Rotavirus Vaccines: Current Controversies and Future Directions

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Rotaviruses are the most important cause of pediatric gastroenteritis worldwide. In August 1998, a new rotavirus vaccine was licensed for general use in the United States. However, 14 months later, the vaccine was withdrawn from the market because of serious gastrointestinal side effects. This paper discusses the need for a rotavirus vaccine, the development of the first rotavirus vaccine, and the safety issues that led to the recall of that vaccine.

Introduction

The first licensed rotavirus vaccine had a short and stormy life. On August 31, 1998, the US Food and Drug Administration licensed it for general use in infants. On July 16, 1999, the Centers for Disease Control and Prevention (CDC) recommended suspension of all rotavirus vaccination because of possible rare but serious vaccine-related side effects. In October 1999, production of the recently licensed vaccine was discontinued, and the CDC revoked its approval of the vaccine after establishing that the vaccine did cause severe gastrointestinal side effects.

The future of rotavirus immunization is now unclear, but the need to prevent rotavirus infection remains. This paper discusses the burden of rotavirus-related disease, the development and licensure of the first rotavirus vaccine, and the recently recognized adverse events associated with that vaccine. It also describes second-generation rotavirus vaccines now being developed.

Rotavirus Disease

Rotavirus is the most common cause of serious gastroenteritis worldwide [1–3]. In both developed and developing nations, it infects almost all children by 3 years of age. In the developing world, it is a major cause of childhood death, killing 480,000 to 640,000 children each year [2,3]. Rotavirus is also a serious pediatric pathogen in developed countries [1,4]. In the United States, rotavirus infections lead to approximately 500,000 outpatient visits; 160,000 emergency department evaluations; and 50,000 hospitalizations each year [1]. Recent reports estimate that one of every 70 infants born in the United States will require hospitalization for rotavirus infection during the first year of life [1,5•]. It is also estimated that 20 to 40 US children die each year of complications of rotavirus infection. In the United States alone, the combined direct health care and indirect societal costs related to rotavirus disease approach one billion dollars annually [6,7••].

Rotavirus disease is most severe in children 3 to 24 months of age, but up to 25% of severe cases of rotavirus gastroenteritis occur in children older than 2 years of age [8]. Of note, infants younger than 3 months of age are relatively protected from clinically significant disease. Maternally derived transplacental and colostral antibodies may lessen the likelihood and severity of infection.

Infants and young children infected with rotavirus typically develop sudden-onset fever, vomiting, and diarrhea [9–11]. Rotavirus infections are more likely than infections with other gastrointestinal pathogens to cause dehydration because of their unique propensity to cause vomiting. In the winter months, more than half of all pediatric patients hospitalized with diarrhea and dehydration are found to be infected with rotavirus [6].

Immunity After Natural Infection

A major challenge to the development of a successful rotavirus vaccine is that immunity induced by natural infection is incomplete and short-lived [12]. Although natural infection provides significant protection against reinfection with rotavirus of the same serotype, symptomatic reinfections do occur [13–15]. Almost 10% of young children have repeated rotavirus infections within the same season [16].

Two observations may explain the short-lived immunity induced by natural rotavirus infection. First, the quantities of rotavirus-specific secretory IgA (sIGA) detected at the intestinal mucosal surface decrease quickly after natural infection. Fecal rotavirus-specific IgA often becomes undetectable within 1 year of infection [16,17]. Although a reproducible immunologic correlate of protection remains elusive, data from animal and human studies suggest that the quantity of rotavirus-specific sIgA at the intestinal sur-

face may determine protection against reinfection [12,18]. Second, the incubation period of rotavirus is short: approximately 1 to 3 days. The process of activation and differentiation of virus-specific memory B or T cells into effector antibody-secreting B or cytotoxic T lymphocytes requires about 3 to 5 days. Therefore, the presence of intestinal rotavirus-specific memory B or T cells is insufficient to prevent reinfection. However, intestinal effector B and T cells derived from preexisting memory cells may contribute to the resolution of acute reinfection. This hypothesis is consistent with the observations that repeated rotavirus infections are usually less severe than primary infections [14] and that previously infected experimental animals shed less virus upon reinfection than naive animals do, even in the absence of intestinal rotavirus-specific sIgA [19].

Development of the First Live, Attenuated Rotavirus Vaccine

A basic review of rotavirus structure is necessary to an understanding of the development of the current vaccine. Rotavirus is a nonenveloped virus with a segmented, double-stranded RNA genome [20]. Each of the 11 gene segments encodes a single viral protein. Rotavirus particles are composed of three concentric viral capsids. Two viral proteins, viral protein 4 and viral protein 7, make up the outermost shell. These proteins have been shown to independently induce antibodies that neutralize virus and, therefore, determine viral serotype. Viral protein 7 is a glycoprotein (often referred to as the *G protein*) and comprises more than 90% of the outer shell. It has been considered the dominant neutralizing antigen. Thus, rotavirus serotypes are often referred to by G type [20]. Initial studies showed that most cases of rotavirus disease in the United States were caused by rotavirus serotypes G1 to G4. However, more recent studies in the United States and worldwide have shown that serotypes G5, G9, and G10 may also be important causes of human disease [21–23].

The first licensed rotavirus vaccine (RotaShield, Wyeth-Lederle, Philadelphia, PA) is a live, attenuated, quadrivalent vaccine that contains human X simian reassortant viruses [24]. The backbone of this vaccine is the simian rotavirus strain RRV, a G3 rotavirus. This virus was initially chosen as a vaccine candidate because it seemed to be naturally attenuated (causing little or no gastrointestinal disease in humans) but capable of inducing high titers of antirotavirus antibodies. However, in clinical trials, it induced inconsistent protection [25,26]. Investigators attempted to enhance the protective efficacy of this virus by generating reassortant viruses—viruses that were essentially simian rotaviruses (and, thus, naturally attenuated) but expressed the single human viral protein 7 on their surfaces. RotaShield contains three reassortant viruses (to induce protection against G1, G2, and G4 rotaviruses) and native RRV (to induce protection against G3 rotaviruses).

Clinical trials in the United States showed that a three-dose series of RotaShield induced 49% to 52% protection against all rotavirus disease [27,28]. However, when only severe or clinically significant rotavirus gastroenteritis was considered, vaccine efficacy was 70% to 80%. Although vaccine-induced immunity, like natural immunity, was incomplete, widespread rotavirus immunization was expected to markedly reduce the burden of rotavirus-related disease [6,7••,29]. A recently published cost-effectiveness analysis [7••] suggested that routine, universal immunization of US infants would prevent approximately one million cases of diarrhea; 227,000 outpatient visits; 95,000 emergency department visits; and 40,000 hospitalizations.

At the time of vaccine licensure, no long-term or serious adverse events had been associated with RotaShield use. However, some systemic side effects had been noted. Approximately 20% of infants developed a temperature greater than 38° C after receiving a first dose of RotaShield [28,30]. One percent to 2% of infants developed temperatures of 39° C or more. In addition, some studies reported that vaccine recipients were more likely than controls to experience irritability and anorexia. In a single study in Finland, diarrhea occurred in 3% of vaccine recipients and 1% of placebo recipients [30].

Vaccine-Related Intussusception

Approximately 11 months after RotaShield was licensed for general use in the United States, concern about possible vaccine-related intussusception led the CDC and the American Academy of Pediatrics to recommend suspension of all rotavirus immunization [31••,32]. Preliminary data from several postlicensure studies have recently become available and have established that RotaShield does cause intussusception. The available data are discussed below.

In phase II and phase III clinical trials, five cases of intussusception occurred among 10,054 recipients of rhesus rotavirus vaccine. In contrast, only one case of intussusception was seen in 4633 placebo recipients [33•]. However, intussusception is the most common cause of intestinal obstruction in infancy, affecting approximately one of every 2000 infants [34]. In addition, only two cases of intussusception occurred among the 8240 persons who received the final formulation of the rotavirus vaccine [33•]. Thus, it was not apparent that the rate of intussusception in vaccine recipients was greater than the rate seen in nonvaccinated infants. Nonetheless, on the package insert for RotaShield, intussusception was listed as a possible adverse event. In addition, a postlicensure study was initiated to gather additional data on possible rare vaccine-related side effects, including intussusception.

Early in July 1999, public health officials were alerted by the Vaccine Adverse Event Reporting System (VAERS) to the fact that 15 recently immunized infants had developed intussusception. All cases were radiographically confirmed, and eight infants had required surgical reduction. On the

Table 1. The relation of intussusception and rotavirus vaccine in infants cared for by the Northern California Kaiser Permanente Health System, December 1, 1998, to August 31, 1999

RotaShield* administration	Person-years	Cases of intussusception, *n*	Rate of intussusception per 100,000 per year, *n*	Age-adjusted relative risk (95% CI)	*P* value
Never	17,140	8	47	–	–
Ever	4764	6	126	1.7 (0.6–5.0)	0.327
<3 weeks earlier	1263	3	238	3.4 (0.9–13.1)	0.080
<1 week earlier	421	2	475	7.1 (1.5– 34.6)	0.015
≥3 weeks earlier	3502	3	86	1.2 (0.3–4.5)	0.815

*Wyeth-Lederle, Philadelphia, PA.

basis of estimates of the number of infants receiving RotaShield, CDC investigators calculated that 14 to 16 cases of intussusception could be expected in recently immunized infants as a result of chance alone [31••]. Further investigation of the cases, however, showed three troubling trends. First, 13 infants had developed intussusception after receiving a first dose of RotaShield. Second, 12 infants had become ill within 1 week of vaccination. And third, the cases of intussusception seen after rotavirus immunization tended to occur in young infants. The median age of the infants reported to VAERS was 3 months, whereas the median age at intussusception in the United States before the introduction of rotavirus vaccination was 7 months [33•]. Because of the recognized risk for underreporting of adverse events with a passive surveillance system such as VAERS [35], rotavirus immunization was suspended on July 16, 1999, while public health officials sought additional information.

Investigators turned to available data compiled within the Northern California Kaiser Permanente Health System, the site commissioned to perform postlicensure vaccine evaluation. Recent analysis of this data showed that approximately 12,000 infants had each received at least one dose of rotavirus vaccine [36]. Since the introduction of RotaShield, six vaccinated infants and eight unvaccinated infants had developed intussusception. Further analysis revealed an increased rate of intussusception in vaccinated infants (126 per 100,000 infant-years) compared with unvaccinated infants (47 per 100,000 infant-years) (Table 1). The difference was not statistically significant. However, when the relationship between intussusception and time of vaccination was examined, recently vaccinated infants were found to have a significantly increased risk for intussusception.

In July 1999, the CDC initiated additional epidemiologic studies. Investigators from the National Immunization Program reviewed hospital records from 19 states to identify all cases of intussusception in vaccinated and unvaccinated infants. Using both case-series and case-control analyses, investigators found an overall 60% to 80% increased risk for intussusception in vaccinated compared with unvaccinated infants [36]. The highest risk for intussusception was noted 3 to 7 days after administration of the first dose of vaccine and did not vary by age at vaccination (Table 2). An intermediate risk for intussusception was noted after the second dose of vaccine.

Table 2. Relative risk for intussusception by age within 3 to 7 days after the first dose of rotavirus vaccine: results of a multistate investigation

Age, mo	Relative risk in case-series analysis	Relative risk in case-control analysis
1–2	28	27
3–5	21	25
6–8	31	16

Several hypotheses may explain the mechanism by which RotaShield may induce intussusception. First, viral replication may induce intestinal lymphoid hyperplasia that, in turn, may lead to intussusception. Previous studies have shown that RRV X human reassortant viruses replicate in vivo [37,38]. After primary vaccination, up to 50% of infants immunized with RotaShield will shed rotavirus. However, the absence of a clear and consistent association between natural rotavirus infection and intussusception challenges this hypothesis. Two studies have shown that the rate of intussusception is relatively constant throughout the year [33•,39]. No seasonal variation in the incidence of intussusception was seen in either study, whereas the incidence of rotavirus infection peaked in the winter months (Fig. 1). In addition, both retrospective and prospective surveys have found no etiologic association between rotavirus infection and intussusception [39,40]. However, in an uncontrolled study, Konno *et al.* [41,42] detected rotavirus particles by electron microscopy in fecal samples from 11 of 30 infants with intussusception.

One possible unifying concept is that natural rotavirus infection may be one of many infectious causes of intussusception. The relatively constant rate of intussusception seen throughout the year may be attributed to the overlapping incidence of infection with a variety of gastrointestinal pathogens, each with its own typical seasonal distribution and propensity to cause intussusception.

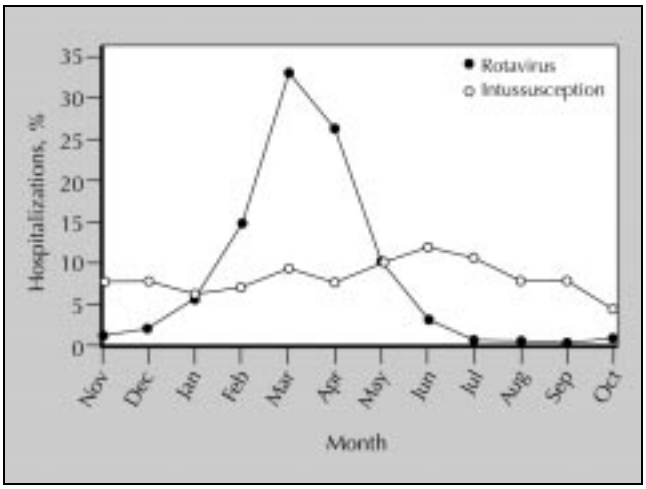

Figure 1. Seasonal distribution of hospitalizations for rotavirus diarrhea and for intussusception among children ages 3 to 23 months in New York State, 1993 to 1995.

Although rotavirus is the most common cause of severe gastroenteritis in children, it may not be the most common infectious cause of intussusception. Therefore, the rate of intussusception may not increase dramatically above baseline rates during rotavirus season. However, because infants with possible vaccine-associated intussusception are younger than those with non–vaccine-associated disease, the putative association between rotavirus immunization and intussusception may be more apparent than the association between natural rotavirus infection and intussusception. Alternatively, there may be a strain-specific propensity to cause intussusception. Infection with human rotavirus may not induce intussusception, but replication of RRV in the human intestinal tract may increase the risk for intussusception.

Another hypothesis that may explain the apparent association between RotaShield use and intussusception is that a nonviral component of the vaccine may stimulate lymphoid hyperplasia or abnormal bowel motility. In addition to including the four strains of rotavirus, RotaShield includes citrate-bicarbonate buffer and trace amounts of fetal bovine serum, neomycin sulfate, and amphotericin B. However, the placebo used in clinical trials was derived from uninfected tissue culture that was diluted in citrate-bicarbonate buffer. Because the nonviral components of the vaccine and the placebo used in clinical trials were identical, the observed trend toward a higher rate of intussusception in vaccine recipients compared with placebo recipients during clinical trials argues against this theory. Finally, unidentified host factors may contribute to the development of intussusception after RotaShield immunization.

Second-Generation Vaccines

Recognizing the global need for a rotavirus vaccine, investigators are now developing second-generation rotavirus vaccines. Several goals for these vaccines can be identified. First, compared with RotaShield, a second-generation rotavirus vaccine should have an enhanced safety profile and fewer gastrointestinal and systemic side effects. Second, the potential global efficacy of a rotavirus vaccine would be improved if it included viral serotypes that predominate in the developing world. Lastly, investigators wish to enhance the protection induced against mild to moderate disease.

Currently, two multivalent human X bovine reassortant candidate vaccines are being evaluated. Preliminary studies have shown that these vaccines are less reactogenic than RotaShield, inducing fewer systemic and no gastrointestinal side effects [43,44]. Efficacy studies are ongoing. In addition, several attenuated human rotavirus vaccine candidates are under evaluation [45,46].

Although the future of rotavirus vaccines remains unclear, development and licensure of a safe and effective rotavirus vaccine would markedly improve the health of infants in both the developed and the developing world.

References and Recommended Reading

Recently published papers of particular interest have been highlighted as:

- • Of importance
- •• Of major importance

1. Glass RI, Kilgore PE, Holman RC, *et al.*: **The epidemiology of rotavirus diarrhea in the United States: surveillance and estimates of disease burden.** *J Infect Dis* 1996, **174:**S5–S11.
2. Huilan S, Zhen LG, Mathan MM, *et al.*: **Etiology of acute diarrhoea among children in developing countries: a multicenter study in five countries.** *Bull WHO* 1991, **69:**549–555.
3. Murray CJ, Lopez AD: **Global mortality, disability, and the contribution of risk factors: global burden of disease study.** *Lancet* 1997, **349:**1436–1442.
4. Ardern-Holmes SL, Lennon D, Pinnock R, *et al.*: **Trends in hospitalization and mortality from rotavirus disease in New Zealand infants.** *Pediatr Infect Dis J* 1999, **18:**614–619.
5. • Parashar UD, Holman RC, Clarke MJ, *et al.*: **Hospitalizations associated with rotavirus diarrhea in the United States, 1993 through 1995; surveillance based on the new ICD-9-CM rotavirus-specific diagnostic code.** *J Infect Dis* 1997, **177:**13–17.

This study documents the burden of rotavirus-related disease in the United States.

6. Smith JC, Haddix AC, Teutsch SM, Glass RI: **Cost-effectiveness analysis of a rotavirus immunization program for the United States.** *Pediatrics* 1998, **96:**609–615.
7. •• Tucker AW, Haddix AC, Bresee JS, *et al.*: **Cost-effectiveness analysis of a rotavirus immunization program for the United States.** *JAMA* 1998, **279:**1371–1376.

This comprehensive analysis demonstrates the cost-effectiveness of universal rotavirus immunization in the United States.

8. Matson DO, Estes MK: **Impact of rotavirus infection at a large pediatric hospital.** *J Infect Dis* 1990, **162:**598–604.
9. Carr M, McKendrick D, Spyridakis T: **The clinical features of infantile gastroenteritis due to rotavirus.** *Scand J Infect Dis* 1987, **8:**241–243.
10. Rodriguez WJ, Kim HW, Arrobio JO, *et al.*: **Clinical features of acute gastroenteritis associated with human reovirus-like agent in infants and young children.** *J Pediatr* 1977, **91:**188–193.

11. Tallett S, MacKenzie C, Middleton P, *et al.*: **Clinical, laboratory, and epidemiologic features of a viral gastroenteritis in infants and children.** *Pediatrics* 1977, **60:**217–222.
12. Offit PA: **Host factors associated with protection against rotavirus disease: the skies are clearing.** *J Infect Dis* 1996, **174:**S59–S64.
13. Ward RL, Bernstein DI: **Protection against rotavirus disease after natural rotavirus infection.** *J Infect Dis* 1994, **169:**900–904.
14. Velazquez FR, Matson DO, Calva JJ, *et al.*: **Rotavirus infections in infants as protection against subsequent infections.** *N Engl J Med* 1996, **335:**1022–1028.
15. Moulton LH, Staat MA, Santosham M, Ward RL: **The protective effectiveness of natural rotavirus infection in an American Indian population.** *J Infect Dis* 1998, **178:**1562–1566.
16. Matson DO, O'Ryan ML, Herrera I, *et al.*: **Fecal antibody responses to symptomatic and asymptomatic rotavirus infections.** *J Infect Dis* 1993, **167:**577–583.
17. Coulson BS: **Typing of human rotavirus VP4 by an enzyme immunoassay using monoclonal antibodies.** *J Clin Microbiol* 1993, **31:**1–8.
18. Offit PA: **Rotaviruses: immunologic determinants of protection against infection and disease.** *Adv Virus Res* 1994, **44:**161–202.
19. Moser CA, Cookinham S, Coffin SE, *et al.*: **Relative importance of rotavirus-specific effector and memory B cells in protection against challenge.** *J Virol* 1998, **72:**1108–1114.
20. Estes MK: **Rotaviruses and their replication.** In *Fields' Virology.* Edited by Fields BN, Knipe DM, Howley PM. New York: Raven Press; 1996:1329–1352.
21. Ramachandran M, Gentsch JR, Parashar UD, *et al.*: **Detection and characterization of novel rotavirus strains in the United States.** *J Clin Microbiol* 1998, **37:**3223–3229.
22. Gentsch JR, Woods PA, Ramachandran M, *et al.*: **Review of G and P typing results from a global collection of rotavirus strains: implications for vaccine development.** *J Infect Dis* 1996, **174:**S30–S36.
23. Alfieri AA, Leite JP, Nakagomi O, *et al.*: **Characterization of human rotavirus genotype P[8]G5 from Brazil by probe-hybridization and sequence.** *Arch Virol* 1996, **141:**2353–2364.
24. Kapikian AZ, Hoshino Y, Chanock RM, Perez-Schael I: **Jennerian and modified Jennerian approach to vaccination against rotavirus diarrhea using a quadrivalent rhesus rotavirus (RRV) and human-RRV reassortant vaccine.** *Arch Virol Suppl* 1996, **12:**163–175.
25. Rennels MB, Losonsky GA, Young AE, *et al.*: **An efficacy trial of the rhesus rotavirus vaccine in Maryland.** *Am J Dis Child* 1990, **144:**601–604.
26. Santosham M, Letson GW, Wolff M, *et al.*: **A field study of the safety and efficacy of two candidate rotavirus vaccines in a Native American population.** *J Infect Dis* 1991, **163:**483–487.
27. Bernstein DI, Glass RI, Rodgers G, *et al.*: **Evaluation of rhesus rotavirus monovalent and tetravalent reassortant vaccines in US children.** *JAMA* 1995, **273:**1191–1196.
28. Rennels MB, Glass RI, Dennehy PH, *et al.*: **Safety and efficacy of high-dose rhesus-human reassortant rotavirus vaccines—report of the National Multicenter Trial. United States Rotavirus Vaccine Efficacy Group.** *Pediatrics* 1996, **97:**7–13.
29. Takala AK, Koskenniemi E, Joensuu J, *et al.*: **Economic evaluation of rotavirus vaccinations in Finland: randomized, double-blind, placebo-controlled trial of tetravalent rhesus rotavirus vaccine.** *Clin Infect Dis* 1998, **27:**272–282.
30. Joensuu J, Koskenniemi E, Vesikari T: **Symptoms associated with rhesus-human reassortant rotavirus vaccine in infants.** *Pediatr Infect Dis J* 1998, **17:**334–340.
31.•• **Intussusception among recipients of rotavirus vaccine—United States, 1998–1999.** *MMWR Morb Mortal Wkly Rep* 1999, **48:**577–581.

This is the original report of the possible association between rotavirus vaccine and intussusception.

32. American Academy of Pediatrics: *AAP Issues Public Health Advisory.* Chicago: AAP; 1999.
33.• Rennels MB, Parashar UD, Holman RC, *et al.*: **Lack of an apparent association between intussusception and wild or vaccine rotavirus infection.** *Pediatr Infect Dis J* 1998, **17:**924–925.

This prelicensure study examined the possible association between intussusception and natural or vaccine-strain rotavirus infection.

34. Pokorny WJ: **Intussusception.** In *Principles and Practice of Pediatrics.* Edited by Oski FA. Philadelphia: JB Lippincott; 1990:1695–1697.
35. Rosenthal C, Chen R: **The reporting sensitivities of two passive surveillance systems for vaccine adverse events.** *Am J Public Health* 1995, **85:**1706–1709.
36. **ACIP revokes recommendation for rotavirus vaccine use.** In *Advisory Committee on Immunization Practices.* Atlanta; 1999.
37. Perez-Schael I, Guntinas MJ, Perez M, *et al.*: **Efficacy of the rhesus rotavirus-based quadrivalent vaccine in infants and young children in Venezuela.** *N Engl J Med* 1997, **337:**1181–1187.
38. Ward RL, Dinsmore A, Goldberg G, *et al.*: **Shedding of rotavirus after administration of the tetravalent rhesus rotavirus vaccine.** *Pediatr Infect Dis J* 1998, **17:**386–390.
39. Mulcahy DL, Kamath KR, de Silva LM, *et al.*: **A two-part study of the aetiological role of rotavirus in intussusception.** *J Med Virol* 1982, **9:**51–55.
40. Nicolas JC, Ingrand D, Fortier B, Bricout F: **A one-year virological survey of acute intussusception in childhood.** *J Med Virol* 1982, **9:**267–271.
41. Konno T, Suzuki H, Kutsuzawa T, *et al.*: **Human rotavirus and intussusception.** *N Engl J Med* 1977, **297:**945.
42. Konno T, Suzuki H, Kutsuzawa T, *et al.*: **Human rotavirus infection in infants and young children with intussusception.** *J Med Virol* 1978, **2:**265–269.
43. Clark HF, Offit PA, Ellis RW, *et al.*: **The development of a multivalent bovine rotavirus (WC3) reassortant vaccine for infants.** *J Infect Dis* 1996, **174:**S73–S80.
44. Hoshino Y, Jones RW, Chanock RM, Kapikian AZ: **Construction of four double gene substitution human x bovine rotavirus reassortant vaccine candidates.** *J Med Virol* 1997, **51:**319–325.
45. Barnes GL, Lund JS, Adams L, *et al.*: **Phase I trial of a candidate rotavirus vaccine (RV3) derived from a human neonate.** *J Paediatr Child Health* 1997, **33:**300–304.
46. Bernstein DI, Sack DA, Rothstein E, *et al.*: **Efficacy of live, attenuated, human rotavirus vaccine 89-12 in infants: a randomised placebo-controlled trial.** *Lancet* 1999, **354:**287–290.