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Probiotics for treating acute infectious diarrhoea (Review)

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[Intervention Review]

Probiotics for treating acute infectious diarrhoea

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ABSTRACT

Background

Probiotics may offer a safe intervention in acute infectious diarrhoea to reduce the duration and severity of the illness.

Objectives

To assess the effects of probiotics in proven or presumed acute infectious diarrhoea.

Search methods

We searched the Cochrane Infectious Diseases Group's trials register (July 2010), the Cochrane Controlled Trials Register (*The Cochrane Library* Issue 2, 2010), MEDLINE (1966 to July 2010), EMBASE (1988 to July 2010), and reference lists from studies and reviews. We also contacted organizations and individuals working in the field, and pharmaceutical companies manufacturing probiotic agents.

Selection criteria

Randomized and quasi-randomized controlled trials comparing a specified probiotic agent with a placebo or no probiotic in people with acute diarrhoea that is proven or presumed to be caused by an infectious agent.

Data collection and analysis

Two reviewers independently assessed the methodological quality of the trial and extracted data. Primary outcomes were the mean duration of diarrhoea, stool frequency on day 2 after intervention and ongoing diarrhoea on day 4. A random-effects model was used.

Main results

Sixty-three studies met the inclusion criteria with a total of 8014 participants. Of these, 56 trials recruited infants and young children. The trials varied in the definition used for acute diarrhoea and the end of the diarrhoeal illness, as well as in the risk of bias. The trials were undertaken in a wide range of different settings and also varied greatly in organisms tested, dosage, and participants' characteristics. No adverse events were attributed to the probiotic intervention.

Probiotics reduced the duration of diarrhoea, although the size of the effect varied considerably between studies.

The average of the effect was significant for mean duration of diarrhoea (mean difference 24.76 hours; 95% confidence interval 15.9 to 33.6 hours; n=4555, trials=35) diarrhoea lasting ≥4 days (risk ratio 0.41; 0.32 to 0.53; n=2853, trials=29) and stool frequency on day 2 (mean difference 0.80; 0.45 to 1.14; n=2751, trials=20).

The differences in effect size between studies was not explained by study quality, probiotic strain, the number of different strains, the viability of the organisms, dosage of organisms, the causes of diarrhoea, or the severity of the diarrhoea, or whether the studies were done in developed or developing countries.

Authors' conclusions

Used alongside rehydration therapy, probiotics appear to be safe and have clear beneficial effects in shortening the duration and reducing stool frequency in acute infectious diarrhoea. However, more research is needed to guide the use of particular probiotic regimens in specific patient groups.

22 March 2019

Update pending

Authors currently updating

The update is due to be published in 2019.

PLAIN LANGUAGE SUMMARY

Probiotics for treating acute infectious diarrhoea

Episodes of acute infectious diarrhoea remain a major disease burden throughout the world, especially in developing countries. They are due to infection by many different organisms. Most episodes are self-limiting and usually investigations are not done to identify the infectious agent. The main risk to health is dehydration and management aims to improve and maintain hydration status. However, rehydration fluids do not reduce the stool volume or shorten the episode of diarrhoea. Probiotics are "friendly" bacteria that improve health and are not harmful in themselves. A number of randomized controlled trials have been done to see whether probiotics are beneficial in acute infectious diarrhoea. We have searched for as many of these trials as possible and collected together the data in a systematic way to try to discover whether or not probiotics are beneficial in acute diarrhoea. We identified 63 trials, which included a total of 8014 people - mainly infants and children. Probiotics were not associated with any adverse effects. Nearly all studies reported a shortened duration of diarrhoea and reduced stool frequency in people who received probiotics compared to the controls. Overall, probiotics reduced the duration of diarrhoea by around 25 hours, the risk of diarrhoea lasting four or more days by 59% and resulted in about one fewer diarrhoeal stool on day 2 after the intervention. However, there was very marked variability in the study findings and so these estimates are approximate. We concluded that these results were very encouraging but more research is needed to identify exactly which probiotics should be used for which groups of people, and also to assess the cost effectiveness of this treatment.

BACKGROUND

Definition

Diarrhoea is defined by the World Health Organization (WHO) as three or more loose or watery stools (taking the shape of the container) in a 24-hour period. Diarrhoea is acute if the illness started less than 14 days previously, and persistent if the episode has lasted 14 days or more (Anonymous 1988). Normal infants who are exclusively breast fed may pass loose, "pasty" stools frequently. In this group the definition is usually based on what the mother considers to be diarrhoea (WHO 1990). Infectious diarrhoea is an episode of diarrhoea that is caused by an infectious agent.

Incidence and disease burden

Infectious diarrhoea occurs much more commonly in developing countries than industrialized countries (Guerrant 1990). Attack rates in developing countries are typically six to 12 episodes per child per year, compared with two in the USA (Savarino 1993). In a systematic analysis of population health data available for 2001, diarrhoeal diseases accounted for 1.78 million deaths (3.7% of total deaths) in low- and middle-income countries (Lopez 2006). Most of these deaths occur in children under five years of age. Although 50% or more children with diarrhoea receive oral rehydration therapy and continued feeding in only six of 60 priority countries, and only seven countries include zinc in diarrhoeal management (Bryce 2006), diarrhoeal deaths have reduced in this age group. However, diarrhoea still accounted for about 1.6 million deaths in 2001 (15% of all deaths in the under fives; Lopez 2006). In industrialized countries deaths from infectious diarrhoea occur mainly in the elderly (Savarino 1993).

Causes

More than 20 viruses, bacteria and parasites are associated with acute diarrhoea (Gadewar 2005). Worldwide, rotavirus is the most common cause of severe diarrhoea and diarrhoea mortality in children (Cunliffe 1998). Other important viral pathogens are astrovirus, human caliciviruses (norovirus and sapovirus) and enteric adenoviruses. Important bacterial pathogens are diarrheogenic *Escherichia coli*, *Salmonella*, *Shigella*, *Yersinia*, *Campylobacter*, and *Vibrio cholerae*. The main parasitic causes of diarrhoea are *Cryptosporidium* and *Giardia* (reviewed by O'Ryan 2005). An aetiological study of young children attending hospitals in China, India, Mexico, Myanmar, and Pakistan showed that rotavirus, enterotoxigenic *E. coli* and *Shigella* spp. were the most commonly isolated pathogens (Huilan 1991). Acute diarrhoea is frequent among travellers, in whom enterotoxigenic *E. coli* is particularly common (Black 1986). In practice, most episodes of acute diarrhoea that are assumed to be caused by an infectious agent are treated without the causative agent being identified. The major causes of acute infectious diarrhoea differ according to local factors, such as availability of clean water and sanitation. In contrast with acute infectious diarrhoea, infection is likely to be only one of several factors that contribute to the pathogenesis of persistent diarrhoea (Walker-Smith 1993).

Treatment

The aim of treatment is to prevent or reverse dehydration, shorten the duration of the illness (important for preventing progression to persistent diarrhoea, which is associated with adverse outcomes such as malnutrition), and to reduce the period that a person is infectious. Treatment options available are oral rehydration solution, antibiotics, and gut motility-suppressing agents such as loperamide, codeine, and probiotics. This review considers the use of probiotics only.

Probiotics

Probiotics have been defined as microbial cell preparations or components of microbial cells that have a beneficial effect on the health and well-being of the host (Salminen 1999). Although organisms used in clinical trials may not have a proven health benefit for the indication being investigated, we have used the term "probiotic" in this review for simplicity. Fermenting foods to enhance their taste and nutritional value is an ancient and widespread practice. Well-known probiotics are the lactic acid bacteria and the yeast *Saccharomyces* (Naidu 1999). The taxonomy of the lactic acid bacteria relied traditionally on their phenotypic characteristics. Modern molecular techniques have shown these to be unreliable, and polyphasic taxonomy using both phenotypical and molecular techniques is now recommended (Klein 1998). Even closely related probiotic strains can have different clinical effects, and the Food and Agricultural Organization (FAO) of the United Nations and WHO expert consultation committee have emphasized that the beneficial effects observed in one strain cannot be assumed to occur in other strains (FAO/WHO 2001). This implies that the reliable identification of organisms at the strain level is necessary for clinical studies.

The rationale for using probiotics in infectious diarrhoea is that they act against enteric pathogens by competing for available nutrients and binding sites, making the gut contents acid, producing a variety of chemicals, and increasing specific and non-specific immune responses (Gismondo 1999; Goldin 1998; Vanderhoof 1998). No serious adverse effects of probiotics have been suggested in well people, but rarely, infections have been reported in people with impaired immune systems or indwelling catheters (Hata 1988; Piarroux 1999; Salminen 1998; Saxelin 1996; Sussman 1986).

Six systematic reviews of probiotics in acute diarrhoea have been published. Szajewska 2001 included only published, randomized, placebo-controlled double-blind studies of acute diarrhoea lasting three or more days in infants and children. A score was used to assess the methodological quality of these trials. The effects of all probiotics and individual strains were analysed. The risk of diarrhoea lasting three or more days was reduced by 0.40 in the probiotic compared with the placebo group (95% confidence interval (CI) 0.28 to 0.57, random-effects model, eight trials including 731 children), and probiotics reduced the duration of diarrhoea by 18.2 hours (95% CI 9.5 to 26.9 hours, random-effects model, eight trials including 773 children). The statistically significant heterogeneity in this result was resolved when one study, which employed a mixture of three probiotic organisms, was excluded. *Lactobacillus* GG was thought to be particularly effective in rotavirus diarrhoea.

A meta-analysis undertaken by Van Niel 2002 was restricted to adequately randomized and blinded studies of several strains of lactobacilli in children. Children who had received recent antibiotics were excluded from the study. Probiotics reduced the duration of diarrhoea by 0.7 days (95% CI 0.3 to 1.2 days, seven studies including 675 children) and diarrhoea frequency on day 2 by 1.6 (95% CI 0.7 to 2.6, three studies including 122 children). The

heterogeneity of results among the studies prevented an analysis of the effects of individual strains of lactobacilli.

Three meta-analyses have focused on randomized controlled trials of specific probiotics in acute infectious diarrhoea in children. Szajewska 2007a analysed trials of *Lactobacillus casei* strain GG where a > 80% follow up was achieved. Trial results published as letters to the editor, abstracts, and proceedings from scientific meetings were not included. *L.casei* GG reduced the duration of diarrhoea by 1.1 days (95% CI 0.3 to 1.9, seven trials, 876 infants) and was particularly effective in rotavirus diarrhoea (duration reduced by 2.1 days, 95% CI 0.6 to 3.6). However, the authors urged caution in the interpretation of the results in view of methodological limitations in the trials and the heterogeneity of the results in the studies. Chmielewska 2008 identified two trials of *Lactobacillus reuteri* strain ATTCC 55730. This probiotic reduced the duration of diarrhoea by 22 hours (95% CI 6 to 38, 106 participants). In an update of a previous review (Szajewska 2007b), Szajewska 2009 pooled data from seven randomized controlled trials of *Saccharomyces boulardii* in 944 otherwise healthy children with acute gastroenteritis. The duration of diarrhoea was reduced by 1.08 days (95% CI 0.53 to 1.64) in children who received the yeast compared with the placebo although there was marked heterogeneity in results among the studies.

A recent review concluded that the beneficial effects of probiotics in acute infectious diarrhoea were dependent on the strain of bacteria and the dose (a greater effect with doses >10^{10}-10^{11} colony-forming units (CFU)/day). They were significant in watery diarrhoea and viral gastroenteritis but absent in invasive bacterial diarrhoea, and were greater when probiotics were administered early in the illness and were more evident in developed countries (Wolvers 2010).

Our review aims to assess the evidence base to inform the use of probiotics in acute infectious diarrhoea. To maximize use of available data, we included participants of all ages, unpublished studies, and non-blinded (open) studies. We assessed the relevant methodological aspects of trials individually (Juni 1999). These were the generation of allocation sequence, allocation concealment, blinding, and loss to follow up. To maximize the relevance of our findings for clinical practice we included studies in which participants with infectious diarrhoea had received antibiotics prior to recruitment.

For primary outcomes, we chose the duration of diarrhoea and diarrhoea lasting ≥ 4 days, as these are directly relevant to the development of persistent diarrhoea, and stool frequency on day 2 after intervention as a marker of diarrhoea severity.

This review is a substantial update of the original version, first published in 2003 (Allen 2003).

OBJECTIVES

To assess the effects of probiotics in proven or presumed acute infectious diarrhoea.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized and quasi-randomized controlled trials reporting the effect of probiotic(s) on acute infectious diarrhoea. Studies of probiotics in acute diarrhoea that reported other outcomes (eg their effect on rotavirus shedding in stools) but no diarrhoea outcomes were not included.

Types of participants

Adults and children with acute diarrhoea (duration < 14 days) that was proven or presumed to be caused by an infectious agent.

Excluded: studies of diarrhoea known or thought to have other causes (eg antibiotic-associated diarrhoea and studies of persistent diarrhoea).

Types of interventions

Intervention

Specific, identified probiotic.

Excluded: yogurt or other fermented foods in which specific probiotic organisms were not identified.

Control

Placebo or no probiotic.

Intervention and control arm to be otherwise treated identically in relation to other treatments and drugs.

Types of outcome measures

Primary

Duration of diarrhoea
Diarrhoea lasting ≥ 4 days
Stool frequency on day 2 after intervention

Secondary

Diarrhoea lasting ≥ 3 days

Stool frequency on day 3 after intervention

Search methods for identification of studies

We have attempted to identify all relevant studies regardless of language or publication status (published, unpublished, in press, and in progress). Searches of all databases was done on 1 July 2010.

We searched the Cochrane Infectious Diseases Group's trials register using the search terms: diarrhea/; diarr$(tw); diarhea(tw); probiotic(tw); Lactobacill$(tw); Lactococc$(tw); Bifidobacter $(tw); Enterococc$(tw); Streptococc$(tw); Saccharomyces(tw). Full details of the Cochrane Infectious Diseases Group's methods and the journals handsearched are published in *The Cochrane Library* in the section on 'Collaborative Review Groups'.

We searched the Cochrane Controlled Trials Register published on *The Cochrane Library* (Issue 2, 2010) using the search terms: diarrhea/; diarr$(tw); diarhea(tw); probiotic(tw); Lactobacill$(tw);

Lactococc$(tw); Bifidobacter$(tw); Enterococc$(tw); Streptococc $(tw); Saccharomyces(tw).

We searched MEDLINE (1966 to 2010) and EMBASE (1988 to 2010 using the search strategy defined by The Cochrane Collaboration (Clarke 2003) and following search terms: diarrhea/; diarr$(tw); diarhea(tw); probiotic(tw); Lactobacill$(tw); Lactococc$(tw); Bifidobacter$(tw); Enterococc$(tw); Streptococc $(tw); Saccharomyces(tw).

The detailed search strategy is shown in Appendix 1.

In preparation for the original review (Allen 2003), we contacted organizations and individuals working in the field, and the following pharmaceutical companies that manufacture probiotic agents to help identify additional published trials and unpublished data: Biogaia Biologicals, Lund, Sweden; Nestle Foundation, Lausanne, Switzerland; Probiotics International Ltd, Somerset, UK; Ross Products Division of Abbott Laboratories, Ohio, USA, and Yakult, London, UK. We have not re-contacted individuals or companies for this update.

We also drew on existing reviews of this topic and checked the citations of all trials identified by the above methods.

Data collection and analysis

Study selection

SA and LD independently reviewed the titles of articles and, where available, abstracts generated by the search to identify potentially relevant studies. All articles that could meet the inclusion criteria as identified by either of the reviewers were selected and the full article reviewed. Eligibility was assessed independently by SA and LD using a form based on the information presented in the article. We planned to contact trial authors if eligibility was unclear. Discrepancies among reviewers' eligibility assessments were resolved by discussion. Trial reports were scrutinized to ensure that multiple publications from the same trial were included only once. Excluded studies and the reasons for their exclusion were listed.

Assessment of methodological quality

Two reviewers (EM, GG), blinded to the origin of the articles, independently assessed the methodological quality of identified studies using generation of allocation sequence, allocation concealment, blinding, and loss to follow up, and we recorded this information on a standard form.

We considered the generation of allocation sequence to be adequate if the study authors stated that they used a method resulting in unpredictable sequences (such as a random number table or list or computer-generated random numbers), unclear if a trial was stated to be randomized but no further information was provided and inadequate where allocation could be related to prognosis and therefore introduced selection bias (for example, the date of birth or date of admission to hospital).

We considered allocation concealment to be adequate if the assignment to arms of the study could not be predicted by the investigators or participants (for example, central randomization or numbered, identical drug containers), unclear if the method used to achieve concealment was not described or inadequate if they used a method such as alternation where the allocation of participants could be predicted.

We considered blinding to be adequate when studies were double blind (when an identical placebo was used and recruitment to intervention or control arms was not known by either the investigator or the participants), unclear if methods of blinding were not described adequately, and inadequate when blinding was not used or where the authors stated that unblinding had occurred.

We considered loss to follow up to be adequate when study endpoints were presented for 90% or more of the participants enrolled at the beginning, inadequate when follow up was less than this and unclear when either or both the number of participants recruited at the beginning of the study and the number of participants who completed the study were not clear.

LD resolved disagreements regarding the assessment of methodological quality.

Data extraction

SA, BO, SP, and SA independently extracted data using standard forms. Key data items were the aetiology and duration of diarrhoea, details of probiotic organism, participants' characteristics (nutritional and human immunodeficiency virus (HIV) status), location (countries classified according to mortality stratum; WHO 2001), and the outcome measures listed above. The number of participants recruited and the number for whom outcome data was reported were extracted and included in the Characteristics of included studies table.

For dichotomous outcomes, the number of participants experiencing the event, and the total number of participants in each intervention group was extracted. For continuous outcomes, arithmetic means, standard deviations (SD), and the numbers of participants in each intervention group was extracted. SDs were calculated from 95% CI and standard errors, where these were reported. The findings of trials that presented data that could not be included in pooled analyses (eg median and inter-quartile range (IQR)), or reported outcomes other than the primary and secondary outcomes employed in this review were reported in the text.

Data analysis

We pooled data from studies that used comparable outcome measures. For the duration of diarrhoea and number of stools per day of intervention, we achieved a pooled estimate of treatment effect by calculating the weighted mean difference. For the number of participants with diarrhoea lasting 3 days or more, or 4 days or more after starting the intervention, we calculated a pooled estimate of the relative risk (RR) among probiotic and non-probiotic groups.

We reported the proportion of participants for whom outcome data were available in a 'Risk of bias' table for each study. We performed analyses according to the intention-to-treat principle using an available case analysis approach.

Where there was significant heterogeneity ($P < 0.1$) in outcomes across studies assessed by the Chi^2 test a random-effects model was used; otherwise a fixed-effect approach was taken.

We inspected the forest plots to detect non-overlapping CIs, applied the Chi^2 test and also implemented the I^2 statistic (with a value of ≥ 50%) to assess heterogeneity in findings. Where there was significant statistical heterogeneity in primary outcomes for the probiotic versus no probiotic group comparisons, we conducted sensitivity analyses according to each of the four parameters of trial methodological quality (Characteristics of included studies).

We proceeded to pool data for meta-analysis to provide a qualitative assessment of probiotic effect as a guide to clinical practice.

We expected that heterogeneity in results among studies would result from clinical diversity, including differences in probiotic(s) used, dose of organisms, types of participants, causes and severity of diarrhoea and the socioeconomic status of countries where the studies were undertaken (Wolvers 2010). Therefore, where there were results for a diarrhoea outcome available from three or more studies we conducted subgroup analyses according to the:

- probiotic strain; single probiotic organisms versus combinations of two or more organisms, dose of live organisms (high dose [> 10^{10} CFU/day] versus lower dose [≤10^{10} CFU/day]); killed organisms;
- age of participants;
- identified diarrhoeal pathogens (rotavirus, bacterial diarrhoea);
- severity of diarrhoea according to whether the participants were likely to have had mild diarrhoea and were, therefore, managed as outpatients;
- mortality stratum for children and adults in the country or countries where the trial was undertaken (WHO 2001) to account for regional differences in major diarrhoeal pathogens and diarrhoea severity related to the availability of clean water and level of sanitation. To facilitate meta-analysis, countries were divided into two groups according to whether either child or adult mortality, or both, was classified as high.

Finally, we inspected funnel plots for the primary outcomes to assess publication bias.

RESULTS

Description of studies

Our search identified 120 potentially relevant studies. Of these, 63 met the inclusion criteria. Overall, 57 studies were excluded, including five that were preliminary or duplicate reports of other included studies (Characteristics of excluded studies). Eligibility regarding inclusion in this review was clear for all studies and clarification from trial authors was not required. We have not been able to locate the reports of two studies (Contreras 1983; Salgado) and one study is ongoing (Freedman 2010). None of the 56 included trials were cluster randomized.

Publication status

Of the 63 included studies, 23 were published in the 1980s-1990s, 37 between 2000-2009 and two in 2010; one study was unpublished.

Study location

According to country mortality strata for children/adults (WHO 2001), 41 trials were undertaken in countries where both child and adult mortality was classified as low or very low and 19 where either child or adult mortality was high. Two international studies recruited participants from countries crossing the mortality strata (Guandalini 2000; Jasinski 2002). Finally, the study by Ritchie 2010 was undertaken in Australia (very low child and low adult mortality) but recruited Aboriginal children who commonly had co-morbidities such as pneumonia and malnutrition related to poverty and social disadvantage in the top end of the Northern Territory. Therefore, data from this study were not included in analysis according to country mortality strata.

A total of 47 studies were conducted in a single centre; 15 recruited participants from two to 150 centres. The number of recruitment centres was unclear in one study (D'Apuzzo 1982).

Participants

The 63 selected studies recruited a total of 8014 participants. There were 6489 infants and children (age < 18 years) and 352 adults. In three studies (1173 participants) the exact ages of participants was not clear: Bruno 1983 studied participants aged 14 years and above, participants in Wunderlich 1989 had a mean age of 33 years (age range not stated) and the age of the participants in Frigerio 1986 was not stated.

Forty-four studies recruited inpatients, seven recruited outpatients and seven recruited both inpatients and outpatients. It was unclear in five studies whether the participants were inpatients or outpatients.

Although all studies recruited participants with acute diarrhoea, the criteria for acute diarrhoea varied considerably among studies (see Characteristics of included studies). Descriptions of stool consistency included watery, loose or liquid stools, or both, semi-liquid, increased fluidity, pasty, mucousy or non-formed in 46 studies but no description was stated in 17 studies. The minimum number of stools/day was specified in 36 studies; this ranged from ≥one to ≥ five stools with the most commonly used criteria being ≥ three (16 studies) and ≥four stools in 24 hours (13 studies). One study specified stool frequency as at least twice normal frequency, one as increased frequency and in one study stool consistency was taken into account. The minimum number of stools was not specified in 24 studies. The maximum duration of diarrhoea at recruitment was specified in 40 studies and varied between one and 14 days. The maximum diarrhoea duration was not specified in 23 studies.

Similarly, criteria used for the end of the diarrhoeal episode varied markedly among studies. The last liquid or watery stool (nine studies) and first normal stool (seven studies) were the most common. Twenty-one studies used a variety of criteria based on stool frequency and consistency in a specified period (eg first formed stool if followed by two consecutive non-watery stools or 12 hours without evacuation; Mao 2008). Four studies also included the resolution of associated symptoms (eg < two stools/day, formed, yellow/brown stools without mucus and no abdominal pains, vomiting, or fever for the whole day; D'Apuzzo 1982). Criteria were not stated in 17 studies.

Eighteen studies were either restricted to children with rotavirus diarrhoea or reported outcomes for a subgroup of children with rotavirus diarrhoea. Children with rotavirus diarrhoea were excluded in one study (Lievin Le-Maol 2007). Ten studies stated that participants with bloody diarrhoea were included whereas these

were excluded in 32 studies. It was unclear whether participants with bloody diarrhoea were included in 21 studies. No study specifically recruited or excluded travellers, and none identified any of the participants as suffering from travellers' diarrhoea.

No study specifically recruited participants known to have HIV infection and no study stated HIV positivity as an exclusion criterion, but many excluded participants with chronic illness or immunosuppression, or both.

Nutritional status was reported in 35 studies, all undertaken in children. Ten studies either recruited malnourished children only or included malnourished children; 20 studies excluded severe malnutrition; five studies recruited well-nourished children only or excluded those with a chronic illness.

Twenty-six studies excluded participants who had received antibiotic treatment before recruitment, eight included participants who had received antibiotic treatment before recruitment and this information was unclear in 29 studies.

The hydration status of the participants was reported in 35 studies; 22 studies included participants with severe dehydration whereas 10 studies recruited only children with mild or moderate dehydration.

Interventions

Many different probiotics were tested. Most studies tested live preparations of lactic acid bacteria and bifidobacteria. Several studies identified the probiotic organisms only by the species name without specific identification details such as a culture collection number. Few studies undertook analyses to confirm the identity or viability of the organism(s).

Forty-six studies tested a single organism and 17 tested combinations of between two to eight organisms. The most common organisms evaluated were *L. casei* strain GG (13 studies), *S. boulardii* (10 studies) and *Enterococcus* lactic acid bacteria (LAB) SF68 (five studies). All other organisms and all combinations were tested in three or fewer studies. Canani 2007 allocated children to one of five different probiotic regimens and compared outcomes with a single control group. For the purposes of this review, we selected the *L. casei GG* group for inclusion because several other studies tested this probiotic and we wanted to maximize the data available for meta-analysis. Grandi 2009 allocated children either to a single organism or a four-organism group and compared outcomes with a single control group. No data extractable for meta-analysis were reported in this study.

Forty-seven studies tested live organisms, five studies tested a killed probiotic preparation (Billoo 2006; Boulloche 1994; Lievin Le-Maol 2007; Simakachorn 2000; Khanna 2005), and one a pasteurized yogurt (Pashapour 2006). The viability of the organisms was unclear in 10 studies.

Three studies compared different dosages (number of organisms) of the same probiotic (Basu 2009, Mao 2008, Shornikova 1997b) with a single control group. We selected the higher probiotic dose group for inclusion in the review but have included results from the lower dose group in the text. Overall, 15 studies used a high dose of organisms (> 10^{10} CFU/day), 26 used a low dose (≤ 10^{10} CFU/day) and the dose was unclear in 22 studies.

As well as differences in dose or organisms, there was a wide variation in the treatment regimens according to timing of intervention, means of administration and duration of treatment. Probiotics were administered directly to the participants or mixed with a variety of fluids and foods. Although expressed breast milk was used to administer probiotics in some studies, some studies excluded exclusively breast-fed infants to minimize the interruption of normal feeding.

Forty-three studies used a placebo in the no probiotic control group; the remaining studies managed participants according to usual clinical practice.

Risk of bias in included studies

Methodological quality varied considerably (see Characteristics of included studies). Twenty-three studies were considered adequate for generation of the allocation sequence, 15 for concealment of allocation, 35 for blinding and 45 for loss to follow up. Ten studies were adequate for all of the four methodological quality assessment parameters and five studies were inadequate for all four parameters.

Effects of interventions

Primary outcomes

The forest plots demonstrate that probiotics reduce the duration of diarrhoea. Values for duration of diarrhoea in the control arm varied widely, from 39.1 to 173.5 hours, and the difference between the intervention groups ranged from -79.2 to 7.0 hours (Analysis 1.1). Similar variability was evident in the other outcomes. Despite the high level of quantitative heterogeneity, the pattern was striking, and meta-analysis shows an important effect which is statistically significant. Using a random effects approach, probiotics reduced the mean duration of diarrhoea (mean difference 24.76 hours; 95% confidence interval 15.9 to 33.6 hours; n=4555, trials=35; Analysis 1.1), diarrhoea lasting ≥4 days (risk ratio 0.41; 0.32 to 0.53; n=2853, trials=29; Analysis 1.2) and stool frequency on day 2 (mean difference 0.80; 0.45 to 1.14; n=2751, trials=20; Analysis 1.3). The differences in these analyses are an average across all studies with quantitative heterogeneity, demonstrating that probiotics have a substantive and significant effect, rather than being a precise estimate of the size of the effect.

The funnel plots for the primary outcomes (Figure 1, Figure 2, Figure 3) did not indicate publication bias as the largest intervention effects were observed in studies with a large number of participants as well as smaller studies.

Figure 1. Funnel plot of comparison: 1 Primary diarrhoea outcomes, outcome: 1.1 Mean duration of diarrhoea.

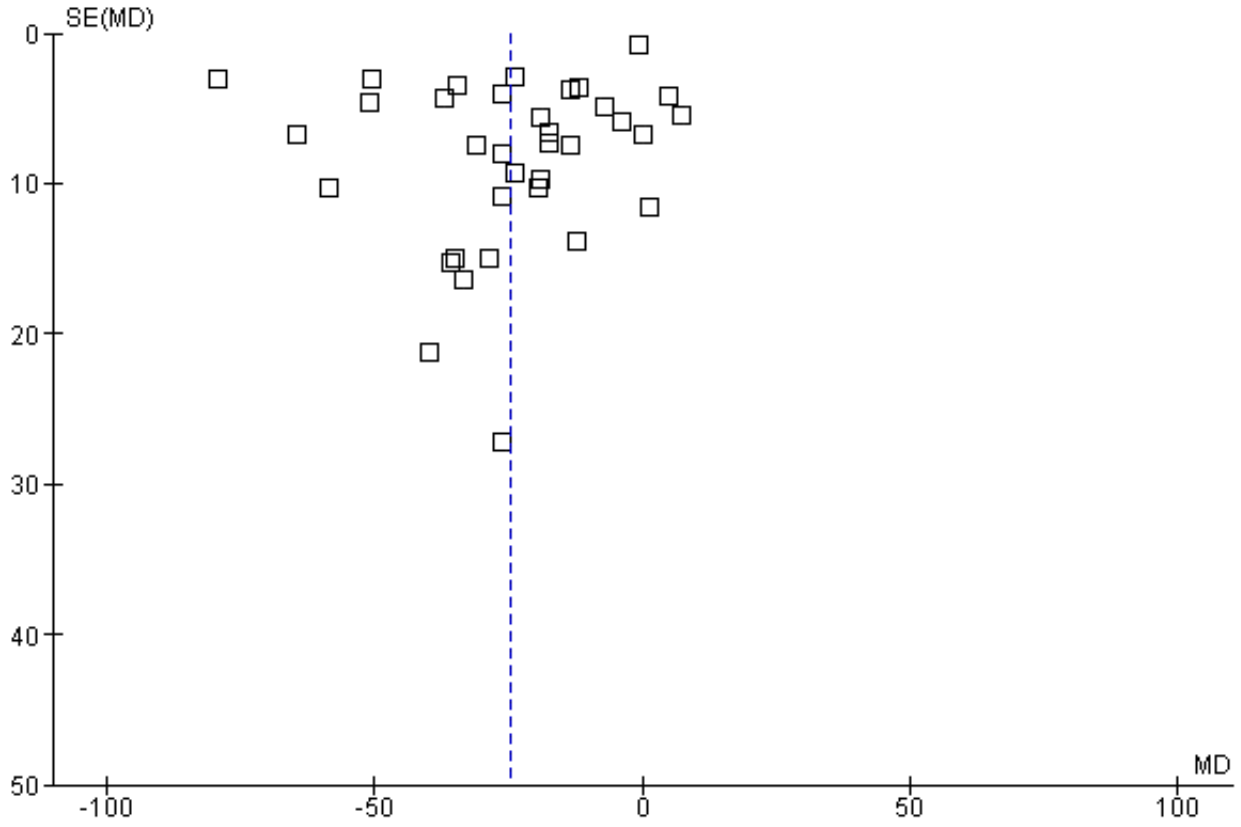


Figure 2. Funnel plot of comparison: 1 Primary diarrhoea outcomes, outcome: 1.2 Diarrhoea lasting ≥ 4 days.

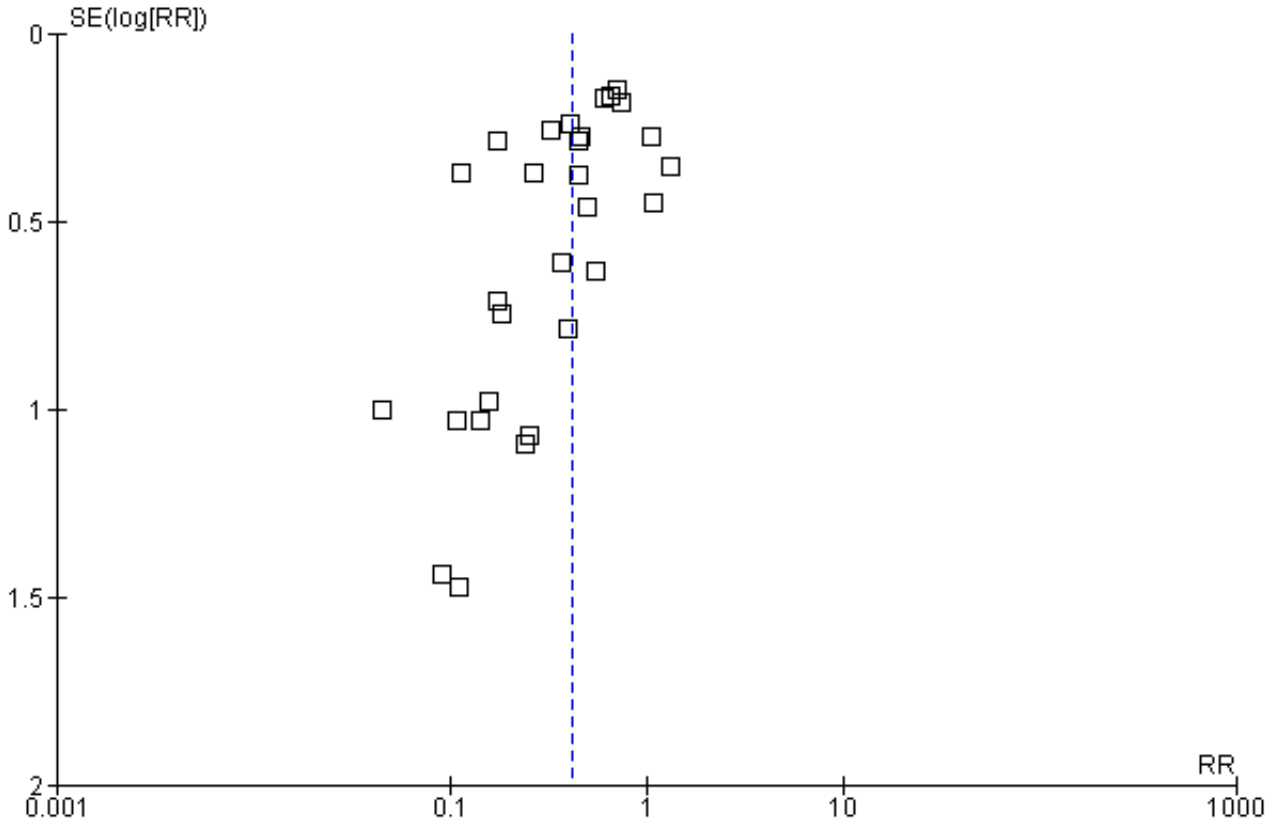
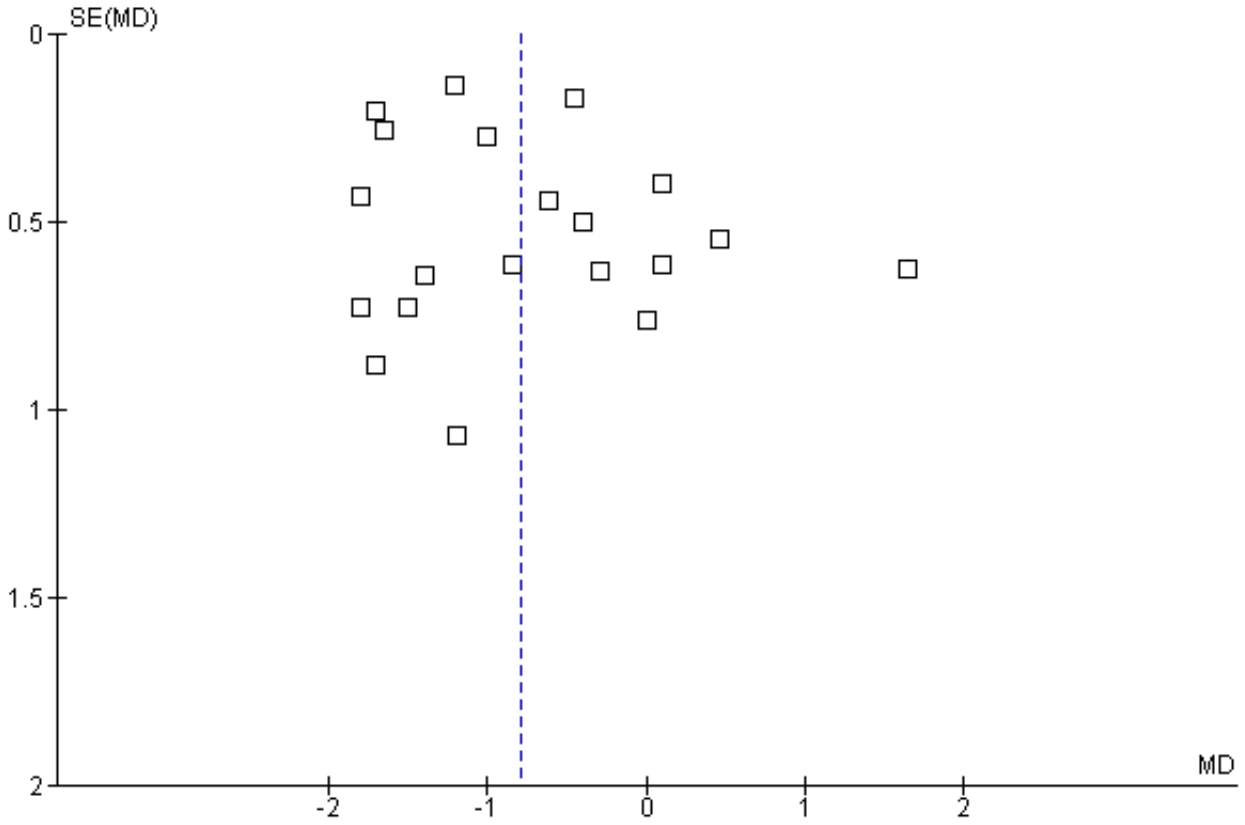


Figure 3. Funnel plot of comparison: 1 Primary diarrhoea outcomes, outcome: 1.3 Mean stool frequency on day 2.



Secondary outcomes

The findings for diarrhoea lasting ≥ 3days (Analysis 2.1) and stool frequency on day 3 after intervention (Analysis 2.2) were broadly similar to the primary outcomes and there was also marked statistical heterogeneity among studies.

Seven studies reported diarrhoea outcomes data that could not be included in analyses. Billoo 2006 evaluated *S. boulardii* in infants and children admitted with acute watery diarrhoea of mild to moderate severity in Pakistan. The mean duration of diarrhoea was reduced in the probiotic compared with the control group (n = 50, 86.4 hours versus n = 50, 115.2 hours, respectively; P = 0.001). Stool frequency on days 3 (P = 0.01) and 6 (P = 0.001) was also reduced in the probiotic group. Czerwionka 2009 evaluated *Lactobacillus rhamnosus* in children with acute diarrhoea in Poland. The total number of stools per child was statistically significantly lower in the probiotic group than the controls. Misra 2009 evaluated *L. rhamnosus* GG in children in India. The mean duration of diarrhoea was 70.6 hours in the probiotic and 78.0 hours in the control group (P = 0.20).

Grandi 2009 allocated young children admitted with acute rotavirus diarrhoea to receive either oral rehydration fluid (ORF) + *S. boulardii*, ORF + *Lactobacillus acidophilus, L. rhamnosus, Bifidobacterium longum* and*S. boulardii,* or ORF alone (control group). The median duration of diarrhoea was shorter in both of the probiotic groups compared with the controls but this was statistically significant only for *S. boulardii* (58 hours versus 84.5 hours, respectively; P = 0.04).

In a short abstract, Frigerio 1986 reported that the duration of diarrhoea was significantly reduced (P < 0.01) among 540 patients with an acute diarrhoeal disorder attending hospitals in Italy who received *Enterococcus* LAB SF 68 compared with 534 who received a placebo.

In a further study, Sepp 1995 evaluated adding *L. casei* GG to trimethoprim-sulfamethoxazole, compared to trimethoprim-sulfamethoxazole alone, in children with acute diarrhoea caused by *shigellosis* in Estonia. The duration of diarrhoea was similar in the probiotic (median 0.5 days) and the control group (1 day; not statistically significant). Also, the proportion of children with ongoing diarrhoea on day 5 was similar in the probiotic and control groups (6/13 (46.3%) versus 9/12 (75.0%); not statistically significant). However, a greater proportion was cured in the probiotic than the control group on day 10 (P < 0.05). Finally, in an open study, Táborská 1997 evaluated live *L. acidophilus* ND in infants and children admitted with acute gastroenteritis in the Czech Republic. The resolution of enteric symptoms during days 1 to 5 of the intervention was similar in the two groups.

Exploration of heterogeneity

Sensitivity analysis for primary outcomes

When analysis was restricted to trials assessed to be adequate for the four criteria of study quality (Characteristics of included studies), highly statistically significant between-study heterogeneity persisted (forest plots not shown (Table 1). This

suggests that differences in outcomes between studies were caused by factors other than differences in methodological quality.

In addition to the methodological quality of studies as a potential source of heterogeneity in the primary outcomes, we explored other prespecified factors in subgroup analyses where outcomes were reported in three or more studies (probiotic strain: Analysis 3.1, Analysis 3.2, Analysis 3.3; single organism versus combinations: Analysis 4.1, Analysis 4.2, Analysis 4.3; live versus killed organisms: Analysis 5.1; dose or organisms: Analysis 6.1, Analysis 6.2, Analysis 6.3; children with rotavirus diarrhoea: Analysis 7.1, Analysis 7.2; severity of diarrhoea: Analysis 8.1 and, finally, mortality stratum for children and adults in the countries where the studies were undertaken: Analysis 9.1, Analysis 9.2, Analysis 9.3). With few exceptions, the magnitude of probiotic effect on diarrhoea outcomes was similar to that for all trials and marked heterogeneity in results persisted in the sub-group analyses.

In three of the sub-group analyses of trials that reported mean stool frequency on day 2, the magnitude of the effect in the intervention group was similar to that for all trials but there was greater consistency in the findings. This occurred in six trials (1335 participants) that assessed *L. casei* strain GG (Analysis 3.3), eight trials (861 participants) that used a high dose of live organisms (> 10^{10} organisms/day; Analysis 6.3) and three trials (164 participants) of children with rotavirus diarrhoea (Analysis 7.2). However, marked heterogeneity persisted in the corresponding sub-group analyses that reported the other primary diarrhoea outcomes (Analysis 3.1 and Analysis 3.2; Analysis 6.1 and Analysis 6.2; Analysis 7.1 respectively). Therefore, the significance of the greater consistency in the sub-group analyses reporting mean stool frequency on day 2 is unclear.

The sub-group analysis according to diarrhoea severity suggested that probiotics resulted in a greater reduction in mean duration of diarrhoea in mild diarrhoea (studies of out-patients) than in more severe diarrhoea (inpatients; Analysis 8.1). However, marked heterogeneity in findings persisted and, therefore, the significance of this finding is unclear.

Finally, probiotics appeared to be less effective in reducing mean stool frequency on day 2 in countries with high child and adult mortality rates compared with those with low or very low mortality rates (Analysis 9.3). However, marked heterogeneity persisted and probiotic effects were similar in both settings for the other diarrhoea outcomes (Analysis 9.1; Analysis 9.2).

On balance, we found no clear evidence that stratification according to the sub-groups modified probiotic effect.

Several studies reported findings relevant to the subgroup analyses that could not be included in the analyses.

Probiotic organisms; strain, single organisms versus combinations and dose

Canani 2007 reported a statistically significantly reduced mean duration of diarrhoea for three different probiotics (live *L. casei* strain GG (Analysis 1.1), a combination of live *Lactobacillus delbrueckii, L. acidophilus, Streptococcus thermophilus* and *Bacillus bifidum,* and *S. boulardii*) compared with controls but there was no effect of live *Enterococcus faecium* SF68 or live *Bacillus clausii* strains O/C84, N/R84, T84, SIN84. These findings were generally supported by effectiveness in reducing stool frequency on d 2 and 3 reported in this study, except that the live *L. casei* strain GG did not reduce stool frequency on day 3 (Analysis 2.2) and *S. boulardii* did not reduce stool frequency on day 2.

Grandi 2009 allocated children with rotavirus diarrhoea to either an *S. boulardii* group or a group treated with a combination of four organisms (*L. acidophilus, L. rhamnosus, B. longum* and*S. boulardii).* The median duration of diarrhoea was shorter in both of the probiotic groups compared with the controls, but this was statistically significant only for *S. boulardii* (58 hours versus 84.5 hours, respectively; P = 0.04).

Three studies directly compared different doses of the same probiotic preparation in infants and children, most of whom had rotavirus diarrhoea. Mao 2008 evaluated two dose levels of a combination of *Bifidobacterium lactis* B12 and *S. thermophilus* TH4. Probiotics were administered in milk powder but the number of organisms administered in each group was not clear. The mean duration of diarrhoea and number of liquid stools/day were similar in the low dose and high dose groups.

Shornikova 1997b evaluated *L. reuteri* 10^7 CFU/day for up to 5 days. In 20 children in the low dose probiotic group, the mean (SD) duration of diarrhoea was 36.0 (26.4) hours, the mean stool frequency on day 2 was 2.0 (2.1), and diarrhoea lasting ≥ 4 days occurred in one (5.0%) child. These outcomes were not statistically significantly different from the control group. In contrast, both the mean duration of diarrhoea and the mean stool frequency on day 2 were statistically significantly improved in the high dose group ($10^{10\text{-}11}$ CFU/day; Analysis 1.1; Analysis 1.3).

Finally, on the basis of their previous study that did not show an effect of a low dose of *L. rhamnosus* GG on acute diarrhoea in a dose of 120 x 10^6 CFU/day (Basu 2007; Analysis 1.1; Analysis 1.3), these researchers evaluated two higher doses of this probiotic (2 x 10^{10} and 2 x 10^{12} CFU/day) in similar participants and a similar study setting (Basu 2009). In contrast to their earlier study, they reported that both higher doses had similar and statistically significant beneficial effects in acute diarrhoea (Analysis 1.1; Analysis 1.3).

Age of participants

It was not possible to assess the effects of probiotics in adults as < three studies reported the same diarrhoea outcomes. The primary analysis of mean duration of diarrhoea did not include studies undertaken in adults (Analysis 1.1). Removing studies of adults from the other primary analyses did not reduce heterogeneity (forest plots not shown). Overall, there was insufficient evidence regarding the efficacy of probiotics according to participants' age.

Children with rotavirus diarrhoea

In keeping with the findings for all children in their study, Simakachorn 2000 reported that fewer children with rotavirus diarrhoea in the probiotic than the control group had watery diarrhoea after 24 hours (3/19 versus 9/16; P = 0.012). Similarly, Boulloche 1994 reported that the resolution of diarrhoea in the probiotic group was similar for rotavirus positive and rotavirus negative participants.

Guandalini 2000 reported that mean stool frequency on day 3 of intervention was lower in the probiotic group (0.4, n = 56) than in the controls (2.0, n = 45; P < 0.05) and this was a greater reduction than that seen in all-cause diarrhoea in this study. In contrast,

Costa-Ribeiro 2003 reported that there was no significant difference in the stool output or duration of diarrhoea between children allocated to probiotics versus placebo.

Bacterial diarrhoea

Only four trials reported outcomes for participants confirmed to have bacterial diarrhoea. Two studies assessed *L. casei* strain GG. Shornikova 1997a reported that the stool frequency was similar in the probiotic (n = 11) and placebo (n = 15) groups (P = 0.42). Guandalini 2000 reported that the mean (SD) duration of diarrhoea was similar in the probiotic and control groups (n = 35, 73.3 (29.3) versus n = 34, 72.0 (32.4) hours, respectively). The mean stool frequency on day 2 was also similar in the probiotic and control groups (5.0 and 5.5, respectively). Chen 2010 evaluated a combination of three organisms and reported that the mean (SD) duration of diarrhoea was not reduced significantly in children receiving probiotics (n = 27, 71.6 (32.8) hours) compared with controls (n = 30, 101.5 (46.8) hours; P = 0.082). In contrast, Htwe 2008 reported that in 21 children with pathogenic *E. coli* in stools, *S. boulardii* significantly improved stool consistency on d 3 (P = 0.004) and 4 (P = 0.025) compared with controls.

Adverse events

Of all 63 selected studies, 43 studies reported no adverse events and 20 gave no information on adverse events. Henker 2008 reported that one participant in the probiotic group had a mild hypersensitivity reaction that was assessed as being possibly related to the intervention. However, these authors commented that the probiotic was safe and well tolerated. With this exception, no authors reported an adverse effect that they considered to be attributable to the probiotic.

Many studies reported on vomiting. Boudraa 2001 reported a similar frequency of vomiting in the probiotic and control groups. Pant 1996 reported that 1/19 children in the control group vomited one dose of the medication, but no vomiting occurred in the 20 children in the probiotic group. Raza 1995 reported that the frequency of vomiting on the second day of intervention was statistically significantly less in children in the probiotic than the placebo group. Shornikova 1997c reported that fewer children in the probiotic than the placebo group vomited from the second day of treatment and this was statistically significant on day 2 and day 4. No child in the probiotic group vomited after the third day of treatment whereas vomiting persisted to the sixth day in 2/21 children in the placebo group. Kurugol 2005 reported that one child had meteorism but the group allocation was not stated.

DISCUSSION

A striking finding of this review is that most trials reported that probiotics improved diarrhoea. A beneficial effect of probiotics was consistent across the different diarrhoea outcomes and was statistically significant in many trials.

With the exception of possible mild hypersensitivity to *E. coli* strain Nissle reported in one participant (Henker 2008), no authors reported adverse events that they attributed to probiotics. Vomiting is common in acute diarrhoea and was the most frequently reported adverse event. Vomiting occurred less frequently in the probiotic than the control groups and, therefore, would appear to be a symptom of the illness rather than an adverse effect of probiotics. The reasons for non-compliance with protocol in some studies were not stated, but were unlikely to be related to the adverse events of probiotics since similar numbers of participants in the probiotic and control groups failed to comply. The causes of the withdrawal of participants from trials were related mostly to their primary illness rather than the interventions. Although this review supports the excellent safety record of probiotics, most of the studies recruited previously healthy people and more studies of susceptible individuals, for example, malnourished children and people with human immunodeficiency virus infection, are required to further evaluate safety.

The marked statistical heterogeneity between studies was expected given the marked clinical diversity in the definitions of diarrhoea and end of the diarrhoeal episode, the probiotic(s) tested, the treatment regimens, the diarrhoeal pathogens identified, the types of participants and the settings in which the trials were undertaken. Although these factors varied greatly among studies, individual studies used the same criteria and outcomes for both the probiotic and control groups. Although there was great variability in the methodological quality of the trials, there was no evidence that poor study design had led to an overestimate of the effects of probiotics.

Few studies reported outcomes for participants with bacterial diarrhoea and it was not possible to extract data for meta-analysis from any of these studies. Many of the other studies that reported a beneficial effect of probiotics included a significant proportion of participants with bacterial diarrhoea or bloody stools, or both. Although this suggests that probiotics are efficacious, more research is needed to assess probiotics in bacterial diarrhoea.

The subgroup analyses did not explain between-study statistical heterogeneity. Therefore, this review does not find important differences in probiotic effect according to probiotic strain, the number of different strains, the viability of the organisms, low versus high dose preparations, the causes or severity of diarrhoea or whether the studies were done in developed or developing countries. These findings are encouraging as effective interventions to prevent the progression from acute to persistent diarrhoea (> 14 days; closely associated with malnutrition in children in developing countries [Walker-Smith 1993]), are a priority.

The persistence of statistical heterogeneity in subgroup analyses is perhaps not surprising given the marked clinical variability among studies. This was demonstrated clearly by the wide range of values for primary outcomes reported in participants allocated to the control groups. There is general consensus that effects of probiotics are strain-specific and that results obtained with one probiotic cannot be extrapolated to other organisms, including closely related strains (Rijkers 2010). However, this review found that studies tested many different probiotics in many different settings yet nearly all reported beneficial outcomes. This suggests that a mechanism common to most probiotics, for example, colonization resistance, is effective against a wide range of gut pathogens. Probiotics are likely to have multiple mechanisms of action in the gut that may include effects on host immunity and gut mucosal barrier integrity as well as effects against diarrhoeal pathogens. Variations in several host and environmental factors that may determine the commensal gut flora may modify probiotic efficacy (Wolvers 2010). These include age, diet and eating practices, level of sanitation and exposure to antibiotics. It is likely that other factors, not considered in this review, underlie the marked among-studies heterogeneity.

The marked clinical variability among studies complicates meta-analysis and, therefore, weakens the evidence base to inform clinical practice. In particular, variability in the definition of diarrhoeal episodes results in misclassification and impairs the comparability of the findings from different studies (Baqui 1991). More large, well-designed studies are needed of specific probiotic regimens in specific settings. In future research, the standardization of definitions of acute diarrhoea, treatment regimens, inclusion criteria and outcome measures are needed to facilitate comparison of results across studies. All studies should try to present data separately for important subgroups, for example, according to participant nutritional status and identified causes of diarrhoea, such as rotavirus or bacterial causes. Guidance on undertaking trials with probiotics, such as reliably identifying the agent used, testing the viability of organisms and confirming their quantity, is readily available (Rijkers 2010; Wolvers 2010). Since most episodes of acute diarrhoea are uncomplicated, self-limiting, and require no specific treatment, cost-effect analyses need to determine whether probiotics should be used in particular groups of people.

AUTHORS' CONCLUSIONS

Implications for practice

Probiotics administered in addition to rehydration therapy resulted in clear reductions in the duration and severity of diarrhoea, and were not associated with adverse effects. This review supports the use of probiotics in acute, infectious diarrhoea. However, marked clinical variability between studies resulted in insufficient studies of specific probiotic regimens in defined groups of children or adults to inform the development of evidence-based treatment guidelines.

Implications for research

Although many different probiotics were effective in reducing diarrhoea, to better inform clinical practice studies of specific probiotic regimens in large numbers of participants with well-defined diarrhoeal illness are needed. Trials need to use standardized definitions for acute diarrhoea and the resolution of the illness. They need to identify infectious causes of diarrhoea and present data separately for important participant subgroups, such as viral and bacterial causes of diarrhoea. All studies should include a reliable identification of the probiotic being tested, and confirm the viability and number of organisms for live probiotics. More research is needed to assess the role of probiotics in developing countries, especially in preventing the progression from acute to persistent diarrhoea and associated malnutrition.

Basic research is needed to identify generic and strain-specific mechanisms underlying the apparent beneficial effects of probiotics in acute diarrhoea.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Basu 2007

Methods	Randomized controlled trial; 1 centre Duration: 1 year (January -December 2003)
Participants	Inclusion criteria: inpatients; infants and children with ≥ 3 watery stools/day without visible blood or mucus (duration not stated); < 10 white blood cells/high power field and no red cells, mucus flakes and bacteria on stool microscopy; negative hanging drop preparation; negative bacterial stool culture. Exclusion criteria: systemic illness other than diarrhoea on admission; systemic complication of diarrhoea during hospital stay; failure to give informed consent. Number completing study: 323/330 (97.9%) in the probiotic group (3 participants had electrolyte imbalance, 2 had septicaemia, 2 withdrew consent); 323/332 (97.3%) in control group (3 participants had electrolyte imbalance, 2 had septicaemia, 2 withdrew consent, 1 was discharged, 1 died).
Interventions	1. Live *L. rhamnosus* GG (120 x 10^6 CFU/day for 7 days) 2. ORF Dehydration was corrected using oral rehydration fluid (ORF) following WHO guidelines
Outcomes	1. Frequency of diarrhoea 2. Duration of diarrhoea (time to 2 consecutive soft or formed stools or no stool for 12 consecutive hours) 3. Duration of vomiting 4. Length of hospital stay No adverse events attributed to probiotic.
Notes	Study location: India (high child and adult mortality) Cause of diarrhoea: bacterial diarrhoea excluded. Rotavirus identified in 241 (74.6%) probiotic and 249 (77.1%) control group. Nutritional status: most participants malnourished: probiotic group; 198/323 moderately malnourished, 31/323 severely malnourished; control group; 185/323 moderately malnourished, 33/323 severely malnourished. Hydration status: all participants dehydrated: probiotic group: 48 mild, 173 moderate, 102 severe dehydration; control group: 51 mild, 168 moderate, 104 severe dehydration.

Basu 2007 *(Continued)*

Source of funding: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	computer randomization
Allocation concealment?	Low risk	concealed in envelopes
Blinding? All outcomes	Low risk	double blind
Incomplete outcome data addressed? All outcomes	Low risk	Follow-up ≥90% in both groups

Basu 2009

Methods	Randomized controlled trial; 1 centre Duration: 1 year (period not stated)
Participants	Inclusion criteria: inpatients; infants and children with ≥3 watery stools/day, without macroscopic blood or mucus, white cells < 10 high power field and absent red blood cells, mucus flakes and bacteria on stool microscopy, negative hanging drop preparation and negative bacterial stool culture. Exclusion criteria: symptoms of illness other than diarrhoea; development of any systemic complication of diarrhoea during hospitalization; failure to give informed consent. Number completing the study: probiotic group: 186/196 (94.9%; withdrawals: 5 electrolyte imbalance, 3 septicaemia, 2 withdrew consent); placebo group: 185/196 (94.4%; withdrawals: 4 electrolyte imbalance, 3 septicaemia, 2 withdrew consent; 1 discharged on request; 1 died).
Interventions	1. Live *L. rhamnosus* GG 2 x 10^{10} CFU/day for minimum 7 days or until diarrhoea stopped (data not extracted for meta-analysis) 2. Live *L. rhamnosus* GG 2 x 10^{12} CFU/day for minimum 7 days or until diarrhoea stopped (data extracted for meta-analysis 3. ORF Interventions started after initial rehydration and stabilization.
Outcomes	1. Frequency of diarrhoea by day 2. Average duration of diarrhoea 3. Average duration of vomiting 4. Average duration of IV therapy 5. Average duration of hospital stay No adverse events attributed to probiotic.
Notes	Study location: India (high child and adult mortality) Cause of diarrhoea: bacterial diarrhoea excluded. Rotavirus identified in 106 (57.0%) probiotic and 102 (55.1%) control group.

Basu 2009 *(Continued)*

Nutritional status: severe malnutrition in 17 (9.1%) probiotic and 12 (6.5%) control group; mild/moderate malnutrition in 102 (54.8%) probiotic and 100 (54.1%) control group.

Hydration status: severe dehydration in 35 (18.8%) probiotic and 39 (21.1%) control group; mild/moderate dehydration in 121 (65.1%) probiotic and 122 (66.0%) control group.

Source of funding not stated but no authors had a financial arrangement regarding this study

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Computer-generated random numbers
Allocation concealment?	Low risk	Opaque, sealed envelopes
Blinding? All outcomes	Low risk	Interventions prepared by pharmacy; packets of similar appearance
Incomplete outcome data addressed? All outcomes	Low risk	Follow up ≥ 90% in both groups

Bhatnagar 1998

Methods	Randomized controlled trial; 2 centres. Duration: 16 months
Participants	Inclusion criteria: inpatients; malnourished boys (weight for height < 80% NCHS median) with diarrhoea (≥ 5 liquid stools in preceding 24 hours) for ≤ 96 hours. Nearly all children were dehydrated (48/49 milk group and 43/47 yogurt group). Exclusion criteria: females; severe non-gastrointestinal illness; gross blood in the stools; exclusive breast-feeding. Number completing study: 47/49 (95.9%) in probiotic group (2 withdrawn because cholera in stool cultures); 49/53 (92.5%) in control group (2 withdrawn because cholera in stool cultures and 2 left against medical advice).
Interventions	1. Yogurt formula (Lactogen-2, Nestle India Ltd; after fermentation with 90 g *S. thermophilus* and *Lactobacillus bulgaricus* standard starter (International Yoghurt Manufacturers Club, Paris) 120 mL/kg/day for at least 72 hours) added to milk formula 2. Non-fermented Lactogen-2 Given after 8 hours initial observation. All participants received rehydration fluids (IV if stool > 4 g/kg/hour), IV cephalosporin and gentamicin, and fed with rice lentil oil gruel.
Outcomes	1. Proportion recovered at 48 hours and 72 hours (defined as 2 consecutive formed stools, ≤3 stools in 24 hours of which at least 2 were formed, or no stool for 12 hours) 2. Median duration of diarrhoea 3. Treatment failures (episode of diarrhoea after 72 hours or stool weight > 150 g/kg on any day) No comment regarding adverse events.
Notes	Study location: India (high child and adult mortality).

Bhatnagar 1998 *(Continued)*

	Cause of diarrhoea: excluded if gross bloody stools. Nutritional status: all malnourished boys (weight for height < 80% NCHS median); mean weight for length and length for age (% NHCS median) similar in both groups. Hydration status: Nearly all children were dehydrated: 43/47 (91.5%) probiotic and 48/49 (98.0%) control group. Source of funding: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	randomisation list
Allocation concealment?	Unclear risk	not stated
Blinding? All outcomes	Unclear risk	probably open study
Incomplete outcome data addressed? All outcomes	Low risk	Follow-up ≥ 90% in both groups

Billoo 2006

Methods	Randomized trial; probably open study; 1 centre Duration: not stated
Participants	Inclusion criteria: inpatients; infants and children with acute watery diarrhoea of mild to moderate severity Exclusion criteria: Severe intercurrent illness; severe diarrhoea and dehydration requiring admission and IV rehydration; temperature > 38.5°C; anti-diarrhoeals or antibiotics in last 24 hours; severe malnutrition Number completing study: 50/50 (100%) in probiotic group; 50/50 (100%) in control group.
Interventions	1. *S. boulardii* (500mg/day for 5 days) 2. ORF and nutritional support only Timing of interventions not stated.
Outcomes	1. Stoppage of diarrhoea (not defined) 2. Weight gain 3. Daily stool frequency and consistency 4. Tolerance and acceptability of intervention No adverse events attributed to probiotic.
Notes	Study location: Pakistan (high child and adult mortality) Cause of diarrhoea: Rotavirus identified in 8 (16.0%) probiotic and 10 (20.0%) control group. Bacterial diarrhoea identified in 13 (26.0%) probiotic and 6 (12.0%) control group.

Billoo 2006 *(Continued)*

	Nutritional status: severe malnutrition excluded; no further data presented
	Hydration status: severe dehydration excluded; no further data presented
	Source of funding: supported by Laboratoires Biocedex (France); Hilton Pharma (Pvt.) Ltd. Pakistan

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Randomized controlled trial but methods not described
Allocation concealment?	Unclear risk	Methods not described
Blinding? All outcomes	High risk	No placebo; probably open study
Incomplete outcome data addressed? All outcomes	Low risk	Follow up ≥90% in both groups

Boudraa 2001

Methods	Randomized controlled trial; 1 centre Duration: not stated
Participants	Inclusion criteria: inpatients; well-nourished children aged 3-24 months with watery diarrhoea < 5 day duration and > 3 watery stools in previous 24 hours. All children were dehydrated, including some with severe dehydration. Exclusion criteria: exclusive breast feeding, history of allergy to cow's milk, severe malnutrition (weight or height < 70% or oedema) Number completing study: 49/56 (87.5%) in probiotic group (3 with urinary tract infection and 1 with bronchopneumonia withdrawn, others withdrawn by parents) and 48/56 (85.7%) in non-probiotic group (2 with urinary tract infection, 1 with amebiasis withdrawn and 1 failed to attend for follow up, others withdrawn by parents). Reasons for withdrawal by parents not stated. Diarrhoea outcomes reported for all randomized children.
Interventions	1. Infant formula (Enapal-Sopad, Nestlé, Courbevoie, France) fermented with *L. bulgaricus* and *S. thermophilus* (Yalacta, Caen, France; total 2 x 10^8 CFU/g). 2. Infant formula acidified with lactic acid to match pH of fermented formula 180 mL/kg/day of either fermented or non-fermented infant formula given after initial oral rehydration. All infants also received other foods.
Outcomes	1. Weight gain 2. Cessation of diarrhoea (defined as last liquid or semi-liquid stool before 2 formed stools). Means and 95% CIs stated 3. Food and liquid intake Frequency of vomiting similar in both groups. No other comment regarding adverse events.
Notes	Study location: Algeria (high child and adult mortality).

Boudraa 2001 *(Continued)*

	Cause of diarrhoea: rotavirus identified in 25/56 (44.6%) probiotic and 26/56 (46.4%) in control group. No bacterial pathogens isolated. Nutritional status: all well-nourished Hydration status: all dehydrated; severe dehydration in 5 (8.9%) in the probiotic and 4 (7.1%) in the control group. Reduced duration of diarrhoea in the probiotic compared with non-probiotic group observed only in children with reducing substances in stools. Source of funding: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Not described
Allocation concealment?	Unclear risk	Not described
Blinding? All outcomes	High risk	Stated as double blind but mothers able to distinguish fermented from non-fermented infant formula
Incomplete outcome data addressed? All outcomes	High risk	Follow up < 90% in both groups

Boulloche 1994

Methods	Randomized controlled trial; 1 centre. Duration: 3 years
Participants	Inclusion criteria: inpatients; young children with acute diarrhoea (definition not stated; 3/4 had diarrhoea < 3 days); weight loss of at least 5%. Exclusion criteria: any treatment that could have affected diarrhoea during hospitalization. Number completing study: 38/38 (100%) in probiotic group and 33/33 (100%) in control group.
Interventions	1. Killed *L. acidophilus* (LB strain, Lacteol Forte, France; 1 sachet thrice daily for first 24 hours, then 1 sachet daily for next 3 days) 2. Placebo (no details provided; same regimen) 3. Loperamide Timing of start of administration not stated. All young infants were given Pregestimil, and older children were given an anti-diarrhoeal diet.
Outcomes	1. Time to first normal stool 2. Failure defined as no improvement by the end of day 2 (clinical criteria) No adverse events attributed to probiotic.
Notes	Study location: France (very low child and adult mortality).

Boulloche 1994 *(Continued)*

	Cause of diarrhoea: 18% all participants had positive stool cultures and 49% positive virology tests (no further details given). Nutritional status: no data presented. Hydration status: all dehydrated with weight loss of at least 5%. Results presented for oral rehydration group only and all children. Resolution of diarrhoea in killed *L. acidophilus* group similar for rotavirus positive and negative participants. Source of funding: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Random number table stratified in groups of 18
Allocation concealment?	Unclear risk	Not described
Blinding? All outcomes	Unclear risk	Not described
Incomplete outcome data addressed? All outcomes	Low risk	Follow up ≥ 90% in both groups

Bruno 1981

Methods	Randomized controlled trial; 1 centre. Duration: not stated
Participants	Inclusion criteria: inpatients; adults with acute enteritis (diarrhoea, fever, vomiting, nausea, abdominal pain with or without toxicity; duration not stated). Exclusion criteria: typhoid cases. Number completing study: stool cultures available after randomization; participants with *Salmonella typhi* withdrawn (number not stated); for non-typhoid participants, results presented for 25/25 (100%) in probiotic group and 24/24 (100%) in control group.
Interventions	1. *Enterococcus LAB* SF68 (Bioflorin; ≥75 x 10^6 lyophilized bacteria tds for 10 days) 2. Placebo Timing of start of administration not stated.
Outcomes	1. Proportion of participants with diarrhoea by day of treatment Resolution of diarrhoea defined as 2 or less formed stools/day and no abdominal pain or fever. No adverse events attributed to probiotic.
Notes	Study location: Italy (very low child and adult mortality). Cause of diarrhoea: non-typhoid. Bacterial stool culture (probiotic group/placebo group): Salmonella 4/3; enteropathogenic *E. coli* 18/20; other enteropathogen 1/3.

Bruno 1981 *(Continued)*

	Nutritional status: no data presented. Hydration status: no data presented. Source of funding: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Not described
Allocation concealment?	Unclear risk	Not described
Blinding? All outcomes	Low risk	Identical placebo
Incomplete outcome data addressed? All outcomes	Low risk	Follow up ≥ 90% in both groups

Bruno 1983

Methods	Randomized controlled trial; 1 centre. Duration: not stated
Participants	Inclusion criteria: inpatients; adults with acute febrile enteritis (duration of diarrhoea not stated). Exclusion criteria: typhoid cases. Number completing study: 10/10 (100%) in the probiotic group and 11/11 (100%) in the control group.
Interventions	1. *Enterococcus LAB* SF68 (Bioflorin; ≥75 x 10^6 lyophilized bacteria thrice daily for at least 10 days) 2. Placebo Intervention started after initial treatment with chloramphenicol (all participants) and after stool culture results available.
Outcomes	1. Proportion of participants with diarrhoea by day of treatment (definition for recovery from diarrhoea not stated). No adverse events attributed to probiotic.
Notes	Study location: Italy (very low child and adult mortality). Cause of diarrhoea: non-typhoid. Nutritional status: no data presented. Hydration status: no data presented. Source of funding: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement

Bruno 1983 *(Continued)*

Adequate sequence generation?	Low risk	Randomization list
Allocation concealment?	High risk	Not described
Blinding? All outcomes	High risk	Not described
Incomplete outcome data addressed? All outcomes	Low risk	Follow up ≥ 90% in both groups

Buydens 1996

Methods	Randomized controlled trial; 2 centres. Duration: not stated
Participants	Inclusion criteria: inpatients and outpatients; adults with acute diarrhoea (>= 3 watery or loose stools in last 24 hours). Exclusion criteria: diarrhoea > 3 days; blood in faeces; faecal leukocytes; temperature > 39 °C; friable and haemorrhagic mucosa in rectosigmoid; history of chronic diarrhoea; polyps; colon cancer; Crohn's disease; ulcerative colitis; malabsorption; use of antidiarrhoeals or antibiotics in past 7 days; severe diarrhoea (dehydration with weight loss >10%); associated major diseases. Number completing study: 93/105 (88.6%) in probiotic group (4 violated protocol, 5 did not comply with study medications, 3 lost to follow up) and 92/106 (86.8%) in control group (5 violated protocol, 7 did not comply with study medications, 2 lost to follow up).
Interventions	1. Enterococcus strain SF68, lyophilized (Bioflorin; 75 x10^6 CFU thrice daily for ≥5 days) 2. Placebo Started on day of presentation.
Outcomes	1. Number of participants with diarrhoea by day of treatment 2. Mean stool frequency by day of treatment Diarrhoea resolved when stool frequency < 3/day and semisolid or solid and no associated symptoms. No adverse events attributed to probiotic.
Notes	Study location: Belgium (very low child and adult mortality). Cause of diarrhoea: bloody diarrhoea excluded. Bacterial diarrhoea identified in 12 (11.4%) in the probiotic and 16 (15.1%) in the control group. Nutritional status: no data presented Hydration status: > 10% dehydration excluded; no further data presented. Highly significant reduction in duration of diarrhoea in the probiotic group confirmed by an intention-to-treat analysis, which included the excluded participants as non-recovered on day 7 (but no data shown). Source of funding: not stated

Risk of bias

Buydens 1996 *(Continued)*

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Randomization by central computer
Allocation concealment?	Low risk	Randomization by central computer
Blinding? All outcomes	Low risk	Identical placebo
Incomplete outcome data addressed? All outcomes	High risk	< 90% follow-up in probiotic and placebo groups

Canani 2007

Methods	Randomized controlled trial; 6 centres Duration: 12 months, October 1999 to September 2000
Participants	Inclusion criteria: outpatients; infants and children aged 3 to 36 months with >2 loose or liquid stools/day for <48 hours. Exclusion criteria; malnutrition, severe dehydration; coexisting acute systemic illness (meningitis, sepsis, pneumonia), immunodeficiency; underlying severe chronic disease; cystic fibrosis; food allergy or other chronic GI diseases; use of probiotics in the previous 3 weeks; antibiotics or any other antidiarrhoeal medication in the previous 3 weeks; poor compliance (< 4 doses of the study medication administered). Number completing study: 95/100 in the probiotic group (2 did not receive the allocated intervention, 1 faster remission, 1 worsening symptoms, 1 poor compliance); 88/92 in the control group (1 did not receive the allocated intervention, 1 worsening symptoms, 1 contracted pneumonia, 1 had coeliac disease).
Interventions	1. Live *Lactoacillus casei rhamnosus* GG (Dicoflor 60; 12 x 10^9 CFU/day for 5 days) 2. Placebo, no details given but same appearance as active intervention. Intervention started within 48 hours of admission. ORF given for 3-6 hours after admission, lactose-containing formula milk or cow's milk according to age.
Outcomes	1. Diarrhoea duration (time of the last loose or liquid stool preceding a normal stool) 2. Number and consistency (scoring system) of stools/day recorded by parents 3. Vomiting 4. Fever (> 37.5°C) 5. Number of hospital admissions 1 patient with poor compliance in the probiotic group; 31 and 34 participants had vomiting in the probiotic and placebo groups, respectively. No adverse events attributed to probiotic.
Notes	Study location: Italy (very low child and adult mortality). Cause of diarrhoea: stool culture in only few participants; no data presented. Nutritional status: malnutrition excluded Hydration status: severe dehydration excluded; no other data presented. Source of funding: none

Canani 2007 *(Continued)*

Single blind trial. Parents instructed to buy probiotic preparation.

This study also allocated children to 4 other probiotic groups: 1) *S. boulardii* It 5 × 10^9 live organisms daily (Codex) for 5 days; 2) *Bacillus clausii* O/C84, N/R84, T84, SIN84 (Enterogermina) 10^9 CFU bd for 5 days; 3) a combination of *L. delbrueckii* var *bulgaricus* LMG-P17550 10^9 CFU daily, *L. acidophilus* LMG-P 17549 109 CFU daily, *S. thermophilus* LMG-P 17503 10^9 CFU daily, *B. bifidum* LMG-P 17500 5 × 10^8 CFU daily (Lactogermina) for 5 d; 4) *Enterococcus faecium* SF 68 (Bioflorin) 7.5×10^7 CFU daily for 5 days and compared each of the probiotic groups with the single control group. Mean duration of diarrhoea and mean stool frequency on day 2 and 3 were significantly shorter than in the control group for intervention groups 1 and 3. These outcomes were similar to the control group for the other probiotic groups.

To avoid a unit-of-analysis error as a result of the multiple comparisons between the intervention groups and the single control group, we elected to include data for the *L.* GG group only in this review. We selected *L.* GG because this was the probiotic most frequently evaluated in acute infectious diarrhoea and we wished to maximize the body of evidence. We rejected the alternative approach of pooling the data from all of the different probiotic intervention groups into a single group because this would not be helpful in selecting a specific probiotic intervention for use in clinical practice.

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Computer-generated randomization list allocation in blocks of 6
Allocation concealment?	Low risk	Concealed until treatment assigned
Blinding? All outcomes	Low risk	Blinded third-party blind assessor
Incomplete outcome data addressed? All outcomes	Low risk	Follow up ≥ 90% in both groups

Carague-Orendain

Methods	Randomized controlled trial; 1 centre Duration: not stated
Participants	Inclusion criteria: inpatients and outpatients; children with non-bloody diarrhoea (not defined) of less than 5 days duration. Exclusion criteria: antimicrobials in the last 72 hours; concomitant illness; severe malnutrition; antidiarrhoeal drugs; immunocompromised. Participants completing study: 35/35 (100%) in probiotic group and 35/35 (100%) in control group.
Interventions	1. *L. acidophilus* and *L. bifidus* (Infloran Berna; dose and duration not stated). 2. Placebo (no details given; unclear whether or not placebo was identical to probiotic). No details of when interventions started.
Outcomes	1. Resolution of diarrhoea (defined as no passage of stool for 12 hours or 2 consecutive formed stools). Assessed in outpatients by phoning the parents. No adverse events attributed to probiotic.

Carague-Orendain *(Continued)*

Notes	Unpublished data. Study location: Philippines (low child and adult mortality). Cause of diarrhoea: bloody diarrhoea excluded. Nutritional status: severe malnutrition excluded; no other data presented. Hydration status: overall, 42 children had some dehydration (none severe) and 28 had no dehydration Source of funding: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Not described
Allocation concealment?	Unclear risk	Not described
Blinding? All outcomes	Unclear risk	Unclear whether placebo identical to probiotic
Incomplete outcome data addressed? All outcomes	Low risk	Follow up ≥ 90% in both groups

Cetina-Sauri 1994

Methods	Randomized controlled trial; 1 centre Duration: 11 months, 1April 1988 to 15 March 1989
Participants	Inclusion criteria: unclear whether inpatients or outpatients, or both; children aged 3 months to 3 years with acute (duration not stated) non-bloody diarrhoea; no dehydration; no concomitant illness; no antibiotics or drugs affecting gut motility. Number completing study: unclear how many participants randomized; participants who deteriorated, developed concomitant illness, and needed other drugs, or who wished to withdraw were excluded from the analysis (details not given).
Interventions	1. *S. boulardii* (live *Saccharomyces cerevisiae Hansen* CBS 5926; 600 mg/day; duration not stated) 2. Glucose placebo (diluted in 5 mL cold water). No details of when interventions started.
Outcomes	1. Number of stools per day 2. First day stools formed 3. Side effects Cure defined as < 4 stools in 24 hours and absence of liquid stools. No adverse events attributed to probiotic.
Notes	Study location: Mexico (low child and adult mortality). Cause of diarrhoea: bloody diarrhoea excluded

Cetina-Sauri 1994 *(Continued)*

Nutritional status: all well nourished.

Hydration status: dehydration excluded.

Source of funding: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Random table
Allocation concealment?	Unclear risk	Not described
Blinding? All outcomes	Unclear risk	Unclear whether placebo was identical to the probiotic
Incomplete outcome data addressed? All outcomes	Unclear risk	Unclear how many participants were randomized at beginning of study

Chapoy 1985

Methods	Intervention study; 1 centre Duration: not stated
Participants	Inclusion criteria: inpatients; infants and children with sudden, recent onset of watery diarrhoea (not defined) of variable importance with or without fever and vomiting. Exclusion criteria: dehydration >10% needing IV rehydration; bloody or purulent stools; fever >39°C; associated pathology. Number completing study: 19/19 (100%) probiotic group and 19/19 (100%) control group.
Interventions	1. Live *S. boulardii* (500 mg/day for 5 days) 2. ORF When the probiotic was administered was not stated.
Outcomes	Mean number of stools, mean stool weight and carmine red transit time on days 1 and 4. Stool consistency on day 4. Stool frequency on day 4 was lower in the probiotic than the control group (n = 19; mean 2.1 [SD 0.9] versus n = 19; 3.4 [1.9] respectively). The reduction in stool frequency from baseline was statistically significantly greater in the probiotic than control group (P < 0.01). No adverse events attributed to probiotic.
Notes	Location: France (very low child and adult mortality) Cause of diarrhoea: bloody or purulent stools excluded; pathogenic bacteria isolated from 9 children in the probiotic and 6 in the control group. Nutritional status: no data presented. Hydration status: dehydration > 10% needing IV rehydration excluded;

Chapoy 1985 *(Continued)*

Source of funding: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	High risk	Infants allocated alternately to the two groups as enrolled in trial
Allocation concealment?	High risk	Alternate allocation
Blinding? All outcomes	High risk	No placebo; open study
Incomplete outcome data addressed? All outcomes	Low risk	Follow up ≥ 90% in both groups

Chen 2010

Methods	Randomized controlled trial; 1 centre Duration: 22 months; February 2006 to November 2007
Participants	Inclusion criteria: inpatients; children aged 3 months to 6 years with acute diarrhoea defined as 3 or more loose or liquid stools per day of less than 72 hours duration. Exclusion criteria: immunodeficiency, severe abdominal distension with risk of bowel perforation, severe infection or sepsis, history with gastrointestinal tract surgery, probiotics use in the preceding 1 week. Number completing study: 304 children enrolled and 293 were included in the analysis (150 in the probiotic and 143 in the control group). Overall, 7 children discontinued medication and 4 were lost to follow up; group allocation unclear.
Interventions	1. Live *Bacillus mesentericus*, *Enterococcus faecalis*, and *Clostridium butyricum* (Bio-three; 2.5 x 10^7 CFU/kg/d) for 7 days 2. Starch powder of identical appearance to probiotic preparation When interventions started not stated.
Outcomes	1. Duration of diarrhoea (time from inclusion into the study until the first normal stool was passed) 2. No. of diarrhoea episodes 3. Mean stool frequency on days 2 and 3 4. Diarrhoea lasting ≥ 3 days 5. Duration of fever 6. Duration of vomiting 7. Appetite/intake score 8. Abdominal pain episodes 9. Length of hospital stay Duration of diarrhoea also reported for children with rotavirus diarrhoea and those with bacterial diarrhoea No adverse events attributed to probiotic.

Chen 2010 *(Continued)*

Notes	Study location: Taiwan (low child and adult mortality). Cause of diarrhoea: 47 (31.3%) of children in probiotic and 44 (30.8%) in control group had rotavirus in stools. Norovirus and adenovirus also identified. 27 (18.0%) children in probiotic and 30 (20.0%) in the control group had bacteria in stools (either *Salmonella enterica* or *Campylobacter jejuni*). Nutritional status: no data presented Hydration status: no data presented Source of funding: The study was supported in part by a grant from Chang Gung Memorial Hospital research project grant XMRPG440021, Northern Taiwan. First author was contacted and asked to clarify • that children who had received antibiotics before recruitment were included • that children with blood in stools were included • whether they could provide outcome results separately for rotavirus diarrhoea • hydration status • nutritional status

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Not described
Allocation concealment?	Unclear risk	Not described
Blinding? All outcomes	Low risk	Identical placebo
Incomplete outcome data addressed? All outcomes	Low risk	Follow up ≥ 90% in both groups

Costa-Ribeiro 2003

Methods	Randomized controlled trial; 1 centre Duration: not stated
Participants	Inclusion criteria: inpatients; boys, age 1 to 24 months with acute diarrhoea (3 or more watery or loose stools per 24 hours during at least one 24 hour period in the 72 hours before admission) with moderate dehydration or severe dehydration after correction by rapid IV fluids. Exclusion criteria: systemic infections requiring antibiotics, severe malnutrition (weight for age < 65% of NCHS standards), bloody diarrhoea. Number completing study: 61/61 (100%) in the probiotic group and 63/63 (100%) in the control group.
Interventions	1. *L. casei* subspecies *rhamnosus* 10 x10^9 CFU/day 2. inulin 320mg/day Interventions started after correction of severe dehydration if required

Costa-Ribeiro 2003 *(Continued)*

Outcomes	1. Duration of diarrhoea (cessation of diarrhoea defined as passage or 2 formed or semi-formed stools or no stools for 24 hours). Note: SDs quoted for mean duration of diarrhoea in each group appeared small in comparison with other trials. Authors contacted and clarification awaited. 2. Diarrhoea lasting 3 or more days 3. Diarrhoea lasting 4 or more days. 4. 24 hour and total stool output 5. Unscheduled IV fluids 6. Vomiting during first 24 hours after randomization 7. Hyponatraemia at 24 hours after randomization No comment regarding adverse events.
Notes	Study location: Brazil (low child and adult mortality). Cause of diarrhoea: bloody diarrhoea excluded; 52% of children in the probiotic and 48% in the control group had rotavirus in stools; no data shown for outcomes in rotavirus diarrhoea although stated as "no significant difference" between groups. Nutritional status: severe malnutrition excluded; median WHZ score -1.13 (IQR −1.63 to −0.43) in control and -1.22 (−1.87 to −0.62) in probiotic group. Hydration status: all dehydrated; moderate or severe dehydration in 92% in the probiotic and 94% in the control group. Source of funding: the study was supported in part by a grant from Pronex/CNPq (661086/1998-4), Brazil.

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Randomization code
Allocation concealment?	High risk	Sequential administration
Blinding? All outcomes	Low risk	Identical placebo
Incomplete outcome data addressed? All outcomes	Low risk	Follow up ≥ 90% in both groups

Czerwionka 2009

Methods	Randomized controlled trial; 1 centre Duration: not stated
Participants	Inclusion criteria: inpatients; infants and children with acute infectious diarrhoea who had failed oral rehydration. Exclusion criteria: bloody stools; coexisting disease that might influence the course of diarrhoea. Number completing study: 50/50 (100%) in the probiotic group and 50/50 (100%) in the control group.
Interventions	1. Live *L. rhamnosus* 50 ml/kg/day of ORF containing 5 x 10^{12} organisms/200 mL

Czerwionka 2009 *(Continued)*

	2. Live *L. rhamnosus* (dose unclear) 3. ORF Interventions started after rapid IV rehydration
Outcomes	1. Duration of treatment 2. No. stools during the whole treatment period 3. No. stools on a typical day of treatment No specific comment regarding adverse events.
Notes	Study location: Poland (low child, low adult mortality). Cause of diarrhoea: bloody diarrhoea excluded; 28/50 in the probiotic and 30/50 in the control group had rotavirus diarrhoea. Nutritional status: no data presented Hydration status: no data presented Source of funding: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Not stated
Allocation concealment?	Unclear risk	Not stated
Blinding? All outcomes	Unclear risk	Not stated
Incomplete outcome data addressed? All outcomes	Low risk	Follow up ≥ 90% in both groups

D'Apuzzo 1982

Methods	Randomized controlled trial; unclear whether single or multi-centre. Duration: not stated
Participants	Inclusion criteria: unclear whether inpatients or outpatients, or both; children with acute enteritis (duration and definition not given). Exclusion criteria: none stated. Number completing study: 21/21 (100%) in the probiotic group and 18/18 (100%) in the control group.
Interventions	1. Live *Streptococcus faecium* (*S. faecium* 68; 75 x10^6 bacteria thrice daily for 7 days) 2. Placebo (details not given). When interventions started not stated.
Outcomes	1. Number of participants with < 2 stools/day. 2. Formed, yellow/brown stools without mucus.

D'Apuzzo 1982 *(Continued)*

	3. No abdominal pains vomiting or fever for the whole day. No adverse events attributed to probiotic.
Notes	Study location: Switzerland (very low child and adult mortality). Cause of diarrhoea: 7 participants in each group had positive stool cultures for bacteria. Nutritional status: no data presented Hydration status: no data presented *S. faecium* 68 also appeared to promote recovery from abdominal pains, fever, and vomiting. Source of funding: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Not described
Allocation concealment?	Unclear risk	Not described
Blinding? All outcomes	Unclear risk	Unclear whether placebo identical to probiotic
Incomplete outcome data addressed? All outcomes	Low risk	Follow up ≥ 90% in both groups

Dubey 2008

Methods	Randomized controlled trial; 1 centre Duration: February 2005 to February 2007
Participants	Inclusion criteria: inpatients; infants and children with watery diarrhoea (defined as watery stools) <72 hours duration due to rotavirus infection, parental consent. Exclusion criteria: systemic infection, chronic disease, body weight <60% NCHS standard, vomiting, need for antibiotics. Number completing study: 113/113 (100%) in the probiotic group and 111/111 (100%) in the control group. Six children did not complete the study; no group allocation or reasons given.
Interventions	1. *L. acidophilus, L. paracasei, L. bulgaricus, L. plantarum, B. breve, B. infantis, B. longum, S. thermophilus* (VSL#3; body weight < 5 kg: 180 billion organisms/day; body weight 5-10 kg: 360 x10^9 organisms/day for 4 days). 2. Placebo (details not given although placed in identical sachets) When interventions started not stated.
Outcomes	Number stools/day; duration diarrhoea; IV fluid requirement; ORF requirement. No adverse effects attributed to probiotic.
Notes	Study location: India (high child and high adult mortality)

Dubey 2008 *(Continued)*

	Cause of diarrhoea: all rotavirus Nutritional status: severe malnutrition excluded; statement that "malnutrition status similar in two groups" Hydration status: dehydration status similar in two groups at baseline but no data presented. Source of funding: supported by grant from VSL

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Not described
Allocation concealment?	Unclear risk	Not described
Blinding? All outcomes	Low risk	identical sachets
Incomplete outcome data addressed? All outcomes	Low risk	Follow up ≥ 90% in both groups

Frigerio 1986

Methods	Randomized controlled trial; 150 hospitals Duration not stated
Participants	Inclusion criteria: acute diarrhoeal disorder; diarrhoea defined as ≥ 3 not formed stools/day; duration not stated Exclusion criteria: not stated Number participants recruited at baseline not reported. 534 patients in the placebo group and 540 in the probiotic group completed the study.
Interventions	1. *Enterococcus* SF 68 (Bioflorin; 3 caps/day for 7 days) 2. Placebo (not details given) When interventions started not stated.
Outcomes	Duration of diarrhoea (only statistical analysis reported; no raw data) No adverse effects attributed to probiotic.
Notes	Study location: Italy (very low child and adult mortality) Cause of diarrhoea: no data presented Nutritional status: no data presented Hydration status: no data presented Source of funding: not stated Probiotic also evaluated in antibiotic-associated diarrhoea

Frigerio 1986 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Random allocation; no details reported
Allocation concealment?	Unclear risk	No details reported
Blinding? All outcomes	Unclear risk	No details regarding placebo reported.
Incomplete outcome data addressed? All outcomes	Unclear risk	Number participants recruited not reported

Grandi 2009

Methods	Randomized controlled trial; 1 centre Duration not stated
Participants	Inclusion criteria: inpatients; children with acute rotavirus diarrhoea Exclusion criteria: not stated Number completing study: overall, 64/70 (91.4%) completed study. Number in each intervention group not stated.
Interventions	1. ORF + *S. boulardii* 2. ORF + *L. acidophilus*, *L. rhamnosus*, *B. longum*, *S. boulardii* 3. ORF only When interventions started not stated.
Outcomes	1. Duration of diarrhoea 2. Duration of fever 3. Duration of vomiting 4. Duration of hospitalization No comment regarding adverse events.
Notes	Study location: Chile (low child and adult mortality) Cause of diarrhoea: all rotavirus Nutritional status: no data presented Hydration status: no data presented Source of funding: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement

Grandi 2009 *(Continued)*

Adequate sequence generation?	Unclear risk	Not described
Allocation concealment?	Unclear risk	Not described
Blinding? All outcomes	Unclear risk	Not described
Incomplete outcome data addressed? All outcomes	Unclear risk	Number children in each intervention group not stated

Guandalini 2000

Methods	Randomized controlled trial; multi-centre Duration: 1 year, 1996
Participants	Inclusion criteria: inpatients and outpatients; infants and children with > 4 liquid or semi-liquid stools/day for 1 to 5 days. Exclusion criteria: previous probiotic usage; underlying chronic untreated small bowel disease; inflammatory bowel disease; any underlying chronic disease or immunosuppressive disease or treatment. Number completing study: 287 forms (269 participants) of total of 323 forms (88.9%) received at the coordinating centre were analysed (36 incomplete data or not compliant with protocol); unclear whether withdrawals occurred at participating centres.
Interventions	1. *L.* GG (ATC 53103, ≥10 x 10^9 CFU/250 ml) with ORF 2. ORF with placebo Interventions added to ORF and started at recruitment.
Outcomes	1. Number of treatment failures (need for IV fluids) 2. Mean duration of diarrhoea (time to last recorded fluid stool) 3. Weight gain 4. Proportion of children with diarrhoea longer than 7 days 5. Mean stool frequency by day of treatment (SDs not given) 6. Mean hospital stay Some outcomes also reported for rotavirus, bacterial, and no organism-isolated subgroups. No comment regarding adverse events.
Notes	Study locations: Poland (low child and adult mortality), Egypt (high child and high adult mortality), Croatia, Italy, Slovenia, The Netherlands, Greece, Israel, United Kingdom, Portugal (all very low child and very low adult mortality). Cause of diarrhoea: rotavirus (56 probiotic/45 placebo); bacteria (35/34); parasites (7/6); no pathogen (45/54). 10 (6.8) probiotic and 15 (10.7) control group had bloody diarrhoea. Nutritional status: no data presented. Hydration status: severe dehydration in 1 (0.7) probiotic and 1 (0.7) control group; mild/moderate dehydration in 107 (72.7%) probiotic and 96 (68.2%) control group. Source of funding: not stated

Guandalini 2000 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Not described
Allocation concealment?	Low risk	Code broken at end of study
Blinding? All outcomes	Unclear risk	Identical placebo
Incomplete outcome data addressed? All outcomes	Unclear risk	Unclear whether withdrawals occurred at participating centres; also 36/323 (11.2%) participant data forms received at the co-ordinating centre were not analysed as incomplete and/or not compliant with protocol.

Guarino 1997

Methods	Randomized controlled trial; 1 centre Duration: 3 months, November 1995 to January 1996
Participants	Inclusion criteria: consecutive outpatients attending 3 family physicians; infants and children with ≥ 3 watery stools/day of < 48 hours duration. Exclusion criteria: antibiotic treatment in preceding 3 weeks, breastfeeding, and weight:height ratio < 5th percentile. Number completing study: 52/52 (100%) in probiotic group and 48/48 (100%) in control group.
Interventions	1. Lyophilized *L. casei* strain GG (Dicloflor 30; 6 x 10^9 million CFU/day for maximum 5 days) re-suspended in milk or formula feed 2. ORF only Interventions started after 6 hours of ORF.
Outcomes	1. Mean duration of diarrhoea (time to last loose or liquid stool assessed by mothers) Results for rotavirus subgroup also presented. No comment regarding adverse events.
Notes	Study location: Italy (very low child and adult mortality). Cause of diarrhoea: Rotavirus identified in 30 (57.7%) probiotic and 31 (64.6%) control group. Nutritional status: weight:height ratio < 5th percentile excluded. Hydration status: all had mild to moderate dehydration. The study author clarified that Figure 1 in the published article reports the mean and standard error for the duration of diarrhoea; SDs derived from graph. We also extracted data from Canani 1997 (abstract), which also reports standard errors. Probiotic also reduced prevalence of rotavirus in stools on day 6. Source of funding: Ministero della Sanità, AIDS Project (9205.30)

Risk of bias

Guarino 1997 *(Continued)*

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Random number table
Allocation concealment?	Unclear risk	Not described
Blinding? All outcomes	High risk	Open study
Incomplete outcome data addressed? All outcomes	Low risk	Follow up ≥ 90% in both groups

Hafeez 2002

Methods	Randomized controlled trial - randomization according to odd and even participant numbers; three centres Duration: 2 months
Participants	Inclusion criteria: outpatients; children aged 6 months to 5 years with acute watery diarrhoea of mild or moderate severity (not defined), suitable for ambulatory treatment. Exclusion criteria: anti-diarrhoeals or antibiotics before admission, grade III malnutrition, bloody diarrhoea, needed IV rehydration, diarrhoea for >14 days. Number completing study: 51/54 (94%) probiotic group and 50/54 (93%) control group.
Interventions	1. Lyophilized *S. boulardii* (500 mg/day for 6 days) 2. standard treatment (oral rehydration and feeds) Unclear whether researchers and participants able to distinguish between interventions.
Outcomes	1. Frequency and consistency (loose vs. formed) of stools 2. Duration of illness (definition of end of diarrhoea not stated). 3. Tolerance of treatment No adverse events attributed to probiotic.
Notes	Study location: Pakistan (high child and adult mortality). Cause of diarrhoea: bloody diarrhoea excluded; stool analysis not done. Nutritional status: grade III malnutrition excluded Hydration status: participants who needed IV rehydration excluded.. Source of funding: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	High risk	Alternate allocation

Hafeez 2002 *(Continued)*

Allocation concealment?	Unclear risk	Not described
Blinding? All outcomes	Unclear risk	Probably open study; no placebo
Incomplete outcome data addressed? All outcomes	Low risk	Follow up ≥ 90% in both groups

Henker 2007a

Methods	Randomized controlled trial; 11 centres Duration: 3 months, February to April 2005
Participants	Inclusion criteria: outpatients; infants and toddlers < 4 years with > 3 watery or loose and non-bloody stools /day for ≤ 3 days. Exclusion criteria: > 5% dehydration; intake of *E. coli* Nissle 1917 in last 3 months; intake of food supplements or drugs which contain living microorganisms or their metabolic products or components within 7 days prior to enrolment or during the trial; other antidiarrhoeal drugs; breast-feeding, premature birth; severe or chronic disease of the bowel or severe concomitant diseases. Antibiotics stated as exclusion criteria but some children included. Number completing study: 54/55 (98.2%) probiotic group and 45/58 (93.8%) control group. Reason for withdrawals in both groups stated as intervention no longer suitable or required other treatment.
Interventions	1. Live *E. coli* strain Nissle 1917 (Mutaflor suspension; 100-300 x10^6 organisms/day according to age) 2. Placebo
Outcomes	1. Number of stools, stool consistency, admixture of blood or mucus 2. Frequency of vomiting, abdominal pain and cramps 3. Fluid intake, concomitant medication and general state of health for up to 10 days Diarrhea resolution: reduction in stool frequency to < 3 watery or loose stools in 24 hours over a period of at least 2 consecutive days. Adverse effects: 1 had rhinitis and 1 had abdominal cramps in the probiotic group. 2 had acute otitis media in the placebo group. 1 participant with poor compliance in the placebo group. No adverse events attributed to probiotic.
Notes	Study location: Ukraine, Russia (low child, high adult mortality) Cause of diarrhoea: bloody diarrhoea excluded; 16/55 (29.1%) probiotic and 19/58 (32.8%) control group had viral diarrhoea. Bacterial pathogens isolated from 9/55 (16.4%) probiotic and 4/58 (6.8%) control group. Nutritional status: most children well nourished. Hydration status: > 5% dehydration excluded; 0/55 probiotic and 1/58 control children had mild dehydration. Better outcomes in probiotic than placebo for abdominal pain (28/30 vs. 24/33) and abdominal cramps (17/18 vs. 21/26). Parents reported slightly better tolerance of probiotic than placebo, although investigators noted no difference. Authors supplied data regarding SDs for diarrhoea duration.

Henker 2007a *(Continued)*

	Source of funding: ARDEYPHARM provided verum and placebo medications and reimbursed study-related expenses

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Computer-generated randomly permuted blocks of 4
Allocation concealment?	Low risk	Sequence concealed from parents and researchers
Blinding? All outcomes	Low risk	Identical placebo
Incomplete outcome data addressed? All outcomes	Low risk	Follow up ≥ 90% in both groups

Henker 2008

Methods	Randomized controlled trial; 11 centres Duration: 3 months, February to April 2005
Participants	Inclusion criteria: inpatients; > 3 loose or watery stools without blood / 24 hours for > 4 days and < 14 days; moderate dehydration (5-10% loss of body weight). Exclusion criteria: other severe organic or infectious disease; participation in another trial; intake of trial preparation in the past 3 months; intake of probiotic preparations within the past 7 days; antibiotics or antidiarrhoeals; severe dehydration (>10% weight loss); weight <5th percentile; growth faltering; breast-feeding; preterm birth. Number completing study: 72/75 (96.0%) probiotic group (trial intervention no longer suitable/different treatment needed - 2; personal reasons - 1); 59/76 (77.6%) control group (trial intervention no longer suitable/different treatment needed - 11; personal reasons - 5f; intolerable adverse event - 1).
Interventions	1. *Escherichia coli* strain Nissle 1917 (Mutaflor Suspension, Germany; participants received 100-300 x10^6 organisms/day according to age) 2. Placebo - Identical suspension
Outcomes	1. Resolution of diarrhoea (<=3 watery or loose stools/24 hours for 4 consecutive days) 2. Clinical improvement 3. General state of health 4. Adverse events 5. Tolerance of intervention 1 participant in the probiotic group had a mild hypersensitivity reaction which was assessed as possibly related to the intervention. In the control group, 1 participant had vomiting, 1 abdominal pain, 1 dermatitis and 1 withdrawn because of influenza. Authors commented that the probiotic was safe and well tolerated.
Notes	Study location: Ukraine, Russia (low child, high adult mortality) Cause of diarrhoea: bloody diarrhoea excluded; 12 (16.0) probiotic and 15 (21.1) control group had viral diarrhoea. Bacterial pathogens isolated from 15 (20.0) probiotic and 19 (25.0) control group.

Henker 2008 *(Continued)*

	Nutritional status: weight < 5th percentile and growth faltering excluded; 2 (2.7) probiotic and 3 (3.9) controls had mild/moderate malnutrition. Hydration status: all had moderate dehydration (5-10% loss of body weight). Fewer children with dehydration at the end of the study in the probiotic than the placebo group. General state of health improved to a greater extent in the probiotic than the placebo group. Significantly fewer children with diarrhoea > 21 days in the probiotic than the placebo group. At the end of the study the rates of mucus in stool, abdominal cramps, and abdominal pain were all lower in the probiotic group. Source of funding: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Computer-generated randomly permuted blocks of 4
Allocation concealment?	Low risk	Study personnel and participants blinded to treatment assignment for the duration of the study
Blinding? All outcomes	Low risk	Identical placebo
Incomplete outcome data addressed? All outcomes	High risk	Follow up < 90% in placebo group

Hernandez 1998

Methods	Randomized controlled trial; 1 centre Duration: not stated
Participants	Inclusion criteria: inpatients; uncomplicated acute diarrhoea (not defined) and mild dehydration. Exclusion criteria: fever; malnutrition; bloody stools. Number completing study: 25/25 (100%) probiotic group; 25/25 (100%) control group.
Interventions	1. *S. boulardii (*200 mg every 8 hours for 5 days) 2. Placebo
Outcomes	1. Stool frequency 2. Persistence of diarrhoea No adverse events attributed to probiotic.
Notes	Study location: Mexico (low child and adult mortality) Cause of diarrhoea: bloody diarrhoea excluded Nutritional status: malnutrition (not defined) excluded. Hydration status: all had mild dehydration.

Hernandez 1998 *(Continued)*

	Source of funding: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Not described
Allocation concealment?	High risk	Not described
Blinding? All outcomes	Unclear risk	Not described
Incomplete outcome data addressed? All outcomes	Low risk	Follow up ≥ 90% in both groups

Hochter 1990

Methods	Randomized controlled trial; multi-centre Duration: not stated
Participants	Inclusion criteria: outpatients attending general practitioners, gastroenterologists, and internal physicians; adults with acute diarrhoea (> 3 liquid stools in last 24 hours; in great majority duration 2 days or less; 1 participant in the placebo group had diarrhoea for >10 days). Exclusion criteria: chronic diarrhoea; blood in stools; drug-induced diarrhoea; antimicrobial treatment; inflammatory bowel disease. Number completing study: 92/107 (86.0%) randomized participants completed study (1 took additional drugs, 14 < 3 liquid stools at presentation). 3 participants dropped out (2 probiotic, 1 placebo) because intervention not effective; results included in analysis.
Interventions	1. *S. boulardii* (Perenterol; 600 mg/day for 2 days then 300 mg/day on days 3 to 7) 2. Placebo Interventions started at presentation.
Outcomes	1. Mean stool frequency on days 1, 3, and 8 2. Score derived from stool frequency and consistency No adverse events attributed to probiotic.
Notes	Study location: Germany (very low child and adult mortality). Cause of diarrhoea: Stool analyses in first 50 participants only: 2 had rotavirus and 3 Salmonella Nutritional status: all well nourished. Hydration status: no data presented. Source of funding: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement

Hochter 1990 *(Continued)*

Adequate sequence generation?	Unclear risk	Not described
Allocation concealment?	Unclear risk	Not described
Blinding? All outcomes	Low risk	identical placebo
Incomplete outcome data addressed? All outcomes	High risk	< 90% in probiotic and placebo groups

Htwe 2008

Methods	Randomized controlled trial - participants alternately assigned to the probiotic or control group on hospital admission; 1 centre Duration: not stated
Participants	Inclusion criteria: inpatients; infants and children aged 3 months to 10 years; acute watery diarrhoea of duration < 7 days. Exclusion criteria: fever > 38°C; severely dehydrated; macroscopic blood in the stools; intake of antifungals; existing severe malnutrition. Number completing the study: 50 (100%) probiotic group, 50 (100%) control group.
Interventions	1. *S. boulardii* (500 mg/day for 5 days) 2. ORF according to WHO protocol Interventions started on admission.
Outcomes	1. Mean duration of diarrhoea (diarrhoea resolution: <3 stools/day or solid stools only) 2. Stool frequency 3. Consistency of stools No adverse events attributed to probiotic.
Notes	Study location: Myanmar (high child and high adult mortality) Cause of diarrhoea: bloody diarrhoea excluded Nutritional status: severe malnutrition excluded, no other data presented Hydration status: severe dehydration excluded, no other data presented SDs for the duration of diarrhoea were not reported. Source of funding: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	High risk	Alternate allocation

Htwe 2008 *(Continued)*

Allocation concealment?	High risk	Alternate allocation
Blinding? All outcomes	High risk	Probably open study; no placebo
Incomplete outcome data addressed? All outcomes	Low risk	Follow up ≥ 90% in both groups

Isolauri 1994

Methods	Randomized controlled trial; 1 centre Duration: not stated
Participants	Inclusion criteria: inpatients; infants and children with > 3 watery stools/day for < 7 days and stools positive for rotavirus. Average dehydration about5% in both groups. Exclusion criteria: not stated. Number completing study: 21/21 (100%) in probiotic group and 21/21 (100%) in control group.
Interventions	1. Live *L. casei* strain GG (2 x 10^{10} CFU/day for 5 days) 2. No probiotic Interventions started after 6 hours ORF.
Outcomes	1. Mean weight gain 2. Mean duration of diarrhoea (definition for recovery from diarrhoea not stated) 3. Proportion of participants with diarrhoea by day of treatment No comment regarding adverse events.
Notes	Study location: Finland (very low child and adult mortality). Cause of diarrhoea: all rotavirus diarrhoea. Nutritional status: all well nourished Hydration status: mean dehydration about 5% in both groups. Source of funding: Academy of Finland and the Foundation for Nutrition Research (Finland).

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	Not defined
Allocation concealment?	Unclear risk	Not defined
Blinding? All outcomes	High risk	Open study; no placebo
Incomplete outcome data addressed?	Low risk	Follow up ≥ 90% in both groups

Isolauri 1994 *(Continued)*
All outcomes

Jasinski 2002

Methods	Randomized controlled trial; 12 centres Duration: not stated
Participants	Inclusion criteria: inpatients and outpatients; age 1month to 3 years; acute diarrhoea (3 or more liquid stools in 12 hours or single liquid or semi-solid stool with mucus or blood, or both, for 5 days or less). Exclusion criteria: antibiotics or probiotics in last 5 days; chronic diseases of small or large intestine (eg coeliac, cow milk protein allergy, inflammatory bowel disease), immunosuppression, phenylketonuria Number completing study: 45/45 (100%) probiotic and 52/52 (100%) placebo
Interventions	1. Live*L.* GG ATCC 53103 (10^{10} organisms in 250 mL ORF). ORF administered at 100 mL/kg over first 4 hours. Then either IV fluids or 10-15 mL/kg ORF per liquid/semi-solid stool. 2. ORF with placebo. Start time for administration unclear.
Outcomes	1. Stool frequency, character 2. Volume and length of use of ORF 3. Duration of diarrhoea (until 2 consecutive normal stools) 4. Use of antibiotics after recruitment No comment regarding adverse events.
Notes	Study location: Europe, Egypt, Africa, and single site (Montevideo) in S. America (variable child and adult mortality) Cause of diarrhoea: bacterial pathogens: probiotic group 29 (64.4%) and placebo group 37 (71.2%); rotavirus: probiotic group 18 (40.0%) and placebo group 21 (40.4%); parasites: probiotic group 2 (4.4%) and placebo group 4 (7.7%); no pathogens identified: probiotic group 11 (24.4%) and placebo group 14 (26.9%). Nutritional status: 15 (33.3%) in the probiotic and 20 (38.5%) in the control group had at least some malnutrition. Hydration status: mild/moderate dehydration in 15 (33.3%) probiotic and 17 (32.7%) control group. Severer dehydration in 0 in the probiotic and 2 (3.8%) control group. Source of funding: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	High risk	Alternate allocation
Allocation concealment?	High risk	Alternate allocation
Blinding? All outcomes	Unclear risk	Not described

Jasinski 2002 *(Continued)*

Incomplete outcome data addressed? All outcomes	Low risk	Follow up ≥ 90% in both groups

Khanna 2005

Methods	Randomized controlled trial; 1 centre Duration: 19 months, April 2001 to September 2002
Participants	Inclusion criteria: inpatients; aged 6 months to 12 years with acute diarrhoea (not defined) Exclusion criteria: systemic infection; encephalopathy; convulsions; use of pharmaceutical probiotics Number completing study: 1/49 (2.0%) in the probiotic group and 3/53 (5.7%) controls left before the completion of the study.
Interventions	1. Tyndalized (heat-killed) *Lactobacilus acidophilus* (Lactrol, Raptakos; 15 x 10^9 bacteria/day for 3 days) 2. Placebo (puffed rice powder) Interventions started on admission. All children received ORF, feeding and IV fluids if needed
Outcomes	1. Duration of diarrhoea (time to first of 3 consecutive semi-formed stools or to last loose stool before gap of no stools for 12 hours). SDs stated for mean duration of diarrhoea in each group appear to be too small, resulting in excessive weight in forest plots. SDs calculated from 95% CI stated in text. 2. Treatment failure (diarrhoea persisting >72 hours, ORF >8L if < 5 years and > 10L if > 5 years, > 200mL/kg IV fluid required) 3. Time to rehydration 4. Duration of hospital stay 5. Weight gain No comment regarding adverse events.
Notes	Study location: India (high child and adult mortality) Cause of diarrhoea: overall, 14/22 (63.6%) children tested were rotavirus positive and 8/98 (8.2%) has a positive culture for cholera. Nutritional status: most children were stunted and some had wasting. Hydration status: 19 in (39.6%) in the probiotic and 15 (30.0%) in the control group had severe dehydration. Source of funding: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Described as "simple randomisation done by a non-departmental colleague"
Allocation concealment?	Low risk	Investigators blinded to group allocation
Blinding? All outcomes	Low risk	Identical placebo

Khanna 2005 *(Continued)*

Incomplete outcome data addressed? All outcomes	Low risk	Follow-up > 90% in both groups

Kianifar 2009

Methods	Randomized controlled trial; 1 centre Duration: 18 months, April 2006 to September 2007
Participants	Inclusion criteria: inpatients; infants and children aged 6 to 36 months with acute non-bloody, non-bacterial diarrhoea (not defined) of less than 2 days' duration and moderate dehydration Exclusion criteria: severe dehydration, antibiotic consumption, severe vomiting, convulsion, inflammatory cells in stool samples Number completing study: 32/34 (94.1%) probiotic and 30/34 (88.2%) placebo; participants excluded because of poor compliance.
Interventions	1. Live *L. acidophilus* 3 x 10^9 and *Bifidobacterium bifidum* 3 x 10^9 /day for 5 days (Infloran; Laboratorio Farmaceutico SIT S.r.l., Mede, Pavia, Italy) in 5–10 mL of water 2. placebo (maltodextran) Start time for administration not stated. All children received IV fluid therapy, oral rehydration solution, and mother's milk in breast-feeding infants, or complementary food according to the patient's age.
Outcomes	1. Duration of diarrhoea 2. Reduction in defecation frequency 3. Weight gain 4. Duration of hospital admission No adverse events attributed to probiotic.
Notes	Study location: Iran (low child and adult mortality) Cause of diarrhoea: non-bloody, non-bacterial diarrhoea (not defined) Nutritional status: not stated. Hydration status: all had moderate dehydration; severe dehydration excluded. Source of funding: grant from the Vice Chancellery for Research, Mashad University of Medical Sciences.

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Random number table sequence
Allocation concealment?	Unclear risk	Not described
Blinding? All outcomes	Low risk	placebo sachets matched for size, shape, and volume of contents; physicians, nurses and parents were blinded to the treatment protocol.

Kianifar 2009 *(Continued)*

Incomplete outcome data addressed? All outcomes	High risk	Follow up < 90% in placebo group

Kowalska-Duplaga 1999

Methods	Randomized controlled trial; 1 centre Duration: not stated
Participants	Inclusion criteria: unclear whether inpatients or outpatients, or both; age < 24 months with acute rotavirus diarrhoea (> 3 loose or watery stools/24 hours lasting < 48 hours prior to inclusion). Exclusion criteria: not stated. Number completing study: 33/33 (100%) in probiotic group and 30/30 (100%) in control group.
Interventions	1. Live *Bifidobacterium ruminatum* (2 x 10^9 CFU/day for 5 days) 2. Placebo Timing of administration not stated.
Outcomes	1. Duration of diarrhoea (definition for recovery from diarrhoea not stated.) 2. Risk of diarrhoea lasting > 72 hours. No adverse events attributed to probiotic.
Notes	Study location: Poland (low child and adult mortality). Cause of diarrhoea: all rotavirus diarrhoea. Nutritional status: no data presented. Hydration status: dehydration status similar in both group; no other data presented. Source of funding: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Not described
Allocation concealment?	Unclear risk	Not described
Blinding? All outcomes	Low risk	Identical placebo
Incomplete outcome data addressed? All outcomes	Low risk	Follow up ≥ 90% in both groups

Kowalska-Duplaga 2004

Methods	Randomized controlled trial; 3 centres Duration: not stated
Participants	Inclusion criteria: inpatients; infants and children with 3 or more loose stools within 24h period of < 72 hours duration Exclusion criteria: history of acute diarrhoea within 14 days preceding the inclusion in the study; antibiotic treatment; received probiotic up to 7 days before the participation in the study; exclusively breast fed; chronic alimentary disease; diagnosis of malabsorption; lack of parental consent; lack of diarrhoea. Number completing study: 86/87 (98.9%) probiotic group and 87/89 (97.8%) placebo group.
Interventions	1. *L. acidophilus, B. bifidum, L. bulgaricus* (*3.2* x 10^9 CFU/day for 5 days) 2. identical placebo (no details given) Interventions administered from recruitment.
Outcomes	1. Duration of diarrhoea (defined as time to last loose stool) 2. Duration of diarrhoea in rotavirus positive children 3. Diarrhoea severity 4. Vomiting 5. Weight gain 6. Duration of hospital stay Mean duration of diarrhoea reported for children with rotavirus diarrhoea. No adverse effects attributed to probiotic.
Notes	Study location: Poland (low child and adult mortality) Cause of diarrhoea: rotavirus identified in 31 (37.3%) probiotic and 22 (26.8%) placebo group. Bacterial pathogens identified in 6 (7.2%) probiotic and 14 (17%) placebo group. Nutritional status: no data presented. Hydration status: no data presented. Source of funding: interventions provided by Allergon, Sweden

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	High risk	Allocated according to order of presentation
Allocation concealment?	High risk	Allocated according to order of presentation
Blinding? All outcomes	Low risk	Identical placebo
Incomplete outcome data addressed? All outcomes	Low risk	Follow up ≥ 90% in both groups

Kurugol 2005

Methods	Randomized controlled trial; 1 centre Duration: not stated
Participants	Inclusion criteria: inpatients; aged 3 months to 7 years with acute diarrhoea (liquid, mucous, or bloody stools passed at least twice as frequently as usual for ≥ 24 hours and < 7 days) Exclusion criteria: chronic disease; malnutrition; use of antibiotics, antidiarrhoeal or other drugs influencing gut motility Number completing study: probiotic group 100/115 (87.0%; 10 required antibiotics, 5 non-compliant); control group 100/117 (85.5%; 13 required antibiotics, 4 non-compliant)
Interventions	1. *S. boulardii* (250mg/d given with water or juice for 5 days) 2. placebo (no details given) Interventions administered from admission. All children received ORF, normal food for age and IV fluids as required
Outcomes	1. Number stools/day and number watery stools/day 2. Duration diarrhoea (time to first normal stool) 3. Duration vomiting 4. Duration fever 5. Duration hospital stay 1 child had meteorism (group allocation unclear). No adverse events attributed to probiotic.
Notes	Study location: Turkey (low child and adult mortality). Cause of diarrhoea: 39 (39.0%) children in probiotic group and 44 (44.0%) controls had rotavirus diarrhoea. Overall, bacterial pathogens were isolated in 9 and parasites in 11 children. Nutritional status: malnutrition excluded; no other data presented. Hydration status: severe or moderate dehydration in 3 (3.0%) probiotic and 5 (5.0%) control group; mild/moderate dehydration in 17 (17.0%) probiotic and 24 (24.0%) control group. Source of funding: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Not described
Allocation concealment?	Unclear risk	Not described
Blinding? All outcomes	Low risk	Identical placebo
Incomplete outcome data addressed? All outcomes	High risk	Follow up < 90% in both groups

Lee 2001

Methods	Randomized controlled trial, non-blinded; 1 centre Duration: 6 months, October 1999 to March 2000
Participants	Inclusion criteria: inpatients; consecutive admissions aged 6-60 months; diarrhoea < 5 days and > 3 watery stools in last 24 hours. Average dehydration about 5% in both groups. Exclusion criteria: bloody stools, antidiarrhoeal or antiperistaltic drugs; children receiving lactose-free, protein hydrolysated formula for malabsorptive disorder; compromised immune system. Number completing study: 50/50 (100%) probiotic and 50/50 (100%) control group.
Interventions	1. Lyophilized *L. acidophilus* and *Bifidobacteria infantis* (Infloran Berna; 3 x 10^9 of each organism/day for 4 days) 2. No additional treatment All children had IV fluids because of vomiting. Interventions administered after initial fluid therapy.
Outcomes	1. Stool frequency by day of intervention 2. Duration of diarrhoea (time until the last watery stool) 3. Recovery rate on day 2 No comment regarding adverse effects.
Notes	Study location: Taiwan (low child and adult mortality). Cause of diarrhoea: bloody diarrhoea excluded. Nutritional status: no data presented. Hydration status: % average dehydration 4.3 (SD 1.5) in probiotic and 4.0 (1.4) in control group. Source of funding: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Not described
Allocation concealment?	Unclear risk	Not described
Blinding? All outcomes	Unclear risk	Probably open study; no placebo
Incomplete outcome data addressed? All outcomes	Low risk	Follow up ≥ 90% in both groups

Lievin Le-Maol 2007

Methods	Randomized controlled trial; 1 centre Duration: not stated
Participants	Inclusion criteria: inpatients; infants and children aged ≤24 months; > 4 liquid stools/24 hours of < 72 hours duration.

Lievin Le-Maol 2007 *(Continued)*

	Exclusion criteria: rotavirus diarrhoea Number completing study: 42/42 (100%) probiotic and 38/38 (100%) control group.
Interventions	1. Heat-killed *L. acidophilus* strain LB (loading dose of 2 sachets, followed by 1 sachet every 12 hours. 1 sachet contained 10^{10} CFU plus 160 mg of spent culture medium) 2. Placebo sachet containing sucrose, ferrous oxides, silicic acid, and banana and orange flavouring All sachets diluted in ORF. Every admitted child was given at least 100 mL/kg of ORF.
Outcomes	1. Duration of diarrhoea (time to passage of first normal stool) 2. Number whose diarrhoea stopped within 4 days. No adverse events attributed to probiotic.
Notes	Study location: Ecuador (high child and high adult mortality) Cause of diarrhoea: rotavirus diarrhoea excluded; bloody diarrhoea included. Nutritional status: no data presented Hydration status: severe dehydration in 0 probiotic and 1 (2.6%) control group; mild/moderate dehydration in 4 (10.5%) probiotic and 7 (23.3%) control group. Source of funding: Laboratoire du Lacte´ol (Houdan, France) provided strain LB and batches of lyophilized, heat-killed LB bacteria plus their culture medium to Dr Servin and Lactéol Fort sachets and placebo sachets to Dr Sarrazin-Davila.

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	High risk	Sequential allocation
Allocation concealment?	High risk	Sequential allocation
Blinding? All outcomes	Low risk	Identical placebo
Incomplete outcome data addressed? All outcomes	Low risk	Follow up ≥ 90% in both groups

Mao 2008

Methods	Randomized controlled trial; 1 centre Duration: not stated
Participants	Inclusion criteria: inpatients; infants and children with severe acute diarrhoea (defined as 1 watery or mucous stool or 3 or more loose stools daily for > 24 hours). Exclusion criteria: moderate or severe malnutrition; total or partial breast feeding; diarrhoea > 48 hours; need for antibiotic treatment; allergy to cow's milk; gastrointestinal or other chronic pathologies.

Mao 2008 *(Continued)*

	12/212 (5.7%; 3 study groups) withdrawn after recruitment as they did not match the age criteria. Number completing study: 70/70 (100%) probiotic and 71/71 (100%) control group.
Interventions	1. Live *B. lactis* Bb12 (10^9 CFU/g milk powder) and *S. thermophilus* TH4 (5 x 10^8 CFU/g milk powder) administered until 24 hours after diarrhoea ended 2. Same probiotic preparation in a lower dose; not included in this review 3. Milk-based, lactose-free formula Interventions administered after oral or parenteral rehydration.
Outcomes	1. Stool frequency and consistency daily until day 7 2. Diarrhoea duration (end of episodes defined as first formed stool if followed by 2 consecutive non-watery stools or 12 hours without evacuation) 3. Failure of treatment No specific comment regarding adverse effects.
Notes	Study location: China; low child and adult mortality Cause of diarrhoea: rotavirus diarrhoea occurred in 87% and bacterial diarrhoea in 13% in both groups. Nutritional status: moderate or severe malnutrition excluded. Hydration status: no data presented. Source of funding:not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Not described
Allocation concealment?	Unclear risk	Not described
Blinding? All outcomes	Unclear risk	Reported as double blind but methods of blinding not described
Incomplete outcome data addressed? All outcomes	Low risk	Follow up ≥ 90% in both groups

Misra 2009

Methods	Randomized controlled trial; 1 centre Duration: not stated
Participants	Inclusion criteria: inpatients; infants and children with diarrhoea (> 3 stools per day, watery or taking the shape of the container); duration not stated. Exclusion criteria: parents refused consent, children living outside the municipal area, bloody diarrhoea, severe dehydration, shock, inability to take and retain oral feeds, suspected systemic infection.

Misra 2009 *(Continued)*

	Number completing study: 105/111 (94.6%) probiotic and 105/118 (89.0%) control group; children withdrawn as they did not complete allocated treatment.
Interventions	1. Live *L. rhamnosus* GG (1 x 10^6 - 10^9 bacteria/day; Culturelle; Amerifit Brands, Cromwell, CT, USAt) 2. Identical placebo (crystalline micro cellulose) Start of interventions not stated
Outcomes	1. Duration of diarrhoea 2. Number of stools on days 3, 6, and 10 3. Difference in number of stool in the same patient at presentation and on days 3, 6, and 10 4. Relative risk of diarrhoea continuing on day 3 No comment regarding adverse effects
Notes	Study location: India; high child and adult mortality Cause of diarrhoea: rotavirus identified in 29/105 (27.6%) probiotic and 25/105 (23.8%) in control group. Bloody diarrhoea excluded but 30/105 (28.6%) in probiotic and 30/105 (28.6%) in control group had white blood cells in stools and, overall, 10 children had bacterial diarrhoea. Nutritional status: no data presented. Hydration status: severe dehydration excluded; mild/moderate dehydration in 18 (17.1%) probiotic and 23 (21.9%) control group. Source of funding: partly by the International Development Fund of the John Nuveen Centre for International Affairs, University of Illinois, Chicago, USA

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Computer-generated randomization
Allocation concealment?	Unclear risk	Not described
Blinding? All outcomes	Low risk	Identical capsules
Incomplete outcome data addressed? All outcomes	High risk	Follow up < 90% in placebo group

Narayanappa 2008

Methods	Randomized controlled trial; 1 centre Duration: not stated
Participants	Inclusion criteria: inpatients; infants and children with acute rotavirus diarrhoea (stool frequency and consistency not stated) of duration of ≤ 3 days. Exclusion criteria: infectious diarrhoea other than rotaviral diarrhoea; serum sodium > 155 mmol/L or <130 mmol/L; history of malabsorption, respiratory or systemic infections

Narayanappa 2008 *(Continued)*

	Number completing study: 40/40 (100%) probiotic and 40/40 (100%) control group.
Interventions	1. Bifilac (species of bacteria not mentioned; information from manufacturers, *Streptococcus faecalis* T-110 30 million bacteria, *Clostridium butyricum* TO-A 2 million bacteria, *Bacillus mesentericus* TO-A 1 million bacteria, *Lactobacillus sporogenes* 50 million bacteria. Total of 249 x 10^6 bacteria/day for < 14 days). 2. Placebo (no details given) When interventions started not stated
Outcomes	1. Frequency of diarrhoea 2. Duration of diarrhoea 3. Amount of IV fluid given 4. Amount of ORF given 5. Rotavirus shedding. No adverse effects attributed to the probiotic.
Notes	Study location: India; high child and adult mortality Cause of diarrhoea: all rotavirus diarrhoea. Nutritional status: no data presented. Hydration status: no data presented. Source of funding: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Not described
Allocation concealment?	Unclear risk	Not described
Blinding? All outcomes	Unclear risk	Reported as double blind but no details given
Incomplete outcome data addressed? All outcomes	Low risk	Follow up ≥ 90% in both groups

Oandasan 1999

Methods	Randomized controlled trial; 1 centre Duration: 1 year, 16 January 1998 to 15 January 1999
Participants	Inclusion criteria: inpatients; infants and children with non-bloody diarrhoea (characteristics not stated) for < 5 days. Exclusion criteria: antibiotics in last 72 hours; antidiarrhoeal drugs; other illness; severe malnutrition; compromised immune system, severe electrolyte disturbance and dehydration. Number completing study: 47/47 (100%) in probiotic group and 47/47 (100%) in placebo group.

Oandasan 1999 *(Continued)*

Interventions	1. Live *L. acidophilius* and *L. bifidus* (Infloran berna; 3 x 10^9 of each organism/day) 2. Placebo When interventions started not stated.
Outcomes	1. Mean duration of diarrhoea (diarrhoea improved when no stool for 12 hours or 2 consecutive formed stools) 2. Proportion of participants with diarrhoea by day of treatment 3. Duration of hospital stay No adverse events attributed to probiotic.
Notes	Study location: Philippines (low child and adult mortality). Cause of diarrhoea: bloody diarrhoea excluded. Nutritional status: severe malnutrition excluded; no other data presented. Hydration status: dehydration excluded. Unpublished data. Source of funding: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Random number table
Allocation concealment?	Low risk	Randomization by independent person
Blinding? All outcomes	Low risk	Administration of interventions by independent person
Incomplete outcome data addressed? All outcomes	Low risk	Follow up ≥ 90% in both groups

Ozkan 2007

Methods	Randomized controlled trial; 1centre Duration: 6 months, October 2004 to March 2005
Participants	Inclusion criteria: inpatients and outpatients; previously healthy children; aged 6 months to 10 years; acute diarrhoea (not defined). Exclusion criteria: severe systemic infection or sepsis; chronic disease; previous antibiotics; anti-diarrhoeal drugs; primary/secondary immune deficiency. Number completing study: 16/16 (100%) for the probiotic group. 11/11(100%) for the control group.
Interventions	1. *S. boulardii* (500 mg/day in 5 mL of water for 7 days) 2. Placebo

Ozkan 2007 *(Continued)*

	Start of intervention unclear.
Outcomes	1. Number, characteristics and frequency of stools; 2. Blood tests (blood count and lymphocyte subsets, C-reactive protein, blood smear, complement, immunoglobulins and cytokines). No adverse events attributed to probiotic.
Notes	Study location: Turkey (low child, low adult mortality) Cause of diarrhoea: 1 (6.3%) child in probiotic and 0 in control group had bacterial diarrhoea. Nutritional status: mild/moderate malnutrition in 2 (12.5%) in the probiotic and 1 (9.1%) in the control group. Hydration status: severe dehydration in 1 (6.3%) in the probiotic and 0 in the control group; mild/moderate dehydration in 3 (18.8%) in the probiotic and 2 (18.2%) in the control group. Source of funding: Sanofi-Aventis (Paris, France) provided laboratory reagents and a commercial preparation of *S. boulardii*

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Not described
Allocation concealment?	Unclear risk	Not described
Blinding? All outcomes	Low risk	Identical placebo
Incomplete outcome data addressed? All outcomes	Low risk	Follow up ≥ 90% in both groups

Pant 1996

Methods	Randomized controlled trial; 1 centre Duration: 6 weeks, July to mid-August 1993.
Participants	Inclusion criteria: inpatients; infants and children with > 3 watery stools in last 24 hours and diarrhoea for < 14 days. . Mean (SD) weight for age z score -1.15 (0.95) in the probiotic group and -1.8 (1.4) in the placebo group. Exclusion criteria: exclusive breast-feeding; septicaemia. Number completing study: 20/20 (100%) in probiotic group and 19/19 (100%) in placebo group. However, data extractable for subset with watery diarrhoea only: 14/20 (70%) in probiotic group and 12/19 (63.2%) in placebo group. No data for children with bloody stools presented.
Interventions	1. Live *L.* GG (10^9 - 10^{10} CFU bd for 2 days) 2. Placebo Interventions started after 6 hours ORF.

Pant 1996 *(Continued)*

Outcomes	1. Mean duration of diarrhoea (time to last watery stool) 2. Mean stool frequency on days 1 and 2 Vomiting occurred in 1 child in the placebo group. No adverse events attributed to probiotic.
Notes	Study location: Thailand (low child and adult mortality). Cause of diarrhoea: bloody stools in 6 children in probiotic and 7 in placebo group. All negative for parasites and cryptosporidium; 2 rotavirus and 1 astrovirus patients in the probiotic group and 5 rotavirus patients in the control group Nutritional status: no data presented Hydration status: severe dehydration in 2 (10%) in the probiotic and 4 (21%) in the control group; mild/moderate dehydration in all remaining children. Source of funding: Scientific Hospital Supplies, UK, provided the probiotic

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Not described
Allocation concealment?	Unclear risk	Not described
Blinding? All outcomes	Low risk	Identical placebo
Incomplete outcome data addressed? All outcomes	Low risk	follow up ≥ 90% in both groups

Pashapour 2006

Methods	Randomized controlled trial; 1 centre Duration: 4 months, September to December 2002
Participants	Inclusion criteria: inpatients; aged 6 to 24 months, breast fed with increased frequency, fluidity and volume of faeces of duration less than 4 days and moderate dehydration. Exclusion criteria: mucoid or bloody stools; oral feeding contra-indicated or intolerance; pneumonia; septicaemia; malnutrition; severe dehydration; stool culture positive for bacteria; recent intake of yogurt; poor compliance with yogurt intervention Number completing study: 3/43 (7.0%) withdrew from probiotic and 3/43 (7.0%) from control group all due to poor compliance with management
Interventions	1. Pasteurized cow's milk yogurt (*L. bulgaricus* 50,000 organisms/mL and *S. thermophilus* 50,000 organisms/mL; 15mL/kg/day yogurt or more) 2. Control group received standard treatment Interventions administered from admission to discharge. All infants received ORF, IV fluids, complementary feeds
Outcomes	1. Duration of hospital admission

Pashapour 2006 *(Continued)*

	2. Weight gain 3. Reduction in diarrhoea frequency (communication from authors: achievement of previous defecation habit) 4. Number of stools on days 2 and 3 of intervention No comment regarding adverse effects.
Notes	Study location: Pakistan (high child and adult mortality). Cause of diarrhoea: no data presented Nutritional status: malnutrition excluded. Hydration status: all had moderate dehydration. Source of funding: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Not described
Allocation concealment?	Unclear risk	Not described
Blinding? All outcomes	High risk	No placebo; probably open study
Incomplete outcome data addressed? All outcomes	Low risk	Follow up ≥ 90% in both groups

Rafeey 2008a

Methods	Randomized controlled trial; 1 centre Duration: 12 months; May 2005 to May 2006
Participants	Inclusion criteria: inpatients; infants and children with 3 or more watery stools/day for less than 48 hours and clinical dehydration. Exclusion criteria: bloody stools; hypovolaemic shock; acute systemic illness; antibiotic or anti-diarrhoeal medication. 18/178 children withdrawn mainly because of parent non-compliance; likely to have been withdrawn before recruitment. Number completing study: 40/40 (100%) in the probiotic group and 40/40 (100%) in the placebo group.
Interventions	Children randomized to one of 4 groups: A, yogurt fermented with *L. acidophilus*, B, *L. acidophilus* supplement, C, conventional yogurt and D, placebo. Groups B and D selected for review. 1. *L. acidophilus* (10 x 10^9 CFU/day; duration of treatment not stated; unclear if live or killed). 2. Placebo (no details given) Start of administration not stated.
Outcomes	1. Weight change

Rafeey 2008a *(Continued)*

	2. Duration of hospital stay 3. Stool frequency on days 1, 2 and 3 4. Signs and symptoms on day 3 No adverse effects attributed to probiotic.
Notes	Study location: Iran; low child and adult mortality Cause of diarrhoea: bloody diarrhoea excluded; no bacteria or parasites identified in stool samples. Nutritional status: severe malnutrition excluded. Hydration status: severe dehydration in 1/40 (2.5%) probiotic and 2/40 (5%); all the rest had mild/moderate dehydration. Source of funding: supported by a grant from Tabriz Medical University

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Restricted randomization using random permuted blocks
Allocation concealment?	Unclear risk	Not described
Blinding? All outcomes	Unclear risk	Not described
Incomplete outcome data addressed? All outcomes	Low risk	Follow up ≥ 90% in both groups

Raza 1995

Methods	Randomized controlled trial; 1 centre Duration: 2 months, July and August 1993
Participants	Inclusion criteria: inpatients; undernourished infants and children with > 3 watery stools in last 24 hours for < 14 days duration and at least moderate dehydration. Exclusion criteria: severe malnutrition; septicaemia. Number completing study: 36/40 participants; 4 withdrawals (2 diagnosed with cholera, 1 developed pneumonia, 1 refused anything by mouth). Results presented for 19/21 (90.5%) in the probiotic group and 17/19 (89.5%) in the placebo group.
Interventions	1. Live *L.* GG (2 x $10^{11\text{-}12}$ CFU/day for 2 days) 2. Placebo Interventions started after 4 to 6 hours ORF.
Outcomes	1. Stool frequency on days 1 and 2. 2. Frequency of vomiting on days 1 and 2. 3. Weight gain.

Raza 1995 *(Continued)*

	Outcomes for watery (non-bloody) diarrhoea also presented: mean (SD) stool frequency day 2 for probiotic (n = 16) versus placebo (n = 16) was 4.4 (2.0) versus 6.6 (4.2), P = < 0.05, and persistent diarrhoea at 48 hours in 5 (31%) versus 12 (75%) patients, P = < 0.01. Definition of persistent diarrhoea not stated. Less vomiting in the probiotic group; myoclonic jerks occurred in one child in each group. No adverse events attributed to probiotic.
Notes	Study location: Pakistan (high child and adult mortality). Cause of diarrhoea: bloody diarrhoea included. Nutritional status: all had mild/moderate malnutrition; severe malnutrition excluded. Hydration status: severe dehydration in 14 (66.7) probiotic and 7 (37) control group; all the rest had moderate dehydration. Duration of diarrhoea not measured (many children discharged before stool character had changed). Source of funding: Scientific Hospital Supplies, UK, provided the probiotic

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Not defined
Allocation concealment?	Unclear risk	Not defined
Blinding? All outcomes	Low risk	Identical placebo
Incomplete outcome data addressed? All outcomes	Low risk	Approximately 90% follow up in both groups

Ritchie 2010

Methods	Randomized controlled trial; 1 centre Duration: 21 months, June 2002 to March 2004.
Participants	Inclusion criteria: inpatients; Aboriginal children aged 4 months to 2 years with acute diarrhoea defined as ≥ 3 loose stools during 24 hours before presentation and duration < 7 days and able to tolerate ORF. Exclusion criteria: oxygen required during the study period; chronic cardiac, renal or respiratory disease; previous gastrointestinal surgery; proven sucrose intolerance; suspected on known immunodeficiency; received probiotic before enrolment; younger than 4 months. Number completing study: 201 assessed for eligibility; 103 refused participation and 28 failed to consent. Probiotic arm: 4 discharged before intervention, 1 parental withdrawal, 33 completed study. Control arm: 1 parental withdrawal, 31 completed study.
Interventions	1. Live *L. casei* strain GG (>15 x 10^9 CFU/day for 3 days) 2. Identical placebo (no details given) Interventions administered within 24 hours of admission.
Outcomes	1. Small intestinal absorption capacity

Ritchie 2010 *(Continued)*

	2. Diarrhoea duration (defined as time to last loose stool in which fewer than 3 loose stools occurred within a 24 hour period) 3. Diarrhoeal frequency 4. Total stool output 5. Proportion of subjects with diarrhoea on days 3 and 4 6. Change in body weight on days 1 and 4 7. Total ORF and IV fluid required 8. Safety and tolerability No adverse events attributed to probiotic.
Notes	Study location: Australia (very low child and low adult mortality). However, this study recruited Aboriginal children who commonly had co-morbidities such as pneumonia and malnutrition related to poverty and social disadvantage in the top end of the Northern Territory. Therefore, data not included in analysis according to country mortality strata. Cause of diarrhoea: bacterial pathogens identified in 4 (12%) probiotic and 4 (13%) in the control group; rotavirus identified in 11 (33%) in the probiotic and 6 (19%) in the control group; parasites identified in 2 (6%) probiotic and 2 (6%) control group. Nutritional status: mild/moderate malnutrition common amongst participants; no other data presented. Hydration status: severe dehydration in 0 probiotic and 1 (3.2%) in the control group; all the rest had mild/moderate dehydration. Source of funding: Project supported by Australian National Health and Medical Research Council

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Computer-generated block randomization
Allocation concealment?	Low risk	Randomization by independent research institute; allocation concealed until recruitment, data collection and analyses were completed
Blinding? All outcomes	Low risk	Identical placebo
Incomplete outcome data addressed? All outcomes	High risk	Follow up < 90% in probiotic group

Rosenfeldt 2002a

Methods	Randomized controlled trial; 2 centres Duration: 6 months, December 1998 to May 1999
Participants	Inclusion: inpatients; children aged 6 to 36 months with 2 or more consecutive loose stools in 24 hours and a duration no more than 7 days. Exclusion criteria: underlying chronic disease or antibiotics prescribed during the study period. Number completing study: 86 children enrolled, of whom 69 (80.2%) completed the study; exclusions were made after randomization because antibiotics were prescribed (3 in the control group and 2 in the

Rosenfeldt 2002a *(Continued)*

	probiotic group), rapid recovery before intervention started (3 in the control group and one in the probiotic group), non-compliance with the protocol (4 in the control group and 4 in the probiotic group).
Interventions	1. Live *L. rhamnosus* 19070-2 and *L. reuteri* DSM 12246 (2 x 10^9 CFU of each organism/day for 5 days) 2. Identical placebo (skimmed milk powder and dextrose anhydrate) Interventions started as soon as possible after randomization and did not await rehydration.
Outcomes	1. Duration of diarrhoea (time from treatment start to appearance of first normal stool as recorded by parents). 2. Persistence of diarrhoea at end of intervention (day 5). No adverse events attributed to probiotic.
Notes	Study location: Denmark (very low child and adult mortality). Cause of diarrhoea: overall, rotavirus was the only pathogen in 40 (58%) children; 6 children had rotavirus and a bacterial pathogen was identified; in addition, *Campylobacter jejuni* was isolated in 3 children and *Salmonella typhimurium* in 1 child. Nutritional status: no data presented. Hydration status: no severe dehydration; mild/moderate dehydration in 5 (16.7%) in the probiotic and 17 (43.6%) in the control group. The probiotics appeared to reduce significantly the duration of diarrhoea in children treated within 60 hours of the onset of diarrhoea. Hospital stay was shorter in the probiotic group than the controls (mean 1.6 (SD 1.0) versus 2.7 (SD 2.0) respectively; P = 0.02). The probiotics also appeared to reduce significantly the number of children excreting rotavirus in stools on day 5. Source of funding: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Not described
Allocation concealment?	Unclear risk	Not described
Blinding? All outcomes	Low risk	Identical placebo
Incomplete outcome data addressed? All outcomes	High risk	Follow up < 90% in both groups

Rosenfeldt 2002b

Methods	Randomized controlled trial; 19 day-care centres Duration: 6 months, December 1998 to May 1999

Rosenfeldt 2002b *(Continued)*

Participants	Inclusion criteria: outpatients; children aged 6 to 36 months with 2 or more consecutive loose stools in 24 hours as assessed by parents and with a duration no more than 7 days. Exclusion criteria: underlying chronic disease; antibiotics prescribed during study period. Number completing study: 50 children enrolled, of whom 43 (86%) participants completed the study. Exclusions were because of hospitalization with excessive vomiting and moderate dehydration (2 in the placebo group and 3 in the probiotic group), 1 because antibiotics were prescribed (placebo group), 1 non-compliant with protocol (placebo group).
Interventions	1. Live *L.rhamnosus* 19070-2 and *L. reuteri* DSM 12246 (2 x 10^9 CFU of each organism/day for 5 days) 2. Identical placebo Interventions started as soon as possible after randomization.
Outcomes	1. Duration of diarrhoea (time from treatment start to appearance of first normal stool as recorded by parents). 2. Persistence of diarrhoea at end of intervention (day 5). One participant in the probiotic group complained of constipation (no stools passed from day 3 for 10 days). No adverse events attributed to probiotic.
Notes	Study location: Denmark (very low child and adult mortality). Cause of diarrhoea: overall, rotavirus was the only pathogen in 25 children, 2 had rotavirus and a bacterial pathogen identified, 2 had an infection with *C. jejuni* and *Salmonella typhimurium*. Nutritional status: no data presented. Hydration status: mild/moderate dehydration in 3 patients (12.5%) in the probiotic and 4 (13.8%) in the control group; no severe dehydration. The probiotics appeared to reduce significantly the duration of diarrhoea in children treated within 60 hours of the onset of diarrhoea. Source of funding: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Not described
Allocation concealment?	Unclear risk	Not described
Blinding? All outcomes	Low risk	Identical placebo
Incomplete outcome data addressed? All outcomes	High risk	Follow up < 90% in both groups

Sarkar 2005

Methods	Randomized controlled trial; 1 centre Duration: 23 months, February 2001 to December 2002

Sarkar 2005 *(Continued)*

Participants	Inclusion criteria: inpatients; boys aged 4 to 24 months of age; acute watery diarrhoea (> 4 liquid stools during 24 hours) of < 48 hours duration. Exclusion criteria: severe malnutrition (< 65% weight for age by the standard of the National Centre for Health Statistics (NCHS)); systemic infection requiring antimicrobial therapy; bloody diarrhoea; spot sample of stool revealed *V. cholerae* by dark-field microscopy; antibiotic treatment in the preceding 2 weeks Number completing study: 112/115 (97.4%) in the probiotic group (3 withdrawn by parents) and 115/115 (100.0%) in the control group.
Interventions	1. Live *Lactobacillus paracasei* strain ST11 (10^{10} CFU/day for 5 days) 2. Placebo (whey-protein and skimmed-milk powder blend) Interventions started after enrolment. All children received ORF and continued feeding, including breast milk if breast fed.
Outcomes	1. Stool output and frequency 2. Oral rehydration solution intake 3. Daily excretion of rotavirus No comment regarding adverse outcomes.
Notes	Study location: Bangladesh (high child and adult mortality). Cause of diarrhoea: bloody diarrhoea excluded. Rotavirus detected in 78 (69.6%) in the probiotic and 73 (63.5%) in the placebo group; *V. cholera* detected in 14 (12.2%) in the probiotic and 16 (13.9%) in the placebo group. Nutritional status: severe malnutrition (weight < 65% weight for age of NCHS standard) excluded no further data presented. Hydration status: mild/moderate dehydration in 54 (47.0%) in the probiotic and 65 (56.5%) in the control group. Source of funding: Nestle Research provided *L. paracasei.* Research supported by the Swedish Agency for Research in Developing Countries , the Karolinska Institute (Stockholm, Sweden), and Nestlé Research Centre (Lausanne, Switzerland).

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Randomly permutated blocks
Allocation concealment?	Low risk	Randomization code generated by an independent statistician
Blinding? All outcomes	Low risk	Identical placebo
Incomplete outcome data addressed? All outcomes	Low risk	Follow up >90% in both groups

Sepp 1995

Methods	Randomized trial; 1 centre Duration: 1 year; November 1992 to October 1993
Participants	Inclusion criteria: inpatients; infants and children with ≥2 loose stools for 1 to 3 days or haemorrhagic colitis, fever ≥ 38.0ºC,or second stage dehydration, or both. All had shigellosis. Exclusion criteria: not stated Number completing study: 13/13 (100%) children in the probiotic group and 12/12 (100%) in the control group.
Interventions	1. *L. casei* strain GG (10^{10-11} CFU/day for either 5 or 10 days) + trimethoprim-sulfamethoxazole (36 mg/kg/day for 5 days) 2. trimethoprim-sulfamethoxazole (36 mg/kg/day for 5 days) When interventions started was not stated.
Outcomes	1. Number cured (defined as < 2 loose stools/24 hours without additional clinical symptoms for at least 3 days) 2. Duration of diarrhoea 3. Duration of hospital stay No comment regarding adverse effects
Notes	Study location: Estonia (low child, high adult mortality) Cause of diarrhoea: all shigellosis. 9 (69.2%) in the probiotic and 4 (33.3%) in the controls had bloody diarrhoea. Nutritional status: no data presented. Hydration status: no data presented. Source of funding: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Not described
Allocation concealment?	Unclear risk	Not described
Blinding? All outcomes	High risk	No placebo; probably open study
Incomplete outcome data addressed? All outcomes	Low risk	Follow up > 90% in both groups

Shornikova 1997a

Methods	Randomized controlled trial; 1 centre Duration: 1 year, 1 April 1994 to 31 May 1995

Shornikova 1997a *(Continued)*

Participants	Inclusion criteria: inpatients; infants and children with ≥ 1 watery stool in the last 24 hours and diarrhoea for < 5 days. Exclusion criteria: not stated. Number completing study: 123/214 (57%) eligible children admitted during the study period enrolled; no reasons given for those not recruited. A total of 59/59 (100%) children allocated to the probiotic group and 64/64 (100%) in the placebo group completed the trial.
Interventions	1. Live *L.* strain GG (American-type culture collection 53 103; 10^{10} CFU/day as a dried powder for 5 days) 2. Placebo Interventions started with oral rehydration solution. All participants with positive stool cultures received antibiotics. Effect of isotonic versus hypotonic oral rehydration solution also assessed.
Outcomes	1. Duration of diarrhoea (defined as last appearance of watery stools) 2. Weight gain 3. Duration of hospital stay No comment regarding adverse events.
Notes	Study location: Russia (low child and high adult mortality). Cause of diarrhoea: rotavirus identified in 13 (22.0%) in the probiotic and 21 (32.8%) in the control group. Bacterial diarrhoea identified in 11 (18.7%) in the probiotic and 15 (23.4%) in the control group. Nutritional status: no data presented. Hydration status: mean dehydration ˜4% in both groups. Among children with rotavirus diarrhoea, the probiotic (n = 13) reduced the number of watery stools compared with the placebo (n = 21; P = 0.02, but no data given). No beneficial effect of the probiotic was seen in those with bacterial diarrhoea (probiotic (n = 11) and placebo (n = 115), P = 0.42). Stool samples tested for rotavirus (Rotazyme, Dakopotts AS, Denmark) and cultured for Salmonella and Shigella. Source of funding: Leiras, Turku, Finland and Valio, Helsinki, Finland

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Randomization schedule
Allocation concealment?	Low risk	Randomization numbers sequentially assigned to participants as enrolled
Blinding? All outcomes	Low risk	Identical placebo
Incomplete outcome data addressed? All outcomes	Low risk	Follow up > 90% in both groups

Shornikova 1997b

Methods	Randomized controlled trial; 2 centres Duration: 6 months, 22 January to 15 July 1996
Participants	Inclusion criteria: inpatients; infants and children with ≥ 3 watery stools in last 24 hours, diarrhoea for < 7 days; stools positive for rotavirus antigen (IDEIA Rotavirus, UK). Mean dehydration about 4% in both groups. Exclusion criteria: 20 participants who received exclusively or mainly IV fluids were excluded. 86/97 (89%) enrolled participants were positive for rotavirus. Number completing study: 21/21 (100%) in the probiotics and 25/25 (100%) in the placebo group. (20 allocated to a low dose probiotic group).
Interventions	Participants randomized to one of 3 groups: 20 in the probiotic small dose (10^7 CFU/day) group, 21 in the probiotic large dose group, 25 in the placebo group. Data from the large dose group were used in this review. 1. Live *L. reuteri* (10^{10}-10^{11} CFU/day for maximum 5 days) 2. Live *L. reuteri* (10^7 CFU/day for maximum 5 days) 3. Placebo Interventions started with ORF
Outcomes	1. Duration of diarrhoea (time to last watery stool in a 24 hour period with no watery stools) 2. Stool frequency on day 2 of treatment 3. Weight gain No comment regarding adverse events.
Notes	Study location: Finland (very low child and adult mortality). Cause of diarrhoea: all rotavirus. Nutritional status: no data presented. Hydration status: mean dehydration about4% in both groups. Data from high dose probiotic group used for continuous outcomes. Duration of diarrhoea before admission greater in probiotic group (4.2 (SD 1.4) days) than in the placebo group (2.9 (SD 1.2) days). Number with persistent diarrhoea on day 3 derived from graph. Source of funding: BioGaia Biologicals AB

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Not described
Allocation concealment?	Unclear risk	Not described
Blinding? All outcomes	Low risk	Identical placebo
Incomplete outcome data addressed? All outcomes	High risk	Participants receiving IV fluids excluded

Shornikova 1997c

Methods	Randomized controlled trial; 1 centre Duration: 5 months, 29 January to 3 July , 1995
Participants	Inclusion criteria: inpatients; infants and children with ≥ 3 watery stools in last 24 hours; diarrhoea for < 7 days; ingested bovine dairy products. Exclusion criteria: immunosuppressive therapy or immune deficiency; allergy to bovine milk; serious underlying disorder; undergoing an investigational product during the preceding month. Number completing study: 41 participants initially enrolled; 19/19 (100%) in the probiotic group and 21/22 (95.5%) in the placebo group (1 participant in the placebo group removed because the probiotic agent (*L. reuteri*) was detected in stool; the probiotic was administered to his sibling).
Interventions	1. Live *L. reuteri* SD 2112 (10^{10}-10^{11} CFU/day for a maximum of 5 days) 2. Placebo Interventions started at recruitment.
Outcomes	1. Weight gain 2. Duration of diarrhoea (last appearance of watery stools) 3. Number of participants with watery diarrhoea according to day of treatment 4. Stool frequency on days 2 and 3 5. Number of participants with vomiting according to day of treatment Less vomiting in the probiotic group. No adverse events attributed to probiotic.
Notes	Study location: Finland (very low child and adult mortality). Cause of diarrhoea: rotavirus identified in 18 (86%) in the probiotic group and 12 (63%) in the control group. Nutritional status: no data presented. Hydration status: mean dehydration at baseline greater in the probiotic (3.9% (SD 1.3)) than the control group (3.0 (SD 1.2)). Source of funding: BioGaia Biologicals, Inc., Raleigh,NC, USA.

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Randomiation schedule
Allocation concealment?	Low risk	Randomization numbers sequentially assigned to participants as enrolled
Blinding? All outcomes	Low risk	Identical placebo
Incomplete outcome data addressed? All outcomes	Low risk	Follow up > 90% in both groups

Simakachorn 2000

Methods	Randomized controlled trial; 1 centre Duration: 1 year, September 1995 to August 1996
Participants	Inclusion criteria: inpatients; infants and children with acute, watery diarrhoea (stool frequency not stated) for ≤ 5 days. Exclusion criteria: mucous bloody stools or major systemic illness. Number completing study: 37/37 (100%) in the probiotic group and 36/36 (100%) in the placebo group.
Interventions	1. Heat-killed *L. acidophilus* LB (MA65/4E; Lacteol Fort sachets, Laboratoire du Lacteol du Docteur Boucard, Houdan, France; 2 x10^{10} organisms and fermented culture medium 5 doses over 48 hours) 2. Placebo Interventions mixed with 5 mL water and started with ORF.
Outcomes	1. Duration of diarrhoea (2 consecutive well formed stools or no stool passed for 12 hours) 2. Recovery from diarrhoea by day of treatment 3. Recovery from diarrhoea at 24 hours in rotavirus positive cases No comment regarding adverse events.
Notes	Study location: Thailand (low child and adult mortality). Cause of diarrhoea: bloody diarrhoea excluded. Nutritional status: severe malnutrition in 1 (2.7%) probiotic participant and 1 (2.8%) in the control group; mild/moderate malnutrition in 8 (21.6%) in the probiotic and 12 (33.3%) in the control group. Hydration status: no severe dehydration; all had mild/moderate dehydration. 40 children (17 probiotic and 23 placebo) had received antibiotics before admission. The effect of the probiotic in shortening the duration of diarrhoea more marked in children who had not received antibiotics before admission. Source of funding: Merck Ltd., Bangkok, Thailand. National Collection of Pasteur Institute provided the probiotic.

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Randomization code
Allocation concealment?	Low risk	Numerically coded packages
Blinding? All outcomes	Low risk	Identical placebo
Incomplete outcome data addressed? All outcomes	Low risk	Follow-up >90% in both groups

Sugita 1994

Methods	Quasi-randomized controlled trial; 1 centre

Sugita 1994 *(Continued)*

	Duration: not stated
Participants	Inclusion criteria: inpatients; infants and children with acute rotavirus diarrhoea (stool characteristics described for each participant; stool frequency x 1-10/day; duration not stated); none had bloody stools. Exclusion criteria: none stated. Number completing study: 16/17 (94.1%) in the probiotic group and 11/15 (73.3%) in the control group.
Interventions	1. Live *L. casei* (1.5 g/day for up to 3 weeks) 2. No additional treatment Not stated when interventions started. All participants received lactase (1.5 g/day in 3 doses) and albumin tannate (0.1/kg/day in 3 doses).
Outcomes	1. Efficacy, as judged by a clinician 2. Time to first formed stool 3. Average stool frequency before and after treatment 4. Persistence of stool rotavirus antigen 1 week after intervention No adverse events attributed to probiotic.
Notes	Study location: Japan (very low child and adult mortality). Cause of diarrhoea: all rotavirus diarrhoea. Nutritional status: no data presented. Hydration status: no data presented. Results for time to first formed stool given for 16/17 (94.1%) participants in the probiotic group and 11/15 (73.3%) in the control group. Reasons for missing data not stated. Rotavirus antigen persisted in the stools of 1/9 (11.1%) children in the probiotic group and 2/8 (25%) in the control group. Source of funding: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	High risk	Allocation in order of hospitalization
Allocation concealment?	High risk	Allocation in order of hospitalization
Blinding? All outcomes	High risk	Open study
Incomplete outcome data addressed? All outcomes	High risk	Overall < 90% follow up in placebo group

Szymanski 2006

Methods	Randomized controlled trial; 1 centre

Szymanski 2006 *(Continued)*

	Duration: 10 months, September 2003 to June 2004
Participants	Inclusion criteria: inpatients and outpatients; aged 2 months to 6 years with acute diarrhoea (3 or more stools/day looser than normal that may contain blood or mucous for > 1 and < 5 days). Exclusion criteria: organic gut disease; underlying chronic illness; immunosuppression, exclusive breast-feeding Number completing study: 46/49 (93.9%) in probiotic group; 41/44 (93.2) controls. Withdrawals stated to be due to non-compliance or incomplete data.
Interventions	1. 3 live strains of *L. rhamnosus* 573L/1, 573L/2, 573L/3 (2.4 x 10^{10} CFU/day; Lakcid L, Biomed, Lublin, Poland) given orally in glucose 2. Identical placebo Onset of intervention delayed >72 hours in many participants.
Outcomes	1. Duration of diarrhoea (either no abnormal movement for the last 12 hours or the time to the second normal stool) 2. Weight gain after rehydration 3. Number of stools/day 4. Duration of IV fluids 5. Number diarrhoea >7 days 6. gGut colonization with probiotics No adverse events attributed to probiotic.
Notes	Study location: Poland (low child and adult mortality) Cause of diarrhoea: bloody diarrhoea included. Overall, 39/87 (45%) had rotavirus (22 probiotic and 17 control group), 5/87 (6%) had adenovirus, 9/87 (10%) had a bacterial pathogen and many children had norovirus infection. Nutritional status: no data presented. Hydration status: no severe dehydration. Mild/moderate dehydration in 34 (73.9%) in the probiotic and 31 (75.6%) in the control group. Source of funding: Wellcome Travel Award

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Computer-generated block randomization
Allocation concealment?	Low risk	Sequential assignment of randomization numbers
Blinding? All outcomes	Low risk	Identical placebo
Incomplete outcome data addressed? All outcomes	Low risk	Follow up > 90% in both groups

Teran 2009

Methods	Randomized, single blind controlled trial; 1 centre Duration: 7 months; August 2007 to February 2008
Participants	Inclusion criteria: inpatients; infants and children with a history of acute watery diarrhoea (defined as ≥3 stools of liquid consistency/day < 72 hours duration) positive for rotavirus and with moderate to severe dehydration. Exclusion criteria: severe malnutrition; systemic infections requiring antibiotic therapy; severe chronic disease; identification of a second pathogen in the stool; ingestion of antibiotics; probiotics or nitazoxanide 3 weeks before admission; recurrence of diarrhoea after discharge. Patients in whom a cause of diarrhoea other than rotavirus were withdrawn (probiotic group: 3 with adenovirus, 2 with *E. histolytica*; control group: 3 with *E. histolytica, 2 with Giardia*, 1 with *S. flexneri*). Number completing study: 25/25 (100%) probiotic group; 25/25 (100%) control group.
Interventions	Participants were allocated to one of three groups: a nitazoxanide, a probiotic and a control group that received rehydration solutions only. Data from the probiotic group and controls used for this review. 1. *L. acidophilus, L. rhamnosus, B.longum, S. boulardii (*total of *2*.5 x 10^9 organisms/day administered for an average of 4.2 days). Unclear if they were live or killed organisms. 2. Control (ORF only) Time when interventions started not described.
Outcomes	1. Duration of diarrhoea (time from admission until the presence of the first soft stool for at least 24 hours) 2. Stool number and consistency 3. Duration of fever 4. Vomiting 5. Duration of hospitalization No adverse events attributed to probiotic.
Notes	Study location: Bolivia (high child and high adult mortality) Cause of diarrhoea: all rotavirus diarrhoea. Nutritional status: severe malnutrition excluded; mild/moderate malnutrition in 5 (20%) in the probiotic and 15 (60%) in the control group. Hydration status: all had moderate to severe dehydration; no further data presented. Source of funding: the research was not sponsored by any pharmaceutical company

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Computerised admissions list
Allocation concealment?	Unclear risk	Not described
Blinding? All outcomes	High risk	Single blind; only parents/caretakers not aware of group allocation. No placebo.
Incomplete outcome data addressed?	Low risk	Follow up > 90% in both groups

Teran 2009 *(Continued)*

All outcomes

Táborská 1997

Methods	Randomized trial; 1 centre Duration: 1994-1995
Participants	Inclusion criteria: inpatients; infants and children Exclusion criteria: nosocomial rotaviral infection Number completing the study: 50/50 (100%) probiotic group; 50/50 (100%) control group.
Interventions	1. Live *L. acidophilus* ND (4 x 10^9 bacteria/day; duration not stated) 2. Standard treatment Time when interventions started:
Outcomes	1. Average number of stools/day 2. stool consistency at 5 days No adverse events attributed to the probiotic.
Notes	Study location: Czech Reublic (very low child and adult mortality) Cause of diarrhoea: nosocomial rotavirus diarrhoea excluded; 16 (32.0%) probiotic and 21 (42.0%) control group had viral diarrhoea. A total of 22 (44.0%) in the probiotic and 24 (48.0%) in the control group had bacterial diarrhoea. Nutritional status: no data presented. Hydration status: severe dehydration in 3 (6.0%) probiotic and 2 (4.0%) in the control group; all the rest had mild/moderate dehydration. No data presented that could be extracted for meta-analysis. Source of funding not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Not described
Allocation concealment?	Unclear risk	Not described
Blinding? All outcomes	High risk	No placebo
Incomplete outcome data addressed? All outcomes	Low risk	Follow up > 90% in both groups

Urganci 2001

Methods	Randomized controlled trial; 1 centre Duration: 1 year, June 200 to May 2001
Participants	Inclusion criteria: consecutive inpatients aged 2 to 29 months with acute, non-bacterial diarrhoea (definition not stated) lasting >48 hours able to receive oral medication. Exclusion criteria: concomitant illness, antimicrobial, antidiarrhoeal or other drugs affecting gut motility, severe electrolyte disturbance or dehydration. Number completing study: 50 cases reported in both arms; number withdrawn because of the deterioration in diarrhoea, concomitant disease requiring other drugs unclear.
Interventions	1. Lyophilized *Saccharomyces cerevisiae* Hansen CBS 5926 (250 mg daily in 5mL cold liquid) 2. 250 mg glucose daily in 5mL cold liquid Time of starting interventions and duration of administration not stated.
Outcomes	1. Stool frequency and consistency at 48 and 96 hours. No adverse events attributed to probiotic.
Notes	Study location: Turkey (low child and adult mortality) Cause of diarrhoea: non-bacterial diarrhoea Nutritional status: no data presented. Hydration status: none dehydrated. Lactose intolerance identified in 8% in the probiotic and 26% in the placebo group. Source of funding: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Not described
Allocation concealment?	Unclear risk	Not described
Blinding? All outcomes	Unclear risk	Unclear if placebo identical or not
Incomplete outcome data addressed? All outcomes	Unclear risk	Number of children withdrawn not stated

Villarruel 2007

Methods	Randomized controlled trial; 1 centre Duration: 1 year
Participants	Inclusion criteria: outpatients; infants and children aged 3 months to 2 years (urban population, middle social class); acute, mild to moderate diarrhoea.

Villarruel 2007 *(Continued)*

	Exclusion criteria: use of probiotic in the preceding 7 days; chronic intestinal disease; short bowel syndrome; malabsorption; ≥ grade 2 malnutrition; severe disease (including dehydration requiring hospitalization at the time of the consultation); known immunodeficiency; immunosuppressant treatment (oral or IV corticoids in the preceding 7 days); oral nystatin; oral or parenteral imidazoles; other systemic antifungal agents; macrolides; drugs that alter intestinal motility (antispasmodics, cisapride, antiemetics and antidiarrhoeal drugs) in the preceding 7 days. Number completing study: 6/50 (12.0%) excluded from the probiotic group and 6/50 (12.0%) from the control group for lack of compliance with protocol medication.
Interventions	1. *S. boulardii* (250-500 mg twice daily. according to age for 6 days) 2. Placebo ORF and antibiotics given when indicated.
Outcomes	1. Number of stools on day 4 and 7 2. Number participants with diarrhoea >7 days 3. Number of participants with liquid stools on days 4 and 7 4. Duration of diarrhoea (time to stool frequency < 3/day or stool consistency improved for at least 24 hours) 5. Effect when treatment was started within 48 hours after the onset of the diarrhoea No comment regarding adverse events.
Notes	Study location: Argentina (low child and adult mortality) Cause of diarrhoea: none had bloody diarrhoea; no other data presented. Nutritional status: ≥ grade 2 malnutrition excluded. Hydration status: dehydration requiring hospitalisation excluded; all had dehydration <7%. Stool frequency significantly lower in probiotic than placebo group on days 4 and 7. Source of funding: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Random computer-generated into blocks of 20
Allocation concealment?	Low risk	Paediatricians recruiting patients received batches of coded containers
Blinding? All outcomes	Low risk	Identical placebo
Incomplete outcome data addressed? All outcomes	High risk	Followup < 90% in both groups

Vivatvakin 2006

Methods	Randomized open study; 1 centre Duration: March 2003 to January 2004; 11 months

Vivatvakin 2006 *(Continued)*

Participants	Inclusion criteria: inpatients and outpatients; infants and children with watery diarrhoea (not defined) for < 5 days. Exclusion criteria: immunocompromised; suspected dysentery; diagnosed with persistent or chronic diarrhoea; chronic cardiac, pulmonary or haematological illness; undergoing antibiotic treatment in the last 2 weeks; severe dehydration or shock. 4/75 withdrawn (1 febrile seizure, 1 urinary tract infection, 2 with pneumonia). Two patients were withdrawn from each group. Number completing study: 36/38 (94.7%) in the probiotic group; 35/37 (94.6%) in the control group.
Interventions	1. *Live L. acidophilus, Bifidobacterium infantis* (Infloran; 6 x 10^9 CFU/day for 2 days) 2. Control group did not receive probiotic Timing of administration not stated
Outcomes	1. Duration of diarrhoea 2. Weight change/day 3. Number bowel motions on day 2 4. Vomiting 5. Duration of hospitalization Duration of diarrhoea reported for rotavirus diarrhoea. No adverse events attributed to probiotic.
Notes	Location: Thailand; low child and adult mortality Cause of diarrhoea: suspected dysentery excluded; overall, 34% had rotavirus and 12.1% Salmonella in stools. Nutritional status: no data presented. Hydration status: severe dehydration excluded; mild/moderate dehydration in 25 (69.4%) probiotic and 23 (65.7%) control group. Source of funding: AIS donation fund, Thai Red Cross Society

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Not described
Allocation concealment?	Unclear risk	Not described
Blinding? All outcomes	High risk	Open study; no placebo
Incomplete outcome data addressed? All outcomes	Low risk	Follow up > 90% in both groups

Wunderlich 1989

Methods	Randomized controlled trial; 10 centres

Wunderlich 1989 *(Continued)*

	Duration: not stated
Participants	Inclusion criteria: adults with acute diarrhoea (characteristics and duration not stated). Exclusion criteria: not stated. 3 participants from each group withdrawn on day 4 or later (causes for dropouts stated to be unrelated to medication); 4 participants assigned to the probiotic group and 5 assigned to the placebo group did not complete the study (reasons not stated). Number completing study (for persisting diarrhoea outcomes): 40/47 (85.1%) in the probiotic group and 38/46 (82.6%) in the placebo group.
Interventions	1. Live *Enterococcus* SF 68 (Bioflorin; 225 x 10^6 bacteria/day for 7 days) 2. Placebo Not stated when interventions started.
Outcomes	1. Number of cases cured by day of treatment (definition of cure not stated). No adverse events attributed to probiotic.
Notes	Study location: Switzerland and Lichtenstein (very low child and adult mortality). Cause of diarrhoea: no data presented. Nutritional status: no data presented. Hydration status: no data presented. Source of funding: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Not described
Allocation concealment?	Unclear risk	Not described
Blinding? All outcomes	Low risk	identical placebo
Incomplete outcome data addressed? All outcomes	High risk	Follow up <90% in both groups

CFU: colony-forming units
IV: intravenous
NCHS: National Centre for Health Statistics
ORF: oral rehydration fluid
RCT: randomized controlled trial
SD: standard deviation

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Agarwal 2001	No non-probiotic group. Participants included in Agarwal 2002 study

Study	Reason for exclusion
Agarwal 2002	No non-probiotic group
Alexander 1971	Not a randomized controlled trial; no non-probiotic group
Alvisi 1982	Intervention groups not treated equally; antibiotics given to the non-probiotic group
Barone 2000	No non-probiotic group
Beck 1961	Not a randomized controlled trial
Bellomo 1979	Cause of diarrhoea unclear. Additional treatment given to children with persisting diarrhoea
Bellomo 1980	No non-probiotic group. Study included children with diarrhoea secondary to antibiotic treatment or associated with respiratory infection
Bellomo 1982	Cause of diarrhoea unclear
Bin Li Xie 1995	Intervention groups not treated equally; antibacterials given to the non-probiotic group
Brewster 2004	Secondary publication to Ritchie 2010
Camarri 1981	Intervention groups not treated equally; antibiotics given to the non-probiotic group
Cetina Sauri 1990	Secondary publication to Cetina-Sauri 1994
Chandra 2002	Prevention of rotavirus diarrhoea study
Chicoine 1973	Unclear if acute diarrhoea
Costa-Ribeiro 2000a	Unclear whether a randomized controlled trial
Costa-Ribeiro 2000b	Prevention of diarrhoea study
Cui 2004	No non-probiotic group
de dios Pozo-O 1978	Assessment of probiotic in the prevention of traveller's diarrhoea
Eren 2010	No non-probiotic group
Fang 2009	Study of effect of probiotic on rotavirus shedding in stools; no diarrhoea outcomes reported
Fourrier 1968	No non-probiotic group
Girola 1995	Children with gastroenteritis and antibiotic-associated diarrhoea studied together
Gracheva 1996	No non-probiotic group
Henker 2007b	Secondary reference to Henker 2007a
Heydarian 2010	No non-probiotic group
Isolauri 1991	No non-probiotic group
Kaila 1992	No non-probiotic group

Study	Reason for exclusion
Kaila 1995	No non-probiotic group
Korviakova 2000	Not a randomized controlled trial; probiotic versus antibiotic
Le Leyur 2010	Intervention group received an adapted lactose-free formula fortified with *S. boulardii* and control group received a standard formula; difference in diarrhoea outcomes between groups cannot be attributed to the probiotic
Lei 2006	Probiotic used was not specified
Lin 2009	Prevention study
Magreiter 2006	No non-probiotic control group
Majamaa 1995	No non-probiotic group
Mazo 2006	Prevention study
Michielutti 1995	Not a randomized controlled trial
Mitra 1990	No non-probiotic group
Moraes 2001	No non-probiotic group
Niv 1963	Not a randomized controlled trial; some children with diarrhoea thought to be caused by antibiotic treatment included
Ortlieb 1974	Participants with acute diarrhoea and antibiotic-associated diarrhoea combined
Pearce 1974	Intervention groups not treated equally; calcium carbonate given as the placebo and may have reduced diarrhoea in the non-probiotic group
Pedone 1999	Prevention of diarrhoea study
Pedone 2000	Prevention of diarrhoea study
Pene 1966	No non-probiotic group; participants with diarrhoea of various causes (infectious, post-antibiotics) grouped together
Rafeey 2008b	Secondary publication to Rafeey 2008a
Rautanen 1998	No data presented for placebo group
Saint-Marc 1991	Not a randomized controlled trial; no non-probiotic group
Salazar-Lindo 2004	Mean duration of diarrhoea reported from responders only; children with ongoing diarrhoea excluded from analysis
Salazar-Lindo 2007	Active placebo
Satoh 1984	Not a randomized controlled trial; no non-probiotic group
Savas-Erdeve 2009	Study of amoebiasis-associated diarrhoea and not acute infectious diarrhoea
Schrezenmeir 2004	Antibiotic-associated diarrhoea included in the study

Study	Reason for exclusion
Singh 1987	No probiotic specified
Sudarmo 2003	Other than the probiotic, unclear whether two intervention groups were treated the same. Probiotic group received high-lactose formula containing *B. bifidum*. Unclear whether control group received high-lactose or normal formula
Szymanski 2005	Preliminary publication of Szymanski 2006
Tojo 1987	Unclear whether diarrhoea acute and whether a randomized controlled trial

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

Contreras 1983

Methods	
Participants	
Interventions	
Outcomes	
Notes	No details of study available

Salgado

Methods	
Participants	
Interventions	Heat-killed *L. acidophilus*, Lacteol strain
Outcomes	
Notes	No other details available

DATA AND ANALYSES

Comparison 1. Primary diarrhoea outcomes

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mean duration of diarrhoea	35	4555	Mean Difference (IV, Random, 95% CI)	-24.76 [-33.61, -15.91]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Diarrhoea lasting ≥4 days	29	2853	Risk Ratio (M-H, Random, 95% CI)	0.41 [0.32, 0.53]
3 Mean stool frequency on day 2	20	2751	Mean Difference (IV, Random, 95% CI)	-0.80 [-1.14, -0.45]

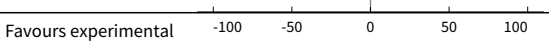
Analysis 1.1. Comparison 1 Primary diarrhoea outcomes, Outcome 1 Mean duration of diarrhoea.

Study or subgroup	Favours experimental N	Favours experimental Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Basu 2007	323	163.2 (50.4)	323	158.4 (55.2)		3.15%	4.8[-3.35,12.95]
Basu 2009	186	122.9 (27.8)	185	173.5 (30.5)		3.19%	-50.6[-56.54,-44.66]
Boudraa 2001	56	44.1 (33.7)	56	61.7 (35.6)		3.03%	-17.6[-30.44,-4.76]
Canani 2007	100	78.5 (35.5)	92	115.5 (23.5)		3.14%	-37[-45.46,-28.54]
Chen 2010	150	60.1 (31.7)	143	86.3 (37.6)		3.15%	-26.2[-34.18,-18.22]
Costa-Ribeiro 2003	61	38.3 (3.8)	63	39.1 (4.6)		3.23%	-0.8[-2.28,0.68]
Guandalini 2000	147	58.3 (27.6)	140	71.9 (35.8)		3.16%	-13.6[-21.02,-6.18]
Guarino 1997	52	76.8 (34.6)	48	141.6 (33.3)		3.01%	-64.8[-78.1,-51.5]
Henker 2007a	54	70.3 (23.5)	45	104.9 (9.1)		3.17%	-34.6[-41.42,-27.78]
Henker 2008	75	57.6 (19.5)	76	136.8 (18.8)		3.18%	-79.2[-85.31,-73.09]
Isolauri 1994	21	36 (16.8)	21	55.2 (19.2)		3.08%	-19.2[-30.11,-8.29]
Jasinski 2002	45	74.6 (47.8)	52	133.4 (53.8)		2.77%	-58.8[-79,-38.6]
Khanna 2005	42	58.8 (27.8)	48	51.8 (22.8)		3.09%	7[-3.6,17.6]
Kianifar 2009	32	81.6 (108.6)	30	108 (105.2)		1.49%	-26.4[-79.63,26.83]
Kowalska-Duplaga 2004	86	54.6 (30)	87	61.6 (34)		3.12%	-7[-16.55,2.55]
Kurugol 2005	100	112.8 (60)	100	132 (76.8)		2.81%	-19.2[-38.3,-0.1]
Lee 2001	50	74.4 (16.8)	50	86.4 (19.2)		3.17%	-12[-19.07,-4.93]
Lievin Le-Maol 2007	42	39.5 (10.5)	38	63.4 (14.9)		3.19%	-23.9[-29.6,-18.2]
Mao 2008	70	67.2 (40.2)	71	67.2 (40.5)		3.01%	0[-13.32,13.32]
Narayanappa 2008	40	104.4 (30.1)	40	130.8 (40.7)		2.94%	-26.4[-42.07,-10.73]
Oandasan 1999	47	42.9 (21.8)	47	94 (22.9)		3.13%	-51.1[-60.12,-42.08]
Pant 1996	14	45.6 (14.4)	12	79.2 (55.2)		2.27%	-33.6[-65.73,-1.47]
Ritchie 2010	33	52.4 (49.8)	31	51.2 (42.4)		2.67%	1.2[-21.42,23.82]
Rosenfeldt 2002a	30	81.5 (37.3)	39	101.1 (47.6)		2.77%	-19.6[-39.63,0.43]
Rosenfeldt 2002b	24	75.9 (39.7)	19	115.7 (85)		1.89%	-39.8[-81.19,1.59]
Sarkar 2005	115	90.4 (45)	115	94.2 (43.3)		3.07%	-3.8[-15.21,7.61]
Shornikova 1997a	59	64.8 (52.8)	64	91.2 (67.2)		2.72%	-26.4[-47.67,-5.13]
Shornikova 1997b	21	36 (26.4)	25	60 (36)		2.85%	-24[-42.07,-5.93]
Shornikova 1997c	19	40.8 (38.4)	21	69.6 (55.2)		2.39%	-28.8[-58.05,0.45]
Simakachorn 2000	37	43.4 (25.9)	36	57 (36.3)		2.98%	-13.6[-28.1,0.9]
Sugita 1994	16	91.2 (36)	11	127.2 (40.8)		2.36%	-36[-65.87,-6.13]
Szymanski 2006	46	83.6 (55.6)	41	96 (71.5)		2.48%	-12.4[-39.55,14.75]
Teran 2009	25	57.1 (25.4)	25	74.6 (26.6)		2.98%	-17.5[-31.92,-3.08]
Villarruel 2007	35	112.8 (46.6)	37	147.8 (76.8)		2.39%	-35[-64.16,-5.84]
Vivatvakin 2006	36	38.4 (16.8)	35	69.6 (40.8)		2.97%	-31.2[-45.79,-16.61]
Total ***	**2289**		**2266**			**100%**	**-24.76[-33.61,-15.91]**

Heterogeneity: Tau^2=630.48; Chi^2=1169.13, df=34(P<0.0001); I^2=97.09%

Favours experimental — Favours control

Study or subgroup	Favours experimental N	Mean(SD)	Control N	Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Test for overall effect: Z=5.48(P<0.0001)							



Analysis 1.2. Comparison 1 Primary diarrhoea outcomes, Outcome 2 Diarrhoea lasting ≥4 days.

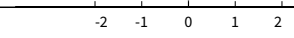
Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Bhatnagar 1998	17/47	17/49		5.08%	1.04[0.61,1.79]
Boudraa 2001	6/56	12/56		3.62%	0.5[0.2,1.24]
Bruno 1981	2/25	11/24		2.24%	0.17[0.04,0.71]
Bruno 1983	1/10	7/11		1.43%	0.16[0.02,1.06]
Buydens 1996	7/93	61/92		4.31%	0.11[0.05,0.23]
Carague-Orendain	0/35	4/35		0.72%	0.11[0.01,1.99]
Cetina-Sauri 1994	16/65	39/65		5.37%	0.41[0.26,0.66]
Chapoy 1985	1/19	4/19		1.23%	0.25[0.03,2.04]
Costa-Ribeiro 2003	31/61	45/63		6.03%	0.71[0.53,0.95]
D'Apuzzo 1982	3/21	7/18		2.72%	0.37[0.11,1.22]
Dubey 2008	12/113	67/111		5.02%	0.18[0.1,0.31]
Guandalini 2000	37/147	58/140		5.86%	0.61[0.43,0.85]
Henker 2007a	13/55	30/58		5.1%	0.46[0.27,0.78]
Henker 2008	30/75	46/76		5.9%	0.66[0.47,0.92]
Hernandez 1998	1/25	7/25		1.31%	0.14[0.02,1.08]
Htwe 2008	2/50	11/50		2.13%	0.18[0.04,0.78]
Jasinski 2002	12/45	43/52		5.25%	0.32[0.2,0.53]
Kowalska-Duplaga 1999	13/33	9/30		4.45%	1.31[0.66,2.62]
Kurugol 2005	8/100	30/100		4.3%	0.27[0.13,0.55]
Oandasan 1999	1/47	22/47		1.37%	0.05[0.01,0.32]
Ritchie 2010	8/33	7/31		3.69%	1.07[0.44,2.61]
Shornikova 1997b	0/21	6/25		0.74%	0.09[0.01,1.52]
Shornikova 1997c	3/19	6/21		2.61%	0.55[0.16,1.91]
Simakachorn 2000	1/37	9/36		1.32%	0.11[0.01,0.81]
Teran 2009	2/25	5/25		1.96%	0.4[0.09,1.87]
Urganci 2001	8/50	18/50		4.27%	0.44[0.21,0.93]
Villarruel 2007	22/44	30/44		5.8%	0.73[0.51,1.05]
Vivatvakin 2006	1/36	4/35		1.19%	0.24[0.03,2.07]
Wunderlich 1989	11/40	23/38		4.98%	0.45[0.26,0.8]
Total (95% CI)	**1427**	**1426**		**100%**	**0.41[0.32,0.53]**
Total events: 269 (Experimental), 638 (Control)					
Heterogeneity: Tau^2=0.27; Chi^2=97.09, df=28(P<0.0001); I^2=71.16%					
Test for overall effect: Z=6.72(P<0.0001)					

Analysis 1.3. Comparison 1 Primary diarrhoea outcomes, Outcome 3 Mean stool frequency on day 2.

Study or subgroup	Experimental N	Experimental Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Basu 2007	323	24.3 (4.8)	323	24.2 (5.3)		5.92%	0.1[-0.68,0.88]
Basu 2009	186	23.2 (6.1)	185	23.5 (6.1)		4.09%	-0.3[-1.54,0.94]
Buydens 1996	93	2 (1)	92	3.7 (1.7)		7.55%	-1.7[-2.1,-1.3]
Canani 2007	100	4 (1.5)	92	5 (2.2)		7%	-1[-1.54,-0.46]
Cetina-Sauri 1994	65	3.8 (2.3)	65	4.4 (2.7)		5.52%	-0.62[-1.49,0.25]
Chen 2010	150	2.7 (1.3)	143	4.4 (2.8)		7.14%	-1.65[-2.16,-1.14]
Khanna 2005	48	6.6 (2.6)	50	5 (3.5)		4.12%	1.64[0.41,2.87]
Lee 2001	50	1.9 (1.9)	50	3.7 (2.4)		5.61%	-1.8[-2.65,-0.95]
Narayanappa 2008	40	4 (2.7)	40	4.8 (2.8)		4.21%	-0.85[-2.05,0.35]
Ozkan 2007	16	3.1 (0.3)	11	4.3 (0.4)		7.98%	-1.21[-1.49,-0.93]
Pant 1996	14	3.5 (1.3)	12	5.2 (2.8)		2.75%	-1.7[-3.42,0.02]
Pashapour 2006	40	6.2 (2.8)	40	5.8 (2.1)		4.7%	0.45[-0.62,1.52]
Rafeey 2008a	40	4 (3.2)	40	4 (3.6)		3.31%	0[-1.49,1.49]
Raza 1995	19	5.8 (3.1)	17	7 (3.3)		2.08%	-1.2[-3.3,0.9]
Ritchie 2010	33	3.3 (2.5)	31	4.7 (2.6)		4.01%	-1.4[-2.66,-0.14]
Shornikova 1997b	20	2 (2.1)	25	3.8 (2.8)		3.48%	-1.8[-3.23,-0.37]
Shornikova 1997c	19	1 (2.3)	21	2.5 (2.3)		3.49%	-1.5[-2.93,-0.07]
Szymanski 2006	46	2.9 (2.8)	41	2.8 (2.9)		4.21%	0.1[-1.1,1.3]
Urganci 2001	50	3.8 (0.7)	50	4.2 (1)		7.79%	-0.46[-0.8,-0.12]
Vivatvakin 2006	36	2.2 (2)	35	2.6 (2.2)		5.06%	-0.4[-1.38,0.58]
Total * **	**1388**		**1363**			**100%**	**-0.8[-1.14,-0.45]**

Heterogeneity: Tau^2=0.38; Chi^2=77.06, df=19(P<0.0001); I^2=75.35%

Test for overall effect: Z=4.47(P<0.0001)



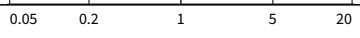
Favours experimental — Favours control

Comparison 2. Secondary diarrhoea outcomes

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Diarrhoea lasting ≥3 days	30	3022	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.56, 0.70]
2 Mean stool frequency on day 3	14	2367	Mean Difference (IV, Random, 95% CI)	-0.63 [-1.18, -0.07]

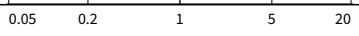
Analysis 2.1. Comparison 2 Secondary diarrhoea outcomes, Outcome 1 Diarrhoea lasting ≥3 days.

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Bhatnagar 1998	27/47	26/49		4.91%	1.08[0.76,1.55]
Boudraa 2001	9/56	23/56		2.12%	0.39[0.2,0.77]
Boulloche 1994	4/38	5/33		0.75%	0.69[0.2,2.38]
Bruno 1981	6/25	17/24		1.82%	0.34[0.16,0.71]
Bruno 1983	3/10	7/11		1.01%	0.47[0.17,1.34]



Favours experimental — Favours control

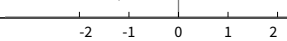
Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Buydens 1996	57/93	88/92		8.31%	0.64[0.54,0.76]
Caragues-Orendain	7/35	8/35		1.32%	0.88[0.36,2.15]
Cetina-Sauri 1994	41/65	58/65		7.6%	0.71[0.58,0.87]
Chen 2010	64/150	97/143		7.35%	0.63[0.51,0.78]
Costa-Ribeiro 2003	31/65	45/63		5.87%	0.67[0.5,0.9]
D'Apuzzo 1982	4/21	10/18		1.15%	0.34[0.13,0.91]
Guandalini 2000	78/147	90/140		7.76%	0.83[0.68,1]
Hafeez 2002	32/51	44/50		7.01%	0.71[0.56,0.9]
Henker 2007a	21/55	32/58		4.27%	0.69[0.46,1.04]
Henker 2008	34/75	49/76		5.86%	0.7[0.52,0.95]
Hernandez 1998	5/25	11/25		1.32%	0.45[0.18,1.12]
Htwe 2008	11/50	22/50		2.5%	0.5[0.27,0.92]
Isolauri 1994	2/21	9/21		0.58%	0.22[0.05,0.91]
Jasinski 2002	25/45	46/52		6.2%	0.63[0.48,0.83]
Khanna 2005	3/42	3/49		0.49%	1.17[0.25,5.48]
Kurugol 2005	20/100	55/100		4.02%	0.36[0.24,0.56]
Lievin Le-Maol 2007	6/42	18/38		1.57%	0.3[0.13,0.68]
Oandasan 1999	9/47	26/47		2.31%	0.35[0.18,0.66]
Ritchie 2010	13/33	12/31		2.47%	1.02[0.55,1.88]
Shornikova 1997b	6/21	11/25		1.58%	0.65[0.29,1.46]
Shornikova 1997c	3/19	11/21		0.9%	0.3[0.1,0.92]
Simakachorn 2000	9/37	11/36		1.79%	0.8[0.38,1.69]
Teran 2009	7/25	16/25		2.03%	0.44[0.22,0.88]
Vivatvakin 2006	2/36	11/35		0.56%	0.18[0.04,0.74]
Wunderlich 1989	19/40	27/38		4.59%	0.67[0.46,0.98]
Total (95% CI)	**1516**	**1506**		**100%**	**0.62[0.56,0.7]**
Total events: 558 (Experimental), 888 (Control)					
Heterogeneity: Tau²=0.03; Chi²=52.06, df=29(P=0.01); I²=44.29%					
Test for overall effect: Z=8.35(P<0.0001)					



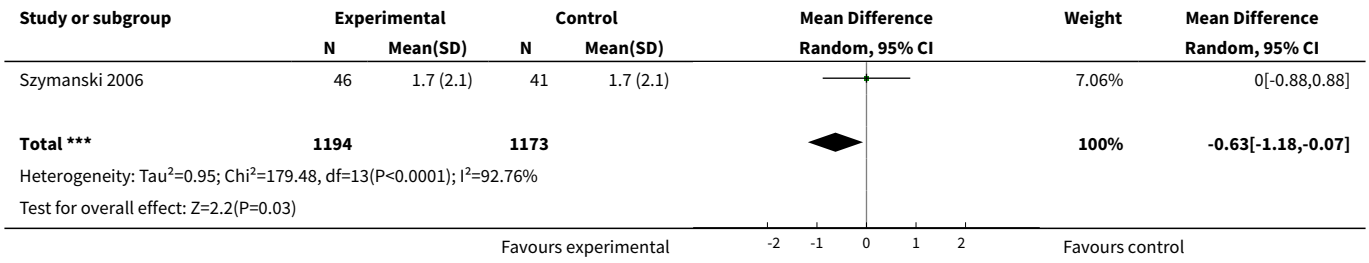
Favours experimental — Favours control

Analysis 2.2. Comparison 2 Secondary diarrhoea outcomes, Outcome 2 Mean stool frequency on day 3.

Study or subgroup	Experimental N	Experimental Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Basu 2007	323	18.4 (3.2)	323	17.3 (3)		8.07%	1.1[0.62,1.58]
Basu 2009	186	22.1 (6)	185	21.7 (5.4)		6.24%	0.4[-0.77,1.57]
Buydens 1996	93	1.1 (0.3)	92	2.5 (1.3)		8.4%	-1.4[-1.67,-1.13]
Canani 2007	100	4 (1.5)	92	4 (1.5)		8.18%	0[-0.42,0.42]
Cetina-Sauri 1994	65	2.5 (1.8)	65	3.6 (2.5)		7.42%	-1.1[-1.85,-0.35]
Chen 2010	150	1.5 (1.2)	143	3.2 (2.1)		8.22%	-1.75[-2.14,-1.36]
Hochter 1990	43	2.4 (2.1)	49	3 (2.8)		6.71%	-0.6[-1.6,0.4]
Narayanappa 2008	40	2 (1.6)	40	3.7 (3)		6.59%	-1.65[-2.7,-0.6]
Ozkan 2007	16	1.7 (0.2)	11	3.4 (0.4)		8.43%	-1.68[-1.93,-1.43]
Pashapour 2006	40	4.2 (1.7)	40	3.7 (1.3)		7.66%	0.5[-0.16,1.16]
Rafeey 2008a	40	1.4 (2.6)	40	2.3 (2.6)		6.32%	-0.9[-2.04,0.24]
Ritchie 2010	33	2.9 (2.5)	31	3.3 (3.7)		5.14%	-0.4[-1.96,1.16]
Shornikova 1997c	19	0.5 (1.9)	21	1.7 (2.6)		5.56%	-1.2[-2.6,0.2]



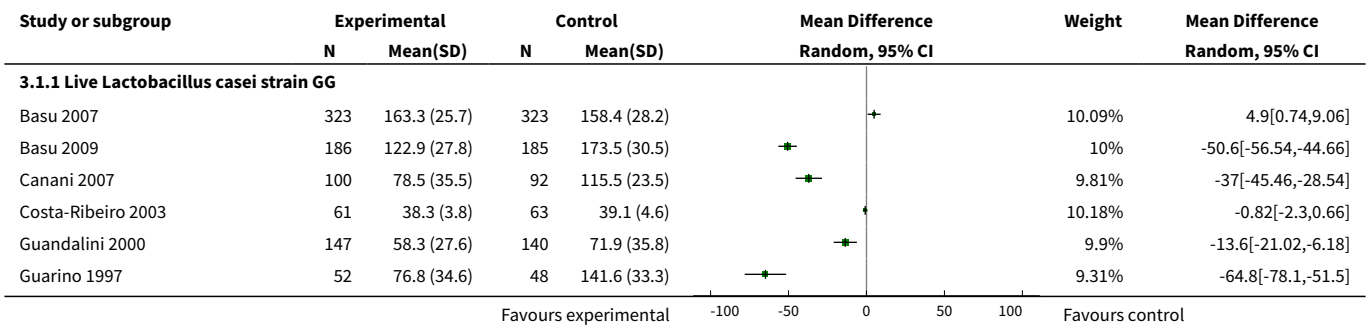
Favours experimental — Favours control



Comparison 3. Strain of probiotic organisms

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Mean duration of diarrhoea	11		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1 Live *Lactobacillus casei* strain GG	11	2072	Mean Difference (IV, Random, 95% CI)	-26.69 [-40.50, -12.88]
2 Diarrhoea lasting ≥4 days	14		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Live *Lactobacillus casei* strain GG	4	572	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.40, 0.87]
2.2 LIve *Enterococcus LAB* SF68	4	333	Risk Ratio (M-H, Random, 95% CI)	0.21 [0.08, 0.52]
2.3 *Saccharomyces boulardii*	6	606	Risk Ratio (M-H, Random, 95% CI)	0.37 [0.21, 0.65]
3 Mean stool frequency on day 2	6		Mean Difference (IV, Random, 95% CI)	Subtotals only
3.1 Live *Lactobacillus casei* strain GG	6	1335	Mean Difference (IV, Random, 95% CI)	-0.76 [-1.32, -0.20]

Analysis 3.1. Comparison 3 Strain of probiotic organisms, Outcome 1 Mean duration of diarrhoea.



Study or subgroup	Experimental N	Experimental Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Isolauri 1994	21	36 (16.8)	21	55.2 (19.2)		9.58%	-19.2[-30.11,-8.29]
Jasinski 2002	45	74.6 (47.8)	52	133.4 (53.8)		8.36%	-58.8[-79,-38.6]
Pant 1996	14	45.6 (14.4)	12	79.2 (55.2)		6.57%	-33.6[-65.73,-1.47]
Ritchie 2010	33	52.4 (49.8)	31	51.2 (42.4)		8%	1.2[-21.42,23.82]
Shornikova 1997a	59	64.8 (52.8)	64	91.2 (67.2)		8.2%	-26.4[-47.67,-5.13]
Subtotal * **	**1041**		**1031**			**100%**	**-26.69[-40.5,-12.88]**
Heterogeneity: Tau²=487.23; Chi²=457.51, df=10(P<0.0001); I²=97.81%							
Test for overall effect: Z=3.79(P=0)							

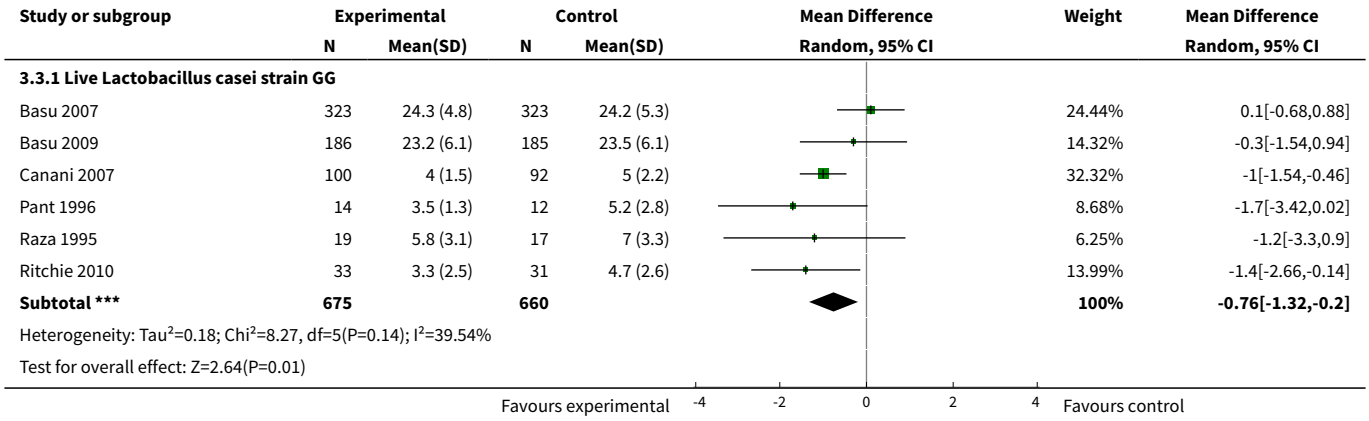
Favours experimental -100 -50 0 50 100 Favours control

Analysis 3.2. Comparison 3 Strain of probiotic organisms, Outcome 2 Diarrhoea lasting ≥4 days.

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
3.2.1 Live Lactobacillus casei strain GG					
Costa-Ribeiro 2003	31/61	45/63		32.74%	0.71[0.53,0.95]
Guandalini 2000	37/147	58/140		30.61%	0.61[0.43,0.85]
Jasinski 2002	12/45	43/52		23.92%	0.32[0.2,0.53]
Ritchie 2010	8/33	7/31		12.72%	1.07[0.44,2.61]
Subtotal (95% CI)	**286**	**286**		**100%**	**0.59[0.4,0.87]**
Total events: 88 (Experimental), 153 (Control)					
Heterogeneity: Tau²=0.09; Chi²=9.01, df=3(P=0.03); I²=66.72%					
Test for overall effect: Z=2.69(P=0.01)					
3.2.2 LIve Enterococcus LAB SF68					
Bruno 1981	2/25	11/24		20.43%	0.17[0.04,0.71]
Bruno 1983	1/10	7/11		14.46%	0.16[0.02,1.06]
Buydens 1996	7/93	61/92		31.24%	0.11[0.05,0.23]
Wunderlich 1989	11/40	23/38		33.87%	0.45[0.26,0.8]
Subtotal (95% CI)	**168**	**165**		**100%**	**0.21[0.08,0.52]**
Total events: 21 (Experimental), 102 (Control)					
Heterogeneity: Tau²=0.56; Chi²=10.47, df=3(P=0.01); I²=71.35%					
Test for overall effect: Z=3.36(P=0)					
3.2.3 Saccharomyces boulardii					
Cetina-Sauri 1994	16/65	39/65		27.09%	0.41[0.26,0.66]
Chapoy 1985	1/19	4/19		5.8%	0.25[0.03,2.04]
Hernandez 1998	1/25	7/25		6.17%	0.14[0.02,1.08]
Htwe 2008	2/50	11/50		10.17%	0.18[0.04,0.78]
Kurugol 2005	8/100	30/100		21.28%	0.27[0.13,0.55]
Villarruel 2007	22/44	30/44		29.48%	0.73[0.51,1.05]
Subtotal (95% CI)	**303**	**303**		**100%**	**0.37[0.21,0.65]**
Total events: 50 (Experimental), 121 (Control)					
Heterogeneity: Tau²=0.24; Chi²=13.76, df=5(P=0.02); I²=63.67%					
Test for overall effect: Z=3.49(P=0)					

Favours experimental 0.001 0.1 1 10 1000 Favours control

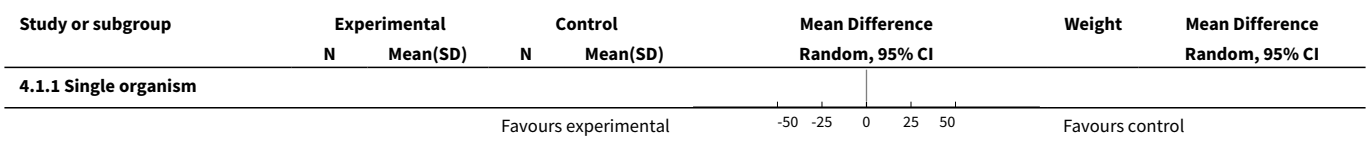
Analysis 3.3. Comparison 3 Strain of probiotic organisms, Outcome 3 Mean stool frequency on day 2.



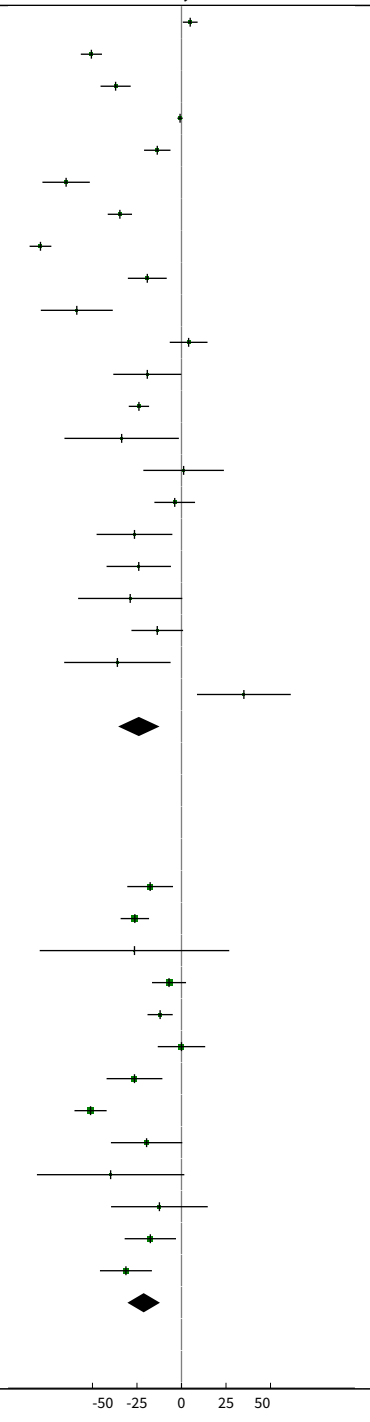
Comparison 4. Single organism versus combinations

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Mean duration of diarrhoea	35		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1 Single organism	22	3196	Mean Difference (IV, Random, 95% CI)	-23.95 [-35.57, -12.32]
1.2 Two or more organisms	13	1375	Mean Difference (IV, Random, 95% CI)	-21.23 [-30.38, -12.09]
2 Diarrhoea lasting ≥4 days	29		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Single organism	22	2136	Risk Ratio (M-H, Random, 95% CI)	0.45 [0.33, 0.60]
2.2 Two or more organisms	7	717	Risk Ratio (M-H, Random, 95% CI)	0.29 [0.12, 0.73]
3 Mean stool frequency on day 2	20		Mean Difference (IV, Random, 95% CI)	Subtotals only
3.1 Single organism	14	2040	Mean Difference (IV, Random, 95% CI)	-0.79 [-1.21, -0.38]
3.2 Two or more organisms	6	711	Mean Difference (IV, Random, 95% CI)	-0.77 [-1.53, 0.00]

Analysis 4.1. Comparison 4 Single organism versus combinations, Outcome 1 Mean duration of diarrhoea.

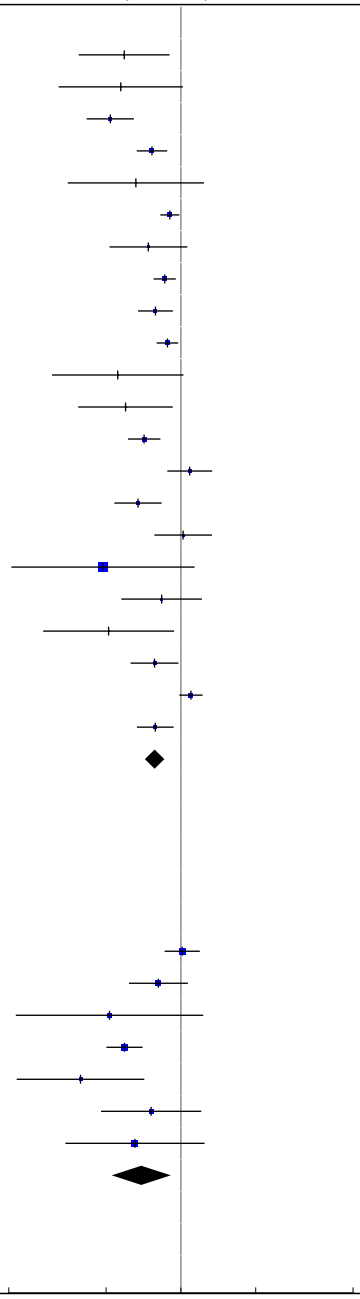


Study or subgroup	Experimental N	Experimental Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Basu 2007	323	163.3 (25.7)	323	158.4 (28.2)		4.97%	4.9[0.74,9.06]
Basu 2009	186	122.9 (27.8)	185	173.5 (30.5)		4.94%	-50.6[-56.54,-44.66]
Canani 2007	100	78.5 (35.5)	92	115.5 (23.5)		4.87%	-37[-45.46,-28.54]
Costa-Ribeiro 2003	61	38.3 (3.8)	63	39.1 (4.6)		5%	-0.8[-2.28,0.68]
Guandalini 2000	147	58.3 (27.6)	140	71.9 (35.8)		4.9%	-13.6[-21.02,-6.18]
Guarino 1997	52	76.8 (34.6)	48	141.6 (33.3)		4.69%	-64.8[-78.1,-51.5]
Henker 2007a	54	70.3 (23.5)	45	104.9 (9.1)		4.92%	-34.6[-41.42,-27.78]
Henker 2008	75	57.6 (19.5)	76	136.8 (18.8)		4.93%	-79.2[-85.31,-73.09]
Isolauri 1994	21	36 (16.8)	21	55.2 (19.2)		4.79%	-19.2[-30.11,-8.29]
Jasinski 2002	45	74.6 (47.8)	52	133.4 (53.8)		4.34%	-58.8[-79,-38.6]
Khanna 2005	42	55.8 (27.8)	48	51.8 (22.8)		4.8%	4.01[-6.59,14.61]
Kurugol 2005	100	112.8 (60)	100	132 (76.8)		4.41%	-19.2[-38.3,-0.1]
Lievin Le-Maol 2007	42	39.5 (10.5)	38	63.4 (14.9)		4.94%	-23.9[-29.6,-18.2]
Pant 1996	14	45.6 (14.4)	12	79.2 (55.2)		3.62%	-33.6[-65.73,-1.47]
Ritchie 2010	33	52.4 (49.8)	31	51.2 (42.4)		4.2%	1.2[-21.42,23.82]
Sarkar 2005	115	90.4 (45)	115	94.2 (43.3)		4.77%	-3.8[-15.21,7.61]
Shornikova 1997a	59	64.8 (52.8)	64	91.2 (67.2)		4.28%	-26.4[-47.67,-5.13]
Shornikova 1997b	21	36 (26.4)	25	60 (36)		4.46%	-24[-42.07,-5.93]
Shornikova 1997c	19	40.8 (38.4)	21	69.6 (55.2)		3.8%	-28.8[-58.05,0.45]
Simakachorn 2000	37	43.4 (25.9)	36	57 (36.3)		4.64%	-13.6[-28.1,0.9]
Sugita 1994	16	91.2 (36)	11	127.2 (40.8)		3.76%	-36[-65.87,-6.13]
Villarruel 2007	44	147.8 (76)	44	112.8 (46.6)		3.98%	35.04[8.7,61.38]
Subtotal ***	**1606**		**1590**			**100%**	**-23.95[-35.57,-12.32]**
Heterogeneity: Tau²=703.62; Chi²=1106, df=21(P<0.0001); I²=98.1%							
Test for overall effect: Z=4.04(P<0.0001)							
4.1.2 Two or more organisms							
Boudraa 2001	56	44.1 (33.7)	56	61.7 (35.6)		8.83%	-17.6[-30.44,-4.76]
Chen 2010	150	60.1 (31.7)	143	86.3 (37.6)		9.89%	-26.2[-34.18,-18.22]
Kianifar 2009	32	81.6 (108.6)	30	108 (105.2)		2.31%	-26.4[-79.63,26.83]
Kowalska-Duplaga 2004	86	54.6 (30)	87	61.6 (34)		9.58%	-7[-16.55,2.55]
Lee 2001	50	74.4 (16.8)	50	86.4 (19.2)		10.05%	-12[-19.07,-4.93]
Mao 2008	70	67.2 (40.2)	71	67.2 (40.5)		8.72%	0[-13.32,13.32]
Narayanappa 2008	40	104.4 (30.1)	40	130.8 (40.7)		8.14%	-26.4[-42.07,-10.73]
Oandasan 1999	47	42.9 (21.8)	47	94 (22.9)		9.69%	-51.07[-60.09,-42.05]
Rosenfeldt 2002a	30	81.5 (37.3)	39	101.1 (47.6)		7.07%	-19.6[-39.63,0.43]
Rosenfeldt 2002b	24	75.9 (39.7)	19	115.7 (85)		3.35%	-39.8[-81.19,1.59]
Szymanski 2006	46	83.6 (55.6)	41	96 (71.5)		5.51%	-12.4[-39.55,14.75]
Teran 2009	25	57.1 (25.4)	25	74.6 (26.6)		8.45%	-17.5[-31.92,-3.08]
Vivatvakin 2006	36	38.4 (16.8)	35	69.6 (40.8)		8.41%	-31.2[-45.79,-16.61]
Subtotal ***	**692**		**683**			**100%**	**-21.23[-30.38,-12.09]**
Heterogeneity: Tau²=203.65; Chi²=72.35, df=12(P<0.0001); I²=83.41%							
Test for overall effect: Z=4.55(P<0.0001)							



Analysis 4.2. Comparison 4 Single organism versus combinations, Outcome 2 Diarrhoea lasting ≥4 days.

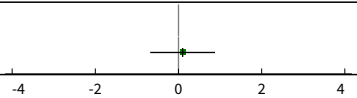
Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
4.2.1 Single organism					
Bruno 1981	2/25	11/24		2.88%	0.17[0.04,0.71]
Bruno 1983	1/10	7/11		1.86%	0.16[0.02,1.06]
Buydens 1996	7/93	61/92		5.33%	0.11[0.05,0.23]
Cetina-Sauri 1994	16/65	39/65		6.53%	0.41[0.26,0.66]
Chapoy 1985	1/19	4/19		1.61%	0.25[0.03,2.04]
Costa-Ribeiro 2003	31/61	45/63		7.25%	0.71[0.53,0.95]
D'Apuzzo 1982	3/21	7/18		3.46%	0.37[0.11,1.22]
Guandalini 2000	37/147	58/140		7.07%	0.61[0.43,0.85]
Henker 2007a	13/55	30/58		6.23%	0.46[0.27,0.78]
Henker 2008	30/75	46/76		7.11%	0.66[0.47,0.92]
Hernandez 1998	1/25	7/25		1.71%	0.14[0.02,1.08]
Htwe 2008	2/50	11/50		2.74%	0.18[0.04,0.78]
Jasinski 2002	12/45	43/52		6.39%	0.32[0.2,0.53]
Kowalska-Duplaga 1999	13/33	9/30		5.5%	1.31[0.66,2.62]
Kurugol 2005	8/100	30/100		5.32%	0.27[0.13,0.55]
Ritchie 2010	8/33	7/31		4.61%	1.07[0.44,2.61]
Shornikova 1997b	0/21	6/25		0.98%	0.09[0.01,1.52]
Shornikova 1997c	3/19	6/21		3.33%	0.55[0.16,1.91]
Simakachorn 2000	1/37	9/36		1.71%	0.11[0.01,0.81]
Urganci 2001	8/50	18/50		5.29%	0.44[0.21,0.93]
Villarruel 2007	30/44	22/44		7.01%	1.36[0.95,1.95]
Wunderlich 1989	11/40	23/38		6.09%	0.45[0.26,0.8]
Subtotal (95% CI)	**1068**	**1068**		**100%**	**0.45[0.33,0.6]**
Total events: 238 (Experimental), 499 (Control)					
Heterogeneity: Tau^2=0.3; Chi^2=87.58, df=21(P<0.0001); I^2=76.02%					
Test for overall effect: Z=5.31(P<0.0001)					
4.2.2 Two or more organisms					
Bhatnagar 1998	17/47	17/49		20.45%	1.04[0.61,1.79]
Boudraa 2001	6/56	12/56		18.07%	0.5[0.2,1.24]
Caragüe-Orendain	0/35	4/35		6.85%	0.11[0.01,1.99]
Dubey 2008	12/113	67/111		20.36%	0.18[0.1,0.31]
Oandasan 1999	1/47	22/47		10.87%	0.05[0.01,0.32]
Teran 2009	2/25	5/25		13.48%	0.4[0.09,1.87]
Vivatvakin 2006	1/36	4/35		9.92%	0.24[0.03,2.07]
Subtotal (95% CI)	**359**	**358**		**100%**	**0.29[0.12,0.73]**
Total events: 39 (Experimental), 131 (Control)					
Heterogeneity: Tau^2=0.98; Chi^2=29.27, df=6(P<0.0001); I^2=79.5%					
Test for overall effect: Z=2.63(P=0.01)					



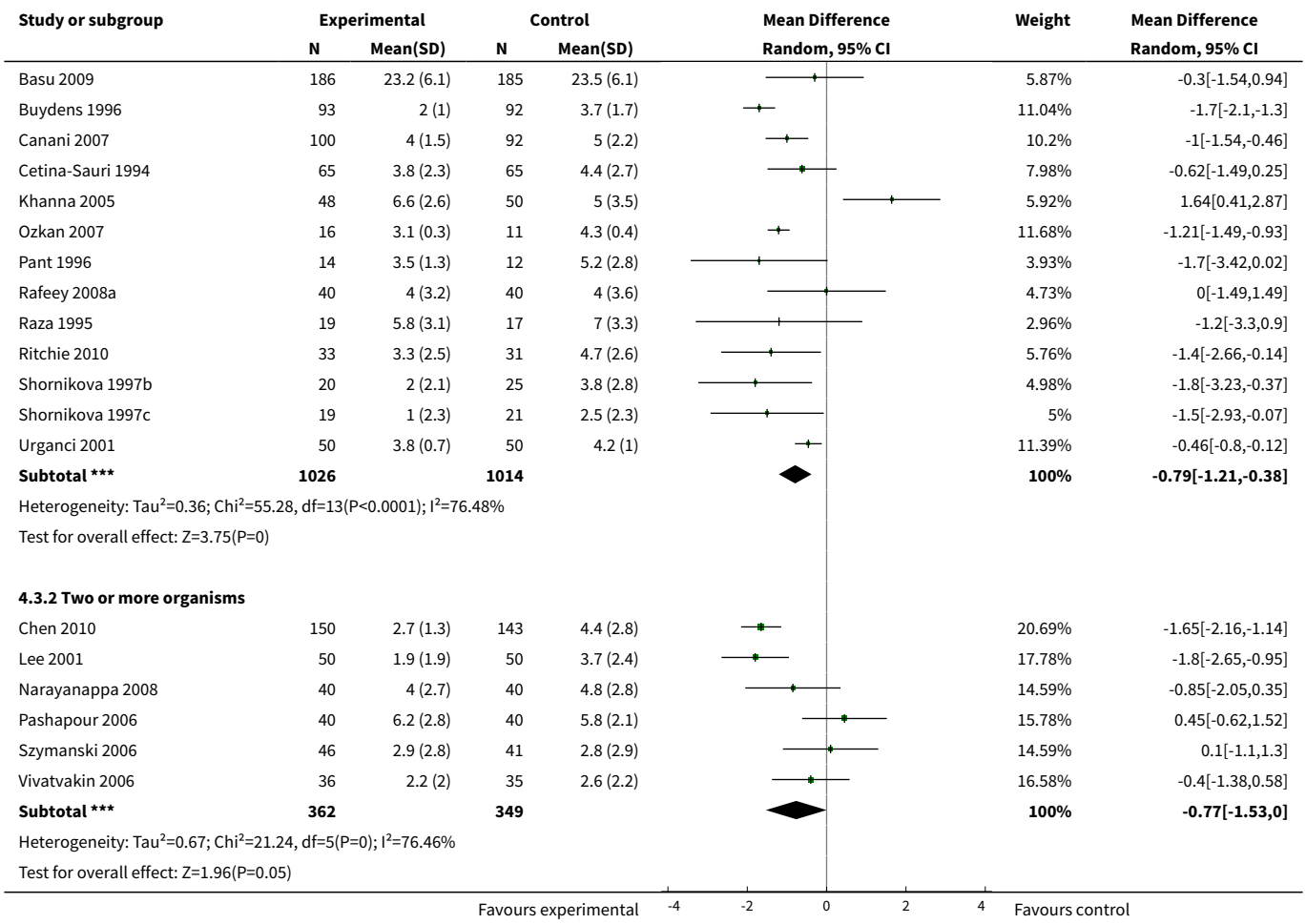
Favours experimental — Favours control

Analysis 4.3. Comparison 4 Single organism versus combinations, Outcome 3 Mean stool frequency on day 2.

Study or subgroup	Experimental N	Experimental Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
4.3.1 Single organism							
Basu 2007	323	24.3 (4.8)	323	24.2 (5.3)		8.57%	0.1[-0.68,0.88]



Favours experimental — Favours control

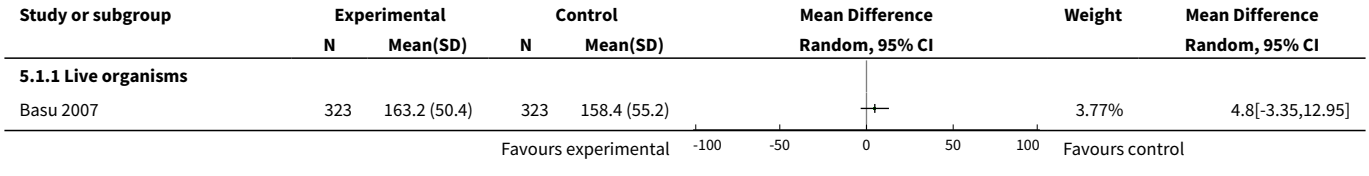


Study or subgroup	Experimental N	Experimental Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Basu 2009	186	23.2 (6.1)	185	23.5 (6.1)		5.87%	-0.3[-1.54,0.94]
Buydens 1996	93	2 (1)	92	3.7 (1.7)		11.04%	-1.7[-2.1,-1.3]
Canani 2007	100	4 (1.5)	92	5 (2.2)		10.2%	-1[-1.54,-0.46]
Cetina-Sauri 1994	65	3.8 (2.3)	65	4.4 (2.7)		7.98%	-0.62[-1.49,0.25]
Khanna 2005	48	6.6 (2.6)	50	5 (3.5)		5.92%	1.64[0.41,2.87]
Ozkan 2007	16	3.1 (0.3)	11	4.3 (0.4)		11.68%	-1.21[-1.49,-0.93]
Pant 1996	14	3.5 (1.3)	12	5.2 (2.8)		3.93%	-1.7[-3.42,0.02]
Rafeey 2008a	40	4 (3.2)	40	4 (3.6)		4.73%	0[-1.49,1.49]
Raza 1995	19	5.8 (3.1)	17	7 (3.3)		2.96%	-1.2[-3.3,0.9]
Ritchie 2010	33	3.3 (2.5)	31	4.7 (2.6)		5.76%	-1.4[-2.66,-0.14]
Shornikova 1997b	20	2 (2.1)	25	3.8 (2.8)		4.98%	-1.8[-3.23,-0.37]
Shornikova 1997c	19	1 (2.3)	21	2.5 (2.3)		5%	-1.5[-2.93,-0.07]
Urganci 2001	50	3.8 (0.7)	50	4.2 (1)		11.39%	-0.46[-0.8,-0.12]
Subtotal ***	**1026**		**1014**			**100%**	**-0.79[-1.21,-0.38]**
Heterogeneity: Tau^2=0.36; Chi^2=55.28, df=13(P<0.0001); I^2=76.48%							
Test for overall effect: Z=3.75(P=0)							
4.3.2 Two or more organisms							
Chen 2010	150	2.7 (1.3)	143	4.4 (2.8)		20.69%	-1.65[-2.16,-1.14]
Lee 2001	50	1.9 (1.9)	50	3.7 (2.4)		17.78%	-1.8[-2.65,-0.95]
Narayanappa 2008	40	4 (2.7)	40	4.8 (2.8)		14.59%	-0.85[-2.05,0.35]
Pashapour 2006	40	6.2 (2.8)	40	5.8 (2.1)		15.78%	0.45[-0.62,1.52]
Szymanski 2006	46	2.9 (2.8)	41	2.8 (2.9)		14.59%	0.1[-1.1,1.3]
Vivatvakin 2006	36	2.2 (2)	35	2.6 (2.2)		16.58%	-0.4[-1.38,0.58]
Subtotal ***	**362**		**349**			**100%**	**-0.77[-1.53,0]**
Heterogeneity: Tau^2=0.67; Chi^2=21.24, df=5(P=0); I^2=76.46%							
Test for overall effect: Z=1.96(P=0.05)							

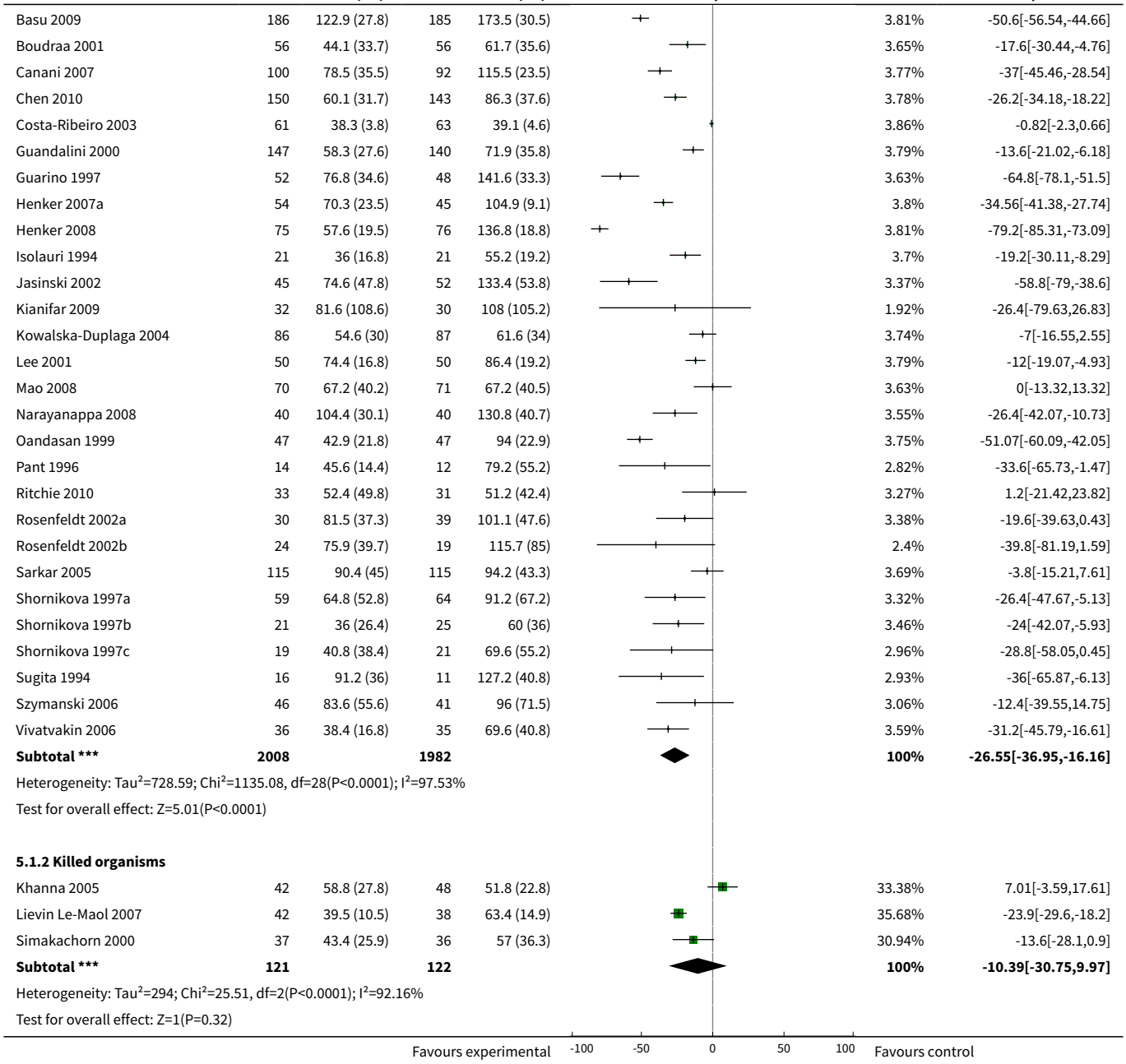
Comparison 5. Live versus killed organisms

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mean duration of diarrhoea	32		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1 Live organisms	29	3990	Mean Difference (IV, Random, 95% CI)	-26.55 [-36.95, -16.16]
1.2 Killed organisms	3	243	Mean Difference (IV, Random, 95% CI)	-10.39 [-30.75, 9.97]

Analysis 5.1. Comparison 5 Live versus killed organisms, Outcome 1 Mean duration of diarrhoea.



Study or subgroup	Experimental N	Experimental Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
5.1.1 Live organisms							
Basu 2007	323	163.2 (50.4)	323	158.4 (55.2)		3.77%	4.8[-3.35,12.95]



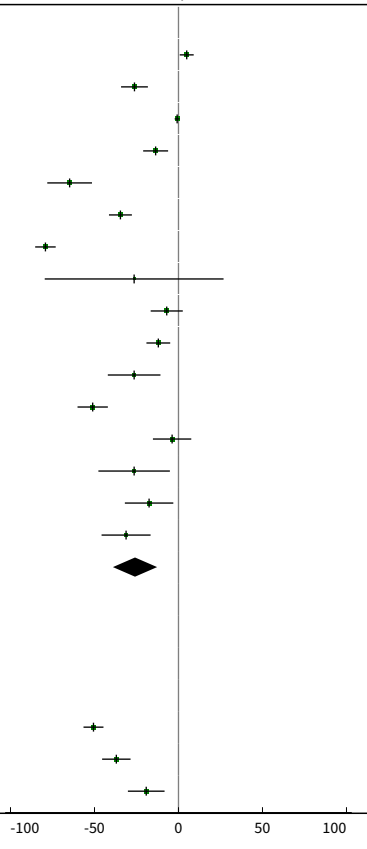
Comparison 6. Dose of probiotic; live organisms

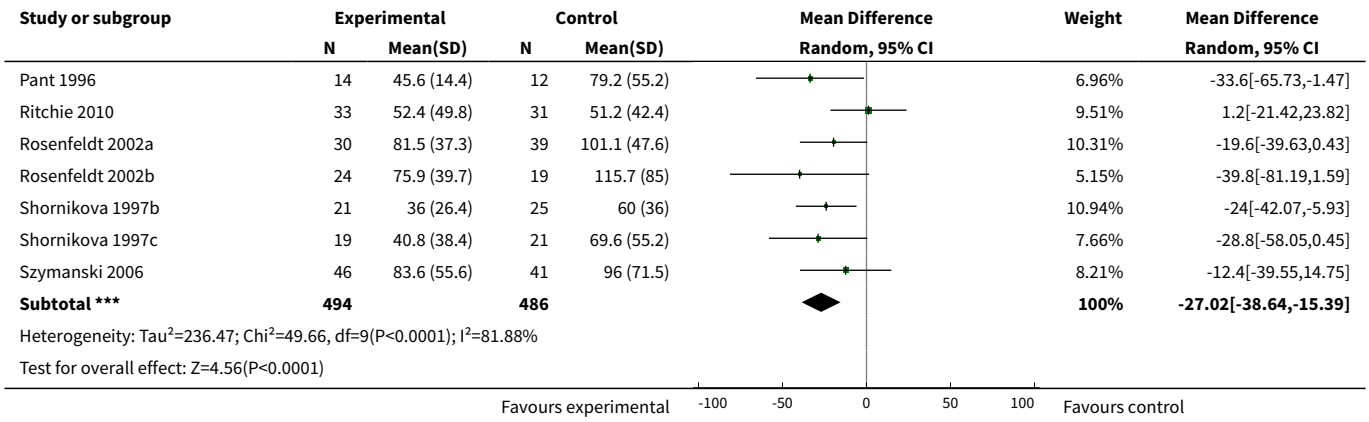
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mean duration of diarrhoea	26		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1 Low dose (≤10,000 million organisms/day)	16	2683	Mean Difference (IV, Random, 95% CI)	-25.88 [-39.04, -12.72]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.2 High dose (>10,000 million organisms/day)	10	980	Mean Difference (IV, Random, 95% CI)	-27.02 [-38.64, -15.39]
2 Diarrhoea lasting ≥4 days	17		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Low dose (≤10,000 million organisms/day)	13	1325	Risk Ratio (M-H, Random, 95% CI)	0.43 [0.29, 0.62]
2.2 High dose (>10,000 million organisms/day)	4	374	Risk Ratio (M-H, Random, 95% CI)	0.37 [0.12, 1.17]
3 Mean stool frequency on day 2	15		Mean Difference (IV, Random, 95% CI)	Subtotals only
3.1 Low dose (≤10,000 million organisms/day)	7	1455	Mean Difference (IV, Random, 95% CI)	-1.01 [-1.61, -0.41]
3.2 High dose (>10,000 million organisms/day)	8	861	Mean Difference (IV, Random, 95% CI)	-0.99 [-1.39, -0.60]

Analysis 6.1. Comparison 6 Dose of probiotic; live organisms, Outcome 1 Mean duration of diarrhoea.

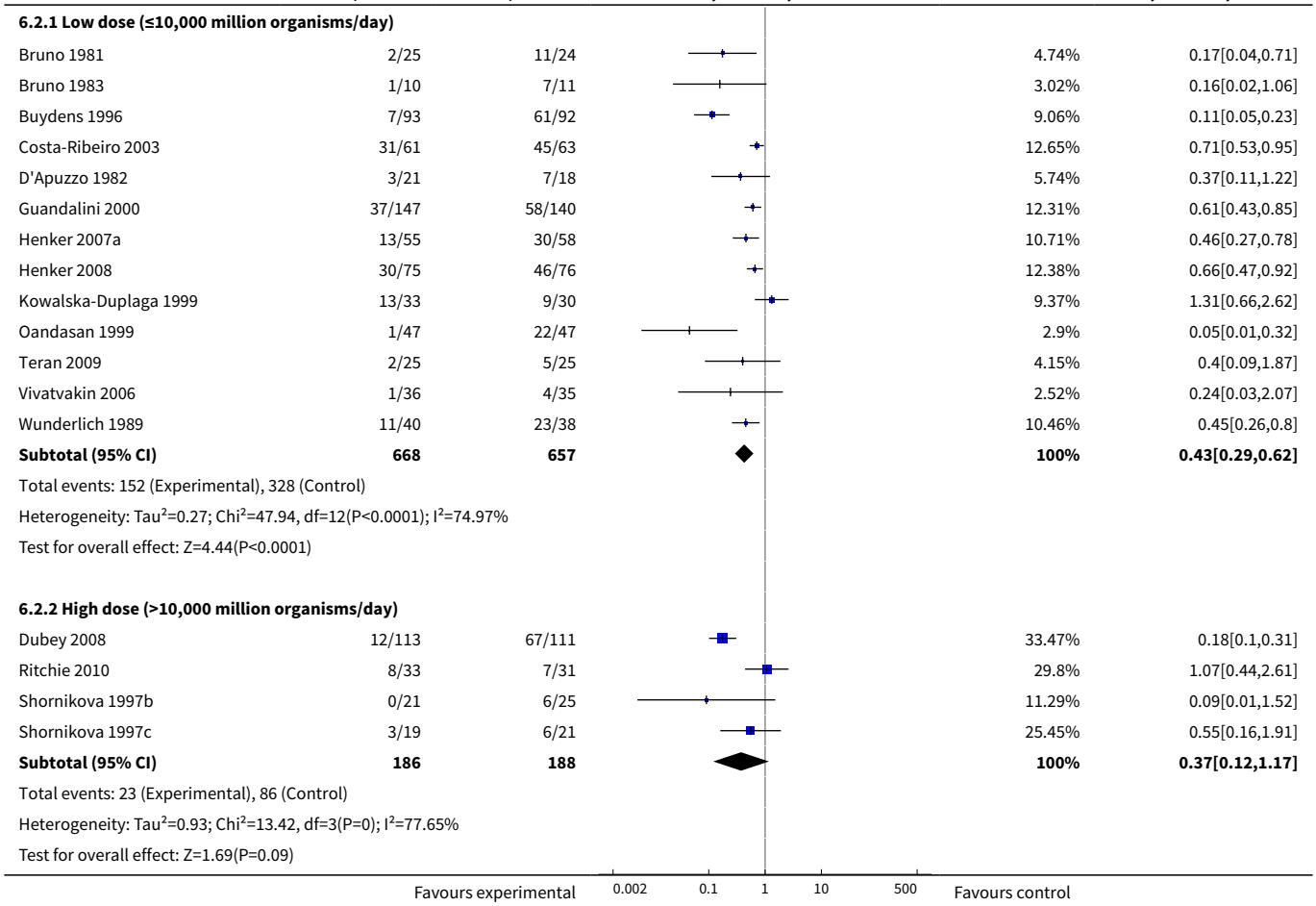
Study or subgroup	Experimental N	Experimental Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
6.1.1 Low dose (≤10,000 million organisms/day)							
Basu 2007	323	163.3 (25.7)	323	158.4 (28.2)		6.71%	4.9[0.74,9.06]
Chen 2010	150	60.1 (31.7)	143	86.3 (37.6)		6.59%	-26.2[-34.18,-18.22]
Costa-Ribeiro 2003	61	38.3 (3.8)	63	39.1 (4.6)		6.75%	-0.8[-2.28,0.68]
Guandalini 2000	147	58.3 (27.6)	140	71.9 (35.8)		6.61%	-13.6[-21.02,-6.18]
Guarino 1997	52	76.8 (34.6)	48	141.6 (33.3)		6.32%	-64.8[-78.1,-51.5]
Henker 2007a	54	70.3 (23.5)	45	104.9 (9.1)		6.63%	-34.56[-41.38,-27.74]
Henker 2008	75	57.6 (19.5)	76	136.8 (18.8)		6.66%	-79.2[-85.31,-73.09]
Kianifar 2009	32	81.6 (108.6)	30	108 (105.2)		3.21%	-26.4[-79.63,26.83]
Kowalska-Duplaga 2004	86	54.6 (30)	87	61.6 (34)		6.52%	-7[-16.55,2.55]
Lee 2001	50	74.4 (16.8)	50	86.4 (19.2)		6.63%	-12[-19.07,-4.93]
Narayanappa 2008	40	104.4 (30.1)	40	130.8 (40.7)		6.16%	-26.4[-42.07,-10.73]
Oandasan 1999	47	42.9 (21.8)	47	94 (22.9)		6.55%	-51.07[-60.09,-42.05]
Sarkar 2005	115	90.4 (45)	115	94.2 (43.3)		6.43%	-3.8[-15.21,7.61]
Shornikova 1997a	59	64.8 (52.8)	64	91.2 (67.2)		5.74%	-26.4[-47.67,-5.13]
Teran 2009	25	57.1 (25.4)	25	74.6 (26.6)		6.25%	-17.5[-31.92,-3.08]
Vivatvakin 2006	36	38.4 (16.8)	35	69.6 (40.8)		6.24%	-31.2[-45.79,-16.61]
Subtotal * **	**1352**		**1331**			**100%**	**-25.88[-39.04,-12.72]**
Heterogeneity: Tau²=667.51; Chi²=910.14, df=15(P<0.0001); I²=98.35%							
Test for overall effect: Z=3.85(P=0)							
6.1.2 High dose (>10,000 million organisms/day)							
Basu 2009	186	122.9 (27.8)	185	173.5 (30.5)		14.32%	-50.6[-56.54,-44.66]
Canani 2007	100	78.5 (35.5)	92	115.5 (23.5)		13.79%	-37[-45.46,-28.54]
Isolauri 1994	21	36 (16.8)	21	55.2 (19.2)		13.15%	-19.2[-30.11,-8.29]





Study or subgroup	Experimental N	Experimental Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Pant 1996	14	45.6 (14.4)	12	79.2 (55.2)		6.96%	-33.6[-65.73,-1.47]
Ritchie 2010	33	52.4 (49.8)	31	51.2 (42.4)		9.51%	1.2[-21.42,23.82]
Rosenfeldt 2002a	30	81.5 (37.3)	39	101.1 (47.6)		10.31%	-19.6[-39.63,0.43]
Rosenfeldt 2002b	24	75.9 (39.7)	19	115.7 (85)		5.15%	-39.8[-81.19,1.59]
Shornikova 1997b	21	36 (26.4)	25	60 (36)		10.94%	-24[-42.07,-5.93]
Shornikova 1997c	19	40.8 (38.4)	21	69.6 (55.2)		7.66%	-28.8[-58.05,0.45]
Szymanski 2006	46	83.6 (55.6)	41	96 (71.5)		8.21%	-12.4[-39.55,14.75]
Subtotal * **	**494**		**486**			**100%**	**-27.02[-38.64,-15.39]**
Heterogeneity: Tau²=236.47; Chi²=49.66, df=9(P<0.0001); I²=81.88%							
Test for overall effect: Z=4.56(P<0.0001)							

Analysis 6.2. Comparison 6 Dose of probiotic; live organisms, Outcome 2 Diarrhoea lasting ≥4 days.



Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
6.2.1 Low dose (≤10,000 million organisms/day)					
Bruno 1981	2/25	11/24		4.74%	0.17[0.04,0.71]
Bruno 1983	1/10	7/11		3.02%	0.16[0.02,1.06]
Buydens 1996	7/93	61/92		9.06%	0.11[0.05,0.23]
Costa-Ribeiro 2003	31/61	45/63		12.65%	0.71[0.53,0.95]
D'Apuzzo 1982	3/21	7/18		5.74%	0.37[0.11,1.22]
Guandalini 2000	37/147	58/140		12.31%	0.61[0.43,0.85]
Henker 2007a	13/55	30/58		10.71%	0.46[0.27,0.78]
Henker 2008	30/75	46/76		12.38%	0.66[0.47,0.92]
Kowalska-Duplaga 1999	13/33	9/30		9.37%	1.31[0.66,2.62]
Oandasan 1999	1/47	22/47		2.9%	0.05[0.01,0.32]
Teran 2009	2/25	5/25		4.15%	0.4[0.09,1.87]
Vivatvakin 2006	1/36	4/35		2.52%	0.24[0.03,2.07]
Wunderlich 1989	11/40	23/38		10.46%	0.45[0.26,0.8]
Subtotal (95% CI)	**668**	**657**		**100%**	**0.43[0.29,0.62]**
Total events: 152 (Experimental), 328 (Control)					
Heterogeneity: Tau²=0.27; Chi²=47.94, df=12(P<0.0001); I²=74.97%					
Test for overall effect: Z=4.44(P<0.0001)					
6.2.2 High dose (>10,000 million organisms/day)					
Dubey 2008	12/113	67/111		33.47%	0.18[0.1,0.31]
Ritchie 2010	8/33	7/31		29.8%	1.07[0.44,2.61]
Shornikova 1997b	0/21	6/25		11.29%	0.09[0.01,1.52]
Shornikova 1997c	3/19	6/21		25.45%	0.55[0.16,1.91]
Subtotal (95% CI)	**186**	**188**		**100%**	**0.37[0.12,1.17]**
Total events: 23 (Experimental), 86 (Control)					
Heterogeneity: Tau²=0.93; Chi²=13.42, df=3(P=0); I²=77.65%					
Test for overall effect: Z=1.69(P=0.09)					

Analysis 6.3. Comparison 6 Dose of probiotic; live organisms, Outcome 3 Mean stool frequency on day 2.

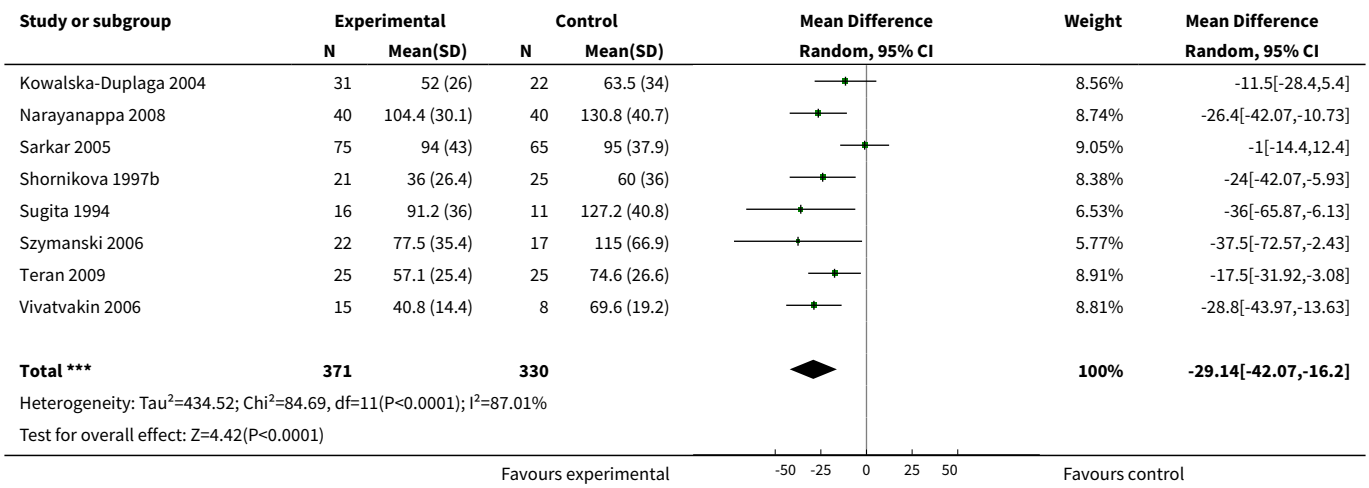
Study or subgroup	Experimental N	Experimental Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
6.3.1 Low dose (≤10,000 million organisms/day)							
Basu 2007	323	24.3 (4.8)	323	24.2 (5.3)		15.23%	0.1[-0.68,0.88]
Buydens 1996	93	2 (1)	92	3.7 (1.7)		18.77%	-1.7[-2.1,-1.3]
Chen 2010	150	2.7 (1.3)	143	4.4 (2.8)		17.9%	-1.65[-2.16,-1.14]
Lee 2001	50	1.9 (1.9)	50	3.7 (2.4)		14.54%	-1.8[-2.65,-0.95]
Narayanappa 2008	40	4 (2.7)	40	4.8 (2.8)		11.26%	-0.85[-2.05,0.35]
Rafeey 2008a	40	4 (3.2)	40	4 (3.6)		9.04%	0[-1.49,1.49]
Vivatvakin 2006	36	2.2 (2)	35	2.6 (2.2)		13.26%	-0.4[-1.38,0.58]
Subtotal ***	**732**		**723**			**100%**	**-1.01[-1.61,-0.41]**
Heterogeneity: Tau²=0.46; Chi²=26.02, df=6(P=0); I²=76.94%							
Test for overall effect: Z=3.3(P=0)							
6.3.2 High dose (>10,000 million organisms/day)							
Basu 2009	186	23.2 (6.1)	185	23.5 (6.1)		9.8%	-0.3[-1.54,0.94]
Canani 2007	100	4 (1.5)	92	5 (2.2)		47.07%	-1[-1.54,-0.46]
Pant 1996	14	3.5 (1.3)	12	5.2 (2.8)		5.09%	-1.7[-3.42,0.02]
Raza 1995	19	5.8 (3.1)	17	7 (3.3)		3.45%	-1.2[-3.3,0.9]
Ritchie 2010	33	3.3 (2.5)	31	4.7 (2.6)		9.47%	-1.4[-2.66,-0.14]
Shornikova 1997b	20	2 (2.1)	25	3.8 (2.8)		7.34%	-1.8[-3.23,-0.37]
Shornikova 1997c	19	1 (2.3)	21	2.5 (2.3)		7.39%	-1.5[-2.93,-0.07]
Szymanski 2006	46	2.9 (2.8)	41	2.8 (2.9)		10.37%	0.1[-1.1,1.3]
Subtotal ***	**437**		**424**			**100%**	**-0.99[-1.39,-0.6]**
Heterogeneity: Tau²=0.01; Chi²=7.18, df=7(P=0.41); I²=2.48%							
Test for overall effect: Z=4.97(P<0.0001)							

Comparison 7. Children with rotavirus diarrhoea

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mean duration of diarrhoea	12	701	Mean Difference (IV, Random, 95% CI)	-29.14 [-42.07, -16.20]
2 Mean stool frequency on day 2	3	164	Mean Difference (IV, Random, 95% CI)	-1.25 [-2.09, -0.41]

Analysis 7.1. Comparison 7 Children with rotavirus diarrhoea, Outcome 1 Mean duration of diarrhoea.

Study or subgroup	Experimental N	Experimental Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Guandalini 2000	56	56.2 (16.9)	45	76.6 (41.6)		9.11%	-20.4[-33.34,-7.46]
Guarino 1997	31	72 (26.7)	30	148.8 (26.3)		9.06%	-76.8[-90.1,-63.5]
Isolauri 1994	21	36 (16.8)	21	55.2 (19.2)		9.36%	-19.2[-30.11,-8.29]
Jasinski 2002	18	62.6 (35)	21	121.2 (36)		7.72%	-58.56[-80.9,-36.22]

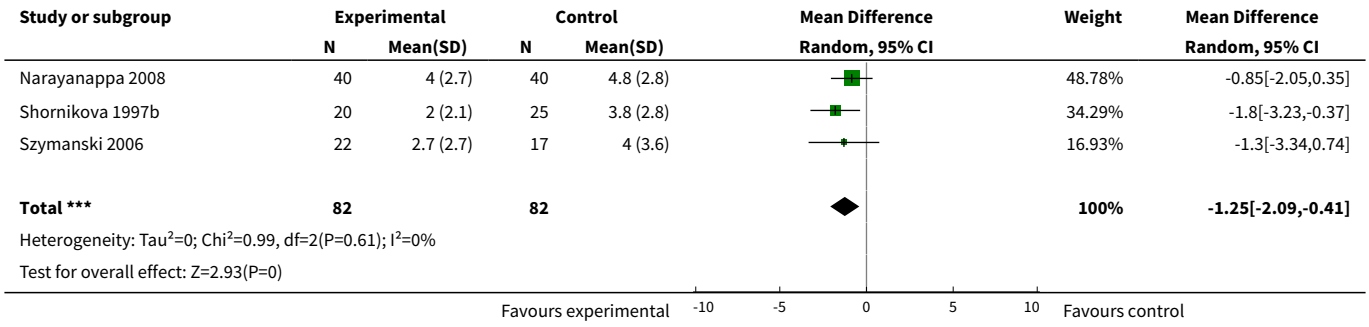


Study or subgroup	Experimental N	Experimental Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Kowalska-Duplaga 2004	31	52 (26)	22	63.5 (34)		8.56%	-11.5[-28.4,5.4]
Narayanappa 2008	40	104.4 (30.1)	40	130.8 (40.7)		8.74%	-26.4[-42.07,-10.73]
Sarkar 2005	75	94 (43)	65	95 (37.9)		9.05%	-1[-14.4,12.4]
Shornikova 1997b	21	36 (26.4)	25	60 (36)		8.38%	-24[-42.07,-5.93]
Sugita 1994	16	91.2 (36)	11	127.2 (40.8)		6.53%	-36[-65.87,-6.13]
Szymanski 2006	22	77.5 (35.4)	17	115 (66.9)		5.77%	-37.5[-72.57,-2.43]
Teran 2009	25	57.1 (25.4)	25	74.6 (26.6)		8.91%	-17.5[-31.92,-3.08]
Vivatvakin 2006	15	40.8 (14.4)	8	69.6 (19.2)		8.81%	-28.8[-43.97,-13.63]
Total ***	**371**		**330**			**100%**	**-29.14[-42.07,-16.2]**

Heterogeneity: Tau²=434.52; Chi²=84.69, df=11(P<0.0001); I²=87.01%

Test for overall effect: Z=4.42(P<0.0001)

Analysis 7.2. Comparison 7 Children with rotavirus diarrhoea, Outcome 2 Mean stool frequency on day 2.



Study or subgroup	Experimental N	Experimental Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Narayanappa 2008	40	4 (2.7)	40	4.8 (2.8)		48.78%	-0.85[-2.05,0.35]
Shornikova 1997b	20	2 (2.1)	25	3.8 (2.8)		34.29%	-1.8[-3.23,-0.37]
Szymanski 2006	22	2.7 (2.7)	17	4 (3.6)		16.93%	-1.3[-3.34,0.74]
Total ***	**82**		**82**			**100%**	**-1.25[-2.09,-0.41]**

Heterogeneity: Tau²=0; Chi²=0.99, df=2(P=0.61); I²=0%

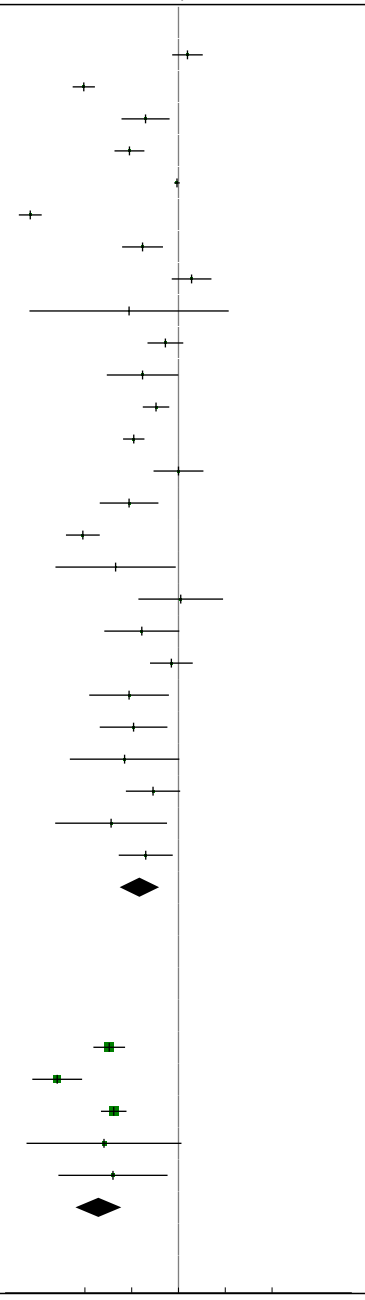
Test for overall effect: Z=2.93(P=0)

Comparison 8. Severity of diarrhoea; studies of outpatients

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mean duration of diarrhoea	31		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1 Studies of inpatients	26	3507	Mean Difference (IV, Random, 95% CI)	-20.90 [-31.44, -10.35]
1.2 Studies of outpatients	5	506	Mean Difference (IV, Random, 95% CI)	-42.81 [-55.07, -30.56]

Analysis 8.1. Comparison 8 Severity of diarrhoea; studies of outpatients, Outcome 1 Mean duration of diarrhoea.

Study or subgroup	Experimental N	Experimental Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
8.1.1 Studies of inpatients							
Basu 2007	323	163.2 (50.4)	323	158.4 (55.2)		4.18%	4.8[-3.35,12.95]
Basu 2009	186	122.9 (27.8)	185	173.5 (30.5)		4.23%	-50.6[-56.54,-44.66]
Boudraa 2001	56	44.1 (33.7)	56	61.7 (35.6)		4.03%	-17.6[-30.44,-4.76]
Chen 2010	150	60.1 (31.7)	143	86.3 (37.6)		4.18%	-26.2[-34.18,-18.22]
Costa-Ribeiro 2003	61	38.3 (3.8)	63	39.1 (4.6)		4.28%	-0.8[-2.28,0.68]
Henker 2008	75	57.6 (19.5)	76	136.8 (18.8)		4.22%	-79.2[-85.31,-73.09]
Isolauri 1994	21	36 (16.8)	21	55.2 (19.2)		4.1%	-19.2[-30.11,-8.29]
Khanna 2005	42	58.8 (27.8)	48	51.8 (22.8)		4.11%	7[-3.6,17.6]
Kianifar 2009	32	81.6 (108.6)	30	108 (105.2)		2.05%	-26.4[-79.63,26.83]
Kowalska-Duplaga 2004	86	54.6 (30)	87	61.6 (34)		4.14%	-7[-16.55,2.55]
Kurugol 2005	100	112.8 (60)	100	132 (76.8)		3.76%	-19.2[-38.3,-0.1]
Lee 2001	50	74.4 (16.8)	50	86.4 (19.2)		4.2%	-12[-19.07,-4.93]
Lievin Le-Maol 2007	42	39.5 (10.5)	38	63.4 (14.9)		4.23%	-23.9[-29.6,-18.2]
Mao 2008	70	67.2 (40.2)	71	67.2 (40.5)		4.01%	0[-13.32,13.32]
Narayanappa 2008	40	104.4 (30.1)	40	130.8 (40.7)		3.91%	-26.4[-42.07,-10.73]
Oandasan 1999	47	42.9 (21.8)	47	94 (22.9)		4.15%	-51.1[-60.12,-42.08]
Pant 1996	14	45.6 (14.4)	12	79.2 (55.2)		3.07%	-33.6[-65.73,-1.47]
Ritchie 2010	33	52.4 (49.8)	31	51.2 (42.4)		3.58%	1.2[-21.42,23.82]
Rosenfeldt 2002a	30	81.5 (37.3)	39	101.1 (47.6)		3.71%	-19.6[-39.63,0.43]
Sarkar 2005	115	90.4 (45)	115	94.2 (43.3)		4.08%	-3.8[-15.21,7.61]
Shornikova 1997a	59	64.8 (52.8)	64	91.2 (67.2)		3.65%	-26.4[-47.67,-5.13]
Shornikova 1997b	21	36 (26.4)	25	60 (36)		3.81%	-24[-42.07,-5.93]
Shornikova 1997c	19	40.8 (38.4)	21	69.6 (55.2)		3.22%	-28.8[-58.05,0.45]
Simakachorn 2000	37	43.4 (25.9)	36	57 (36.3)		3.96%	-13.6[-28.1,0.9]
Sugita 1994	16	91.2 (36)	11	127.2 (40.8)		3.19%	-36[-65.87,-6.13]
Teran 2009	25	57.1 (25.4)	25	74.6 (26.6)		3.97%	-17.5[-31.92,-3.08]
Subtotal * **	**1750**		**1757**			**100%**	**-20.9[-31.44,-10.35]**
Heterogeneity: Tau^2=675.78; Chi^2=990.04, df=25(P<0.0001); I^2=97.47%							
Test for overall effect: Z=3.88(P=0)							
8.1.2 Studies of outpatients							
Canani 2007	100	78.5 (35.5)	92	115.5 (23.5)		28.3%	-37[-45.46,-28.54]
Guarino 1997	52	76.8 (34.6)	48	141.6 (33.3)		23.61%	-64.8[-78.1,-51.5]
Henker 2007a	54	70.3 (23.5)	45	104.9 (9.1)		29.7%	-34.6[-41.42,-27.78]
Rosenfeldt 2002b	24	75.9 (39.7)	19	115.7 (85)		6.92%	-39.8[-81.19,1.59]
Villarruel 2007	35	112.8 (46.6)	37	147.8 (76.8)		11.47%	-35[-64.16,-5.84]
Subtotal * **	**265**		**241**			**100%**	**-42.81[-55.07,-30.56]**
Heterogeneity: Tau^2=119.62; Chi^2=16.3, df=4(P=0); I^2=75.46%							
Test for overall effect: Z=6.85(P<0.0001)							

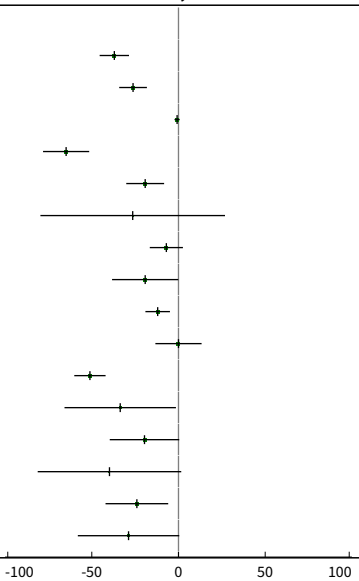


Comparison 9. Mortality stratum for children and adults in the countries where trials were undertaken (children/adults)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mean duration of diarrhoea	32		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1 Child and adult mortality low or very low	21	2075	Mean Difference (IV, Random, 95% CI)	-24.83 [-34.42, -15.23]
1.2 Either child or adult mortality high	11	2032	Mean Difference (IV, Random, 95% CI)	-24.75 [-43.40, -6.10]
2 Diarrhoea lasting ≥4 days	26		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Child and adult mortality low or very low	19	1559	Risk Ratio (M-H, Random, 95% CI)	0.35 [0.23, 0.51]
2.2 Either child or adult mortality high	7	846	Risk Ratio (M-H, Random, 95% CI)	0.45 [0.26, 0.76]
3 Mean stool frequency on day 2	19		Mean Difference (IV, Random, 95% CI)	Subtotals only
3.1 Child and adult mortality low or very low	14	1456	Mean Difference (IV, Random, 95% CI)	-0.99 [-1.35, -0.63]
3.2 Either child or adult mortality high	5	1231	Mean Difference (IV, Random, 95% CI)	0.00 [-0.78, 0.78]

Analysis 9.1. Comparison 9 Mortality stratum for children and adults in the countries where trials were undertaken (children/adults), Outcome 1 Mean duration of diarrhoea.

Study or subgroup	Experimental N	Experimental Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
9.1.1 Child and adult mortality low or very low							
Canani 2007	100	78.5 (35.5)	92	115.5 (23.5)		5.72%	-37[-45.46,-28.54]
Chen 2010	150	60.1 (31.7)	143	86.3 (37.6)		5.75%	-26.2[-34.18,-18.22]
Costa-Ribeiro 2003	61	38.3 (3.8)	63	39.1 (4.6)		5.98%	-0.8[-2.28,0.68]
Guarino 1997	52	76.8 (34.6)	48	141.6 (33.3)		5.37%	-64.8[-78.1,-51.5]
Isolauri 1994	21	36 (16.8)	21	55.2 (19.2)		5.56%	-19.2[-30.11,-8.29]
Kianifar 2009	32	81.6 (108.6)	30	108 (105.2)		2.11%	-26.4[-79.63,26.83]
Kowalska-Duplaga 2004	86	54.6 (30)	87	61.6 (34)		5.65%	-7[-16.55,2.55]
Kurugol 2005	100	112.8 (60)	100	132 (76.8)		4.84%	-19.2[-38.3,-0.1]
Lee 2001	50	74.4 (16.8)	50	86.4 (19.2)		5.8%	-12[-19.07,-4.93]
Mao 2008	70	67.2 (40.2)	71	67.2 (40.5)		5.37%	0[-13.32,13.32]
Oandasan 1999	47	42.9 (21.8)	47	94 (22.9)		5.69%	-51.07[-60.09,-42.05]
Pant 1996	14	45.6 (14.4)	12	79.2 (55.2)		3.58%	-33.6[-65.73,-1.47]
Rosenfeldt 2002a	30	81.5 (37.3)	39	101.1 (47.6)		4.75%	-19.6[-39.63,0.43]
Rosenfeldt 2002b	24	75.9 (39.7)	19	115.7 (85)		2.83%	-39.8[-81.19,1.59]
Shornikova 1997b	21	36 (26.4)	25	60 (36)		4.94%	-24[-42.07,-5.93]
Shornikova 1997c	19	40.8 (38.4)	21	69.6 (55.2)		3.85%	-28.8[-58.05,0.45]



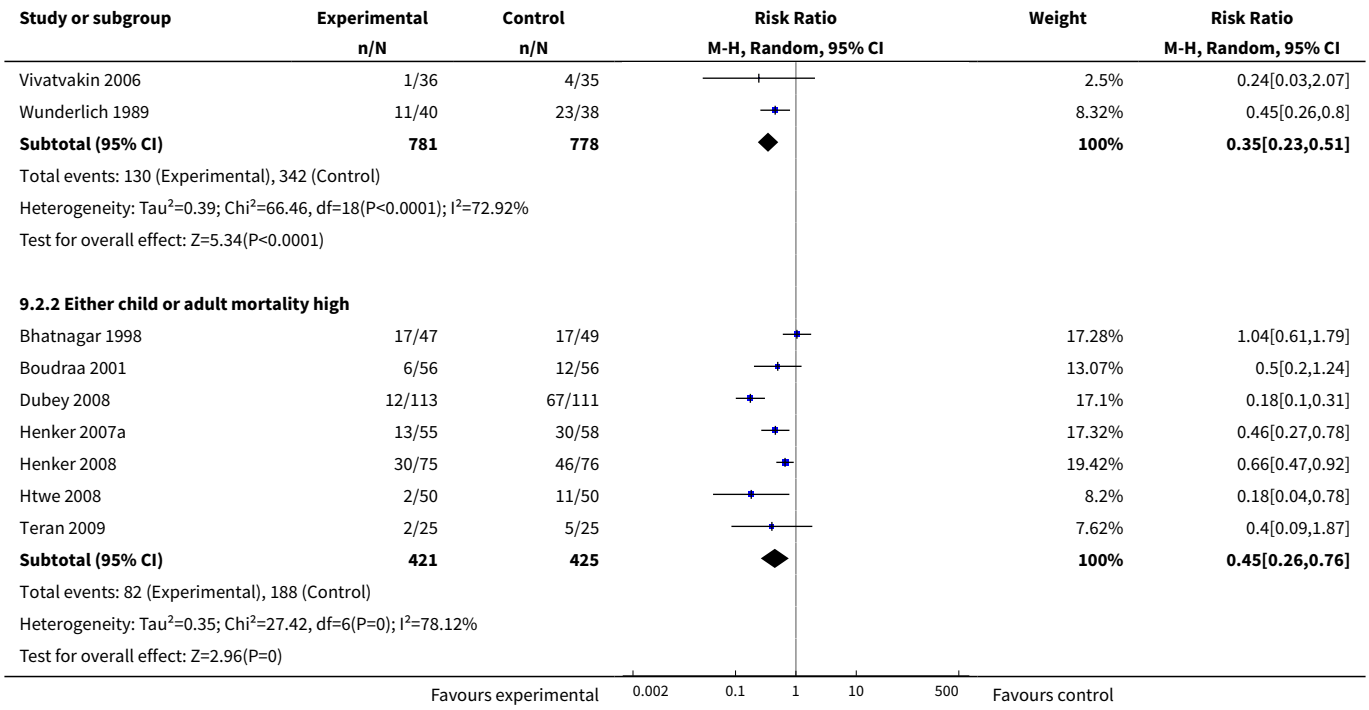
Study or subgroup	Experimental N	Experimental Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Simakachorn 2000	37	43.4 (25.9)	36	57 (36.3)		5.27%	-13.6[-28.1,0.9]
Sugita 1994	16	91.2 (36)	11	127.2 (40.8)		3.79%	-36[-65.87,-6.13]
Szymanski 2006	46	83.6 (55.6)	41	96 (71.5)		4.05%	-12.4[-39.55,14.75]
Villarruel 2007	35	112.8 (46.6)	37	147.8 (76.8)		3.86%	-35.04[-64.2,-5.88]
Vivatvakin 2006	36	38.4 (16.8)	35	69.6 (40.8)		5.26%	-31.2[-45.79,-16.61]
Subtotal ***	**1047**		**1028**			**100%**	**-24.83[-34.42,-15.23]**
Heterogeneity: Tau²=400.3; Chi²=339.75, df=20(P<0.0001); I²=94.11%							
Test for overall effect: Z=5.07(P<0.0001)							
9.1.2 Either child or adult mortality high							
Basu 2007	323	163.3 (25.7)	323	158.4 (28.2)		9.37%	4.9[0.74,9.06]
Basu 2009	186	122.9 (27.8)	185	173.5 (30.5)		9.32%	-50.6[-56.54,-44.66]
Boudraa 2001	56	44.1 (33.7)	56	61.7 (35.6)		9.01%	-17.6[-30.44,-4.76]
Henker 2007a	54	70.3 (23.5)	45	104.9 (9.1)		9.3%	-34.56[-41.38,-27.74]
Henker 2008	75	57.6 (19.5)	76	136.8 (18.8)		9.32%	-79.2[-85.31,-73.09]
Khanna 2005	42	55.8 (27.8)	48	51.8 (22.8)		9.13%	4.01[-6.59,14.61]
Lievin Le-Maol 2007	42	39.5 (10.5)	38	63.4 (14.9)		9.33%	-23.9[-29.6,-18.2]
Narayanappa 2008	40	104.4 (30.1)	40	130.8 (40.7)		8.83%	-26.4[-42.07,-10.73]
Sarkar 2005	115	90.4 (45)	115	94.2 (43.3)		9.09%	-3.8[-15.21,7.61]
Shornikova 1997a	59	64.8 (52.8)	64	91.2 (67.2)		8.39%	-26.4[-47.67,-5.13]
Teran 2009	25	57.1 (25.4)	25	74.6 (26.6)		8.91%	-17.5[-31.92,-3.08]
Subtotal ***	**1017**		**1015**			**100%**	**-24.75[-43.4,-6.1]**
Heterogeneity: Tau²=961.55; Chi²=624.63, df=10(P<0.0001); I²=98.4%							
Test for overall effect: Z=2.6(P=0.01)							

Favours experimental -100 -50 0 50 100 Favours control

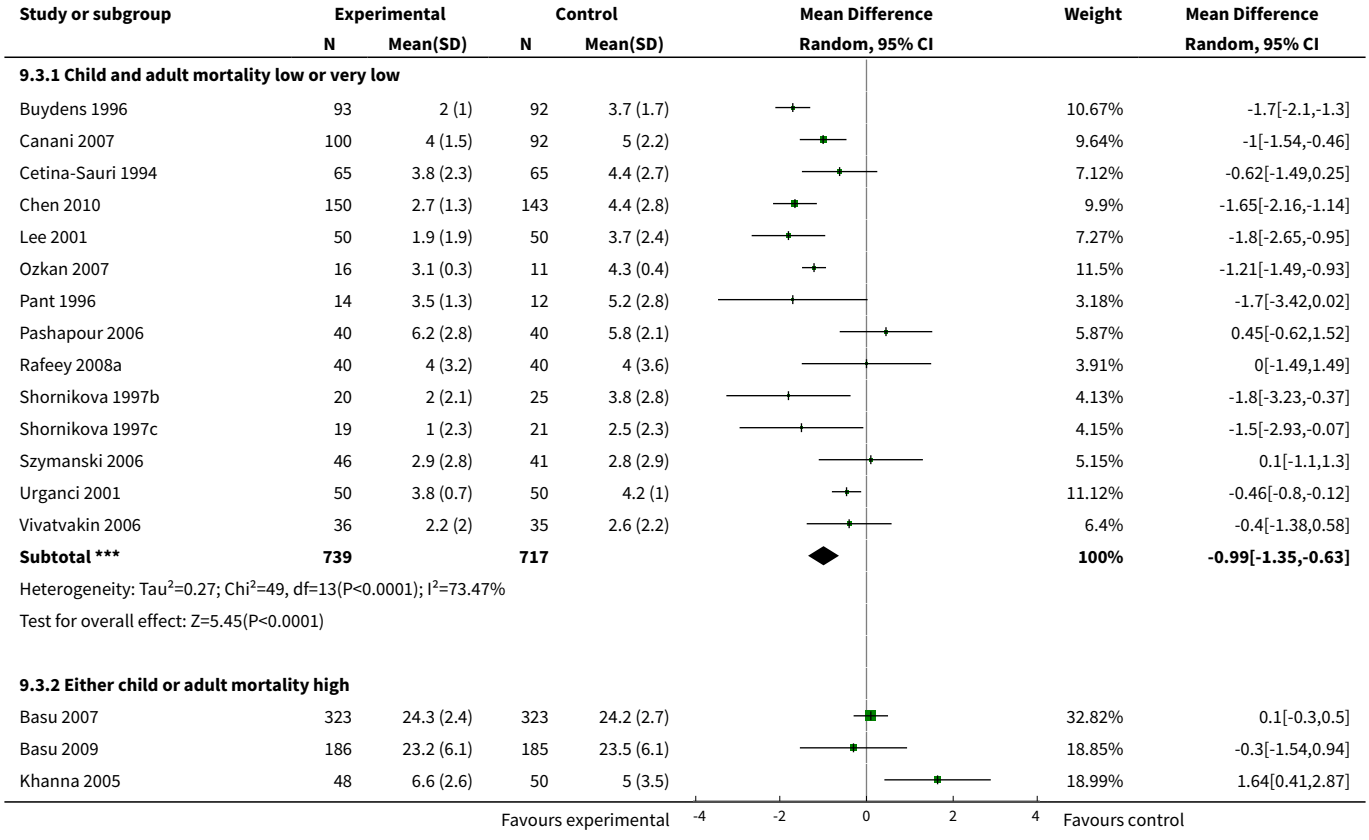
Analysis 9.2. Comparison 9 Mortality stratum for children and adults in the countries where trials were undertaken (children/adults), Outcome 2 Diarrhoea lasting ≥4 days.

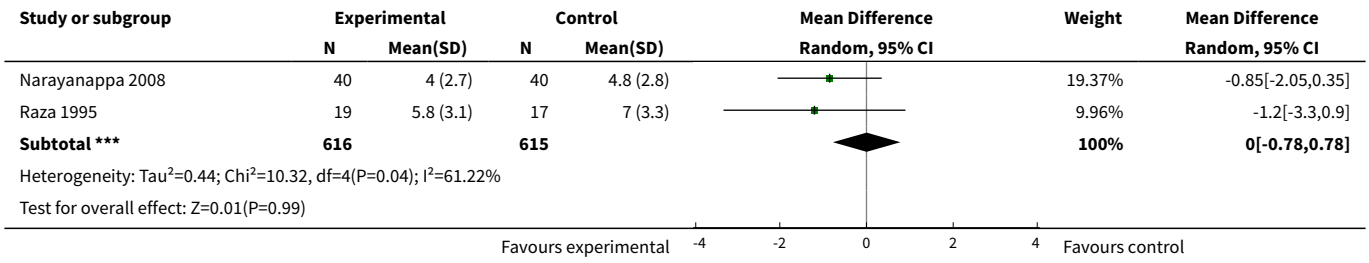
Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
9.2.1 Child and adult mortality low or very low					
Bruno 1981	2/25	11/24		4.39%	0.17[0.04,0.71]
Bruno 1983	1/10	7/11		2.95%	0.16[0.02,1.06]
Buydens 1996	7/93	61/92		7.47%	0.11[0.05,0.23]
Caragues-Orendain	0/35	4/35		1.55%	0.11[0.01,1.99]
Cetina-Sauri 1994	16/65	39/65		8.8%	0.41[0.26,0.66]
Chapoy 1985	1/19	4/19		2.58%	0.25[0.03,2.04]
Costa-Ribeiro 2003	31/61	45/63		9.54%	0.71[0.53,0.95]
D'Apuzzo 1982	3/21	7/18		5.17%	0.37[0.11,1.22]
Hernandez 1998	1/25	7/25		2.72%	0.14[0.02,1.08]
Kowalska-Duplaga 1999	13/33	9/30		7.66%	1.31[0.66,2.62]
Kurugol 2005	8/100	30/100		7.46%	0.27[0.13,0.55]
Oandasan 1999	1/47	22/47		2.84%	0.05[0.01,0.32]
Shornikova 1997b	0/21	6/25		1.61%	0.09[0.01,1.52]
Shornikova 1997c	3/19	6/21		5%	0.55[0.16,1.91]
Simakachorn 2000	1/37	9/36		2.73%	0.11[0.01,0.81]
Urganci 2001	8/50	18/50		7.43%	0.44[0.21,0.93]
Villarruel 2007	22/44	30/44		9.3%	0.73[0.51,1.05]

Favours experimental 0.002 0.1 1 10 500 Favours control



Analysis 9.3. Comparison 9 Mortality stratum for children and adults in the countries where trials were undertaken (children/adults), Outcome 3 Mean stool frequency on day 2.





ADDITIONAL TABLES

Table 1. Heterogeneity in sensitivity analysis of primary outcomes[1]

Sensitivity analysis	Outcome	Studies (no.)	χ^2	P value	I^2 (%)
Generation of allocation sequence	Mean duration diarrhoea	16	1077.2	< 0.00001	99
	Diarrhoea ≥4 days	13	46.2	< 0.00001	74
	Stool frequency day 2	9	26.9	0.0007	70
Concealment of allocation sequence	Mean duration diarrhoea	14	438.3	< 0.00001	97
	Diarrhoea ≥4 days	8	34.2	< 0.0001	8%
	Stool frequency day 2	8	42.4	< 0.00001	83
Blinding	Mean duration diarrhoea	26	1070.9	< 0.00001	98
	Diarrhoea ≥4 days	16	64.8	< 0.00001	77
	Stool frequency day 2	14	48.8	< 0.00001	73
Follow-up	Mean duration diarrhoea	25	672.3	< 0.00001	96
	Diarrhoea ≥4 days	19	52.3	< 0.0001	66
	Stool frequency day 2	15	54.5	< 0.00001	74

1. Only trials considered adequate for quality assessment included; forest plots not shown

APPENDICES

Appendix 1. Detailed search strategy

Search set	CIDG SR[a]	CENTRAL	MEDLINE[b]	EMBASE[b]	LILACS[b]
1	Diarrhea*	DIARRHEA	DIARRHEA	INFECTIOUS DIARRHEA	Diarrhea$

(Continued)

2	Diarrhoea*	Diarrhoea*	Diarrhoea*	Diarrhoea*	Diarrhoea$
3	1 or 2	1 or 2	1 or 2	1 or 2	1 or 2
4	Probiotic*	Probiotic*	PROBIOTICS	PROBIOTIC AGENT	Probiotic$
5	Lactobacill*	Lactobacill*	Lactobacill*	Lactobacill$	Lactobacill$
6	Lactococc*	Lactococc*	Lactococc*	Lactococc$	Lactococc$
7	Bifidobacter*	Bifidobacter*	Bifidobacter*	Bifidobacter$	Bifidobacter$
8	Enterococc*	Enterococc*	Enterococc*	Enterococc$	Enterococc$
9	Streptococc*	Streptococc*	Streptococc*	Streptococc$	Streptococc$
10	saccharomyces	saccharomyces	saccharomyces	saccharomyces	saccharomyces
11	4 or 5 or 6 or 7 or 8 or 9 or 10	4 or 5 or 6 or 7 or 8 or 9 or 10	4 or 5 or 6 or 7 or 8 or 9 or 10	4 or 5 or 6 or 7 or 8 or 9 or 10	4 or 5 or 6 or 7 or 8 or 9 or 10
12	3 and 11	3 and 11	3 and 11	3 and 11	3 and 11
13			Limit 12 to Humans	Limit 12 to Human	

Footnotes

[a] Cochrane Infectious Diseases Group Specialized Register

[b] Search terms used in combination with the search strategy for retrieving trials developed by The Cochrane Collaboration (Higgins 2008); Upper case: MeSH or EMTREE heading; Lower case: free text term

WHAT'S NEW

Date	Event	Description
9 November 2010	Amended	Detailed search strategy added to appendices

HISTORY

Protocol first published: Issue 2, 2001
Review first published: Issue 2, 2004

Date	Event	Description
11 August 2010	New citation required but conclusions have not changed	Title changed ("acute" added) to emphasise that persistent diarrhoea is not considered. The authorship of the update has changed due to the untimely death of Dr Okoko.
11 August 2010	New search has been performed	The table showing clinical variability among studies has been removed and this information added to the Characteristics of included studies table. A table has been added to show the marked

Date	Event	Description
		statistical heterogeneity in primary outcomes and subgroup analyses (Table 1). The following secondary outcomes have been removed as they were either uncommon or not reported: need for unscheduled intravenous (IV) rehydration after randomization; deaths; adverse events, such as vomiting; withdrawal from study. Details regarding adverse events and reasons for withdrawal are included in the "details of included studies" table.
22 July 2008	Amended	Converted to new review format.
8 December 2007	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Stephen Allen and Leonila Dans identified articles for inclusion in the review. Leonila Dans, Elizabeth Martinez, and Germana Gregorio assessed study quality, and Leonila Dans settled any disagreements. Stephen Allen extracted data. Stephen Allen took the main responsibility for analysis and writing the review. All reviewers contributed to the final version.

DECLARATIONS OF INTEREST

Stephen Allen is participating in ongoing research studies of lactobacilli and bifidobacteria provided by Cultech Ltd, UK, in the prevention of atopic disorders in infants and antibiotic-associated diarrhoea in older people. In previous research, Scientific Hospital Supplies, UK, and Valio Ltd, Finland, have provided *L. casei* strain GG and also supported his attendance at a training workshop. Elizabeth Martinez is a Medical Manager for United Laboratories Inc., Philippines.

SOURCES OF SUPPORT

Internal sources

- Swansea School of Medicine, UK.

External sources

- Cochrane Infectious Disease Group, Liverpool School of Tropical Medicine, UK.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The following secondary outcomes have been removed as they were either uncommon or not reported: need for unscheduled intravenous (IV) rehydration after randomization; deaths; adverse events, such as vomiting; withdrawal from study.

NOTES

This review is a substantial update of the original version, first published in 2003 (Allen 2003).

INDEX TERMS

Medical Subject Headings (MeSH)

Acute Disease; Diarrhea [microbiology] [parasitology] [*therapy]; Probiotics [*therapeutic use]

MeSH check words

Adult; Child; Child, Preschool; Humans; Infant