. Anti Infect. Ther. **5:**591–612.
71. **Rennels, M. B., R. I. Glass, P. H. Dennehy, D. I. Bernstein, M. E. Pichichero, E. T. Zito, M. E. Mack, B. L. Davidson, A. Z. Kapikian, et al.** 1996. Safety and efficacy of high-dose rhesus-human reassortant rotavirus vaccines—report of the National Multicenter Trial. Pediatrics **97:**7–13.
72. **Rodriguez, W. J., H. W. Kim, C. D. Brandt, B. Bise, A. Z. Kapikian, R. M. Chanock, G. Curlin, and R. H. Parrott.** 1980. Rotavirus gastroenteritis in the Washington, DC, area: incidence of cases resulting in admission to the hospital. Am. J. Dis. Child. **134:**777–779.
73. **Ruiz-Palacios, G. M., I. Perez-Schael, F. R. Velazquez, H. Abate, T. Breuer, S. C. Clemens, B. Cheuvart, F. Espinoza, P. Gillard, B. L. Innis, Y. Cervantes, A. C. Linhares, P. Lopez, M. Macias-Parra, E. Ortega-Barria, V. Richardson, D. M. Rivera-Medina, L. Rivera, B. Salinas, N. Pavia-Ruz, J. Salmeron, R. Ruttimann, J. C. Tinoco, P. Rubio, E. Nunez, M. L. Guerrero, J. P. Yarzabal, S. Damaso, N. Tornieporth, X. Saez-Llorens, R. F. Vergara, T. Vesikari, A. Bouckenooghe, R. Clemens, B. De Vos, and M. O'Ryan.** 2006. Safety and efficacy of an attenuated vaccine against severe rotavirus gastroenteritis. N. Engl. J. Med. **354:**11–22.
74. **Santos, N., and Y. Hoshino.** 2005. Global distribution of rotavirus serotypes/genotypes and its implication for the development and implementation of an effective rotavirus vaccine. Rev. Med. Virol. **15:**29–56.
75. **Santosham, M., L. H. Moulton, R. Reid, J. Croll, R. Weatherholt, R. Ward, J. Forro, E. Zito, M. Mack, G. Brenneman, and B. L. Davidson.** 1997. Efficacy and safety of high-dose rhesus-human reassortant rotavirus vaccine in Native American populations. J. Pediatr. **131:**632–638.
76. **Steele, A. D., and B. Ivanoff.** 2003. Rotavirus strains circulating in Africa during 1996–1999: emergence of G9 strains and P[6] strains. Vaccine **21:** 361–367.
77. **Svensson, L., H. Sheshberadaran, T. Vesikari, E. Norrby, and G. Wadell.** 1987. Immune response to rotavirus polypeptides after vaccination with heterologous rotavirus vaccines (RIT 4237, RRV-1). J. Gen. Virol. **68:**1993–1999.
78. **Torok, T. J., P. E. Kilgore, M. J. Clarke, R. C. Holman, J. S. Bresee, R. I. Glass, et al.** 1997. Visualizing geographic and temporal trends in rotavirus activity in the United States, 1991 to 1996. Pediatr. Infect. Dis. J. **16:**941–946.
79. **Turcios, R. M., A. T. Curns, R. C. Holman, I. Pandya-Smith, A. LaMonte, J. S. Bresee, and R. I. Glass.** 2006. Temporal and geographic trends of rotavirus activity in the United States, 1997–2004. Pediatr. Infect. Dis. J. **25:**451–454.
80. **Velazquez, F. R., D. O. Matson, J. J. Calva, L. Guerrero, A. L. Morrow, S. Carter-Campbell, R. I. Glass, M. K. Estes, L. K. Pickering, and G. M. Ruiz-Palacios.** 1996. Rotavirus infections in infants as protection against subsequent infections. N. Engl. J. Med. **335:**1022–1028.
81. **Velazquez, F. R., D. O. Matson, M. L. Guerrero, J. Shults, J. J. Calva, A. L. Morrow, R. I. Glass, L. K. Pickering, and G. M. Ruiz-Palacios.** 2000. Serum antibody as a marker of protection against natural rotavirus infection and disease. J. Infect. Dis. **182:**1602–1609.
82. **Vesikari, T., E. Isolauri, and E. D'Hondt.** 1984. Protection of infants against rotavirus diarrhea by RIT 4237 attenuated bovine rotavirus strain vaccine. Lancet **i:**977–981.
83. **Vesikari, T., A. Karvonen, R. Prymula, V. Schuster, J. C. Tejedor, R. Cohen, F. Meurice, H. H. Han, S. Damaso, and A. Bouckenooghe.** 2007. Efficacy of human rotavirus vaccine against rotavirus gastroenteritis during the first 2 years of life in European infants: randomised, double-blind controlled study. Lancet **370:**1757–1763.
84. **Vesikari, T., A. V. Karvonen, J. Majuri, S. Q. Zeng, X. L. Pang, R. Kohberger, B. D. Forrest, Y. Hoshino, R. M. Chanock, and A. Z. Kapikian.** 2006. Safety, efficacy, and immunogenicity of 2 doses of bovine-human (UK) and rhesus-rhesus-human rotavirus reassortant tetravalent vaccines in Finnish children. J. Infect. Dis. **194:**370–376.
85. **Vesikari, T., D. O. Matson, P. Dennehy, P. Van Damme, M. Santosham, Z. Rodriguez, M. J. Dallas, J. F. Heyse, M. G. Goveia, S. B. Black, H. R. Shinefield, C. D. Christie, S. Ylitalo, R. F. Itzler, M. L. Coia, M. T. Onorato, B. A. Adeyi, G. S. Marshall, L. Gothefors, D. Campens, A. Karvonen, J. P. Watt, K. L. O'Brien, M. J. DiNubile, H. F. Clark, J. W. Boslego, P. A. Offit, and P. M. Heaton.** 2006. Safety and efficacy of a pentavalent human-bovine (WC3) reassortant rotavirus vaccine. N. Engl. J. Med. **354:**23–33.
86. **Vesikari, T., T. Ruuska, H. P. Koivu, K. Y. Green, J. Flores, and A. Z. Kapikian.** 1991. Evaluation of the M37 human rotavirus vaccine in 2- to 6-month-old infants. Pediatr. Infect. Dis. J. **10:**912–917.
87. **Ward, R. L.** 2003. Possible mechanisms of protection elicited by candidate rotavirus vaccines as determined with the adult mouse model. Viral Immunol. **16:**17–24.
88. **Wenman, W. M., D. Hinde, S. Feltham, and M. Gurwith.** 1979. Rotavirus infection in adults. Results of a prospective family study. N. Engl. J. Med. **301:**303–306.
89. **Westerman, L. E., H. M. McClure, B. Jiang, J. W. Almond, and R. I. Glass.** 2005. Serum IgG mediates mucosal immunity against rotavirus infection. Proc. Natl. Acad. Sci. USA **102:**7268–7273.
90. **Widdowson, M. A., J. S. Bresee, J. R. Gentsch, and R. I. Glass.** 2005. Rotavirus disease and its prevention. Curr. Opin. Gastroenterol. **21:**26–31.
91. **Zissis, G., J. P. Lambert, P. Marbehant, D. Marissens, M. Lobmann, P. Charlier, A. Delem, and N. Zygraich.** 1983. Protection studies in colostrum-deprived piglets of a bovine rotavirus vaccine candidate using human rotavirus strains for challenge. J. Infect. Dis. **148:**1061–1068.

ROTAVIRUS DISEASE AND PREVENTION THROUGH VACCINATION

GUEST EDITOR
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This CME supplement is jointly sponsored by Boston University School of Medicine and Med Learning Group. Publication of this supplement is supported by an educational grant from Merck & Co., Inc.

The Pediatric Infectious Disease Journal®

CME Overview

Rotavirus Disease and Prevention Through Vaccination

Program Overview
Rotavirus is the most common cause of acute infectious gastroenteritis in children and is associated with substantial morbidity in the United States and morbidity and mortality in the developing world. Two orally administered vaccines, a live bovine reassortant vaccine (RV5; licensed in 2006) and a live attenuated human vaccine (RV1; licensed in 2008), are now being employed in a universal infant vaccination program in the United States. There is already ecological evidence and data from post-licensure effectiveness studies that this program will be an unequivocal success in reducing the impact of rotavirus disease. This overview presents the structure, pathogenesis, and mechanisms of natural immunity to rotavirus, key concepts in understanding the rationale behind vaccine-induced protection. The history of rotavirus vaccine development is also included, along with a discussion of the safety, efficacy, and recommended use of the approved vaccines.

CME Release Date: April 1, 2009

CME Expiration Date: March 31, 2010

Estimated Time to Complete: 1.0 Hour

Jointly sponsored by Boston University School of Medicine and Med Learning Group

Supported by an educational grant from Merck & Co., Inc.

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Target Audience
This activity has been designed to meet the educational needs of physicians, nurses, and physician assistants who wish to learn about vaccination strategies for the prevention of rotavirus.

Learning Objectives
1. Outline the epidemiology of rotavirus infection, including transmission, seasonality, and year-to-year serotype variation.
2. Calculate rotavirus disease burden in the United States, including outpatient episodes of gastroenteritis and hospitalizations for dehydration.
3. Compare and contrast available rotavirus vaccines.
4. Summarize the ACIP recommendations for rotavirus vaccination.

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1. Read the educational objectives and faculty disclosures.
2. Study all parts of the educational activity.
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Rotavirus Disease and Prevention Through Vaccination

Gary S. Marshall, MD

Abstract: Rotavirus is the most common cause of acute infectious gastroenteritis in children and is associated with substantial morbidity in the United States and morbidity and mortality in the developing world. Two orally administered vaccines, a live bovine reassortant vaccine (RV5; licensed in 2006) and a live attenuated human vaccine (RV1; licensed in 2008), are now being used in a universal infant vaccination program in the United States. There is already ecologic evidence and data from post-licensure effectiveness studies that this program will be an unequivocal success in reducing the impact of rotavirus disease. This overview presents the structure, pathogenesis, and mechanisms of natural immunity to rotavirus, key concepts in understanding the rationale behind vaccine-induced protection. The history of rotavirus vaccine development is also included, along with a discussion of the safety, efficacy, and recommended use of the approved vaccines.

Key Words: rotavirus, gastroenteritis, RV5, RV1

(*Pediatr Infect Dis J* 2009;28: 355–362)

Since its discovery in 1973, rotavirus has come to be recognized as the most common cause of acute infectious gastroenteritis in children.[1] Morbidity because of rotavirus in the United States is significant, and morbidity and mortality in the developing world are staggering. Fortunately, there is already evidence that universal vaccination programs have the potential to curtail this burden of disease.

Virus Structure

Rotavirus, named from the Latin "rota" for its wheel-like appearance (Fig. 1),[2] is a nonenveloped virus in the Reoviridae family.[2,3] The particle contains 11 segments of double-stranded RNA in its core[2,3]; each strand codes for a different viral protein (VP), but only 6 proteins are incorporated into the virion. The core of the virus is contained within an inner capsid, comprised mostly of VP6.[2,3] This is surrounded by an outer capsid, primarily comprised of VP7, which forms a Wiffle-ball-like shell around the virion; and VP4, which forms spikes that protrude from the particle.[2,3] VP7 and VP4 are the major targets of neutralizing antibodies.

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Supported by an educational grant from Merck & Co., Inc. Jointly sponsored by Boston University School of Medicine and Med Learning Group.

Disclosures: G.S.M. receives grant/research support from GlaxoSmithKline, Merck & Co., Inc, Novartis, and sanofi pasteur and is an ad-hoc consultant for GlaxoSmithKline, Merck & Co., Inc, Novartis, and sanofi pasteur. He is on the speaker's bureau for GlaxoSmithKline. Merck & Co., Inc, and sanofi pasteur and receives support for CME activities from GlaxoSmithKline, MedImmune, Inc., and Merck & Co., Inc.

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ISSN: 0891-3668/09/2804-0355
DOI: 10.1097/INF.0b013e318199494a

Rotavirus is classified according to antigenic specificities by serogroup, subgroup, and serotype.[2] Seven infectious serogroups of rotavirus, labeled A through G, infect various species.[2,3] However, only groups A, B, and C are human pathogens.[2,3] These groups are distinguished by antigenic differences within the virus core and by migration of RNA gene segments.[3] Group A is the primary pathogenic type for humans worldwide and is responsible for the majority of outbreaks.[2,3] Epidemic infection caused by group B has been limited to Asia and the Indian subcontinent.[2,3] Endemic infections caused by group C are generally not detectable by commercial assays and often go unrecognized.[2,3]

Serogroup and subgroup specificities are determined by VP6, which is abundantly represented in the virion.[2] This also happens to be the antigen most commonly detected by diagnostic assays.[2,3]

Rotaviruses are also classified by their VP7 and VP4 antigens.[2,3] VP7, also referred to as the G protein (for "glycoprotein"), occurs in at least 14 different serotypes, 10 of which are important for humans.[4] These serotypes are referred to as Arabic numerals (G1, G2, G3, etc.); those numerals simultaneously designate genotypes. The most common G type in the United States and worldwide is G1 (Fig. 2).[5]

VP4, also referred to as the P protein (for "protease-sensitive"), also occurs in at least 14 different serotypes, 9 of which are important for humans.[4] These serotypes are referred to by Arabic numerals and lowercase letters (P1a, P1b, etc.); unlike G types, the genotype is referred to by a separate Arabic numeral in brackets (P1a[8], P1b[4], etc.). In this article, only the genotype will be referenced to avoid confusion. The most common P type in the United States and worldwide is P[8] (Fig. 2). Proteolytic cleavage of VP4 enhances rotavirus infectivity, and although VP4 plays a role in virulence, increased disease severity has not been linked to any particular serotype.[2,3]

The G and P proteins segregate independently as the gene segments that encode them reassort.[4] Although various combinations of G and P types are possible, there seems to be a preferential association between particular G and P types. Thus, serotypes G1, G3, and G4 are most often associated with P[8] and G2 is most often associated with P[4].[3] The mechanism of this segregation is not well understood.

Pathophysiology

After ingestion, rotavirus particles are carried to the small intestine, where they attach to enterocytes via glycolipids on the cell surface[3] and enter directly or through calcium-dependent endocytosis.[2,3,6] Replication occurs in mature enterocytes, allowing new rotavirus particles to infect distal portions of the small intestine or be excreted in the stool.[2,3] Viral replication leads to notable pathophysiologic changes, including mitochondrial swelling; distension of the endoplasmic reticulum; denudation of microvilli; mononuclear cell infiltration; shortening, flattening, and atrophy of the villi; and decreased disaccharidase activity.[2,3] These changes lead to an increased osmotic load in the gut lumen because of decreased absorption of salt and water, as well as the failure to process and absorb complex sugars. Symptoms may resolve as mature villous epithelial cells are replaced by less mature enterocytes, which may be less susceptible to rotavirus infection.[2,3]

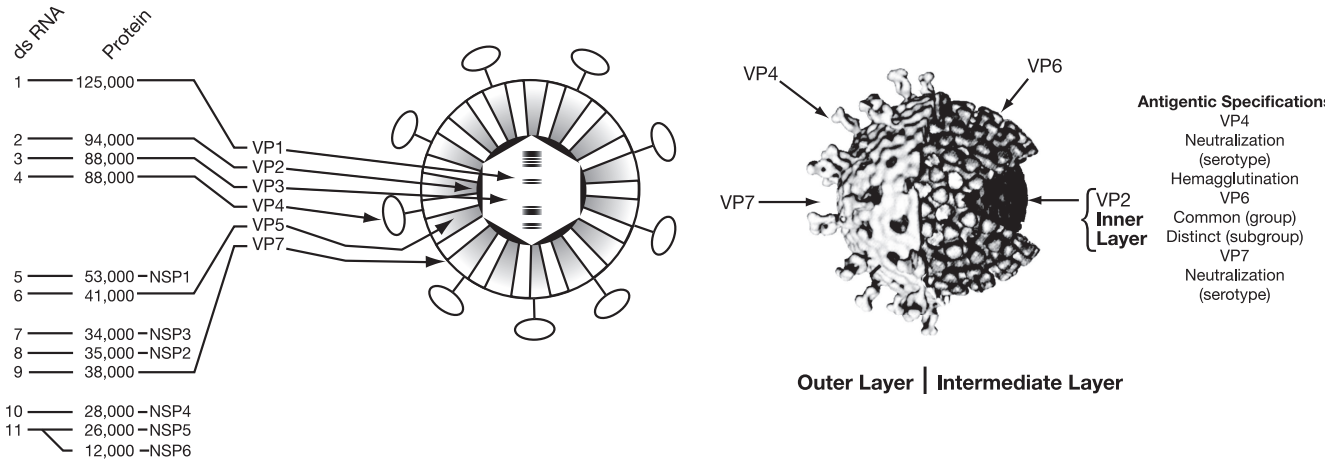
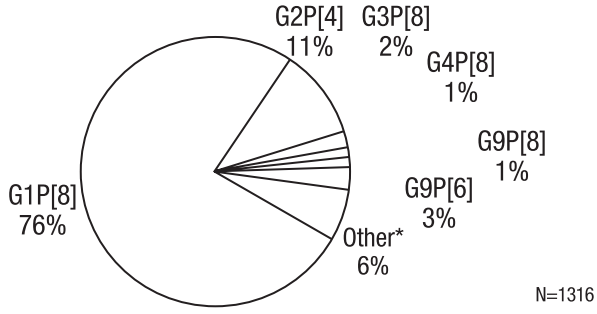


FIGURE 1. Structure of rotavirus. Left: Schematic representation of the rotavirus particle. Right: Surface representations of the 3D structures of the outer layer of the complete particle (*left*) and the particle (*right*) in which the outer layer and a small triangular portion of the intermediate layer have been removed, exposing the inner layer (Modified from Reference 260, with permission. The 3D figure on the right is courtesy of B.V.V. Prasad.)



*Other includes typed uncommon strains, mixed infections, and nontypeable infections.

FIGURE 2. Distribution of human rotavirus serotypes in the United States, November 1997–March 1999 (Adapted from Griffin). Serotypes G1, G3, and G4 with genotype P[8] and serotype G2 with genotype P[4] represented approximately 90% of the strains that were analyzed.

Nonstructural protein 4, an endoplasmic reticulum-specific glycoprotein, that is produced in cells but is not packaged into the mature virion, acts as an enterotoxin and contributes to the genesis of diarrhea.[2,3] It is hypothesized that nonstructural protein 4 interacts with a cellular receptor in the gut epithelium,[2] stimulating a calcium-dependent signal transduction pathway that increases plasma membrane chloride permeability and potentiates chloride secretion, leading to secretory diarrhea.[2] Stimulation of the enteric nervous system also may enhance fluid secretion.

Disease Burden

Most rotavirus infections in infants are symptomatic. After a 2-day incubation period, symptoms begin with fever and vomiting followed shortly thereafter by diarrhea. The whole illness lasts about 3 or 4 days, but loose stools can persist for weeks.[7,8] Early on, vomiting may be rate limiting in terms of attempts at oral rehydration.

Most children have experienced at least 1 rotavirus infection by their second birthday,[7] and almost all are infected in the first 5 years of life.[9] The virus is highly infectious and spreads by the fecal-oral route.[2,3,7] The amount of rotavirus excreted by infected children is very high, more than 10^{10} to 10^{11} viral particles per gram of feces.[2,3] This, combined with the fact that children begin shedding before they are symptomatic and for up to 2 weeks after onset of symptoms[7,10] and that infants do not have good stool hygiene, helps to explain why rotavirus spreads so quickly through daycare centers, families, and communities. The peak incidence of disease is between 6 months and 2 years of age; neonates may be relatively protected by maternal antibody.[3]

Estimates hold that rotavirus is responsible for 111 million worldwide episodes of gastroenteritis, 25 million clinician office visits, 2 million hospitalizations, and 440,000 deaths annually in children <5 years of age.[9] By 5 years of age, 1 in 5 children will have visited a clinic for treatment of rotavirus disease, and 1 in 65 will have been hospitalized. One in 293 children will have died of rotavirus-induced dehydration before the fifth birthday.

In the United States, mortality associated with rotavirus is much lower. Eighty percent of children contract rotavirus by their fifth birthday.[11] Of these, 1 in 200,000 children will die of the disease.[11] However, rotavirus morbidity is still high. Annual direct and indirect costs of rotavirus disease in the United States are estimated at $1 billion.[11] One in 7 children require a clinic or an emergency department (ED) visit because of rotavirus, and 1 in 70 will be hospitalized.[11] Interestingly, the proportion of hospital cases of acute gastroenteritis caused by rotavirus is approximately the same in the developed world as it is in the developing world. This emphasizes the importance of person-to-person transmission, as opposed to water- or food-borne transmission, in the epidemiology of rotavirus infection.

Rotavirus is responsible for at least 18% of pediatric hospital admissions associated with gastroenteritis in the United States, according to retrospective analysis of National Hospital Discharge Survey data from 1993 to 2002.[12] Survey data also indicate that the number of rotavirus hospitalizations has steadily increased from 15.4% during 1993 to 1995 to 20.8% during 2000 to 2002, whereas the rates of all-cause gastroenteritis-associated hospitalizations remained stable at 95 per 10,000 children <5 years of age. Children hospitalized for rotavirus also had significantly longer hospital stays (3.2 vs. 2.9 days).

In a separate analysis, the Kids' Inpatient Database was used to estimate the number of diarrhea- and rotavirus-related hospitalizations in US children <5 years of age in 1997 and 2000.[13] Diarrhea was associated with 173,220 and 150,465 hospitalizations in 1997 and 2000, respectively, accounting for about 13% of all hospitalizations in that age group. This suggests that 1 out of every 23 to 27 children <5 years of age will be hospitalized for diarrhea. Most (62%) hospitalizations were of unspecified etiology; however, 35% were identified as viral, and rotavirus was specifically identified in 18% and 19% of cases in 1997 and 2000, respectively. Annual costs for rotavirus hospitalizations in 1997 and 2000 were estimated to be between $140 and $180 million. The authors concluded that a rotavirus vaccine would likely decrease hospitalizations for diarrhea by about 30% for children <5 years of age.

Even when it doesn't result in hospitalization, rotavirus places a tremendous burden upon caregivers and the healthcare system.[8] An analysis of 5 independent prospective cohort studies found that 40% of 284 stool samples collected from outpatients <36 months of age with acute gastroenteritis were positive for rotavirus.[8] The proportion of patients with follow-up medical care was similar among those with rotavirus and those with some other cause of acute gastroenteritis; 57% of patients had a follow-up visit, 8% were seen in an ED, and 5% were hospitalized. However, the data suggested that rotavirus gastroenteritis was more severe than other forms of gastroenteritis: caregivers of patients with rotavirus were more likely to make follow-up calls to healthcare providers (73% vs. 57%); twice as many children with rotavirus required ≥4 healthcare contacts (28% vs. 14%); patients with rotavirus missed significantly more daycare; and in turn, caregivers of children with rotavirus missed significantly more work. Median lost work time was 2 days for caregivers of children with rotavirus, but there was no lost work time for caregivers of children with gastroenteritis that was caused by an agent other than rotavirus.

Given the clinical significance of rotavirus infection, understanding the risk factors for severe disease is important. A case-control study nested within a surveillance study was conducted at Cincinnati Children's Hospital Medical Center, Children's Hospital of New Orleans, and Hasbro Children's Hospital.[14] Data from 349 children ≤59 months of age admitted for rotavirus gastroenteritis from April 1, 2000, through June 31, 2001, were compared with 1242 controls selected from birth certificate registries (Cincinnati and Providence [Hasbro]) and a large-practice consortium patient registry (New Orleans). Breastfeeding was found to protect against hospitalization in infants <6 months of age, although breastfeeding likely postponed rotavirus disease rather than prevented it. Factors associated with hospitalization of children <24 months of age included birth weight <2500 g (odds ratio [OR], 2.8), being a Medicaid recipient or lacking health insurance (OR, 2.1), living with another child <24 months of age (OR, 1.6), and daycare attendance the month before hospitalization (OR, 1.5).

Seasonality

In temperate climates such as the continental United States, rotavirus occurs in predictable seasonal epidemics.[3] An analysis of rotavirus samples reported weekly by the National Respiratory and Enteric Virus Surveillance System from July 1991 to June 1996 found that, in general, rotavirus season began from late November to late December, peaked in mid-February to mid-March, and ended by May, with a mean duration of 23 weeks.[15] Activity tends to begin and peak earlier in the southwest United States and later in the northeast United States (Fig. 3).[15,16]

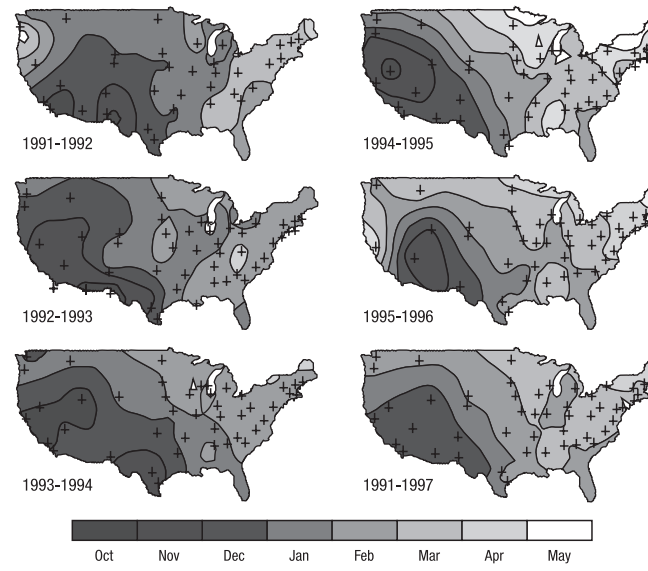


FIGURE 3. Rotavirus activity: United States, July 1991–June 1997 National Respiratory and Enteric Virus Surveillance System. Reprinted with permission from Tõrõk TJ, et al. Pediatr Infect Dis J. 1997;16:941–946.

Strain Prevalence

In a study of 45,571 samples collected worldwide between 1973 and 2003, G1P[8], G2P[4], G3P[8], and G4P[8] strains were found to be responsible for most (89%) of episodes of rotavirus infection in children.[4] However, the predominant serotypes varied by continent. In North America, for example, 73% of infections were caused by G1P[8] strains, and G1, G2, G3, and G4 strains collectively accounted for 98% of infections. G9P[6], originally detected in Philadelphia, Pennsylvania, represented 4% of global rotavirus infections and is believed to be persistent in the United States and emergent worldwide.[4,5]

Another study looked at samples collected from 1981 to 1989 from hospitalized children in the north-central United States (Ohio, New York, Pennsylvania, West Virginia, Kentucky, Indiana, and Michigan) and samples collected from 1979 to 1989 in Harris County (Houston) and other parts of Texas.[16] G1 strains were identified in 61% of infections, followed by G3 (23%), G4 (7%), G2 (4%), and a small number of nontypeable and mixed specimens. Serotype prevalence also varied by season, but the prevalent serotype tended to predominate early in each season. No significant differences in serotypes were noted in different age groups. However, geographic differences were marked. The ratio of G1:G3 was about 10:1 in the north central states compared with about 1:1 in Harris County and 2:1 in other parts of Texas. G4 was also significantly more prevalent in Texas than in the north central states. When this trend was mapped, G3 and G4 decreased in prevalence from the southwest to the northeast.

Natural Infection Confers Protection

After rotavirus infection, children develop serum and intestinal antibody responses that protect against severe diarrhea upon reinfection.[6] Viral antigens are transported to Peyer patches, where they are processed by macrophages and dendritic cells and presented to B cells and helper T cells.[2,3] The end result is the generation of rotavirus-specific B cells and expansion of cytotoxic T lymphocytes.[2,3]

Protection is thought to be largely due to humoral immunity.[2,3] In infants and young children, rotavirus-specific IgM can be detected in duodenal fluid and serum during the first week of illness.[3] Months later, rotavirus-specific IgG and IgA can be detected in duodenal fluid, and rotavirus-specific IgG and monomeric IgA can be detected in serum.[3] One year postinfection, rotavirus-specific IgG but not IgA can be detected in the serum.[3] Serum IgG antibody against rotavirus is considered the most consistent marker of rotavirus immunity, although definitive correlates of protection have not been established.[2,3,6] Fecal or duodenal IgA is considered an excellent marker for recent primary infection or reinfection.[3]

The initial antibody response to rotavirus is serotype specific, and production of cross-protective antibodies is limited.[2,3,6] However, cross-reactive antibodies arise after repeated infections.[2,3,6] In this regard, it is important to differentiate homotypic from heterotypic antibody responses. Infection with a G1P[8] strain would be expected to protect against subsequent infections with G8 strains as well as other G serotypes associated with P[8]; this is an example of homotypic immunity. Protection against infection with a G2P[4] strain, if present, would be mediated by heterotypic immunity or cross-reactive antibodies.

In a classic prospective cohort study, 200 newborns in Mexico City were followed through 2 years of age. Home visits were made and stool samples were collected each week.[17] Additional stool samples were collected when children had symptoms of diarrhea. This study clearly demonstrated that natural infection was protective against reinfection. As shown in Figure 4,[17] the cumulative probability of 1 rotavirus infection by age 2 was nearly 100%, testifying to the universality of infection in childhood. However, the cumulative probability of a second infection was lower, and a third infection even lower, implying a protective effect of the prior infections. Subsequent infections were also less severe than prior infections; in fact, no child who had 2 rotavirus infections had a third infection that was judged to be moderate to severe. This was true even if the prior infections were asymptomatic. The implications of this study were clear: a vaccine that could mimic natural infection in an immunologic sense would be expected, after multiple doses, to protect against moderate-to-severe rotavirus gastroenteritis.

Vaccine Development

Given the disease burden described above, development of a rotavirus vaccine has been considered an important public health initiative for several decades. Rhesus rotavirus vaccine, tetravalent (RRV-TV), licensed in 1998 under the trade name RotaShield (Wyeth), was the first rotavirus vaccine approved in the United States. The vaccine was based on a G3P[3] rhesus rotavirus strain that was naturally attenuated for humans. The vaccine was comprised of 4 live viruses: 3 reassortants, each the parental rhesus virus with 1 gene segment substitution from a human strain leading to expression of either G1, G2, or G4, and the native G3P[3] strain. The vaccine was administered as a 3-dose series given orally at 2, 4, and 6 months of age. Efficacy against severe rotavirus gastroenteritis was 70% to 95%.[18]

Use of RRV-TV was short-lived. Within a year, the vaccine was found to be associated with intussusception and the recommendation for universal use was withdrawn.[19] The attributable risk of intussusception to the vaccine is now estimated to be somewhere around 1 in 11,000 vaccine recipients,[20–22] with most cases occurring in the first 2 weeks after dose 1, the time of peak viral replication. The mechanism by which RRV-TV caused intussusception is not fully understood, but is believed to be related to biologic characteristics of the native rhesus strain.

Two newer generation rotavirus vaccines are now available in the United States. Rotavirus vaccine, 5-valent (RV5), licensed under the trade name RotaTeq (Merck) in February 2006, is a live, oral, bovine reassortant vaccine.[23] Rotavirus vaccine, monovalent (RV1), licensed under the trade name Rotarix (GlaxoSmithKline) in April 2008, is a live, attenuated, oral vaccine made from a human strain of rotavirus.[24] Both vaccines were tested in more than 70,000 infants before approval.

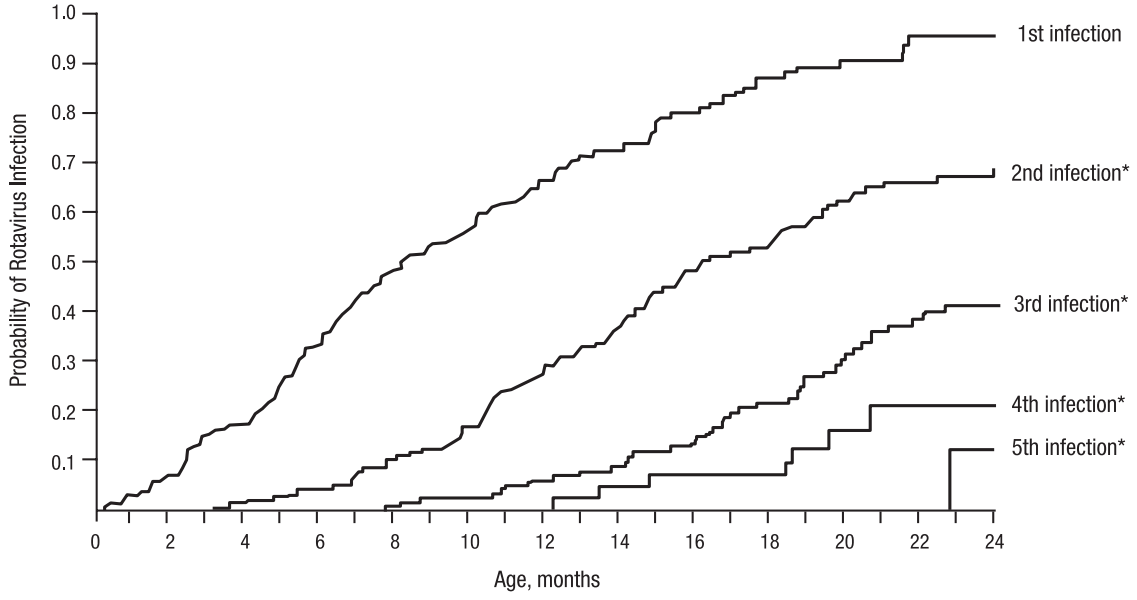


FIGURE 4. Cumulative probability of first and future rotavirus infection during the first 2 years of life. *Subsequent infections were usually caused by a different serotype. Reprinted with permission from Velaquez FR, Matson DO, Calva JJ, et al. *N Engl J Med.* 1996;335:1022–1028. Copyright 1996 Massachusetts Medical Society.

RV5 Efficacy and Safety

RV5 was developed from the bovine rotavirus strain WC3, a G6P[5] virus that is attenuated for humans. WC3 was reassorted with human strains to yield the 5 viruses that comprise the licensed vaccine: each the parental bovine virus with 1 gene segment substitution from a human strain, leading to expression of either G1, G2, G3, or G4, each with the bovine P[5], or P[8] along with the bovine G6.

The pivotal phase 3 study called REST (*R*otavirus *E*fficacy and *S*afety *T*rial) was conducted primarily in the United States and Finland, but with other sites worldwide.[25] A total of 70,301 healthy infants were enrolled; 34,644 were assigned to receive RV5 and 34,630 were assigned to receive placebo. A total of 3 doses were given: the first doses at 6 to 12 weeks of age and subsequent doses at 4 to 10 week intervals. Among infants who received at least 1 dose, 67,756 were followed for 42 days after their last dose. Six RV5 recipients and 5 placebo recipients had confirmed cases of intussusception within the 42-day period after any dose (relative risk, 1.6; 95% confidence interval [CI], 0.4–6.4). No cases of intussusception were reported within 42 days after the first dose, the highest risk period that was noted for RRV-TV. These results met the study's prespecified safety criteria for no association with intussusception. The incidence of serious adverse events was similar between RV5 and placebo recipients (2.4% vs. 2.5%). Forty-four deaths occurred during the study, mostly attributable to sudden infant death syndrome. No deaths were considered related to RV5 administration.

In a detailed safety substudy, the incidence rates of fever, vomiting, diarrhea, and hematochezia were similar for RV5 (n = 4806) and placebo (n = 4799) recipients within 42 days after any dose. However, the incidence of the following solicited adverse events was higher for vaccinees versus placebo recipients: vomiting (6.7% vs. 5.4%) and diarrhea (10.4% vs. 9.1%) after dose 1, and diarrhea (8.6% vs. 6.4%) after dose 2.[23] This is perhaps not surprising for an orally administered, live-attenuated vaccine.

In a detailed efficacy cohort nested within the Rotavirus Efficacy and Safety Trial that compared approximately 2800 vaccinees and placebo recipients, efficacy against rotavirus gastroenteritis of any severity (caused by serotypes G1 through G4) was 74% (95% CI, 66.8–79.9) through 1 season and 71.3% (95% CI, 64.7–76.9) through 2 seasons. Efficacy against severe rotavirus gastroenteritis through 1 season was 98.0% (95% CI, 88.3–100.0) and in the second season only was 88.0% (95% CI, 49.4–98.7). The numbers were similar when efficacy was considered without regard to serotype. The large-scale efficacy study looking at health resource utilization involved approximately 28,000 to 34,000 vaccinees and equal numbers of placebo recipients. Hospitalizations due to rotavirus serotypes G1 through G4 during the 2 years after dose 3 were reduced by 95.8% among vaccinees and ED visits were reduced by 93.7%.

RV1 Efficacy and Safety

RV1 was developed from a human strain of rotavirus (G1P[8]) isolated from a child in Cincinnati in 1989. The virus was serially passaged in tissue culture to achieve attenuation. The vaccine is considered monovalent because it contains only 1 strain of virus; in fact, 2 major neutralizing proteins—G1 and P[8]—are included.

The pivotal clinical trial was conducted primarily in Latin America and Finland; 6 to 13 week old healthy infants were enrolled and scheduled to receive vaccine or placebo at approximately 2 and 4 months of age.[26] In all, 31,673 infants received RV1 and 31,552 received placebo. Six RV1 recipients and 7 placebo recipients had definite intussusception within 31 days, after either dose (respective incidence rates, 1.89 and 2.21 per 10,000 infants; difference in risk −0.32 per 10,000 infants; 95% CI, −2.91 to 2.18). There was no statistically significant difference between RV1 and placebo recipients in intussusception occurring within 31 days of vaccine (relative risk, 0.85), after the 31-day window (3 vs. 9), or during the entire safety surveillance period (9 vs. 16). These results met the study's prespecified safety criteria for no association with intussusception.

Significantly fewer RV1 recipients experienced serious adverse events than placebo recipients (293.0 vs. 331.8 events per 10,000 infants). Ninety-nine deaths occurred during the study. Although overall mortality did not differ between RV1 and placebo recipients, more RV1 recipients died of pneumonia (16 vs. 6). However, the distribution of pneumonia-related deaths within 31 days of vaccine administration did not differ between groups, and further analyses did not detect a difference in pneumonia-related serious adverse events. There were no differences in the incidence of solicited adverse events between RV1 and placebo.[24] However, RV1 recipients did experience significantly more irritability (11.4% vs. 8.7%) and flatulence (2.2% vs. 1.3%).[24]

Efficacy was evaluated in 9009 infants who received RV1 and 8858 infants who received placebo, and were followed until they were 1 year old.[26] Efficacy against severe rotavirus gastroenteritis was 84.7% (95% CI, 71.7–92.4) and efficacy against hospitalization for severe rotavirus gastroenteritis was 85.0% (95% CI, 69.6–93.5).

Efficacy against severe rotavirus gastroenteritis caused by G1P[8] strains (homotypes of the vaccine strain) was 91.8% (95% CI, 74.1–98.4). For severe rotavirus gastroenteritis caused by strains with heterotypic G types (G3, G4, and G9) but with homotypic P types (P[8]), efficacy was 87.3% (95% CI, 64.1–96.7). Efficacy against rotavirus gastroenteritis caused by G2P[4], which does not share any antigens with the vaccine strain, was 41.0% (95% CI, −79.2 to 82.4); the small number of cases here is responsible for the wide confidence interval.

Efficacy also was assessed in a separate double-blind trial of RV1 limited to Europe.[27] The primary end point was vaccine efficacy against rotavirus gastroenteritis of any severity. Subjects were followed through the end of the second rotavirus season after vaccination. Overall, 2646 subjects received RV1 and 1348 subjects received placebo; 3883 infants (97%) completed the follow-up visit. RV1 efficacy against rotavirus gastroenteritis of any severity was 78.9% (95% CI, 72.7%–83.8%); efficacy against severe gastroenteritis was 90.4% (95% CI, 85.1%–94.1%). Efficacy against rotavirus gastroenteritis of any severity due to G1, G3, G4, G9, and G2 was 89.8%, 84.8%, 83.1%, 72.9%, and 58.3%, respectively. Efficacy against severe rotavirus gastroenteritis due to the same strains was 96.4%, 93.7%, 95.4%, 85.0%, and 85.5%.

Vaccine Comparison

Both RV5 and RV1 were found to be safe and effective in these large-scale clinical trials, and each has been licensed in many countries, including the United States. Table 1 presents a comparison of RV5, RV1, and the discontinued RRV-TV.[28] It is important to note that the vaccines have not been directly compared in head-to-head controlled clinical trials.

Evidence of Effectiveness of the US Rotavirus Vaccination Program

The recommendation to immunize all infants in the United States against rotavirus disease was issued in August 2006, shortly after the licensure of RV5.[11] The Centers for Disease Control and Prevention (CDC) recently analyzed data from the National

TABLE 1. Comparison of Rotavirus Vaccines (The Vaccine Quarterly)*

Characteristic	Vaccines		
	No Longer Available	Currently Licensed in the United States	
	Rhesus Rotavirus Vaccine-Tetravalent	Pentavalent Rotavirus Vaccine	Human Rotavirus Vaccine
Common abbreviation	RRV-TV	RV5 (rotavirus vaccine, 5-valent)	RV1 (rotavirus vaccine, monovalent)
Trade name	RotaShield	RotaTeq	Rotarix
Manufacturer	Wyeth	Merck	GlaxoSmithKline
Licensure	1998	2006	2008
Description	Live rhesus rotavirus reassortant	Live bovine rotavirus reassortant	Live attenuated human rotavirus
Method of attenuation	Heterologous host	Heterologous host serial in vitro passage	Serial in vitro passage
Cell type used for production	Fetal rhesus diploid cells	Vero (African green monkey kidney) cells	Vero (African green monkey kidney) cells
Serotypes actually contained in the vaccine (origin)	G1 (human) G2 (human) G3-like (rhesus) G4 (human) P5[3] (rhesus)	G1 (human) G2 (human) G3 (human) G4 (human) G6 (bovine) P1[8] (human) P7[5] (bovine)	G1 (human) P1[8] (human)
Serotypes for which vaccine is labeled as protective	G1, G2, G3, G4	G1, G2, G3, G4	G1, G3, G4, G9
Route	Oral	Oral	Oral
Dose	2.5 mL	2 mL	1 mL
Presentation	Lyophilized in a single-dose vial Reconstitution required using plastic ampoule containing liquid diluent	Liquid in a single-dose, squeezable, plastic tube	Lyophilized in a single-dose vial Reconstitution required using oral applicator containing liquid diluent
Dosing schedule	2, 4, 6 mos of age	2, 4, 6 mos of age	2, 4 mos of age
Age at first dose according to the package insert	≥6 wks	6–12 wks	≥6 wks
Age at first dose according to the 2009 ACIP recommendations	N/A	6 wk–14 wk 6 days	6 wk–14 wk 6 days
Minimum interval between doses	3 wks	4 wks	4 wks
Maximum age for last dose according to the package insert	6 mos	32 wks	24 wks
Maximum age for last dose according to the ACIP recommendations	N/A	8 mos 0 days	8 mos 0 days
Storage	Vials and diluent stored in refrigerator or room temperature Reconstituted vaccine stable for 1 h at room temperature and 4 h in refrigerator	Refrigerator	Vials in refrigerator and diluent at room temperature Reconstituted vaccine stable for 24 h at room temperature or in refrigerator
Approximate number of children involved in mature pre-licensure trials	11,000	72,000	72,000
Efficacy against any rotavirus disease through the first season	49%–83%	73%–74%	87%
Efficacy against severe rotavirus disease through the first season	70%–95%	98%–100%	85%–96%
Shedding and transmission	50% of vaccines Low-level horizontal transmission documented	9% after first dose only Horizontal transmission not evaluated	26% Horizontal transmission not evaluated
Solicited adverse events statistically higher than placebo during first week	Fever Decreased appetite Irritability Decreased activity	Slight excess of vomiting and diarrhea	None
Risk of intussusception attributable to the vaccine	1 in 11,000 vaccinees	No attributable risk detected	No attributable risk detected

*Data on safety and efficacy are based on information provided in the respective package inserts. It is important to point out that the vaccines were not compared to each other in a head-to-head clinical trial.

Respiratory and Enteric Virus Surveillance System and the New Vaccine Surveillance Network to see if there has been an impact of the rotavirus vaccine program.[29] On average, the rotavirus seasons between 1991 and 2006 began in mid-November and peaked in early February (Fig. 5).[29] During the height of the season, about 40% of stool specimens submitted were positive for rotavirus. The 2007–2008 season was very different—the onset was delayed and the season peaked around April. What's more, at the height of the season, <20% of tests were positive. Several additional studies presented in abstract form at the recent Infectious Diseases Society of America/International Conference on Antimicrobial Agents and Chemotherapy meeting confirm these observations and suggest that the rotavirus program is working. Investigators have reported dramatic reductions in hospitalizations and positive laboratory tests[30–35]; these benefits have been seen despite the fact that only 1 vaccine has been in general use since 2006, and fewer than half of infants have received all 3 doses. A formal postlicensure effectiveness study[36] among 33,135 fully-vaccinated infants and 27,954 control infants who were not vaccinated demonstrated a 100% reduction in hospitalizations and ED visits and a 96% reduction in physician visits for rotavirus gastroenteritis.

Recommendations

The following recommendations were recently published by the Advisory Committee for Immunization Practices (ACIP).[37] There are some important differences between the information in the respective package inserts and the ACIP recommendations, particularly with respect to the timing of doses (Table 1). In practice, ACIP recommendations generally trump product labeling, although in a technical sense, the timing suggested by the ACIP is off-label.

All infants should be vaccinated against rotavirus. There is no preference for 1 vaccine over the other, and either vaccine can be given concomitantly with the other vaccines recommended in infancy. The usual schedule for RV5 is 3 oral doses at 2, 4, and 6 months of age and the usual schedule for RV1 is 2 oral doses at 2 and 4 months of age. The first dose of either product should be given between 6 weeks and 14 weeks 6 days of age. The last dose (second dose of RV1 or third dose of RV5) should be given before 8 months 0 days of age. Effort should be made to complete the series with the same product; however, vaccination should not be deferred if the same product is not available or not known. If any dose in the series is RV5 or is unknown, a total of 3 doses should be given. If the infant spits up a dose, repeat administration is not necessary (although the RV1 package insert says that a single replacement dose at the same visit may be considered).

Vaccination is recommended in the following circumstances:

- Infants who have already had an episode of rotavirus gastroenteritis
- Infants who are breastfed
- Premature infants who are clinically stable and are being or have been discharged from the nursery (infants who remain in the nursery should not be vaccinated)
- Infants living in the home of immunocompromised or pregnant individuals (standard precautions should be followed to minimize horizontal transmission)

Vaccine should not be given to infants who have had an allergic reaction to a previous dose or any vaccine components. Rotavirus vaccine should be used with precaution (this means weighing the risks and benefits) in infants with moderate or severe acute illness; moderate or severe acute gastroenteritis; immunodeficiency or immunosuppression (infants with or at risk for HIV infection may be vaccinated); pre-existing gastrointestinal disease such as congenital malabsorption syndromes, chronic diarrhea and failure to thrive, previous abdominal surgery, Hirschsprung's disease, short-gut syndrome, persistent vomiting of unknown cause (history of uncorrected congenital malformation of the gastrointestinal tract that might predispose to intussusception [eg, Meckel diverticulum] is listed in the package insert as a contraindication for RV1); and previous history of intussusception. In addition, whereas receipt of an antibody-containing blood product could impair the immune response to the vaccine, vaccination should not be deferred in this situation.

Routine vaccination of infants against rotavirus is considered the most effective public-health intervention for reducing the burden of rotavirus disease.[38]

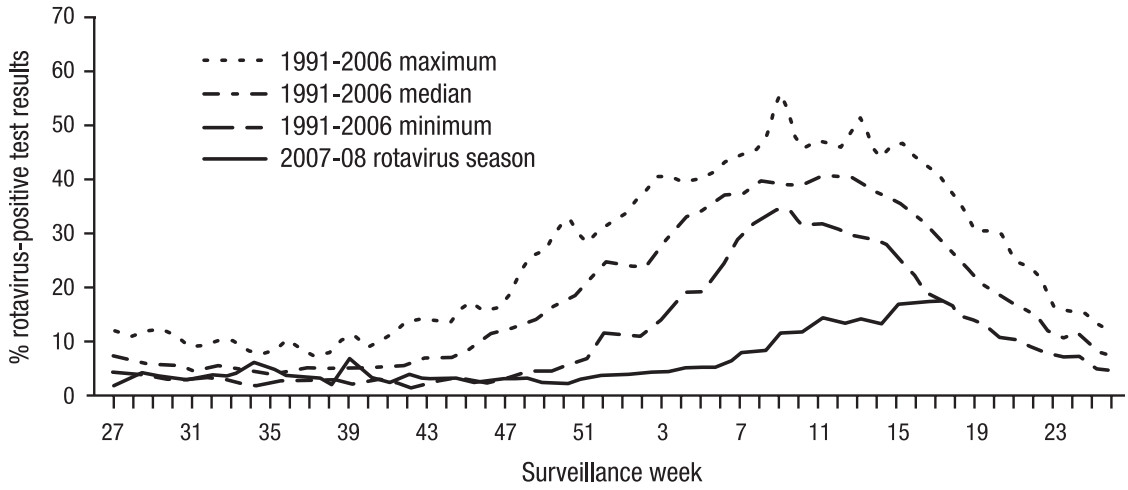


FIGURE 5. Percentage of rotavirus tests with positive results from participating laboratories, by week of the year—-National Respiratory and Enteric Virus Surveillance System, United States; 1991–2006 rotavirus seasons and 2007–2008 rotavirus season* (*MMWR* 6/27/08). *2008 data current through week ending May 3, 2008. Data from July 2006–June 2007 were excluded from the (1991–2006) baseline data.

ACKNOWLEDGMENTS

The author thanks Tara Hun-Dorris, MMC, ELS, of THD Editorial, Inc., for assistance in preparation of this manuscript.

REFERENCES

1. Anderson EJ, Weber SG. Rotavirus infection in adults. *Lancet Infect Dis*. 2004;4:91–99.
2. Kapikian AZ, Hoshino Y, Chanoock RM. Rotaviruses. In: Knipe DM, Howley PM, eds. *Fields Virology*. Philadelphia, PA: Lippincott Williams and Wilkins; 2001:1787–1808.
3. Offit PA, Clark HF. Rotavirus. In: Mandell GL, Bennett JE, Dolin R, eds. *Principles and Practice of Infectious Disease*. Philadelphia, PA: Churchill Livingstone; 2000:1696–1703.
4. Santos N, Hoshino Y. Global distribution of rotavirus serotypes/genotypes and its implications for the development and implementation of an effective rotavirus vaccine. *Rev Med Virol*. 2005;15:29–56.
5. Griffin DD, Kirkwood CD, Parashar UD, et al. Surveillance of rotavirus strains in the United States: identification of unusual strains. *J Clin Microbiol*. 2000;38:2784–2787.
6. Jiang B, Gentsch JR, Glass RI. The role of serum antibodies in the protection against rotavirus disease: an overview. *Clin Infect Dis*. 2002;34: 1351–1361.
7. Musher DM, Musher BL. Contagious acute gastrointestinal infections. *N Engl J Med*. 2004;351:2417–2427.
8. Coffin SE, Elser J, Marchant C, et al. Impact of acute rotavirus gastroenteritis on pediatric outpatient practices in the United States. *Pediatr Infect Dis J*. 2006;25:584–589.
9. Parashar UD, Hummelman EG, Bresee JS, et al. Global illness and death caused by rotavirus disease in children. *Emerg Infect Dis.* 2003;9:565–572.
10. Pickering LK, Bartlett AV, Reves RR, et al. Asymptomatic excretion of rotavirus before and after rotavirus diarrhea in children in day care centers. *J Pediatr*. 1988;112:361–365.
11. Parashar UD, Alexander JP, Glass RI, Advisory Committee on Immunization Practices (ACIP), Centers for Disease Control and Prevention. Prevention of rotavirus gastroenteritis among infants and children: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 2006;55(RR-12):1–13.
12. Charles MD, Holman RC, Curns AT, et al. Hospitalizations associated with rotavirus gastroenteritis in the United States, 1993 to 2002. *Pediatr Infect Dis J*. 2006;25:489–493.
13. Maleck MA, Curns AT, Holman RC, et al. Diarrhea- and rotavirus-associated hospitalization among children less than 5 years of age: United States, 1997 and 2000. *Pediatrics*. 2006;117:1887–1892.
14. Dennehy PH, Cortese MM, Begue RE, et al. A case-control study to determine risk factors for hospitalization for rotavirus gastroenteritis in US children. *Pediatr Infect Dis J*. 2006;25:1123–1131.
15. Török TJ, Kilgore PE, Clarke MJ, et al. Visualizing geographic and temporal trends in rotavirus activity in the United States, 1991 to 1996. *Pediatr Infect Dis J*. 1997;16:941–945.
16. Matson DO, Estes MK, Burns JW, et al. Serotype variation of human group A rotaviruses in two regions of the USA. *J Infect Dis.* 199;162:605–614.
17. Velazquez FR, Matson DO, Calva JJ, et al. Rotavirus infection in infants as protection against subsequent infections. *N Engl J Med*. 1996;335:1022–1028.
18. RotaShield prescribing information. Philadelphia, PA: Wyeth-Ayerst; August 1998.
19. Centers for Disease Control and Prevention. Suspension of rotavirus vaccine after reports of intussusception—United States, 1999. *MMWR.* 2004; 53:786–789.
20. Murphy TV, Gargiullo PM, Massoudi MS, et al. Intussusception among infants given an oral rotavirus vaccine. *N Engl J Med*. 2001;344:564–572.
21. Kramarz P, France EK, DeStefano F, et al. Population-based study of rotavirus vaccination and intussusception. *Pediatr Infect Dis J*. 2001;20: 410–416.
22. Simonsen L, Viboud C, Elixhauser A, et al. More on RotaShield and intussusception: the role of age at the time of vaccination. *J Infect Dis*. 2005;192(suppl 1):S36–S43.
23. RotaTeq prescribing information. Whitehouse Station, NJ: Merck and Co. Inc; 2008.
24. Rotarix prescribing information. Research Triangle Park, NC: GlaxoSmith-Kline; 2008.
25. Vesikari T, Matson DO, Dennehy P, et al; the Rotavirus Efficacy and Safety Trial Study Team. Safety and efficacy of a pentavalent human-bovine (WC3) reassortant rotavirus vaccine. *N Engl J Med*. 2006;354:23–33.
26. Ruiz-Palacios GM, Perez-Schael I, Velazquez FR, et al; Human Rotavirus Vaccine Study Group. Safety and efficacy of an attenuated vaccine against severe rotavirus gastroenteritis. *N Engl J Med*. 2006;354:11–22.
27. Vesikari T, Karvonen A, Prymula R, et al. Efficacy of human rotavirus vaccine against rotavirus gastroenteritis during the first 2 years of life in European infants, randomized, double-blind controlled study. *Lancet*. 2007; 370:1757–1763.
28. Marshall GS. Rotavirus vaccines. *Vaccine Quart*. 2008;2:17.
29. Centers for Disease Control and Prevention. Delayed onset and diminish magnitude of rotavirus activity—United States, November 2007–May 2008. *MMWR.* 2008;57:697–700.
30. Clark HF, Lawley D, Mallette L, et al. Decline in rotavirus (RV) gastroenteritis (GE) presenting to the Children's Hospital of Philadelphia (CHOP) after introduction of pentavalent rotavirus vaccine (PRV). Poster (G1-413) presented at ICAAC/IDSA Meeting; October 2008; Washington, DC.
31. Daskalaki I, Wood SJ, Inumerable YM, et al. Epidemiology of rotavirus-associated hospitalizations pre- and post-implementation of immunization: North Philadelphia, 2000–2008. Poster (G1-432) presented at ICAAC/IDSA Meeting; October 2008; Washington, DC.
32. Harrison CJ, Jackson M, Olson-Burgess C, et al. Fewer 2008 hospitalizations for rotavirus (RV) in Kansas City, two years post RV vaccine. Poster (G1-435) presented at ICAAC/IDSA Meeting; October 2008; Washington, DC.
33. Hatch S, Fontecchio S, Gibson L, et al. Rapid decline in pediatric rotavirus cases following introduction of rotavirus vaccine. Poster (G1-436) presented at ICAAC/IDSA Meeting; October 2008; Washington, DC.
34. Lieberman JM, Huang X, Koski E, et al. Decline in rotavirus cases in the US after licensure of a live, oral rotavirus vaccine. Poster (G1-437) presented at ICAAC/IDSA Meeting; October 2008; Washington, DC.
35. Patel JA, Loeffelholz M. Reduction of severe rotavirus gastroenteritis following the routine use of live, oral, pentavalent rotavirus vaccine. Poster (G1-434) presented at ICAAC/IDSA Meeting; October 2008; Washington, DC.
36. Mast T, Wang F, Goli V, et al. Post-licensure effectiveness of RotaTeq in preventing gastroenteritis. Poster (G1-433) presented at ICAAC/IDSA Meeting; October 2008; Washington, DC.
37. Centers for Disease Control and Prevention. Prevention of rotavirus gastroenteritis among infants and children: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR*. 2009;58(RR-2):1–25.
38. Rotavirus vaccination coverage and adherence to the Advisory Committee on Immunization Practice (ACIP)-recommended vaccination schedule—United States, February 2006–May 2007. *MMWR.* 2008;57:398–401.

CME Posttest

Rotavirus Disease and Prevention Through Vaccination

1. Which of the following rotavirus serogroups are human pathogens?
    a. A
    b. D
    c. F
    d. All of the above
    e. None of the above

2. Which protein is the "glycoprotein" in rotavirus?
    a. VP4
    b. VP6
    c. VP7
    d. NSP4
    e. None of the above

3. When is the peak incidence of rotavirus infection?
    a. <6 months of age
    b. 6 months to 1 year of age
    c. 6 months to 2 years of age
    d. 6 months to 5 years of age
    e. Birth to 5 years of age

4. Which of the following statements is true regarding the disease burden of rotavirus in the United States?
    a. Annual direct and indirect costs associated with rotavirus are estimated at $100 million
    b. 1 in 20,000 children will die from rotavirus
    c. Children hospitalized for rotavirus have significantly shorter hospital stays
    d. Rotavirus is responsible for at least 18% of pediatric hospitalizations
    e. All children will contract rotavirus by their fifth birthday

5. Natural rotavirus infection does not confer protection against future disease.
    a. True
    b. False

6. Which of the following is true about the seasonality of rotavirus in the United States?
    a. Rotavirus activity tends to begin in the southwest
    b. The season begins in late November/early December
    c. The season peaks in mid-February/mid-March
    d. None of the above
    e. All of the above

7. Which rotavirus strain tends to be most prevalent in North America?
    a. G1P[8]
    b. G2P[4]
    c. G3P[8]
    d. G4P[8]
    e. None of the above

8. There is evidence that the rotavirus vaccine program is working.
    a. True
    b. False

9. According to ACIP, which of the following infants can receive the rotavirus vaccine?
    a. Prior rotavirus gastroenteritis
    b. Breastfeeding
    c. Clinically stable premature infants who are/have been discharged from the nursery
    d. None of the above
    e. All of the above

10. How did the RRV-TV vaccine differ from the currently approved rotavirus vaccines?
    a. It was tested in a smaller population in clinical trials prior to approval
    b. It caused shedding in approximately 50% of patients
    c. It was associated with a higher risk of intussusception attributable to vaccine
    d. None of the above
    e. All of the above

Evaluation - please complete

Rotavirus Monograph Journal Supplement
Rotavirus Disease and Prevention Through Vaccination

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For Physicians Only: I certify my actual time spent to complete this educational activity to be:
__ I participated in the entire activity and claim 1.0 credits.
__ I participated in only part of the activity and claim ___ credits.

Posttest Answer Key

__	__	__	__	__	__	__	__	__	__
1	2	3	4	5	6	7	8	9	10

1. How would you rate this educational activity overall?
(5 = excellent, 1 = poor, please circle one) 5 4 3 2 1

2. In your opinion, did you perceive any commercial bias in any of the presentations?
☐ Yes If yes, please explain:
☐ No

3. Do you plan on making any changes in your practice as a result of this activity?
☐ Yes If yes, please explain:
☐ No

4. Do you feel each of the following objectives were met?
I am now better able to:

• Outline the epidemiology of rotavirus infection, including transmission, seasonality, and year-to-year serotype variation.	☐Yes ☐No ☐Partially ☐N/A
• Calculate rotavirus disease burden in the United States, including outpatient episodes of gastroenteritis and hospitalizations for dehydration.	☐Yes ☐No ☐Partially ☐N/A
• Compare and contrast available rotavirus vaccines.	☐Yes ☐No ☐Partially ☐N/A
• Summarize the ACIP recommendations for rotavirus vaccination.	☐Yes ☐No ☐Partially ☐N/A

5. Do you feel that the information presented was based on the best evidence available?
☐ Yes
☐ No If no, please explain:

6. Which of the following competency areas do you feel have been improved as a result of this activity? (Check all that apply)
☐ Patient Care ☐ Professionalism ☐ Practice Based Learning
☐ Medical Knowledge ☐ System Base Practice ☐ Communication Skills

7. Please suggest topics for future activities.

_____

8. Please rate the quality of the content. (5 = Excellent, 1 = Poor)
Rotavirus Disease and Prevention Through Vaccination 5 4 3 2 1
Comments:

General Comments: