Rotavirus disease and its prevention

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Purpose of review

Rotavirus infection is the foremost cause of severe gastroenteritis of young children worldwide. Efforts to develop safe and effective vaccines resulted in licensure of the first live oral vaccine, tetravalent, rhesus-based rotavirus vaccine (RRV-TV), which was incorporated into the US immunization schedule in 1998. Less than 1 year later, however, the vaccine was withdrawn when reports of cases of intussusception were linked to recent vaccination. This setback created significant hurdles as well as new opportunities for the development of the next generation of rotavirus vaccines. This review focuses on new information related to the clinical presentation and pathogenesis of rotavirus infection, the associated global disease burden, and the ongoing efforts to develop and introduce the next generation of rotavirus vaccines for widespread use.

Recent findings

Recent studies have confirmed that rotavirus infection is not confined only to the gut but can have extraintestinal manifestations, including viremia. Estimates of the global disease burden of rotavirus diarrhea have been refined and suggest that mortality has not declined, and that among hospitalized cases of diarrhea, the fraction associated with rotavirus has increased in many countries. In the United States, the estimated number of hospitalizations attributed to rotavirus has increased. Debate continues about the magnitude of the attributable risk of the association between RRV-TV and intussusception. Several new rotavirus vaccines are in late stages of development. One vaccine was licensed in Mexico in 2004 and a second has completed clinical trials in the United States and Europe and may be licensed within 2 to 3 years.

Summary

The tremendous burden of rotavirus diarrhea among children all over the world continues to drive the remarkable pace of vaccine development and the variety of approaches to creating rotavirus vaccines.

Keywords

rotavirus, vaccine, disease burden, intussusception

Curr Opin Gastroenterol 21:26–31. © 2004 Lippincott Williams & Wilkins.

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Current Opinion in Gastroenterology 2005, 21:26–31

Abbreviations

ICD	International Classification of Disease
RRV-TV	rhesus rotavirus tetravalent
VP	viral protein

0267-1379

Introduction

Rotavirus infection remains the most common cause of severe, dehydrating gastroenteritis among children worldwide. Almost every child in the world, in both developed and developing countries, will be infected with rotavirus in the first 5 years of life. Globally, approximately 500,000 children die every year from rotavirus gastroenteritis, with the vast majority of these deaths occurring in the poorest countries. In developed nations, rotavirus infection rarely results in death but remains the most common cause of hospitalizations for acute gastroenteritis in children and leads to major medical and societal costs.

In 1998, the first vaccine against rotavirus, tetravalent, rhesus-based rotavirus vaccine (RRV-TV), was approved by the US Food and Drug Administration and recommended for inclusion in the 1999 US schedule for routine childhood immunizations. In July 1999, this vaccine was withdrawn in the United States following reports of cases of intussusception among recently vaccinated children.

Since 1999, several important developments have improved our understanding of the natural history of rotavirus infection and of intussusception, as well as the disease burden of rotavirus-associated gastroenteritis. Moreover, efforts to develop other vaccines have been stimulated by the withdrawal of RRV-TV, and at least two vaccines are now in the final stages of clinical trials.

Pathogenesis

Rotavirus infects the mature absorptive enterocytes in the proximal two thirds of the ileum, and is thought to cause diarrhea by several mechanisms. First, virus-associated cell death, with subsequent sloughing of the villus epithelium and proliferation of the secretory crypt cells, results in reduced absorptive capacity of the gut, leading to fluid and electrolyte loss into the lumen. Epithelial

Table 1. Rotavirus vaccines

	Concept	Status
Reassortant vaccines		
Rotateq	Pentavalent bovine–human reassortants with G1, G2, G3, G4, P[1a] types	Phase III
Rotashield	Tetravalent rhesus–human reassortants with G1, G2, G3, G4 types	Licensed in United States (1998) but withdrawn from market in 1999
Human-bovine (United Kingdom)	Quadrivalent bovine–human reassortants with G1, G2, G3, G4 types	Phase II
Monovalent vaccines		
Rotarix	Human strain P[8]G1	Licensed in Mexico, Dominican Republic, and Kuwait; phase III elsewhere
LLR	Lamb strain P[12]G10	Licensed in China (2001)
Neonatal strain vaccines		
RV3	Neonatal strain P[6]G3	Phase II
I-321	Neonatal strain P[11]G9	Phase I

Modified from Glass *et al.* [51].

dysfunction also leads to reduced expression of certain digestive enzymes such as sucrase and isomaltase, and the osmotic pull of accumulated sugars in the small intestine further exacerbates fluid loss. In addition, a nonstructural protein (NSP4) expressed by rotavirus is thought to trigger an intracellular Ca^{++}-dependent signaling pathway, which leads to an increased membrane permeability to electrolytes. Lastly, rotavirus seems to activate the secretormotor neurons of the enteric nervous system that stimulate secretion of fluids and solutes, an effect recently found to be mediated via vasoactive intestinal peptide [1].

Rotavirus infection has traditionally been thought to be limited to the gastrointestinal tract, but several recent case reports have challenged this paradigm. Evidence of rotavirus RNA has been found by polymerase chain reaction in the cerebrospinal fluid of rotavirus-infected children who have seizures [2] and in liver and kidney sections of immunocompromised children [3]. A recent study used reverse transcriptase polymerase chain reaction, immunohistochemistry, and in situ hybridization to detect rotavirus in a variety of internal organs of two children who died with severe rotavirus-associated vomiting and diarrhea and who also had neurologic disease [4•]. One elegant study used a commercial enzyme immunoassay test designed to detect rotavirus antigen in stool but applied it to serum and found that 22 of 33 immunocompetent children with confirmed rotavirus gastroenteritis had rotavirus antigenemia, providing evidence that rotavirus may commonly escape the gastrointestinal tract [5••]. The clinical significance of these findings remains unclear but is under active investigation.

Rotavirus disease burden

The Institute of Medicine estimated in 1985 that rotavirus is associated with 9 million cases of severe diarrhea globally and 870,000 deaths [6]. In the past two decades, however, successive studies have documented a sustained decrease in global mortality due to diarrheal illness. However, the incidence of diarrheal illness has not declined appreciably in the same time frame [7•]. The reasons for this decline in mortality and not incidence remain poorly delineated although increased measles vaccination and better access to oral rehydration therapy cannot be ruled out. Estimates of mortality caused by rotavirus diarrhea appear to have declined along with those of overall diarrheal mortality; the most recent global estimate is of 352,000 to 592,000 deaths (median 440 000) attributable to rotavirus [8•]. However, this recent estimate relies on multiplying overall diarrheal mortality data from a variety of different countries by the proportion of hospitalizations for severe diarrhea attributed to rotavirus reported in studies in the 1990s, which in developing countries averages at about 22 to 25%. In the past few years, evidence suggests that the proportion of hospitalizations attributable to rotavirus in poorer countries may actually be much higher [9•,10,11], and therefore that the estimated number of deaths caused by rotavirus infection may have been substantially underestimated.

In developed countries, studies have focused on assessing the burden of hospitalizations due to rotavirus. The risk of hospitalization with rotavirus diarrhea among children under 5 years of age in the United States has been estimated to be 1 in 73, or about 55,000 hospitalizations annually in studies reliant upon hospital discharge International Classification of Disease (ICD) codes for diarrhea [12]. Since 1993, rotavirus-specific ICD 9 and ICD 10 codes have been introduced, but since rotavirus is not routinely detected, these codes are underused and will severely underestimate the number of hospitalizations attributable to rotavirus diarrhea. A study among hospitalized children in New York State in the period 1993 to 2000 found that 8.7% of all diarrhea-associated illnesses were coded for rotavirus; however, 54% of hospitals never used the new code, while 12% of hospitals coded rotavirus in more than 30% of diarrheal episodes [13•]. Specific rotavirus codes, however, were found in this study to be highly predictive of rotavirus disease; 94% of codes were associated with laboratory confirmation of rotavirus infection. The same study also found that chil-

dren of white race and those with private insurance were more likely to be coded for rotavirus, pointing to differences in the diagnosis and management of diarrhea among children from different socioeconomic backgrounds. In 2000, an active surveillance system for rotavirus in three pediatric hospitals in different states that used a broad case definition to enroll and subsequently test children for rotavirus found that 21 (9%) of 234 rotavirus-positive children initially presented not with diarrhea, but with only fever (3%), only vomiting (2%), or both fever and vomiting (4%) [14]. These findings further suggest that analyses of ICD codes specific for diarrhea will underestimate rotavirus hospitalizations. A further analysis of data at one of these hospital sites combined discharge data and laboratory results from active rotavirus surveillance to validate the ICD-9 codes and has confirmed the high specificity of diagnosis of discharges using the rotavirus ICD code [15••]. The authors estimated that as many 80,000 hospitalizations annually may be attributable to rotavirus in the United States, corresponding to 1 in 43 children under 5 years hospitalized for rotavirus diarrhea. This is closer to estimates in other developed countries, which include 1 in 38 children less than 5 years of age in the United Kingdom [16], 1 in 33 in Finland [17], and 1 in 44 recently reported in Spain [18].

Rationale for vaccination

Initial observations of the natural history of rotavirus infection noted that a child's first infection with rotavirus occurs early in life, is usually the most clinically severe, and results in immunity against subsequent illness. Prospective studies subsequently showed that this protective immunity against severe disease is boosted by subsequent infections. The rationale, therefore, for vaccination is that administration of an attenuated rotavirus strain early in life will mimic the initial natural infection and induce immunity. An additional reason for this vaccine approach is that while oral rehydration therapy may have been effective in prevention of severe dehydration and death in poorer countries [7•], it has had limited impact on diarrheal hospitalizations in the United States. Lastly, the cost of rotavirus disease in the United States, including both medical costs and societal costs such as loss of earnings due to caring for child, has been estimated to be more than $1 billion annually [19].

Rotavirus strains

The rotavirus virion consists of double-stranded RNA surrounded by a triple-layered capsid. The genome is divided into 11 segments, a characteristic that allows reassortment during natural co-infection to yield new and unusual strains and that is used to advantage in the development of vaccines. The outer capsid shell comprises two viral proteins (VPs), the G-protein (or VP7) and the P-protein (or VP4), which both induce neutralizing antibodies in natural infection and are the basis for the serotype classification of rotaviruses. At least fourteen different G-serotypes and 11 different P-serotypes have been described, and although in principle these serotypes could assort into a large number of combinations, only four strains predominate: P[8]G1, P[8]G3, P[8]G4, and P[4]G2 [20]. Recent studies, however, have found a variety of novel G- and P-serotypes combinations that contribute very substantially to rotavirus strain diversity [21]. For example, G9 rotaviruses in two strains, P[6]G9 and P[8]G9, have been reported with increased frequency around the world [22,23,24•,25•]and indicate that G9 should be considered the fifth most important rotavirus serotype. In addition, several serotypes that are uncommon globally have been identified as regionally important, such as P[8]G5 in Brazil [26] and P[6]G8 in Malawi [27]. Frequent natural reassortment between animal and human rotaviruses is suggested by the detection of rotaviruses in humans that have close genetic relationships to both animal and human rotaviruses. Examples include serotype G6, G8, G9, and G10 rotaviruses with one to several gene segments each derived from bovine and human strains [28,29] and G5 human rotaviruses with genes from porcine and human strains [30•]. Other uncommon human rotaviruses that are very closely related in all 11 gene segments to animal rotavirus strains appear to represent examples of interspecies infections of children by animal rotaviruses [31•,32].

Rotavirus vaccines

Early efforts at vaccine development focused on a "Jennerian" approach using attenuated live bovine and simian strains to vaccinate children. These monovalent vaccines relied on heterotypic immunity to protect children from infection with human rotaviruses of different serotypes. However, the efficacy of these vaccines varied widely in trials around the world, and some evidence suggested that homotypic immunity provided better protection against rotavirus illness. This led to the development of multivalent human–animal reassortant vaccines.

Tetravalent rhesus–based rotavirus vaccine and intussusception

The first licensed rotavirus vaccine, RRV-TV (Rotashield, Wyeth Laboratories), was composed of the parent rhesus strain with G3 specificity and three human–rhesus reassortants each with the VP7 capsid gene of either G1, G2, or G4 specificity, and 10 other rhesus genes. Trials of this vaccine demonstrated efficacies of up to 91% against severe rotavirus diarrhea.

Between September 1998 and July 1999, more than 1 million doses of RRV-TV were administered to approximately 500,000 children—13.4% of all eligible children [33]. In July 1999, the vaccine was withdrawn after 15 cases of intussusception among recent vaccinees had been reported to the Vaccine Adverse Event Reporting System. Subsequent epidemiologic studies confirmed an association between receipt of the vaccine and the development of intussusception during the 2 weeks after

the first and second doses of vaccine. The initial risk attributed to the vaccine was one case of intussusception for every 5000 to 11,000 children vaccinated [34]. Subsequent ecological studies have estimated a lower risk associated with the vaccine and raised the possibility that the small increased risk of intussusception in children aged 2 to 5 months may in fact be compensated by a decrease in risk of intussusception in children aged 6 to 11 months [35]. However, controversy continues over the decision to withdraw the recommendation for RRV-TV [36••,37••]. It remains unclear whether natural rotavirus infection causes intussusception; early reports documented rotavirus in children hospitalized with intussusception, but these studies were uncontrolled, and rotavirus can be a common cause of nosocomial infection. In New York state, cases of intussusception occurred year-round whereas rotavirus hospitalizations had a distinct peak confined to the 3 months of winter [38]. A recent case-control study, however, has found evidence of increased distal wall thickness and lymphadenopathy by use of ultrasound in 13 children with rotavirus disease, establishing a possible biologic mechanism by which natural rotavirus infection may cause intussusception [39•].

New-generation live oral rotavirus vaccines

Two vaccines have been or will soon be licensed and may be available in the next 2 to 3 years (Table 1). Each vaccine has been tested in very large phase III clinical trials (more than 60,000 children) that are designed to assess safety with respect to intussusception.

One vaccine candidate is a pentavalent vaccine (Rotateq, Merck) composed of five human–bovine reassortant strains containing single-gene reassortants expressing human VP7 genes with G1, G2, G3, G4 specificity and one strain with a human VP4 gene with P1 specificity, all in the parent bovine rotavirus strain. A trial of a prototype quadrivalent vaccine found the vaccine to be 75% effective at preventing all episodes of rotavirus gastroenteritis and 100% at preventing severe disease [40]. Moreover, the vaccine was well tolerated by infants, with no increase in fever, vomiting, diarrhea, or irritability in recipients of vaccine compared with placebo. This contrasts with RRV-TV, a more reactogenic vaccine that provoked side effects, including fever, among vaccinees [41].

In addition, a live attenuated, monovalent P[8]G1 human rotavirus strain (Rotarix, GSK Biologicals, Rixensart, Belgium) has been developed and recently licensed in Mexico, the Dominican Republic, and Kuwait. Rationale for development of this vaccine include the observation that rotaviruses of G1 or P [8] serotypes account for more than 75% of rotavirus infections worldwide and, compared with multivalent reassortant vaccines, vaccine manufacture of a monovalent, human strain may be simpler and less expensive. This vaccine strain has been found to be virtually nonreactogenic and highly immunogenic when administered orally at a high titer [42]. A trial of more than 6000 children in Mexico, Brazil, and Venezuela demonstrated an efficacy of more than 70% against severe rotavirus diarrhea and protected not only against rotavirus disease caused by the homologous serotype (G1) but also against a single heterologous serotype (G9). Protection against the full range of rotavirus strains in circulation remains to be demonstrated [43].

At least two other vaccines have been tested in phase I or II clinical trials. One is a quadrivalent human–bovine vaccine consisting of four strains derived from the reassortment of four human rotaviruses (G-types 1, 2, 3, and 4) with a bovine rotavirus. Small clinical trials have indicated that this vaccine is well tolerated and immunogenic [44] although induced neutralizing antibodies seem to be directed more toward the bovine strain than toward the human G serotypes [45].

A further approach to vaccine development exploits the fact that some strains of rotavirus seem to cause asymptomatic infection in neonates, and this infection may lead to later protection against subsequent rotavirus illness. A recent study followed up 72 children for 2 years and found the 44 children infected as neonates with a P[11]G10 rotavirus strain were much less likely to develop diarrhea than those who were not (2.3% compared with 39.3%) [46•]. This strain is currently being tested as a live-vaccine candidate. A second neonatal strain, P[6]G3, has been tested in a limited phase II clinical trial, in which children were vaccinated at 3, 5, and 7 months of age and were partially protected against rotavirus disease in the subsequent winter epidemic (efficacy 54%) [47].

Experimental vaccines

The association of intussusception with live strains administered orally has provided a stimulus to develop nonreplicating vaccines based on either inactivated strains or expressed proteins. The relative role of levels of serum antibody and gut antibody in protection against rotavirus infection remains unclear [48]; however, animal models have shown that injected formalin-inactivated vaccines [49] and intranasal delivery of rotavirus proteins [50] will result in some protection against oral rotavirus challenge.

Conclusion

Rotavirus remains a major cause of morbidity and mortality worldwide and the need for effective, safe vaccines remains strong. Debate continues over the association of Rotashield with intussusception and over the ethical issues raised by the withdrawal of a vaccine that could save hundreds of thousands of lives globally because of a small risk found in US children. However, the withdrawal of Rotashield has spurred the competition to develop new vaccines that have proven effective in large

trials, and the first of these (Rotarix) is newly licensed, although not in the United States. An additional vaccine (Rotateq) could be licensed in the United States in 2006 or 2007.

The World Health Organisation and the Global Initiative for Vaccines and Immunization—an alliance of interested partners in the private and public sector—have made the accelerated development and introduction of rotavirus vaccines a priority [51]. Now, with a variety of different approaches to manufacture and marketing, a vaccine against rotavirus disease both in developed and developing countries should become a reality in the next few years.

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