ClinicalEvidence

Gastroenteritis in children

Search date August 2007

Jacqueline Dalby-Payne and Elizabeth Elliott

ABSTRACT

INTRODUCTION: Diarrhoea is defined as the frequent passage of unformed, liquid stools. Regardless of the cause, the mainstay of management of acute gastroenteritis is provision of adequate fluids to prevent and treat dehydration. METHODS AND OUTCOMES: We conducted a systematic review and aimed to answer the following clinical questions: What are the effects of interventions to prevent acute gastroenteritis? What are the effects of treatments for acute gastroenteritis? We searched: Medline, Embase, The Cochrane Library, and other important databases up to August 2007 (Clinical Evidence reviews are updated periodically; please check our website for the most up-to-date version of this review). We included harms alerts from relevant organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA). RESULTS: We found 20 systematic reviews, RCTs, or observational studies that met our inclusion criteria. We performed a GRADE evaluation of the quality of evidence for interventions. CONCLUSIONS: In this systematic review, we present information relating to the effectiveness and safety of: rotavirus vaccines for the prevention of gastroenteritis; enteral rehydration solutions (oral or gastric), lactose-free feeds, and loperamide for the treatment of gastroenteritis; and ondansetron for the treatment of vomiting.

QUESTIONS

INTERVENTIONS

Key points

- Gastroenteritis in children worldwide is usually caused by rotavirus, which leads to considerable morbidity and mortality.

  Bacterial causes of gastroenteritis are more common in developing countries.
- Rotavirus vaccines are both safe and effective in preventing and minimising harm from gastroenteritis caused by rotavirus, particularly in preventing severe disease.
- Enteral rehydration solutions containing sugar or food plus electrolytes are as effective as intravenous fluids at correcting dehydration and reducing the duration of hospital stay, and may have fewer major adverse effects.
- Lactose-free feeds may reduce the duration of diarrhoea in children with mild-to-severe dehydration compared with feeds containing lactose, but studies have shown conflicting results.
- Loperamide can reduce the prevalence of acute diarrhoea in children in the first 48 hours after initiation of treatment, but there is an increased risk of adverse effects compared with placebo.
- Ondansetron reduces vomiting but increases diarrhoea in children with gastroenteritis compared with placebo.

DEFINITION

Acute gastroenteritis results from infection of the gastrointestinal tract, most commonly with a virus. It is characterised by rapid onset of diarrhoea with or without vomiting, nausea, fever, and abdominal pain. [1] In children, the symptoms and signs can be non-specific. [2] Diarrhoea is defined as the frequent passage of unformed, liquid stools. [3] Regardless of the cause, the mainstay of management of acute gastroenteritis is provision of adequate fluids to prevent and treat dehydration. In this review, we examine the benefits and harms of interventions to prevent and treat gastroenteritis, irrespective of its cause.

INCIDENCE/ PREVALENCE

Worldwide, diarrhoea causes the death of about 2 million children under 5 years of age each year; [4] of these deaths, up to 600,000 are caused by rotavirus. [5] Gastroenteritis leads to hospital admission in 7/1000 children under 5 years of age each year in the UK, [6] and diarrhoea results in the hospital admission in 1/23 to 1/27 children in the USA by the age of 5 years. [7] In Australia, gastroenteritis accounts for 6% of all hospital admissions in children under 15 years. [8] Acute gastroenteritis accounts for 204/1000 general practitioner consultations in children under 5 years in the UK. [6] In the USA, rotavirus results in hospital admission in 1/67 to 1/85 children by the age of 5 years. [7]

AETIOLOGY/ RISK FACTORS

In developed countries, acute gastroenteritis is predominantly caused by viruses (87%), of which rotavirus is the most common. [8] [9] [10] [11] [12] Worldwide, rotavirus causes almost 40% of cases of severe diarrhoea in infants. [13] Rotavirus outbreaks exhibit a seasonal pattern in temperate climates, and infections peak during winter months. In countries closer to the equator, seasonality is less noticeable, but the disease is more pronounced in the drier and cooler months. The reason for rotavirus seasonality is not known. Bacteria, predominantly *Campylobacter*, *Salmonella*, *Shigella,* and *Escherichia coli*, cause most of the remaining cases of acute gastroenteritis. In developing countries, where bacterial pathogens are more frequent, rotavirus is still a major cause of gastroenteritis; 82% of worldwide deaths caused by rotavirus occur in these countries. [5]

PROGNOSIS

Acute gastroenteritis is usually self-limiting, but if untreated it can result in morbidity and mortality secondary to water loss, and electrolyte and acid–base disturbance. Acute diarrhoea causes 4 million deaths each year in children under 5 years in Asia (excluding China), Africa, and Latin America, and more than 80% of deaths occur in children under 2 years of age. [14] Although death is uncommon in developing countries, dehydration secondary to gastroenteritis is a significant cause of morbidity and hospital admission. [8] [9] [15]

AIMS OF INTERVENTION

To prevent gastroenteritis, to prevent diarrhoea in children with gastroenteritis, to reduce the duration of diarrhoea, quantity of stool output, and duration of hospital stay; to prevent and treat dehydration; to promote weight gain after rehydration; to prevent persistent diarrhoea associated with lactose intolerance in children with gastroenteritis of any cause; and to prevent vomiting.

OUTCOMES

Prevention: episodes of diarrhoea, episodes of vomiting, and admissions to hospital with diarrhoea and/or vomiting. **Treatment:** total stool volume; duration of diarrhoea (time until permanent cessation); failure rate of oral rehydration treatment (as defined by individual RCTs); weight gain after rehydration; length of hospital stay; adverse events; mortality. For the antiemetic ondansetron, we report episodes of vomiting.

METHODS

Clinical Evidence search and appraisal August 2007. The following databases were used to identify studies for this systematic review: Medline 1966 to August 2007, Embase 1980 to August 2007, and The Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled Clinical Trials 2007, Issue 3. Additional searches were carried out using these websites: NHS Centre for Reviews and Dissemination (CRD) — for Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment (HTA), Turning Research into Practice (TRIP), and National Institute for Health and Clinical Excellence (NICE). We also searched for retractions of studies included in the review. Abstracts of the studies retrieved from the initial search were assessed by an information specialist. Selected studies were then sent to the author for additional assessment, using pre-determined criteria to identify relevant studies. Study design criteria for inclusion in this review were: published systematic reviews and RCTs in any language, at least single blinded, and containing more than 20 individuals of whom more than 80% were followed up. There was no minimum length of follow-up required to include studies. We excluded all studies described as "open", "open label", or not blinded unless blinding was impossible. In addition we use a regular surveillance protocol to capture harms alerts from organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA), which are added to the reviews as required. To aid readability of the numerical data in our reviews, we round percentages to the nearest whole number. Readers should be aware of this when relating percentages to summary statistics such as relative risks (RRs) and odds ratios (ORs). For GRADE evaluation of interventions for gastroenteritis in children, see table, p 20 .

QUESTION What are the effects of interventions to prevent acute gastroenteritis in children?

OPTION ROTAVIRUS VACCINES New

Episodes of diarrhoea caused by rotavirus

Compared with placebo Rotavirus vaccines may be more effective at decreasing episodes of diarrhoea caused by rotavirus (moderate-quality evidence).

Admissions to hospital
Compared with placebo Rotavirus vaccines may be more effective at decreasing admissions to hospital with diarrhoea caused by rotavirus (moderate-quality evidence).

Adverse effects
Rotavirus vaccines do not seem to be associated with an increased risk of intussusception (low-quality evidence).

For GRADE evaluation of interventions for gastroenteritis in children, see table, p 20 .

Benefits:

We found one systematic review (search date 2003; 64 RCTs; 21,060 healthy children) [16] and eight subsequent RCTs [17] [18] [19] [20] [21] [22] [23] [24] [25] comparing rotavirus vaccines versus placebo; one RCT was reported in two papers. [17] [18] The systematic review examined rhesus rotavirus vaccines, live-attenuated bovine rotavirus vaccines, and human-attenuated rotavirus vaccines. However, the tetravalent rhesus rotavirus vaccine was voluntarily withdrawn from the market in October 1999 because of an association with intussusception, [26] and the monovalent rhesus rotavirus vaccine is not licensed, so only data for live-attenuated bovine rotavirus vaccines and human-attenuated rotavirus vaccines are reported here. The results of the review are summarised in table 1, p 10 .

The systematic review found that both live-attenuated bovine rotavirus vaccine and human-attenuated rotavirus vaccine significantly reduced the total number of episodes of diarrhoea caused by rotavirus, episodes of severe diarrhoea caused by rotavirus, and admissions to hospital with diarrhoea caused by rotavirus, compared with placebo. [16] It also found that live-attenuated bovine rotavirus vaccine significantly reduced the number of episodes of all-cause diarrhoea, but it found no significant difference in the number of episodes of all-cause diarrhoea between human-attenuated rotavirus vaccine and placebo. The review found no significant difference in the number of episodes of severe all-cause diarrhoea, and no significant difference in the number of admissions to hospital with all-cause diarrhoea, between live-attenuated bovine rotavirus vaccine and placebo. The effects of human-attenuated rotavirus vaccine versus placebo on episodes of all-cause diarrhoea and hospitalisations for all-cause diarrhoea were not reported. Of the 64 RCTs evaluated in the systematic review, 49 did not report information about the generation of the allocation sequence, three RCTs did not provide information on blinding, and six RCTs did not provide information on withdrawals before study end. The authors of the review noted statistical heterogeneity among RCTs for many of the outcomes assessed ($P < 0.10$ for the outcome of episodes of diarrhoea [either caused by rotavirus or all-cause]; statistical heterogeneity set by review as significant if $P < 0.10$). The authors of the review suggest that the wide variation in protection across the individual RCTs may be related to the study design, study population, or the response of the immune system to different strains of rotavirus or rotavirus vaccine.

Of the eight subsequent RCTs, two large RCTs assessed the safety and efficacy of human–bovine and human rotavirus vaccines in over 60,000 children each. [19] [20] The other six RCTs evaluated different combinations and dosages of the vaccines on a variety of outcomes. [17] [18] [21] [22] [23] [24] [25] One RCT compared both bovine–human rotavirus reassortant tetravalent vaccine (2 doses) and rhesus–human rotavirus reassortant tetravalent vaccine versus placebo; we report only data for bovine–human rotavirus reassortant tetravalent vaccine versus placebo. [24] The results of the eight RCTs are summarised in table 1, p 10 . The RCTs found that the human rotavirus vaccine and human–bovine vaccine decreased episodes of diarrhoea caused by rotavirus, severe episodes of diarrhoea caused by rotavirus, severe episodes of diarrhoea from any cause, and admissions to hospital with diarrhoea caused by rotavirus or from any cause, compared with placebo. The RCTs also showed that the vaccines were effective against the wild-type G1 strain of the rotavirus.

Two RCTs randomly allocated children at a vaccine-to-placebo ratio of 2:1, [21] [24] and one RCT had an uneven distribution of children in each group because of a short supply of one of the vaccines. [25] In all the RCTs, stools were analysed for rotavirus antigen by enzyme immunoassay or enzyme-linked immunosorbent assay; however, some RCTs did not report the percentage of stools that were analysed. [19] [20] [23] [24] In one RCT, 23% of children were excluded from the per-protocol analysis because they were not evaluable with regard to the case definition for rotavirus gastroenteritis. [25] In the other RCTs, the percentage of stools that were not analysed was 7%, [21] 26%, [18] and 41%. [22]

Harms:

The tetravalent rhesus rotavirus vaccine was voluntarily withdrawn from the market in October 1999 because of an association with intussusception. The systematic review gave no information on the incidence of intussusception or death from any cause for either the human-attenuated rotavirus vaccine or live-attenuated bovine rotavirus vaccine. [16] The systematic review found no significant difference in fever and vomiting between the human-attenuated rotavirus vaccine and placebo, and between the live-attenuated bovine rotavirus vaccine and placebo. It found that the human-attenuated rotavirus increased irritability compared with placebo, but the difference between

groups was of borderline significance. It found no significant difference in irritability between the live-attenuated bovine rotavirus vaccine and placebo (data summarised in table 1, p 10). [16] The subsequent RCTs found no significant difference between human or human–bovine rotavirus vaccines and placebo in adverse effects, including fever, vomiting, diarrhoea, loss of appetite, or irritability (table 1, p 10). [17] [18] [19] [20] [21] [22] [23] [24] [25] The two large RCTs designed to look for safety found no significant difference in the incidence of intussusception between either the human and human–bovine vaccines and placebo. There was no difference in other potential severe adverse effects. [19] [20]

Comment:

The case definitions and scoring systems for severe gastroenteritis differed between RCTs, and the criteria for admission to hospital was likely to have varied between centres and countries; these factors make the comparison between vaccines difficult. The percentage of stools analysed also varied between RCTs, with a number of studies not reporting this information. In one RCT, participants whose stool specimens were not analysed were excluded from the analysis, [25] thus increasing the likelihood of bias and reducing the quality of the RCT. Monitoring for intussusception in infants is ongoing after the market introduction of rotavirus vaccine in developing communities. This ongoing surveillance follows the voluntary withdrawal of the quadrivalent rhesus rotavirus vaccine because of an association with intussusception.

Clinical guide:

Rotavirus vaccines are effective at preventing rotavirus gastroenteritis, and large safety studies of the currently available vaccines have shown no increased risk of adverse events, including intussusception. Given that rotavirus is a major cause of severe diarrhoeal illness worldwide, rotavirus vaccination would be equally beneficial for both developed and developing communities. Rotavirus vaccination is part of the routine vaccination schedule in a number of countries, including the US and Australia.

QUESTION What are the effects of treatments for acute gastroenteritis in children?

OPTION ENTERAL REHYDRATION SOLUTIONS

Duration of diarrhoea

Compared with intravenous rehydration We don't know whether enteral rehydration is more effective at reducing the duration of diarrhoea or at promoting weight gain (very low-quality evidence).

Duration of hospital stay

Compared with intravenous rehydration Enteral rehydration may be more effective at reducing the duration of hospital stay (very low-quality evidence).

For GRADE evaluation of interventions for gastroenteritis in children, see table, p 20 .

Benefits:

We found three systematic reviews. [27] [28] [29] Of these, we report results from the two with the most relevant outcomes. [27] [28] The third review [29] focused on the outcome of treatment failure, which is defined variably in different studies, and can be difficult to define with intravenous therapy. The first review (search date 2003) found that enteral rehydration significantly reduced the duration of hospital stay compared with intravenous rehydration (3 RCTs, 161 children; WMD –0.88 days, 95% CI –1.45 days to –0.32 days). [27] However, it found no significant difference between enteral and intravenous rehydration in weight gain or duration of diarrhoea (weight gain: 5 RCTs, 276 children; WMD –26 g, 95% CI –60.8 g to +9.7 g; duration of diarrhoea: 8 RCTs, 946 children; WMD –6.39 hours, 95% CI –13.73 hours to +0.94 hours). [27] Subgroup analysis found that, compared with intravenous rehydration, nasogastric rehydration significantly reduced the duration of diarrhoea, whereas oral rehydration did not (nasogastric rehydration: 2 RCTs, 494 children; WMD –17.77 hours, 95% CI –27.55 hours to –7.99 hours; oral rehydration: 5 RCTs, 415 children; WMD +1.76 hours, 95% CI –0.91 hours to +4.42 hours). The results for nasogastric rehydration were heavily influenced by one large study in 470 children with severe gastroenteritis. Results for weight gain in the first review excluded one RCT in a population of under-nourished children. Inclusion of this study in meta-analyses resulted in significant heterogeneity.

The second review (search date 2006, including children up to 18 years of age with acute gastroenteritis) found that the hospital stay was shorter for those treated with oral rehydration (6 RCTs, 526 children; WMD –1.2 days, 95% CI –2.38 to –0.02 days), but there was no significant difference in weight gain (6 RCTs, 369 children; WMD –26.33 g, 95% CI –206.92 g to +154.26 g) or duration of diarrhoea (8 RCTs, 960 children; WMD –5.90 hours, 95% CI –12.70 hours to +0.89 hours). The risk of failure to rehydrate was higher for oral rehydration than for intravenous rehydration (18 RCTs, 1811 children: 5% with oral rehydration *v* 1% with intravenous rehydration; risk difference 4%, 95% CI 1% to 7%), but the definitions of failure varied. [28] The RCTs included in the system-

atic reviews were of variable quality, and many did not report sufficient information about randomisation, blinding, and allocation concealment to enable quality assessment of included trials. [27] [28] RCTs in both systematic reviews included children with a wide age range, with variable degrees of dehydration, and with different socioeconomic backgrounds; they also included RCTs with different modes of oral therapy (by mouth or nasogastric tube).

Harms: The first systematic review found significantly fewer major adverse events (death or seizure) with enteral rehydration than with intravenous rehydration (16 RCTs, 1545 children; AR for death or seizure: 5/886 [1%] with enteral *v* 15/659 [2%] with intravenous; RR 0.36, 95% CI 0.14 to 0.89). [27] Analysis of major adverse events (death or seizure) was strongly weighted by a large RCT conducted in a developing community in 1985 in children with severe gastroenteritis, exclusion of which rendered the results not significant. Oral rehydration had a failure rate (need to convert to intravenous rehydration) of 4%, and nasogastric rehydration had a failure rate of 3%. The review did not report on minor adverse events. [27] The second systematic review found that only three of the 17 trials reported deaths, with all reported deaths occurring in low- to middle-income countries. [28] They found that phlebitis was more common in those given intravenous rehydration (NNT 50, 95% CI 25 to 100). Paralytic ileus was more common in those treated with oral rehydration (NNT 33, 95% CI 20 to 100).

Comment: **Clinical guide:**
There is evidence from systematic reviews that enteral and intravenous rehydration are equally effective for the management of mild-to-moderate dehydration. It is accepted practice in developed communities that children who are shocked or severely dehydrated require intravenous fluids.

OPTION LACTOSE-FREE FEEDS

Duration of diarrhoea
Compared with feeds containing lactose Lactose-free feeds may be more effective at reducing the duration of diarrhoea and stool frequency in children with mild-to-severe dehydration (low-quality evidence).

For GRADE evaluation of interventions for gastroenteritis in children, see table, p 20 .

Benefits: We found one systematic review (search date not reported) [30] and five subsequent RCTs [31] [32] [33] [34] [35] comparing feeds containing lactose versus lactose-free feed (see table 2, p 18). The review was limited by flaws in its methods. It found that feeds containing lactose significantly increased "treatment failure" compared with lactose-free feeds (13 RCTs, 873 children with mild-to-severe dehydration; treatment failure rate: 89/399 [22%] with lactose *v* 56/474 [12%] with lactose free; RR 2.1, 95% CI 1.6 to 2.7). [30] However, the definition of treatment failure varied among trials, and included increasing severity or persistence of diarrhoea or recurrence of dehydration. The review found that lactose-free feeds significantly reduced the mean duration of diarrhoea compared with feeds containing lactose (9 RCTs, 826 children with mild or no dehydration receiving oral rehydration treatment; 92 hours with lactose *v* 88 hours with lactose free; P = 0.001). When the three RCTs that included children given additional solid food were excluded, the review found that lactose-free feeds also significantly reduced the duration of diarrhoea compared with feeds containing lactose (6 RCTs, 604 children; 95 hours with lactose *v* 82 hours with lactose free; P < 0.001). Children receiving lactose-free feeds had significantly reduced stool frequency compared with children receiving feeds containing lactose (4 RCTs, 387 children; 4.0 stool movements/day with lactose *v* 3.5 stool movements/day with lactose free; P < 0.004). Total stool volume was greater in children who received feeds containing lactose (4 RCTs, 209 children; P = 0.002). Differences in weight gain during treatment could not be assessed, because of the use of solid food in two studies, and considerable heterogeneity among studies. Although the systematic review stated criteria for inclusion and exclusion of RCTs, only published studies were included, and the method of determining RCT quality was not reported. [30] There was considerable heterogeneity among studies, which limits the validity of the meta-analyses. Lactose-free feeds were superior to feeds containing lactose for decreasing the duration of diarrhoea. Differences for other outcomes, although statistically significant, were not clinically important. Of the five subsequent RCTs, three found that lactose-free feeds significantly reduced the duration of diarrhoea compared with feeds containing lactose (see table 2, p 18). [31] [34] [35] The other two RCTs found no significant difference. [32] [33] The results of other outcomes are also summarised in table 2, p 18 .

Harms: The RCT assessing adverse effects reported none in the treatment or control groups. [33]

Comment: A protocol on "Lactose avoidance for acute diarrhoea in children less than five years" has been published in the Cochrane Library. [36]

Clinical guide:
There is evidence that lactose-free feeds can decrease the duration of diarrhoea compared with lactose-containing feeds, but the existing systematic review is limited by weaknesses in the methods used. Routine use of lactose-free feeds is currently not recommended. We await the results of the Cochrane Review that is under way.

OPTION LOPERAMIDE

Duration of diarrhoea
Compared with placebo Loperamide may be more effective at reducing the duration of diarrhoea in children but we are not certain as results were sensitive to the method of analysis used (low-quality evidence).

Adverse effects
Loperamide may be associated with an increased risk of adverse effects such as ileus and lethargy.

For GRADE evaluation of interventions for gastroenteritis in children, see table, p 20 .

Benefits: We found one systematic review (search date 2006; 13 RCTs, 1788 children) [37] comparing loperamide versus placebo. It found that loperamide significantly reduced the mean duration of diarrhoea compared with placebo (6 RCTs, 976 children; mean reduction 0.8 days, 95% CI 0.7 days to 0.9 days). The review did not pool data for stool volume or admission to hospital because there were insufficient data for analysis reported in the identified RCTs. The authors of the review reported statistical heterogeneity among RCTs for the outcome of duration of diarrhoea ($P < 0.01$); subgroup analyses did not identify the source of heterogeneity. When the random effects method was used in a meta-analysis of the RCTs that satisfied all four indicators of quality (generation of allocation sequence, allocation concealment, double-blind RCT, and >90% of children randomised to treatment), the difference in the outcome of diarrhoea duration was no longer significant (mean difference –0.67 days, 95% CI –1.35 days to +0.01 days). The systematic review included open-label studies (4 RCTs), and reported that some of the RCTs did not report generation of allocation sequence (6 RCTs) or allocation concealment (6 RCTs). [37]

Harms: The review found that loperamide was associated with a significant increase in the proportion of children with adverse effects compared with placebo (12 RCTs, 1691 children; 94/927 [10%] with loperamide *v* 16/764 [2%] with placebo; ARI 8.6%, 95% CI 6.4% to 10.9%). [37] It found no significant difference in serious adverse effects (defined as ileus, lethargy, or death) between loperamide and placebo (12 RCTs; 8/927 [1%] with loperamide *v* 0/764 [0%] with placebo; ARI +0.8%, 95% CI –0.1% to +1.8%). However, when abdominal distension and sleepiness were also included in the definition of serious adverse effects, loperamide was associated with a significant increase in the proportion of children with adverse effects compared with placebo (21/927 [2%] with loperamide *v* 4/764 [1%] with placebo; ARI 1.8%, 95% CI 0.6% to 3.1%). Serious adverse effects occurred only in children under 3 years of age. One death occurred in a child taking loperamide caused by *Salmonella typhi* bacteraemia.

Comment: The quality of some of the studies included in the systematic review was poor due to lack of allocation-concealment reporting and non-blinding. These factors may have resulted in bias in favour of the intervention compared with placebo.

Clinical guide:
Although loperamide reduces the persistence of acute diarrhoea in children, it is not recommended for children under 3 years of age because the risk of adverse effects outweighs the benefits in this group.

OPTION ONDANSETRON New

Episodes of vomiting
Compared with placebo Ondansetron may be more effective at reducing episodes of vomiting within 24 hours of treatment (very low-quality evidence).

Admissions to hospital
Compared with placebo Ondansetron may be more effective at reducing admissions to hospital (very low-quality evidence).

Adverse effects
Ondansetron may be associated with an increased risk of episodes of diarrhoea (low-quality evidence).

For GRADE evaluation of interventions for gastroenteritis in children, see table, p 20 .

Benefits: We found one systematic review (search date 2005, 3 RCTs; 396 children with vomiting caused by gastroenteritis) comparing ondansetron with placebo. [38] The systematic review did not pool data because of clinical heterogeneity among the RCTs and a paucity of data. The results of the individual RCTs identified by the review are summarised in table 3, p 19 . The RCTs found that, during the initial period in the emergency department, [39] within 24 hours of treatment, [40] or during oral rehydration, [41] ondansetron significantly reduced the mean number of episodes of vomiting, and the proportion of children with vomiting, compared with placebo. However, one of the RCTs found no significant difference in either of these outcomes within the first 24 hours of treatment. [39] One of the RCTs found that ondansetron significantly reduced admissions to hospital compared with placebo, [39] whereas another RCT found no significant difference between the groups. [41] One trial did not recruit the calculated sample size because of the time constraints relating to the gastroenteritis season. [39]

Harms: The systematic review reported harms data from each RCT individually. [38] All three RCTs found that ondansetron was significantly associated with an increased risk of diarrhoeal episodes compared with placebo (table 3, p 19). [39] [40] [41] A rash was reported in one patient taking ondansetron, [39] and one trial reported drowsiness in 90% of children in all treatment groups. [40]

Comment: One RCT evaluated multiple doses of ondansetron; it found that the first dose was associated with a reduction in the episodes of vomiting, but that no benefit was derived from subsequent doses. [39] The other two RCTs assessed single doses of ondansetron and found significant reductions in the number of episodes of vomiting. [40] [41] In one RCT, the authors commented that a large proportion of children had spontaneous remission of vomiting, which indicates that the criteria for assessing vomiting severity was too low. [39] The same RCT also eliminated children with diarrhoea, which may have resulted in the recruitment of children with gastritis only, rather than gastroenteritis. All three RCTs found an association between ondansetron and an increased incidence of diarrhoea. [39] [40] [41] However, the reported incidence was between one and two episodes, which in developing countries would be of little clinical significance compared with the reduction in vomiting and the avoidance of the need for intravenous fluids. The results may not be applicable to developing communities where the aetiology of gastroenteritis is different, and where dehydration because of diarrhoea results in higher mortality. The relatively small sample size of the RCTs does not allow us to make definite conclusions regarding adverse effects. The systematic review does not provide adequate evidence to guide clinicians on the most effective dose or route of administration of ondansetron. Further trials are in progress. [38]

Clinical guide:
RCTs indicate that a single dose of ondansetron reduces vomiting in children with acute gastroenteritis, but care should be taken in populations where diarrhoea causes significant morbidity and mortality.

GLOSSARY

Lactose intolerance Malabsorption of lactose can occur for a short period after acute gastroenteritis because of mucosal damage and temporary lactase deficiency.
Low-quality evidence Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Moderate-quality evidence Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Very low-quality evidence Any estimate of effect is very uncertain.

SUBSTANTIVE CHANGES

Rotavirus vaccines New option for which we found one systematic review [16] and eight subsequent RCTs; [17] [18] [19] [20] [21] [22] [23] [24] [25] one RCT was reported in two papers. [17] [18] The systematic review found that live-attenuated bovine rotavirus vaccine and human-attenuated rotavirus vaccine were safe, and significantly reduced the number of episodes and severe episodes of gastroenteritis caused by rotavirus, and admissions to hospital with gastroenteritis caused by rotavirus, compared with placebo. The eight subsequent RCTs found similar results. Categorised as Beneficial.
Ondansetron New option for which we found one systematic review. [38] The review did not pool data because of clinical heterogeneity among the RCTs and a paucity of data. Three RCTs identified by the review found that ondansetron reduced episodes of vomiting compared with placebo. [39] [40] [41] The RCTs found that ondansetron was associated with an increased risk of diarrhoea compared with placebo, but the RCTs were small in size and, taken together, do not provide sufficient evidence to draw a definitive conclusion regarding adverse effects of ondansetron. Categorised as Likely to be beneficial.
Loperamide One systematic review added, [37] which found that loperamide significantly reduced the mean duration of diarrhoea compared with placebo. However, the incidence of adverse effects was significantly higher in children treated with loperamide compared with placebo; all serious adverse effects occurred in children under 3 years of age. Categorisation changed from Likely to be beneficial to Trade-off between benefits and harms.

REFERENCES

1. Armon K, Elliott EJ. Acute gastroenteritis. In: Moyer VA, Elliott EJ, Davis RL, eds. Evidence based pediatrics and child health, 2nd ed. London: BMJ Books, 2004;377–392.
2. American Academy of Pediatrics (APP). Practice parameter: the management of acute gastroenteritis in young children. American Academy of Pediatrics, Provisional Committee on Quality Improvement, Subcommittee on Acute Gastroenteritis. *Pediatrics* 1996;97:424–435.[PubMed]
3. Critchley M. Butterworths medical dictionary, 2nd ed. London: Butterworths, 1986.
4. World Health Organization. Children's environmental health. http://www.who.int/ceh/en/ (last accessed 14 July 2009).
5. Parashar UD, Hummelman EG, Bresee JS, et al. Global illness and deaths caused by rotavirus disease in children. *Emerg Infect Dis* 2003;9:565–572.[PubMed]
6. OPCS. Morbidity statistics from general practice. Fourth national study, 1991–1992. London: HMSO, 1993.
7. Malek MA, Curns AT, Holman RC. Diarrhea- and Rotavirus-associated hospitalizations among children less than 5 years of age: United States, 1997 and 2000. *Pediatrics* 2006;117:1887–1892.
8. Elliott EJ, Backhouse JA, Leach JW. Pre-admission management of acute gastroenteritis. *J Paediatr Child Health* 1996;32:18–21.[PubMed]
9. Conway SP, Phillips RR, Panday S. Admission to hospital with gastroenteritis. *Arch Dis Child* 1990;65:579–584.[PubMed]
10. Finkelstein JA, Schwartz JS, Torrey S, et al. Common clinical features as predictors of bacterial diarrhea in infants. *Am J Emerg Med* 1989;7:469–473.[PubMed]
11. DeWitt TG, Humphrey KF, McCarthy P. Clinical predictors of acute bacterial diarrhea in young children. *Pediatrics* 1985;76:551–556.[PubMed]
12. Ferson MJ. Hospitalisations for rotavirus gastroenteritis among children under five years of age in New South Wales. *Med J Aust* 1996;164:273–276.[PubMed]
13. World Health Organisation. Diarrhoeal diseases (updated February 2009); Rotavirus. http://www.who.int/vaccine_research/diseases/diarrhoeal/en/index5.html (last accessed 14 July 2009).
14. World Health Organization. A manual for the treatment of diarrhoea. Programme for the control of diarrhoeal diseases. Geneva: WHO, 1990. http://www.popline.org/docs/1443/273264.html (last accessed 14 July 2009).
15. Glass RI, Lew JF, Gangarosa RE, et al. Estimates of morbidity and mortality rates for diarrheal diseases in American children. *J Pediatr* 1991;118:S27–S33.[PubMed]
16. Soares Weiser K, Goldberg E, Tamimi G, et al. Rotavirus vaccine for preventing diarrhoea. In: The Cochrane Library, Issue 3, 2007. Chichester, UK: John Wiley & Sons, Ltd. Search date 2003.[PubMed]
17. Linhares AC, Ruiz-Palacios GM, Guerrero ML, et al. A short report on highlights of world-wide development of RIX4414: a Latin American experience. *Vaccine* 2006;24:3784–3785.[PubMed]
18. Salinas B, Perez Schael I, Linhares AC, et al. Evaluation of safety, immunogenicity and efficacy of an attenuated rotavirus vaccine, RIX4414: a randomized, placebo-controlled trial in Latin American infants. *Pediatr Infect Dis J* 2005;24:807–816.[PubMed]
19. Vesikari T, Matson DO, Dennehy P, et al. Safety and efficacy of a pentavalent human-bovine (WC3) reassortant rotavirus vaccine. *N Eng J Med* 2006;354:23–33.[PubMed]
20. Ruiz-Palacios GM, Perez-Schael I, Velazquez FR, et al. Safety and efficacy of an attenuated vaccine against severe rotavirus gastroenteritis. *N Eng J Med* 2006;354:11–22.[PubMed]
21. Vesikari T, Karvonen A, Puustinen L, et al. Efficacy of RIX4414 live attenuated human rotavirus vaccine in Finnish infants. *Pediatr Infect Dis J* 2004;23:937–943.[PubMed]
22. Phua KB, Quak SH, Lee BW, et al. Evaluation of RIX4414, a live, attenuated rotavirus vaccine, in a randomized, double-blind, placebo-controlled phase 2 trial involving 2464 Singaporean infants. *J Infect Dis* 2005;192:S6–S16.[PubMed]
23. Clark HF, Bernstein DI, Dennehy PH, et al. Safety, efficacy, and immunogenicity of a live, quadrivalent human-bovine reassortant rotavirus vaccine in healthy infants. *J Pediatr* 2004;144:184–190.[PubMed]
24. Vesikari T, Karvonen AV, Majuri J, et al. Safety, efficacy, and immunogenicity of 2 doses of bovine-human (UK) and rhesus-rhesus-human rotavirus reassortant tetravalent vaccines in Finnish children. *J Infect Dis* 2006;194:370–376.[PubMed]
25. Vesikari T, Clark HF, Offit PA, et al. Effects of the potency and composition of the multivalent human-bovine (WC3) reassortant rotavirus vaccine on efficacy, safety and immunogenicity in healthy infants. *Vaccine* 2006;24:4821–4829.[PubMed]
26. MMWR. Withdrawal of rotavirus vaccine recommendation. Available at http://www.cdc.gov/mmwr/preview/mmwrhtml/mm4843a5.htm (last accessed 10 August 2009).
27. Fonseca BK, Holdgate A, Craig JC. Enteral vs intravenous rehydration therapy for children with gastroenteritis: a meta-analysis of randomized controlled trials. *Arch Pediatr Adolesc Med* 2004;158:483–490. Search date 2003; primary sources Medline, Embase, Cochrane Central Register of Controlled Trials.[PubMed]
28. Hartling L, Bellemare S, Wiebe N, et al. Oral versus intravenous rehydration for treating dehydration due to gastroenteritis in children. In: The Cochrane Library: Issue 3, 2007. Chichester, UK: John Wiley & Sons, Ltd. Search date 2006.[PubMed]
29. Bellemare S, Hartling L, Wiebe N, et al. Oral rehydration versus intravenous therapy for treating dehydration due to gastroenteritis in children: a meta-analysis of randomised controlled trials. *BMC Med* 2004;2:11. Available online at http://www.biomedcentral.com/1741-7015/2/11 (last accessed 14 July 2009). Search date 2003; primary sources Medline, Embase, Cochrane Central Register of Controlled Trials.[PubMed]
30. Brown KH, Peerson JM, Fontaine O. Use of nonhuman milks in the dietary management of young children with acute diarrhea: a meta-analysis of clinical trials. *Pediatrics* 1994;93:17–27. Search date not reported; primary sources Medline, hand searches of reference lists, and contact with researchers.[PubMed]
31. Allen UD, McLeod K, Wang EE. Cow's milk versus soy-based formula in mild and moderate diarrhea: a randomized, controlled trial. *Acta Paediatr* 1994;83:183–187.[PubMed]
32. Clemente YF, Tapia CC, Comino AL, et al. Lactose free formula versus adapted formula in acute infantile diarrhea. *An Esp Pediatr* 1993;39:309–312.[PubMed]
33. Lozano JM, Cespedes JA. Lactose vs. lactose free regimen in children with acute diarrhoea: a randomized controlled trial. *Arch Latinoam Nutr* 1994;44:6–11.[PubMed]
34. Fayad IM, Hashem M, Husseine A, et al. Comparison of soy-based formulas with lactose and with sucrose in the treatment of acute diarrhoea in infants. *Arch Pediatr Adolesc Med* 1999;153:675–680.[PubMed]
35. Wall CR, Webster J, Quirk P, et al. The nutritional management of acute diarrhea in young infants: effect of carbohydrate ingested. *J Pediatr Gastroenterol Nutr* 1994;19:170–174.[PubMed]
36. MacGillivray SA, Fahey T, McGuire W. Lactose avoidance for acute diarrhoea in children less than five years (Protocol). In: The Cochrane Library, Issue 3, 2007. Chichester, UK: John Wiley & Sons, Ltd.
37. Li ST, Grossman DC, Cummings P. Loperamide therapy for acute diarrhea in children: Systematic review and meta-analysis. *PLoS Med* 2007;4:495–505.[PubMed]
38. Alhashimi D, Alhashimi H, Fedorowicz Z, et al. Antiemetics for reducing vomiting related to acute gastroenteritis in children and adolescents. In: The Cochrane Library, Issue 3, 2007. Chichester, UK: John Wiley & Sons, Ltd. Search date 2005.[PubMed]
39. Ramsook C, Sahagun-Carreon I, Kozinetz CA, et al. A randomized clinical trial comparing oral ondansetron with placebo in children with vomiting from acute gastroenteritis *Ann Emerg Med* 2002;39:397–403.[PubMed]
40. Cubeddu LX, Trujillo LM, Talmaciu I, et al. Antiemetic activity of ondansetron in acute gastroenteritis. *Aliment Pharmacol Ther* 1997;11:185–191.[PubMed]
41. Freedman SB, Adler M, Seshadri R, et al. Oral ondansetron for gastroenteritis in a pediatric emergency department. *N Eng J Med* 2006;354:1698–1705.[PubMed]

Jacqueline R Dalby-Payne
Consultant Paediatrician
The Children's Hospital at Westmead
Sydney
Australia

Elizabeth J Elliott
Associate Professor
Discipline of Paediatrics and Child Health
University of Sydney, Consultant Paediatrician, The Children's Hospital at Westmead
Sydney
Australia

Competing interests: EE is co-contributor for one review [1] and one study referenced in this review. [8] JDP declares that she has no competing interests.

Disclaimer

The information contained in this publication is intended for medical professionals. Categories presented in Clinical Evidence indicate a judgement about the strength of the evidence available to our contributors prior to publication and the relevant importance of benefit and harms. We rely on our contributors to confirm the accuracy of the information presented and to adhere to describe accepted practices. Readers should be aware that professionals in the field may have different opinions. Because of this and regular advances in medical research we strongly recommend that readers' independently verify specified treatments and drugs including manufacturers' guidance. Also, the categories do not indicate whether a particular treatment is generally appropriate or whether it is suitable for a particular individual. Ultimately it is the readers' responsibility to make their own professional judgements, so to appropriately advise and treat their patients. To the fullest extent permitted by law, BMJ Publishing Group Limited and its editors are not responsible for any losses, injury or damage caused to any person or property (including under contract, by negligence, products liability or otherwise) whether they be direct or indirect, special, incidental or consequential, resulting from the application of the information in this publication.

TABLE 1 **RCTs comparing rotavirus vaccines versus placebo in healthy children.**

RCTs comparing rotavirus vaccines versus placebo in healthy children.

Comparison

Human-attenuated rotavirus vaccine *v* placebo [16]

Study details

Population: 1 SR (6 RCTs, 2703 healthy children aged 1.5–60 months)
Follow-up time: 6–15 months
Location: 1 RCT Australia; 1 RCT Brazil, Mexico, and Venezuela; 1 RCT Finland; 2 RCTs USA; and 1 RCT Venezuela

Episodes of diarrhoea and proportion of children with episodes of diarrhoea

Caused by rotavirus

Any serotype

Episodes of any severity:
3 RCTs, 2482 children; 67/1730 (4%) with human vaccine *v* 91/752 (12%) with placebo; RR 0.42, 95% CI 0.21 to 0.85
Severe episodes:
2 RCTs, 2201 children; 25/1590 (2%) with human vaccine *v* 53/611 (9%) with placebo; RR 0.21, 95% CI 0.13 to 0.35

G serotype

NA

All-cause

Episodes of any severity:
1 RCT, 281 children; 27/140 (19%) with human vaccine *v* 30/141 (21%) with placebo; RR 0.91, 95% CI 0.57 to 1.44

Admissions to hospital

Caused by rotavirus

2 RCTs, 2201 children; 8/1590 (1%) with human vaccine *v* 15/611 (2%) with placebo; RR 0.21, 95% CI 0.09 to 0.48

All-cause

NA

Treatment-related adverse effects

1 week after receipt of vaccine or placebo:
Fever: 5 RCTs, 716 children; 61/372 (16%) with human vaccine *v* 30/344 (9%) with placebo; RR 1.75, 95% CI 0.85 to 3.64
Vomiting: 2 RCTs, 331 children; 24/169 (14%) with human vaccine *v* 12/162 (7%) with placebo; RR 1.94, 95% CI 1.00 to 3.75
Irritability: 1 RCT, 215 children; 37/108 (34%) with human vaccine *v* 52/107 (49%) with placebo; RR 0.70, 95% CI 0.51 to 0.98

Mortality

NA

Comparison

Human strain RIX4414 ($10^{4.7}$ffu, $10^{5.5}$ffu, or $10^{5.8}$ffu; all 2 doses) *v* placebo [17] [18]

Study details

Population: 2155 healthy infants aged 6–12 weeks
Follow-up time: until 1 year of age
Location: Brazil, Mexico, and Venezuela

Episodes of diarrhoea and proportion of children with episodes of diarrhoea

Caused by rotavirus

Any serotype

G serotype

All-cause

RCTs comparing rotavirus vaccines versus placebo in healthy children.

Episodes of any severity:
21/468 (4%) with $10^{4.7}$ffu vaccine *v* 22/460 (5%) with $10^{5.2}$ffu vaccine *v* 15/464 (3%) with $10^{5.8}$ffu vaccine *v* 51/454 (11%) with placebo; significance not assessed

Proportion of children with episodes of any severity:
21/468 (4%) with $10^{4.7}$ffu vaccine *v* 22/460 (5%) with $10^{5.2}$ffu vaccine *v* 15/464 (3%) with $10^{5.8}$ffu vaccine *v* 49/454 (11%) with placebo; all comparisons between vaccine groups and placebo had P < 0.001; $10^{4.7}$ffu vaccine efficacy 58%, 95% CI 29% to 76%; $10^{5.2}$ffu vaccine efficacy 56%, 95% CI 25% to 75%; $10^{5.8}$ffu vaccine efficacy 70%, 95% CI 46% to 84%

Proportion of children with severe episodes:
12/468 (3%) with $10^{4.7}$ffu vaccine *v* 10/460 (2%) with $10^{5.2}$ffu vaccine *v* 5/464 (1%) with $10^{5.8}$ffu vaccine *v* 34/454 (7%) with placebo; all comparisons between vaccine groups and placebo had P < 0.001; $10^{4.7}$ffu vaccine efficacy 66%, 95% CI 32% to 84%; $10^{5.2}$ffu vaccine efficacy 71%, 95% CI 40% to 87%, $10^{5.8}$ffu vaccine efficacy 86%, 95% CI 63% to 96%

Episodes of any severity:

G1 wild-type:
12/468 (3%) with $10^{4.7}$ffu vaccine *v* 6/460 (1%) with $10^{5.2}$ffu vaccine *v* 7/464 (2%) with $10^{5.8}$ffu vaccine *v* 30/454 (7%) with placebo

G2:
0/468 (0%) with $10^{4.7}$ffu vaccine *v* 0/460 (0%) with $10^{5.2}$ffu vaccine *v* 1/464 (0.2%) with $10^{5.8}$ffu vaccine *v* 3/454 (0.7%) with placebo

G3:
1/468 (0.2%) with $10^{4.7}$ffu vaccine *v* 0/460 (0%) with $10^{5.2}$ffu vaccine *v* 0/464 (0%) with $10^{5.8}$ffu vaccine *v* 2/454 (0.4%) with placebo

G4:
0/468 (0%) with $10^{4.7}$ffu vaccine *v* 0/460 (0%) with $10^{5.2}$ffu vaccine *v* 1/464 (0.2%) with $10^{5.8}$ffu vaccine *v* 0/454 (0%) with placebo

G9:
8/468 (2%) with $10^{4.7}$ffu vaccine *v* 14/460 (3%) with $10^{5.2}$ffu vaccine *v* 7/464 (2%) with $10^{5.8}$ffu vaccine *v* 15/454 (3%) with placebo

Canine:
0/468 (0%) with $10^{4.7}$ffu vaccine *v* 0/460 (0%) with $10^{5.2}$ffu vaccine *v* 0/464 (0%) with $10^{5.8}$ffu vaccine *v* 1/454 (0.2%) with placebo

Unknown:
0/468 (0%) with $10^{4.7}$ffu vaccine *v* 2/460 (0.4%) with $10^{5.2}$ffu vaccine *v* 0/464 (0%) with $10^{5.8}$ffu vaccine *v* 0/454 (0%) with placebo; significance not assessed for all outcomes above

Proportion of children with severe episodes:

G1 wild-type:
7/468 (1%) with $10^{4.7}$ffu vaccine (P = 0.057) *v* 4/460 (1%) with $10^{5.2}$ffu vaccine (P = 0.006) *v* 2/464 (0.4%) with $10^{5.8}$ffu vaccine (P < 0.001) *v* 16/454 (4%) with placebo (P values are for comparisons with the placebo group); $10^{4.7}$ffu vaccine efficacy +58%, 95% CI –9% to +85%; $10^{5.2}$ffu vaccine efficacy 75%, 95% CI 24% to 94%; $10^{5.8}$ffu vaccine efficacy 88%, 95% CI 48% to 99%

G9:
4/468 (1%) with $10^{4.7}$ffu vaccine (P = 0.027) *v* 6/460 (1%) with $10^{5.2}$ffu vaccine (P = 0.109) *v* 3/464 (0.6%) with $10^{5.8}$ffu vaccine (P = 0.011) *v* 13/454 (3%) with placebo (P values are for comparisons with the placebo group); $10^{4.7}$ffu vaccine efficacy 70%, 95% CI 3% to 93%; $10^{5.2}$ffu vaccine efficacy +54%, 95% CI –29% to +86%; $10^{5.8}$ffu vaccine efficacy 77%, 95% CI 18% to 96%

Episodes of any severity:
1216/1392 (87%) with vaccine *v* 419/454 (92%) with placebo; significance not assessed

Proportion of children with episodes of any severity:
573/1392 (41%) with pooled vaccine groups *v* 214/454 (47%) with placebo; significance not assessed. Data for individual vaccine doses not reported

Admissions to hospital

Caused by rotavirus

9/1392 (0.6%) with pooled vaccine groups *v* 14/454 (3%) with placebo; pooled vaccine efficacy 79%, 95% CI 48% to 92%. Data for individual vaccine doses not reported

All-cause

NA

Treatment-related adverse effects

15 days after receipt of any dose of vaccine or placebo:
Rates of fever, diarrhoea, vomiting, irritability, loss of appetite, and cough/runny nose were similar among groups; data presented graphically, significance not assessed

Mortality

3 deaths

RCTs comparing rotavirus vaccines versus placebo in healthy children.

Comparison

Human strain RIX4414 (2 doses) *v* placebo [20]

Study details

Population: 63,225 healthy infants aged 6–13 weeks included in a safety cohort, 20,169 of which were included in the efficacy cohort
Follow-up time: until 1 year of age
Location: Argentina, Brazil, Chile, Colombia, the Dominican Republic, Finland, Honduras, Mexico, Nicaragua, Panama, Peru, and Venezuela

Episodes of diarrhoea and proportion of children with episodes of diarrhoea

Caused by rotavirus

Any serotype

Proportion of children with severe episodes:
12/9009 (0.1%) with vaccine *v* 77/8858 (0.9%) with placebo; RR 0.153, CI not reported; vaccine efficacy 84.7%, 95% CI 71.7% to 92.4%; P < 0.001

G serotype

Proportion of children with episodes of any severity:
G1P[8]:
3/9009 (0.03%) with vaccine *v* 36/8858 (0.4%) with placebo; RR 0.082, CI not reported; vaccine efficacy 91.8%, 95% CI 74.1% to 98.4%
G3P[8], G4P[8], G9P[8]:
4/9009 (0.04%) with vaccine *v* 31/8858 (0.3%) with placebo; RR 0.126, CI not reported; vaccine efficacy 87.3%, 95% CI 64.1% to 96.7%
G2P[4]:
6/9009 (0.07%) with vaccine *v* 10/8858 (0.1%) with placebo; RR 0.59, CI not reported; vaccine efficacy +41%, 95% CI –79.2% to +82.4%
Proportion of children with severe episodes:
G1P[8]:
3/9009 (0.03%) with vaccine *v* 32/8858 (0.4%) with placebo; RR 0.092, CI not reported; vaccine efficacy 90.8%, 95% CI 70.5% to 98.2%
G3P[8], G4P[8], G9P[8]:
4/9009 (0.04%) with vaccine *v* 30/8858 (0.3%) with placebo; RR 0.130, CI not reported; vaccine efficacy 86.9%, 95% CI 62.8% to 96.6%
G2P[4]:
5/9009 (0.06%) with vaccine *v* 9/8858 (0.1%) with placebo; RR 0.55 CI not reported; vaccine efficacy +45.4%, 95% CI –81.5% to +85.6%

All-cause

Proportion of children with severe episodes:
183/9009 (2%) with vaccine *v* 300/8858 (3%) with placebo; RR 0.600, CI not reported; vaccine efficacy 40%, 95% CI 27.7% to 50.4%

Admissions to hospital

Caused by rotavirus

9/9009 (0.1%) with vaccine *v* 59/8858 (0.7%) with placebo; RR 0.150, CI not reported; vaccine efficacy 85%, 95% CI 69.6% to 93.5%; P < 0.001

All-cause

145/9009 (1.6%) with vaccine *v* 246/8858 (3%) with placebo; RR 0.580, CI not reported; vaccine efficacy 42%, 95% CI 28.6% to 53.1%

Treatment-related adverse effects

Whole study period:
Serious adverse effects: (any untoward medical occurrence that resulted in death, was life-threatening, required hospitalisation, prolonged existing hospitalisation, or resulted in disability or incapacity): 928/31,673 (3%) with vaccine *v* 1047/31,552 (3%) with placebo; RR 0.88, 95% CI 0.81 to 0.96; P = 0.005
Intussusception: 9/31,673 (0.03%) with vaccine *v* 16/31,552 (0.05%) with placebo; RR 0.56, 95% CI 0.25 to 1.24; P = 0.16
Hospitalisation: 886/31,673 (3%) with vaccine *v* 1003/31,552 (3%) with placebo; RR 0.88, 95% CI 0.81 to 0.96; P = 0.005

Mortality

56/31,673 (0.2%) with vaccine *v* 43/31,552 (0.1%) with placebo; RR 1.30, 95% CI 0.87 to 1.93; P = 0.20

Comparison

RCTs comparing rotavirus vaccines versus placebo in healthy children.

Human strain RIX4414 (2 doses) *v* placebo [21]

Study details

Population: 405 healthy infants aged 6–12 weeks.
Follow-up time: 18– 22 months
Location: Finland

Episodes of diarrhoea and proportion of children with episodes of diarrhoea

Caused by rotavirus		**All-cause**
Any serotype	**G serotype**	
Episodes of any severity: 14/245 (6%) with vaccine *v* 24/123 (20%) with placebo; significance not assessed **Proportion of children with episodes of any severity:** 13/245 (5%) with vaccine *v* 23/123 (19%) with placebo; vaccine efficacy 72%, 95% CI 42% to 87%; P < 0.001 **Proportion of children with severe episodes:** 3/245 (1%) with vaccine *v* 10/123 (8%) with placebo; vaccine efficacy 85%, 95% CI 42% to 97%; P = 0.001	NA	**Proportion of children with episodes of any severity:** 66% with vaccine *v* 65% with placebo; absolute numbers not reported, significance not assessed **Proportion of children with severe episodes:** 5% with vaccine *v* 9% with placebo; absolute numbers not reported, significance not assessed

Admissions to hospital

Caused by rotavirus	**All-cause**
NA	NA

Treatment-related adverse effects

15 days after receipt of the first dose of vaccine or placebo:
Fever: 12/265 (5%) with vaccine *v* 11/133 (8%) with placebo
Diarrhoea: 8/265 (3%) with vaccine *v* 5/133 (4%) with placebo
Vomiting: 9/265 (3%) with vaccine *v* 5/133 (4%) with placebo
Irritability: 62/265 (23%) with vaccine *v* 60/133 (45%) with placebo
Loss of appetite: 24/265 (9%) with vaccine *v* 17/133 (13%) with placebo; significance not assessed for all outcomes listed above
Whole study period:
Intussusception: 0 cases; significance not assessed

Mortality

NA

Comparison

Human strain RIX4414 ($10^{4.7}$ffu, $10^{5.2}$ffu, or $10^{6.1}$ffu; all 2 doses) *v* placebo [22]

Study details

Population: 2464 healthy infants aged 11–17 weeks
Follow-up time: until 18 months of age
Location: Singapore

Episodes of diarrhoea and proportion of children with episodes of diarrhoea

Caused by rotavirus		**All-cause**
Any serotype	**G serotype**	

RCTs comparing rotavirus vaccines versus placebo in healthy children.

Episodes of any severity:
2/501 (0.4%) with $10^{4.7}$ffu vaccine *v* 0/639 (0%) with $10^{5.2}$ffu vaccine *v* 0/639 (0%) with $10^{6.1}$ffu vaccine *v* 4/642 (0.6%) with placebo; pooled vaccine efficacy 82%; P = 0.046
Severe episodes:
0/501 (0%) with $10^{4.7}$ffu vaccine *v* 0/639 (0%) with $10^{5.2}$ffu vaccine *v* 0/639 (0%) with $10^{6.1}$ffu vaccine *v* 1/642 (0.2%) with placebo; significance not assessed

NA

Episodes of any severity:
98/501 (20%) with $10^{4.7}$ffu vaccine *v* 85/639 (13%) with $10^{5.2}$ffu vaccine *v* 93/639 (15%) with $10^{6.1}$ffu vaccine *v* 111/642 (17%) with placebo; significance not assessed
Severe episodes:
2/501 (0.4%) with $10^{4.7}$ffu vaccine *v* 4/639 (0.6%) with $10^{5.2}$ffu vaccine *v* 5/639 (0.8%) with $10^{6.1}$ffu vaccine *v* 10/642 (2%) with placebo; significance not assessed
Proportion of children with episodes of any severity:
74/501 (15%) with $10^{4.7}$ffu vaccine *v* 73/639 (11%) with $10^{5.2}$ffu vaccine *v* 84/639 (13%) with $10^{6.1}$ffu vaccine *v* 100/642 (16%) with placebo; significance not assessed

Admissions to hospital

Caused by rotavirus

NA

All-cause

NA

Treatment-related adverse effects

15 days after receipt of the first dose of vaccine or placebo:
Fever: 30/510 (6%) with $10^{4.7}$ffu vaccine *v* 28/648 (4%) with $10^{5.2}$ffu vaccine *v* 25/653 (4%) with $10^{6.1}$ffu vaccine *v* 28/653 (4%) with placebo
Diarrhoea: 1/510 (0.2%) with $10^{4.7}$ffu vaccine *v* 1/648 (0.2%) with $10^{5.2}$ffu vaccine *v* 3/653 (0.5%) with $10^{6.1}$ffu vaccine *v* 2/653 (0.3%) with placebo
Vomiting: 5/510 (1%) with $10^{4.7}$ffu vaccine *v* 5/648 (1%) with $10^{5.2}$ffu vaccine *v* 7/653 (1%) with $10^{6.1}$ffu vaccine *v* 6/653 (1%) with placebo
Whole study period:
Serious adverse effects (those that prevent normal daily activity):
Serious adverse effects in 4 children were deemed to be possibly related to vaccination, including 1 case of intussusception in a boy who received $10^{5.2}$ffu vaccine; significance not assessed for all outcomes listed above

Mortality

3 deaths: 2 in the $10^{6.1}$ffu group and 1 in the $10^{5.2}$ffu group

Comparison

Live-attenuated bovine rotavirus vaccine *v* placebo [16]

Study details

Population: 1 SR (22 RCTs, 6087 healthy children aged from newborn to 60 months)
Follow-up time: 1 week to 32 months
Location: 1 RCT Austria, 1 RCT Central African Republic, 5 RCTs Finland, 1 RCT Gambia, 1 RCT Peru, 1 RCT Rwanda, 1 RCT UK, and 11 RCTs USA

Episodes of diarrhoea and proportion of children with episodes of diarrhoea

Caused by rotavirus

Any serotype

Episodes of any severity:
17 RCTs, 5283 children; 393/2967 (13%) with bovine vaccine *v* 413/2316 (18%) with placebo; RR 0.59, 95% CI 0.45 to 0.76
Severe episodes:
10 RCTs, 3643 children; 118/1933 (6%) with bovine vaccine *v* 218/1710 (13%) with placebo; RR 0.38, 95% CI 0.24 to 0.60

G serotype

NA

All-cause

Episodes of any severity:
11 RCTs, 3309 children; 523/1797 (29%) with bovine vaccine *v* 572/1512 (38%) with placebo; RR 0.73, 95% CI 0.60 to 0.89
Severe episodes:
3 RCTs, 714 children; 39/398 (10%) with bovine vaccine *v* 69/316 (22%) with placebo; RR 0.51, 95% CI 0.21 to 1.26

Admissions to hospital

RCTs comparing rotavirus vaccines versus placebo in healthy children.

Caused by rotavirus

4 RCTs, 1693 children; 13/962 (1%) with bovine vaccine *v* 23/731 (3%) with placebo; RR 0.37, 95% CI 0.18 to 0.74

All-cause

3 RCTs, 799 children; 8/424 (2%) with bovine vaccine *v* 13/375 (3%) with placebo; RR 0.55, 95% CI 0.16 to 1.91

Treatment-related adverse effects

5 days to 4 weeks after receipt of vaccine or placebo:
Fever: 12 RCTs, 2168 children; 140/1182 (12%) with bovine vaccine *v* 118/986 (12%) with placebo; RR 0.95, 95% CI 0.73 to 1.23
Vomiting: 10 RCTs, 2016 children; 262/1109 (24%) with bovine vaccine *v* 202/907 (22%) with placebo; RR 1.05, 95% CI 0.90 to 1.22
Irritability: 3 RCTs, 512 children; 95/255 (37%) with bovine vaccine *v* 89/257 (35%) with placebo; RR 1.08, 95% CI 0.86 to 1.36

Mortality

NA

Comparison

Pentavalent human-bovine (WC3) reassortant rotavirus vaccine (3 doses) *v* placebo [19]

Study details

Population: 70,301 healthy infants aged 6–12 weeks. A large-scale study (assessing intussusception plus hospitalisations and emergency department visits for rotavirus gastroenteritis) evaluated 68,038 children; a detailed safety substudy (assessing non-serious adverse events) evaluated 9605 children; and a clinical-efficacy substudy (assessing efficacy against all rotavirus gastroenteritis and office visits for rotavirus gastroenteritis) evaluated 5673 children
Follow-up time: 1 year for the large-scale safety study; 42 days after each dose for the detailed safety substudy; 1 year for the clinical-efficacy substudy
Location: Belgium, Costa Rica, Finland, Germany, Guatemala, Italy, Jamaica, Mexico, Puerto Rico, Sweden, Taiwan, and the USA. The clinical-efficacy substudy included only children from Finland and the USA

Episodes of diarrhoea and proportion of children with episodes of diarrhoea

Caused by rotavirus

Any serotype

Proportion of children with episodes of any severity during the first season (per protocol):
82/2207 (4%) with vaccine *v* 315/2305 (14%) with placebo; vaccine efficacy 74%, 95% CI 66.8% to 79.9%
Proportion of children with severe episodes during the first season:
Vaccine efficacy 98%, 95% CI 88.3% to 100%; absolute numbers not reported

G serotype

Proportion of children with episodes of any severity during the first season (ITT analysis: participants who received at least 1 dose of vaccine):
G1:
72/2834 (3%) with vaccine *v* 286/2839 (10%) with placebo; vaccine efficacy 74.9%, 95% CI 67.3% to 80.9%
G2:
6/2834 (0.2%) with vaccine *v* 17/2839 (0.6%) with placebo; vaccine efficacy 63.4%, 95% CI 2.6% to 88.2%
G3:
1/2834 (0.04%) with vaccine *v* 6/2839 (0.2%) with placebo; vaccine efficacy 82.7%, 95% CI <0% to 99.6%
G4:
3/2834 (0.1%) with vaccine *v* 6/2839 (0.2%) with placebo; vaccine efficacy 48.1%, 95% CI <0% to 91.6%
G9:
1/2834 (0.04%) with vaccine *v* 3/2839 (0.1%) with placebo; vaccine efficacy 65.4%, 95% CI <0% to 99.3%

All-cause

NA

Admissions to hospital

Caused by rotavirus

6/28,646 (0.02%) with vaccine *v* 138/28,488 (0.5%) with placebo; vaccine efficacy 95.8%, 95% CI 90.5% to 98.2%

All-cause

Vaccine efficacy 59%, 95% CI 52% to 65%; absolute data not reported

RCTs comparing rotavirus vaccines versus placebo in healthy children.

Treatment-related adverse effects

42 days after receipt of any dose of vaccine or placebo:
Fever: 41% with vaccine *v* 43% with placebo
Diarrhoea: 20% with vaccine *v* 19% with placebo
Vomiting: 13% with vaccine *v* 13% with placebo
Haematochezia: 0.6% with vaccine *v* 0.6% with placebo; absolute data not reported and significance not assessed for all outcomes listed above
Whole study period:
Intussusception: 12/34,035 (0.04%) with vaccine *v* 15/34,003 (0.04%) with placebo; RR 0.8, 95% CI 0.3 to 1.8

Mortality

24/34,035 (0.07%) with vaccine *v* 20/34,003 (0.06%) with placebo; significance not assessed

Comparison

Quadrivalent human-Bovine (WC3) reassortant rotavirus vaccine (QRV) (3 doses) *v* placebo [23]

Study details

Population: 439 healthy infants aged 2–6 months
Follow-up time: Mean 154.3 days for vaccine recipients and 141.9 days for placebo recipients
Location: USA

Episodes of diarrhoea and proportion of children with episodes of diarrhoea

Caused by rotavirus		**All-cause**
Any serotype	**G serotype**	
Episodes of any severity: 11/187 (6%) with vaccine *v* 39/183 (21%) with placebo; vaccine efficacy 74.6%, 95% CI 49.5% to 88.3%, P < 0.001 **Severe episodes:** 0/187 (0%) with vaccine *v* 8/183 (4%) with placebo; vaccine efficacy 100%, 95% CI 43.5% to 100%	**Episodes of any severity:** **G1:** 10/187 (5%) with vaccine *v* 26/183 (14%) with placebo **G2:** 1/187 (0.5%) with vaccine *v* 2/183 (1%) with placebo **G3:** 0/187 (0%) with vaccine *v* 10/183 (5%) with placebo **G4:** 0/187 (0%) with vaccine *v* 1/183 (0.5%) with placebo; significance not assessed for all outcomes above	NA

Admissions to hospital

Caused by rotavirus	**All-cause**
NA	NA

Treatment-related adverse effects

14 days after receipt of any dose of vaccine or placebo:
Fever: 70/218 (32%) with vaccine *v* 73/220 (33%) with placebo; risk difference –1.1%, 95% CI –10.9% to +8%
Diarrhoea: 97/218 (45%) with vaccine *v* 80/220 (36%) with placebo; risk difference +8.1%, 95% CI –1.5% to +17.8%
Vomiting: 58/218 (27%) with vaccine *v* 52/220 (24%) with placebo; risk difference +3%, 95% CI –5.9% to +12%
Irritability: 86/218 (39%) with vaccine *v* 93/220 (42%) with placebo; risk difference –2.8%, 95% CI –12.8% to +6.5%

Mortality

NA

Comparison

RCTs comparing rotavirus vaccines versus placebo in healthy children.

Bovine-human rotavirus reassortant tetravalent vaccine (2 doses) *v* placebo [24]

Study details

Population: 258 healthy infants aged 50–122 days
Follow-up time: The first rotavirus season was 7–9 months; second rotavirus season was 12–21 months
Location: Finland

Episodes of diarrhoea and proportion of children with episodes of diarrhoea

Caused by rotavirus

Any serotype

Episodes of any severity during the first season:
8/161 (5%) with vaccine *v* 13/80 (16%) with placebo; vaccine efficacy 69%, 95% CI 29% to 86%; P = 0.006
Severe episodes during the first season:
1/161 (0.6%) with vaccine *v* 4/80 (5%) with placebo; vaccine efficacy 90%, 95% CI 36% to 99%; P = 0.016
Episodes of any severity during the first and second seasons:
12/161 (7%) with vaccine *v* 15/80 (19%) with placebo; vaccine efficacy 60%, 95% CI 20% to 80%; P = 0.015
Severe episodes during the first and second seasons:
1/161 (0.6%) with vaccine *v* 5/80 (6%) with placebo; vaccine efficacy 90%, 95% CI 36% to 99%; P = 0.016

G serotype

NA

All-cause

Episodes of any severity (ITT analysis: entire population):
84/172 (49%) with vaccine *v* 68/86 (80%) with placebo; vaccine efficacy 38%, 95% CI 25% to 49%; P < 0.001
Severe episodes:
1/172 (0.6%) with vaccine *v* 5/86 (6%) with placebo; vaccine efficacy 90%, 95% CI 35% to 99%; P = 0.017

Admissions to hospital

Caused by rotavirus

NA

All-cause

NA

Treatment-related adverse effects

7 days after receipt of the first dose of vaccine or placebo:
Fever: 16.1% with vaccine *v* 12.3% with placebo; P = 0.42
Diarrhoea: 7.1% with vaccine *v* 7.2% with placebo; P = 1.00
Vomiting: 11.8% with vaccine *v* 20.5% with placebo; P = 0.04
Loss of appetite: 7.5% with vaccine *v* 6.4% with placebo, P = 0.83
Antipyretic use: 6.9% with vaccine *v* 5.1% with placebo, P = 0.64; absolute data not reported for all outcomes listed above. In the safety analysis, vaccine recipients were compared with pooled placebo recipients

Mortality

NA

Comparison

High-potency pentavalent vaccine, middle-potency pentavalent vaccine, low-potency pentavalent vaccine, high-potency G1-G4 vaccine, high-potency P1A and monovalent vaccine (all human-bovine reassortant rotavirus vaccines, administered at 3 doses each) *v* placebo [25]

Study details

Population: 1946 healthy infants aged 2–8 months
Follow-up time: 1 season: 7 months; 2 seasons: 19 months; 3 seasons: 31 months
Location: Finland

Episodes of diarrhoea and proportion of children with episodes of diarrhoea

Caused by rotavirus

All-cause

RCTs comparing rotavirus vaccines versus placebo in healthy children.

Any serotype

Episodes of any severity during the first season (per protocol analysis: excluded participants without a case definition of rotavirus gastroenteritis):
19/276 (7%) with high-potency pentavalent vaccine *v* 12/237 (5%) with middle-potency pentavalent vaccine *v* 20/253 (8%) with low-potency pentavalent vaccine *v* 14/198 (7%) with high-potency G1-G4 vaccine *v* 27/270 (10%) with high-potency P1A monovalent vaccine *v* 43/264 (16%) with placebo; high-potency pentavalent vaccine efficacy 61.2%, 95% CI 31.9% to 78.6%; middle-potency pentavalent vaccine efficacy 70.5%, 95% CI 43.1% to 85.8%; low-potency pentavalent vaccine efficacy 53.8%, 95% CI 19.7% to 74.2%; high-potency G1-G4 vaccine efficacy 59.2%, 95% CI 24.0% to 79.4%; high-potency P1A monovalent vaccine efficacy 41.6%, 95% CI 3.4% to 65.3%

G serotype

Episodes of any severity during the first season (ITT analysis: participants who received 3 doses of vaccine):
G1, G2, G3, and G4:
13/303 (4%) with high-potency pentavalent vaccine *v* 8/264 (3%) with middle-potency pentavalent vaccine *v* 16/280 (6%) with low-potency pentavalent vaccine *v* 8/225 (4%) with high-potency G1-G4 vaccine *v* 22/294 (7%) with high-potency P1A monovalent vaccine *v* 33/281 (12%) with placebo; high-potency pentavalent vaccine efficacy 65.8%, 95% CI 27.7% to 85.0%; middle-potency pentavalent vaccine efficacy 75.1%, 95% CI 39.9% to 91.3%; low-potency pentavalent vaccine efficacy 53.1%, 95% CI 5.3% to 77.9%; high-potency G1-G4 vaccine efficacy 71.5%, 95% CI 37.2% to 88.6%; high-potency P1A monovalent vaccine efficacy +38.5%, 95% CI –8.7% to +65.8%

NA

Admissions to hospital

Caused by rotavirus

NA

All-cause

NA

Treatment-related adverse effects

7 days after receipt of any dose of vaccine or placebo:
Fever: Similar rates among the groups; data presented graphically, significance not assessed
Whole study period:
Intussusception: 1 case of intussusception was reported in the low-potency pentavalent vaccine group

Mortality

No deaths

Ffu, focus-forming units; ITT, intention to treat; NA, not assessed

TABLE 2 **Feeds containing lactose versus lactose-free feeds in children with mild-to-severe dehydration: results of subsequent RCTs.**

Intervention	Participants (age)	Duration of diarrhoea	Weight gain	Total stool output (mL/kg body weight)	Treatment failure
Cows' milk *v* soy-based formula [31]	76 children with acute diarrhoea and mild-to-moderate dehydration (2–12 months)	L > LF; 6.6 days *v* 4.5 days; P < 0.01	NS	NR	NS
Lactose *v* lactose-free formula [32]	60 children with acute diarrhoea (<1 year)	NS	NS	NR	NR
Lactose *v* lactose-free formula [33]	52 children with acute diarrhoea and mild-to-moderate dehydration (1–24 months)	NS	NS	NR	NS
Soy-based formula with lactose *v* soy-based formula with sucrose [34]	200 boys with acute diarrhoea (3–18 months)	L > LF; 39 hours *v* 23 hours; P < 0.001	NS	L > LF; mean 164 (95% CI 131 to 208) *v* 69 (95% CI 55 to 87); P < 0.001	NS
Lactose-free *v* low lactose *v* lactose formula [35]	91 children with acute gastroenteritis (<24 months)	L > LF; 38 hours *v* 25 hours; P < 0.03	L < LF; 7.48 kg *v* 7.84 kg; P < 0.05	NR	NR

NR, not recorded; NS, non-significant; L, lactose-containing; LF, lactose free.

TABLE 3 **RCTs comparing ondansetron versus placebo in children with acute gastroenteritis and vomiting.**

Comparison	Population	Episodes of vomiting	Proportion of children with episodes of vomiting	Admissions to hospital	Treatment-induced adverse effects
Ondansetron (single intravenous) *v* placebo [40]	36 children aged 6 months to 8 years who had vomited twice within 1 hour. All children were hospitalised for a minimum of 24 hours	Mean number of episodes reported <24 hours after treatment: 2 with ondansetron *v* 5 with placebo; P = 0.049	<24 hours after treatment: 5/12 (42%) with ondansetron *v* 10/12 (83%) with placebo; P = 0.04	Not reported	**Episodes of diarrhoea:** More diarrhoeal episodes with ondansetron than placebo; absolute data not reported; P = 0.013 **Other adverse effects:** Drowsiness in >90% of children in all groups. Cough in 3/12 (25%) with ondansetron *v* 0/12 (0%) with placebo
Ondansetron (oral, 8 hourly for 1 or 2 days) *v* placebo [39]	145 children aged 6 months to 12 years with at least 5 episodes of vomiting in the preceding 24 hours	Mean number of episodes reported. In ED: 0.18 with ondansetron *v* 0.83 with placebo; P = 0.001; <24 hours after treatment: 0.75 with ondansetron *v* 0.96 with placebo; P = 0.96	In ED: AR 10/74 (14%) with ondansetron *v* 25/71 (35%) with placebo; P = 0.004; <24 hours after treatment: AR 27/64 (42%) with ondansetron *v* 26/56 (46%) with placebo; P = 0.8	Reported to be significantly lower with ondansetron compared with placebo; P = 0.007	**Episodes of diarrhoea:** Mean number of episodes reported; In ED: 0.7 with ondansetron *v* 0.61 with placebo; P = 0.622; <24 hours after treatment: 4.7 with ondansetron *v* 1.37 with placebo; P = 0.002 **Other adverse effects:** Macular rash, without urticaria or respiratory symptoms, in 1 patient 30 minutes after receiving ondansetron
Ondansetron (single oral) *v* placebo [41]	215 children aged 6 months to 10 years with non-bloody vomiting within the 4 hours preceding triage, and mild-to-moderate dehydration	Mean number of episodes reported: 0.18 with ondansetron *v* 0.65 with placebo; RR 0.30, 95% CI 0.18 to 0.50; P < 0.001	During oral rehydration: 15/107 (14%) with ondansetron *v* 37/107 (35%) with placebo; RR 0.40, 95% CI 0.26 to 0.61; P < 0.001	4/107 (4%) with ondansetron *v* 5/107 (5%) with placebo; RR 0.80, 95% CI 0.22 to 2.90; P = 1.00	**Episodes of diarrhoea:** Mean number of episodes reported; post intervention: 1.4 with ondansetron *v* 0.5 with placebo; P < 0.001 **Other adverse effects:** No cardiovascular or respiratory events occurred. 1 child in the placebo group developed urticaria

ED, emergency department

TABLE **GRADE evaluation of interventions for gastroenteritis in children**

Important outcomes	Prevention of gastroenteritis, admissions to hospital, duration of diarrhoea, duration of hospital stay, episodes of vomiting, adverse effects								
Number of studies (participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
What are the effects of treatments to prevent acute gastroenteritis?									
28 (37,037) [16] [17] [18] [19] [20] [21] [22] [23] [24] [25]	Episodes of diarrhoea caused by rotavirus	Rotavirus vaccines *v* placebo	4	–1	–1	0	+1	Moderate	Quality point deducted for weak methods. Consistency point deducted for statistical heterogeneity. Effect-size point added for RR >0.2 but <0.5
9 (80,741) [16] [17] [18] [19] [20] [21] [22] [23] [24] [25]	Admissions to hospital	Rotavirus vaccines *v* placebo	4	–1	–1	0	0	Low	Quality point deducted for weak methods. Consistency point deducted for statistical heterogeneity.
2 (131,263) [19] [20]	Adverse effects	Rotavirus vaccines *v* placebo	4	–1	0	0	0	Moderate	Quality point deducted for incomplete analysis
What are the effects of treatments for acute gastroenteritis?									
At least 8 RCTs (at least 960 children) [27] [28]	Duration of diarrhoea	Enteral rehydration solutions *v* intravenous rehydration	4	−2	0	−2	0	Very low	Quality points deducted for uncertainties about randomisation and blinding. Directness points deducted for including children of different age ranges, socioeconomic backgrounds, disease severities, and different modes of oral therapies
9 (687) [27] [28]	Duration of hospital stay	Enteral rehydration solutions *v* intravenous rehydration	4	−2	0	−2	0	Very low	Quality points deducted for uncertainties about randomisation and blinding. Directness points deducted for including children of different age ranges, socioeconomic backgrounds, disease severities, and different modes of oral therapies
14 (1305) [30] [31] [32] [33] [34] [35]	Duration of diarrhoea	Lactose-free feeds *v* lactose feeds	4	−1	−1	0	0	Low	Quality point deducted for weak methods. Consistency point deducted as results sensitive to methods of analysis used in meta-analysis
6 (976) [37]	Duration of diarrhoea	Loperamide *v* placebo	4	–2	−1	0	0	Low	Quality points deducted for incomplete reporting and inclusion of open-label RCTs. Consistency point deducted for conflicting results between studies
3 (396) [39] [40] [41]	Episodes of vomiting	Ondansetron *v* placebo	4	0	–1	–2	0	Very low	Consistency point deducted for conflicting results among RCTs. Directness points deducted for clinical heterogeneity among trials and inclusion of only highly selected population in one RCT
2 (360) [39] [41]	Admissions to hospital	Ondansetron *v* placebo	4	0	–1	–2	0	Very low	Consistency point deducted for conflicting results among RCTs. Directness points deducted for clinical heterogeneity among trials and inclusion of only highly selected population in one RCT
3 (396) [39] [40] [41]	Adverse effects	Ondansetron *v* placebo	4	0	0	–2	0	Low	Directness points deducted for clinical heterogeneity among trials and inclusion of only highly selected population in one RCT

Important outcomes	Prevention of gastroenteritis, admissions to hospital, duration of diarrhoea, duration of hospital stay, episodes of vomiting, adverse effects								
Number of studies (participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consis-tency**	**Direct-ness**	**Effect size**	**GRADE**	**Comment**

Type of evidence: 4 = RCT; 2 = Observational
Consistency: similarity of results across studies
Directness: generalisability of population or outcomes
Effect size: based on relative risk or odds ratio