

Rotavirus vaccine for preventing diarrhoea (Review)

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ABSTRACT

Background

Rotaviruses cause viral gastroenteritis and result in more deaths from diarrhoea in children under 5 years of age than any other single agent, particularly in low- and middle-income countries.

Objectives

To assess rotavirus vaccines in relation to preventing rotavirus diarrhoea, death, and adverse events.

Search strategy

We searched the Cochrane Infectious Diseases Group's trial register (October 2003), the Cochrane Central Register of Controlled Trials (*The Cochrane Library* Issue 3, 2003), MEDLINE (1966 to October 2003), EMBASE (January 1980 to October 2003), LILACS (1982 to October 2003), Biological Abstracts (January 1982 to October 2003), reference lists of articles, and contacted researchers and rotavirus vaccine manufacturers.

Selection criteria

Randomized controlled trials comparing rotavirus vaccines to placebo, no intervention, or other rotavirus vaccines in children and adults.

Data collection and analysis

Two reviewers independently extracted data and assessed trial methodological quality, and contacted trial authors for additional information.

Main results

Sixty-four trials provided information on efficacy and safety of three main types of rotavirus vaccine (bovine, human, and rhesus) for 21,070 children. Different levels of efficacy were demonstrated with different vaccines varying from 22 to 89% to prevent one episode of rotavirus diarrhoea, 11 to 44% to prevent one episode of all-cause diarrhoea, and 43 to 90% to prevent one episode of severe rotavirus diarrhoea. Rhesus vaccine demonstrated a similar efficacy against one episode of rotavirus diarrhoea (37 and 44% respectively), and one episode of all-cause diarrhoea (around 15%) for trials performed in high and middle-income countries. Results on mortality and safety of the vaccines were scarce and incomplete. We noticed important heterogeneity among the pooled studies and were unable to discard a biased estimation of effect.

Authors' conclusions

Current evidence shows that rhesus rotavirus vaccines (particularly RRV-TV) and the human rotavirus vaccine 89-12 are efficacious in preventing diarrhoea caused by rotavirus and all-cause diarrhoea. Evidence about safety, and about mortality or prevention of severe outcomes, is scarce and inconclusive. Bovine rotavirus vaccines were also efficacious, but safety data are not available. Trials of new rotavirus vaccines will hopefully improve the evidence base. Randomized controlled trials should be performed simultaneously in high-, middle-, and low-income countries.

SUPPLEMENT ARTICLE

Rotavirus Types in Europe and Their Significance for Vaccination

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Abstract: The degree of diversity of cocirculating human rotavirus wild-type strains is high. This article reviews the occurrence and frequency of rotavirus types in European children younger than 5 years of age during the past 10–15 years. To enable greater understanding of the overall epidemiologic situation, rotavirus types found in animals in Europe are described. In addition, rotavirus types occurring in children outside Europe are considered. Taken together, these data provide an essential background to the development of rotavirus vaccines. The different concepts of immunization with the 2 main rotavirus candidate vaccines are briefly discussed, and their potential impact on the epidemiology of cocirculating rotavirus wild-type viruses is considered. A case is made for comprehensive surveillance of cocirculating human rotavirus types in Europe after the implementation of rotavirus vaccination.

Key Words: rotavirus types, epidemiology, vaccination

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Rotaviruses (RVs) are a major cause of acute gastroenteritis in infants and young children worldwide and in the young of a wide variety of other species.^{1,2} RVs form the genus *Rotavirus* of the Reoviridae family and possess a genome consisting of 11 segments of double stranded RNA. The genome and several enzymes necessary for viral replication (VP1, VP3) are enclosed in a triple layer of proteins: the core layer (VP2); the middle layer (VP6); and the outer layer (VP7 and VP4). VP6 determines the group specificity (A–G), VP7 the G type and VP4 the P type. For G types, a complete concordance of serotypes and genotypes has been achieved, while for P types this is not the case. Accordingly the P serotype is indicated by a free arabic number (eg, P1, P2), and the G genotype is indicated by numbers in brackets (eg, P[12]). At least 15 G types and 23 P types are known, of

which 10 and 11, respectively, have been found in viruses isolated from humans. Because RV proteins are encoded by different double stranded RNA segments that can reassort readily in doubly infected cells (as long as they are within the same group), various combinations of proteins in progeny viruses have been observed. Correspondingly there is a great diversity of cocirculating RV wild-type (wt) strains (for review, see References 1–3). In addition to G and P types, strain designations also contain the group and species of origin; for example, the human Wa strain is designated A/hu/Wa G1P1A[8], the simian strain SA11 is A/sim/SA11 G3P6[11], etc (for details, see Reference 2).

The pathogenesis, RV-specific immune response, immunologic correlates of RV-specific protection and treatment of RV disease have been reviewed elsewhere.^{4–13} The epidemiology of RV infections is complex (for review, see Reference 1). Most human infections are caused by group A RVs. Globally, for countries in temperate climates (including Europe), mainly 4 RV serotypes (G1P[8], G2P[4], G3P[8] and G4P[8]), have been linked to 90–95% of all hospitalized RV cases.¹⁴ There are, however, some exceptions (see below). By contrast, in tropical regions the variability of cocirculating RV types is much higher.^{15,16} Novel RV types have emerged in different parts of the world. For example, G9 strains have recently entered the human population, not only in the tropics but also in countries of temperate climates. In Australia and Belgium, G9 strains have become the predominant strains in recent RV seasons.^{17–19} Furthermore G5, G6 and G8 strains have been isolated from humans in tropical regions (for review see Reference 15).

The genetic mechanisms underlying the diversity of cocirculating RV wild-type (wt) strains can be summarized as follows^{14,15}: (1) accumulation of point mutations that can lead to antigenic changes and failure to serotype or genotype^{20–22}; (2) ability of cocirculating human RVs to reassort,^{23,24} reassortment not being restricted to the VP4, VP7 and VP6 genes²⁴; (3) ability of cocirculating animal RV strains to reassort with human strains and thus to introduce animal RV genes into strains circulating in humans^{15,16,25}; (4) ability of animal RVs to infect humans and to “emerge” by circulating in humans^{25–29}; and (5) ability of RVs to rearrange their genomes (for review, see Reference 30).

Thus RVs have various ways of constantly mutating and emerging as “novel” strains in humans. Although there is not much evidence that reassortment between animal and human RV strains is happening easily or frequently in Europe,³¹ it cannot be excluded. On the other hand, such events are not infrequent in tropical regions.^{15,32–35} Through

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shedding G9 strains and those infected with other G type RVs.⁴⁸ With respect to the more uncommon strains, a study in Hungary suggested relatively severe disease for G6 strains. All children infected with G6 were inpatients.⁴² In the United Kingdom, it has been reported that all 11 patients infected with G3P[6] strains were hospitalized.¹²⁵ Nevertheless no differences in disease severity between G9 and other G types were seen in a study from the United States.¹²⁸ Again, in studies attempting to correlate disease severity with uncommon RV types, case numbers are small, and this may have led to the different conclusions.

DISCUSSION

Given the unpredictable RV type diversity in and outside Europe, it would be difficult to design vaccines to cover the antigenic variation of all cocirculating RV wt strains. The perception of this difficulty is based on the notion that vaccine-induced protection is mainly achieved by eliciting RV type-specific neutralizing antibodies. On the other hand, empiric observations from RV vaccine trials speak differently. Heterologous RV vaccines of bovine origin, which do not share G or P types with commonly circulating human group A RVs, induced significant protection, particularly against severe RV disease.¹²⁹ Moreover it has been observed in a prospective follow-up study of children during their first 2 years of life that cross-protection is accumulated through successive natural infections and that disease is then prevented even in case of exposure to RV types not previously encountered.¹³

A rhesus rotavirus-based, tetravalent, human reassortant vaccine (Rotashield; Wyeth) was licensed in August 1998 for universal use but was subsequently withdrawn because of a likely association with intestinal intussusception (for detailed review, see References 1, 127, and 129–133).

The 2 major vaccine candidates of today are designed on the basis of very different principles:

1. The pentavalent RV vaccine RotaTeq[®] (developed by Merck & Co.) is based on the notion that RV type-specific neutralizing antibodies matter most. Thus RotaTeq is designed to elicit antibodies against antigens G1–G4 and P1A[8], which occur on >90% of RV strains isolated in countries of temperate climates. Thus the pentavalent vaccine might require modification for rapidly changing epidemiologic situations, analogous to the procedures used for influenza virus vaccines.¹³⁴ Vaccine adaptation would have to account for the worldwide emergence of G9 RV type,^{23,25,31,43,46,48,49,68,70,71,121,123} and particularly in tropical regions, a high incidence of G5, G6, G8 and G10 RV strains.^{28,42,102,113,117}
2. The monovalent RV vaccine Rotarix[™] (developed by GlaxoSmithKline) builds on the observation of cross-protection after repeated natural infections,¹³ and on the finding of cross-protection by bovine and rhesus RV human reassortant vaccines.^{129,135} Indeed after 2 doses of oral vaccination with the G1P1A[8] Rotarix vaccine, protection was achieved against severe disease from not only homologous, but also heterologous RV infection,¹³⁶ including the worldwide emerging G9 strain.¹³⁷

It remains to be seen whether vaccination with Rotarix will also protect against new heterologous strains that may emerge in the future. Rotarix has been licensed in Mexico since January 2005 on the basis of extensive, worldwide clinical data. For both vaccines, applications for licensure in European countries are pending.

In addition to immunity mediated by neutralizing antibodies, partial cross-protection via nonneutralizing VP6-specific antibodies has been seen in some (but not all) animal models. These observations can be explained by the fact that VP6 genes of group A RV strains are more conserved than their VP7 and VP4 genes; blockage of RV replication by the formation of intracellular DLP-VP6 antibody complexes (in which DLP indicates double layered particles) may be the molecular mechanism responsible for anti-VP6 immunity.^{138,139}

As with any new vaccine, a postvaccination surveillance system will be required to monitor the safety and whether either of the main 2 candidate vaccines will provide full heterogeneous protection. Such surveillance will have to account for the possibility of viral transmission from vaccinees, as well as the possibility that vaccine virus may reassort with cocirculating RV wt strains. This will allow the effectiveness of the vaccines to be monitored, as well as to discover expected effects on the composition of cocirculating RV wt strains. The surveillance system must include monitoring of animal RV strains, particularly among animals in close contact with humans (house animals, pets). Because animals constitute a potential reservoir for human RV infection and disease in particular settings, it will be vital to monitor whether animal RVs may be transmitted to humans after reduction or removal of the normally circulating (human) RVs by universal vaccination. There is evidence that asymptomatic RV infections do occur in humans; the replication and transmission of RV in this circumstance contributes to the overall RV epidemiology. Close surveillance will reveal at an early stage whether transition of such RVs into the pool of pathogenic human RVs will occur. Thus continuous and comprehensive surveillance will be critical and necessary for the implementation and further development of human RV vaccines.

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SUPPLEMENT ARTICLE

Clinical Trials of Rotavirus Vaccines in Europe

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Abstract: Clinical trials of a live oral candidate rotavirus vaccine were started in 1982 and soon demonstrated that severe rotavirus disease can be prevented by vaccination. The first bovine candidate vaccine was withdrawn because of inconsistent efficacy, and studies of a rhesus rotavirus vaccine were initiated. A field trial of rhesus-human reassortant tetravalent rotavirus vaccine in Finland was pivotal for the licensure of this vaccine (RotaShield®) in the United States in 1998. However, this vaccine was withdrawn in 1999 because of association with intussusception. Safety therefore became a major issue in the development of new candidate rotavirus vaccines. A pentavalent bovine-human reassortant rotavirus vaccine (RotaTcq®) showed about 70% efficacy against any rotavirus disease and 100% efficacy against severe disease in Finland, according to the Clark scale. A large, multinational safety trial indicated no association of this vaccine with intussusception, and its licensure is under review in the EU. An attenuated human rotavirus vaccine (RIX4414; Rotarix™) was developed from GI rotavirus strain 89-12. A trial in Finland showed efficacy comparable with that of RotaShield, and a larger trial is under way in several European countries. In the first epidemic season, vaccine efficacy was 73% against any and 90% against severe rotavirus (mostly GI) gastroenteritis, according to the Vesikari scale. A large scale safety trial, conducted in Latin America plus Finland, indicated no increased risk of intussusception among recipients of Rotarix compared with placebo. The licensure of Rotarix is in process in the European Union.

Key Words: rotavirus vaccine, bovine rotavirus, rhesus rotavirus, reassortant rotaviruses, human rotavirus

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The discovery of human rotaviruses in Australia and the United Kingdom in 1973 was key to understanding the viral etiology of winter diarrhea among young children in industrialized countries.^{1,2} Appreciation of the paramount clinical importance of rotavirus infection stimulated interest in development of vaccines for the prevention of rotaviral gastroenteritis in both industrialized and developing countries.

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By 1982, the first live oral heterologous rotavirus vaccine, a bovine rotavirus candidate vaccine designated as strain RIT 4237, had been developed by SmithKline-RIT.³ Its testing was an early European joint effort to prevent rotavirus disease. A historic record of studies of RIT 4237 vaccine has been presented previously,⁴⁻⁶ and is only summarized here.

A second candidate, rhesus rotavirus vaccine, was developed by Kapikian et al at the National Institutes of Health in the United States.^{7,8} This was tested at an early stage in Finland and Sweden and, at a similar time, rhesus-human reassortants were also investigated. An efficacy trial of the rhesus-human reassortant tetravalent rotavirus vaccine (RRV-TV; RotaShield®, Wyeth, Collegeville, PA) in Finland significantly contributed to the licensure of this vaccine in the United States in 1998.⁹

After the withdrawal of RRV-TV in 1999 because of an apparent, albeit rare, association with intussusception, safety became a major issue in the development of any new candidate rotavirus vaccine. Two new rotavirus vaccines, a bovine-human reassortant pentavalent vaccine (RotaTcq®; Merck, Whitehouse Station, NJ) and a monovalent human rotavirus vaccine (Rotarix™; GlaxoSmithKline, Rixensart, Belgium) have recently undergone extensive testing for safety and efficacy, and the licensure of these vaccines in Europe is now anticipated.

This article provides a short review of the clinical development of the major historical rotavirus vaccines, as well as the 2 new vaccines awaiting licensure. The focus is on clinical trials of these vaccines in Europe.

RIT 4237 BOVINE ROTAVIRUS VACCINE

Trials with RIT 4237 vaccine began in Finland in 1982 and consisted first of sequential safety and immunogenicity studies in adults and children.^{10,11} The vaccine was initially found to be immunogenic yet devoid of detectable side effects, so studies progressed to phase II.

Three efficacy trials were conducted in Tampere, Finland (Table 1). In the first study, infants 8-11 months of age were immunized with a single dose of RIT 4237 vaccine immediately before the 1983 rotavirus epidemic season.¹² In the second trial, infants 6-12 months of age received 2 doses of the vaccine in the autumn before the 1984 rotavirus season.¹³ The third trial included 3 groups of neonates vaccinated in 1984-1985.¹⁴⁻¹⁶ Of these, 1 group of infants received the first dose at birth and the second dose at 7 months of age; the other 2 groups received a single dose 5 days after birth. In all 3 studies, the vaccine was administered before the rotavirus season, and all yielded similar results during follow-up for 1 or 2 rotavirus seasons. The efficacy of the vaccine against any rotavirus gastroenteritis was 43-62% and 80-89% against moderately severe and severe rotavirus

TABLE 1. Summary of 3 Efficacy Trials of RIT 4287 Bovine Rotavirus Vaccine in Finland*

Age at Vaccination (mo)	No. of Doses	Protective Efficacy for Rotavirus Diarrhea		
		Any (%)	Moderately Severe to Severe	Refractive
8–11	1	55	99	12
6–12	2 (1-mo interval)	62	80	13
0 and 7	2	43	89	14

*In each study, the follow-up period was 2 rotavirus seasons.

gastroenteritis (Table 1). In these early studies, “clinically significant rotavirus diarrhea” was used to describe moderately severe and severe cases; that is, diarrhea lasting >24 hours and requiring specific therapeutic measures (rehydration, additional fluids given).

The key findings of the first efficacy trials in Finland included the following: (1) the vaccine protected against disease rather than infection; (2) vaccine protection was greater against severe than mild rotavirus diarrhea (ie, the vaccine ameliorated the clinical severity of rotavirus disease in the vaccinees, shifting a potentially severe case to a mild one and a mild case to a subclinical one). After these observations, it became customary to use a numeric symptom score to describe clinical severity of rotavirus disease as well as the effect on severity of a rotavirus vaccine¹⁷; (3) these observations related to a situation where at least 1 dose of rotavirus vaccine was given close to the onset of the rotavirus season. In contrast, when a single dose of RIT 4237 vaccine was given to neonates in June (half a year before the rotavirus season), there was no protective efficacy for any rotavirus gastroenteritis and only moderate protection against severe rotavirus gastroenteritis, suggesting waning vaccine-induced immunity over time in neonates.¹⁶

In addition to the efficacy trials reviewed above, a series of safety, immunogenicity and interference studies of RIT 4237 vaccine were conducted in several European countries. Studies in Finland looked at dose response and the effect of feeding, particularly breast milk, on immune response to the vaccine.^{18–20} The key findings were that buffering (with milk) against stomach acidity was necessary for optimal immune response, and breast milk or breast-feeding did not suppress the response. Studies focused on the effect of feeding were also performed by Zoppi et al in Italy. These showed no differences in immune response to RIT 4237 between breast- and bottle-fed infants,²¹ whereas soy formula seemed to interfere with vaccine response.²² The effect of concomitant vaccination was investigated in Italy, Yugoslavia and Switzerland (M. Just, unpublished observations): interference was found between oral rotavirus and poliovirus vaccines.^{23,24} Efficacy studies were initiated in Austria and England, but these had not been completed when RIT 4237 was withdrawn by the manufacturer in 1986.^{25,26} Several reasons led to the withdrawal, including poor performance in African studies.^{27,28} European awareness of rotavirus disease, among physicians and the public, remained low in the 1980s.

RHESUS AND RHESUS-HUMAN REASSORTANT ROTAVIRUS VACCINES, RRV-TV

Rhesus rotavirus was developed as a candidate heterologous rotavirus vaccine at the National Institute of Allergy and Infectious Diseases (part of the National Institutes of Health) by Kapikian et al.^{7,8} Rhesus rotavirus vaccine (RRV) was studied in Finnish and Swedish children in the mid-1980s.^{29–31} In these studies, RRV was found to be highly reactogenic. In Finland, for example, 64% of infants 6–8 months of age developed febrile reactions to RRV at a dose of 10⁵ plaque-forming units (PFU)²⁹; such reactogenicity was regarded as unacceptable. Administration of a lower dosage of RRV to younger infants reduced its reactogenicity, but its efficacy was also lower than previously seen with the bovine rotavirus vaccine: 38% against any rotavirus disease and 75% against severe rotavirus disease.³⁰

In Sweden, an efficacy trial of RRV was conducted at the original high dosage. In this trial, the vaccinees were 4–12 months of age and received a single dose of RRV or placebo before the rotavirus epidemic season. The protective efficacy against any rotavirus gastroenteritis was only 48%, and reactogenicity was unacceptably high (febrile reaction rate, 79%).³¹

Subsequently rhesus-human reassortant rotaviruses were developed at the National Institute of Allergy and Infectious Diseases as second generation versions of RRV.³² Rhesus-human reassortant rotaviruses express human G-type 1, 2 and 4 VP7 surface antigens on rhesus rotavirus particles. Rhesus rotavirus itself is G3. The biologic profile of the reassortants, including febrile reaction, is very similar to rhesus rotavirus; this was observed in phase I trials of rhesus rotavirus type 1 and 2 reassortants in Finland.³³ Reassortant rotaviruses induce a neutralizing antibody response to the human VP7 antigens according to G type. However, the proportion of recipients developing such neutralizing antibody responses is usually <50%, and it is not clear what role the neutralizing antibody plays in protective immunity. An efficacy trial of G1 and G2 single serotype rhesus-human reassortant rotavirus vaccines was conducted in Finland in the rotavirus seasons of 1988 and 1989, with conflicting results.³⁴ A low dose G1 reassortant (10⁴ PFU) provided only 44% protection against severe rotavirus disease (predominantly G1), whereas a high dose G2-reassortant vaccine (10⁵ PFU) provided 89% protection against severe, and 67% protection against any, rotavirus gastroenteritis.³⁴ Although the result could not be explained by the G-type-specific immunity, it was the best result in any rotavirus vaccine trial up to that point.

RRV-TV contains all 4 viruses (G1, G2 and G4 reassortants and rhesus rotavirus for G3). The only trial of RRV-TV in Europe, at the final dose of 4 × 10⁵ PFU, was conducted in Finland in 1993–1995.⁹ In this trial, a total of 2398 Finnish infants were randomly assigned to receive 3 doses of vaccine or placebo, between the ages of 2 and 7 months. The recruitment period was over a full calendar year with vaccination performed irrespective of the seasonality of rotavirus; thus the study simulated incorporation of the vaccine into routine immunization schedules.

The intention-to-treat analysis showed that, in children who had received all 3 doses of vaccine, the protective efficacy was 68% against any and 91% against severe rotavirus diarrhea (Table 2). Furthermore vaccine protection was 78% against rotavirus diarrhea requiring a physician visit, 97% against clinic admission and 100% against hospitalization.⁹ Of note, 89% of children who received the third dose of vaccine had a specific antirotavirus IgA response. There was a trend toward lower efficacy against any rotavirus gastroenteritis in infants whose vaccination was completed long before the onset of the rotavirus epidemic season, whereas in all children efficacy against severe disease was high.⁹ The results of this study set a standard for the efficacy of new rotavirus vaccines in Europe or elsewhere. Furthermore the results were used in disease burden estimates and a cost-benefit analysis of rotavirus vaccination in Finland.³⁵ Overall the vaccine reduced the incidence of severe gastroenteritis (rotavirus or not) by 64%. The Finnish study, together with U.S. trials,^{36,37} was pivotal for the licensure of RotaShield in the United States in August 1998. Licensure of this vaccine in the European Union (EU) was imminent when its association with intussusception was detected in the United States in 1999. One case of intussusception had in fact been seen in the Finnish trial (involving 1191 RRV-TV vaccine recipients).³⁸

WC3 BOVINE-HUMAN REASSORTANT ROTAVIRUS VACCINES

WC3 bovine strain rotavirus vaccine was developed at the Wistar Institute, Philadelphia, PA.³⁹ The vaccine, produced by Pasteur Mérieux, was tested in a small trial in France,⁴⁰ but studies were discontinued because the WC3 vaccine showed low efficacy in a trial in Cincinnati, OH,⁴¹ and no efficacy in Africa.⁴²

Subsequently bovine-human reassortants based on the WC3 strain were developed, starting with a G1 reassortant. These reassortants are similar to the rhesus-human reassortants, in that they express human VP7 antigens on the surface of bovine rotavirus.^{43,44} The reassortants were adopted by Merck, and bivalent (G1, G2) as well as tetravalent (G1-G4) combinations were tested in double blind, placebo-controlled trials in the United States with promising results, indicating good general safety and efficacy.^{45,46}

Next a pentavalent vaccine that contained, in addition to human G1-G4, a VP4 reassortant with human rotavirus P-type P1A, was developed. Because P1A is the most common human P-type, detected in ~90% of the strains causing

gastroenteritis, it was believed that the addition of this reassortant might broaden coverage and increase protective efficacy of the multivalent vaccine. Thus the pentavalent vaccine contains 5 different viruses. A dose-ranging study was conducted in Finland; the results with the final composition of the vaccine (aggregate potency, 7.92×10^6 PFU) are shown in Table 3. The vaccine was well-tolerated, and its efficacy against any rotavirus gastroenteritis was 74%, with up to 100% efficacy against severe rotavirus gastroenteritis.⁴⁷ However, a scoring system was used that was different from the one in studies of the previous rotavirus vaccine (dehydration was reported not as an independent sign, but only with the addition of behavioral signs),¹⁷ preventing direct comparison of efficacy against "severe" disease. A single case of intussusception was encountered in a child in this trial involving 1946 children, who received the first dose of vaccine at the age of 7.6 months.⁴⁷ In this trial, the recruitment was over a broad age range, 2–8 months, and vaccinations were performed before the rotavirus season to maximize efficacy.

A large scale safety trial of the pentavalent vaccine, with intussusception as an endpoint, was started in Finland and the United States in 2001.⁴⁸ In this study, infants were recruited at 6–12 weeks of age and received 3 doses of the vaccine or placebo. Recruitment was continued throughout the calendar year. As the study progressed well, with no safety signal detected, other countries joined in, including Germany, Belgium and Sweden. By the end of enrollment in 2004, ~70,000 children had been vaccinated, of whom 43% were European.

The results indicated no increased risk of intussusception among recipients of the vaccine compared with placebo in the primary follow-up period of 42 days after each dose of vaccine or placebo. Altogether there were 12 cases of intussusception in the vaccine group versus 15 in the placebo group during a follow-up period of 1 year after the first dose.⁴⁸ The study also examined the impact of the pentavalent vaccine to prevent hospitalization caused by rotavirus gastroenteritis; the overall effectiveness was 94%.⁴⁹ Results for individual countries, including Finland, Germany, Belgium and Sweden, will soon be available.

The pentavalent bovine-human reassortant vaccine was filed for licensure in the United States and EU (RotaTeq) in April 2005.

TABLE 2. Efficacy of 3 Doses of Rhesus-Human Reassortant Tetravalent Rotavirus Vaccine (RRV-TV) in Finnish Infants During a Follow-up Period of 1 Year⁹

Rotavirus Disease	No. of Cases		Vaccine Efficacy* (%)
	RRV-TV (n = 1128)	Placebo (n = 1145)	
Any	64	172	68
Severe	8	100	91

*P < 0.001 for both comparisons of RRV-TV versus placebo.

TABLE 3. Efficacy of 3 Doses of Pentavalent Bovine-Human Rotavirus Vaccine (PRV) in Finnish Infants During the First Rotavirus Season After Vaccination⁴⁷

Rotavirus Disease	No. of Cases		Vaccine Efficacy* (%)
	PRV (n = 328)	Placebo (n = 322)	
Any	8	39	74
Moderate to severe	5	28	81
Severe	0	8	100

*P < 0.001 for both comparisons of PRV versus placebo.

HUMAN ROTAVIRUS VACCINE

A live, attenuated human rotavirus G1, P1A, vaccine (strain 89-12) was originally developed in Cincinnati, OH,⁵⁰ by tissue culture passaging from a wild-type human rotavirus isolate. The vaccine was mildly reactogenic in infants 3–5 months of age. In a small efficacy trial during a predominantly G1 rotavirus season, the 89-12 vaccine showed 89% efficacy against any and 100% efficacy against severe rotavirus gastroenteritis.⁵¹ Strain 89-12 was adopted by Glaxo-SmithKline and developed further. It was cloned and passaged 12 more times in Vero cells, and the new vaccine strain was designated as RIX4414.

Human rotavirus vaccine RIX4414 was first tested for safety and immunogenicity in adults in Belgium, in toddlers in Germany and finally in young infants in Finland.⁵² It was found that in comparison with the parent rotavirus vaccine strain 89-12, RIX4414 was more attenuated, as evidenced by a very mild reactogenicity profile in the clinical trials. The immunogenicity of the vaccine at $10^{5.8}$ PFU, measured by rotavirus-specific IgA in the serum after 2 doses, was 96%, and the vaccine was shed in ~50–60% of vaccine recipients at 7 days postvaccination, indicating effective multiplication in the human host.⁵² There were no febrile reactions attributable to the vaccine.

A pilot efficacy trial of RIX4414 vaccine was conducted in Finland after a traditional study design: vaccination with 2 doses, administered at 2 and 4 months of age, immediately before the rotavirus epidemic season. In the first epidemic season, vaccine efficacy was 73% against any and 90% against severe rotavirus (mostly G1) gastroenteritis, according to the Vesikari scale.^{17,53} Vaccine efficacy persisted at this level through the second rotavirus epidemic season (Table 4). In retrospect, it was realized that the vaccine dose in this trial ($10^{4.7}$ PFU) was suboptimal, given that it induced only an 80% seroconversion rate compared with 96% in the previous immunogenicity trial.

The first year results of the pilot efficacy trial in Finland were encouraging, and subsequent efficacy studies of the RIX4414 vaccine were conducted in Latin America while studies in Europe were postponed. In a trial involving 2155 children in Mexico, Venezuela and Brazil, a high dose of the vaccine ($10^{5.8}$ PFU) showed 70% efficacy against any rotavirus vaccine and 86% efficacy against severe rotavirus gastroenteritis (Vesikari scale).^{17,54} This study also provided evidence of the efficacy of the vaccine against G types other than G1. For example, protection against severe gastroenteritis associated with G9 rotavirus was observed.⁵⁴

TABLE 4. Efficacy of 2 Doses of Human G1 Rotavirus Vaccine RIX4414 in Finnish Infants During a Follow-up Period Covering 2 Rotavirus Seasons⁵³

Rotavirus Disease	No. of Cases		Vaccine Efficacy* (%)
	RIX4414 (n = 246)	Placebo (n = 129)	
Any	13	23	72
Severe	9	10	85

*P < 0.05 for both comparisons of RIX4414 versus placebo.

A large scale, double blind, placebo-controlled trial (vaccine-placebo ratio, 1:1) was conducted in Latin America to evaluate the risk of intussusception with RIX4414 vaccine. A total of 63,225 infants were enrolled in 11 Latin American countries, with a small participation (2060 infants) from Finland during a period of 7 months. The vaccine was administered at 2 and 4 months of age. During a 31-day period after each dose, there was no increase of intussusception among recipients of vaccine compared with placebo. After a follow-up period of 100 days, when the infants were ~6 months of age, there was actually a trend (nonsignificant) toward a decrease in intussusception cases among RIX4414 vaccine recipients.⁵⁵

A subset of 20,000 infants in this large trial was followed for efficacy. The results confirmed the previous observations, with a high protection rate (>85%) against severe rotaviral gastroenteritis and 100% protection against the most severe dehydrating rotaviral gastroenteritis episodes.⁵⁶

RIX4414 (Rotarix) was licensed in Mexico in July 2004, thus becoming the first licensed rotavirus vaccine in 5 years after withdrawal of RotaShield. Rotarix has been registered in 10 other countries and filed for licensure in a large number of others, including the EU in December 2004.

As there were relatively few European efficacy data for RIX4414, a new efficacy trial was initiated in 2004 in 6 European countries (Czech Republic, Finland, France, Germany, Italy and Spain). This trial also followed the "classic" design of vaccination shortly before rotavirus epidemic season, with 2 doses given at the ages of 2–3 and 4–5 months, respectively. Substudies of the same protocol will examine the immunogenicity of the vaccine when coadministered with routine childhood vaccinations. An interim analysis is expected in the autumn of 2005, but the study will cover 2 full rotavirus epidemic seasons and end in mid-2006.

DISCUSSION

Two new rotavirus vaccines are in the process of being reviewed for licensure in EU countries. The key issue now is safety, given that the efficacy of both of these vaccines appears similar to that of the previously licensed RotaShield vaccine, particularly against severe rotavirus disease. Large scale studies of both new vaccines, RotaTeq and Rotarix, have indicated no increased risk of intussusception versus placebo.

To compare the new vaccines with RotaShield in terms of intussusception risk, it is necessary to reconsider the actual risks that were associated with RotaShield vaccination. The use of this vaccine was suspended in July 1999 because of a possible link with intussusception, and it was withdrawn by the manufacturer in October 1999 when studies confirmed a temporal association.^{57–59} The risk was initially estimated to be 1 in 4300, but a later consensus meeting revised the figure to 1 in 10,000.⁶⁰ More recently, a reappraisal of the risk has challenged even this estimate and suggested that it might have been only 1 in 32,000.⁶¹ Furthermore a reanalysis has shown that the risk was correlated with age, being lowest in infants younger than 3 months of age.⁶²

The sample size calculations of the safety studies (for intussusception) of the new rotavirus candidate vaccines were

based on the initial risk estimates for RotaShield. Moreover the safety studies of the new rotavirus vaccines were conducted in young infants; that is, the first dose of the vaccine was usually given to infants younger than 3 months of age. Therefore the safety conclusions are limited to this age group.

The practical conclusions from the present situation are obvious: the administration of the first dose of the new rotavirus vaccines, RotaTeq and Rotarix, should be restricted to young infants; and any use of the vaccines in older subjects should be monitored with a postlicensure surveillance system for intussusception.

The efficacy of both the pentavalent bovine-human reassortant vaccine and the monovalent human rotavirus vaccine against severe rotavirus disease appears well-established, regardless of serotype. It also seems that the monotypic G1 vaccine will protect against severe disease caused by other G types. As for protection against any (including mild) rotavirus gastroenteritis, the situation is less clear. For example, efficacy against G2 rotavirus may be less than that against other G types.

Although the efficacy rates of RotaTeq and Rotarix appear similar, the available data do not permit direct comparison of the efficacy of the 2 products, because different scoring systems were used in their trials. In the studies of Rotarix, the "standard" 20-point Vesikari scale was used,¹⁷ enabling direct comparison with the previous studies of RotaShield. However, in the RotaTeq studies, a 24-point scale was used,⁴⁶ in which the cutoff for severe disease (16 of 24 points) is clearly higher than in the Vesikari scale (11 of 20 points).

A year-round immunization study to generate clinical efficacy data for Rotarix in Europe would be valuable in demonstrating the feasibility of integrating Rotarix into national immunization schedules irrespective of the rotavirus season. Such a study could also include long term efficacy evaluation.

In conclusion, the licensure of 2 new rotavirus vaccines is now anticipated in Europe. The vaccines are different in terms of their virologic characteristics, but clinical trials indicate that their efficacy and safety, including absence of vaccine-associated intussusception in young infants, are remarkably similar. It may be assumed that proper use of either of these vaccines could produce significant reductions in rotavirus disease in Europe.

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