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Rotavirus vaccine for preventing diarrhoea (Review)

Soares-Weiser K, Goldberg E, Tamimi G, Leibovici L, Pitan F

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TABLE OF CONTENTS

HEADER	1
ABSTRACT	1
PLAIN LANGUAGE SUMMARY	2
BACKGROUND	3
OBJECTIVES	4
METHODS	4
RESULTS	6
Figure 1.	10
DISCUSSION	10
AUTHORS' CONCLUSIONS	12
ACKNOWLEDGEMENTS	12
REFERENCES	13
CHARACTERISTICS OF STUDIES	20
DATA AND ANALYSES	70
Analysis 1.1. Comparison 1 Drop outs before end of study, Outcome 1 Drop outs before end of study.	71
Analysis 2.1. Comparison 2 Rotavirus diarrhoea, Outcome 1 Episodes.	72
Analysis 2.2. Comparison 2 Rotavirus diarrhoea, Outcome 2 Severe episodes.	74
Analysis 2.3. Comparison 2 Rotavirus diarrhoea, Outcome 3 Episodes requiring hospitalization.	74
Analysis 2.4. Comparison 2 Rotavirus diarrhoea, Outcome 4 Episodes of more than four days.	75
Analysis 3.1. Comparison 3 All-cause diarrhoea, Outcome 1 Episodes (number of episodes/number of person-years).	77
Analysis 3.2. Comparison 3 All-cause diarrhoea, Outcome 2 Episodes (number of cases/number of participants).	77
Analysis 3.3. Comparison 3 All-cause diarrhoea, Outcome 3 Episodes during first week after vaccine (one or multiple doses). ..	78
Analysis 3.4. Comparison 3 All-cause diarrhoea, Outcome 4 Severe episodes (clinical or measured by any scale).	80
Analysis 3.5. Comparison 3 All-cause diarrhoea, Outcome 5 Episodes requiring re-hydration.	80
Analysis 3.6. Comparison 3 All-cause diarrhoea, Outcome 6 Episodes requiring hospitalization.	81
Analysis 4.1. Comparison 4 Death, Outcome 1 All-cause death.	81
Analysis 5.1. Comparison 5 Exploration of heterogeneity: methodological quality, Outcome 1 Adequate allocation concealment (A).	83
Analysis 5.2. Comparison 5 Exploration of heterogeneity: methodological quality, Outcome 2 Unclear allocation concealment (B).	84
Analysis 5.3. Comparison 5 Exploration of heterogeneity: methodological quality, Outcome 3 Exclusions after randomization reported.	85
Analysis 5.4. Comparison 5 Exploration of heterogeneity: methodological quality, Outcome 4 Exclusions after randomization not reported.	85
Analysis 5.5. Comparison 5 Exploration of heterogeneity: methodological quality, Outcome 5 Sample size of less than 1000 participants.	86
Analysis 5.6. Comparison 5 Exploration of heterogeneity: methodological quality, Outcome 6 Sample size of at least 1000 participants.	87
Analysis 6.1. Comparison 6 Exploration of heterogeneity: multiple versus single dose, Outcome 1 Multiple doses (two or more) of rotavirus vaccine.	89
Analysis 6.2. Comparison 6 Exploration of heterogeneity: multiple versus single dose, Outcome 2 Single dose of rotavirus vaccine.	89
Analysis 7.1. Comparison 7 Exploration of heterogeneity: administered with other vaccines, Outcome 1 Concomitant use of DPT or OPV allowed.	91
Analysis 7.2. Comparison 7 Exploration of heterogeneity: administered with other vaccines, Outcome 2 Concomitant use of DPT or OPV not allowed.	92
Analysis 7.3. Comparison 7 Exploration of heterogeneity: administered with other vaccines, Outcome 3 No information.	93
Analysis 8.1. Comparison 8 Exploration of heterogeneity: breastfeeding, Outcome 1 Breastfeeding allowed during vaccination.	94
Analysis 8.2. Comparison 8 Exploration of heterogeneity: breastfeeding, Outcome 2 Breastfeeding not allowed for at least one hour before and after vaccination.	95
Analysis 8.3. Comparison 8 Exploration of heterogeneity: breastfeeding, Outcome 3 No information.	95
Analysis 9.1. Comparison 9 Exploration of heterogeneity: one season versus multiple seasons follow up, Outcome 1 One season.	97

Analysis 9.2. Comparison 9 Exploration of heterogeneity: one season versus multiple seasons follow up, Outcome 2 Two or more seasons.	97
Analysis 10.1. Comparison 10 Exploration of heterogeneity: different rotavirus vaccines, Outcome 1 Rotavirus diarrhoea: episodes.	100
Analysis 10.2. Comparison 10 Exploration of heterogeneity: different rotavirus vaccines, Outcome 2 Rotavirus diarrhoea: severe episodes.	101
Analysis 10.3. Comparison 10 Exploration of heterogeneity: different rotavirus vaccines, Outcome 3 All-cause diarrhoea: episodes (number of cases/number of participants).	103
Analysis 11.1. Comparison 11 Exploration of heterogeneity: country of origin - income status, Outcome 1 Rotavirus diarrhoea: episodes.	107
Analysis 11.2. Comparison 11 Exploration of heterogeneity: country of origin - income status, Outcome 2 Rotavirus diarrhoea: severe episodes.	108
Analysis 11.3. Comparison 11 Exploration of heterogeneity: country of origin - income status, Outcome 3 Rotavirus diarrhoea: severe episodes requiring hospitalization.	110
Analysis 11.4. Comparison 11 Exploration of heterogeneity: country of origin - income status, Outcome 4 All-cause diarrhoea: episodes (number of cases/number of participants).	111
Analysis 11.5. Comparison 11 Exploration of heterogeneity: country of origin - income status, Outcome 5 All-cause diarrhoea: severe episodes (clinical or measured by any scale).	112
Analysis 11.6. Comparison 11 Exploration of heterogeneity: country of origin - income status, Outcome 6 All-cause diarrhoea: episodes requiring hospitalization.	113
Analysis 11.7. Comparison 11 Exploration of heterogeneity: country of origin - income status, Outcome 7 All-cause diarrhoea: episodes requiring re-hydration.	113
Analysis 12.1. Comparison 12 Adverse events, Outcome 1 Bowel obstruction and/or intussusception.	115
Analysis 12.2. Comparison 12 Adverse events, Outcome 2 Fever (one or multiple doses of vaccine).	115
Analysis 12.3. Comparison 12 Adverse events, Outcome 3 Vomiting (one or multiple doses of vaccine).	117
Analysis 12.4. Comparison 12 Adverse events, Outcome 4 Irritability (one or multiple doses of vaccine).	118
APPENDICES	118
WHAT'S NEW	122
HISTORY	123
CONTRIBUTIONS OF AUTHORS	123
DECLARATIONS OF INTEREST	123
SOURCES OF SUPPORT	123
DIFFERENCES BETWEEN PROTOCOL AND REVIEW	123
INDEX TERMS	124

[Intervention Review]

Rotavirus vaccine for preventing diarrhoea

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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 methods

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.

2010 Editor's Note: Several of the vaccines investigated in this review are no longer in routine clinical use (for example, live attenuated rhesus-human reassortant tetravalent vaccine) and further new vaccines have been tested and approved for use since this review was written in 2004. For an up-to-date assessment of rotavirus vaccines currently approved for use, please see : Soares-Weiser K, MacLehose H, Ben-Aharon I, Goldberg E, Pitan F, Cunliffe N. Vaccines for preventing rotavirus diarrhoea: vaccines in use. *Cochrane Database of Systematic Reviews* 2010, Issue 5. Art. No.: CD008521. DOI: 10.1002/14651858.CD008521.

23 April 2019

No update planned

Review superseded

This Cochrane Review has been superseded by Soares-Weiser 2019 <https://doi.org/10.1002/14651858.CD008521.pub4>

PLAIN LANGUAGE SUMMARY

Rotavirus vaccines can prevent diarrhoea caused by rotavirus, but we are still not clear about safety and whether they prevent deaths

Rotavirus diarrhoea causes illness and death in young children. The benefits of the vaccine were different depending on the type of vaccine. The reviewers are unable to make conclusive recommendations regarding the use of rotavirus vaccines.

BACKGROUND

Rotaviruses cause viral gastroenteritis, and result in more deaths from diarrhoea than any other single agent (Vesikari 1997). In middle- and low-income countries, rotavirus kills an estimated 1600 to 2400 children every day (600,000 to 870,000 per year), and can cause up to 6% of all mortality in children under 5 years of age. It is estimated that rotavirus is responsible for 20 to 25% of all deaths due to diarrhoeal disease worldwide (Bresee 1999; Glass 1999).

Biology

People become infected with rotavirus by direct faecal-oral spread, and symptoms develop 1 to 4 days after exposure. Babies in the first 3 months tend to have infections without symptoms because of the protection of antibodies transferred to the baby via the placenta and breastfeeding. In older infants, the disease can be without symptoms, or with mild or severe symptoms, which are characterized by vomiting, fever, watery diarrhoea, and dehydration (AAP 1998). Infants and children develop immunity to rotavirus infection during the first 2 or 3 years of life, which is thought to protect from subsequent episodes of severe disease (Vesikari 1997).

Rotaviruses have two proteins that induce neutralizing antibodies. These proteins have two different specific antibody-inducing sections, called the P and G types (P is short for the VP4 protease-cleaved protein, and G for the glycoprotein VP7) (Matson 1990). Children that are infected for the first time usually develop specific antibodies to the infecting rotavirus type, but with subsequent infections develop a broader immunity to other types.

Control

Efforts to prevent disease by improving sanitary conditions have not reduced exposure (Glass 1999; Peter 2002). More than 90% of children, in any region of the world, have been exposed and have measurable rotavirus antibody titres by the ages of 3 to 5 years. Hence, the high priority placed on the development of a safe and effective vaccine (Peter 2002).

Vaccines

Several rotavirus vaccines have been developed (Appendix 1) (Vesikari 1997; Bresee 1999). Early vaccine candidates were developed from an animal virus strain, but the efficacy of such vaccines was highly variable due to a predominant homotypic response of these so called monovalent vaccines. In an effort to induce a heterotypic response (tetravalent vaccines), combinations of animal or human-animal reassortant strains or attenuated human strains of rotaviruses have been included in the second generation of vaccines (Henchal 1996).

The first vaccine tested in the early 1980s was a bovine, monovalent, live-oral rotavirus vaccine for children (NCDV - RIT 4237) (Appendix 1). The first trials were conducted in Finland (Vesikari 1997), and the vaccine seemed effective both against mild and severe rotavirus infection (Vesikari 1997). After this initial success, the monovalent, live-oral bovine vaccines (RIT 4237 and WC3) were tested in low- and middle-income countries, and much lower efficacy was reported. The hypothesis generated for such lower efficacy was that in these countries the rotavirus diarrhoea was caused by a different strain, not available in the vaccine. Both bovine rotavirus vaccines were

therefore withdrawn and have not been used since then (Vesikari 1997).

Monovalent rhesus (RRV) and human attenuated (M37) vaccines were tested next. These vaccines appeared to be promising, but efficacy varied greatly between different countries. This variability was suggested to occur due to serotype-specific protection produced by the monovalent vaccine. This finding was demonstrated in controlled trials conducted in Venezuela in the early 1990s (Perez-Schael 1990b), and led to the development of a polyvalent reassortant vaccine protecting against the four major serotypes of rotavirus that were in common circulation worldwide.

To broaden the antigenic spectrum of the vaccine, rhesus-human reassortant rotaviruses were developed. These polyvalent vaccines provide serotype-specific immunity against all four predominant human rotavirus serotypes (G1, G2, G3, and G4), and were described as efficacious in reducing the rate of severe rotavirus diarrhoea by 80% - a rate similar to the protection conferred by natural infection (Vesikari 1997).

In August 1998, the rhesus rotavirus tetravalent vaccine (RRV-TV, RotaShield, Wyeth-Lederle Vaccines and Pediatrics, Philadelphia, PA) was licensed by the US Food and Drug Administration for oral administration to infants at 2, 4, and 6 months of age. This vaccine is a live-attenuated, orally administered product derived from four group A rotavirus. Three of the rotaviruses are single gene reassortants of the VP7 gene of human origin (types G1, G2, and G4), and the fourth strain is rhesus rotavirus (type G3), which is antigenically similar to human G3. No data are available to indicate whether this rotavirus vaccine protects against diarrhoea attributable to rotavirus strains not contained in the vaccine (Vesikari 1997).

Several studies in the USA, Finland, and Venezuela have found that RRV-TV is very effective in rotavirus disease (Perez-Schael 1997; Vesikari 1997; AAP 1998). However, other studies conducted in Peru and Brazil produced conflicting results that showed a much lower efficacy (Lanata 1996a; Linhares 1996).

Since the introduction of RRV-TV, several cases of bowel obstruction and intussusception following administration of the vaccine have been reported, which have led to the vaccine being withdrawn. In July 1999, the US Centers for Disease Control and Prevention advised doctors to temporarily stop giving children the vaccine against rotavirus after counting at least 20 infants who developed intussusception in the weeks after vaccination with RRV-TV (CDC 1999; CDC 1999a; MMWR 1999a; MMWR 1999b). In October 1999, the vaccine's manufacturer decided to voluntarily withdraw the vaccine from the market because reports of intussusception possibly linked to the product have reached about 100 (MMWR 1999b).

RRV-TV was also thought to cause febrile reactions 3 to 4 days after vaccination due to the viral antigens. These reactions seem to be more frequent and severe in older children who lack maternally acquired antibodies. Therefore the first dose of the vaccine was recommended to be given between age 2 and 6 months in the USA.

Using the same strategy as RRV-TV, a quadrivalent, human-bovine, reassortant vaccine has been tested. This vaccine incorporates human VP7 with bovine genes (G1 to G3) and VP4 reassortants. Results of efficacy trials with this vaccine are due to be published

(Dr Penny Heaton, Vaccine Infectious Diseases - Merck, personal communication).

Other vaccines have been developed (Bresee 1999; Merck 1999; Jones 2001). In Japan, an inactivated parenteral vaccine (BIRVI) with strains of human origin has been tested. In China, a live oral vaccine that uses a lamb strain appeared to be safe and immunogenic in phase II trials, and efficacy trials are now being planned. Vaccine-like particles for use as an inactivated vaccine are being developed in Korea (Cunliffe 2002).

Sources of heterogeneity

The wide variation in protection observed in randomized controlled trials may be related to the response of the immune system to different strains of the rotavirus or of rotavirus vaccine, the study population, or the study design.

Rotavirus

Cross-immunization is induced between some, but not all, human and animal strains. The differences in efficacy found in the various studies can be attributed in part to differences in serotypes of circulating strains and the failure of animal strains to elicit heterotypic protection.

Vaccines

Different vaccine formulations may have different efficacy. Premature conclusions about effectiveness were drawn from trials of bovine rotavirus vaccine in low- and middle-income countries, and the same should not be repeated for other vaccines.

Study population

One possible explanation for low efficacy of rotavirus vaccine in low- and middle-income countries may be the interference by other enteric viruses, which are a common cause of diarrhoea in children in such countries (Vesikari 1997). The epidemiology of rotavirus differs in low- and middle-income compared to high-income countries. In low- and middle-income countries, the disease occurs all the year round (compared with seasonal peaks in high-income countries), children are infected at an early age (6 to 9 months), immunization efforts require greater levels of coverage to be effective, and children are often subject to infections with strains that are not included in the current vaccines (Bresee 1999).

As a result, it has been speculated that rotavirus vaccine could be more efficacious if given at an earlier age, not associated with other vaccines (particularly 'diphtheria-pertussis-tetanus' (DPT) and oral polio vaccine (OPV)), or breastfeeding. Additionally, it has been suggested that higher titre and multiple doses of the vaccine are more efficacious (Vesikari 1997; Bresee 1999).

Study design

It is also plausible that some methodological issues, such as allocation concealment (adequate or unclear), exclusions after randomization (reported or not reported), sample size (< 1000, ≥ 1000), and length of follow up (one rotavirus season or more than one rotavirus season) could provide different levels of efficacy.

Significance of rotavirus vaccine

Finding that a rotavirus vaccine is efficacious might encourage immunization in the countries with the highest burden (Tucker

1998). This has to be weighed against the available resources (Griffiths 1995). Hence, to become a worthwhile intervention, vaccines against rotavirus will not only have to be proven to be efficacious and not related to major adverse events, but also affordable and cost-effective in comparison with other potential interventions (Glass 1999).

Efficacy levels of as low as 50 to 60% against severe rotavirus disease could prevent a large number of deaths (Josefson 1997). Because rotavirus disease causes up to 6% of all mortality among children less than 5 years of age in low- and middle-income countries, universal immunization with rotavirus vaccine may prevent a significant number of deaths, and the trade off against rare severe adverse effects may well be different from the situation in high-income countries.

OBJECTIVES

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

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled trials.

Types of participants

Children and adults.

Types of interventions

We included the following interventions and controls regardless of doses and/or schedules used in the different trials.

Intervention

- Live-attenuated bovine rotavirus vaccine (RIT-4237, WC3, W179-9, QHBRV).
- Rhesus rotavirus vaccine (RRV, RRV-TV).
- Human-attenuated rotavirus vaccine (M37, 89-12).
- Other rotavirus vaccines (BIRVI, Lamb RV).

Control

- Placebo or no vaccination.
- Any of the interventions mentioned above.

Types of outcome measures

Primary

Rotavirus diarrhoea

- Episodes.
- Severe episodes (defined as an episode that last for more than 24 hour of duration, with more than six stools in 24 hours, presence of vomiting, fever, and dehydration (WHO 1995)).
- Episodes requiring hospitalization.
- Episodes of more than four days duration.

Secondary

All-cause diarrhoea

- Episodes.
- Episodes during first week after vaccine.
- Severe episodes (defined as an episode that last for more than 24 hour of duration, with more than six stools in 24 hours, presence of vomiting, fever, and dehydration (WHO 1995)).
- Episodes requiring re-hydration.
- Episodes requiring hospitalization.
- Death: all-cause.
- Death: from rotavirus infection.
- Malnutrition at follow up.
- Drop outs before the end of the study.

Adverse events

- Bowel obstruction and/or intussusception related to the use of the rotavirus vaccine.
- Serious adverse events that are fatal, life threatening, or require hospitalization.
- Systemic reaction, such as fever, related to the use of the rotavirus vaccine.
- Adverse events that require discontinuation of vaccination schedule.

We excluded studies collecting only immunological data.

Search methods for identification of studies

We attempted to identify all relevant studies regardless of language or publication status (published, unpublished, in press, and in progress).

We searched the Cochrane Infectious Diseases Group's trials register for relevant trials up to October 2003 using the search terms: rotavirus; diarrhoea; diarrhea; gastroenteritis; and vaccine. Full details of the Cochrane Infectious Diseases Group methods and the journals handsearched are published in *The Cochrane Library* in the section on Collaborative Review Groups.

We searched the Cochrane Central Register of Controlled Trials (CENTRAL), published in *The Cochrane Library* (Issue 3, 2003), using the search terms: rotavirus; diarrhoea; diarrhea; gastroenteritis; and vaccine. We also searched the following electronic databases using the search terms in combination with the search strategy developed by The Cochrane Collaboration (Clarke 2003); MEDLINE (1966 to October 2003) using the search terms: rotavirus; rotavirus-infections; diarrhoea; diarrhea; gastroenteritis; vaccines-attenuated; and viral-vaccines; EMBASE (January 1980 to October 2003) using the search terms: rotavirus; diarrhoea; diarrhea; gastroenteritis; vaccines-attenuated; and viral-vaccines; and LILACS (www.bireme.br; 1982 to October 2003) using the search terms: rotavirus; diarrhoea; diarrhea; gastroenteritis; and vaccine. Biological Abstracts (January 1982 to October 2003) using the search terms: rotavirus vaccine; diarrhoea; and diarrhea.

We checked the reference lists of all trials identified by the above methods. We also contacted the first or corresponding author of each included study as well as researchers active in the field, and a rotavirus vaccine manufacturer (Merck Sharp & Dohme)

for information regarding unpublished trials or complementary information on their own trial.

Data collection and analysis

Selection of studies

Two reviewers (Karla Soares-Weiser (KSW), Elad Goldberg (EG)) independently inspected the abstract of each reference identified by the search and determined the potential relevance of each article. For potentially relevant articles, or in cases of disagreement, we obtained the full article and independently inspected it and applied the inclusion criteria. Where we were unable to resolve the disagreement through discussion, we added the article to those 'awaiting assessment' and contacted the authors of the study for clarification. In an event of no reply from the authors within 6 months, a third reviewer (Leonard Leibovici (LL)) checked the article to solve disagreements. We also documented our justification for excluding studies from the review.

Data extraction and management

Two reviewers (KSW, EG) independently extracted data from the included trials. In case of any disagreement between the two reviewers, a third reviewer (LL) extracted the data. We discussed the data extraction, documented decisions, and where necessary, contacted the study authors for clarification.

We identified trials by the name of the first author and year in which the trial was first published. We extracted, checked, and recorded the following data.

1. Characteristics of trials.

- Date location and setting of trial.
- Publication status.
- Case definitions used (clinical, serological, virological).
- Sponsor of trial (specified, known or unknown).

2. Characteristics of participants.

- Number of participants in each group.
- Age, gender, nationality, ethnic group, and risk category.
- Previous immunization status (if known).
- Use of breast-bottle feed during the vaccination.
- Presence of any immunodeficiency.

3. Characteristics of interventions.

- Type of vaccine, type of control, dose, and immunization schedule.

4. Characteristics of outcome measures.

- Number of people who died in the vaccine and control group.
- Number of people who developed rotavirus diarrhoea.
- Number of people who developed any diarrhoea.
- Number of hospitalizations for diarrhoea, dehydration, or malnutrition.
- Systemic adverse events, specifically bowel obstruction.
- Any adverse events.
- Length of follow up (in months).
- Loss to follow up (drop outs) before end of study.

We individually extracted adverse event data for each adverse event wherever possible. For trials reporting adverse events for more than one dose, we recorded the average number of people reporting each adverse event for each dose was recorded.

Assessment of risk of bias in included studies

Two reviewers (KWS, EG) assessed the included trials for methodological quality. We extracted information about the method of treatment allocation (random, quasi-random, sequential, not stated), concealment of allocation (adequate (A), unclear (B), inadequate (C) according to [Juni 2001](#)), blinding (double, single, or not blind), sample size (< 1000 , ≥ 1000), and exclusions after randomization (reported, not reported), and the follow-up period (one rotavirus season after immunization, two or more rotavirus seasons).

Data synthesis

We analysed dichotomous data by calculating the risk ratio (RR) for each trial with the uncertainty in each result being expressed using 95% confidence intervals (CI). Additionally, we tested variability according to differences in type of vaccine (bovine, human, or rhesus).

Using the method of Newcombe-Wilson hybrid score (not continuity corrected ([Newcombe 1998](#))) and the correspondent 95% CI, we estimated the number of children needed to take rotavirus vaccine to avoid one case of rotavirus diarrhoea (NNT) for trials that tested each specific vaccine.

Heterogeneity and publication bias

We initially assessed heterogeneity on the results of the trials by inspecting of graphical presentations and by calculating a test of heterogeneity (chi-squared test). However, we were aware of the fact that the chi-squared test has a poor ability to detect statistically significant heterogeneity among studies. Therefore, we have also quantified the impact of heterogeneity in the meta-analysis using a measure of the degree of inconsistency in the studies' results ([Higgins 2003](#)). This measure (I^2) describes the percentage of total variation across studies that are due to heterogeneity rather than the play of chance ([Higgins 2003](#)). The values of I^2 lies between 0 and 100%, and a simplified categorization of heterogeneity could be low, moderate, and high to I^2 values of 25, 50, and 75% ([Higgins 2003](#)).

We anticipated between-trial variation in estimation of vaccine efficacy for trials that used different rotavirus strains and were conducted in different geographic locations. We performed subgroup analyses in order to assess the impact of these possible sources of heterogeneity. In addition, we performed sensitivity analyses for the main outcome (rotavirus diarrhoea) in order to assess the robustness of the findings to different aspects of the trials methodology: concealment of allocation (adequate or unclear); exclusions after randomization (reported or not reported); sample size (< 1000 , ≥ 1000); and length of follow up (one rotavirus season or more than one rotavirus season). We carried out further exploratory sensitivity analyses to test the impact of different types of vaccines, concomitant use of diphtheria-tetanus-pertussis (DPT) and/or oral polio vaccine (OPV), breastfeeding during vaccination, and number of doses of vaccine (single dose, two to three doses) in the pooled efficacy.

We used a fixed effect model throughout the review, except in the event of statistically significant heterogeneity between the trials ($P < 0.10$), when we chose the random effects model. And because we demonstrated heterogeneity in most of the outcomes when we performed the analyses using odds ratio or RR either on a fixed effect or random effects model (see [Appendix 2](#) for an example), we chose to present the results using the RR with the correspondent 95% CI and a random effects model.

We observed moderate to high statistically heterogeneity among most of the outcomes evaluated on this review. Even when we analysed the vaccines separately, we observed heterogeneity in the combined trials for the following vaccines and outcomes: RRV-TV (episodes of rotavirus diarrhoea, episodes of severe rotavirus diarrhoea), RRV (all-cause diarrhoea), RIT-4237 (episodes of rotavirus diarrhoea, episodes of severe rotavirus diarrhoea, all-cause diarrhoea), and WC3 (episodes of rotavirus diarrhoea) vaccines.

We examined a funnel plot estimating the precision of trials (plots of logarithm of the RR for efficacy against the sample size) in order to estimate potential asymmetry.

Personal communication with authors and pharmaceutical industry

We contacted the corresponding authors of the 64 included trials, of which 25 replied and 20 provided additional data. We initially sought data on study design, death, bowel obstruction and/or intussusception, and dehydration. Because of the low response rate in the first round, we attempted to contact the authors for a second time using only e-mail and requesting information only for deaths and adverse events. The results of the personal communication with the authors are summarized in [Appendix 3](#). These data were previously published for only three of the trials ([Joensuu 1997](#); [Santosham 1997](#); [Bresee 2001](#)).

We also contacted Merck Sharp & Dohme – the pharmaceutical industry organizing the field trials of the new bovine quadrivalent vaccine – for further details on their trials. Dr Penny Heaton (Vaccine Infectious Diseases, Clinical Research) replied and informed us that most of the trials will be published, and they would prefer not to release any further information until after publication (e-mail on 11 March 2002).

RESULTS

Description of studies

Eligibility

We identified 138 potentially relevant references through our search strategy, and 1 trial through contact with authors, who also provided unpublished data ([Perez-Schael 2002](#)). Of these, we included 64 trials (90 references), which are described below and in the '[Characteristics of included studies](#)', and excluded 31 studies (33 references) and 16 reviews of the literature.

We have described the 31 excluded studies in the '[Characteristics of excluded studies](#)'. Our main reasons for excluding these studies were because they were not randomized or had an inadequate allocation concealment (7), did not measure any clinical outcome (21), and because all participants received the vaccine and were randomized to different dietary components (3).

Two randomized controlled trials are still awaiting assessment because currently only an abstract without the required information has been published ([Seth 2000](#); [Vesikari 2002](#)).

Participants

All but one study tested vaccines or placebo in children, age ranging from newborns to 12 years old; [Barnes 1997](#) is a small safety study included a group of 10 adults (21 to 30 years old). Studies included only healthy children; in a single study, we found a description that children were included if they did not have any debilitating disease ([Perez-Schael 1990c](#)).

Interventions

Details of the six different types of vaccines assessed in the included studies can be found in [Appendix 4](#). Only one trial did not use placebo in the control group ([Vesikari 1986a](#)). In another trial ([Santosham 1991a](#) and [Santosham 1991b](#)), children were allocated to three groups: RIT 4237 (106 children); MMU18006 (108 children); placebo (107 children); the placebo group was arbitrarily divided into two arms, and we report each arm as a separate study.

Outcomes

Of the 64 included trials, 49 trials provided information on the safety of rotavirus vaccine in 16,602 children, and 40 trials provided information on the effectiveness of the vaccine to prevent rotavirus diarrhoea in 21,070 children. See the '[Characteristics of included studies](#)' for the complete list of outcomes provided by each study; no study reported on malnourishment.

Rotavirus was detected in all studies using serology and stool analysis by the ELISA method. An episode of diarrhoea was defined in the majority of the studies as at least two liquid or semi-liquid stools in 24 hours. The definition of severity of diarrhoea varied according to the criteria used in the trial. Thirty-seven studies used only a clinical definition of severe diarrhoeal diseases. The other studies used either the [Clark 1988](#) scale (4 studies), [Flores 1987](#) scale (7 studies), [Rennels 1996](#) scale (3 studies), [Ruuska 1990](#) scale (6 studies) or the World Health Organization (WHO) criteria ([WHO 1995](#); 7 studies) for diarrhoea to measure the severity of diarrhoeal diseases.

Twenty-three trials had an unbalanced randomization with more than one experimental group, which may affect the calculation of the NNT: 10 trials tested different strains of the same vaccine in two to four experimental groups; 10 trials tested different dosages of the same vaccine; and 3 trials tested different vaccines in two experimental groups. Of these three trials two provided data only on safety of the vaccine (children were followed up for up to 10 days after vaccination) ([Flores 1990](#); [Perez-Schael 1994](#)); we used data on the placebo and rhesus vaccines groups and discarded data on the M37 vaccine. The other trial provided data on the efficacy of two rotavirus vaccines (RIT 4237, MMU18006) against placebo ([Santosham 1991a](#); [Santosham 1991b](#)).

Study location

We divided the trials according to the classification of high-, middle-, and low-income countries of the World Bank ([World Bank 2003](#)). Trials were conducted in high-income countries: Australia (2), Austria (1), Finland (12), Israel (1), Spain (1), Sweden (1), the United Kingdom (1), the United States of America (29); middle-income countries: Brazil (1), Peru (3), and Venezuela (9); and low-income

countries: Bangladesh (1), Central African Republic (1), Gambia (1), Rwanda (1).

Risk of bias in included studies

Generation of allocation sequence

Seven trials reported information about generation of allocation sequence in the published version. They used random code assignment or computer-generated randomization. The code was kept by the pharmaceutical industry or academic institutions (including World Health Organization and National Institute of Health, USA) and not broken until the end of the study. In eight trials, randomization was generated by a central computer, and pre-coded vessels were administered sequentially to the children. It was not possible to determine the method used in the remaining 49 trials.

Concealment of allocation

Fifteen trials had adequate allocation concealment (information was available in the publication in seven trials and sought from authors in eight trials), and scored A. In the remained 49 trials it was not possible to determine the method used to conceal the allocation and these trials scored B (unclear).

Blinding

All trials used placebo in the control arm. Sixty-one trials were reported to be double blind, and three studies provided no information. Only 29 out of the 61 studies reported a procedure to guarantee double blinding. The vaccine and placebo were of identical appearance in 28 trials. In another trial ([Vesikari 1986a](#)), parents and paediatricians were unaware of the code given to vaccine and placebo.

Exclusions after randomization

Exclusion of participants from the trials after randomization varied from 0 to 23%, except in [Hanlon 1987](#), where 43% of the randomized children were excluded because they were absent during the epidemic period or too young to be vaccinated.

From the 40 included trials that provided data on efficacy: 6 did not provide any information about drop outs before end of study; in the other trials exclusion of participants from the trials after randomization varied from 0 to 23%, except in [Hanlon 1987](#), where 43% of the randomized children were excluded because they were absent during the epidemic period or were too young to be vaccinated. Nineteen trials (n = 12,493) provided data for each group (vaccine or placebo) on the number of children dropped out before the end of the study. There was no statistically significant difference in the number of people who dropped out between the vaccine and placebo arms of the rhesus rotavirus vaccine trials (RR 0.95, 95% CI 0.85 to 1.06; [Analysis 1.1](#)).

Follow-up period

The follow-up period was less than a month in 21 trials, up to one year (one season) in 20 trials, and of one to four years (two or more seasons) in 23 trials.

We have provided additional information about the methodological quality of the trials in the '[Characteristics of included studies](#)'.

Effects of interventions

Rotavirus diarrhoea

Episodes

Forty trials provided information for 21,070 children regarding diarrhoeal disease caused by rotaviruses. Rotavirus vaccine prevents rotavirus diarrhoea in all three groups of vaccines: rhesus (RR 0.59, 95% CI 0.50 to 0.70); bovine (RR 0.59, 95% CI 0.45 to 0.76); and human (RR 0.42, 95% CI 0.21 to 0.85) ([Analysis 2.1](#)).

Converting these RR values to vaccine efficacy gives the following estimates for preventing one episode of rotavirus diarrhoea: 41% (95% CI 30 to 50%) for rhesus vaccines; 41% (95% CI 24 to 55%) for bovine vaccines; and 58% (95% CI 15 to 79%) for human vaccines.

Severe episodes

Rotavirus vaccines also showed a highly statistically significant benefit in preventing severe episodes of rotavirus infection ([Analysis 2.2](#)): rhesus (RR 0.42, 95% CI 0.31 to 0.57); bovine (RR 0.38, 95% CI 0.24 to 0.60); and human (RR 0.21, 95% CI 0.13 to 0.35).

Converting these RR values to vaccine efficacy gives the following estimates to prevent one episode of severe rotavirus diarrhoea: 58% (95% CI 43 to 69%) for rhesus vaccines; 62% (95% CI 40 to 76%) for bovine vaccines; and 79% (95% CI 65 to 87%) for human vaccines.

Episodes requiring hospitalization

Rotavirus vaccines also showed a highly statistically significant benefit in preventing severe rotavirus infection requiring hospitalization ([Analysis 2.3](#)): rhesus (RR 0.48, 95% CI 0.27 to 0.86); bovine (RR 0.37, 95% CI 0.18 to 0.74); and human (RR 0.21, 95% CI 0.09 to 0.48).

Converting these RR values to vaccine efficacy gives the following estimates to prevent one episode of rotavirus diarrhoea requiring hospitalization: 52% (95% CI 14 to 73%) for rhesus vaccines; 63% (95% CI 26 to 82%) for bovine vaccines; and 79% (95% CI 52 to 91%) for human vaccines.

Episodes of more than four days duration

Only the rhesus vaccine significantly reduced the number of cases of rotavirus diarrhoea with more than four days of duration (rhesus: RR 0.61, 95% CI 0.42 to 0.87; bovine: RR 1.01, 95% CI 0.51 to 1.99; [Analysis 2.4](#)).

All-cause diarrhoea

Episodes

Twenty-three trials provided information about all-cause diarrhoea for 11,296 children. A further nine trials provided information on episodes of diarrhoeal disease per person-year in 3944 children. We could not combine the latter in a meta-analysis and have summarized them in [Analysis 3.1](#). Meta-analysis was also not possible for human vaccines, as only one trial provided data on this outcome.

We found a statistically significant beneficial effect of the rhesus vaccines (RR 0.86, 95% CI 0.80 to 0.92; [Analysis 3.2](#)) and bovine vaccines (RR 0.73, 95% CI 0.60 to 0.89; [Analysis 3.2](#)), and no

statistically significant difference for human vaccines (RR 0.91, 95% CI 0.57 to 1.44; [Analysis 3.2](#)).

Converting these RR values to vaccine efficacy gives the following estimates to prevent one episode of diarrhoea: 14% (95% CI 8 to 20%) for rhesus vaccines; and 27% (95% CI 11 to 40%) for bovine vaccines.

Episodes during first week after vaccine (one or multiple doses)

The data indicated a non statistically significant difference between vaccine and placebo in the number of cases of diarrhoea in the first week after inoculation of the vaccine for both rhesus (RR 1.06, 95% CI 0.98 to 1.14) and bovine vaccines (RR 1.02, 95% CI 0.89 to 1.17), and a slightly statistically significant difference for the human vaccines (RR 1.94, 95% CI 1.03 to 3.65) ([Analysis 3.3](#), fixed effect model).

Severe episodes

Rotavirus vaccines showed a non-statistically significant benefit in preventing episodes of severe diarrhoeal diseases: rhesus (RR 0.85, 95% CI 0.72 to 1.00); and bovine (RR 0.51, 95% CI 0.21 to 1.26) ([Analysis 3.4](#)).

Episodes requiring re-hydration

Rotavirus vaccines also showed a statistically significant benefit in preventing diarrhoeal diseases requiring re-hydration: rhesus (RR 0.51, 95% CI 0.30 to 0.88); and bovine (RR 0.42, 95% CI 0.26 to 0.67) ([Analysis 3.5](#)).

Converting these RR values to vaccine efficacy gives the following estimates to prevent one episode of diarrhoea requiring re-hydration: 49% (95% CI 12 to 70%) for rhesus vaccines; and 58% (95% CI 33 to 74%) for bovine vaccines.

Episodes requiring hospitalization

Rotavirus vaccines also showed a non statistically significant benefit in preventing cases of diarrhoea requiring hospitalization: rhesus (RR 0.81, 95% CI 0.66 to 0.99); and bovine (RR 0.55, 95% CI 0.16 to 1.91) ([Analysis 3.6](#)).

Death

All-cause death

Published information about deaths was available in five studies. We received additional information for a further 18 studies after contacting the study authors. Overall, 57 cases of deaths occurred among the different trials. They occurred in trials of rhesus rotavirus vaccine (1 in a RRV-MV trial, 36 in 6 RRV-TV trials), live-attenuated bovine rotavirus vaccines (8 in a RIT-4237 trial, 11 in a WC3 trial), and human-attenuated rotavirus vaccine (1 in a 89-12 trial). Meta-analysis was possible for 4 studies of rhesus rotavirus vaccines, accounting for 10 deaths in 6029 children. An additional 47 deaths occurred during the trials, but we have no information about the specific group to which these participants were allocated, and we could not pool these data together (see [Appendix 3](#) for details). The pooled data indicated a non-statistically significant difference between children randomized to receive rhesus rotavirus vaccines or placebo in the number of deaths (RR 0.72, 95% CI 0.16 to 3.12; [Analysis 4.1](#)).

Exploration of heterogeneity

We could not explore heterogeneity with the human rotavirus vaccines because of the small number of trials testing the vaccine. However, we were able to explore heterogeneity with trials from other classes, and the results are described below.

Risk of bias (Methodological quality)

Trials with adequate (A) or unclear (B) allocation concealment demonstrated a similar ratio of efficacy on preventing rotavirus diarrhoea for rhesus vaccines (A: RR 0.58, 95% CI 0.45 to 0.76; B: RR 0.57, 95% CI 0.48 to 0.67). As for bovine vaccines the comparison between adequate and unclear allocation concealment could not be undertaken because of small number of trials in at least one subgroup ([Analysis 5.1](#) and [Analysis 5.2](#)).

We also observed a similar RR in trials of rhesus vaccines that did report exclusions after randomization (RR 0.59, 95% CI 0.48 to 0.71) compared to those that did not (RR 0.58, 95% CI 0.44 to 0.76). Levels of efficacy were higher for bovine vaccine trials that reported exclusions (RR 0.50, 95% CI 0.26 to 0.96) than for trials that did not report exclusions after randomization (RR 0.61, 95% CI 0.46, 0.82) ([Analysis 5.3](#) and [Analysis 5.4](#)).

Regarding different sample size rhesus vaccine trials presented a slightly higher ratio of efficacy for larger trials when compared to trials with smaller sample size (< 1000 participants: RR 0.66, 95% CI 0.56 to 0.79; ≥ 1000 participants: RR 0.50, 95% CI 0.39 to 0.65). Once again we could not make the comparison for bovine vaccines because only one trial had a sample size of at least 1000 participants ([Analysis 5.5](#) and [Analysis 5.6](#)).

Multiple versus single dose

Trials with multiple dose of rhesus rotavirus vaccine had a higher ratio of efficacy (RR 0.55, 95% CI 0.44 to 0.69) when compared to trials that used single dose of the vaccine (RR 0.64, 95% CI 0.50 to 0.82). Bovine vaccine trials in the other hand had similar ratio of efficacy for both multiple or single doses (multiple doses: RR 0.58, 95% CI 0.39 to 0.86; single dose: RR 0.57, 95% CI 0.40 to 0.83) ([Analysis 6.1](#) and [Analysis 6.2](#)). All trials using multiple doses of vaccine were performed in the 1990s.

Administered with other vaccines

Rhesus vaccine trials that allowed the concomitant use of DPT and/or OPV and rotavirus vaccine demonstrated a higher ratio of efficacy on preventing rotavirus diarrhoea (RR 0.57, 95% CI 0.44 to 0.73) than trials that did not allow the concomitant use of DPT and/or OPV (RR 0.71, 95% CI 0.52 to 0.97). We could not make a comparison among bovine vaccine trials because many trials did not provide this information ([Analysis 7.1](#), [Analysis 7.2](#), and [Analysis 7.3](#)).

Breastfeeding

Rhesus vaccine trials that allowed breastfeeding had a smaller RR (0.52, 95% CI 0.32 to 0.86) than trials that did not allow breastfeeding at least one hour before or after vaccination (0.61, 95% CI 0.51 to 0.73). Conversely, bovine vaccine trials had a higher RR for trials that allowed breastfeeding at least one hour before or after vaccination (0.64, 95% CI 0.48 to 0.85) than the ones that did not (0.45, 95% CI 0.21 to 0.94) ([Analysis 8.1](#) and [Analysis 8.2](#)). No information was provided about breastfeeding in four trials ([Analysis 8.3](#)).

Number of seasons of follow up

Rhesus vaccine trials had a similar ratio of efficacy for trials where children were followed up for one or at least two seasons (one season: RR 0.57, 95% CI 0.42 to 0.78; two or more seasons: RR 0.60, 95% CI 0.48 to 0.74). We found a slight difference among bovine vaccine trials that followed up for one season (RR 0.52, 95% CI 0.32 to 0.83) or at least two seasons (RR 0.60, 95% CI 0.43 to 0.84) ([Analysis 9.1](#) and [Analysis 9.2](#)).

Different rotavirus strains

We analysed the following vaccines separately for rotavirus diarrhoea, severe rotavirus diarrhoea, and all-cause diarrhoea: rhesus tetravalent vaccine (RRV-TV), rhesus monovalent vaccines (RRV, RRV-D, RRV-DS1, or RRV-ST3), bovine vaccines (RIT-4237 or WC3), bovine-human vaccine (WC3-QV), and human vaccines (89-12 or M37). We observed a statistically significant beneficial effect for most vaccines, except for the bovine vaccine WC3 and the human vaccine M37 for rotavirus diarrhoea and severe episodes of rotavirus diarrhoea. The complete results are presented in [Appendix 5](#) and [Analysis 10.1](#), [Analysis 10.2](#), and [Analysis 10.3](#).

The NNT for each specific vaccine is available in [Appendix 5](#). Eleven of the 40 trials that dealt with vaccine efficacy had more than one group of vaccine combined for the meta-analysis ([Lanata 1989](#); [Mutz 1989](#); [Vesikari 1992](#); [Flores 1993](#); [Bernstein 1995](#); [Rennels 1995](#); [Rennels 1996](#); [Lanata 1996a](#); [Lanata 1996b](#); [Santosham 1997](#); [Perez-Schael 2002](#)), which generated an imbalance in the number of participants and might imply possible bias on the calculation of the NNT ([Altman 2002](#)).

Country of origin: income status

We also analysed rotavirus vaccines according to the income status of country of origin. Trials of rhesus and human rotavirus vaccines were performed only in high- and middle-income countries; only three small trials of bovine vaccine were performed in low-income countries. We could only do subgroup analyses for rhesus rotavirus vaccine in high- and middle-income countries. The results did not tend to be significantly different for any of the main outcomes. The complete results are presented in [Analysis 11.1](#), [Analysis 11.2](#), [Analysis 11.3](#), [Analysis 11.4](#), [Analysis 11.5](#), [Analysis 11.6](#), and [Analysis 11.7](#).

Adverse events

Forty-nine trials provided information on the safety of rotavirus vaccines for 16,602 children. We have summarized the results according to the outcomes collected in the published trials and personal communication with several authors.

Bowel obstruction and/or intussusception

Published information about cases of bowel obstruction and/or intussusception was available in two studies. We received additional information for a further 20 studies after contacting the study authors. Overall, four cases of intussusception were reported among trials of the rhesus rotavirus vaccine RRV-TV. Additional cases of intussusception in trials conducted with RRV-TV were described in the literature ([Rennels 1998](#); [Murphy 2001](#); [Niu 2001](#); [Zanardi 2001](#); [Murphy 2002](#)), but we failed to get this information after three attempts of contacting the authors.

The intussusception cases occurred between 6 and 44 days after vaccination: one was reported in the vaccine and three in the placebo group. A meta-analysis was possible for three studies of rhesus rotavirus vaccines with a total of 4123 children. The pooled data indicated a non statistically significant difference in the number of intussusception between children randomized to receive rhesus rotavirus vaccines or placebo (RR 0.42, 95% CI 0.07 to 2.42; [Analysis 12.1](#)).

Minor adverse events

Fever occurred more frequently among those taking rhesus vaccines (RR 2.00, 95% CI 1.51 to 2.64), and there was a non statistically significant difference between vaccine and placebo for

bovine vaccines (RR 0.95, 95% CI 0.73 to 1.23) and human vaccines (RR 1.75, 95% CI 0.85 to 3.64) ([Analysis 12.2](#)).

There was no statistically significant difference between vaccine and placebo in the numbers of episodes of vomiting (rhesus: RR 0.96, 95% CI 0.90 to 1.03; bovine: RR 1.05, 95% CI 0.90 to 1.22; human: RR 1.94, 95% CI 1.00 to 3.75; [Analysis 12.3](#), fixed effect model), and irritability (rhesus: RR 1.01, 95% CI 0.85 to 1.20; bovine: RR 1.08, 95% CI 0.86 to 1.36; human: RR 0.70, 95% CI 0.51 to 0.98; [Analysis 12.4](#), fixed effect model).

Funnel plot

Regarding the presence of possible publication bias, the funnel plot of the precision (inverse of the standard error) against the logarithm of the RR does not show an important asymmetry ([Figure 1](#)).

Figure 1. The size of the circle is proportional to the size of the trial.

DISCUSSION

Vaccine efficacy

Different rotavirus vaccines afforded different levels of efficacy. The pooled analysis showed an efficacy against one episode of rotavirus diarrhoea of 41% for rhesus and bovine vaccines, and of 58% for human vaccines. Efficacy against one episode of severe rotavirus diarrhoea varied from 79% for human vaccines

to 58% for rhesus vaccines. Statistically significant, but lower efficacy was demonstrated against one episode of all-cause diarrhoea, varying from 14% for rhesus vaccines to 27% for bovine vaccines. Heterogeneity among studies, however, compromise the results described here and should be taken into account. The pooled analysis for each specific vaccine showed that rhesus rotavirus vaccines (RRV-TV, RRV-MV), live-attenuated bovine rotavirus vaccine (RIT-4237), and human-attenuated rotavirus

vaccine (89-12) were moderate to highly efficacious against one episode of rotavirus diarrhoea (42, 40, 35, and 68% respectively); and rhesus rotavirus vaccine (RRV-TV), live-attenuated bovine rotavirus vaccine (RIT-4237), and human-attenuated rotavirus vaccine (89-12) were highly efficacious against one episode of severe rotavirus diarrhoea (60, 62, and 79% respectively).

Vaccine and mortality

We failed to demonstrate any impact of the tested vaccines on mortality because the included trials did not provide the relevant information. However, as a result of gathering together published and unpublished information, we became aware of 57 deaths that occurred in the rotavirus vaccine trials (rhesus rotavirus vaccines: 1 on RRV-MV, 36 on RRV-TV; bovine rotavirus vaccines: 8 on RIT-4237, 11 on WC3; human rotavirus vaccine: 1 on 89-12); all but six of these deaths occurred in low- or middle-income countries. We could not combine these data because information about the allocation of children in the vaccine or placebo arms of the trial was provided only in three cases. However if one speculates that the non-reported deaths might have happened in the vaccine arm of the trials one could say that one death occurred for every 200 children vaccinated with rhesus tetravalent vaccine (RRV-TV), for every 150 children vaccinated with the bovine vaccine RIT-4237, and for every 35 children vaccinated with the bovine vaccine WC3 (roughly estimations of the number of children needed to be vaccinated to cause one death, not based on accurate information). Yet, according to the investigators the cause of deaths on these trials was not related to the vaccine (see Appendix 3 for more details).

Furthermore, in our communication with investigators of the trials performed in South America (Brazil, Peru, and Venezuela), it became clear that these trials were conducted under ideal circumstances (ie rigorous surveillance and prompt treatment of children participating in the trials) that might not reflect the reality of treating rotavirus diarrhoea in poor communities worldwide. The investigators stated that if a child developed an episode of diarrhoea they would immediately start oral re-hydration and daily visits to the house. This rigorous surveillance might have impacted on the relatively low mortality described in the trials. In addition, most of the trials reportedly tested the vaccine in low risk individuals, however, higher morbidity and mortality occurs in high-risk children, particularly the malnourished ones.

Rare adverse events

We fail to provide any evidence about the possible link of the rhesus rotavirus vaccine RRV-TV and intussusception (Murphy 2001; Cale 2002). In our communication with the principal investigators we also identified two cases of intussusception that occurred in a small trial conducted in China with the bovine vaccine WC3 (Dr Ho, personal communication).

Disease severity

Insufficient or no information was provided for the outcomes measuring the severity of the episodes of all-cause diarrhoea and/or rotavirus diarrhoea (diarrhoea requiring hospitalization, re-hydration, and malnutrition at follow up). In addition, the severity of the episode of diarrhoea was measured using different scales and might not represent the same spectrum of disease severity. Furthermore, once again the rigorous surveillance of children – particularly in the South American trials – might have influenced

the low frequency of severe diarrhoea measured by hospitalization and dehydration.

High-, middle-, and low-income countries

Rhesus rotavirus vaccines trials were performed in high- and middle-income countries (South America). Contrary to what has been described in the literature (Josefson 1997; Bresee 1999; Cunliffe 2002; WHO/UNICEF 2002), when comparing the pooled results of studies performed in these two group of countries, rhesus vaccine demonstrated a similar efficacy against one episode of rotavirus diarrhoea (44% and 36%, respectively), or against one episode of diarrhoea (around 15%), and a slight difference favouring high-income countries for the efficacy of the vaccine against one episode of severe rotavirus diarrhoea (61% and 50%, respectively). As for bovine vaccines, although they were tested in high-, middle-, and low-income countries, we could only pool data for high-income countries showing a 50% of efficacy against one episode of rotavirus diarrhoea, 69% against severe rotavirus diarrhoea, and 31% against all-cause diarrhoea in such countries. We could not stratify or pool data for the three trials performed with the human rotavirus vaccines.

Another important issue for the future implementation of rotavirus vaccines is whether rotavirus vaccines can become part of the World Health Organization's 'Expanded Program of Immunization'. From the sensitivity analyses performed on this review the concomitant use of DPT and/or OPV did not impact on the efficacy of the rotavirus vaccines. This is particularly relevant for the implementation of rotavirus vaccines in low- and middle-income countries.

Limitations of this systematic review

To avoid publication bias, we have searched different databases and retrieved relevant publications regardless of language, and have contacted authors and checked the references of the included trials. We also performed a funnel plot for the main outcome, which showed no relevant asymmetry. We also made an additional effort in writing every contact author of the included trials in order to obtain further information about methodological issues and results of the published trials. Nevertheless, we were able to identify the procedure used to guarantee the concealment of the allocation in only 15 out of the 64 trials included in this review. Moreover, only 29 out of the 64 trials described the procedure used to guarantee the double blinding in their trials, and only in 19 out of the 40 trials reporting data on efficacy of rotavirus vaccines was it possible to perform the meta-analysis on an intention-to-treat basis.

In addition, we could not fully determine the reasons for heterogeneity among studies, although we have tried to use different statistics to account for the given heterogeneity. Because of this we decided not to perform an overall meta-analysis, which could provide an 'average' statement not easy to interpret quantitatively in relation to the benefits that might accumulate from any rotavirus vaccine. The percentage of total variation across studies due to heterogeneity (Higgins 2003) was around 70% for all group of vaccines in the main outcome (rotavirus diarrhoea) and for rhesus and bovine vaccines on severe rotavirus infection. This level of heterogeneity was maintained for the rhesus vaccine RRV-TV and the bovine vaccine RIT-4237, even when the meta-analysis pooled together only trials that tested specifically these vaccines. Possible reasons that have been suggested in the literature are

the concomitant use of other vaccines, the number of doses of the vaccines, whether mothers were allowed to breastfeed children during the vaccination, and whether trials were performed in low-, middle-, or high-income countries. We performed subgroup analyses to evaluate the impact of these issues and observed that the concomitant use of rotavirus vaccine and DPT or OPV vaccines, and breastfeeding during vaccination did not appear to impact on the pooled data. Conversely, when trials were performed in high-, middle-, or low-income countries, and used a single or multiple doses of vaccine, we observed a statistically significant difference between groups.

AUTHORS' CONCLUSIONS

Implications for practice

Based on the available information gathered on this review, we cannot recommend rotavirus vaccines in routine clinical practice.

Rhesus, bovine, and human rotavirus vaccines were moderate to highly efficacious against rotavirus diarrhoea, and showed lower, but statistically significant levels of efficacy for all-cause diarrhoea. However, results on mortality and adverse events during the follow up period of the different trials might have served to draw different conclusions about the efficacy of the vaccines. For example, we were unable to obtain detailed information about 47 of the 57 deaths occurred during follow up of different trials, and the lack of data on intussusception precludes the present use of the rhesus vaccine RRV-TV. The high level of heterogeneity observed among different vaccines in the main outcomes could also make the results prone to possible overestimation of effects.

In addition, the current results are mainly based on trials performed in high- and middle-income countries. Only three small trials were performed in low-income countries. It is also important to state that the trials performed in South America countries were done under rigorous surveillance and might not reflect the reality of treating diarrhoea (with or without dehydration and malnutrition) in middle- and low-income countries. Research has been performed on lamb and another human rotavirus vaccine, but efficacy trials are still not available.

Implications for research

Based on the current evidence, we recommend the performance of additional placebo-controlled randomized trials, particularly with the new bovine, human, lamb, and inactivated vaccines. The trials should be conducted in parallel in high-, middle-, and low-income countries, have a simple design, and involve tens of thousands of children. Trials carried out this far had enough power to elucidate efficacy, but safety remains to be clarified. Outcomes of major importance, such as severe diarrhoea, intussusception, and death, should be collected (Verstraeten 2001). The lively debate that took place after the rhesus tetravalent rotavirus vaccine (RRV-TV) was withdrawn from the market suggests that researchers and sponsors of rotavirus vaccine trials are concerned about the costs of trials if sample size is to aim at rare adverse events (Jacobson 2001).

However, uncertainty regarding safety of rotavirus vaccines could end up being harmful and costly, particularly for those in middle- and low-income countries where the vaccine is most needed. Even if use of intussusception as a primary outcome is precluded by the enormous sample size needed, data can be carefully collected for later use in systematic reviews and meta-analyses.

The design and outcomes of trials are often tailored to the type of the disease occurring in high-income countries, and to the outcomes of interest in these countries, but this might not be appropriate for use in low- and middle-income countries (WHO/UNICEF 2002). This approach already led to early research being abandoned on bovine vaccines that appeared to be efficacious, and every effort should be made to avoid a repetition of the same mistake.

The proposed trials should account for the different agenda of rotavirus vaccines in different regions of the world (Josefson 1997; Weijer 2000). The design should take into account that rotavirus infections are caused by different strains, have a different severity and seasonability in high, middle and low-income countries. In particular, trials should take into consideration that, although rotavirus diarrhoea accounts for a high number of hospitalization in high-income countries, death is a rare event. Conversely, in middle- and low-income countries diarrhoea accounts for approximately 13% of all deaths among children under 5 years of age and 20% of such deaths are related to rotavirus (Weijer 2000; Perez-Schael 2001, WHO 2003).

Future trials should have a careful mechanism to promptly identify, treat, and record rare adverse events. Death should be considered a main outcome in such trials and a detailed report on mortality should be made available. Trials should be simple and aim to test the vaccine in real-life situations, especially in middle- and low-income countries.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Anderson 1986

Methods	Randomization: no details
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Anderson 1986 (Continued)

Allocation concealment: no details

Blinding: single (placebo and vaccine looked similar)

Data collection: no details

Intention to treat: yes

Interim analysis: none

Exclusion from analysis: none

Follow-up period: 8 days after vaccination

Participants	<p>Age: 8 to 60 months</p> <p>Health status: healthy</p> <p>Breastfeeding: 50 to 75%</p> <p>Immunization status: no information</p> <p>Clinical symptoms: clinical evaluation, no further details</p> <p>Laboratory studies: serology and stool analysis by ELISA</p>
Interventions	<p>1. Rhesus vaccine (MMU 18006), $10^{6.5}$ PFU single dose (n = 13)</p> <p>2. Placebo (similac formula), 30 ml single dose (n = 10)</p> <p>30 ml similac formula given with vaccine or placebo</p>
Outcomes	<p>1. Safety: clinical symptoms within 8 days</p>
Notes	<p>Study location: USA</p> <p>Two separate trials</p>

Barnes 1997

Methods	<p>Randomization: no details</p> <p>Allocation concealment: no details</p> <p>Blinding: double (vaccine and placebo ampoules identified by participant number only)</p> <p>Data collection: no details</p> <p>Intention to treat: yes</p> <p>Interim analysis: none</p> <p>Exclusion from analysis: none</p> <p>Follow-up period: 4 weeks after vaccination</p>
Participants	<p>Age: 3 to 360 months</p> <p>Health status: healthy</p> <p>Immunization status: no information</p> <p>Breastfeeding: no information</p>

Rotavirus vaccine for preventing diarrhoea (Review)

Barnes 1997 (Continued)

	Clinical symptoms: clinical evaluation, no further details
	Laboratory studies: serology and stool analysis by ELISA
Interventions	1. Human vaccine (RV3), 6.5×10^5 PFU, single dose (n = 15). 2. Placebo (uninfected monkey kidney culture fluids), single dose (n = 15) 1 h fasting and then 30 ml soy formula given before vaccine or placebo
Outcomes	1. Safety: clinical symptoms within 4 weeks of vaccination
Notes	Study location: Australia

Barnes 2002

Methods	Randomization: block randomization in groups of 6 independently done by the University of Melbourne Statistical Consulting Centre Allocation concealment: no details Blinding: double (vaccine and placebo ampoules identical) Data collection: no details Intention to treat: no Interim analysis: none Exclusion from analysis: 1/60 withdrawn from follow up by parents; 5/59 excluded from analysis due to wild-type infection before or during trial Follow-up period: 7 days after vaccination; 2 rotavirus seasons after completion of all vaccinations
Participants	Age: 3 months Health status: healthy Immunization status: vaccine administered not closer than 14 days to routine immunizations Breastfeeding: > 75%
Interventions	1. Human vaccine (RV3), 6.5×10^5 PFU with soy-based formula (n = 20) or without soy-based formula (n = 20), 3 doses 2. Placebo (uninfected monkey kidney culture fluids) with soy-based formula, 3 doses (n = 20) 1 h fasting and then 10 ml soy formula given before vaccine (only in 1 of 2 vaccine groups) or placebo 400 mg of sodium bicarbonate given to all groups before vaccination
Outcomes	1. Safety: clinical symptoms within 7 days of vaccination. 2. Efficacy: diarrhoea within 2 rotavirus seasons of beginning of trial
Notes	Study location: Australia Clinical symptoms: clinical evaluation, severity score measured by Flores 1987 scale

Barnes 2002 (Continued)

Laboratory studies: serology by ELISA, stool analysis by ELISA and PCR

Bernstein 1990

Methods	Randomization: randomization code provided by Institut Merieux Allocation concealment: no details Blinding: double (no further details) Data collection: 7 September 1987 to 30 June 1989 Intention to treat: no Interim analysis: none Exclusion from analysis: 1\206 not evaluated; 42\205 not followed over the second year because of no consent Follow-up period: 7 days after vaccination; 2 rotavirus seasons after beginning of trial
Participants	Age: 2 to 12 months Health status: healthy Breastfeeding: < 50% Immunization status: DTP and OPV vaccination not allowed within 2 weeks of WC3 vaccination
Interventions	1. Bovine vaccine (WC3), 10^7 PFU, single dose (n = 103) 2. Placebo (diluent), 2 ml single dose (n = 103) 30 ml formula or 1 ml/kg antacid given before vaccine or placebo
Outcomes	1. Safety: clinical symptoms within 7 days of vaccination 2. Efficacy: diarrhoea within 2 rotavirus seasons of beginning of trial
Notes	Study location: USA Feeding was withheld from infants for at least 1 h before vaccine. Breastfeeding also withheld for 1 h after vaccine Clinical symptoms: clinical evaluation (diarrhoea defined as ≥ 2 watery stools in 24 h); severity score measured by Clark 1988 scale Laboratory studies: serology by ELISA and fluorescent focus reduction assay; stool analysis by plaque assay and ELISA

Bernstein 1995

Methods	Randomization: random code prepared by the pharmaceutical industry Allocation concealment: no details Blinding: double (identical appearing vials) Data collection: 10 October 1989 to 1 July 1991
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Rotavirus vaccine for preventing diarrhoea (Review)

Bernstein 1995 (Continued)

	<p>Intention to treat: no</p> <p>Interim analysis: performed after first season; no changes made on the study protocol as a result of the interim analysis</p> <p>Exclusion from analysis: 17\1006 not vaccinated 91\989 not included in first year follow up; 34\898 not included in second year follow up</p> <p>Follow-up period: 5 days after vaccination; 2 rotavirus seasons after beginning of trial</p>
Participants	<p>Age: 1 to 6.5 months</p> <p>Health status: healthy</p> <p>Breastfeeding: < 50%</p> <p>Immunization status: OPV vaccination given within 2 weeks of RRV vaccination in 120 participants</p>
Interventions	<p>1. Rhesus + human tetravalent vaccine (RRV-TV), 4×10^4 PFU, single dose (n = 332).</p> <p>2. Monovalent vaccine (D x RRV), 4×10^4 PFU, single dose (n = 327)</p> <p>3. Placebo (uninfected tissue culture fluids), single dose (n = 330)</p> <p>400 mg sodium bicarbonate in 30 ml cow milk or soy formula given before vaccine or placebo</p>
Outcomes	<p>1. Safety: clinical symptoms within 5 days of vaccination</p> <p>2. Efficacy: gastrointestinal illness within 2 rotavirus seasons of beginning of trial</p>
Notes	<p>Country: USA</p> <p>Clinical symptoms: clinical evaluation (diarrhoea defined as ≥ 3 watery or loose stools in 24 h); severity score measured by Flores 1987 scale</p> <p>Laboratory studies: serology by ELISA and focus reduction assay; stool analysis by ELISA</p> <p>All other vaccines given as scheduled</p>

Bernstein 1998

Methods	<p>Randomization: no details</p> <p>Allocation concealment: code was not available until end of study</p> <p>Blinding: double (no details)</p> <p>Data collection: enrolment between August 1995 and November 1995, end of vaccination December 1995</p> <p>Intention to treat: no</p> <p>Interim analysis: none</p> <p>Exclusion from analysis: 1\116 not followed because of persistent otitis</p> <p>Follow-up period: 1 week after each vaccination</p>
Participants	<p>Age: 1.5 to 60 months</p> <p>Health status: no information</p>

Bernstein 1998 (Continued)

Breastfeeding: no information

Immunization status: no vaccination allowed within 2 weeks of rotavirus vaccination

Clinical symptoms: clinical evaluation, diarrhoea was defined as 3 or more unformed stools within 48 h.
Fever was defined as a rectal temperature > 38.1 °C in paediatric participants, confirmed within 20 minutes

Laboratory studies: stool analysis by ELISA and PCR

Serology by plaque reduction neutralization and ELISA

Interventions	<p>1. Human (89-12), 10⁵ PFU single dose for adults and children (n = 40), 2 doses for infants (n = 21)</p> <p>2. Placebo (n = 55), no further details</p> <p>50 ml sodium bicarbonate for adults and 0.5 ml/kg Mylanta-DS for infants and children given before vaccine or placebo</p>
Outcomes	<p>1. Safety: clinical symptoms within 7 days of each vaccination</p>
Notes	<p>Study location: USA</p> <p>Clinical symptoms: clinical evaluation (diarrhoea defined as ≥ 3 watery or loose stools in 24 h, fever defined as > 100.4 °F)</p> <p>Laboratory studies: serology and stool analysis by ELISA</p> <p>Immunization with other vaccines separated by at least 2 weeks from the RV</p> <p>3 separate trials: adults and children (2 to 12 years) for initial trials; infants (6 to 26 weeks) for last trial</p>

Bernstein 1999

Methods	<p>Randomization: computer generated, blocks of 10, provided by sponsor</p> <p>Allocation concealment: code was not available until end of study</p> <p>Blinding: double (no further details)</p> <p>Data collection: August 1997 to May 1999</p> <p>Intention to treat: no</p> <p>Interim analysis: none</p> <p>Exclusion from analysis: 1\215 not vaccinated because of persistent fever; 1\214 not re-vaccinated because of congenital malformation; 1\213 died of pneumococcal sepsis; 28\212 were not available for second season follow up, no further details</p> <p>Follow-up period: 1 week after each vaccination; 2 rotavirus season after beginning of trial</p>
Participants	<p>Age: 10 to 16 weeks</p> <p>Health status: healthy</p> <p>Breastfeeding: 50 to 75%</p> <p>Immunization status: no other vaccine allowed within 2 weeks of vaccination</p>
Interventions	<p>1. Human (89-12), 10⁵ PFU, two doses (n = 108)</p>

Bernstein 1999 (Continued)

	2. Placebo (tissue culture medium), 1 ml, 2 doses (n = 107) 2 ml antacid given before vaccine or placebo
Outcomes	1. Safety: clinical symptoms within 7 days of each vaccination. 2. Efficacy: gastroenteritis (rotavirus or other) within the study period (18 months)
Notes	Study location: USA Feeding withheld for at least 1 h before and after vaccine Clinical symptoms: clinical evaluation (gastroenteritis defined as vomiting, ≥ 3 loose stools), severity score measured by Flores 1987 scale Laboratory studies: serology by ELISA and antigen reduction assay; stool analysis by ELISA All other immunizations separated from RV by at least 2 weeks

Bresee 2001

Methods	Randomization: block randomization in groups of 6 Allocation concealment: no details Blinding: double (vaccine and placebo that tasted and appeared identical) Data collection: October 1998 to February 1998 enrolment, no further details Intention to treat: no Interim analysis: none Exclusion from analysis: 9\120 not vaccinated because of parental refusal (8) or death (1 case due to severe pneumonia); 2\111 did not complete trial because of death (1 case due to suspected sudden infant death syndrome) or relocation (1) Follow-up period: 1 week after each vaccination
Participants	Age: 2 to 6 weeks Health status: healthy, full term Breastfeeding: no information Immunization status: no information
Interventions	1. Rhesus + human tetravalent vaccine (RRV-TV), 4×10^5 PFU, 3 doses (n = 60) 2. Placebo (lyophilized growth medium with 10% SPG), 3 ml, 3 doses (n = 60)
Outcomes	Safety: clinical symptoms within 7 days of each vaccination
Notes	Study location: Bangladesh Clinical symptoms: clinical evaluation, no further details Laboratory studies: serology by ELISA and by neutralizing antibody titers; stool analysis by ELISA, polyacrylamide gel electrophoresis (PAGE) and by reverse transcriptase (RT)-PCR

Christy 1988

Methods	Randomization: sequential enrolment and vaccination according to table of random numbers Allocation concealment: no details Blinding: double (similar appearance to vaccine and placebo vials) Data collection: October 1986 to July 1986 Intention to treat: no Interim analysis: none Exclusion from analysis: 1\176 for "reasons unrelated to trial" Follow-up period: 10 days after each vaccination; 10 months after beginning of trial
Participants	Age: 2 to 4 months Health status: healthy Breastfeeding: < 50% Immunization status: DPT and polio vaccinations not allowed within 4 weeks before and 3 weeks after vaccination
Interventions	1. Rhesus (MMU 18006), 10^4 PFU, single dose (n = 88) 2. Placebo (soy formula), 1 ml single dose (n = 88) 400 mg sodium bicarbonate in 30 ml soy formula given before vaccine or placebo
Outcomes	1. Safety: clinical symptoms within 10 days of each vaccination. 2. Efficacy: gastroenteritis (rotavirus or other) within 10 months of beginning of trial
Notes	Study location: USA All feedings withheld for 1 h before and after vaccine Clinical symptoms: clinical evaluation, severity measured by WHO criteria (fever (≥ 38) vomiting, dehydration, > 6 stools in 24 h, and illness duration ≥ 24 h) Laboratory studies: serology by micro neutralization assay and ELISA; stool analysis by ELISA

Christy 1993

Methods	Randomization: block randomization scheme Allocation concealment: no details Blinding: double (no further details) Data collection: 21 November 1991 to 1 June 1992 Intention to treat: no Interim analysis: none Exclusion from analysis: 4/31 excluded for having diarrhoea from wild-type rotavirus; 1/27 did not receive second dose "for reasons unrelated to vaccination"
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Christy 1993 (Continued)

Follow-up period: 10 days after each vaccination; 6 months after beginning of trial

Participants	<p>Age: 2 to 6 months</p> <p>Health status: no information</p> <p>Breastfeeding: no information</p> <p>Immunization status: no information</p>
Interventions	<p>1. Bovine + human reassortant (WI79-9), $10^{7.5}$ PFU, 2 doses (n = 16)</p> <p>2. Placebo (cell culture medium with cherry syrup), 2.5 ml, 2 doses (n = 15)</p> <p>400 mg sodium bicarbonate in 30 ml soy formula given before vaccine or placebo</p>
Outcomes	<p>1. Safety: clinical symptoms within 10 days of each vaccination</p> <p>2. Efficacy: gastroenteritis within 6 months of beginning of trial</p>
Notes	<p>Study location: USA</p> <p>Breastfeeding withheld for 1 h before vaccine</p> <p>Clinical symptoms: clinical evaluation (significant diarrhoea defined as ≥ 2 watery stools in 24 h)</p> <p>Laboratory studies: stool analysis by ELISA; serology by micro-neutralization</p>

Clark 1988

Methods	<p>Randomization: serial coding according to table of random numbers</p> <p>Allocation concealment: code unbroken until end of trial, no further details</p> <p>Blinding: double (numbered identical vials)</p> <p>Data collection: September 1985 to June 1986</p> <p>Intention to treat: unknown (only number of infants completing the trial mentioned)</p> <p>Interim analysis: none</p> <p>Exclusion from analysis: unknown</p> <p>Follow-up period: 1 week after each vaccination; 10 months after beginning of trial</p>
Participants	<p>Age: 3 to 12 months</p> <p>Health status: healthy</p> <p>Breastfeeding: < 50%</p> <p>Immunization status: DPT vaccination not allowed within 1 week before vaccination</p>
Interventions	<p>1. Bovine (WC3), $10^{7.5}$ PFU, single dose (n = 49)</p> <p>2. Placebo (cell culture medium with 0.5 ml cherry syrup), 2.5 ml single dose (n = 55)</p> <p>30 ml formula or 85 mg antacid given before vaccine or placebo</p>
Outcomes	<p>1. Safety: clinical symptoms within 7 days of each vaccination</p>

Clark 1988 (Continued)

2. Efficacy: gastroenteritis (rotavirus or other) within 10 months of beginning of trial

Notes	<p>Study location: USA</p> <p>No feeding 1 h before vaccine, and no breastfeeding 1 h after vaccine</p> <p>Clinical symptoms: clinical evaluation (significant diarrhoea defined as ≥ 2 watery stools in 24 h); severity score measured by Clark 1988 (modified Duffy 1986) scale</p> <p>Laboratory studies: serology by plaque reduction neutralization; stool analysis by PAGE-SS analysis and ELISA</p> <p>At least 1 week between DTP and RV</p>
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Clark 1990

Methods	<p>Randomization: table of random numbers</p> <p>Allocation concealment: no details</p> <p>Blinding: double (numbered vials)</p> <p>Data collection: September 1987 to July 1988</p> <p>Intention to treat: no details, only number of infants completing the trial mentioned</p> <p>Interim analysis: none</p> <p>Exclusion from analysis: no details</p> <p>Follow-up period: 1 week after each vaccination; 17 weeks after vaccination</p>
Participants	<p>Age: 2 to 11 months</p> <p>Health status: healthy</p> <p>Breastfeeding: < 50%</p> <p>Immunization status: DPT and polio vaccinations not allowed within 7 days of vaccination</p>
Interventions	<p>1. Bovine + human reassortant (WI79-9), 2×10^7 PFU, 2 doses (n = 38)</p> <p>2. Placebo (cell culture medium with 20% cherry syrup), 2 doses (n = 39)</p> <p>30 ml formula or 85 mg antacid given before vaccine or placebo</p>
Outcomes	<p>1. Safety: clinical symptoms within 7 days of each vaccination</p> <p>2. Efficacy: gastroenteritis within 17 weeks of vaccination</p>
Notes	<p>Study location: USA</p> <p>Clinical symptoms: clinical evaluation; severity score measured by modified Duffy 1986 scale</p> <p>Laboratory studies: serology by plaque reduction neutralization test; stool analysis by latex agglutination test</p> <p>At least 7 days between DTP and RV</p>

Clark 1995

Methods	Randomization: no details Allocation concealment: no details Blinding: double (no further details) Data collection: no information Intention to treat: no Interim analysis: none Exclusion from analysis: 12/417 were not evaluated, no further details Follow-up period: 1 week after each vaccination; 1 rotavirus season after vaccination
Participants	Age: 2 to 6 months Health status: no information Breastfeeding: no information Immunization status: no information
Interventions	1. Human-bovine QHBRV, 4×10^7 PFU, 3 doses (n = 199) 2. Placebo (no details), 3 doses (n = 206)
Outcomes	1. Safety: clinical symptoms within 7 days of each vaccination 2. Efficacy: gastroenteritis within 1 rotavirus season of vaccination
Notes	Study location: USA Clinical symptoms: clinical evaluation; severity score measured by modified Duffy 1986 scale Laboratory studies: stool analysis by solid phase immunoassay and electropherotype analysis

Clements-Mann 1999

Methods	Randomization: no details Allocation concealment: no details Blinding: double (no further details) Data collection: no information Intention to treat: no Interim analysis: none Exclusion from analysis: 5/182 were excluded for exceeding the age limit Follow-up period: 1 week after each vaccination
Participants	Age: 1.5 to 60 months Health status: no information Breastfeeding: no information

Clements-Mann 1999 (Continued)

Immunization status: no vaccination allowed within 2 weeks of rotavirus vaccination

Interventions	<ol style="list-style-type: none"> Human-bovine D x UK, $10^{4.8}$ PFU, single dose (n = 17) Human-bovine D x UK, $10^{5.8}$ PFU, single dose (n = 20) Human-bovine DS-1 x UK, $10^{4.3}$ PFU, single dose (n = 18) Human-bovine DS-1 x UK, $10^{5.3}$ PFU, single dose (n = 11) Human-bovine P x UK, $10^{4.3}$ PFU, single dose (n = 10) Human-bovine P x UK, $10^{5.3}$ PFU, single dose (n = 21) Human-bovine ST3 x UK, $10^{4.8}$ PFU, single dose (n = 8) Human-bovine ST3 x UK, $10^{5.8}$ PFU, single dose (n = 14). Placebo (buffered solution), single dose (n = 63) <p>30 ml of formula mixed with 0.4 g of sodium bicarbonate given before vaccine or placebo</p>
Outcomes	<ol style="list-style-type: none"> Safety: clinical symptoms within 7 days of each vaccination
Notes	<p>Study location: USA</p> <p>1 h fasting before vaccination</p> <p>Clinical symptoms: clinical evaluation; diarrhoea was defined as 3 or more unformed stools within 48 h; fever was defined as a rectal temperature $> 38.1^{\circ}\text{C}$ in paediatric participants, confirmed within 20 minutes</p> <p>Laboratory studies: stool analysis by ELISA and PCR; serology by plaque reduction neutralization and ELISA</p>

Dagan 1992

Methods	<p>Randomization: no details</p> <p>Allocation concealment: no details</p> <p>Blinding: double (vaccine and placebo vials looked alike and were coded)</p> <p>Data collection: study started July 1988, no further details.</p> <p>Intention to treat: no</p> <p>Interim analysis: none</p> <p>Exclusion from analysis: 19\240 did not receive second vaccine</p> <p>Follow-up period: 10 days after each vaccine, 1 year after beginning of trial</p>
Participants	<p>Age: 2 days old infants</p> <p>Health status: healthy</p> <p>Breastfeeding: $> 75\%$</p> <p>Immunization status: no OPV vaccines allowed within 2 weeks of vaccination</p>

Dagan 1992 (Continued)

Interventions	1. Rhesus + human tetravalent vaccine (D x RRV + DS1 x RRV + RRV + ST3 x RRV), 4×10^4 PFU, 2 doses (n = 183) 2. Placebo (uninfected cell culture fluid), 2 doses (n = 57) 200 mg citrate-bicarbonate in 20 ml similac formula given before vaccine or placebo
Outcomes	1. Safety: clinical symptoms within 10 days of each vaccination
Notes	Study location: Israel Clinical symptoms: clinical evaluation, no further details Laboratory studies: serology by ELISA At least 14 days were allowed between OPV and RV

De Mol 1986

Methods	Randomization: no details Allocation concealment: no details Blinding: double (no further details) Data collection: April 1985 to August 1985 Intention to treat: no information Interim analysis: none Exclusion from analysis: no information Follow-up period: 4 months after beginning of trial
Participants	Age: 3 to 8 months Health status: without fever Breastfeeding: > 75% Immunization status: no OPV vaccines allowed within 2 weeks of vaccination
Interventions	1. Bovine RIT 4237, single dose (n = 122), no further details 2. Placebo (no further details), single dose (n = 123)
Outcomes	1. Efficacy: gastroenteritis within 4 months of vaccination
Notes	Study location: Rwanda Clinical symptoms: clinical evaluation, no further details Laboratory studies: serology and stool analysis by ELISA

Dennehy 1996

Methods	Randomization: no details
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Rotavirus vaccine for preventing diarrhoea (Review)

Dennehy 1996 (Continued)

Allocation concealment: no details

Blinding: double (vaccine and placebo vials looked identical)

Data collection: 1 July 1991 to 1 December 1991

Intention to treat: no

Interim analysis: none

Exclusion from analysis: 2\195 were not followed

Follow-up period: 5 days after each vaccine

Participants	<p>Age: 6 to 24 weeks</p> <p>Health status: healthy</p> <p>Breastfeeding: no information</p> <p>Immunization status: no DTP, OPV, or Hib vaccines allowed within 2 weeks of vaccination</p>
Interventions	<p>1. Rhesus + human tetravalent vaccine (RRV-TV), 4×10^6 PFU, single dose (n = 69)</p> <p>2. Rhesus + human tetravalent vaccine (RRV-TV), 4×10^5 PFU, single dose (n = 60)</p> <p>3. Placebo (tissue culture medium), single dose (n = 64)</p> <p>3 ml sodium citrate-bicarbonate given with vaccine or placebo</p>
Outcomes	<p>1. Safety: clinical symptoms within 5 days of vaccination</p>
Notes	<p>Study location: USA</p> <p>At least 2 weeks were allowed between DTP, OPV, Hib, and RV</p> <p>Clinical symptoms: clinical evaluation; diarrhoea defined as ≥ 3 looser than normal stools in 24 h and 1 or more vomiting; fever defined as $> 38^\circ\text{C}$</p> <p>Laboratory studies: serology by ELISA</p>

Eichelberger 2002

Methods	<p>Randomization: no details</p> <p>Allocation concealment: no details</p> <p>Blinding: double (no further details)</p> <p>Data collection: no information</p> <p>Intention to treat: yes</p> <p>Interim analysis: none</p> <p>Exclusion from analysis: none</p> <p>Follow-up period: 1 week after each vaccination</p>
Participants	<p>Age: 1.5 to 60 months</p> <p>Health status: no information</p>

Eichelberger 2002 (Continued)

	Breastfeeding: no information
	Immunization status: no vaccination allowed within 2 weeks of rotavirus vaccination
Interventions	1. Human-bovine Wa x UK, $10^{6.3}$ PFU, single dose (n = 21) 2. Human-bovine Wa x UK, $10^{7.3}$ PFU, single dose (n = 21) 3. Human-bovine Wa x (DS-1xUK), $10^{6.4}$ PFU, single dose (n = 14) 4. Human-bovine Wa x (DS-1xUK), $10^{7.4}$ PFU, single dose (n = 22) 5. Placebo (buffered soy-based formula), single dose (n = 37) 30 ml of formula mixed with 0.4 g of sodium bicarbonate given before vaccine or placebo
Outcomes	1. Safety: clinical symptoms within 7 days of each vaccination
Notes	Study location: USA 1 h fasting before vaccination Clinical symptoms: clinical evaluation; diarrhoea was defined as 3 or more unformed stools within 48 h; fever was defined as a rectal temperature $> 38.1^{\circ}\text{C}$ in paediatric participants, confirmed within 20 minutes Laboratory studies: stool analysis by ELISA and PCR; serology by plaque reduction neutralization and ELISA

Escobar 1988

Methods	Randomization: no details Allocation concealment: no details Blinding: double (vaccine and placebo were identical) Data collection: no details Intention to treat: no information Interim analysis: no information Exclusion from analysis: no information Follow-up period: 3 weeks after vaccination
Participants	Age: 6 to 18 months Health status: without diarrhoea, no further details Breastfeeding: no information Immunization status: no information
Interventions	1. Bovine RIT 4237, 0.5 ml, 10^8 DICT 50, single dose (n = 52) 2. Placebo (same preparation without the virus), single dose (n = 51) 110 ml of formula given before vaccine or placebo

Escobar 1988 (Continued)

Outcomes	1. Efficacy: rotavirus diarrhoea within 3 weeks of vaccination
Notes	Study location: Spain Clinical symptoms: clinical evaluation, no further details Laboratory studies: serology and stool analysis by ELISA

Flores 1988

Methods	Randomization: no details Allocation concealment: no details Blinding: double (no details) Data collection: no details Intention to treat: yes Interim analysis: none Exclusion from analysis: none Follow up-period: 10 days after vaccination
Participants	Age: newborns Health status: healthy newborns and mothers, normal pregnancy Breastfeeding: > 75% Immunization status: no information
Interventions	1. Rhesus (MMU18006) vaccine, 10 ⁴ PFU, single dose (n = 20) 2. Placebo (buffered formula), single dose (n = 20) 200 mg citrate-bicarbonate in 15 ml formula given before vaccine or placebo
Outcomes	1. Safety: clinical symptoms within 10 days of vaccination
Notes	Study location: Venezuela Clinical symptoms: clinical evaluation; diarrhoea defined as ≥ 3 liquid or semi-liquid stools in 24 h Laboratory studies: serology by ELISA, complement-fixation assay, plaque reduction neutralization assay, tube neutralization assay, and VP-7 competition assay; stool analysis by ELISA

Flores 1989

Methods	Randomization: random code assignment to 5 groups Allocation concealment: code prepared in advance, not disclosed to field team, broken at NIH laboratory after follow up ended Blinding: double (same size of ampoules given to each group). Data collection: no details
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Rotavirus vaccine for preventing diarrhoea (Review)

Flores 1989 (Continued)

Intention to treat: no

Interim analysis: none

Exclusion from analysis: 20\116 excluded from study for having diarrhoea, nausea, or vomiting in the week prior to vaccination.

Follow-up period: 1 week after vaccination

Participants	<p>Age: 1 to 5 months</p> <p>Health status: healthy</p> <p>Breastfeeding: no information</p> <p>Immunization status: polio vaccine not given within 2 weeks of vaccination</p>
Interventions	<p>1. Rhesus + human (D x RRV), 10^4 PFU, single dose (n = 24)</p> <p>2. Rhesus + human (DS1 x RRV), 10^4 PFU, single dose (n = 25)</p> <p>3. Rhesus (RRV 3), 10^4 PFU, single dose (n = 21)</p> <p>4. Rhesus + human (D x RRV + RRV), 5×10^3 PFU, single dose (n = 23)</p> <p>5. Placebo (formula alone or with red soda), 1 ml single dose (n = 23)</p> <p>400 mg citrate-bicarbonate in 30 ml similac formula given before vaccine or placebo</p>
Outcomes	<p>1. Safety: clinical symptoms within 1 week of vaccination</p>
Notes	<p>Study location: Venezuela</p> <p>Clinical symptoms: clinical evaluation; diarrhoea defined as ≥ 3 watery or loose stools in 24 h; severity score measured by Flores 1987 scale</p> <p>Laboratory studies: serology by ELISA and plaque reduction neutralization assay; stool analysis by ELISA and cultures</p>

Flores 1990

Methods	<p>Randomization: random order assignment to 4 groups</p> <p>Allocation concealment: code not disclosed to field team until end of analysis, broken at NIH</p> <p>Blinding: double (no further details)</p> <p>Data collection: no details</p> <p>Intention to treat: yes</p> <p>Interim analysis: none</p> <p>Exclusion from analysis: none</p> <p>Follow-up period: 1 week after vaccination</p>
Participants	<p>Age: 10 to 20 weeks</p> <p>Health status: no information</p> <p>Breastfeeding: no information</p>

Rotavirus vaccine for preventing diarrhoea (Review)

Flores 1990 (Continued)

	Immunization status: no information
Interventions	<ol style="list-style-type: none"> 1. Rhesus + human quadrivalent vaccine (3 RRV + D x RRV + DS1 x RRV + ST3 x RRV), 10^4 PFU, single dose (n = 23) 2. Rhesus + human quadrivalent vaccine (3 RRV + D x RRV + DS1 x RRV + ST3 x RRV), 5×10^4 PFU, single dose (n = 22) 3. Human vaccine (M37), 10^4 PFU, single dose (n = 23) 4. Placebo (formula), 1 ml, single dose (n = 22) <p>400 mg citrate-bicarbonate in 30 ml similac formula given before vaccine or placebo</p>
Outcomes	1. Safety: clinical symptoms within 1 week of vaccination
Notes	<p>Study location: Venezuela</p> <p>Clinical symptoms: clinical evaluation; diarrhoea defined as ≥ 3 watery or loose stools in 24 h</p> <p>Laboratory studies: serology by ELISA and plaque reduction neutralization assay; stool analysis by ELISA and cultures</p>

Flores 1993

Methods	<p>Randomization: no details</p> <p>Allocation concealment: code not revealed at any time to field team, no further details</p> <p>Data collection: no details</p> <p>Blinding: double (no further details)</p> <p>Intention to treat: no</p> <p>Interim analysis: yes</p> <p>Exclusion from analysis: 22\302 dropped from study, no further details</p> <p>Follow-up period: 1 week after each vaccination, passive follow up for 8 months</p>
Participants	<p>Age: newborns</p> <p>Health status: healthy</p> <p>Breastfeeding: no information</p> <p>Immunization status: OPV and DPT vaccinations were given 2 weeks after each RRV dose</p>
Interventions	<ol style="list-style-type: none"> 1. Rhesus + human quadrivalent vaccine (3 RRV + D x RRV + DS1 x RRV + ST3 x RRV), 10^5 PFU, 3 doses (n = 101) 2. Rhesus + human quadrivalent vaccine (3 RRV + D x RRV + DS1 x RRV + ST3 x RRV), 10^6 PFU, 3 doses (n = 99) 3. Placebo (uninfected tissue culture fluids), 3 doses (n = 102) <p>400 mg citrate-bicarbonate in 30 ml similac formula given before vaccine or placebo</p>
Outcomes	1. Safety: clinical symptoms within 1 week of vaccination

Flores 1993 (Continued)

2. Efficacy: diarrhoea (rotavirus or other) within 8 months

Notes	<p>Study location: Venezuela</p> <p>Clinical symptoms: clinical evaluation; diarrhoea defined as ≥ 3 watery or loose stools in 24 h</p> <p>Laboratory studies: serology by ELISA and plaque reduction neutralization assays; stool analysis by ELISA</p> <p>Vaccine given between OPV and DPT vaccines.</p>
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Georges-Courbot 1991

Methods	<p>Randomization: table of random numbers, administered in numeric order in the first dose</p> <p>Allocation concealment: no details</p> <p>Blinding: double (identical precoded vials)</p> <p>Data collection: no information</p> <p>Intention to treat: no</p> <p>Interim analysis: yes</p> <p>Exclusion from analysis: 69/539 did not receive vaccine (7 deaths), 56/470 did not finish follow up (4 deaths)</p> <p>Follow-up period: 9 months after first vaccination</p>
Participants	<p>Age: 3 months</p> <p>Health status: healthy</p> <p>Breastfeeding: > 75%</p> <p>Immunization status: DTCP vaccine given with rotavirus vaccine</p>
Interventions	<p>1. Bovine (WC3), 10^7 PFU, 2 doses (n = 237)</p> <p>2. Placebo (sacharose and lactose substrates), 2 doses (n = 235)</p> <p>Milk given before vaccine or placebo</p>
Outcomes	<p>1. Safety: clinical symptoms within 1 week of vaccination</p> <p>2. Efficacy: diarrhoea within 9 months of first vaccination</p>
Notes	<p>Country: Central African Republic</p> <p>Clinical symptoms: clinical evaluation; diarrhoea defined as ≥ 3 watery or loose stools in 24 h; severity score measured by Clark 1988 (modified Duffy 1986) scale</p> <p>Laboratory studies: stool analysis by latex agglutination and ELISA; serology by plaque reduction neutralization assay</p>

Gothefors 1989

Methods	Randomization: no details
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Rotavirus vaccine for preventing diarrhoea (Review)

Gothefors 1989 (Continued)

Allocation concealment: no details

Blinding: no details

Data collection: started December 1984, lasted 2 winter seasons

Intention to treat: no

Interim analysis: none

Exclusion from analysis: 2\106 excluded for infection with serotype distinct from vaccine strain

Follow-up period: 2 winter seasons.

Participants	<p>Age: 4 to 12 months</p> <p>Health status: no information</p> <p>Breastfeeding: < 50%</p> <p>Immunization status: no information</p>
Interventions	<p>1. Rhesus (MMU18006), 1 ml vaccine diluted 1\10 orally, single dose (n = 54)</p> <p>2. Placebo (distilled water with added color), single dose (n = 52)</p>
Outcomes	<p>1. Safety: clinical symptoms within 1 week of vaccination</p> <p>2. Efficacy: diarrhoea within 2 winter seasons (rotavirus or other)</p>
Notes	<p>Country: Sweden</p> <p>Clinical symptoms: clinical evaluation; diarrhoea defined as ≥ 3 watery or loose stools in 24 h, clinically significant diarrhoea defined as > 3 loose stools\24 h and symptoms > 48 h, WHO criteria</p> <p>Laboratory studies: stool analysis and serology by ELISA</p>

Hanlon 1987

Methods	<p>Randomization: no details</p> <p>Allocation concealment: no details</p> <p>Blinding: none (one group not blinded because of IM vaccination)</p> <p>Data collection: January 1985 to March 1986</p> <p>Intention to treat: no</p> <p>Interim analysis: none</p> <p>Exclusion from analysis: 180\433 excluded (absent during epidemic period or too young to be vaccinated)</p> <p>Follow-up period: 7 days after vaccination; 1 rotavirus season</p>
Participants	<p>Age: > 2.5 months</p> <p>Health status: no information</p> <p>Breastfeeding: no information</p>

Hanlon 1987 (Continued)

	Immunization status: OPV and IPV given with rotavirus vaccine, no further details
Interventions	1. Bovine (RIT 4237) $10^{7.8}$ per monodose vial and OPV, 3 doses (n = 78) 2. Bovine (RIT 4237) $10^{7.8}$ per monodose vial and IPV, 3 doses (n = 92) 3. Placebo (uninfected primary monkey kidney cells) 0.5 ml and OPV, 3 doses (n = 83) Vaccine given with OPV or IM polio vaccine
Outcomes	1. Efficacy: diarrhoea (rotavirus) within 1 rotavirus season
Notes	Study location: Gambia Mothers encouraged to breastfeed before and after vaccination Clinical symptoms: clinical evaluation; diarrhoea defined as ≥ 3 loose to watery stools in 24 h; severity measured by WHO criteria (fever ($\geq 38^{\circ}\text{C}$) vomiting, dehydration, > 6 stools in 24 h, and illness duration ≥ 24 h) Laboratory studies: stool analysis by ELISA and silver staining polyacrylamide gel technique; serology by standard viral neutralization methods

Ho 1989

Methods	Randomization: no details Allocation concealment: no details Blinding: double for 2 groups (no further details) Data collection: September 1987 to January 1988 Intention to treat: no information Interim analysis: no information Exclusion from analysis: no information Follow-up period: 5 days after vaccination
Participants	Age: 2 to 3 months Health status: healthy Breastfeeding: $< 50\%$ Immunization status: DPT/OPV given with RRV in one group, and 2 weeks apart in a second group
Interventions	1. Rhesus (MMU18006) 10^4 PFU alone, single dose (n = 30). 2. Rhesus (MMU18006) 10^4 PFU with OPV/DTP, single dose (n = 36) 3. Placebo (soybean formula) with OPV/DTP single dose (n = 36) 400 mg sodium bicarbonate in 30 ml soybean formula given before vaccine or placebo 1 group received the vaccine together with OPV\DTP (this group received acetaminophen prophylactically for 24 h) The second group received the vaccine after 2 weeks of OPV\DTP

Ho 1989 (Continued)

Outcomes	1. Safety: clinical symptoms within 5 days of vaccination
Notes	Study location: USA Breast or bottle feeding delayed for 1 h before and after RV Clinical symptoms: clinical evaluation (irritability defined as > 20 minutes unexplained crying, gastroenteritis defined as diarrhoea and vomiting) Laboratory studies: serology by ELISA

Ing 1991

Methods	Randomization: prepared randomization schedule Allocation concealment: no details Blinding: none Data collection: January 1989 to November 1989 Intention to treat: yes Interim analysis: none Exclusion from analysis: none Follow-up period: 5 days after vaccination; 2 months after vaccination
Participants	Age: 1.5 to 4 months Health status: healthy
Interventions	1. Rhesus + human tetravalent vaccine (RRV-TV), 4×10^5 PFU, with OPV/DTP vaccination, single dose (n = 135). 2. OPV/DTP alone (n = 39) 400 mg sodium bicarbonate in 25 ml soybean formula given before vaccine
Outcomes	1. Safety: clinical symptoms within 5 days of vaccination 2. Illness or diarrhoea within 2 months of vaccination
Notes	Study location: USA Clinical symptoms: clinical evaluation (diarrhoea defined as ≥ 3 loose to watery stools in 24 h) Laboratory studies: serology by ELISA

Joensuu 1997

Methods	Randomization: computer-generated randomization schedule, blocks of four, provided by the pharmaceutical industry Allocation concealment: code sent to investigator in sealed envelopes and returned to pharmaceutical industry unbroken at the end of the study
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Joensuu 1997 (Continued)

Blinding: double (except 4th year of follow up), identically appearing vaccine and placebo

Data collection: September 1993 to June 1997

Intention to treat: yes

Interim analysis: none

Exclusion from analysis: 38\2398 excluded, no further details

Follow-up period: 5 days after vaccination; 4 rotavirus seasons after vaccination

Participants	<p>Age: 1.5 to 4.5 months</p> <p>Health status: healthy</p> <p>Breastfeeding: no information</p> <p>Immunization status: all other vaccinations given according to schedule without delays</p>
Interventions	<p>1. Rhesus + human tetravalent vaccine (RRV-TV), 4×10^5 PFU, 3 doses (n = 1191)</p> <p>2. Placebo (tissue culture fluid), 3 ml, 3 doses (n = 1207)</p> <p>3 ml sodium bicarbonate and citric acid buffer given before vaccine or placebo</p>
Outcomes	<p>1. Safety: clinical symptoms within 5 days of vaccination.</p> <p>2. Efficacy: gastroenteritis (rotavirus or other) within 4 rotavirus seasons</p>
Notes	<p>Study location: Finland</p> <p>Clinical symptoms: clinical evaluation (gastroenteritis defined as ≥ 3 looser than normal stools or ≥ 3 loose stools and one vomiting episode in 24 h); severity score measured by Ruuska 1990 scale</p> <p>Laboratory studies: stool analysis by ELISA and PCR; serology by ELISA</p>

Lanata 1989

Methods	<p>Randomization: no details</p> <p>Allocation concealment: no details</p> <p>Blinding: double (identical pre-coded vials)</p> <p>Data collection: November 1984 to July 1986</p> <p>Intention to treat: no</p> <p>Interim analysis: none</p> <p>Exclusion from analysis: 32\43 excluded for not receiving all 3 doses; 50/391 did not finish surveillance (8 deaths, no details)</p> <p>Follow-up period: 7 days after vaccination; 18 months after vaccination</p>
Participants	<p>Age: 2 to 18 months</p> <p>Health status: no information</p> <p>Breastfeeding: 50 to 75% (vaccinees only)</p>

Lanata 1989 (Continued)

	<p>Immunization status: no information</p> <p>Clinical symptoms: clinical evaluation (diarrhoea defined as ≥ 3 liquid or semi-liquid stools in 24 h), WHO dehydration criteria used</p> <p>Laboratory studies: stool analysis by ELISA; serology by CF.</p>
Interventions	<p>1. Bovine (RIT 4237), $10^{8.3}$ TCID₅₀, 3 doses (n = 358 child years).</p> <p>2. Placebo (uninfected primary monkey kidney cells), 0.5 ml, 3 doses (n = 127 child years)</p> <p>100 ml evaporated milk given before vaccine or placebo</p>
Outcomes	<p>1. Safety: clinical symptoms within 7 days of vaccination</p> <p>2. Efficacy: diarrhoea within 18 months of vaccination</p>
Notes	<p>Study location: Peru</p>

Lanata 1996a

Methods	<p>Randomization: 12 letter codes allocated by block randomization</p> <p>Allocation concealment: code kept at NIH and WHO, and not revealed until study ended</p> <p>Blinding: double (identical appearing vaccine and placebo vials)</p> <p>Data collection: August 1987 to October 1990</p> <p>Intention to treat: no</p> <p>Interim analysis: none</p> <p>Exclusion from analysis: 115\800 not followed 24 months (13 deaths unrelated to vaccine)</p> <p>Follow-up period: 6 days after vaccination; 24 months after vaccination</p>
Participants	<p>Age: 2 months</p> <p>Health status: healthy</p> <p>Breastfeeding: no information</p> <p>Immunization status: DPT and OPV vaccination began 1 month after rotavirus vaccination</p>
Interventions	<p>1. Rhesus (MMU18006) 10^4 PFU, single dose (n = 200)</p> <p>2. Rhesus + human (D x RRV) 10^4 PFU, single dose (n = 200)</p> <p>3. Rhesus + human (DS1 x RRV), 10^4 PFU, single dose (n = 200)</p> <p>4. Placebo (milk or minimum essential media), single dose (n = 200)</p> <p>400 mg sodium bicarbonate in 30 ml milk given before vaccine or placebo</p>
Outcomes	<p>1. Safety: clinical symptoms within 6 days of vaccination.</p> <p>2. Efficacy: diarrhoea (rotavirus or other) within 24 months of vaccination</p>
Notes	<p>Study location: Peru</p>

Lanata 1996a (Continued)

Clinical symptoms: clinical evaluation (diarrhoea defined as ≥ 3 liquid or semi-liquid stools in 24 h), WHO dehydration criteria used

Laboratory studies: stool analysis by ELISA; serology by ELISA and plaque reduction neutralization assay

Lanata 1996b

Methods	<p>Randomization: computerized randomization, blocks of 12</p> <p>Allocation concealment: pre-coded vessels administered sequentially to children; code kept at pharmaceutical industry and not broken until end of study</p> <p>Blinding: double (identical appearing vaccine and placebo vials)</p> <p>Data collection: October 1988 to October 1990</p> <p>Intention to treat: no</p> <p>Interim analysis: none</p> <p>Exclusion from analysis: 60\700 excluded for not completing 3 doses of vaccine; 60\640 not followed for 24 months (6 deaths unrelated to vaccine)</p> <p>Follow-up period: 6 days after vaccination; 24 months after vaccination</p>
Participants	<p>Age: 2 months</p> <p>Health status: healthy</p> <p>Breastfeeding: no information</p> <p>Immunization status: DPT and polio vaccinations given with RRV</p>
Interventions	<p>Rhesus + human tetravalent vaccine (RRV + D x RRV + DS1 x RRV + ST3 x RRV), 10^4 PFU, 3 doses (n = 467)</p> <p>Placebo (uninfected cell cultures), 1 ml, 3 doses (n = 232)</p> <p>400 mg sodium bicarbonate in 30 ml milk given before vaccine or placebo</p>
Outcomes	<p>1. Safety: clinical symptoms within 6 days of vaccination</p> <p>2. Efficacy: diarrhoea (rotavirus or other) within 24 months of vaccination</p>
Notes	<p>Study location: Peru</p> <p>Breastfeeding withheld for 1 h before and after RV</p> <p>Clinical symptoms: clinical evaluation (diarrhoea defined as ≥ 3 liquid or semi-liquid stools in 24 h), WHO dehydration criteria used; severity score measured by Kapikian's scale (modified Flores 1987)</p> <p>Laboratory studies: stool analysis by ELISA; serology by ELISA and plaque reduction neutralization assay</p> <p>Children were concurrently immunized with IPV, DTP, BCG (at birth), and MMR</p>

Linhares 1996

Methods	Randomization: block randomization, numbered serially Allocation concealment: code kept by pharmaceutical industry and WHO and not broken until end of study Blinding: double (identical appearing vaccine and placebo vials) Data collection: February 1990 to January 1991 Intention to treat: no Interim analysis: none Exclusion from analysis: 74\540 not followed 24 months (8 deaths, no further details) Follow-up period: 7 days after each vaccination; 24 months after vaccination
Participants	Age: 1 to 2 months Health status: healthy Breastfeeding: no information Immunization status: OPV vaccine given at least 15 days before or after RRV
Interventions	1. Rhesus + human tetravalent vaccine (RRV-TV), 10^4 PFU, 3 doses (n = 270) 2. Placebo (uninfected cell cultures), 1.2 ml, 3 doses (n = 270) 400 mg sodium bicarbonate in 30 ml milk given before vaccine or placebo
Outcomes	1. Safety: clinical symptoms within 7 days of vaccination. 2. Efficacy: diarrhoea (rotavirus or other) within 24 months of vaccination
Notes	Study location: Brazil Breastfeeding or bottle feeding withheld for 1 h before or after vaccine OPV given at an interval of at least 2 weeks before or after RV Clinical symptoms: clinical evaluation (diarrhoea defined as ≥ 3 liquid or semi-liquid stools in 24 h), WHO dehydration criteria used; severity score measured by Flores scale Laboratory studies: stool analysis by ELISA; serology by ELISA and plaque reduction neutralization assay

Madore 1992

Methods	Randomization: table of random numbers Allocation concealment: no details Blinding: double (identical placebo and vaccine vials) Data collection: 15 September 1987 to 8 August 1990 Intention to treat: yes Interim analysis: none Excluded subjects: none
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Madore 1992 (Continued)

Follow-up period: 10 days after vaccination; 3 years after enrolment

Participants	Age: 2 to 4 months Health status: healthy Breastfeeding: < 50% Immunization status: DPT and OPV vaccinations not given 4 weeks before and 3 weeks after RRV
Interventions	1. Rhesus (MMU 18006), 10^4 PFU, single dose (n = 76) 2. Rhesus + human (RRV x D), 10^4 PFU, single dose (n = 74) 3. Placebo (soy formula), 1 ml single dose (n = 73) 400 mg sodium bicarbonate in 30 ml soy formula given before vaccine or placebo
Outcomes	1. Safety: clinical symptoms within 10 days of vaccination 2. Efficacy: gastroenteritis (rotavirus or other) within 3 years of enrolment
Notes	Study location: USA Clinical symptoms: clinical evaluation (diarrhoea defined as ≥ 3 loose stools in 24 h), severity measured by WHO criteria (fever (≥ 38) vomiting, dehydration, > 6 stools in 24 h and illness duration ≥ 24 h) Laboratory studies: serology by micro-neutralization assay and ELISA; stool analysis by ELISA All other vaccines withheld for 4 weeks before and 3 weeks after RV

Maldonado 1986

Methods	Randomization: block randomization 2:2:1 Allocation concealment: no details Blinding: double (coded preparations) Data collection: enrolment between June 1984 and January 1985, no further details Intention to treat: no Interim analysis: none Exclusion from analysis: 11\54 excluded for non-compliance Follow-up period: 7 days before and 7 days after vaccination
Participants	Age: < 1 month Health status: no information Breastfeeding: no information Immunization status: no information
Interventions	1. Bovine (RIT 4237), 10^8 TCID ₅₀ , 2 doses (n = 19) 2. Bovine (RIT 4237), 10^7 TCID ₅₀ , 2 doses (n = 20) 3. Placebo (uninfected tissue culture fluid), 0.5 ml, 2 doses (n = 10)

Rotavirus vaccine for preventing diarrhoea (Review)

Maldonado 1986 *(Continued)*

Formula given before vaccine or placebo

Outcomes	1. Safety: clinical symptoms within 7 days of vaccination
Notes	Study location: USA Clinical symptoms: clinical evaluation (diarrhoea defined as any noticeable change in frequency of stools or development of watery/loose stools) Laboratory studies: serology by plaque reduction neutralization; stool analysis by ELISA

Mutz 1989

Methods	Randomization: confirmed by investigator, no further details Allocation concealment: no details Blinding: double (confirmed by investigator), no further details Data collection: no details Intention to treat: no Interim analysis: none Exclusion from analysis: no details Follow-up period: 3 to 4 weeks after vaccination; 6 months after end of safety period
Participants	Age: > 1 month Health status: no information Breastfeeding: no information Immunization status: no information
Interventions	1. Bovine (RIT 4237), $10^{6.5}$ TCID ₅₀ , 1 dose (n = 243) 2. Placebo (n = 103), no further details
Outcomes	1. Safety: clinical symptoms within 3 to 4 weeks of vaccination 2. Efficacy: diarrhoea within 6 months of safety period ending
Notes	Study location: Austria Clinical symptoms: clinical evaluation, no further details Laboratory studies: serology by ELISA; stool analysis (no details)

Perez-Schael 1990a

Methods	Randomization: code assigned to vials Allocation concealment: vials administered serially to participants; codes partially disclosed at NIH before end of trial to analyse reactions to vaccine, and kept at NIH until end of study Blinding: double (vaccine and placebo looked alike)
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Rotavirus vaccine for preventing diarrhoea (Review)

Perez-Schael 1990a (Continued)

Data collection: vaccination between February 1985 and February 1986, end of study February 1987

Intention to treat: no

Interim analysis: yes, after phase 1

Exclusion from analysis: 63\320 dropped from follow up

Follow-up period: 1 week after vaccination, 1 year after safety period

Participants	<p>Age: 1 to 10 months</p> <p>Health status: no information</p> <p>Breastfeeding: no information</p> <p>Immunization status: no information</p>
Interventions	<p>1. Rhesus (MMU-18006), 10^4 PFU, single dose (n = 151)</p> <p>2. Placebo (buffered formula), single dose (n = 151)</p> <p>400 mg citrate-bicarbonate in 30 ml similac formula given before vaccine or placebo</p>
Outcomes	<p>1. Safety: clinical symptoms within 1 week of vaccination</p> <p>2. Efficacy: diarrhoea within 1 year of vaccination</p>
Notes	<p>Study location: Venezuela</p> <p>Clinical symptoms: clinical evaluation (diarrhoea defined as ≥ 3 watery or loose stools in 24 h)</p> <p>Laboratory studies: serology by ELISA and plaque reduction neutralization assay; stool analysis by ELISA</p>

Perez-Schael 1990c

Methods	<p>Randomization: code, no further details</p> <p>Allocation concealment: code broken at NIH after completion of safety analysis but not disclosed to field team</p> <p>Blinding: double, no further details</p> <p>Data collection: no information</p> <p>Intention to treat: yes</p> <p>Interim analysis: yes, doses were evaluated sequentially</p> <p>Exclusion from analysis: none</p> <p>Follow-up period: 1 week after vaccination</p>
Participants	<p>Age: 2.5 to 5 months</p> <p>Health status: no debilitating disease</p> <p>Breastfeeding: no information</p> <p>Immunization status: no information</p>

Perez-Schael 1990c (Continued)

Interventions	1. Rhesus + human quadrivalent vaccine (3 RRV + D x RRV + DS1 x RRV + ST3 x RRV), 0.25×10^4 PFU or 0.5×10^4 PFU or 10^4 PFU, single dose (n = 67) 2. Placebo (buffered formula), single dose (n = 63) 400 mg citrate-bicarbonate in 30 ml similac formula given before vaccine or placebo
Outcomes	1. Safety: clinical symptoms within 1 week of vaccination
Notes	Study location: Venezuela Clinical symptoms: clinical evaluation, no further details Laboratory studies: serology by ELISA and plaque reduction neutralization assay; stool analysis by ELISA

Perez-Schael 1994

Methods	Randomization: confirmed by letter to author, no further details. Allocation concealment: no details Blinding: double (confirmed by letter to author), no further details Data collection: no details Intention to treat: no details Interim analysis: none Exclusion from analysis: no details Follow-up period: 1 week after vaccination
Participants	Age: 2.5 to 5 months Health status: no information Breastfeeding: no information Immunization status: no information
Interventions	1. Rhesus + human quadrivalent vaccine (3 RRV + D x RRV + DS1 x RRV + ST3 x RRV), 10^4 PFU or 5×10^4 PFU, 2 doses (n = 87) 2. Placebo, 2 doses (n = 82), no further details 400 mg bicarbonate in 30 ml similac formula given before vaccine or placebo
Outcomes	1. Safety: clinical symptoms within 1 week of vaccination
Notes	Study location: Venezuela Clinical symptoms: clinical evaluation, no further details Laboratory studies: serology by ELISA and plaque reduction neutralization assay; stool analysis by ELISA and cultures

Perez-Schael 1997

Methods	<p>Randomization: computerized randomization algorithm that balanced the number of children in groups of 500 numbers</p> <p>Allocation concealment: sequential code numbers</p> <p>Blinding: double (identical looking vaccine and placebo)</p> <p>Data collection: March 1992 to October 1995</p> <p>Intention to treat: yes for safety, no for efficacy</p> <p>Interim analysis: none</p> <p>Exclusion from analysis: 443\2480 dropped from study, similar distribution in vaccine and placebo groups according to author, no further details</p> <p>Follow-up period: 6 days after each vaccination; 19 to 20 months after vaccination</p>
Participants	<p>Age: newborns (< 1 month)</p> <p>Health status: healthy</p> <p>Breastfeeding: > 75%</p> <p>Immunization status: DPT vaccination given with RRV, OPV not given within 2 to 4 weeks of RRV</p>
Interventions	<p>1. Rhesus + human quadrivalent vaccine (RRV-TV), 4 x 10⁵ PFU, 3 doses (n = 1247)</p> <p>2. Placebo (uninfected tissue culture fluids), 2.5 ml, 3 doses (n = 1233)</p> <p>400 mg citrate-bicarbonate in 30 ml simlac formula given before vaccine or placebo</p>
Outcomes	<p>1. Safety: clinical symptoms within 6 days of vaccination</p> <p>2. Efficacy: gastroenteritis within 19 to 20 months of vaccination</p>
Notes	<p>Study location: Venezuela</p> <p>Clinical symptoms: clinical evaluation (gastroenteritis defined as ≥ 3 watery or loose stools or 1 bloody stool with or without vomiting in 24 h); WHO dehydration criteria used; severity score measured by Ru-uska 1990 scale</p> <p>Laboratory studies: stool analysis by ELISA and PCR; serology by ELISA</p> <p>Children were concurrently immunized with DTP; IPV was separated from RV by at least 2 weeks</p> <p>85 to 95% of children were breastfeeding while receiving at least 1 of the doses of RV</p>

Perez-Schael 2002

Methods	<p>Randomization: no details</p> <p>Allocation concealment: no details</p> <p>Blinding: double, no further details</p> <p>Data collection: no details</p> <p>Intention to treat: no details</p> <p>Interim analysis: yes</p>
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Perez-Schael 2002 (Continued)

	Exclusion from analysis: no details
	Follow-up period: 6 months after vaccination
Participants	Age: 1.5 to 3 months Health status: healthy Breastfeeding: no information Immunization status: DPT, HBV, and HiB vaccination given with RRV; OPV not given within 2 weeks of RRV
Interventions	1. Human 89-12 (RIX4414) 105.0 PFU/dose, 2 doses (n = 493) 2. Human 89-12 (RIX4414) 105.5 PFU/dose, 2 doses (n = 496) 3. Human 89-12 (RIX4414) 106.0 PFU/dose, 2 doses (n = 493) 4. Placebo, 2 doses (n = 504), no further details
Outcomes	1. Efficacy: rotavirus gastroenteritis within 6 months of vaccination
Notes	Study location: Venezuela, Brazil, Mexico Clinical symptoms: clinical evaluation; severity score measured by Ruuska 1990 scale Laboratory studies: stool analysis by ELISA Data taken from poster presented at ICAAC 2002 This is an interim analysis of an ongoing trial

Pichichero 1990

Methods	Randomization: code supplied by pharmaceutical industry Allocation concealment: no details Blinding: double (coded vials) Data collection: before September 1987, no further details Intention to treat: no Interim analysis: none Exclusion from analysis: 1\96 gave only safety information because of no consent Follow-up period: 1 week after each vaccination
Participants	Age: 2 to 5 months Health status: healthy Breastfeeding: < 50% Immunization status: no medication given within 2 weeks before vaccination
Interventions	1. Rhesus (MMU 18006), 10 ³ PFU, single dose (n = 22) 2. Rhesus (MMU 18006), 10 ⁴ PFU, single dose (n = 25)

Rotavirus vaccine for preventing diarrhoea (Review)

Pichichero 1990 (Continued)

3. Rhesus (MMU 18006), 10^5 PFU, single dose (n = 23)
 4. Placebo (buffered formula), 1ml, single dose (n = 25)
- Half the infants received 30 ml formula before vaccine or placebo

Outcomes	1. Safety: clinical symptoms within 7 days of vaccination
Notes	<p>Study location: USA</p> <p>All feedings withheld for 1 h before and after RV</p> <p>Clinical symptoms: clinical evaluation (diarrhea defined as ≥ 3 looser than usual stools in 24 h)</p> <p>Laboratory studies: serology by ELISA and plaque reduction neutralization assay; stool analysis by ELISA and cultures</p>

Pichichero 1993

Methods	<p>Randomization: no details</p> <p>Allocation concealment: no details</p> <p>Blinding: double (identical appearing vials)</p> <p>Data collection: 31 May 1988 to 2 March 1988</p> <p>Intention to treat: no</p> <p>Interim analysis: none</p> <p>Exclusion from analysis: 1\213 did not supply safety information</p> <p>Follow-up period: 1 week after each vaccination</p>
Participants	<p>Age: 1.5 to 4 months</p> <p>Health status: healthy</p> <p>Breast feeding: > 75%</p> <p>Immunization status: no medication given within 2 weeks before vaccination</p>
Interventions	<ol style="list-style-type: none"> 1. RRV S1, 10^4 or 10^5 PFU, single dose (n = 40) 2. RRV S2, 10^4 or 10^5 PFU, single dose (n = 37) 3. RRV S3, 10^4 or 10^5 PFU, single dose (n = 39) 4. RRV S4, 10^4 or 10^5 PFU, single dose (n = 39) 5. RRV-TV, 10^4 or 10^5 PFU, single dose (n = 38) 6. Placebo, single dose (n = 19), no details
Outcomes	1. Safety: clinical symptoms within 7 days of vaccination
Notes	<p>Study location: USA</p> <p>No buffer or formula given with vaccine; feeding allowed after vaccination</p> <p>Clinical symptoms: clinical evaluation (diarrhoea defined as ≥ 3 looser than usual stools in 24 h)</p>

Rotavirus vaccine for preventing diarrhoea (Review)

Pichichero 1993 (Continued)

Laboratory studies: serology by ELISA and plaque reduction neutralization

Rennels 1987

Methods	Randomization: code, no further details Allocation concealment: no details Blinding: double (coded preparations) Data collection: May 1985 to October 1985 Intention to treat: yes Interim analysis: none Excluded subjects: none Follow-up period: 7 days after vaccination
Participants	Age: 3 to 12 months Health status: healthy Breastfeeding: < 50% Immunization status: no other vaccines allowed within 2 weeks of vaccination
Interventions	1. Rhesus (MMU 18006), 10^4 PFU, single dose (n = 12) 2. Rhesus (MMU 18006), 10^3 PFU, single dose (n = 8) 3. Placebo (buffered formula), 1 ml, single dose (n = 11) 400 mg sodium bicarbonate in 30 ml formula given before vaccine or placebo
Outcomes	1. Safety: clinical symptoms within 7 days of vaccination
Notes	Study location: USA Breastfeeding or bottle feeding withheld for 1 h before or after vaccine Clinical symptoms: clinical evaluation (diarrhea defined as ≥ 3 loose stools in 24 h) Laboratory studies: serology by plaque reduction neutralization assay; stool analysis by ELISA and cultures

Rennels 1990

Methods	Randomization: no details Allocation concealment: no details Blinding: double (coded preparations) Data collection: no information Interim analysis: none Excluded subjects: 2\114 did not complete surveillance
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Rotavirus vaccine for preventing diarrhoea (Review)

Rennels 1990 (Continued)

Follow-up period: 7 days after vaccination, 2 years after vaccination

Participants	<p>Age: 2 to 5 months</p> <p>Health status: healthy</p> <p>Breastfeeding: < 50%</p> <p>Immunization status: all other vaccinations not given within 2 weeks of RRV</p>
Interventions	<p>1. Rhesus (MMU 18006), 10^4 PFU, single dose (n = 64)</p> <p>2. Placebo (formula), single dose (n = 50)</p> <p>30 ml formula containing 400 mg sodium bicarbonate given before vaccine or placebo</p>
Outcomes	<p>1. Safety: clinical symptoms within 7 days of vaccination.</p> <p>2. Efficacy: diarrhoea (rotavirus or other) within 2 years of vaccination</p>
Notes	<p>Study location: USA</p> <p>Clinical symptoms: clinical evaluation (diarrhoea defined as ≥ 3 looser than normal stools in 24 h); severity score measured by Flores 1987 scale</p> <p>Laboratory studies: serology by plaque reduction neutralization assay; stool analysis by ELISA</p>

Rennels 1995

Methods	<p>Randomization: no details</p> <p>Allocation concealment: no details</p> <p>Blinding: double, no further details</p> <p>Data collection: vaccination between 10 August 1989 and 16 July 1990</p> <p>Intention to treat: no</p> <p>Interim analysis: none</p> <p>Excluded participants: 173\989 did not complete surveillance</p> <p>Follow-up period: 2 years after vaccination</p>
Participants	<p>Age: 1 to 6.5 months</p> <p>Health status: healthy</p> <p>Breastfeeding: < 50%</p> <p>Immunization status: no information</p>
Interventions	<p>1. Rhesus + human monovalent vaccine (RRV-S1), 4×10^4 PFU, 3 doses (n = 280)</p> <p>2. Rhesus + human quadrivalent vaccine (RRV-TV), 4×10^4 PFU, 3 doses (n = 264)</p> <p>3. Placebo (tissue culture medium), 3 doses (n = 272)</p> <p>30 ml formula containing 400 mg sodium bicarbonate given before vaccine or placebo</p>

Rennels 1995 (Continued)

Outcomes	1. Efficacy: gastroenteritis (rotavirus related) within 2 years of vaccination
Notes	Study location: USA Clinical symptoms: clinical evaluation (gastroenteritis defined as ≥ 3 loose stools in 24 h or emesis) Laboratory studies: serology by ELISA and fluorescent focus reduction assay

Rennels 1996

Methods	Randomization: code provided by pharmaceutical industry, no further details Allocation concealment: no details Blinding: double (identical appearing vials) Data collection: vaccination between 5 July 1991 and 24 January 1992 Intention to treat: no Interim analysis: none Excluded participants: 91\1278 did not complete efficacy surveillance Follow-up period: 5 days after vaccination, 1 rotavirus season after vaccination
Participants	Age: 1.25 to 6.25 months Health status: healthy Breastfeeding: < 50% Immunization status: all other vaccines allowed with RRV
Interventions	1. Rhesus + human monovalent vaccine (RRV-S1), 4×10^5 PFU, 3 doses (n = 425) 2. Rhesus + human quadrivalent vaccine (RRV-TV), 4×10^5 PFU, 3 doses (n = 428) 3. Placebo (tissue culture medium), 3 doses (n = 425) 3 ml sodium bicarbonate given before vaccine or placebo
Outcomes	1. Safety: clinical symptoms within 5 days of vaccination 2. Efficacy: gastroenteritis (rotavirus or other) within 1 rotavirus season
Notes	Study location: USA Clinical symptoms: clinical evaluation (diarrhoea defined as ≥ 3 loose stools in 24 h; gastroenteritis defined as diarrhea, vomiting, or both); severity score measured by Rennels 1996 (modified Flores 1987) scale Laboratory studies: serology and stool analysis by ELISA Other vaccines allowed with RV but not required

Ruuska 1990

Methods	Randomization: no details
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Rotavirus vaccine for preventing diarrhoea (Review)

Ruuska 1990 (Continued)

	Allocation concealment: no details
	Blinding: double (identical vaccine and placebo appearance)
	Data collection: October 1984 to June 1987
	Intention to treat: no
	Interim analysis: none
	Exclusion from analysis: 22% of first group and 13% of second group did not finish follow up, no further details
	Follow-up period: 7 days after vaccination, 24 to 32 months after safety period
Participants	Age: newborns
	Health status: healthy
	Immunization status: no vaccine except BCG given before rotavirus vaccine
Interventions	1. Bovine (RIT 4237), $10^{8.3}$ TCID, single dose (n = 519 person years)
	2. Placebo (uninfected tissue culture), single dose (n = 481 person years)
Outcomes	1. Safety: clinical symptoms within 7 days of vaccination
	2. Efficacy: diarrhoea within 2 seasons of vaccination
Notes	Study location: Finland
	Clinical symptoms: definitions and laboratory methods mentioned in different paper
	No buffer or formula given with vaccine

Santosham 1991a

Methods	Randomization: table of random numbers
	Blinding: no details
	Data collection: 1 January 1992 to 31 January 1994
	Intention to treat: no
	Interim analysis: none
	Exclusion from analysis: 11/332 were not followed because they left the area
	Follow-up period: 5 days after vaccination, 17 months after vaccination
Participants	Age: 2 to 5 months
	Health status: no illness or immunodeficiency
	Breastfeeding: < 50%
	Immunization status: OPV vaccination not given within 3 weeks of rotavirus vaccination
Interventions	1. Rhesus (MMU18006), 10^4 PFU, single dose (n = 108)
	2. Placebo (soy formula), 1 ml, single dose (n = 107)

Rotavirus vaccine for preventing diarrhoea (Review)

Santosham 1991a (Continued)

400 mg sodium bicarbonate in 30 ml soy formula given before vaccine or placebo

Outcomes	1. Safety: clinical symptoms within 5 days of vaccination. 2. Efficacy: diarrhoeal illness (rotavirus or other) within 17 months of vaccination
Notes	Study location: USA Clinical symptoms: diarrhoea $\geq$ 3 watery stools in 24 h Laboratory studies: serology and stool analysis by ELISA OPV given at an interval of at least 3 weeks before or after RV Breastfeeding allowed during vaccination

Santosham 1991b

Methods	Santosham 1991a and 1991b are two arms of a single trial See Santosham 1991a for details
Participants	See Santosham 1991a for details
Interventions	1. Bovine (RIT 4237), 10^8 PFU, single dose (n = 106) 2. Placebo (soy formula), 1 ml, single dose (n = 107) 400 mg sodium bicarbonate in 30 ml soy formula given before vaccine or placebo
Outcomes	See Santosham 1991a for details
Notes	See Santosham 1991a for details

Santosham 1997

Methods	Randomization: blocks of 6 to receive either RRV-TV, RRV-S1, or placebo. Packages containing 3 doses of study drug, code-labelled, were provided to the study sites Allocation concealment: schedule generated by the biostatistics division at Wyeth Ayerst Blinding: no details Data collection: enrolment between September 1985 and February 1987, no further details Intention to treat: yes Interim analysis: none Exclusion from analysis: 101/1185 did not complete 2 years follow up, 171/1084 did not complete 2 years follow up, no further details Follow-up period: 5 days after vaccination, 2 years after beginning of trial
Participants	Age: 1.5 to 6 months Health status: healthy

Santosham 1997 (Continued)

	Breastfeeding: no information
	Immunization status: all other vaccines allowed with RRV
Interventions	1. Rhesus + human tetravalent vaccine (RRV-TV), 10^5 PFU, 3 doses (n = 396) 2. Rhesus + human monovalent vaccine (RRV-S1), 4×10^5 PFU, 3 doses (n = 398) 3. Placebo (tissue culture medium), 3 doses (n = 391) 3 ml sodium citrate bicarbonate given with vaccine or placebo
Outcomes	1. Safety: clinical symptoms within 5 days of vaccination 2. Efficacy: gastroenteritis within 2 years of beginning of trial
Notes	Study location: USA Clinical symptoms: clinical evaluation (gastroenteritis defined as ≥ 3 watery or loose stools in 24 h); severity score measured by Rennels 1996 (modified from Flores 1987) scale Laboratory studies: serology and stool analysis by ELISA Simultaneous administration of routine childhood vaccines was permitted but not required

Senturia 1987

Methods	Randomization: no details Allocation concealment: no details Blinding: double, no further details Data collection: winter 1985 to 1986 Intention to treat: yes Interim analysis: none Exclusion from analysis: none Follow-up period: 1 winter season after vaccination
Participants	Age: 8 to 48 months Health status: no information Breastfeeding: < 50% Immunization status: no information
Interventions	1. Bovine (RIT 4237), single dose (n = 105), no further details 2. Placebo (no details), single dose (n = 106) Milk drink given before vaccine or placebo
Outcomes	1. Efficacy: diarrhoea (rotavirus or other) within 1 winter season of vaccination
Notes	Study location: UK Clinical symptoms: clinical evaluation, no further details

Rotavirus vaccine for preventing diarrhoea (Review)

Senturia 1987 (Continued)

Laboratory studies: stool analysis by ELISA; serology by serum neutralization

Treanor 1995

Methods	Randomization: block 2:1 (Rochester), 1:1 (Philadelphia), no further details Allocation concealment: no details Blinding: double, no further details Data collection: 18 June 1992 to 15 June 1993 Intention to treat: no information Interim analysis: no information Exclusion from analysis: 13/325 did not complete the study because of relocation out of the area or negative compliance Follow-up period: 7 days after vaccination, 1 winter season after vaccination
Participants	Age: 2 to 8 months Health status: healthy Breastfeeding: < 50% Immunization status: no other vaccine given within 7 days of rotavirus vaccination
Interventions	1. Bovine + human (WI79-9), $10^{7.3}$ PFU, 3 doses (n = 207). 2. Placebo (cell culture media and cherry syrup), 2.5 ml, 3 doses (n = 118) 30 ml soy or milk formula or 400 mg sodium bicarbonate in 30 ml soy formula given before vaccine or placebo
Outcomes	1. Safety: clinical symptoms within 7 days of vaccination 2. Efficacy: gastroenteritis (rotavirus or other) within 1 winter season
Notes	Study location: USA Breastfeeding and bottle feeding withheld for 1 h before and after RV Clinical symptoms: clinical evaluation (gastroenteritis defined as ≥ 1 watery stool or ≥ 3 liquid stools and/or ≥ 1 vomiting episode in 24 h); severity score measured by Clark 1988 (modified Duffy 1986) scale Laboratory studies: stool analysis by ELISA, gel electrophoresis, and PCR Other vaccines given at least 7 days after RV

Vesikari 1984

Methods	Randomization: no details Allocation concealment: code not available until end of study Blinding: double (code-labelled vials)
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Vesikari 1984 (Continued)

	Data collection: January 1983 to June 1983
	Intention to treat: no
	Interim analysis: none
	Exclusion from analysis: 12/190 did not complete vaccination or follow up
	Follow-up period: 10 days after vaccination, 5 months after vaccination
Participants	Age: 8 to 11 months Health status: healthy Breastfeeding: no information Immunization status: no information
Interventions	1. Bovine (RIT 4237), $10^{8.1}$ TCID ₅₀ , single dose (n = 86) 2. Placebo (uninfected primary monkey kidney cells), 0.5 ml, single dose (n = 92)
Outcomes	1. Clinical symptoms within 10 days of vaccination 2. Diarrhoea and other gastrointestinal upsets within 5 months of vaccination
Notes	Study location: Finland No restriction on breastfeeding or bottle feeding were imposed Clinical symptoms: clinical evaluation (clinically significant diarrhoea defined as watery stools > 24 h) Laboratory studies: serology and stool analysis ELISA

Vesikari 1985a

Methods	Randomization: predetermined scheme Allocation concealment: code unavailable until end of study Blinding: double (indistinguishable vaccine and placebo) Data collection: September 1983 to April 1985 Intention to treat: no Interim analysis: yes Exclusion from analysis: 19/347 were not followed until end of study Follow-up period: 10 days after vaccination, 2 rotavirus season after vaccination
Participants	Age: 6 to 12 months Health status: healthy Breastfeeding: 50 to 75% Immunization status: no information
Interventions	1. Bovine (RIT 4237), $10^{8.1}$ TCID ₅₀ , single dose (n = 168)

Vesikari 1985a (Continued)

	2. Placebo (uninfected primary monkey kidney cells), 0.5 ml, single dose (n = 163)
Outcomes	1. Clinical symptoms within 10 days of vaccination 2. Diarrhoea and other gastrointestinal upsets within 2 rotavirus seasons of vaccination
Notes	Study location: Finland Clinical symptoms: clinical evaluation (clinically significant diarrhoea defined as diarrhoea requiring re-hydration) Laboratory studies: serology and stool analysis by ELISA No specific orders concerning feeding

Vesikari 1986a

Methods	Randomization: coded list of the 2 vaccines Allocation concealment: code not broken until end of trial Blinding: double (parents and paediatricians unaware of the code) Data collection: vaccination between 10 December 1984 and 17 December 1984, no further details Intention to treat: no Interim analysis: none Exclusion from analysis: 2/51 excluded for lost incomplete data Follow-up period: 7 days after vaccination
Participants	Age: 8 months Health status: healthy Breastfeeding: no information Immunization status: no information
Interventions	1. Bovine (RIT 4237), $10^{8.3}$ TCID ₅₀ , single dose (n = 24) 2. Rhesus (MMU18006), 10^5 PFU, single dose (n = 25) Ordinary meal or breast milk given before vaccines
Outcomes	1. Safety: clinical symptoms within 7 days of vaccination
Notes	Study location: Finland Clinical symptoms: clinical evaluation, no definitions given Laboratory studies: serology by ELISA CF and plaque reduction neutralization assay; stool analysis by ELISA

Vesikari 1987b

Methods	Randomization: done at pharmaceutical industry Allocation concealment: code kept at pharmaceutical industry until end of study Blinding: double (identical vaccine and placebo appearance). Data collection: enrolment at October 1984 Intention to treat: no information Interim analysis: yes Exclusion from analysis: no information Follow-up period: 10 days after vaccination, 16 months after vaccination
Participants	Age: newborns Health status: healthy Breastfeeding: > 75% Immunization status: no other vaccine given before rotavirus vaccination
Interventions	1. Bovine (RIT 4237), $10^{8.3}$ TCID ₅₀ , single dose (n = 119) 2. Placebo (uninfected tissue culture fluid), 0.6 ml, single dose (n = 120) Ordinary meal or breast milk given before vaccine or placebo
Outcomes	1. Clinical symptoms within 10 days of vaccination 2. Diarrhoea (rotavirus or other) within 16 months
Notes	Study location: Finland Clinical symptoms: clinical evaluation, no definitions given Laboratory studies: stool analysis and serology by ELISA

Vesikari 1990

Methods	Randomization: no details Allocation concealment: code kept at WHO until end of trial Blinding: double (identical vaccine and placebo appearance) Data collection: July 1985 to June 1987 Intention to treat: yes to efficacy, no to safety Interim analysis: none Exclusion from analysis: 5/200 did not finish safety follow up Follow-up period: 7 days after vaccination, 2 rotavirus seasons after vaccination
Participants	Age: 2 to 5 months Health status: healthy

Vesikari 1990 (Continued)

	Breastfeeding: > 75%
	Immunization status: no information
Interventions	1. Rhesus (MMU18006), 10^4 PFU, single dose (n = 100). 2. Placebo (minimal essential medium), 1 ml, single dose (n = 100) 30 ml soy milk formula given before vaccine or placebo
Outcomes	1. Clinical symptoms within 7 days of vaccination 2. Diarrhoea (rotavirus or other) within 2 rotavirus seasons
Notes	Study location: Finland Most of the infants were breastfed. Feeding withheld for 90 minutes before vaccination and 2 h after vaccination Clinical symptoms: clinical evaluation (diarrhoea defined as ≥ 3 unformed stools); severity score by Vesikari 1990 scale Laboratory studies: stool analysis by ELISA; serology by plaque reduction neutralization assay and tube neutralization assay

Vesikari 1991a

Methods	Randomization: sequentially numbered code from 1 to 252 Allocation concealment: no details Blinding: double (identical vaccine and placebo appearance) Data collection: February 1985 to June 1987 Intention to treat: no Interim analysis: none Exclusion from analysis: 41/252 did not finish follow up Follow-up period: 2 rotavirus seasons
Participants	Age: newborns Health status: healthy Breastfeeding: > 75% Immunization status: no information
Interventions	1. Bovine (RIT 4237), $10^{8.3}$ TCID ₅₀ , 2 doses (n = 244 person years) 2. Placebo (uninfected tissue culture fluid), 2 doses (n = 217 person years) 0.5% sodium bicarbonate in 50 ml 5% glucose solution given before vaccine or placebo
Outcomes	1. Diarrhoea (rotavirus or other) within 2 rotavirus seasons
Notes	Study location: Finland All infants breastfed at first vaccination, 64% breastfed at second vaccination

Rotavirus vaccine for preventing diarrhoea (Review)

Vesikari 1991a (Continued)

Clinical symptoms: clinical evaluation, severity score by [Ruuska 1990](#) scale

Laboratory studies: stool analysis by latex test and ELISA; serology by ELISA

Vesikari 1991b

Methods	Randomization: computer-generated randomization list Allocation concealment: code kept at WHO, not available until end of trial Blinding: double, no further details Data collection: October 1989 to June 1990 Intention to treat: yes for efficacy, no for safety Interim analysis: none Exclusion from analysis: 2/282 excluded from safety analysis. Follow-up period: 7 days after vaccination, 6 to 8 months after vaccination
Participants	Age: 2 to 7 months Health status: healthy Breastfeeding: no information Immunization status: all other vaccinations not given within 2 weeks of rotavirus vaccination
Interventions	1. Human (M37), 10^4 PFU, (n = 102) single dose 2. Human (M37), 10^5 PFU, (n = 39) single dose 3. Placebo (dilution medium), single dose (n = 141) 400 mg sodium bicarbonate in 30 ml soy milk formula given before vaccine or placebo
Outcomes	1. Safety: clinical symptoms within 7 days of vaccination. 2. Efficacy: diarrhoea (rotavirus or other) within 6 to 8 months of vaccination
Notes	Study location: Finland Clinical symptoms: clinical evaluation (diarrhoea defined as ≥ 3 watery or loose stools in 24 h); severity score by Ruuska 1990 scale Laboratory studies: stool analysis by ELISA; serology by ELISA and plaque reduction neutralization assay

Vesikari 1991c

Methods	Randomization: randomization list Allocation concealment: no details Blinding: no details Data collection: no information
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Vesikari 1991c (Continued)

	<p>Intention to treat: no</p> <p>Interim analysis: none</p> <p>Exclusion from analysis: 6/89 excluded from analysis</p> <p>Follow-up period: 7 days after vaccination</p>
Participants	<p>Age: 2 to 4 months</p> <p>Health status: healthy</p> <p>Breastfeeding: no information</p> <p>Immunization status: no information.</p>
Interventions	<p>1. Rhesus + human monovalent vaccine (D x RRV or DS1 x RRV), 10^4 PFU, single dose (n = 61)</p> <p>2. Placebo (dilution medium), single dose (n = 24)</p> <p>400 mg sodium bicarbonate in 40 ml soy milk formula given before vaccine or placebo</p>
Outcomes	<p>1. Safety: clinical symptoms within 7 days of vaccination</p>
Notes	<p>Study location: Finland</p> <p>Clinical symptoms: clinical evaluation, no further details</p> <p>Laboratory studies: stool analysis by ELISA; serology by ELISA and plaque reduction neutralization assay</p>

Vesikari 1992

Methods	<p>Randomization: computer-generated randomization list</p> <p>Allocation concealment: code kept at WHO, not available until end of trial</p> <p>Blinding: double, no details</p> <p>Data collection: August 1987 to June 1989</p> <p>Intention to treat: yes for efficacy, no for safety</p> <p>Interim analysis: none</p> <p>Exclusion from analysis: None</p> <p>Follow-up period: 7 days after vaccination, 7 to 10 months after vaccination</p>
Participants	<p>Age: 2 to 5 months</p> <p>Health status: healthy</p> <p>Breastfeeding: no information</p> <p>Immunization status: no information</p>
Interventions	<p>1. Rhesus + human monovalent vaccine (D x RRV or DS1 x RRV), 10^4 or 10^5 PFU, single dose (n = 239)</p> <p>2. Placebo (essential medium), single dose (n = 120)</p>

Vesikari 1992 (Continued)

400 mg sodium bicarbonate in 30 ml soy milk formula given before vaccine or placebo

Outcomes	1. Safety: clinical symptoms within 7 days of each dose 2. Efficacy: diarrhoea (rotavirus or other) within 7 to 10 months of vaccination
Notes	Study location: Finland Clinical symptoms: clinical evaluation (diarrhoea defined as ≥ 3 watery or loose stools in 24 h); severity score by Ruuska 1990 scale Laboratory studies: serology and stool analysis by ELISA

Vesikari 1999

Methods	Randomization: schedule generated by pharmaceutical industry Allocation concealment: no details Blinding: double (code-labelled package) Data collection: no data Intention to treat: no Interim analysis: none Exclusion from analysis: 6\249 did not receive 3 doses because of medical problems Follow-up period: 5 days after each dose
Participants	Age: 2.5 to 3.5 months Health status: healthy Breastfeeding: no information Immunization status: pentavalent DTP + Hib + polio vaccine and HBV vaccine given with RRV-TV
Interventions	1. Rhesus + human tetravalent vaccine (RRV-TV), 4×10^5 PFU, 3 doses ($n = 126$). 2. Placebo (identical preparation without vaccine), 3 doses ($n = 123$) 2.5 ml citric acid and bicarbonate given with vaccine or placebo
Outcomes	1. Safety: clinical symptoms within 5 days of each dose
Notes	Study location: Finland Clinical symptoms: clinical evaluation, no further details Laboratory studies: serology by ELISA Vaccine given with pentavalent (DTP + Hib + IPV) vaccine and hepatitis B vaccine

Wright 1987

Methods	Randomization: no details
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Wright 1987 (Continued)

	Allocation concealment: code broken at the end of the trial, no further details
	Blinding: yes, no details
	Data collection: winter 1984 to spring 1986
	Intention to treat: yes
	Interim analysis: none
	Exclusion from analysis: none
	Follow-up period: 3 days before vaccination and 9 days after vaccination
Participants	Age: 4 to 70 months Health status: no information Breastfeeding: no information Immunization status: no information.
Interventions	1. Rhesus (MMU18006), 3.6×10^4 to 7.5×10^6 TCID, single dose (n = 41) 2. Placebo (no details), single dose (n = 39) Sodium bicarbonate tablet or in formula given before vaccine or placebo
Outcomes	1. Safety: clinical symptoms within 9 days of vaccination 2. Efficacy: fever, gastrointestinal illness, and upper respiratory illness during 2 winter seasons
Notes	Study location: USA Clinical symptoms: clinical evaluation (fever defined as ≥ 38.3 °C; gastrointestinal illness defined as > 3 stools in 24 h or 1 vomiting in 24 h; upper respiratory tract illness defined as any respiratory sign leading to clinical impression of illness) Laboratory studies: stool analysis by cell culture and ELISA; serology by ELISA, complement fixation, immune adherence haemagglutination, and tube neutralization assays

Vaccines: BCG: Bacillus Calmette-Guerrin vaccine; DTP: diphtheria-tetanus-pertussis vaccine; HiB: haemophilus influenza B vaccine; IPV: intramuscular polio vaccine; MMR: measles-mumps-rubella vaccine; OPV: oral polio vaccine; RRV: rhesus rotavirus vaccine; RV: rotavirus vaccine; DTCP: diphtheria-tetanus-coqueluche-polio; RRV-TV: rhesus-human reassortant rotavirus vaccine.

Institutions: NIH: National Institute of Health; WHO: World Health Organization.

Serology: PFU: plaque-forming units; ELISA: enzyme-linked immunosorbent assay; PCR: polymerase chain reaction; SPG: Shirasu porous glass; CF: complement fixation; TCID: tissue culture infectious doses; PAGE-SS: polyacrylamide gel electrophoresis and silver stain.

IM vaccination: intra-muscular vaccination; ICAAC: Interscience Conference on Antimicrobial Agents and Chemotherapy HBV: hepatitis B virus.

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Ceyhan 1993	Randomization of children to breastfeed or bottle feed, not to vaccine. Only collected immunological data. Study design: RCT. Study location: Turkey.
Christy 1986	Not randomized. Study design: clinical trial.

Rotavirus vaccine for preventing diarrhoea (Review)

Study	Reason for exclusion
	Study location: USA.
Clements-Mann 2001	Only collected immunological data. Study design: RCT. Study location: USA.
Friedman 1993	Not randomized, only collected immunological data. Study design: clinical trial. Study location: Israel.
Giammanco 1988	Only collected immunological data. Study design: RCT. Study location: Italy.
Halsey 1988	Not randomized. Study design: clinical trial. Study location: USA.
Isolauro 1995	Randomization of children to receive Lactobacillus casei GG or not with the rotavirus vaccine. All children received the rotavirus vaccine. Study design: RCT. Study location: Finland.
Jalil 1991	Not randomized. All children received the rotavirus vaccine. Study design: CCT. Study location: Pakistan.
Jin 1996	Only collected immunological data. Study design: RCT. Study location: USA.
Kobayashi 1993	Only collected immunological data. Study design: RCT. Study location: USA.
Kobayashi 1994	Only collected immunological data. Study design: RCT. Study location: USA.
Losonsky 1988	Only collected immunological data. Study design: RCT. Study location: USA.
Markwick 1998	Only collected immunological data. Study design: RCT. Study location: USA.
Midthun 1989	Only collected immunological data. Study design: RCT. Study location: Venezuela.
Padilla 1992	Only collected immunological data. Study design: clinical trial. Study location: USA.
Pang 1999a	Only collected immunological data. Study design: RCT.

Study	Reason for exclusion
	Study location: Finland.
Pang 1999b	Only collected immunological data. Study design: RCT. Study location: Finland.
Pang 1999c	Only collected immunological data. Study design: RCT. Study location: Finland.
Pang 1999d	Only collected immunological data. Study design: RCT. Study location: Finland.
Pickering 1995	Only collected immunological data. Study design: RCT. Study location: USA.
Simasathien 1994	Only collected immunological data. Study design: RCT. Study location: Thailand.
Tajima 1990	Only collected immunological data. Study design: RCT. Study location: USA.
Ukae 1994	Not randomized. Study design: CCT. Study location: Japan.
Vesikari 1983	Not randomized. Study design: clinical trial. Study location: Finland.
Vesikari 1985b	Only collected immunological data. Study design: RCT. Study location: Finland.
Vesikari 1986b	Only collected immunological data. Study design: RCT. Study location: Finland.
Vesikari 1987a	Only collected immunological data. Study design: RCT. Study location: Yugoslavia.
Vodopija 1986	Only collected immunological data. Study design: RCT. Study location: Yugoslavia.
Wright 1991	Only collected immunological data. Study design: RCT. Study location: USA.
Zoppi 1986	Randomization of children to receive milk or soy formula, not to vaccine. Only collected immunological data. Study design: RCT.

Study	Reason for exclusion
	Study location: Italy.
Zoppi 1989	Randomization of children to receive milk or soy formula, not to vaccine. Only collected immunological data. Study design: RCT. Study location: Italy.

RCT: randomized controlled trial

CCT: controlled clinical trial (not randomized)

Characteristics of studies awaiting assessment *[ordered by study ID]*

[Seth 2000](#)

Methods	—
Participants	—
Interventions	—
Outcomes	—
Notes	—

[Vesikari 2002](#)

Methods	—
Participants	—
Interventions	—
Outcomes	—
Notes	—

DATA AND ANALYSES

Comparison 1. Drop outs before end of study

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Drop outs before end of study	19		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Rhesus rotavirus vaccines	14	11128	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.85, 1.06]
1.2 Bovine rotavirus vaccines	5	1365	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.56, 1.22]

[Rotavirus vaccine for preventing diarrhoea \(Review\)](#)

Analysis 1.1. Comparison 1 Drop outs before end of study, Outcome 1 Drop outs before end of study.

Comparison 2. Rotavirus diarrhoea

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Episodes	40		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Rhesus rotavirus vaccines	20	13305	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.50, 0.70]
1.2 Bovine rotavirus vaccines	17	5283	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.45, 0.76]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.3 Human rotavirus vaccines	3	2482	Risk Ratio (M-H, Random, 95% CI)	0.42 [0.21, 0.85]
2 Severe episodes	23		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Rhesus rotavirus vaccines	11	10606	Risk Ratio (M-H, Random, 95% CI)	0.42 [0.31, 0.57]
2.2 Bovine rotavirus vaccines	10	3643	Risk Ratio (M-H, Random, 95% CI)	0.38 [0.24, 0.60]
2.3 Human rotavirus vaccines	2	2201	Risk Ratio (M-H, Random, 95% CI)	0.21 [0.13, 0.35]
3 Episodes requiring hospitalization	13		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 Rhesus rotavirus vaccines	7	7803	Risk Ratio (M-H, Random, 95% CI)	0.48 [0.27, 0.86]
3.2 Bovine rotavirus vaccines	4	1693	Risk Ratio (M-H, Random, 95% CI)	0.37 [0.18, 0.74]
3.3 Human rotavirus vaccines	2	2201	Risk Ratio (M-H, Random, 95% CI)	0.21 [0.09, 0.48]
4 Episodes of more than four days	8		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 Rhesus rotavirus vaccines	5	631	Risk Ratio (M-H, Random, 95% CI)	0.61 [0.42, 0.87]
4.2 Bovine rotavirus vaccines	3	252	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.51, 1.99]

Analysis 2.1. Comparison 2 Rotavirus diarrhoea, Outcome 1 Episodes.

Analysis 2.2. Comparison 2 Rotavirus diarrhoea, Outcome 2 Severe episodes.

Analysis 2.3. Comparison 2 Rotavirus diarrhoea, Outcome 3 Episodes requiring hospitalization.

Analysis 2.4. Comparison 2 Rotavirus diarrhoea, Outcome 4 Episodes of more than four days.

Comparison 3. All-cause diarrhoea

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Episodes (number of episodes/number of person-years)			Other data	No numeric data
1.1 Rhesus rotavirus vaccines			Other data	No numeric data
1.2 Bovine rotavirus vaccines			Other data	No numeric data
1.3 Human rotavirus vaccines			Other data	No numeric data
2 Episodes (number of cases/number of participants)	23		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Rhesus rotavirus vaccines	11	7706	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.80, 0.92]
2.2 Bovine rotavirus vaccines	11	3309	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.60, 0.89]
2.3 Human rotavirus vaccines	1	281	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.57, 1.44]
3 Episodes during first week after vaccine (one or multiple doses)	40		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 Rhesus rotavirus vaccines	29	12673	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.98, 1.14]
3.2 Bovine rotavirus vaccines	10	2125	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.89, 1.17]
3.3 Human rotavirus vaccines	3	376	Risk Ratio (M-H, Fixed, 95% CI)	1.94 [1.03, 3.65]
4 Severe episodes (clinical or measured by any scale)	6		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 Rhesus rotavirus vaccines	3	1663	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.72, 1.00]
4.2 Bovine rotavirus vaccines	3	714	Risk Ratio (M-H, Random, 95% CI)	0.51 [0.21, 1.26]
5 Episodes requiring re-hydration	11		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
5.1 Rhesus rotavirus vaccines	5	5559	Risk Ratio (M-H, Random, 95% CI)	0.51 [0.30, 0.88]
5.2 Bovine rotavirus vaccines	5	2148	Risk Ratio (M-H, Random, 95% CI)	0.42 [0.26, 0.67]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.3 Human rotavirus vaccines	1	215	Risk Ratio (M-H, Random, 95% CI)	0.14 [0.01, 2.71]
6 Episodes requiring hospitalization	7		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
6.1 Rhesus rotavirus vaccines	4	5023	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.66, 0.99]
6.2 Bovine rotavirus vaccines	3	799	Risk Ratio (M-H, Random, 95% CI)	0.55 [0.16, 1.91]

Analysis 3.1. Comparison 3 All-cause diarrhoea, Outcome 1 Episodes (number of episodes/number of person-years).

Study	Episodes (number of episodes/number of person-years)			
	Episodes (vaccine)	Person-years vaccine	Episodes (placebo)	Person-years placebo
Rhesus rotavirus vaccines				
Gothefors 1989	75	53	79	51
Lanata 1996a	9104	1032	3000	339
Lanata 1996b	6518	758	3200	386
Linhares 1996	2579	361	2803	363
Perez-Schael 1990a	294	141	290	130
Santosham 1991a	397	130	383	125
Santosham 1997	2559	1391	1331	680
Bovine rotavirus vaccines				
Bernstein 1990	153	102 (patients)	179	103 (patients)
Lanata 1989	3432	358	1343	127
Santosham 1991b	404	125	383	125
Human rotavirus vaccines				
Barnes 1997	62	40 (patients)	23	20 (patients)
Georges-Courbot 1991	503	232 (patients)	455	230 (patients)

Analysis 3.2. Comparison 3 All-cause diarrhoea, Outcome 2 Episodes (number of cases/number of participants).

Study or subgroup	Vaccine n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
3.2.1 Rhesus rotavirus vaccines					
Vesikari 1990	37/100	52/100		3.93%	0.71[0.52,0.98]
Flores 1993	90/200	58/102		6.59%	0.79[0.63,0.99]
Wright 1987	17/41	11/32		1.24%	1.21[0.66,2.2]
Vesikari 1992	85/239	70/120		6.59%	0.61[0.49,0.77]
Christy 1988	59/88	58/88		7.41%	1.02[0.82,1.25]
Escobar 1988	14/52	24/51		1.56%	0.57[0.34,0.98]
Rennels 1990	52/64	45/50		11.2%	0.9[0.78,1.05]
Madore 1992	77/150	48/73		6.62%	0.78[0.62,0.98]
Perez-Schael 1997	724/1247	808/1233		19.9%	0.89[0.83,0.94]
Rennels 1996	448/853	236/425		15.17%	0.95[0.85,1.05]
Joensuu 1997	689/1191	795/1207		19.79%	0.88[0.82,0.94]
Subtotal (95% CI)	4225	3481		100%	0.86[0.8,0.92]
Total events: 2292 (Vaccine), 2205 (Placebo)

Analysis 3.3. Comparison 3 All-cause diarrhoea, Outcome 3 Episodes during first week after vaccine (one or multiple doses).

Analysis 3.4. Comparison 3 All-cause diarrhoea, Outcome 4 Severe episodes (clinical or measured by any scale).

Analysis 3.5. Comparison 3 All-cause diarrhoea, Outcome 5 Episodes requiring re-hydration.

Analysis 3.6. Comparison 3 All-cause diarrhoea, Outcome 6 Episodes requiring hospitalization.

Comparison 4. Death

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause death	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Rhesus rotavirus vaccines	4	6029	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.16, 3.12]

Analysis 4.1. Comparison 4 Death, Outcome 1 All-cause death.

Comparison 5. Exploration of heterogeneity: methodological quality

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Adequate allocation concealment (A)	12		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Rhesus rotavirus vaccines	9	8963	Risk Ratio (M-H, Random, 95% CI)	0.58 [0.45, 0.76]
1.2 Bovine rotavirus vaccines	1	239	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.33, 1.56]
1.3 Human vaccine rotavirus	2	496	Risk Ratio (M-H, Random, 95% CI)	0.49 [0.12, 1.99]
2 Unclear allocation concealment (B)	28		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Rhesus rotavirus vaccines	11	4423	Risk Ratio (M-H, Random, 95% CI)	0.57 [0.48, 0.67]
2.2 Bovine rotavirus vaccines	16	5040	Risk Ratio (M-H, Random, 95% CI)	0.57 [0.43, 0.76]
2.3 Human vaccine rotavirus	1	1986	Risk Ratio (M-H, Random, 95% CI)	0.35 [0.24, 0.51]
3 Exclusions after randomization reported	20		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 Rhesus rotavirus vaccines	15	12009	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.48, 0.71]
3.2 Bovine rotavirus vaccines	5	1361	Risk Ratio (M-H, Random, 95% CI)	0.50 [0.26, 0.96]
4 Exclusions after randomization not reported	20		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 Rhesus rotavirus vaccines	5	1377	Risk Ratio (M-H, Random, 95% CI)	0.58 [0.44, 0.76]
4.2 Bovine rotavirus vaccines	12	3918	Risk Ratio (M-H, Random, 95% CI)	0.61 [0.46, 0.82]
4.3 Human vaccine rotavirus	3	2482	Risk Ratio (M-H, Random, 95% CI)	0.42 [0.21, 0.85]
5 Sample size of less than 1000 participants	33		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
5.1 Rhesus rotavirus vaccines	15	4975	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.56, 0.79]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.2 Bovine rotavirus vaccines	16	4279	Risk Ratio (M-H, Random, 95% CI)	0.55 [0.41, 0.74]
5.3 Human vaccine rotavirus	2	496	Risk Ratio (M-H, Random, 95% CI)	0.49 [0.12, 1.99]
6 Sample size of at least 1000 participants	7		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
6.1 Rhesus rotavirus vaccines	5	8411	Risk Ratio (M-H, Random, 95% CI)	0.50 [0.39, 0.65]
6.2 Bovine rotavirus vaccines	1	1000	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.61, 1.41]
6.3 Human vaccine rotavirus	1	1986	Risk Ratio (M-H, Random, 95% CI)	0.35 [0.24, 0.51]

Analysis 5.1. Comparison 5 Exploration of heterogeneity: methodological quality, Outcome 1 Adequate allocation concealment (A).

Analysis 5.2. Comparison 5 Exploration of heterogeneity: methodological quality, Outcome 2 Unclear allocation concealment (B).

Analysis 5.3. Comparison 5 Exploration of heterogeneity: methodological quality, Outcome 3 Exclusions after randomization reported.

Analysis 5.4. Comparison 5 Exploration of heterogeneity: methodological quality, Outcome 4 Exclusions after randomization not reported.

Analysis 5.5. Comparison 5 Exploration of heterogeneity: methodological quality, Outcome 5 Sample size of less than 1000 participants.

Analysis 5.6. Comparison 5 Exploration of heterogeneity: methodological quality, Outcome 6 Sample size of at least 1000 participants.

Comparison 6. Exploration of heterogeneity: multiple versus single dose

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Multiple doses (two or more) of rotavirus vaccine	15		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Rhesus rotavirus vaccines	8	9698	Risk Ratio (M-H, Random, 95% CI)	0.55 [0.44, 0.69]
1.2 Bovine rotavirus vaccines	5	2148	Risk Ratio (M-H, Random, 95% CI)	0.58 [0.39, 0.86]
1.3 Human rotavirus vaccines	2	2201	Risk Ratio (M-H, Random, 95% CI)	0.32 [0.23, 0.45]
2 Single dose of rotavirus vaccine	25		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Rhesus rotavirus vaccines	12	3607	Risk Ratio (M-H, Random, 95% CI)	0.64 [0.50, 0.82]
2.2 Bovine rotavirus vaccines	12	3135	Risk Ratio (M-H, Random, 95% CI)	0.57 [0.40, 0.83]
2.3 Human rotavirus vaccines	1	281	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.45, 2.25]

Analysis 6.1. Comparison 6 Exploration of heterogeneity: multiple versus single dose, Outcome 1 Multiple doses (two or more) of rotavirus vaccine.

Analysis 6.2. Comparison 6 Exploration of heterogeneity: multiple versus single dose, Outcome 2 Single dose of rotavirus vaccine.

Comparison 7. Exploration of heterogeneity: administered with other vaccines

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Concomitant use of DPT or OPV allowed	12		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Rhesus rotavirus vaccines	8	10052	Risk Ratio (M-H, Random, 95% CI)	0.57 [0.44, 0.73]
1.2 Bovine rotavirus vaccines	3	1071	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.44, 1.18]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.3 Human rotavirus vaccines	1	1986	Risk Ratio (M-H, Random, 95% CI)	0.35 [0.24, 0.51]
2 Concomitant use of DPT or OPV not allowed	15		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Rhesus rotavirus vaccines	6	1367	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.52, 0.97]
2.2 Bovine rotavirus vaccines	7	2110	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.40, 1.00]
2.3 Human rotavirus vaccines	2	496	Risk Ratio (M-H, Random, 95% CI)	0.49 [0.12, 1.99]
3 No information	13		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 Rhesus rotavirus vaccines	6	1886	Risk Ratio (M-H, Random, 95% CI)	0.55 [0.43, 0.71]
3.2 Bovine rotavirus vaccines	7	2102	Risk Ratio (M-H, Random, 95% CI)	0.47 [0.28, 0.79]

Analysis 7.1. Comparison 7 Exploration of heterogeneity: administered with other vaccines, Outcome 1 Concomitant use of DPT or OPV allowed.

Analysis 7.2. Comparison 7 Exploration of heterogeneity: administered with other vaccines, Outcome 2 Concomitant use of DPT or OPV not allowed.

Analysis 7.3. Comparison 7 Exploration of heterogeneity: administered with other vaccines, Outcome 3 No information.

Comparison 8. Exploration of heterogeneity: breastfeeding

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Breastfeeding allowed during vaccination	13		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Rhesus rotavirus vaccines	4	3652	Risk Ratio (M-H, Random, 95% CI)	0.52 [0.32, 0.86]
1.2 Bovine rotavirus vaccines	9	3452	Risk Ratio (M-H, Random, 95% CI)	0.64 [0.48, 0.85]
2 Breastfeeding not allowed for at least one hour before and after vaccination	23		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Rhesus rotavirus vaccines	15	8468	Risk Ratio (M-H, Random, 95% CI)	0.61 [0.51, 0.73]
2.2 Bovine rotavirus vaccines	6	954	Risk Ratio (M-H, Random, 95% CI)	0.45 [0.21, 0.94]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.3 Human rotavirus vaccines	2	496	Risk Ratio (M-H, Random, 95% CI)	0.49 [0.12, 1.99]
3 No information	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 Rhesus rotavirus vaccines	1	1185	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.56, 0.87]
3.2 Bovine rotavirus vaccines	2	877	Risk Ratio (M-H, Random, 95% CI)	0.58 [0.20, 1.71]
3.3 Human rotavirus vaccines	1	1986	Risk Ratio (M-H, Random, 95% CI)	0.35 [0.24, 0.51]

Analysis 8.1. Comparison 8 Exploration of heterogeneity: breastfeeding, Outcome 1 Breastfeeding allowed during vaccination.

Analysis 8.2. Comparison 8 Exploration of heterogeneity: breastfeeding, Outcome 2 Breastfeeding not allowed for at least one hour before and after vaccination. **Analysis 8.3. Comparison 8 Exploration of heterogeneity: breastfeeding, Outcome 3 No information.**

Comparison 9. Exploration of heterogeneity: one season versus multiple seasons follow up

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 One season	15		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Rhesus rotavirus vaccines	8	2885	Risk Ratio (M-H, Random, 95% CI)	0.57 [0.42, 0.78]
1.2 Bovine rotavirus vaccines	7	1798	Risk Ratio (M-H, Random, 95% CI)	0.52 [0.32, 0.83]
1.3 Human rotavirus vaccines	1	1986	Risk Ratio (M-H, Random, 95% CI)	0.35 [0.24, 0.51]
2 Two or more seasons	24		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Rhesus rotavirus vaccines	12	10172	Risk Ratio (M-H, Random, 95% CI)	0.60 [0.48, 0.74]
2.2 Bovine rotavirus vaccines	10	3726	Risk Ratio (M-H, Random, 95% CI)	0.60 [0.43, 0.84]
2.3 Human rotavirus vaccines	2	496	Risk Ratio (M-H, Random, 95% CI)	0.49 [0.12, 1.99]

Analysis 9.1. Comparison 9 Exploration of heterogeneity: one season versus multiple seasons follow up, Outcome 1 One season.

Analysis 9.2. Comparison 9 Exploration of heterogeneity: one season versus multiple seasons follow up, Outcome 2 Two or more seasons.

Comparison 10. Exploration of heterogeneity: different rotavirus vaccines

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Rotavirus diarrhoea: episodes	40		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Rhesus tetravalent vaccine (RRV-TV)	11	11590	Risk Ratio (M-H, Random, 95% CI)	0.58 [0.47, 0.72]
1.2 Rhesus monovalent vaccine (RRV, RRV-D, RRV-DS1, or RRV-ST3)	9	1715	Risk Ratio (M-H, Random, 95% CI)	0.60 [0.46, 0.78]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.3 Bovine vaccine (RIT-4237)	10	3663	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.48, 0.86]
1.4 Bovine vaccine (WC3)	3	782	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.46, 1.28]
1.5 Bovine-human vaccine (W179-9)	3	433	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.19, 0.56]
1.6 Bovine-human vaccine (WC3-QV)	1	405	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.19, 0.58]
1.7 Human vaccine (89-12)	2	2201	Risk Ratio (M-H, Random, 95% CI)	0.32 [0.23, 0.45]
1.8 Human vaccine (M37)	1	281	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.45, 2.25]
2 Rotavirus diarrhoea: severe episodes	23		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Rhesus tetravalent vaccine (RRV-TV)	7	9569	Risk Ratio (M-H, Random, 95% CI)	0.40 [0.28, 0.57]
2.2 Rhesus monovalent vaccine (RRV-MMU 18006)	4	1037	Risk Ratio (M-H, Random, 95% CI)	0.52 [0.27, 0.97]
2.3 Bovine vaccine (RIT-4237)	5	2131	Risk Ratio (M-H, Random, 95% CI)	0.38 [0.19, 0.79]
2.4 Bovine vaccine (WC3)	3	782	Risk Ratio (M-H, Random, 95% CI)	0.57 [0.29, 1.12]
2.5 Bovine-human vaccine (W179-9)	1	325	Risk Ratio (M-H, Random, 95% CI)	0.14 [0.05, 0.42]
2.6 Bovine-human vaccine (QHBRV)	1	405	Risk Ratio (M-H, Random, 95% CI)	0.31 [0.16, 0.62]
2.7 Human vaccine (89-12)	2	2201	Risk Ratio (M-H, Random, 95% CI)	0.21 [0.13, 0.35]
3 All-cause diarrhoea: episodes (number of cases/number of participants)	23		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 Rhesus tetravalent vaccine (RRV-TV)	5	6561	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.84, 0.93]
3.2 Rhesus monovalent vaccine (RRV, RRV-D, RRV-DS1, or RRV-ST3)	6	1145	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.69, 0.98]
3.3 Bovine vaccine (RIT-4237)	7	2772	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.67, 1.01]
3.4 Bovine vaccine (WC3)	1	104	Risk Ratio (M-H, Random, 95% CI)	0.48 [0.28, 0.84]
3.5 Bovine-human vaccine (W179-9)	3	433	Risk Ratio (M-H, Random, 95% CI)	0.60 [0.50, 0.72]
3.6 Human vaccine (M37)	1	281	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.57, 1.44]

Analysis 10.1. Comparison 10 Exploration of heterogeneity: different rotavirus vaccines, Outcome 1 Rotavirus diarrhoea: episodes.

Analysis 10.2. Comparison 10 Exploration of heterogeneity: different rotavirus vaccines, Outcome 2 Rotavirus diarrhoea: severe episodes.

Analysis 10.3. Comparison 10 Exploration of heterogeneity: different rotavirus vaccines, Outcome 3 All-cause diarrhoea: episodes (number of cases/number of participants).

Comparison 11. Exploration of heterogeneity: country of origin - income status

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Rotavirus diarrhoea: episodes	40		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Rhesus vaccines: high-income countries	14	8182	Risk Ratio (M-H, Random, 95% CI)	0.56 [0.46, 0.68]
1.2 Rhesus vaccines: middle-income countries	6	5123	Risk Ratio (M-H, Random, 95% CI)	0.64 [0.48, 0.83]
1.3 Bovine vaccines: high-income countries	14	4073	Risk Ratio (M-H, Random, 95% CI)	0.50 [0.35, 0.71]
1.4 Bovine vaccines: middle-income countries	1	485	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.62, 0.97]
1.5 Bovine vaccines: low-income countries	2	725	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.57, 1.18]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.6 Human vaccines: high-income countries	2	496	Risk Ratio (M-H, Random, 95% CI)	0.49 [0.12, 1.99]
1.7 Human vaccines: middle-income countries	1	1986	Risk Ratio (M-H, Random, 95% CI)	0.35 [0.24, 0.51]
2 Rotavirus diarrhoea: severe episodes	23		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Rhesus vaccines: high-income countries	7	6585	Risk Ratio (M-H, Random, 95% CI)	0.39 [0.25, 0.61]
2.2 Rhesus vaccines: middle-income countries	4	4021	Risk Ratio (M-H, Random, 95% CI)	0.50 [0.35, 0.72]
2.3 Bovine vaccines: high-income countries	8	2918	Risk Ratio (M-H, Random, 95% CI)	0.31 [0.20, 0.46]
2.4 Bovine vaccines: low-income countries	2	725	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.58, 1.09]
2.5 Human vaccines: high-income countries	1	215	Risk Ratio (M-H, Random, 95% CI)	0.14 [0.04, 0.46]
2.6 Human vaccines: middle-income countries	1	1986	Risk Ratio (M-H, Random, 95% CI)	0.23 [0.14, 0.40]
3 Rotavirus diarrhoea: severe episodes requiring hospitalization	13		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 Rhesus vaccine: high-income countries	3	3782	Risk Ratio (M-H, Random, 95% CI)	0.15 [0.02, 1.33]
3.2 Rhesus vaccine: middle-income countries	4	4021	Risk Ratio (M-H, Random, 95% CI)	0.58 [0.35, 0.95]
3.3 Bovine vaccines: high-income countries	2	736	Risk Ratio (M-H, Random, 95% CI)	0.18 [0.03, 0.99]
3.4 Bovine vaccines: middle-income countries	1	485	Risk Ratio (M-H, Random, 95% CI)	0.35 [0.14, 0.93]
3.5 Bovine vaccines: low-income countries	1	472	Risk Ratio (M-H, Random, 95% CI)	0.57 [0.17, 1.91]
3.6 Human vaccines: high-income countries	1	215	Risk Ratio (M-H, Random, 95% CI)	0.20 [0.01, 4.08]
3.7 Human vaccines: middle-income countries	1	1986	Risk Ratio (M-H, Random, 95% CI)	0.21 [0.09, 0.50]
4 All-cause diarrhoea: episodes (number of cases/number of participants)	23		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Rhesus vaccines: high-income countries	9	4924	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.77, 0.94]
4.2 Rhesus vaccines: middle-income countries	2	2782	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.83, 0.93]
4.3 Bovine vaccines: high-income countries	10	3064	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.55, 0.86]
4.4 Bovine vaccines: low-income countries	1	245	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.83, 1.17]
4.5 Human vaccines: high-income countries	1	281	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.57, 1.44]
5 All-cause diarrhoea: severe episodes (clinical or measured by any scale)	6		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
5.1 Rhesus vaccines: high-income countries	2	1361	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.73, 1.02]
5.2 Rhesus vaccines: middle-income countries	1	302	Risk Ratio (M-H, Random, 95% CI)	0.47 [0.20, 1.11]
5.3 Bovine vaccines: high-income countries	3	714	Risk Ratio (M-H, Random, 95% CI)	0.51 [0.21, 1.26]
6 All-cause diarrhoea: episodes requiring hospitalization	7		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
6.1 Rhesus vaccine: high-income countries	4	5023	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.66, 0.99]
6.2 Bovine vaccines: high-income countries	2	337	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.04, 12.07]
6.3 Bovine vaccines: low-income countries	1	472	Risk Ratio (M-H, Random, 95% CI)	0.57 [0.17, 1.91]
7 All-cause diarrhoea: episodes requiring re-hydration	11		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
7.1 Rhesus vaccine: high-income countries	1	1278	Risk Ratio (M-H, Random, 95% CI)	0.31 [0.14, 0.68]
7.2 Rhesus vaccine: middle-income countries	4	4281	Risk Ratio (M-H, Random, 95% CI)	0.58 [0.33, 1.05]
7.3 Bovine vaccines: high-income countries	5	2148	Risk Ratio (M-H, Random, 95% CI)	0.42 [0.26, 0.67]
7.4 Human vaccines: high-income countries	1	215	Risk Ratio (M-H, Random, 95% CI)	0.14 [0.01, 2.71]

Analysis 11.1. Comparison 11 Exploration of heterogeneity: country of origin - income status, Outcome 1 Rotavirus diarrhoea: episodes.

Analysis 11.2. Comparison 11 Exploration of heterogeneity: country of origin - income status, Outcome 2 Rotavirus diarrhoea: severe episodes.

Analysis 11.3. Comparison 11 Exploration of heterogeneity: country of origin - income status, Outcome 3 Rotavirus diarrhoea: severe episodes requiring hospitalization.

Analysis 11.4. Comparison 11 Exploration of heterogeneity: country of origin - income status, Outcome 4 All-cause diarrhoea: episodes (number of cases/number of participants).

Analysis 11.5. Comparison 11 Exploration of heterogeneity: country of origin - income status, Outcome 5 All-cause diarrhoea: severe episodes (clinical or measured by any scale).

Analysis 11.6. Comparison 11 Exploration of heterogeneity: country of origin - income status, Outcome 6 All-cause diarrhoea: episodes requiring hospitalization.

Analysis 11.7. Comparison 11 Exploration of heterogeneity: country of origin - income status, Outcome 7 All-cause diarrhoea: episodes requiring re-hydration.

Comparison 12. Adverse events

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Bowel obstruction and/or intussusception	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Rhesus rotavirus vaccines	3	4123	Risk Ratio (M-H, Random, 95% CI)	0.42 [0.07, 2.42]
2 Fever (one or multiple doses of vaccine)	47		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Rhesus rotavirus vaccines	32	13718	Risk Ratio (M-H, Random, 95% CI)	2.00 [1.51, 2.64]
2.2 Bovine rotavirus vaccines	12	2168	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.73, 1.23]
2.3 Human rotavirus vaccines	5	716	Risk Ratio (M-H, Random, 95% CI)	1.75 [0.85, 3.64]
3 Vomiting (one or multiple doses of vaccine)	28		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 Rhesus rotavirus vaccines	16	10289	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.90, 1.03]
3.2 Bovine rotavirus vaccines	10	2016	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.90, 1.22]
3.3 Human rotavirus vaccines	2	331	Risk Ratio (M-H, Fixed, 95% CI)	1.94 [1.00, 3.75]
4 Irritability (one or multiple doses of vaccine)	9		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Rhesus rotavirus vaccines	5	807	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.85, 1.20]
4.2 Bovine rotavirus vaccines	3	512	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.86, 1.36]
4.3 Human rotavirus vaccines	1	215	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.51, 0.98]

Analysis 12.1. Comparison 12 Adverse events, Outcome 1 Bowel obstruction and/or intussusception.

Analysis 12.2. Comparison 12 Adverse events, Outcome 2 Fever (one or multiple doses of vaccine).

Analysis 12.3. Comparison 12 Adverse events, Outcome 3 Vomiting (one or multiple doses of vaccine).

Analysis 12.4. Comparison 12 Adverse events, Outcome 4 Irritability (one or multiple doses of vaccine).

APPENDICES

Appendix 1. Types of oral rotavirus vaccines in research field trials

Vaccine	Years on trial	Serotype
Live attenuated bovine rotavirus (NCDV - RIT 4237)	1982 to 1987	G6, P6
Live attenuated rhesus monovalent rotavirus (RRV - MMU18006)	1984 to 1988	G3, P3
Live attenuated bovine rotavirus (WC3)	1986 to 1990	G6, P5
Live attenuated human rotavirus (M37)	1990 to 1994	G1
Live attenuated rhesus-human reassortant rotavirus tetravalent (RRV-TV: RRV-D + RRV-DS1 + RRV + RRV-ST3)	1989 to present	G1-4, P3
Live attenuated bovine-human reassortant multivalent (QHBRV)	1994 to present	G1-3, P5, P8

(Continued)

Live attenuated human rotavirus (HRV 89-12)	1996 to present	G1
Live attenuated human-bovine rotavirus (W179-9)	1988 to present	G1, P8

Appendix 2. Rotavirus diarrhoea: overall effect by vaccine (random vs fixed effect model)

Type of vaccine	Random-effects model		Fixed-effect model		Heterogeneity test
	Risk ratio (95% CI)	Z statistics	Risk ratio (95% CI)	Z statistics	
Rhesus tetravalent vaccine (RRV-TV)	0.58 (0.47 to 0.72)	4.96, P < 0.00001	0.59 (0.54 to 0.64)	11.96, P < 0.00001	Chi squared 51.64, df 10, P < 0.00001, I squared 80.6%
Rhesus monovalent vaccine (RRV, RRV-D, RRV-DS1, or RRV-ST3)	0.60 (0.46 to 0.78)	3.85, P 0.0001	0.59 (0.47 to 0.75)	4.42, P < 0.00001	Chi squared 9.80, df 8, P 0.28, I squared 18.4%
Bovine vaccine (RIT-4237)	0.65 (0.48 to 0.86)	2.96, P 0.003	0.68 (0.58 to 0.79)	4.84, P < 0.00001	Chi squared 19.77, df 9, P 0.02, I squared 54.5%
Bovine vaccine (WC3)	0.77 (0.46 to 1.28)	1.00, P 0.32	0.85 (0.66 to 1.10)	1.22, P 0.22	Chi squared 5.09, df 2, P 0.08, I squared 60.7%
Bovine-human vaccine (W179-9)	0.33 (0.19 to 0.56)	4.00, P 0.00001	0.29 (0.17 to 0.51)	4.36, P < 0.0001	Chi squared 1.58, df 2, P 0.45, I squared 0%
Human vaccine (89-12)	0.32 (0.23 to 0.45)	6.52, P < 0.00001	0.31 (0.22 to 0.44)	6.60, P < 0.00001	Chi squared 0.79, df 1, P 0.37, I squared 0%

CI: confidence interval.

Appendix 3. Data on number of deaths and intussusception (published/unpublished)

Trial	Type of vaccine	Intussusceptions	Deaths	Cause of deaths
Gothefors 1989	RRV-MV	No cases	No information	No information
Perez-Schael 1990a	RRV-MV	No cases	1 case, group allocation unknown	Described by authors as "not related to vaccine"
Wright 1987	RRV-MV	No cases	No cases	No cases
Wright 1991	RRV-MV	No cases	No cases	No cases
Bresee 2001	RRV-TV	No cases	2 cases, 1 case placebo group and 1 case vaccine group	Pneumonia and sudden death syndrome

(Continued)

Ing 1991	RRV-TV	No cases	No cases	No cases
Dennehy 1996	RRV-TV	No cases	No cases	No cases
Joensuu 1997	RRV-TV	Vaccine: 1 case, 6 days after third dose; Placebo: 1 case, 44 days after second dose	1 case, placebo group	Suffocation due to foreign body in the bronchia, 11 months old boy
Lanata 1996a	RRV-TV	No cases	13 cases, group allocation unknown	Described by authors as "not related to vaccine"
Lanata 1996b	RRV-TV	No cases	6 cases, group allocation unknown	Described by authors as "not related to vaccine"
Linhares 1996	RRV-TV	Placebo: 1 case, during follow up	7 cases, group allocation unknown	Gastrointestinal reflux + asphyxia, measles + sepsis, poisoning, gastroenteritis + pneumonia, acute respiratory distress
Perez-Schael 1997	RRV-TV	No cases	3 cases, placebo group	Bronchial aspiration + diarrhoea + dehydration, pneumonia + sepsis, accidental intoxication
Santosham 1997	RRV-TV	Placebo: 1 case	4 cases, vaccine group, all after one month of receiving the vaccine	HiB (hemophilus influenza B vaccine), sudden death syndrome, asphyxia, unknown
Lanata 1989	RIT-4237	No cases	8 cases	No information
Maldonado 1986	RIT-4237	No cases	No cases	No cases
Senturia 1987	RIT-4237	No cases	No cases	No cases
Mutz 1989	RIT-4237	No cases	No cases	No cases
Christy 1993	W179-9	No cases	No cases	No cases
Bernstein 1998	HRV89-12	No cases	No cases	No cases
Bernstein 1999	HRV89-12	No cases	1 case	Pneumococcal sepsis
Georges-Courbot 1991	WC3	No cases	11 cases, group allocation unknown	Described by authors as "not related to vaccine"
Ho 1989	WC3	Vaccine: 2 cases (1 week and 1 month after)	No cases	No cases

Appendix 4. Type of rotavirus vaccines assessed in the included trials

Rotavirus vaccine	Trials	Dosage
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(Continued)

RIT-4237: live attenuated bovine	Hanlon 1987 , Lanata 1989 , Maldonado 1986 Ruuska 1990 , Santosham 1991a , Santosham 1991b , Senturia 1987 Vesikari 1984 , Vesikari 1985a , Vesikari 1986a , Vesikari 1987b Vesikari 1991a	10 ^{7.8} to 10 ^{8.3} TCID ₅₀ or 10 ^{6.5} to 10 ⁸ PFU
WC3: live attenuated bovine	Bernstein 1990 , Clark 1988	10 ⁷ to 10 ^{7.5} PFU
W179-9: live attenuated human-bovine	Clark 1990 , Christy 1993 , Treanor 1995	10 ⁷ to 10 ^{7.5} PFU
RRV-MV (RRV or RRV-D or RRV-DS1 or RRV-ST3): live attenuated rhesus monovalent	Anderson 1986 , Barnes 1997 , Christy 1988 , Flores 1988 , Flores 1989 , Gothers 1989 , Ho 1989 , Madore 1992 , Perez-Schael 1990a , Pichichero 1990 , Rennels 1987 , Santosham 1991a , Santosham 1991b Vesikari 1990 , Wright 1987 , Wright 1991	10 ³ to 10 ⁵ PFU
RRV-TV: live attenuated rhesus tetravalent	Bernstein 1995 , Dagan 1992 Dennehy 1996 Escobar 1988 , Flores 1990 Flores 1993 , Ing 1991 , Joensuu 1997 , Lanata 1996a Lanata 1996b Linhares 1996 , Perez-Schael 1997 , Pichichero 1993 , Rennels 1995 , Rennels 1996 , Santosham 1997 , Vesikari 1999	4 x 10 ⁴ to 4 x 10 ⁶ PFU
HRV 89-12: live attenuated human	Bernstein 1998 Bernstein 1999	10 ⁴ to 10 ⁵ PFU
QHBRV: live attenuated human-bovine quadrivalent or pentavalent	Clark 1995	4 x 10 ⁷ PFU

PFU: plaque-forming units.

Appendix 5. Exploration of heterogeneity: different rotavirus vaccines

Outcome	Vaccine	No. trials	No. participants	RR (95% CI)	NNT (95% CI)	Analysis
Rotavirus diarrhoea: episodes	Rhesus tetravalent (RRV-TV)	11	11,590	0.58 (0.47 to 0.72)	19 (15 to 25)	Analysis 10.1
	Rhesus monovalent (RRV, RRV-D, RRV-DS1, or RRV-ST3)	9	1715	0.60 (0.46 to 0.78)	13 (9 to 22)	Analysis 10.1
	Bovine (RIT-4237)	10	3663	0.65 (0.48 to 0.86)	—	Analysis 10.1
	Bovine (WC3)	3	782	0.77 (0.46 to 1.28)	—	Analysis 10.1
	Bovine-human (W179-9)	3	433	0.33 (0.19 to 0.56)	7 (5 to 12)	Analysis 10.1
	Bovine-human (WC3-QV)	1	405	0.33 (0.19 to 0.58)	7 (5 to 13)	Analysis 10.1

(Continued)

	Human (89-12)	2	2201	0.32 (0.23 to 0.45)	11 (8 to 15)	Analysis 10.1
	Human (M37)	1	281	1.01 (0.45 to 2.25)	—	Analysis 10.1
Rotavirus diarrhoea: severe episodes	Rhesus tetravalent (RRV-TV)	7	9569	0.40 (0.28 to 0.57)	18 (15 to 22)	Analysis 10.2
	Rhesus monovalent (RRV-MMU 18006)	4	1037	0.52 (0.27 to 0.97)	23 (13 to 72)	Analysis 10.2
	Bovine (RIT-4237)	5	2131	0.38 (0.19 to 0.79)	24 (16 to 53)	Analysis 10.2
	Bovine (WC3)	3	782	0.57 (0.29 to 1.12)	14 (8 to 37)	Analysis 10.2
	Bovine-human (W179-9)	1	325	0.14 (0.05 to 0.42)	—	Analysis 10.2
	Bovine-human (QHBRV)	1	405	0.31 (0.16 to 0.62)	—	Analysis 10.2
	Human (89-12)	2	2201	0.21 (0.13 to 0.35)	14 (10 to 20)	Analysis 10.2
All-cause diarrhoea: episodes	Rhesus tetravalent (RRV-TV)	5	6561	0.89 (0.84 to 0.93)	12 (10 to 17)	Analysis 10.3
	Rhesus monovalent (RRV or RRV-D or RRV-DS1 or RRV-ST3)	6	1145	0.82 (0.69 to 0.98)	8 (5 to 13)	Analysis 10.3
	Bovine (RIT-4237)	7	2772	0.82 (0.67 to 1.01)	16 (10 to 35)	Analysis 10.3
	Bovine (WC3)	1	104	0.48 (0.28 to 84)	—	Analysis 10.3
	Bovine-human (W179-9)	3	433	0.60 (0.50 to 0.72)	4 (3 to 7)	Analysis 10.3
	Human (M37)	1	281	0.91 (0.57 to 1.44)	—	Analysis 10.3

WHAT'S NEW

Date	Event	Description
4 August 2010	Amended	Several of the vaccines investigated in this review are no longer in routine clinical use (for example, live attenuated rhesus-human reassortant tetravalent vaccine) and further new vaccines have been tested and approved for use since this review was written in 2004. For an up-to-date assessment of rotavirus vaccines currently approved for use, please see : Soares-Weiser K, MacLehose H, Ben-Aharon I, Goldberg E, Pitan F, Cunliffe N. Vaccines for preventing rotavirus diarrhoea: vaccines in use.

Date	Event	Description
		<i>Cochrane Database of Systematic Reviews</i> 2010, Issue 5. Art. No.: CD008521. DOI: 10.1002/14651858.CD008521.

HISTORY

Protocol first published: Issue 4, 2000

Review first published: Issue 1, 2004

Date	Event	Description
11 August 2009	Amended	Text added to abstract to highlight current actions: The authors are aware that further trials have been conducted for some of the vaccines included in this review. Authors are preparing new reviews that will update the evidence for vaccines approved for use and vaccines in development.
22 October 2008	Amended	Converted to new review format with minor editing.

CONTRIBUTIONS OF AUTHORS

Karla Soares-Weiser: protocol writing, searching, trial selection, data extraction and assimilation, statistical analyses, and review writing. Elad Goldberg: trial selection, data extraction and assimilation, and review writing. Ghandi Tamimi: protocol writing; location of information on rare adverse events. Femi Pitan: protocol writing. Leonard Leibovici: data extraction and assimilation (as third author to resolve disagreements), statistical analyses, and review writing.

DECLARATIONS OF INTEREST

None declared.

SOURCES OF SUPPORT

Internal sources

- Al-Ahli Hospital, Palestine Authority, Not specified.
- Lagos University Teaching Hospital, Nigeria.
- Rabin Medical Center, Beilinson Campus, Israel.

External sources

- Nuffield Trust, UK.
- Cochrane Child Health Field Bursary Scheme, Canada.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

1. Objectives: we re-worded the objectives to make them clearer.

2. Change in interventions. We added: W179-9 (live-attenuated bovine rotavirus vaccine); QHBRV (live-attenuated bovine rotavirus vaccine); 89-12 (human attenuated rotavirus vaccine); and other rotavirus vaccines (BIRVI, Lamb RV). We removed NCDV (live-attenuated bovine rotavirus vaccine); WC-QV (live-attenuated bovine rotavirus vaccine); and M37 (human attenuated rotavirus vaccine).

3. Types of outcome measures. We re-worded the following outcomes to make them clearer:

- "Number of people who developed diarrhoea from rotavirus infection" becomes "Rotavirus diarrhoea: episodes".
- "Number of deaths from rotavirus infection" becomes "Death: from rotavirus infection".
- "Hospitalization with rotavirus infection" becomes "Rotavirus diarrhoea: episodes requiring hospitalization".
- "Diarrhoea from any cause" becomes "All-cause diarrhoea: episodes".

Rotavirus vaccine for preventing diarrhoea (Review)

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- "Diarrhoea requiring hospitalization" becomes "All-cause diarrhoea: episodes requiring hospitalization".
- "Diarrhoea requiring intravenous infusion" becomes "Rotavirus diarrhoea: episodes requiring re-hydration" and "All-cause diarrhoea: episodes requiring re-hydration"

The outcome "Death from diarrhoea" is no longer used (incorporated in the other 'death' outcomes).

4. The following outcomes are used in the review but were not pre-specified in the protocol, because severity of rotavirus vaccine was measured in different ways and we thought that it would be useful to provide all information: rotavirus diarrhoea: severe episodes; rotavirus diarrhoea: episodes of more than four days duration; all-cause diarrhoea: episodes during first week after vaccine; and all-cause diarrhoea: severe episodes.

5. Elad Goldberg and Leonard Leibovici joined the review team. Prof Shai Ashkenazi left the review team.

INDEX TERMS

Medical Subject Headings (MeSH)

Cause of Death; Diarrhea [mortality] [*prevention & control] [virology]; Randomized Controlled Trials as Topic; Rotavirus Infections [*prevention & control]; Rotavirus Vaccines [*therapeutic use]; Vaccines, Attenuated [therapeutic use]

MeSH check words

Adult; Child; Humans