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ADVANCES IN PEDIATRICS

Rotavirus Infection

An Update on Management and Prevention

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Key Points
- Rotavirus vaccines have reduced the burden of rotavirus disease in the United States.
- The real-world effectiveness data for both vaccines are consistent with efficacy data obtained from clinical trials.
- Herd immunity has also been seen after vaccine introduction.
- Vaccine introduction has led to no significant strain shifts or escape mutants as yet.

Rotavirus infection is the leading cause of severe acute diarrhea among young children worldwide. An estimated 527,000 children aged less than 5 years die from rotavirus diarrhea each year, with greater than 85% of these deaths occurring in the low-income countries of Africa and Asia [1]. Rotavirus-related deaths represent approximately 5% of all deaths in children younger than 5 years worldwide. Each year rotavirus causes approximately 114 million episodes of gastroenteritis requiring only home care, 24 million clinic visits, and 2.4 million hospitalizations in children less than 5 years of age worldwide [2]. 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 [2]. Recent results from the World Health Organization (WHO) rotavirus surveillance networks indicate that approximately 36% of diarrhea hospitalizations among children aged less than 5 years worldwide can be attributed to rotavirus infection [3]. 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.

In the United States, before the introduction of rotavirus vaccine in 2006, rotavirus caused an estimated 20 to 60 deaths, 55,000 to 70,000 hospitalizations,

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205,000 to 272,000 emergency department visits, and 410,000 outpatient visits annually [4]. Nearly every child in the United States was infected with rotavirus by 5 years of age and most developed gastroenteritis [5]. One child in 7 required a clinic or emergency room visit and 1 in 70 was hospitalized [5,6]. Rotavirus was responsible for 22% to 54% of the acute gastroenteritis cases in the United States and caused more severe disease than did other enteric pathogens, accounting for 30% to 50% of all hospitalizations for gastroenteritis among children less than 5 years of age and more than 70% of hospitalizations for gastroenteritis during the seasonal peaks of rotavirus disease in the United States [7–9]. Annual direct and indirect costs were estimated at approximately 1 billion dollars, primarily due to the cost of time lost from work to care for an ill child [10,11]. Rotavirus activity in the United States decreased significantly after introduction of rotavirus vaccine in 2006.

EPIDEMIOLOGY AND TRANSMISSION OF INFECTION

Rotavirus outbreaks exhibit a seasonal pattern. In temperate climates, disease is more prevalent during fall and winter. In the United States, before introduction of rotavirus vaccine, annual epidemics began in the southwest during November and December, progressing north and east and reaching the northeast by April or May [12]. The reason for this seasonal pattern is unknown. In tropical climates, the disease is less seasonal than in temperate areas but is more pronounced during drier and cooler months.

The reservoir of rotavirus is the gastrointestinal tract and stool of infected humans. Although rotavirus infection occurs in many nonhuman mammals, transmission of animal rotaviruses to humans is believed to be rare and probably does not lead to clinical illness. Although immunodeficient persons may shed rotavirus for a prolonged period, a true carrier state has not been described.

Rotavirus is highly communicable, with a small infectious dose of less than 100 virus particles [13]. Viruses are shed in high concentration in the stool of rotavirus-infected persons. Children shed large numbers of viruses in stool, from 100 to 1000 viruses per milliliter, during the acute illness. Shedding may occur beginning 2 days before the onset of diarrhea and for up to 10 days after onset of symptoms. Rotavirus may be detected in the stool of immunodeficient persons for more than 30 days after infection.

Transmission is by fecal-oral spread, both through close person-to-person contact and by fomites (such as toys and other environmental surfaces contaminated by stool). The virus may also be transmitted by respiratory droplets [14]. Rotaviruses are also probably transmitted by other modes such as fecally contaminated food and water. These routes of transmission are probably uncommon as rates of rotavirus illness among children in industrialized and resource poor countries are similar, indicating that clean water supplies and good hygiene have had little effect on virus transmission.

Spread within families, institutions, hospitals, and childcare settings is common. From 30% to 50% of adult contacts of infected infants become infected, although most are asymptomatic. The virus survives well in the environment and only 10

to 100 infectious virus particles are needed to cause infection. This amount of virus can readily be acquired through contact with contaminated surfaces facilitating spread to household contacts.

Rotavirus is a major cause of acute gastroenteritis in children attending child care. Most children in childcare will have their first infection in that setting. In child care centers rotavirus is introduced from the community and quickly spreads to most of the children in the center [15]. During these outbreaks toys, food preparation areas, and toilet facilities are usually heavily contaminated with rotaviruses.

Rotavirus is also a common hospital-acquired infection on pediatric wards in the winter months [16]. These infections result in prolonged hospital stays and increased medical costs. One in 5 children hospitalized during rotavirus season may acquire a nosocomial rotavirus infection. The likelihood of infection increases with duration of hospitalization.

CONTROL MEASURES TO PREVENT INFECTION

The single most important procedure to minimize transmission of rotavirus is frequent hand hygiene measures [17]. Rotavirus can rapidly contaminate environmental surfaces because of the large number of viruses shed in an infected child's stool. Rotavirus is very stable and may remain viable in the environment for weeks or months if not disinfected [18]. Hands may be contaminated from environmental surfaces further facilitating spread of infection. Skin disinfectants such as chlorhexidine are ineffective against rotavirus. Studies have shown that hand washing with soap and water removes only 75% of virus from the hands. Agents containing alcohol are the most effective against rotavirus. To control the spread of rotavirus hands should be cleaned of visible stool with soap and water and then an alcohol-containing hand rub should be used. Because general disinfectants, such as bleach, are ineffective against rotavirus, potentially contaminated surfaces, such as changing tables, should be cleaned of all visible stool and then disinfected with 95% ethanol or other alcohol-containing disinfectant [17]. Although hand hygiene and cleaning of potentially contaminated surfaces are important control measures, vaccination is the only measure likely to have a significant impact on the incidence of severe dehydrating rotavirus disease.

PATHOPHYSIOLOGY OF ROTAVIRUS DISEASE

Rotavirus enters the body through the mouth. The virus is thought to cause diarrhea by at least three different mechanisms. The first is by infecting the mature enterocytes on the tips of the absorptive intestinal villi of the small intestine [19]. Histopathology of jejunal and duodenal mucosal small intestinal biopsies in children performed 24 to 129 hours after the onset of illness shows patchy irregularities that consist of shortening and blunting of villi and increased infiltration of the lamina propria with mononuclear cells [20]. Blunting of the villus tips causes a loss of absorptive surface in the small intestine resulting in decreased absorption of salt and water. This net secretion of salt and water leads to the production of voluminous watery stools. In addition, rotavirus infection of the enterocytes destroys intestinal brush border enzymes, such as maltase, sucrase, and lactase,

which are located on the villus tips and are involved in the digestion of carbohydrates. The resulting complex sugar malabsorption and osmotic diarrhea contribute to the diarrhea seen in rotavirus infections.

The second mechanism that rotavirus uses to cause diarrhea is a viral enterotoxin that works much like cholera toxin. Rotavirus nonstructural protein NSP4 has been shown to have direct toxic effects on the gastrointestinal mucosa [21]. Diarrhea is induced when NSP4 triggers chloride secretion via a calcium-dependent signaling pathway.

Finally, rotavirus-induced diarrhea may also be the result of activation of the enteric nervous system by infection. This results in net intestinal fluid and electrolyte secretion and diarrhea [22].

Rotavirus infection is usually localized to the intestine; however, studies have reported antigenemia is common in children with rotavirus diarrhea. Rotavirus viremia is less commonly detected [23–28]. Rarely, involvement of extraintestinal sites, including the respiratory tract, liver, kidney, lymph nodes, and central nervous system (CNS), has been reported [29–37].

CLINICAL ILLNESS

The incubation period for rotavirus diarrhea is short, usually less than 48 hours. The clinical manifestations of infection vary and depend on whether it is the first infection or reinfection. Rotavirus predominantly infects children, but infection also occurs in adults. Immunosuppressed hosts, including children, seem to develop a more severe and protracted infection.

Studies of children with rotavirus infection have shown a spectrum of disease, ranging from asymptomatic shedding to severe dehydration, seizures, and even death. Rotavirus gastroenteritis typically begins with acute onset of fever and vomiting followed 24 to 48 hours later by watery diarrhea [38]. On average, there are up to 10 to 20 bowel movements per day. Symptoms generally persist for 3 to 8 days, although protracted episodes have been noted on occasion. Fever is usually low-grade and occurs in up to half of all infected children. Some children may have high fevers. Rotavirus infection with fever may trigger seizures in children with a propensity for febrile seizures. Vomiting is nonbilious and occurs in 80% to 90% of infected children. Vomiting is usually brief, lasting 24 hours or less in most children. Dehydration and electrolyte disturbances are the major sequelae of rotavirus infection and occur most often in the youngest children. Studies of hospitalized children have indicated that cases of gastroenteritis associated with rotavirus have tended to be more severe than cases in which rotavirus was not detected, with more severe dehydration and higher incidences of vomiting and fever. Respiratory symptoms may be seen in 30% to 50% of children with rotavirus gastroenteritis.

Although infection can occur at any age, rotavirus most commonly causes clinically significant disease in young infants and children. In industrialized countries severe, dehydrating rotavirus gastroenteritis primarily occurs among infants and children aged 3 to 24 months, although 25% of cases of severe disease occur after 2 years of age. Infants younger than 3 months of age have relatively low rates of

rotavirus infection, probably because of passive maternal antibody, and possibly breastfeeding. In developing countries, 60% to 80% of severe rotavirus disease occurs by 12 to 15 months of age.

Most children are infected with rotavirus more than once. First infections are more likely to result in severe gastroenteritis than are subsequent infections. Protective immunity develops after rotavirus infection and is strongest against moderate to severe disease. Subsequent infections are usually milder or may even be asymptomatic. Adults usually have asymptomatic or mild disease because of immunity from previous exposure.

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. An exception is the preterm infant, who is at greater risk of severe illness than the term infant is because of the lack of transplacental maternal antibodies [39]. Exposure of neonates (asymptomatically) to rotavirus is associated with a reduced likelihood of their developing severe rotavirus diarrhea later in infancy [40,41].

Although rotavirus gastroenteritis most commonly affects small children, adults may also develop symptomatic infections [42]. Among adults in the United States, rotavirus infection occurs most often in travelers returning from developing countries, persons caring for children with rotavirus gastroenteritis, immunocompromised persons, and older adults [43]. The clinical manifestations in adults seem similar to those in children but are usually less severe. Dehydration and severe disease have been reported in adults.

Severe and prolonged rotavirus gastroenteritis has been reported in children with immunodeficiency, particularly those with T-cell immunodeficiencies or severe combined immunodeficiency (SCID), and after bone marrow transplantation. In these cases, rotavirus may be associated with severe disease and may be fatal, and extraintestinal replication has been reported. Rotavirus infection of children after solid organ transplantation is usually self-limited but more severe than in healthy children. Rotavirus does not seem to be a common cause of severe or persistent diarrhea in individuals with HIV infection.

Rotavirus gastroenteritis has occurred in association with multiple other clinical syndromes, which may or may not be causally associated with rotavirus. These clinical syndromes include gastrointestinal complications or CNS complications.

The gastrointestinal syndromes that may be associated with rotavirus include necrotizing enterocolitis, intussusception, biliary atresia, and prolonged diarrhea. Necrotizing enterocolitis has been associated with nosocomial rotavirus infections in neonates. Intussusception was reported in association with rotavirus gastroenteritis shortly after recognition of this virus. However, subsequent studies have never established a definitive causal link with natural rotavirus infection. Biliary atresia has also been reported in association with rotavirus infection. Although most children recover from rotavirus gastroenteritis completely, some children continue to have protracted diarrhea. Carbohydrate intolerance or lactase intolerance may persist after resolution of diarrhea.

Epidemiologic studies have suggested that rotavirus infection does not increase the risk for subsequent persistent diarrhea in childhood.

Rotavirus gastroenteritis may be associated with CNS complications, particularly seizures and encephalopathy. Rotavirus has been detected by polymerase chain reaction (PCR) in cerebrospinal fluid (CSF) in some cases. However, it is unclear whether detection of rotavirus represents actual replication in the CNS, contamination at the time of lumbar puncture, or carriage of rotavirus RNA in CSF lymphocytes.

DIAGNOSIS AND MANAGEMENT OF INFECTION

Enzyme immunoassays and latex agglutination assays for detection of group A rotavirus antigen in stool are available commercially and are widely used for diagnosing rotavirus infection. Virus also can be identified in stool by electron microscopy and by reverse transcriptase-PCR, but these techniques are primarily used in the research setting.

No antiviral is currently available to treat rotavirus infection. The current mainstay of treatment of acute rotavirus gastroenteritis consists of oral rehydration and early introduction of feedings [44]. Adequate fluid and electrolyte replacement and maintenance is the key to managing rotavirus gastroenteritis. Oral rehydration is the preferred method unless the child has intractable vomiting that would require intravenous (IV) rehydration. Hydration status in children can be assessed based on easily observed signs and symptoms. Children who are not thirsty, have moist mucous membranes, wet diapers and tears are not dehydrated and do not require oral rehydration solution (ORS). In the absence of dehydration, ORS should be used to replace ongoing stool losses only in severe cases in which the patient has already required rehydration and still has ongoing diarrhea. Children who are mildly or moderately dehydrated should receive 50 to 100 mL/kg of ORS over 4 hours and should be reevaluated often for changes in hydration status. Children who are vomiting generally tolerate ORS. ORS is contraindicated in the child who is obtunded or at risk for aspiration. When ORS is complete, regular feeding should be resumed.

Children who are severely dehydrated with changes in vital signs or mental status require emergency IV fluid resuscitation. Hypotension is a late manifestation of shock in children. Mental status, heart rate, and perfusion are better indicators of severe dehydration and incipient shock. After initial treatment with IV fluids, these children can be given ORS.

Early refeeding is recommended in managing acute rotavirus gastroenteritis because oral feedings help facilitate mucosal repair following rotavirus infection. Introducing a regular diet within a few hours of rehydration or continuing the diet during diarrhea without dehydration has been shown to shorten the duration of the disease. Early refeeding has not been associated with increased morbidity, such as electrolyte disturbances or a need for IV fluids.

ADJUNCTIVE THERAPY

Although oral rehydration treats dehydration, it is not effective in shortening the duration of rotavirus-induced diarrhea. There is a growing body of literature establishing the effectiveness of selected probiotics as an adjunct to rehydration therapy. In developed countries, *Lactobacillus rhamnosus* GG given in a daily dose of 10 billion colony-forming units per day has proven efficacy in rotavirus gastroenteritis to reduce the duration of diarrhea, the risk of protracted diarrhea, and the duration of hospitalization [45–47]. The duration of diarrhea may be reduced as much as 1 to 2 days with the use of probiotics.

Nitazoxanide is a thiazolidine antimicrobial with activity against anaerobic bacteria, protozoa, and viruses. Three randomized double-blind clinical trials have demonstrated effectiveness of nitazoxanide in treating rotavirus gastroenteritis in young children with significant reductions in time to resolution of symptoms [48–50]. More data on nitazoxanide is needed before it can be considered for routine use.

Antidiarrheal drugs are generally not recommended for treatment of rotavirus gastroenteritis [44,51]. Over-the-counter medicines such as loperamide and bismuth subsalicylate can help relieve gastroenteritis symptoms in adults but are not recommended for children.

Antiemetics should not be routinely used in the management of children with acute rotavirus gastroenteritis [52,53]. Although ondansetron use may decrease vomiting during the first hours after presentation, decrease the need for IV fluids in the emergency department, and decrease hospitalization rates in those patients who require IV fluids, its use may increase diarrheal episodes. In addition, most studies of ondansetron in children with acute gastroenteritis have been performed only on mildly dehydrated children. Of greatest concern is the use of ondansetron may increase risk of developing prolongation of the Q-T interval. For more information, see http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm272041.htm. Patients at risk for adverse outcomes include those with underlying heart conditions, such as congenital long QT syndrome, those who are predisposed to low levels of potassium and magnesium in the blood, and those taking other medications that lead to QT prolongation.

ROTAVIRUS STRUCTURE AND CLASSIFICATION

Human rotaviruses are part of a large family of viruses causing neonatal diarrhea in a variety of domestic animals and birds. Animal strains are antigenically distinct from those causing human infection, and rarely cause infection in humans. Rotaviruses are classified into at least seven distinct groups (A through G). Only groups A, B, and C infect humans. Group A rotaviruses are the most important cause of severe acute gastroenteritis in infants and young children worldwide.

Rotaviruses were first described as a causative agent of gastroenteritis in humans in 1973 when they were seen in electron micrographs of duodenal mucosal biopsies from children with acute gastroenteritis. Rotaviruses have a distinctive wheel-shape on electron microscopy giving rise to their name which is derived from the Latin word "rota" meaning wheel.

To understand how vaccines have been developed to prevent rotavirus disease, one must understand the structure of the rotavirus virion. Rotavirus is a double-stranded RNA virus composed of three concentric shells that enclose 11 gene segments. 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.

The outermost shell of the rotavirus virion contains two important structural proteins, VP7, the glycoprotein (G protein), and VP4, the protease-cleaved protein (P protein) [28]. VP7 and VP4 define the serotype of the virus and are considered critical to vaccine development because they are targets for neutralizing antibodies that may provide both serotype specific and, in some instances, cross-reactive protection [54]. A typing system has been developed for each protein. Fourteen G serotypes and 11 P serotypes have been identified in humans.

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 G-P serotype combinations [55]. Until recently, four rotavirus strains (G1, G3, G4 combined with P[8], and G2 combined with P[4]) made up 96% of the globally identified strains [56]. Recently, previously rare G serotypes, such as G5, G6, G8, G10, and in particular G9, have emerged [55].

Predominant serotypes vary from year to year and region to region. G1P[8] is the globally predominant strain, representing over 70% of rotavirus infections in North America, Europe, and Australia, but only about 30% of the infections in South America and Asia, and 23% of those in Africa [57]. G9 strains now constitute the predominant strains in some parts of Asia and Africa and G8 strains are proportionally more frequent in Africa. In South America, G5 strains have emerged in children with diarrhea and G9 is associated with more severe disease in Latin America [58]. Similarly, the distribution of the P[6] antigen differs according to region. P[6] strains now constitute over 50% of the circulating strains in Africa, whereas P[8] is associated with most rotavirus strains from the rest of the world [59]. The development of successful rotavirus vaccines may require inclusion of all the major G or P types causing disease in a specific region.

NATURAL PROTECTION

Naturally acquired rotavirus infections provide the greatest protection against reinfection causing severe disease [60]. 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. After a single natural infection, 40% of children are protected against any subsequent infection with rotavirus, 75% are protected against diarrhea caused by a subsequent rotavirus infection, and 88% are protected against severe rotavirus diarrhea. Second, third, and fourth infections confer progressively greater protection. In observation studies, no child with two previous infections has subsequently developed severe rotavirus diarrhea.

Despite three decades of research, the components of the immune response that protect children from rotavirus infection and disease are not completely understood. Both serum and mucosal antibodies are probably important. Antibodies to both VP4 and VP7 proteins neutralize virus infectivity. However, in vaccine studies, correlation between these antibodies and protection has been poor. The first infection with rotavirus elicits serum-neutralizing antibody response to the serotype of the infecting virus. Subsequent infections elicit a broader, cross-reactive response. Studies have suggested that antibody is important in the resolution of infection and in protection against subsequent infection, whereas cell-mediated immunity is most important in the resolution of rotavirus infections [61]. Local immunity in the gut also seems to be important for protection against subsequent infection. Total serum antirotavirus IgA, measured shortly after infection, generally reflects intestinal IgA levels and seems to be the best marker of protection [62]. However, gut immunity seems to be of short duration and has been hard to measure. Because a reliable immune correlate of protection has not been found, 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. Effective rotavirus vaccines should decrease the number of children admitted to the hospital with dehydration or seen in emergency departments and should decrease the burden on the practicing primary care practitioner by reducing the number of office visits or telephone calls due to rotavirus gastroenteritis.

Effective rotavirus vaccines are most needed in resource-poor countries where mortality associated with rotavirus is high. The development and introduction of rotavirus vaccines for children in the resource-poor countries of the world has been given high priority by the WHO. In 2003, GAVI (Global Alliance for Vaccines and Immunizations) sponsored a new public-private organization, the Rotavirus Vaccine Program at PATH (Program for Appropriate Technology in Health), whose role was to accelerate the development and introduction of rotavirus vaccines in developing countries.

DEVELOPMENT OF ROTAVIRUS VACCINES

Human-rhesus rotavirus reassortant vaccine

The first multivalent live oral reassortant vaccine developed was a human-rhesus rotavirus reassortant vaccine (RotaShield; RRV-TV). This tetravalent vaccine contained four virus strains representing the most commonly seen G types, G1 to G4; three rhesus-human reassortant strains containing the VP7 genes of human serotype G1, G2 and G4 strains were substituted for the VP7 gene of the parent rhesus rotavirus (RRV), and the fourth strain comprised serotype G3 of RRV [63]. RRV-TV was extensively evaluated in field trials in the United

States, Finland, and Venezuela and was found to be 80% to 100% effective in preventing severe diarrhea due to rotavirus in each of these settings [64–67]. 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 [68].

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 [69]. The period of greatest risk of intussusception was shown to be 3 to 10 days after the first of three oral doses [70–72]. Although the true overall incidence of this adverse event proved difficult to assess, a group of international experts suggested a consensus rate of 1 per 10,000 vaccinated infants [73]. The pathogenic mechanisms involved in intussusception following vaccination are currently unknown. As a consequence of this rare but potentially dangerous adverse effect, the manufacturer withdrew RotaShield from the market in the United States 14 months after its introduction.

CURRENTLY LICENSED VACCINES

There are two rotavirus vaccines currently licensed for use in the United States. The two rotavirus vaccine products differ in composition and schedule of administration. RV5 (RotaTeq) is a live oral vaccine manufactured by Merck and licensed by the US Food and Drug Administration (FDA) in February 2006. RV5 is routinely recommended as a three-dose schedule at 2, 4, and 6 months of age. RV1 (Rotarix), a live oral vaccine manufactured by GlaxoSmithKline, was licensed by the FDA in April 2008. RV1 is routinely recommended as a two-dose schedule at 2 and 4 months of age.

Human-bovine rotavirus reassortant vaccine (RV5, RotaTeq)

RV5 contains five reassortant rotaviruses developed from human and bovine parent rotavirus strains. 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 important in protection; therefore, RV5 includes human VP7 or VP4 genes to provide protective immune responses. Four reassortant rotaviruses express the VP7 protein (G1, G2, G3, or G4) from the human rotavirus parent strain and the attachment protein (P[5]) from the bovine rotavirus parent strain WC3. The fifth reassortant virus expresses the attachment protein (P[8]) from the human rotavirus parent strain and the outer capsid protein G6 from the bovine rotavirus parent strain.

RV5 was tested in a large phase III trial in 11 countries, with the United States and Finland accounting for more than 80% of all enrolled subjects [74]. The trial included more than 70,000 children and was primarily designed 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 RV5 group versus 5 cases of intussusception in the placebo group. The data did not suggest an increased risk of intussusception in vaccine recipients relative to placebo. Among vaccine recipients, there were no confirmed cases of intussusception within the 42-day period 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-day 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 RV5 the incidence of fever and irritability did not differ between vaccine and placebo recipients. Diarrhea and vomiting occurred more frequently among vaccine versus placebo recipients (10.4% vs 9.1% and 6.7% vs 5.4%, respectively).

The efficacy of RV5 was evaluated in two phase III trials [74,75]. In these trials, the efficacy of a 3-dose regimen of RV5 against rotavirus gastroenteritis of any severity was 74% and against severe rotavirus gastroenteritis was 98%. RV5 also proved 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 (G3 83% efficacy, G4 48% efficacy, and G9 65% efficacy).

The efficacy of RV5 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 [74]. RV5 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 cause was 59%. The efficacy of RV5 in the second rotavirus season after immunization was 63% against rotavirus gastroenteritis of any severity and 88% against severe rotavirus gastroenteritis [74].

To assess the efficacy of RV5 between doses of a 3-dose series and with less than 3 doses (incomplete regimen) post hoc analyses of the large study of the efficacy of RV5 were conducted. RV5 reduced the rates of combined hospitalizations and emergency department visits for G1 to G4 rotavirus gastroenteritis by 100% between doses 1 and 2, and 91% between doses 2 and 3. RV5 reduced the rates of rotavirus gastroenteritis, regardless of serotype, by 82% between doses 1 and 2, and 84% between doses 2 and 3 [76].

Efficacy and safety trials of RV5 in Asia and Africa have been conducted. The efficacy of an RV5 against severe rotavirus gastroenteritis in Ghana, Kenya, and Mali was 39% [77]. Vaccine efficacy of RV5 in Vietnam and Bangladesh was 48% against severe disease during nearly 2 years of follow-up [78].

Live, attenuated human rotavirus vaccine (RV1, Rotarix)

A live, attenuated human rotavirus vaccine (strain 89–12) was originally developed in Cincinnati, OH, USA, by tissue culture passage of a wild-type human rotavirus isolate [79]. This vaccine is a G1P[8] 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 GSK Biologicals, who further modified the vaccine by cloning and tissue culture passaging of the parent 89–12 vaccine strain. The resulting vaccine, RIX4414 (RV1), underwent initial trials in Finland that showed 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 [80]. 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 the placebo in terms of fever, diarrhea, or vomiting. During a 31-day period after each dose, there was no increase of intussusception among recipients of vaccine compared with 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 followed for efficacy [80]. 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 strongly efficacious in preventing rotavirus gastroenteritis of any severity caused by the predominant G1 serotype (92% efficacy) and for serotypes G3, G4, or G9 (88% efficacy). Efficacy against the G2 serotype (41%) was not significant in this large trial.

Although RV1 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 in a European trial with two seasons follow-up. In this study, efficacy was 79% against rotavirus gastroenteritis of any severity, 90% against severe rotavirus disease, and 96% against hospitalization due to rotavirus. For severe rotavirus gastroenteritis the vaccine had efficacy of 96% against G1P[8] and 88% against non-G1P[8] RV strains, including G2P[4] [81].

Efficacy and safety trials of RV1 have been conducted in Asia and Africa. In a large phase III trial (>9000 infants) in Singapore, Hong-Kong, and Taiwan vaccine efficacy was 96% against severe rotavirus gastroenteritis, 100% against wild-type G1P[8] and 94% against circulating non-G1 rotavirus types. No intussusception cases were reported within 31 days postvaccination [82]. In a phase III trial in South Africa and Malawi, RV1 showed an overall efficacy of 61% by 1 year of age. Vaccine efficacy was lower in Malawi than in South Africa (49% vs 77%); however, the number of episodes of severe rotavirus gastroenteritis that were prevented was greater in Malawi than in South Africa (6.7 vs 4.2 cases prevented per 100 infants vaccinated per year) [83]. Efficacy against all-cause severe gastroenteritis was 30%.

WORLDWIDE IMPLEMENTATION OF ROTAVIRUS VACCINES

In 2007, after RV5 and RV1 became available, the WHO recommended inclusion of rotavirus vaccine in the immunization programs of Europe and the Americas and, in 2009, expanded the recommendation to all infants over the age of 32 weeks worldwide [84].

Currently rotavirus vaccines are licensed in over 125 countries and are available in the private sector in many countries. These vaccines are part of the national immunization program in 29 (15%) of 193 countries worldwide. Over 50% of these countries are in Latin America and none are the low-income countries where rotavirus disease is most severe. With donor support, GAVI plans to introduce rotavirus vaccine in more than 40 low-income countries by 2015.

ROTAVIRUS VACCINE USE IN THE UNITED STATES

Recommendations for the use of rotavirus vaccine

The current recommendations for the use of rotavirus vaccine in the United States were published by the Advisory Committee on Immunization Practices (ACIP) of the Centers for Disease Control and Prevention (CDC) in February 2009 and by the American Academy of Pediatrics (AAP) in May 2009 [7,85]. Because of similar estimates of efficacy and safety, neither the ACIP nor AAP state a preference for one vaccine versus the other.

The AAP and ACIP recommend routine rotavirus vaccination of all infants. The vaccine should be administered as a series of either two or three oral doses, for RV1 and RV5, respectively, beginning at 2 months of age. Rotavirus vaccine should be given at the same visit as other vaccines given at these ages. The vaccination series for both vaccines may be started as early as 6 weeks of age. The minimum interval between doses of both rotavirus vaccines is 4 weeks. The AAP and ACIP did not define a maximum interval between doses. It is preferable to adhere to the recommended interval of 8 weeks. But if the interval is prolonged, the infant can still receive the vaccine as long as it can be given on or before 8-months of age. It is not necessary to restart the series or add doses because of a prolonged interval between doses.

The maximum age for any dose of RV1 approved by the FDA is 24 weeks, whereas the maximum FDA-approved age for any dose of RV5 is 32 weeks. The AAP and ACIP developed age recommendations that vary from those of the manufacturers. The AAP and ACIP recommendations state that the maximum age for the first dose of both vaccines is 14 weeks 6 days. This is an off-label recommendation for RV5 because the approved maximum age for the first dose of that vaccine is 12 weeks. The maximum age for any dose of either rotavirus vaccine is 8 months 0 days. This is an off-label recommendation for both vaccines because the labeled maximum age for RV1 is 24 weeks and the labeled maximum age for RV5 is 32 weeks.

Infants for whom the first dose of rotavirus vaccine was inadvertently administered at age 15 weeks or older should receive the remaining doses of the series at the routinely recommended intervals. Timing of the first dose should not

affect the safety and efficacy of the remaining doses. Rotavirus vaccine should not be given after age 8 months 0 days even if the series is incomplete.

There are currently no data on schedules that include both RV1 and RV5. The AAP and ACIP recommend that the rotavirus vaccine series should be completed with the same product whenever possible. However, vaccination should not be deferred if the product used for a prior dose or doses is not available or is not known. In this situation, the provider should continue or complete the series with the product that is available. If any dose in the series was RV5 or the vaccine brand used for any prior dose in the series is not known, a total of three doses of rotavirus vaccine should be administered.

The AAP and ACIP recommend that providers not repeat the dose if the infant spits out or regurgitates the vaccine. Any remaining doses should be administered on schedule.

Breastfeeding does not seem to diminish immune response to rotavirus vaccine. Infants who are being breastfed should be vaccinated on schedule.

There are at least five serotypes of rotavirus that may cause diarrheal disease in the United States. In addition, infants may experience multiple episodes of rotavirus diarrhea because the initial infection may provide only partial immunity. Infants documented to have had rotavirus gastroenteritis before receiving the full course of rotavirus vaccinations should still begin or complete the 2-dose or 3-dose schedule.

Rotavirus vaccine is contraindicated for infants who are known to have had a severe allergic reaction (anaphylactic) to a vaccine component or following a prior dose of vaccine. Latex rubber is contained in the RV1 oral applicator, so infants with a severe allergy to latex should not receive RV1. The RV5 dosing tube is latex free.

Chronic, wild-type rotavirus infection has been reported in infants with SCID, with resulting prolonged diarrhea or shedding of rotavirus [86]. In 2010, in response to reported cases of vaccine-acquired rotavirus infection in infants with SCID following rotavirus vaccine administration, the prescribing information and patient labeling for RV5 and RV1were revised to include SCID as a contraindication for administration of rotavirus vaccine [87–89]. The CDC updated the list of contraindications for rotavirus vaccine (RV1 and RV5) to include infants diagnosed with SCID [90].

Available data suggest that infants with a history of intussusception might be at higher risk for a repeat episode than are other infants. In 2011, the CDC updated the contraindications for rotavirus vaccine (RV1 and RV5) to include history of intussusception [91]. Previously, the CDC had considered history of intussusception a precaution but not a contraindication.

Precautions are those conditions that may increase the chance of a vaccine adverse reaction or reduce the efficacy of the vaccine. In general, infants with precautions to vaccination (see later discussion) should not receive rotavirus vaccine until the condition improves unless the benefit of vaccination outweighs the risk of an adverse reaction. However, clinicians may consider use of the vaccine on a case-by-case basis.

Children who are immunocompromised because of congenital immunodeficiency, or hematopoietic stem cell or solid organ transplantation sometimes experience severe, prolonged, and even fatal rotavirus gastroenteritis. However, no safety or efficacy data are available regarding administration of rotavirus vaccine to infants who are, or are potentially, immunocompromised due to either disease or drugs, except for those with SCID. Consultation with an immunologist or infectious disease specialist is advised for infants with known or suspected altered immunocompetence before rotavirus vaccine is administered [7]. General guidelines on immunodeficiency and use of live virus vaccines are available in the *2009 Red Book*, Table 1.14 [92].

HIV-infected infants acquire rotavirus at the same frequency as uninfected infants but may have more severe disease if there are concurrent nutritional deficiencies or opportunistic infections [93]. However, there are few data on the safety and immunogenicity of rotavirus vaccines in HIV-infected infants. In a study in South Africa, administration of three doses of RV1 were well tolerated by a group of infants with HIV and demonstrated immunogenicity comparable to HIV-uninfected infants living in the same country [94]. The vaccinated cohort had no evidence of increased rate of CD4 decline, which is relevant to the concern that vaccine administration could accelerate HIV disease progression. The ACIP and AAP recommend that rotavirus vaccine be administered during early infancy. In addition to the safety and immunogenicity data from South Africa, two considerations support vaccination of HIV-exposed and potentially infected infants. First, the HIV diagnosis might not be established in infants born to HIV-infected mothers by the time they reach the age of the first rotavirus vaccine dose and only 1.5% to 3% of HIV-exposed infants in the United States will eventually be determined to be HIV infected. Second, vaccine strains of rotavirus are considerably attenuated and exposure to an attenuated rotavirus is preferable to exposure to wild-type rotavirus.

Rotavirus vaccine should generally not be administered to infants with acute, moderate, or severe gastroenteritis, or other acute illness, until the condition improves. However, infants with mild acute gastroenteritis or other mild acute illness can be vaccinated, particularly if the delay in vaccination will delay the first dose of vaccine beyond 15 weeks 0 days of age.

No data are available on the immune response to rotavirus vaccine in infants who have recently received a blood product. In theory, infants who have recently received an antibody-containing blood product might have a reduced immunologic response to a dose of oral rotavirus vaccine. However, two or three doses of vaccine are administered in the full rotavirus vaccine series and no increased risk for adverse events is expected. ACIP now recommends that rotavirus vaccine may be administered at any time before, concurrent with, or after administration of any blood product.

Available data suggest that preterm infants (ie, infants born at less than 37-week gestation) are at increased risk for hospitalization from rotavirus during the first 1 to 2 years of life. In clinical trials, rotavirus vaccines seemed to be generally well tolerated in preterm infants, although a relatively small number of preterm

infants have been evaluated [95,96]. The AAP and ACIP consider the benefits of rotavirus vaccination of preterm infants to outweigh the risks of adverse events. The AAP and ACIP support vaccination of a preterm infant according to the same schedule and precautions as a full-term infant, provided the following conditions are met: the infant's chronologic age is at least 6 weeks, the infant is clinically stable, and the vaccine is administered at the time of discharge or after discharge from the neonatal intensive care unit or nursery. Although the lower level of maternal antibody to rotavirus in very preterm infants theoretically could increase the risk for adverse reactions from rotavirus vaccine, the AAP and ACIP believes the benefits of vaccinating the infant when age eligible, clinically stable, and no longer in the hospital outweigh the theoretic risks.

Vaccine strains of rotavirus are shed in the feces of vaccinated infants. So if an infant were to be vaccinated with rotavirus vaccine while still needing care in the hospital, a theoretic risk exists for vaccine virus being transmitted to infants in the same unit who are acutely ill and to preterm infants who are not age eligible for vaccine. The AAP and ACIP consider that, in usual circumstances, the risk from shedding outweighs the benefit of vaccinating an infant who will remain in the hospital and recommends that these infants not be vaccinated until they meet the conditions described above.

Although rotavirus is shed in the feces of vaccinated infants, transmission of vaccine virus has been documented in only a few cases [97,98]. Infants living in households with persons who have or are suspected of having an immunodeficiency disorder or impaired immune status can be vaccinated. The AAP and ACIP believe that the indirect protection of the immunocompromised household member provided by vaccinating the infant in the household, and thereby preventing wild-type rotavirus disease, outweighs the small risk for transmitting vaccine virus to the immunocompromised household member.

Infants living in households with pregnant women should be vaccinated according to the same schedule as infants in households without pregnant women. Because most women of childbearing age have preexisting immunity to rotavirus, the risk for infection by the attenuated vaccine virus is considered to be very low. Although transmission of vaccine virus has not been documented, it is prudent for all members of the household to use measures such as good hand washing after changing a diaper or otherwise coming in contact with the feces of the vaccinated infant.

IMPLEMENTATION OF THE ROTAVIRUS VACCINE PROGRAM IN THE UNITED STATES

Vaccine uptake

The uptake of rotavirus vaccine in the United States has been rapidly increasing. Estimates of rotavirus vaccination coverage were not available before 2009. Since 2009, rotavirus vaccine coverage has been included in the National Immunization Survey (NIS). NIS monitors vaccination coverage among children aged 19 to 35 months using a random-digit–dialed sample of telephone numbers of households. Coverage with a full series of rotavirus vaccine increased to 59.2% in 2010 from

43.9% in 2009 [99]. Within the 2010 sample, rotavirus vaccination coverage increased from 51.9% among children born during January to June 2007, to 69.8% among children born during January to June 2009. Coverage varied by race or ethnicity. Among black children, coverage with rotavirus vaccine was lower compared with white children. Coverage among children living below poverty level was lower than coverage among children living at or above poverty level. In 2010, coverage with rotavirus vaccine significantly increased in 40 states compared with 2009, and coverage ranged from 42.1% in Maine to 82.1% in Delaware.

Postlicensure safety-monitoring data from the United States

As the rotavirus vaccination program is implemented, it is important to continue to assess the safety profile of the vaccines to detect rare or unusual events as well as to continue to monitor the potential for intussusception following vaccination. Current rotavirus vaccines were not associated with intussusception in large prelicensure trials. However, recent postlicensure data from international settings suggest the possibility of a low-level elevated risk, primarily in the first week after the first vaccine dose [100,101]. Two recently reported studies have been conducted to examine the risk of intussusception following RV5 in United States infants. The first study, a cohort study that included infants 4 to 34 weeks of age enrolled in the Vaccine Safety Datalink, found the risk of intussusception in vaccinated infants was not increased compared with infants not receiving the rotavirus vaccine [102]. A second study identified and followed infants with a health insurance claim for RV5 during the first 2 years of RV5 availability. The relative risk of intussusception in 85,000 children receiving RV5 was 0.8 compared with a control group and the general safety evaluation did not identify any specific diagnoses or patterns of diagnoses that might suggest other safety concerns [103]. No published data is available on the risk of intussusception following RV1 in United States infants.

In 2010, researchers using novel laboratory techniques found that rotavirus vaccines contain DNA or DNA fragments from porcine circovirus (PCV) [104]. PCV is a virus that commonly infects pigs and has been detected in 5% of stool samples from United States adults, likely as a result of dietary consumption of pork products. PCV is not believed to cause illness among humans. Based on available evidence regarding a theoretical risk of PCV infection among humans and the observed benefits of rotavirus vaccines in preventing severe acute gastroenteritis among infants, the FDA expressed reassurance that the detection of DNA and DNA fragments from PCV in rotavirus vaccines was not likely to cause harm to humans and recommended continued use of the vaccines [105]. Subsequent investigation suggests that PCV DNA was introduced into both rotavirus vaccines through porcine-derived trypsin, a reagent used in the cell-culture growth process of vaccine production.

Rotavirus surveillance in the United States

Rotavirus gastroenteritis is not a reportable disease in the United States and testing for rotavirus infection is not often performed when a child seeks medical

care for acute gastroenteritis. Methods of surveillance for rotavirus disease at the national level include review of national hospital discharge databases for rotavirus-specific or rotavirus-compatible diagnoses, surveillance for rotavirus disease at three sites that participate in the New Vaccine Surveillance Network, and reports of rotavirus detection from a sentinel system of laboratories, the CDC National Respiratory and Enteric Virus Surveillance System (NREVSS). At the state and local levels, surveillance efforts at sentinel hospitals or by review of hospital discharge databases are used to monitor the impact of the vaccine program. Special studies, such as case-control studies and retrospective cohort studies, are used to measure the effectiveness of rotavirus vaccine under routine use in the United States. CDC has established a national strain surveillance system of sentinel laboratories to monitor circulating rotavirus strains before and after the introduction of rotavirus vaccine. This system is designed to detect new or unusual strains causing gastroenteritis that might not be prevented effectively by vaccination, which might affect the success of the vaccination program.

The effectiveness of rotavirus vaccination in the prevention of rotavirus disease

The effect of vaccine on rotavirus disease and epidemiology needs to be evaluated for several reasons [106]. First, routine immunization occurs in conditions different from the ideal clinical trial setting. Monitoring postlicensure effectiveness of rotavirus vaccine is important to assure that the expected benefits of rotavirus vaccine programs are achieved. Second, assessing protection in infants through the first and second years of life is crucial for the success of a rotavirus vaccination program because infancy is when most severe disease and mortality from rotavirus occur. Third, assessing whether vaccination results in herd immunity is important because a vaccine with indirect protection could provide substantially greater benefits than expected based on direct efficacy. Fourth, changes in the epidemiology of rotavirus disease may occur postlicensure, such as duration of protection, changes in age-specific and seasonal incidence of disease, and timing of epidemics. These changes may be important in immunization program planning. Fifth, surveillance is important to describe serotype distribution to identify newly emerging strains or changes in strain distribution because these may compromise the effectiveness of rotavirus vaccines.

Unlike efficacy studies that are done in a carefully controlled setting, studies on vaccine effectiveness compare the risks of disease outcomes in vaccinated or nonvaccinated populations in a real-life setting. Because the introduction of rotavirus vaccines into the national immunization program in 2006, seven studies have been conducted to assess vaccine effectiveness of RV5 in the United States [107–113]. A complete series of RV5 showed effectiveness ranging from 78% to 100% in preventing severe rotavirus disease (hospitalizations and/or emergency department visits) and 96% in preventing outpatient visits. There have no studies to evaluate the vaccine effectiveness of RV1 in the United States.

The real-world effectiveness data for RV5 are consistent with efficacy data obtained from clinical trials and strengthen the argument for the introduction

of rotavirus vaccination as an effective means for controlling severe childhood diarrhea. Additionally, no indication of waning vaccine-induced immunity has yet been observed during the rotavirus vaccine postlicensure period [108,114].

The impact of rotavirus vaccination on the health burden of rotavirus disease in the United States

Vaccine impact studies have demonstrated that the burden of rotavirus disease in the United States has been reduced significantly since the introduction of rotavirus vaccines. Since 2009, eight studies have assessed the impact of vaccination on use of health care resources in the United States [115–122]. These include studies using national surveillance data as well as studies evaluating the impact of introduction of vaccines in specific regions or hospitals. Three studies used prospective surveillance data [117,121,122]. The remaining studies were based on retrospective analyses of data sources that included hospital records, data from laboratory reports, and health-insurance claims databases. The impact of vaccination on rotavirus-related hospitalizations was the most frequently reported outcome. Evaluation of the prevaccination and postvaccination periods demonstrated that rotavirus vaccination significantly reduced the burden of rotavirus-related hospitalizations; ranging from 60% to 93% depending on vaccine coverage, age group, and rotavirus season studied.

Studies have also evaluated the impact of rotavirus vaccination on all-cause gastroenteritis or diarrhea-related hospitalizations, emergency visits, and outpatient or physician office visits. Reductions were seen in all these parameters. All-cause gastroenteritis or diarrhea-related hospitalizations declined 16% to 50% in the United States. Three studies also found significant reductions in emergency department and office visits after the introduction of rotavirus vaccine [109,115,118].

Studies comparing the numbers or proportions of rotavirus-positive tests before and after introduction of the rotavirus vaccination program are useful in evaluating vaccine impact. Sentinel laboratory surveillance data from the NREVSS demonstrated a decline in the numbers or proportions of rotavirus-positive tests in the United States during the first two seasons after the introduction of RV5 when compared with the period of 1991 to 2006 [123]. These reductions have sustained through the 2009 to 2010 rotavirus season [124].

Herd immunity after rotavirus vaccination

Herd immunity has been noted after routine rotavirus vaccination in the United States. Herd immunity occurs as a result of decreased transmission of rotavirus in the community and provides indirect protection to unvaccinated individuals. The rotavirus vaccination schedule should be completed by 32 weeks of age in the United States and there have been no catch-up vaccination programs in older children. Evidence suggestive of herd immunity after the widespread use of rotavirus vaccines comes, therefore, from older children who were unlikely to have been vaccinated. Postvaccination data in the early years after introduction of rotavirus vaccines show significant reductions in

rotavirus disease among members of age groups who were too old and/or too young to be vaccinated [115,116,118,119,121,123,125].

Changing epidemiology and seasonality of rotavirus disease after vaccine introduction in the United States

Surveillance and disease monitoring after vaccine introduction can supply information on changes in age-specific incidence of disease. Rotavirus vaccines have shown sustained efficacy for first 2 to 3 years of life in the United States and Europe with no changes in expected age-specific incidence of disease [74,81,126].

In the United States, there were alterations in the rotavirus season following the introduction of rotavirus vaccine. The CDC compared the onset, duration, and magnitude of the 2007 to 2008, 2008 to 2009, and 2009 to 2010 rotavirus seasons with median values for the previous 15 years. In 2007 to 2008, onset was delayed by 2 to 4 months, the duration was reduced by 12 weeks (14 vs 26 weeks), and the median was 11 weeks later than the median onset during 2000 to 2006. The rotavirus season was longer during 2008 to 2009 compared with 2007 to 2008 rotavirus activity [124].

Before introduction of vaccine, rotavirus had a predictable winter-spring seasonality and geographic pattern in the United States, with activity beginning in the west from December to January, extending across the country, and ending in the northeast from May to June [12]. Studies from the United States show a shift in the onset of the epidemic by 1 to 2 months has occurred after rotavirus vaccination; during the 2010 rotavirus season in the United States, rotavirus activity was below the epidemic threshold, a finding that had never occurred in the previous 19 years of rotavirus surveillance [124]. In addition, impressive alterations in the spatiotemporal spread of rotavirus disease in the United States occurred after vaccination [127].

Effect of vaccination on rotavirus strain circulation and emergence

Rotavirus vaccines need to provide cross-protection against multiple rotavirus serotypes because circulating strains vary and multiple strains can circulate within the same region at the same time. RV1 differs from G2P[4] strains by both G-type and P-type and genogroup. Although RV5 contains either the G or P antigen for all common strains, serotype-specific immune responses varied by strain with the lowest response against G3P[8] in the pivotal clinical trial [74]. Despite the potential for decreased efficacy, both RV5 and RV1 vaccines provided good cross-protection against the common circulating strains in trials in Europe and the United States [74,80]. In the Latin American trial, RV1 seemed to provide less protection against the fully heterotypic G2P[4] rotavirus strains (vaccine efficacy was 44%). However, it is important to note that the G2P[4] strain was not circulating in Latin America during the study period; thus the study was not powered to conclusively assess protection against this strain [80]. However, in a 2-year efficacy study conducted in six European countries, RV1 provided 85% protection against severe rotavirus gastroenteritis caused by G2P[4] strains [81]. In more recently published trials from

Asia and Africa, both vaccines had similar efficacy against a wide range of strains circulating during the study period [77,78].

Both RV5 and RV1 vaccines provided good cross-protection against the common circulating strains in postlicensure vaccine studies. In two vaccine effectiveness studies from Brazil that were conducted during 2 years when G2P[4] strain circulation predominated, RV1 effectiveness ranged from 75% to 81% against severe rotavirus disease caused by this strain during the first year of life [128,129]. In a similar case-control study from Australia, during an outbreak of G2P[4]-related gastroenteritis among an indigenous population, effectiveness of RV1 was 86% [130]. A postlicensure study from the United States reported high effectiveness of RV5 against severe disease due to G3P [8] strains [131]. In a case-control study from Mexico, after the emergence of a novel G9P[4] strain, effectiveness of RV1 against severe rotavirus gastroenteritis was 94% [132].

Three nationwide longitudinal strain surveillance studies address the issue of strain ecology before and after routine childhood vaccination. A nationwide predominance of G2P[4] strains was noticed in Brazil in the first 2 years after introduction of RV1 [133]. In the United States, a higher prevalence of G3P[8] strains occurred in some cities after introduction of RV5 [134]. In Australia individual states used either RV1 or RV5 exclusively. A higher prevalence of G2P[4] strains was noted in states that were exclusively using RV1 compared with states using RV5 and the RV5 states had a higher prevalence of G3P[8] strains than states using RV1 [135].

Both effectiveness studies and clinical trial efficacy data suggest that a natural shift in strain, unrelated to vaccination, is the most plausible explanation for the observed short-term changes postvaccination. However, the studies showing shifts in strain predominance highlight the need for robust longitudinal surveillance and epidemiologic studies to better assess the long-term effect of rotavirus vaccination on strain ecology. These longer term studies could help assess whether the continued high level of immunity to vaccine serotypes eventually leads to evolution of strains that evade vaccine immunity.

SUMMARY

Rotavirus infection is the most common cause of severe diarrhea disease in infants and young children worldwide and continues to have a major global impact on childhood morbidity and mortality. Vaccination is the only control measure likely to have a significant impact on the incidence of severe dehydrating rotavirus disease.

Rotavirus vaccines have reduced the burden of rotavirus disease in the United States. Long-term monitoring will need to continue to assess the effects of rotavirus immunization programs and epidemiologic strain surveillance is necessary to determine whether changes in strain ecology will affect the rotavirus vaccine effectiveness and whether rotaviruses with the ability to evade vaccine immunity emerge.

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