Probiotics for treating infectious diarrhoea (Review)

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[Intervention Review]

Probiotics for treating infectious diarrhoea

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ABSTRACT

Background

Probiotics are microbial cell preparations or components of microbial cells that have a beneficial effect on the health and well being of the host. 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 infectious diarrhoea.

Search strategy

We searched the Cochrane Infectious Diseases Group's trials register (December 2002), the Cochrane Controlled Trials Register (*The Cochrane Library* Issue 4, 2002), MEDLINE (1966 to 2002), EMBASE (1988 to 2002), 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 controlled trials comparing a specified probiotic agent with 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 trial methodological quality and extracted data.

Main results

Twenty-three studies met the inclusion criteria with a total of 1917 participants, mainly in countries with low overall mortality rates. Trials varied in relation to the probiotic(s) tested, dosage, methodological quality, and the diarrhoea definitions and outcomes.

Probiotics reduced the risk of diarrhoea at 3 days (risk ratio 0.66, 95% confidence interval 0.55 to 0.77, random effects model; 15 studies) and the mean duration of diarrhoea by 30.48 hours (95% confidence interval 18.51 to 42.46 hours, random effects model, 12 studies). Subgroup analysis by probiotic(s) tested, rotavirus diarrhoea, national mortality rates, and age of participants did not fully account for the heterogeneity.

Authors' conclusions

Probiotics appear to be a useful adjunct to rehydration therapy in treating acute, infectious diarrhoea in adults and children. More research is needed to inform the use of particular probiotic regimens in specific patient groups.

PLAIN LANGUAGE SUMMARY

Probiotics for treating infectious diarrhoea

Plain language summary pending.

BACKGROUND

Definition

Diarrhoea is defined by the World Health Organization (WHO) as 3 or more loose or watery stools (taking the shape of the container) in a 24-hour period. Diarrhoea is acute if the illness started under 14 days previously, and persistent if the episode has lasted 14 days or more (Anonymous 1988). Normal infants who are exclusively breastfed 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 mortality

Infectious diarrhoea occurs much more commonly in developing countries than industrialized countries (Guerrant 1990). Attack rates in developing countries are typically 6 to 12 episodes per child per year, compared with 2 in the USA (Savarino 1993). In developing countries, deaths are most common in children younger than 5 years, and account for 2.4 to 3.3 million deaths each year (Bern 1992). In industrialized countries, deaths are mainly in the elderly (Savarino 1993).

Causes

Many infectious agents cause diarrhoea. Worldwide, rotavirus is the most common cause of severe diarrhoea and diarrhoea mortality in children (Cunliffe 1998). Other important viral pathogens are adenoviruses and enteroviruses. Important bacterial pathogens are: enterotoxigenic *Escherichia coli*, *Salmonella*, *Shigella*, *Yersinia*, *Campylobacter*, and *Vibrio cholera*. The main parasitic causes of diarrhoea are *Cryptosporidium* and *Giardia*. 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. Major causes of acute infectious diarrhoea will 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 length of the illness, 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). 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 phenotypic characteristics. Modern molecular techniques have shown these to be unreliable, and "polyphasic taxonomy" using both phenotypic and molecular techniques is now recommended (Klein 1998). Even closely related probiotic strains can have different clinical effects, and the Food and Agricultural Organization of the United Nations (FAO) and WHO expert consultation committee emphasized that beneficial effects observed with one strain cannot be assumed to occur with other strains (FAO/WHO 2001). This implies that 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 infections have been reported in people with impaired immune systems (Hata 1988; Piarroux 1999; Salminen 1998; Saxelin 1996; Sussman 1986).

Two 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 3 or more days in infants and children. A score was used to assess methodological quality. The effects of all probiotics and of individual strains were analysed. The risk of diarrhoea lasting 3 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; 8 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; 8 trials including 773 children). 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. Probiotics reduced the duration of diarrhoea by 0.7 days (95% CI 0.3 to 1.2 days; 7 studies including 675 children) and diarrhoea frequency on day 2 by 1.6 (95% CI 0.7 to 2.6; 3 studies including 122 children). Heterogeneity of results between studies prevented the analysis of the effects of individual strains of lactobacilli.

Our review aims to maximize use of available data by including participants of all ages, unpublished studies, and non-blinded ('open') studies. Also, rather than using a score, 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.

OBJECTIVES

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

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled trials.

Types of participants

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

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

Types of interventions

Intervention

Specific, identified probiotic.

Excluded: yoghurt or other fermented foods in which a specific probiotic agent was 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

- Diarrhoea lasting 3+ and 4+ days.
- Duration of diarrhoea.
- Stool frequency and volume.

Secondary

- Need for unscheduled intravenous rehydration after randomization.
- Deaths.
- Adherence.
- Adverse events, such as vomiting.
- Withdrawal from trial.

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).

We searched the Cochrane Infectious Diseases Group's trials register in December 2002 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 CIDG 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 4, 2002) 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 2002) and EMBASE (1988 to 2002) 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).

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 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

Stephen Allen (SD) and Leonila Dans (LD) independently reviewed the titles of papers 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.

Assessment of risk of bias (methodological quality)

Two reviewers (Elizabeth Martinez, Germana Gregorio), blinded to the origin of the papers, independently assessed the risk of bias (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 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; or *inadequate* where allocation could be related to prognosis and therefore introduce selection bias, for example, 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 study authors did not describe the method used to achieve concealment; 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, that is, an identical placebo was used and recruitment to intervention or control arms was not known by either the investigator or the participants; *unclear* when the study authors provided no details; or *open* when they did not use blinding.

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; or *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 and Brown Okoko independently extracted data using standard forms. Key data items were aetiology and duration of diarrhoea, details of probiotic organism, participant characteristics (nutritional and HIV status), location (countries classified according to mortality stratum; WHO 2001), and the outcome measures listed above.

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 mean difference. For 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 risk

ratio (RR) among probiotic and non-probiotic groups. We used either a fixed effect or random effects model approach according to the heterogeneity in outcomes across studies assessed by the chi-squared (chi^2) test.

Where there was statistically significant heterogeneity in outcomes across studies, we conducted sensitivity analyses according to each of the four parameters of trial methodological quality.

We expected that differences between studies in probiotic(s) used, types of participants, and major causes of diarrhoea would result in heterogeneity in results. To address this likely heterogeneity, we conducted the following subgroup analyses.

- Probiotic type.
- Identified diarrhoeal pathogens (eg rotavirus).
- Background mortality rate (trials classified according to mortality stratum for children and adults in the country or countries where the trial was undertaken (WHO 2001) because of likely regional differences in major diarrhoeal pathogens related to the availability of clean water and level of sanitation).
- Age of participants.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of studies awaiting classification.

Our search identified 64 potentially relevant studies. Of these, 23 met the inclusion criteria and we excluded 35 (*see* 'Characteristics of excluded studies'). We have not been able to locate the reports of four potentially relevant studies to date and are awaiting a translation of one study (Taborska 1997) and the report of an unpublished study (Salazar-Lindo).

Publication status

Of the 23 included studies, 4 were published in the 1970s and 1980s, 18 in 1990 or later, and 1 is unpublished.

Study location

Two studies were performed in countries classified by the WHO as having high child and adult mortality, five in countries with low child and adult mortality, and one in a country with low child and high adult mortality (Shornikova 1997a), 14 classified as very low child and adult mortality, and 1 multicentre study pooled data from countries classified as having high and very low mortality rates (Guandalini 2000).

Sixteen studies were conducted in a single centre, five studies recruited participants from two or more centres within the same country, one study was a multicentre international study, and the number of recruitment centres was unclear in one study (D'Apuzzo 1982).

Participants

The 23 selected studies recruited a total of 1917 participants. There were 1449 infants or children (age < 18 years) divided into the probiotic (n = 740) and control (n = 709) groups, and 352 adults (age ≥ 18 years; 173 probiotic/179 control groups). Bruno 1983 studied participants aged 14 years and above, and participants in Wunderlich 1989 had a mean age of 33 years (age range not stated); these two studies accounted for 58 participants in each of the probiotic and control groups.

Fifteen studies recruited inpatients, three recruited outpatients, and three recruited both inpatients and outpatients; it was unclear in two studies whether the participants were inpatients and/or outpatients (Cetina-Sauri 1994; D'Apuzzo 1982).

Although all studies recruited participants with acute diarrhoea, the criteria for diarrhoea and for the duration of acute diarrhoea varied considerably between studies (*see* 'Characteristics of included studies'). Three or more loose or watery stools in the last 24 hours was the most common definition of diarrhoea (six studies); nine studies did not specify the definition of diarrhoea. The most commonly used criteria for the duration of acute diarrhoea was diarrhoea of < 5 days (four studies) or < 7 days (five studies), but criteria varied from < 48 hours to < 14 days, and the maximum duration of diarrhoea was not specified in eight 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; no study stated HIV positivity as an exclusion criterion, but many excluded participants with chronic illness and/or immunosuppression.

Two studies specifically recruited malnourished children (Bhatnagar 1998; Raza 1995), and a further two studies included malnourished children (Pant 1996; Simakachorn 2000). Three studies excluded severely malnourished children (Caragué-Orendain; Oandasan 1999; Raza 1995), and one excluded moderately malnourished children (Guarino 1997). Many studies did not comment specifically on nutritional status but excluded participants with underlying severe or chronic illness.

The hydration status of participants varied considerably between studies. Three studies included infants and children with severe dehydration (> 10%; Guandalini 2000; Pant 1996; Raza 1995), another 3 studies were restricted to infants and children with moderate (5 to 10%) or mild (< 5%) dehydration (Boulloche 1994; Guarino 1997; Simakachorn 2000), and 4 studies stated the average degree of dehydration (Isolauri 1994; Shornikova 1997a; Shornikova 1997b; Shornikova 1997c). Three studies excluded participants with moderate or severe dehydration (Buydens 1996; Cetina-Sauri 1994; Oandasan 1999). In the 4 studies that classi-

fied infants and children according to hydration status, 82 with no dehydration, 205 with mild, 123 with moderate, and 29 with severe dehydration were recruited (Guandalini 2000; Pant 1996; Raza 1995; Simakachorn 2000).

Ten studies specified that they excluded participants with bloody stools or grossly bloody stools, including three studies that were restricted to participants with rotavirus diarrhoea (Isolauri 1994; Shornikova 1997b; Sugita 1994). Participants with bloody stools were included in four studies. Nine studies did not state whether they excluded participants with dysentery. Four studies reported outcomes for the subgroup of children with rotavirus diarrhoea (Boulloche 1994; Guandalini 2000; Guarino 1997; Shornikova 1997a). Guandalini 2000 reported outcomes for the subgroup of children with bacterial diarrhoea, and Pant 1996 reported results for the subgroup of children with watery, non-bloody diarrhoea.

Interventions

Several different probiotics were tested: all were lactic acid bacilli, except in two studies that tested the yeast *Saccharomyces boulardii* (Cetina-Sauri 1994; Hochter 1990). Two studies tested a heat-killed probiotic preparation (Boulloche 1994; Simakachorn 2000). Few studies reported specific identification details beyond the species name, for example, by stating a culture collection number, and few undertook analyses to confirm the identity or viability of the organism. There was also wide variation in the treatment regimens according to number of organisms administered, 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, two studies excluded breastfed infants to minimize interruption of normal feeding.

Two studies compared the probiotic to standard treatment without a placebo (Guarino 1997; Isolauri 1994). One study administered milk formula to the comparison group (Bhatnagar 1998). The remaining 20 studies used a matching placebo.

Outcomes

In addition to the outcome measures identified a priori, we also extracted data for the number of participants with diarrhoea lasting 3 days or more and 4 days or more following the intervention. These outcomes were often reported and allowed several studies that did not report data for the other predefined outcomes to be included.

There was great variation between studies in the definition for the resolution of diarrhoea. The most commonly used criteria were the appearance of the last liquid or watery stool (five studies) or the first formed stool (four studies). Several studies used various combinations of stool consistency and stool frequency, and three studies included resolution of associated symptoms (fever, abdominal pain) in the definition. The criteria for resolution of diarrhoea were not stated in three studies. Raza 1995 did not follow children until resolution of diarrhoea but reported stool frequency by day of intervention.

There was also considerable variation between studies in outcome measures, and many studies reported more than one outcome. The most commonly reported outcomes were the number of participants with diarrhoea lasting 3 or more days (15 studies) and 4 or more days (13 studies) following the intervention, and the mean duration of diarrhoea from the start of the intervention (12 studies). Less commonly reported outcomes were weight change at intervals following the intervention (as a measure of rehydration), stool frequency according to day of intervention, length of hospital stay, and stool output. Although there was great variability between studies in definitions and reported outcomes, individual studies used the same criteria and outcomes for the probiotic and control groups.

Risk of bias in included studies

Methodological quality varied considerably (Appendix 1). Generation of the allocation sequence was adequate in 10 studies, inadequate in 1 study, and unclear in 12 studies. Concealment of allocation was adequate in only 5 studies, inadequate in 1 study, and unclear in 17 studies. Blinding was adequate in 14 studies, unclear in 6 studies, and 3 studies did not use blinding. Loss to follow up was adequate in 14 studies, inadequate in 7 studies, and unclear in 2 studies. Three studies were adequate for all of the four methodological quality assessment parameters (Oandasan 1999; Shornikova 1997c; Simakachorn 2000). Only one study stated that they conducted an analysis by "intention to treat" (Buydens 1996).

Effects of interventions

The results of trials according to reported outcomes are shown in Analysis 1.1 to Analysis 1.5 with trials grouped according to the probiotic(s) tested. With the exception of a trial of live *Streptococcus thermophilus* and *Lactobacillus bulgaricus* (Bhatnagar 1998; Analysis 1.4 and Analysis 1.5), all trials reported for all outcomes a beneficial effect in the probiotic group compared to the controls, and this was statistically significant in many studies. For several studies reporting continuous outcomes, standard deviations were large in comparison to mean values, suggesting that outcome data were not normally distributed. Therefore, caution is needed in the interpretation of the pooled results.

Diarrhoea lasting 3+ and 4+ days

3+ days

The persistence of diarrhoea on day 3 of intervention was the most frequently reported outcome (1341 participants/15 studies; Analysis 1.1). Participants taking probiotics were less likely to have diarrhoea lasting 3+ days, but there was heterogeneity between studies (0.67, 95% CI 0.61 to 0.74 (fixed effect model); 0.66; 95% CI 0.55 to 0.77 (random effects model; chi^2 = 26.24, degrees of freedom (df) = 14, P = 0.02). A sensitivity analysis that pooled the results from the four studies with adequate allocation concealment showed a similar reduction in risk ratio of ongoing diarrhoea (Analysis 2.2). Between-study heterogeneity persisted in sensitivity analyses for other parameters of study methodological quality (Analysis 2.1, Analysis 2.3, Analysis 2.4).

4+ days

The risk ratio of diarrhoea lasting 4 or more days in the probiotic group was 0.36 (95% CI 0.30 to 0.44), again with heterogeneity in results between studies (Analysis 1.2). The reduced risk of diarrhoea in the probiotic group was similar in a random effects analysis but had a wider confidence interval (0.31; 95% CI 0.19 to 0.50). Again, results were more homogeneous when the analysis was restricted to 4 studies with adequate allocation concealment (Analysis 3.2), and this analysis showed a greater reduction in diarrhoea (RR 0.12; 95% CI 0.07 to 0.22). Heterogeneity between studies persisted in sensitivity analyses for the other parameters of study methodological quality. Differences in allocation concealment may have accounted for the heterogeneity in results between studies for the risk ratio of ongoing diarrhoea on days 3 and 4 of intervention. However, similar or greater effects of probiotics on stopping diarrhoea were seen when the analysis was restricted to studies with adequate allocation concealment.

Duration of diarrhoea

Mean duration of diarrhoea was reported in 12 studies, all performed in infants and children, and was reduced by 29.20 hours in people taking probiotics (95% CI 25.14 to 33.25, fixed effect model; 30.48 hours, 95% CI 18.51 to 42.46, random effects model, chi^2 = 76.51, df = 11, P $\leq$ 0.00001) (Analysis 1.3). In the subgroups and in the studies of live *Lactobacillus casei* strain GG, one study demonstrated a particularly dramatic effect with a long mean duration of diarrhoea in the control group (Guarino 1997). These data were recorded by mothers at home rather than by health staff, which may account for the difference. Statistically significant between-study heterogeneity persisted in sensitivity analyses (Analysis 4.1 to Analysis 4.4) suggesting that differences in outcomes between studies were caused by factors other than differences in methodological quality.

Stool frequency

Participants in the probiotic group had on average 1.51 fewer stools on day 2 of intervention (95% CI 1.17 to 1.85; Analysis 1.4) and 1.31 fewer stools on day 3 (95% CI 1.07 to 1.56; Analysis 1.5) compared to participants in the control group. Although the results across studies were not statistically heterogeneous, mean stool frequency on day 2 was reported in only 5 trials and on day 3 in only 4 trials.

Need for unscheduled intravenous rehydration after randomization

Occasionally children developed severe dehydration and required intravenous rehydration (*see* 'Adverse events' below), but in no case was this attributable to probiotic treatment.

Death

No trial reported any deaths amongst participants.

Exploration of heterogeneity

We have explored methodological quality of studies as a potential source of heterogeneity in the primary analyses above and explored other pre-specified factors below.

Probiotic type

There were three or more trials of *L. casei* strain GG and *Enterococcus* LAB strain SF68 that reported the same outcomes. Two of three pooled analyses showed statistically significant between-study heterogeneity (Analysis 1.2 and Analysis 1.5). Although the combination of live *Lactobacillus acidophilus* and *Lactobacillus bifidus* appeared to be particularly effective in reducing diarrhoea (Analysis 1.2 and Analysis 1.4), this combination was tested in few participants. In contrast to most other regimens, live *S. thermophilus* and *L. bulgaricus* appeared to have no effect on diarrhoea, but this combination was tested in one trial only and the confidence width is wide and does not exclude potentially clinically significant values (Bhatnagar 1998; Analysis 1.1 and Analysis 1.2).

Identified diarrhoeal pathogen

Mean duration of diarrhoea in the subset of children with rotavirus diarrhoea was reported in two trials (Guandalini 2000; Guarino 1997) and in two studies that recruited only children with rotavirus diarrhoea (Isolauri 1994; Sugita 1994). Duration of diarrhoea was reduced by 38.10 hours (95% CI 8.10 to 68.10) in the probiotic group compared to the controls (random effects model; Analysis 5.1) – similar to that observed in the analysis of all-cause diarrhoea (Analysis 1.3). Again there was marked between-study heterogeneity in results. Isolauri 1994 also reported that in children with rotavirus diarrhoea, the risk ratio of diarrhoea lasting 3 or more days was markedly reduced (0.22; 95% CI 0.05 to 0.91; Analysis 1.1). However, this analysis was based on relatively few participants. Guandalini 2000 reported that in

rotavirus diarrhoea, stool frequency on day 3 of intervention was lower in children receiving *L. casei* strain GG (0.4, n = 56) than in the controls (2.0, n = 45; P < 0.05), which would appear to a greater reduction than seen in all-cause diarrhoea. Shornikova 1997a reported statistically significantly (P = 0.02) fewer watery stools in 13 children receiving *L. casei* strain GG compared with 21 receiving placebo, but presented no data. Boulloche 1994 commented that killed *L. acidophilus* reduced the duration of rotavirus diarrhoea to a similar extent as diarrhoea due to other causes.

Only two trials reported outcomes for participants confirmed to have bacterial diarrhoea, and both tested *L. casei* strain GG (Guandalini 2000; Shornikova 1997a). Both trials reported that diarrhoea was not reduced in the probiotic group compared to the control group.

Background mortality rate

We used the WHO mortality rates to reflect likely differences in the major causes of diarrhoea as a consequence of differences in the availability of clean water and level of sanitation in countries where trials were undertaken. We excluded the multicentre study by Guandalini 2000 because participants were recruited from countries with very low child and adult mortality and Egypt, which has high child and adult mortality. Only three trials were undertaken in countries with either high child or adult mortality (Bhatnagar 1998; Raza 1995; Shornikova 1997a). We observed statistically significant between-study heterogeneity in results where there were four or more trials in each classification (Analysis 6.1 to Analysis 6.5). There was no consistent trend in the efficacy of probiotics according to this classification.

Age of participants

Statistically significant between-study heterogeneity was present for both the trials of adults and those of infants and children for the risk of diarrhoea lasting 3 or 4 or more days (Analysis 7.1 and Analysis 7.2). We observed similar estimates of the effect of probiotics using the random effects model. Probiotics tended to reduce diarrhoea more in adults than children (Analysis 7.1 to Analysis 7.4), especially for the risk of diarrhoea lasting 4 or more days (Analysis 7.2). All trials reporting the mean duration of diarrhoea were conducted in infants and children.

Statistically significant between-study heterogeneity persisted in these subgroup analyses. Variability between studies may have persisted within subgroups. For example, the number of organisms and means of administration differed markedly even in studies of the same probiotic (*see* 'Characteristics of included studies'), and major causes of diarrhoea may have differed between countries with similar mortality rates. Also, other factors may have contributed to the between-study heterogeneity in the main analyses. Appendix 2 lists differences between studies in factors that may have influenced the progression of diarrhoea, such as antibiotic treatment before recruitment and nutritional differences in participants.

Adherence

Adherence to interventions was reported in only a few studies. Bhatnagar 1998 reported that in malnourished children the amount of milk consumed (control group) was statistically significantly greater than the amount of yoghurt (probiotic group). Boulloche 1994 reported that five participants receiving the probiotic and seven receiving the placebo did not comply with the study medication. Guandalini 2000 reported that one child in the probiotic group and three in the placebo group refused oral solutions. Rosenfeldt 2002a reported that four participants in the control group and four in the probiotic group were non-compliant with the trial protocol, and Rosenfeldt 2002b reported that 1 participant in the control group was non-compliant with the trial protocol, but no further details were given in either study.

Adverse events

Of all 23 selected studies, 12 studies reported that clinical observation of the participants revealed no adverse events, 8 did not collect or report information on adverse events, and 3 studies reported that an adverse event occurred (Pant 1996; Raza 1995; Shornikova 1997c).

Vomiting was reported as an adverse event; adverse events that led to withdrawal from treatment are described under 'Withdrawal from trial'. Pant 1996 reported that 1/19 children in the control group vomited 1 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 had vomiting from the second day of treatment and this was statistically significant on days 2 and 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.

No authors reported an adverse effect that they considered to be attributable to the probiotic.

Withdrawal from trial

Cetina-Sauri 1994 excluded from the analysis participants who deteriorated, developed concomitant illness and needed other drugs, or who wished to withdraw from the study. However, the number of participants withdrawn was not stated. In one multicentre study, it was not clear whether withdrawals occurred at the participating research centres (Guandalini 2000).

The study of *L. casei* strain GG in malnourished children reported that four children were removed from the study (Raza 1995); two

siblings with cholera developed severe dehydration (one in each intervention group), and one of a pair of twins developed pneumonia and the other refused anything by mouth (one in each intervention group). Also, myoclonic jerks occurred in one participant receiving *L. casei* strain GG and one receiving placebo; both had severe dehydration on admission. Rosenfeldt 2002a excluded participants after randomization because antibiotics were prescribed (3 control group/2 probiotic group), rapid recovery occurred before intervention started (3 control group/1 probiotic group), or non-compliance with the trial protocol (4 control group/4 probiotic group). Rosenfeldt 2002b excluded participants after enrolment because of hospitalization with excessive vomiting and moderate dehydration (2 placebo group/3 probiotic group), because antibiotics were prescribed (1 placebo group) and because of non-compliance with protocol (1 placebo group). Shornikova 1997c withdrew one child from the placebo group after stool culture identified the probiotic under trial. Wunderlich 1989 withdrew three participants from the probiotic group and three from the control group on or after day 4 of the intervention, but stated that this was for reasons unrelated to medication. No other trial reported that participants in either probiotic or placebo groups had been withdrawn from the study. Therefore, where reported, in total 15 participants were withdrawn from the probiotic and 20 from the control groups.

DISCUSSION

The striking finding of this review is that nearly all trials reported that probiotics had a beneficial effect in reducing diarrhoea, and this was statistically significant in many studies. This is despite great variability between studies in setting, participants recruited, probiotic tested, treatment regimens, and definitions of outcome measures. Given this marked variability in study design, it is not surprising that results varied markedly between studies. 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. The small number of studies limited the ability to assess whether other factors may have accounted for between study heterogeneity, especially with regards to the probiotic(s) used and identified diarrhoeal pathogens. However, it did not appear that differences between studies in either regional differences in major pathogens or the age of participants were responsible for the heterogeneity in results. Between-study heterogeneity may have been due to the many other differences between studies, such as differences between participants according to prior antibiotic treatment, nutritional status and proportion with bacterial diarrhoea, and marked differences in probiotic dosages and methods of administration (*see* 'Characteristics of included studies' and Appendix 2).

This statistically significant between-study heterogeneity for nearly all reported outcomes indicates that the summary analyses of treatment effect should be interpreted with caution. However, when we conducted the analysis using the random effects model, which accounts for between study differences, we found broadly similar estimates of treatment effect.

There was a scarcity of information regarding the effects of probiotics for specific infectious agents. *L. casei* strain GG may be particularly effective for rotavirus diarrhoea, but more data are needed. Interpretation of the results of the subgroup analyses, in which studies were classified according to national mortality rates, is complicated because it is not clear whether this classification reflects important regional differences in the major causes of diarrhoea. However, it appeared that the effects of probiotics were similar in developing and developed countries. Probiotics may be more effective in acute diarrhoea in adults than infants and children.

The adverse event of vomiting was reported in three studies, all of which recruited children (including some malnourished children). Because vomiting is common in children with acute diarrhoea and it occurred less frequently in the probiotic than the control groups, it seems unlikely to be caused by the probiotics. The causes of the withdrawal of participants from trials appeared to be related mostly to their primary illness rather than the interventions. 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. No authors reported adverse events that they considered to be attributable to probiotics. However, with the exception of malnourished children, most studies recruited previously healthy people. Therefore, no conclusions can be drawn regarding the safety of probiotics in other groups, for example, immunocompromised individuals, from this review.

Overall, we suggest that a variety of probiotics reduced infectious diarrhoea in children and adults in various settings. This suggests that a mechanism common to most probiotics, for example, colonization resistance, is effective against a wide range of gut pathogens. There were insufficient studies of specific probiotic regimens in defined groups of children or adults to allow for the development of definitive treatment guidelines. More well-designed studies are needed to advance the understanding of the efficacy of individual probiotics. Although trials of different probiotics in different participant groups and settings are to be encouraged, standardization of definitions of acute diarrhoea, treatment regimens, inclusion criteria, and outcome measures are needed to compare results across studies. All studies should try to present data separately for important subgroups, for example, according to identified causes of diarrhoea such as rotavirus or bacterial causes, or whether participants had received an antibiotic before recruitment. 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 (Reid 1999).

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 patient groups. For example, the apparent efficacy of probiotics in reducing the duration of acute diarrhoea may be particularly important in developing countries where acute diarrhoea in children is a risk factor for persistent diarrhoea (> 14 days) which, in turn, is closely associated with malnutrition (Walker-Smith 1993).

AUTHORS' CONCLUSIONS

Implications for practice

In individual studies, probiotics appeared to be moderately effective as adjunctive therapy in reducing the duration of diarrhoea. However, there were insufficient studies of specific probiotic regimens in defined groups of children or adults to inform the development of evidence-based treatment guidelines.

Most studies were performed in healthy individuals living in industrialized countries with uncomplicated diarrhoea, but some studies included malnourished children living in developing countries.

Implications for research

More studies of specific probiotic regimens in well-defined patient groups are needed to inform their role in clinical management. Trials need to use standardized definitions for acute diarrhoea and resolution of the illness, and they need to present data separately for important participant subgroups. All studies should include reliable identification of the probiotic being tested and confirm viability and number of organisms for live probiotics. Researchers should report whether the probiotic prevented or reversed dehydration − the most important complication of acute diarrhoea. In particular, the safety and potential of specific regimens to reduce the risk of persistent diarrhoea and associated malnutrition in children with acute diarrhoea in developing countries merits further study.

Basic research is needed to determine the mechanisms underlying the apparent beneficial effects of probiotics in acute diarrhoea.

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REFERENCES

References to studies included in this review

Bhatnagar 1998 *{published data only}*

* Bhatnagar S, Singh KD, Sazawal S, Saxena SK, Bhan MK. Efficacy of milk versus yogurt offered as part of a mixed diet in acute noncholera diarrhea among malnourished children. *Journal of Pediatrics* 1998;**132**(6):999–1004.

Boulloche 1994 *{published data only}*

* Boulloche J, Mouterde O, Mallet E. Management of acute diarrhoea in infants and young children. Controlled study of the anti-diarrheal efficacy of killed L. acidophilus (LB strain) versus a placebo and a reference drug (loperamide). *Annales de Pediatrie* 1994;**41**:457–63.

Bruno 1981 *{published data only}*

* Bruno F, Frigerio G. A new therapeutic alternative for the treatment of enteritis -- controlled double-blind tests with the strain SF 68 [Eine neuartige möglichkeit zur behandlung der enteritis – kontrollierte doppel–blindversuche mit dem Stamm SF 68]. *Schweizerische Rundschau fur Medizin Praxis* 1981;**70**(39):1717–20.

Bruno 1983 *{published data only}*

* Bruno F, Nastasi A, Bruno M. Double-blind controlled study of the effect of the lactogenic enterococcus SF68 strain on various enterocolitis associated manifestations and on salmonella infections [Studio controllato dopio–cieco sull'effecto dell'enterococco lattoproduttore ceppo SF 68 su manifestazione associate a forme enterocolitiche variee a salmonellosi]. *La Clinica Terapeutica* 1983; **105**(3):203–7.

Buydens 1996 *{published data only}*

* Buydens P, Debeuckelaere S. Efficacy of SF68 in the treatment of acute diarrhea. A placebo-controlled trial. *Scandanavian Journal of Gastroenterology* 1996;**31**(9):887–91.

Caragues-Orendain *{unpublished data only}*

* Carragues-Orendain A. Randomized, double blind placebo-controlled trial on the efficacy and safety of lactobacillus (Infloran Berna capsules) in the treatment of acute non-bloody diarrhoea in children two to five years of age.

Cetina-Sauri 1994 *{published data only}*

* Cetina-Sauri G, Sierra Basto G. Evaluation of Saccharomyces boulardii in children with acute diarrhea [Evaluation therapeutique de Saccharomyces boulardii chez des enfants souffrant de diarrhee aigue]. *Annales de Pediatrie* 1994;**41**(6):397–400.

D'Apuzzo 1982 *{published data only}*

* D'Apuzzo V, Salzberg R. The treatment of acute diarrhoea in paediatrics using Streptococcus faecium: results of a double blind trial [Die Behandlung der akuten Diarrho in der Padiatrie mit

Streptococcus faecium: Resultae einer doppleblindstudie]. *Therapeutische Umschau* 1982;**39**:1033–5.

Guandalini 2000 *{published data only}*

* Guandalini S, Pensabene L, Zikri MA, Dias JA, Casali LB, Hoekstra H, et al.Lactobacillus GG administered in oral rehydration solution to children with acute diarrhoea: a multicenter European trial. *Journal of Pediatric Gastroenterology and Nutrition* 2000;**30**(1):54–60.

Guarino 1997 *{published data only}*

Canani RB, Albano F, Spagnuolo MI, Di Benedetto L, Stabile A, Guarino A. Effect of oral administration of Lactobacillus GG on the duration of diarrhea and on rotavirus excretion in ambulatory children (Abstract). *Journal of Pediatric Gastroenterology and Nutrition* 1997;**24**:469.

* Guarino A, Canani RB, Spagnuolo MI, Albano F, Di Benedetto L. Oral bacterial therapy reduces the duration of symptoms and viral excretion in children with mild diarrhoea. *Journal of Pediatric Gastroenterology and Nutrition* 1997;**25**(5):516–9.

Hochter 1990 *{published data only}*

* Höchter W, Chase D, Hagenhoff G. Saccharomyces boulardii in the treatment of acute adult diarrhoea. [Saccharomyces boulardii bei acuter Erwachsenendiarrhoea]. *Münchener medizinische Wochenschrift* 1990;**132**:188–92.

Isolauri 1994 *{published data only}*

* Isolauri E, Kaila M, Mykkanen H, Ling WH, Salminen S. Oral bacteriotherapy for viral gastroenteritis. *Digestive Diseases and Sciences* 1994;**39**(12):2595–600.

Oandasan 1999 *{unpublished data only}*

* Oandasan M, Gatcheco F, Kapahmgan S. Randomized, double blind placebo-controlled clinical trial on the efficacy and safety of Infloran berna capsules in the treatment of acute non-bloody diarrhea in infants.

Pant 1996 *{published data only}*

* Pant AR, Graham SM, Allen SJ, Harikul S, Sabchareon A, Cuevas L, et al.Lactobacillus GG and acute diarrhoea in young children in the tropics. *Journal of Tropical Pediatrics* 1996;**42**(3):162–5.

Raza 1995 *{published data only}*

* Raza S, Graham SM, Allen SJ, Sultana S, Cuevas L, Hart CA. Lactobacillus GG promotes recovery from acute nonbloody diarrhoea in Pakistan. *The Pediatric Infectious Disease Journal* 1995; **14**(2):107–11.

Rosenfeldt 2002a *{published data only}*

* Rosenfeldt V, Michaelsen KF, Jakobsen M, Larsen CN, Moller PL, Pedersen P. Effect of probiotic Lactobacillus strains in young children hospitalized with acute diarrhea. *The Pediatric Infectious Disease Journal* 2002;**21**(5):411–6.

Rosenfeldt 2002b *{published data only}*

* Rosenfeldt V, Michaelsen KF, Jakobsen M, Larsen CN, Moller PL, Tvede M, et al.Effect of probiotic Lactobacillus strains on acute diarrhea in a cohort of nonhospitalized children attending day-care centers. *The Pediatric Infectious Disease Journal* 2002;**21**(5):417–9.

Shornikova 1997a *{published data only}*

* Shornikova AV, Isolauri E, Burkanova L, Lukovnikova S, Vesikari T. A trial in the Karelian Republic of oral rehydration and Lactobacillus GG for treatment of acute diarrhoea. *Acta Paediatrica* 1997;**86**(5):460–5.

Shornikova 1997b *{published data only}*

* Shornikova AV, Casas IA, Mykkanen H, Salo E, Vesikari T. Bacteriotherapy with Lactobacillus reuteri in rotavirus gastroenteritis. *The Pediatric Infectious Disease Journal* 1997;**16**(12): 1103–7.

Shornikova 1997c *{published data only}*

* Shornikova AV, Casas IA, Isolauri E, Mykkanen H, Vesikari T. Lactobacillus reuteri as a therapeutic agent in acute diarrhea in young children. *Journal of Pediatric Gastroenterology and Nutrition* 1997;**24**(4):399–404.

Simakachorn 2000 *{published data only}*

* Simakachorn N, Pichaipat V, Rithipornpaisarn P, Kongkaew C, Tongpradit P, Varavithya W. Clinical evaluation of the addition of lyophilized, heat-killed Lactobacillus acidophilus LB to oral rehydration therapy in the treatment of acute diarrhoea in children. *Journal of Pediatric Gastroenterology and Nutrition* 2000;**30**(1): 68–72.

Simakachorn N, Pichaipat V, Rithipornpaisarn P, Kongkaew C, Tongpradit P, Varavithya W. Erratum. *Journal of Pediatric Gastroenterology* 2000;**30**(2):228.

Sugita 1994 *{published data only}*

* Sugita T, Togawa M. Efficacy of Lactobacillus preparation bioloactis powder in children with rotavirus enteritis. *Japan Journal of Pediatrics* 1994;**47**:2755–62.

Wunderlich 1989 *{published data only}*

* Wunderlich PF, Braun L, Fumagalli I, D'Apuzzo V, Heim F, Karly M, et al.Double-blind report of the efficacy of lactic acid-producing Enterococcus SF68 in the prevention of antibiotic-associated diarrhoea and in the treatment of acute diarrhoea. *The Journal of International Medical Research* 1989;**17**(4):333–8.

References to studies excluded from this review

Alexander 1971 *{published data only}*

* Alexander JG. Lactobacillus casei tablets in the treatment of intestinal infection. *The Journal of the Royal College of General Practitioners* 1971;**21**(111):623–4.

Alvisi 1982 *{published data only}*

* Alvisi V, Tralli M, Loponte A, Pavani F, Massari M. Double-blind study of treatment with SF 68 or with antibiotics in acute enteritis in adults [Studio in doppio cieco sul trattamento con SF68 o con antibiotici nelle enteritis acute dell'adulto]. *La Clinica Terapeutica* 1982;**101**(6):581–6.

Barone 2000 *{published data only}*

* Barone C, Pettinato R, Avola E, Alberti A, Greco D, Failla P, et al.Comparison of three probiotics in the treatment of acute diarrhea in mentally retarded children. *Minerva Pediatrica* 2000;**52**(3): 161–5.

Beck 1961 *{published data only}*

* Beck C, Necheles H. Beneficial effects of administration of Lactobacillus acidophilus in diarrheal and other intestinal disorders. *The American Journal of Gastroenterology* 1961;**35**:522–30.

Bellomo 1979 *{published data only}*

* Bellomo G, Finocchiaro C, Frigerio G. A new approach for the treatment of enteritides in paediatrics [Une novelle approche pour

le traitement des entérites en pédiatrie]. *Medecine et Hygiene* 1979; **37**:3781–4.

Bellomo 1980 ***{published data only}***

* Bellomo G, Mangiagle A, Nicastro L, Frigeria G. A controlled double-blind study of SF68 strain as a new biological preparation for the treatment of diarrhoea in pediatrics. *Current Therapeutic Research: clinical and experimental* 1980;**28**:927–35.

Bellomo 1982 ***{published data only}***

* Bellomo G, Finocchiaro C, Frigerio G, Mangiagli A, Nicastro L. Controlled study of Enterococcus LAB strain SF68 in acute enteritis in children with concomitant respiratory infection [Studio controllato sull'enterococco L.A.B. ceppo SF 68 nelle enteriti acute del bambino concomitanti ad infezioni delle vie respiratorie]. *Clinica Pediatrica* 1982;**64**:219–27.

Bin Li Xie 1995 ***{published data only}***

* Bin Li Xie. Controlled clinical trial of Lacteol Fort Sachet versus furazolidone or berberine in treatment of acute diarrhoea in children [Étude contrôlée du Lactéol Fort sachets versus furazolidone ou berbérine dans le traitement des diarrhées aiguës de l'enfant]. *Annales de Pediatrie* 1995;**42**:396–401.

Camarri 1981 ***{published data only}***

* Camarri E, Belvisi A, Guidoni G, Marini G, Frigerio G. A double-blind comparison of two different treatments for acute enteritis in adults. *Chemotherapy* 1981;**27**(6):466–70.

Chapoy 1985 ***{published data only}***

* Chapoy P. Treatment of acute infantile diarrhea: controlled trial of Saccharomyces boulardii [Traitement des diarrhées aiguës infantiles]. *Annales de Pediatrie* 1985;**32**(6):561–3.

Chicoine 1973 ***{published data only}***

* Chicoine L, Joncas JH. Use of lactic enzymes in non-bacterial gastroenteritis [Emploi des ferments lactiques dans la gastro–entérite non bactérienne]. *L'Union Médicale du Canada* 1973;**102**(5):1114–5.

Costa-Ribeiro 2000a ***{published data only}***

* Costa-Ribeiro H, Ribeiro TCM, Mattos AP, Almeida PS, Valois SS, Vanderhoof JA. Use of Lactobacillus GG in the treatment of severe, acute diarrhoea in adverse environmental conditions.. *Journal of Pediatric Gastroenterology* 2000;**31 Suppl 2**:251–2.

Costa-Ribeiro 2000b ***{published data only}***

* Costa-Ribeiro H, Ribeiro TCM, Mattos AP, Lins EV, Neri DA, Valois SS, Vanderhoof JA. Prophylactic administration of Lactobacillus GG to children in a daycare center. *Journal of Pediatric Gastroenterology and Nutrition* 2000;**31 Suppl 2**:252.

de dios Pozo-O 1978 ***{published data only}***

* de dios Pozo-Olano J, Warram JH Jr, Gomez RG, Cavazos MG. Effect of a lactobacilli preparation on traveler's diarrhoea. A randomised, double blind clinical trial. *Gastroenterology* 1978;**74**(5 Pt 1):829–30.

Frigerio 1986 ***{published data only}***

* Frigerio G. A lactic acid producer enterococcus in the prevention of antibiotic-associated diarrhoea and in the treatment of acute diarrhoeal disorders: a double-blind multicentre placebo-controlled clinical trial (Abstract). *Digestive Diseases and Sciences* 1986;**31 Suppl**:496.

Girola 1995 ***{published data only}***

* Girola M, Ventura P. Efficacy of probiotic preparation with living, freeze-dried lactic acid bacteria and yeast on child diarrhoea [Efficacia di un prodotto probiotico a base di fermenti lattici e lievito vitali liofilizzati nel trattamento della diarrea del bambino]. *Archivio di Medicina Interna* 1995;**47**(2-3):61–72.

Gracheva 1996 ***{published data only}***

* Gracheva NM, Gavrilov AF, Solov'eva AI, Smirnov VV, Sorokulova IB, Reznik SR, et al.The efficacy of the new bacterial preparation biosporin in treating acute intestinal infections. *Zhurnal Mikrobiologii, Epidemiologii, i Immunobiologii* 1996;**1**: 75–7.

Isolauri 1991 ***{published data only}***

* Isolauri E, Juntunen M, Rautanen T, Sillanaukee P, Koivula T. A human Lactobacillus strain (Lactobacillus casei GG) promotes recovery from acute diarrhea in children. *Pediatrics* 1991;**88**(1): 90–7.

Kaila 1992 ***{published data only}***

* Kaila M, Isolauri E, Soppi E, Virtanen E, Laine S, Arvilommi H. Enhancement of the circulating antibody secreting cell response in human diarrhea by a human Lactobacillus strain. *Pediatric Research* 1992;**32**(2):141–4.

Kaila 1995 ***{published data only}***

* Kaila M, Isolauri E, Saxelin M, Arvilommi H, Vesikari T. Viable versus inactivated lactobacillus strain GG in acute rotavirus diarrhoea. *Archives of Disease in Childhood* 1995;**72**(1):51–3.

Korviakova 2000 ***{published data only}***

* Korviakova EP. Use of loading doses of Bifidumbacterin forte for the treatment of patients with acute enteric infections. *Zhurnal Mikrobiologii, Epidemiologii, i Immunobiologii* 2000, (6):58–61.

Majamaa 1995 ***{published data only}***

* Majamaa H, Isolauri E, Saxelin M, Vesikari T. Lactic acid bacteria in the treatment of acute rotavirus gastroenteritis. *Journal of Pediatric Gastroenterology and Nutrition* 1995;**20**(3):333–8.

Michielutti 1995 ***{published data only}***

* Michielutti F, Bertini M, Presciuttini B, Andreotti G. Clinical assessment of a new oral bacterial treatment for children with acute diarrhea [Valutazione clinica di un nuovo batterioterapico orale in pazienti di eta pediatrica con diarrea acuta]. *Minerva Medica* 1996; **87**(11):545–50.

Mitra 1990 ***{published data only}***

* Mitra AK, Rabbini GH. A double-blind, controlled trial of bioflorin (Streptococcus faecium SF68) in adults with acute diarrhea due to Vibrio chlolerae and entertoxigenic Escherichia coli. *Gastroenterology* 1990;**99**(4):1149–52.

Niv 1963 ***{published data only}***

* Niv M, Levy W, Greenstein NM. Yogurt in the treatment of infantile diarrhea. *Clinical Pediatrics* 1963;**2**:407–11.

Ortlieb 1974 ***{published data only}***

* Ortlieb R. Randomized comparative testing of a new drug in intestinal disorders in a child. *Therapie der Gegenwart* 1974;**113**(1): 76–8.

Pearce 1974 ***{published data only}***

* Pearce JL, Hamilton JR. Controlled trial of orally administered lactobacilli in acute infantile diarrhea. *The Journal of Pediatrics* 1974;**84**(2):261–2.

Pedone 1999 *{published data only}*

* Pedone CA, Bernabeu AO, Postaire ER, Bouley CF, Reinert P. The effect of supplementation with milk fermented by Lactobacillus casei (strain DN-114 001) on acute diarrhoea in children attending day care centres. *International Journal of Clinical Practice* 1999;**53**(3):179–84.

Pedone 2000 *{published data only}*

* Pedone CA, Arnaud CC, Postaire ER, Bouley CF, Reinert P. Multicentric study of the effect of milk fermented by Lactobacillus casei on the incidence of diarrhoea. *International Journal of Clinical Practice* 2000;**54**(9):568–71.

Pene 1966 *{published data only}*

* Pene P, Linhard J, Bernou JC. The colibacillus-lactobacillus combination in the treatment of diarrhea in adults, children and infants [L'association colibacilles–lactobacilles dans le traitement des diarrhées de l'adulte, de l'enfant et du nourrisson]. *La Semaine Des Hopitaux* 1966;**42**(4):241–4.

Rautanen 1998 *{published data only}*

* Rautanen T, Isolauri E, Salo E, Vesikari T. Management of acute diarrhoea with low osmolarity oral rehydration solutions and Lactobacillus strain GG. *Archives of Disease in Childhood* 1998;**79** (2):157–60.

Saint-Marc 1991 *{published data only}*

* Saint-Marc T, Rossello-Prats L, Touraine JL. Efficacy of Saccharomyces boulardii in the treatment of diarrhea in AIDS [Efficacite de Saccharomyces boulardii dans le traitement des diarrhees du SIDA]. *Annales de Medecine Interne* 1991;**142**(1):64–5.

Satoh 1984 *{published data only}*

* Satoh Y, Iwata S, Iwata Y, Yamashita N, Oikawa T, Osano M, et al.Effect of Bifidobacterium breve administration on clinical course and intestinal flora in children with acute diarrhea [Abstract]. *Nippon Shonikagakkai Zasshi* 1984;**88**:2178–9.

Sepp 1995 *{published data only}*

* Sepp E, Tamm E, Torm S, Lutsar I, Mikelsaar M, Salminen S. Impact of a Lactobacillus probiotic on the faecal microflora in children with shigellosis. *Microecology and Therapy* 1995;**23**:74–80.

Singh 1987 *{published data only}*

* Singh T. Yoghurt feeding during acute diarrhea. *Indian Pediatrics* 1987;**24**(6):530.

Tojo 1987 *{published data only}*

* Tojo M, Oikawa T, Morikawa Y, Yamashita N, Iwata S, Satoh Y, et al.The effects of Bifidobacterium breve administration on camylobacter enteritis. *Acta Paediatrica Japonica; Overseas edition* 1987;**29**(1):160–7.

References to studies awaiting assessment

Cetina-Sauri 1990 *{published data only}*

* Cetina-Sauri G, Sierra Basto G. Therapeutic evaluation of Saccharomyces boulardii in children with acute diarrhoea [Evaluacion terapeutica de Saccharomyces boulardii en ninos con diarrea aguda]. *Tribuna Medica (Bogota)* 1990;**81**(3):141–4.

Contreras 1983 *{published data only}*

* Contreras G. *Compend Invest Clin Latinoam* 1983;**3**:114–6.

Fourrier 1968 *{published data only}*

* Fourrier A, Lequien P. The treatment of infantile gastroenteritis by the use solely of a combination of colibacillus and lactobacillus. Apropos of 56 cases. *Annales de Pediatrie* 1968;**15**:491–5.

Salazar-Lindo ***{published data only (unpublished sought but not used)}***

Salazar-Lindo E. [LGG versus placebo in infants with acute watery diarrhoea, Peru, 1990s].

Salgado *{published data only}*

* Salgado AJ, Garcia Jara JA. Use of heat-killed Lactobacillus acidophilus, Lacteol strain in the treatment of acute diarrhoea. Open trial. *Revista del Hospital de la Muyer* **2**.

Taborska 1997 *{published data only}*

* Táborská J, Pazdiora P. [Smecta a Lactobacillus acidophilus ND v lécbe akutních detských prujmu]. *Cs. Pediat.* 1997;**1**:29–33.

Additional references

Anonymous 1988

Anonymous. Persistent diarrhoea in children in developing countries: memorandum from a WHO meeting. *Bulletin of the World Health Organization* 1988;**66**(6):709–17.

Bern 1992

Bern C. The magnitude of the global problem of diarrhoeal disease: a ten-year update. *Bulletin of the World Health Organization* 1992; **70**(6):705–14.

Black 1986

Black RE. Pathogens that cause traveler's diarrhea in Latin America and Africa. *Reviews of Infectious Diseases* 1986;**8 Suppl 2**:131–5.

Clarke 2003

Clarke M, Oxman A, editors. Optimal search strategy. Cochrane Reviewers' Handbook 4.2 [updated March 2003]; Appendix 5c. In: The Cochrane Library. The Cochrane Collaboration. Chichester, UK: John Wiley & Sons, Ltd.; 2003, Issue 3.

Cunliffe 1998

Cunliffe NA, Kilgore PE, Bresee JS, Steele AD, Luo N, Hart CA, et al.Epidemiology of rotavirus diarrhoea in Africa: a review to assess the need for rotavirus immunization. *Bulletin of the World Health Organization* 1998;**76**(5):525–37.

FAO/WHO 2001

Food and Agriculture Organization of the United Nations (FAO)/ World Health Organization (WHO). Joint FAO/WHO expert consultation on evaluation of health and nutritional properties of probiotics in food including powder milk and live lactic acid bacteria. ftp://ftp.fao.es/esn/food/probio_report_en.pdf 2001.

Gismondo 1999

Gismondo MR, Drago L, Lombardi A. Review of probiotics available to modify gastrointestinal flora. *International Journal of Antimicrobial Agents* 1999;**12**(4):287–92.

Goldin 1998

Goldin BR. Health benefits of probiotics. *The British Journal of Nutrition* 1998;**80 Suppl**(4):203–7.

Guerrant 1990

Guerrant RL, Hughes JM, Lima NL, Crane J. Diarrhea in developed and developing countries: magnitude, special settings,

and etiologies. *Reviews of Infectious Diseases* 1990;**12 Suppl 1**: 41–50.

Hata 1988
Hata D, Yoshida A, Ohkubo H, Mochizuki Y, Hosoki Y, Tanaka R, et al.Meningitis caused by Bifidobacterium in an infant. *The Pediatric Infectious Disease Journal* 1988;**7**(9):669–71.

Huilan 1991
Huilan S, Zhen LG, Mathan MM, Mathew MM, Olarte J, Espejo R, et al.Etiology of acute diarrhoea among children in developing countries: a multicentre study in five countries. *Bulletin of the World Health Organization* 1991;**69**(5):549–55.

Juni 1999
Juni P, Witschi A, Bloch R, Egger M. The hazards of scoring the quality of clinical trials for meta-analysis. *JAMA* 1999;**282**(11): 1054–60.

Klein 1998
Klein G, Pack A, Bonaparte C, Reuter G. Taxonomy and physiology of the probiotic lactic acid bacteria. *International Journal of Food Microbiology* 1998;**41**(2):103–25.

Naidu 1999
Naidu AS, Bidlack WR, Clemens RA. Probiotic spectra of lactic acid bacteria (LAB). *Critical Reviews in Food Science and Nutrition* 1999;**39**(1):13–126.

Piarroux 1999
Piarroux R, Millon L, Bardonnet K, Vagner O, Koenig H. Are live saccharomyces yeasts harmful to patients?. *Lancet* 1999;**353**(9167): 1851–2.

Reid 1999
Reid G. Testing the efficacy of probiotics. In: Tannock GW editor (s). *Probiotics: a critical review*. Norfolk, UK: Horizon Scientific Press, 1999:129–40. [: ISBN: 1–898486–15–8]

Salminen 1998
Salminen S, von Wright A, Morelli L, Marteau P, Brassart D, de Vos WM, et al.Demonstration of safety of probiotics -- a review. *International Journal of Food Microbiology* 1998;**44**(1-2):93–106.

Salminen 1999
Salminen S, Ouwehand A, Benno Y, Lee YK. Probiotics: how should they be defined?. *Trend Food Sci Technol* 1999;**10**:107–10.

Savarino 1993
Savarino SJ, Bourgeois AL. EpiDiarrhoeal disease: current concepts and future challenges. Epidemiology of diarrhoeal diseases in developed countries. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 1993;**87 Suppl 3**:7–11.

Saxelin 1996
Saxelin M, Chuang NH, Chassy B, Rautelin H, Makela PH, Salminen S, et al.Lactobacilli and bacteremia in southern Finland, 1989-1992. *Clinical Infectious Diseases* 1996;**22**(3):564–6.

Sussman 1986
Sussman J, Baron E, Goldberg S, Kaplan M, Pizzarello R. Clinical manifestations and therapy of Lactobacillus endocarditis: report of a case and review of the literature. *Reviews of Infectious Diseases* 1986;**8**(5):771–6.

Szajewska 2001
Szajewska H, Mrukowicz JZ. Probiotics in the treatment and prevention of acute infectious diarrhoea in infants and children; a systematic review of published randomized, double-blind, placebo-controlled trials. *Journal of Pediatric Gastroenterology and Nutrition* 2001;**33 Suppl 2**:17–25.

Van Niel 2002
Van Niel CW, Feudtner C, Garrison MM, Christakis DA. Lactobacillus therapy for acute infectious diarrhoea in children: a meta-analysis. *Pediatrics* 2002;**109**(4):678–84.

Vanderhoof 1998
Vanderhoof JA, Young RJ. Use of probiotics in childhood gastrointestinal disorders. *Journal of Pediatric Gastroenterology and Nutrition* 1998;**27**(3):323–32.

Walker-Smith 1993
Walker-Smith JA. Diarrhoeal disease: current concepts and future challenges. Malnutrition and infection. *Transactions of the Royal Society of Tropical Medicine* 1993;**87 Suppl 3**:13–5.

WHO 1990
Division of Diarrhoeal and Acute Respiratory Disease Control. *The treatment of diarrhoea. A manual for physicians and other senior health workers*. Geneva: World Health Organization, 1990:20–1.

WHO 2001
World Health Organization. *The world health report : 2001: Mental health : new understanding, new hope*. Geneva: World Health Organization, 2001.

* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Bhatnagar 1998

Methods	Study design: RCT; 2 centres.
Participants	Inclusion criteria: inpatients; malnourished boys (weight for height < 80% NCHS median) with diarrhoea (≥ 5 liquid stools in preceding 24 h) for ≤ 96 h. 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 Streptococcus thermophilus and Lactobacillus bulgaricus standard starter (International Yoghurt Manufacturers Club, Paris) 120 ml/kg/day for at least 72 h) added to milk formula. (2) Non-fermented Lactogen-2. Given after 8 h initial observation. All participants received rehydration fluids (IV if stool > 4 g/kg/h), IV cephalosporin and gentamicin, and fed with rice lentil oil gruel.
Outcomes	(1) Proportion recovered at 48 h and 72 h (defined as 2 consecutive formed stools, ≤ 3 stools in 24 h of which at least 2 were formed, or no stool for 12 h). (2) Median duration of diarrhoea. (3) Treatment failures (episode of diarrhoea after 72 h or stool weight > 150 g/kg on any day). No comment regarding adverse events.
Notes	Study location: India (high child and adult mortality).

Boulloche 1994

Methods	Study design: RCT; 1 centre.
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 Lactobacillus acidophilus (LB strain, Lacteol Forte, France; 1 sachet tds for first 24 h, then 1 sachet bd 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 observed.

Boulloche 1994 (*Continued*)

Notes	Study location: France (very low child and adult mortality). 18% all participants had positive stool cultures and 49% positive virology tests (no further details given). 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.

Bruno 1981

Methods	Study design: RCT; 1 centre.
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; $\geq$ 75 million 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 observed.
Notes	Study location: Italy (very low child and adult mortality). Bacterial stool culture (probiotic group/placebo group): Salmonella 4/3; enteropathogenic E. coli 18/20; other enteropathogen 1/3.

Bruno 1983

Methods	Study design: RCT; 1 centre.
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; $\geq$ 75 million lyophilized bacteria tds 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 observed.
Notes	Study location: Italy (very low child and adult mortality).

Buydens 1996

Methods	Study design: RCT; 2 centres.
Participants	Inclusion criteria: inpatients and outpatients; adults with acute diarrhoea (≥ 3 watery or loose stools in last 24 h). 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 antidiarrheals 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 million CFU tds 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 observed.
Notes	Study location: Belgium (very low child and adult mortality). 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).

Caragueorendain

Methods	Study design: RCT; 1 centre.
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 h; concomittent illness; severe malnutrition; antidiarrhoeal drugs; immunocompromise. Participants completing study: 35/35 (100%) in probiotic group and 35/35 (100%) in control group.
Interventions	(1) Lactobacillus acidophilus and Lactobacillus bifidus (Infloran Berna). (2) Placebo (no details given; unclear whether or not placebo was identical to probiotic). No details of dose, when treatment started, or duration of treatment.
Outcomes	(1) Resolution of diarrhoea (defined as no passage of stool for 12 h or 2 consecutive formed stools). Assessed in outpatients by phoning the parents. No adverse events observed.
Notes	Unpublished data. Study location: Philippines (low child and adult mortality). 42 children had some dehydration (none severe) and 28 had no dehydration.

Cetina-Sauri 1994

Methods	Study design: RCT; 1 centre.
Participants	Inclusion criteria: unclear whether inpatients and/or outpatients; 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) Saccharomyces boulardii (live Saccharomyces cerevisiae Hansen CBS 5926) 200 mg tds. (2) Glucose placebo (diluted in 5 ml cold water). Start and duration of treatment not stated.
Outcomes	(1) Number of stools per day. (2) First day stools formed. (3) Side effects. Cure defined as < 4 stools in 24 h and absence of liquid stools. No adverse events observed.
Notes	Study location: Mexico (low child and adult mortality).

D'Apuzzo 1982

Methods	Study design: RCT; unclear whether single or multicentre.
Participants	Inclusion criteria: unclear whether inpatients and/or outpatients; children with acute enteritis (duration and definition not given). Exclusion criteria: none stated. Number completing study: 21/21 (100%) in probiotic group and 18/18 (100%) in control group.
Interventions	(1) Streptococcus faecium (Streptococcus faecium 68; 75 million live bacteria tds 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. (3) No abdominal pains vomiting or fever for the whole day. No adverse events observed.
Notes	Study location: Switzerland (very low child and adult mortality). 7 participants in each group had positive stool cultures for bacteria. Streptococcus faecium 68 also appeared to promote recovery from abdominal pains, fever, and vomiting.

Guandalini 2000

Methods	Study design: RCT; multicentre.

Guandalini 2000 (*Continued*)

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 co-ordinating center were analysed (36 incomplete data or not compliant with protocol); unclear whether withdrawals occurred at participating centres.
Interventions	(1) Lactobacillus GG (ATC 53103, ≥ 10,000 million 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 (standard deviations not given). (6) Mean hospital stay. Some outcomes also reported for rotavirus, bacterial, and no organisms isolated subgroups. No comment regarding adverse events.
Notes	Study locations: Poland (low child and low 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). Stool analyses: rotavirus (56 probiotic/45 placebo); bacteria (35/34); parasites (7/6); no pathogen (45/54).

Guarino 1997

Methods	Study design: RCT; 1 centre.
Participants	Inclusion criteria: consecutive outpatients attending 3 family physicians; infants and children with ≥ 3 watery stools/day of < 48 h 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 Lactobacillus casei strain GG (Dicloflor 30; 3,000 million CFU bd for maximum 5 days) resuspended in milk or formula feed. (2) ORF only. Interventions started after 6 h of ORF.
Outcomes	(1) Mean duration of diarrhoea. Recovery from diarrhoea defined as time to last loose or liquid stools and assessed by mothers. Results for rotavirus subgroup also presented. No comment regarding adverse events.
Notes	Study location: Italy (very low child and adult mortality). The study author clarified that Figure 1 in the published article reports the mean and standard error for the duration of diarrhoea; standard deviations derived from graph. We also extracted data from Canani 1997 (abstract), which

Guarino 1997 (*Continued*)

	also reports standard errors. Duration of diarrhoea derived from graph. Probiotic also reduced prevalence of rotavirus in stools on day 6.

Hochter 1990

Methods	Study design: RCT; multicentre.
Participants	Inclusion criteria: outpatients attending general practitioners, gastroenterologists, and internal physicians; adults with "acute diarrhoea" (> 3 liquid stools in last 24 h; 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) Saccharomyces boulardii (Perenterol) 200 mg tds for 2 days then 100 mg tds on days 3 to 7. (2) Placebo. Interventions started at presentation.
Outcomes	(1) Mean stool frequency on days 1, 3, and 8; score derived from stool frequency and consistency. No adverse events observed.
Notes	Study location: Germany (very low child and adult mortality).

Isolauri 1994

Methods	Study design: RCT; 1 centre.
Participants	Inclusion criteria: inpatients; infants and children with > 3 watery stools/day for < 7 days and stools positive for rotavirus. Exclusion criteria: not stated. Definition of recovery from diarrhoea not stated. Number completing study: 21/21 (100%) in probiotic group and 21/21 (100%) in control group.
Interventions	(1) Freeze-dried Lactobacillus casei strain GG (10,000 million CFU bd for 5 days). (2) No probiotic. Interventions started after 6 h ORF.
Outcomes	(1) Mean weight gain. (2) Mean duration of diarrhoea. (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). Stools positive for rotavirus antigen (Rotazyme, Abbott) in all cases.

Oandasan 1999

Methods	Study design: RCT; 1 centre.
Participants	Inclusion criteria: inpatients; infants and children with non-bloody diarrhoea (characteristics not stated) for < 5 days. Exclusion criteria: antibiotics in last 72 h; antidiarrhoeal drugs; other illness; severe malnutrition; immunocompromise. Number completing study: 47/47 (100%) in probiotic group and 47/47 (100%) in placebo group.
Interventions	(1) Lyophilized Lactobacillus acidophilius and Lactobacillus bifidus (Infloran berna; 1,000 million organisms tds). (2) Placebo. When interventions started not stated.
Outcomes	(1) Mean duration of diarrhoea. (2) Proportion of participants with diarrhoea by day of treatment. (3) Mean hospital stay. Diarrhoea improved when no stool for 12 h or 2 consecutive formed stools. No adverse events observed.
Notes	Unpublished data. Study location: Philippines (low child and adult mortality). Unpublished data.

Pant 1996

Methods	Study design: RCT; 1 centre.
Participants	Inclusion criteria: inpatients; infants and children with > 3 watery stools in last 24 h and diarrhoea for < 14 days. Exclusion criteria: exclusive breastfeeding; 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) Freeze dried Lactobacillus GG (10,000 million to 100,000 thousand million CFU bd for 2 days). (2) Placebo. Interventions started after 6 h ORF.
Outcomes	(1) Mean duration of diarrhoea (time to last watery stool). (2) Mean stool frequency on days 1 and 2. Vomiting occurred in one child in the placebo group but did nt occur in the probiotic group. No other comment regarding adverse effects.
Notes	Study location: Thailand (low child and adult mortality). Mean (standard deviation) weight for age z score -1.15 (0.95) in the probiotic group and -1.8 (1.4) in the placebo group. Bloody stools in 6 children in probiotic and 7 in placebo group. All stools negative for parasites and cryptosporidium; electron microscopy showed 2 rotavirus and 1 astrovirus cases in the probiotic group and 5 rotavirus cases in the placebo group.

Raza 1995

Methods	Study design: RCT; 1 centre.
Participants	Inclusion criteria: inpatients; undernourished infants and children with > 3 watery stools in last 24 h 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 probiotic group and 17/19 (89.5%) in placebo group.
Interventions	(1) Freeze dried Lactobacillus GG (100,000 million to one billion CFU bd for 2 days). (2) Placebo. Interventions started after 4 to 6 h ORF.
Outcomes	(1) Stool frequency on days 1 and 2. (2) Frequency of vomiting on days 1 and 2. (3) Weight gain. (4) Outcomes for watery (non-bloody) diarrhoea also presented: mean (standard deviation) stool frequency day 2 for probiotic (n = 16) versus placebo (n = 16) was 4.4 (2.0) versus 6.6 (4.2), $P \leq 0.05$, and persistent diarrhoea at 48 h was 5 (31%) versus 12 (75%), $P \leq 0.01$. Definition of persistent diarrhoea not stated. Less vomiting in the probiotic group; myoclonic jerks occurred in one child in each group; no other comment regarding adverse events.
Notes	Study location: Pakistan (high child and adult mortality). Children with bloody stools included. Duration of diarrhoea not measured (many children discharged before stool character had changed).

Rosenfeldt 2002a

Methods	Study design: RCT; 2 centres.
Participants	Inclusion: inpatients; children aged 6 to 36 months with 2 or more consecutive loose stools in 24 h and duration no more than 7 days. Exclusion criteria: underlying chronic disease or antibiotics prescribed during study period. Number completing study: 86 children enrolled of which 69 (80.2%) completed the study; exclusions after randomization were because antibiotics prescribed (3 control group/2 probiotic group), rapid recovery before intervention started (3 control group/1 probiotic group), non-compliant to protocol (4 control group/4 probiotic group).
Interventions	(1) Lyophilized Lactobacillus rhamnosus 19070-2 and Lactobacillus reuteri DSM 12246 (10,000 million CFU of each given twice daily for 5 days). (2) Identical placebo (skim 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 comment regarding adverse events.
Notes	Study location: Denmark (very low child and adult mortality). Stool analysis showed rotavirus as the only pathogen in 40 (58%) children; 6 children had rotavirus and a bacterial pathogen identified; in addition, Campylobacter jejuni was isolated in 3 children and Salmonella typhimurium in 1

Rosenfeldt 2002a (*Continued*)

	child. 32 children (15 probiotic group, 17 control group) had mild/moderate dehydration on admission; none were severely dehydrated. 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 (standard deviation 1.0) versus 2.7 (standard deviation 2.0) respectively; P = 0.02). The probiotics also appeared to reduce significantly the number of children excreting rotavirus in the stools on day 5.

Rosenfeldt 2002b

Methods	Study design: RCT; 19 day-care centres.
Participants	Inclusion criteria: outpatients; children aged 6 to 36 months with 2 or more consecutive loose stools in 24 h 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 which 43 (86%) participants completed the study. Exclusions were because of hospitalization with excessive vomiting and moderate dehydration (2 placebo group/3 probiotic group), 1 antibiotics prescribed (placebo group), 1 non-compliant with protocol (placebo group).
Interventions	(1) Lyophilized Lactobacillus rhamnosus 19070-2 and Lactobacillus reuteri DSM 12246 (10,000 million CFU of each given twice daily 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). No serious adverse events observed.
Notes	Study location: Denmark (very low child and adult mortality). Stool analysis showed rotavirus as the only pathogen in 25 children, 2 had rotavirus and a bacterial pathogen identified, 2 had infection with Campylobacter jejuni and Salmonella typhimurium. 7 children (3 probiotic group, 4 placebo group) had mild/moderate dehydration on presentation; none were severely dehydrated. The probiotics appeared to reduce significantly the duration of diarrhoea in children treated within 60 h of the onset of diarrhoea. One participant in the probiotic group complained of constipation (no stools passed from day 3 for 10 days).

Shornikova 1997a

Methods	Study design: RCT; 1 centre.
Participants	Inclusion criteria: inpatients; infants and children with $\geq$ 1 watery stool in last 24 h 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 enrolled. 59/59 children allocated to probiotic group and 64/64 (100%) in placebo group completed the trial.

Shornikova 1997a (*Continued*)

Interventions	(1) Lactobacillus strain GG (American type culture collection 53 103; 5000 million CFU bd 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). Amongst children with rotavirus diarrhoea, the probiotic (n = 13) reduced the number of watery stools compared with placebo (n = 21; P = 0.02, but no data given). A beneficial effect of the probiotic was not 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.

Shornikova 1997b

Methods	Study design: RCT; 2 centres.
Participants	Inclusion criteria: inpatients; infants and children with $\geq$ 3 watery stools in last 24 h, diarrhoea for < 7 days; stools positive for rotavirus antigen (IDEIA Rotavirus, UK). Exclusion criteria: not stated. Number completing study: 86/97 (89%) enrolled participants were positive for rotavirus. 20 participants who received exclusively or mainly IV fluids were excluded. Results presented for 66/86 (77%) participants who received oral rehydration (20 in small dose group, 21 in large dose group, 25 in placebo group).
Interventions	(1) Freeze-dried Lactobacillus reuteri (low dose: 10 million CFU o.d. for maximum 5 days; high dose: 10,000 million to 100,000 million CFU o.d. for maximum 5 days). (2) Placebo. Interventions started with ORF.
Outcomes	(1) Duration of diarrhoea (time to last watery stool in a 24-h 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). Data from high dose probiotic group used for continous outcomes. Data from low and high dose groups combined for non-continous outcomes. Duration of diarrhoea before admission greater in probiotic group (4.2 (standard deviation 1.4) days) than placebo group (2.9 (standard deviation 1.2) days). Number with persistent diarrhoea on day 3 derived from graph.

Shornikova 1997c

Methods	Study design: RCT; 1 centre.
Participants	Inclusion criteria: inpatients; infants and children with ≥ 3 watery stools in last 24 h; diarrhoea for < 7 days; ingested bovine dairy products. Exclusion criteria: immunosuppressive therapy or immune deficiency; allergy to bovine milk; serious underlying disorder; taken 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 probiotic agent (Lactobacillus reuteri) was detected in stool; probiotic was administered to his sibling).
Interventions	(1) Freeze-dried Lactobacillus reuteri SD 2112 (10,000 million to 100,000 million CFU o.d.) for a maximum of 5 days. (2) Placebo for a maximum of 5 days. 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 other comment regarding adverse events.
Notes	Study location: Finland (very low child and adult mortality). 12 (63%) of placebo group and 18 (86%) of probiotic group had stools positive for rotavirus antigen by enzyme immunoassay. Mean (standard deviation) percentage dehydration was greater in probiotic group (n = 19; 3.9 (1.3)) versus placebo group (n = 21; 3.0 (1.2); P = 0.02).

Simakachorn 2000

Methods	Study design: RCT; 1 centre.
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 probiotic group and 36/36 (100%) in placebo group.
Interventions	(1) Lyophilized, heat-killed Lactobacillus acidophilus LB (MA65/4E; Lacteol Fort sachets, Laboratoire du Lacteol du Docteur Boucard, Houdan, France; 20,000 million organisms and fermented culture medium 5 doses over 48 h). (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 h). (2) Recovery from diarrhoea by day of treatment. (3) Recovery from diarrhoea at 24 h in rotavirus-positive cases. No comment regarding adverse events.

Simakachorn 2000 (*Continued*)

Notes	Study location: Thailand (low child and adult mortality). 40 children (17 probiotic and 23 placebo) had received antibiotics before admission. Effect of probiotic in shortening duration of diarrhoea more marked in children who had not received antibiotics before admission.

Sugita 1994

Methods	Study design: quasi-RCT; 1 centre.
Participants	Inclusion criteria: inpatients; infants and children < 2 years 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 probiotic group and 11/15 (73.3%) in control group.
Interventions	(1) Live Lactobacillus casei (1.5 g/day in 3 doses) 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 observed.
Notes	Study location: Japan (very low child and adult mortality). 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.

Wunderlich 1989

Methods	Study location: RCT; 10 centres.
Participants	Inclusion criteria: adults with "acute diarrhoea" (characteristics and duration not stated). Exclusion criteria: not stated. Number completing study (for persisting diarrhoea outcomes): 40/40 (100%) in probiotic group and 38/38 (100%) in placebo group; 3 participants from each group withdrawn on day 4 or later (causes for drop outs stated to be unrelated to medication); 4 participants assigned to probiotic group and 5 assigned to placebo group did not complete the study (reasons not stated).
Interventions	(1) Lyophilized Enterococcus SF 68 (Bioflorin; 75 million bacteria tds 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 observed.

Wunderlich 1989 (*Continued*)

Notes	Study location: Switzerland and Lichtenstein (very low child and adult mortality).

bd: twice daily; CFU: colony-forming units; IV: intravenous; NCHS: National Centre for Health Statistics; o.d.: once daily ORF: oral rehydration fluid; RCT: randomized controlled trial; tds: three times daily.

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

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 extractable outcome data for meta-analysis: 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.
Camarri 1981	Intervention groups not treated equally; antibiotics given to the non-probiotic group.
Chapoy 1985	No extractable outcome data for meta-analysis.
Chicoine 1973	No extractable outcome data for meta-analysis.
Costa-Ribeiro 2000a	Unclear whether a randomized controlled trial.
Costa-Ribeiro 2000b	Assessment of Lactobacillus GG in the prevention of diarrhoea.
de dios Pozo-O 1978	Assessment of probiotic in the prevention of traveller's diarrhoea.
Frigerio 1986	No extractable data for meta-analysis.
Girola 1995	Children with gastroenteritis and antibiotic-associated diarrhoea studied together.
Gracheva 1996	No non-probiotic group; details of randomization and allocation concealment not given.

(*Continued*)

Isolauri 1991	No non-probiotic group.
Kaila 1992	No non-probiotic group.
Kaila 1995	No non-probiotic group.
Korviakova 2000	Not a randomized controlled trial; probiotic versus antibiotic.
Majamaa 1995	No non-probiotic group.
Michielutti 1995	Not a randomized controlled trial.
Mitra 1990	No non-probiotic group.
Niv 1963	Not a randomized controlled trial; some children with diarrhoea thought to be caused by antibiotic treatment also included.
Ortlieb 1974	No extractable outcome data for meta-analysis; 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	Assessment of milk fermented by Lactobacillus casei (strain DN-114 001) in the prevention of diarrhoea.
Pedone 2000	Assessment of milk fermented by Lactobacillus casei (strain DN-114 001) in the prevention of diarrhoea.
Pene 1966	No non-probiotic group; participants with diarrhoea of various causes (infectious, post-antibiotics) grouped together.
Rautanen 1998	No extractable outcome data for meta-analysis; no data presented for placebo group.
Saint-Marc 1991	Not a randomized controlled trial; no non-probiotic group.
Satoh 1984	Not a randomized controlled trial; no non-probiotic group.
Sepp 1995	No extractable outcome data for meta-analysis; duration of diarrhoea given as median value only; proportion of participants cured stated for days 5 and 10 only.
Singh 1987	No probiotic specified.
Tojo 1987	Unclear whether diarrhoea acute and whether a randomized controlled trial.

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

Cetina-Sauri 1990

Methods	-
Participants	
Interventions	-
Outcomes	
Notes	-

Contreras 1983

Methods	-
Participants	-
Interventions	-
Outcomes	-
Notes	-

Fourrier 1968

Methods	-
Participants	-
Interventions	-
Outcomes	-
Notes	-

Salazar-Lindo

Methods	-
Participants	-
Interventions	-
Outcomes	-

Salazar-Lindo (*Continued*)

Notes	-

Salgado

Methods	-
Participants	-
Interventions	-
Outcomes	-
Notes	-

Taborska 1997

Methods	-
Participants	-
Interventions	-
Outcomes	-
Notes	-

DATA AND ANALYSES

Comparison 1. Probiotic versus control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Diarrhoea lasting 3 or more days	15	1341	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.55, 0.77]
1.1 Live Lactobacillus casei strain GG	2	329	Risk Ratio (M-H, Random, 95% CI)	0.51 [0.14, 1.83]
1.2 Live Lactobacillus reuteri	2	106	Risk Ratio (M-H, Random, 95% CI)	0.49 [0.26, 0.94]
1.3 Live Enterococcus LAB strain SF68	5	372	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.47, 0.74]
1.4 Live Lactobacillus acidophilus and Lactobacillus bifidus	2	164	Risk Ratio (M-H, Random, 95% CI)	0.52 [0.21, 1.28]
1.5 Live Streptococcus thermophilus and Lactobacillus bulgaricus	1	96	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.76, 1.55]
1.6 Killed Lactobacillus acidophilus LB strain	2	144	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.40, 1.46]
1.7 Saccharomyces boulardii	1	130	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.58, 0.87]
2 Diarrhoea lasting 4 or more days	13	1228	Risk Ratio (M-H, Random, 95% CI)	0.31 [0.19, 0.50]
2.1 Live Lactobacillus casei strain GG	1	287	Risk Ratio (M-H, Random, 95% CI)	0.61 [0.43, 0.85]
2.2 Live Lactobacillus reuteri	2	106	Risk Ratio (M-H, Random, 95% CI)	0.29 [0.06, 1.51]
2.3 Live Enterococcus LAB strain SF68	5	372	Risk Ratio (M-H, Random, 95% CI)	0.23 [0.11, 0.49]
2.4 Live Lactobacillus acidophilus and Lactobacillus bifidus	2	164	Risk Ratio (M-H, Random, 95% CI)	0.06 [0.01, 0.31]
2.5 Live Streptococcus thermophilus and Lactobacillus bulgaricus	1	96	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.61, 1.79]
2.6 Killed Lactobacillus acidophilus LB strain	1	73	Risk Ratio (M-H, Random, 95% CI)	0.11 [0.01, 0.81]
2.7 Saccharomyces boulardii	1	130	Risk Ratio (M-H, Random, 95% CI)	0.41 [0.26, 0.66]
3 Mean duration of diarrhoea (hours)	12	970	Mean Difference (IV, Random, 95% CI)	-30.48 [-42.46, -18.51]
3.1 Live Lactobacillus casei strain GG	5	578	Mean Difference (IV, Random, 95% CI)	-31.18 [-51.62, -10.75]
3.2 Live Lactobacillus reuteri	2	86	Mean Difference (IV, Random, 95% CI)	-25.33 [-40.70, -9.95]
3.3 Live Lactobacillus casei	1	27	Mean Difference (IV, Random, 95% CI)	-36.0 [-65.87, -6.13]
3.4 Live Lactobacillus rhamnosus and Lactobacillus reuteri	2	112	Mean Difference (IV, Random, 95% CI)	-23.43 [-41.47, -5.40]

3.5 Live Lactobacillus acidophilus and Lactobacillus bifidus	1	94	Mean Difference (IV, Random, 95% CI)	-51.07 [-60.09, -42.05]
3.6 Killed Lactobacillus acidophilus LB strain	1	73	Mean Difference (IV, Random, 95% CI)	-13.60 [-28.10, 0.90]
4 Mean stool frequency on day 2	5	417	Mean Difference (IV, Fixed, 95% CI)	-1.51 [-1.85, -1.17]
4.1 Live Lactobacillus casei strain GG	2	62	Mean Difference (IV, Fixed, 95% CI)	-1.50 [-2.83, -0.17]
4.2 Live Lactobacillus reuteri	1	40	Mean Difference (IV, Fixed, 95% CI)	-1.5 [-2.93, -0.07]
4.3 Live Enterococcus LAB strain SF68	1	185	Mean Difference (IV, Fixed, 95% CI)	-1.70 [-2.10, -1.30]
4.4 Saccharomyces boulardii	1	130	Mean Difference (IV, Fixed, 95% CI)	-0.62 [-1.49, 0.25]
5 Mean stool frequency on day 3	4	447	Mean Difference (IV, Fixed, 95% CI)	-1.31 [-1.56, -1.07]
5.1 LIve Lactobacillus reuteri	1	40	Mean Difference (IV, Fixed, 95% CI)	-1.2 [-2.60, 0.20]
5.2 Live Enterococcus LAB strain SF68	1	185	Mean Difference (IV, Fixed, 95% CI)	-1.4 [-1.67, -1.13]
5.3 Saccharomyces boulardii	2	222	Mean Difference (IV, Fixed, 95% CI)	-0.92 [-1.52, -0.32]

Comparison 2. Sensitivity analysis; diarrhoea lasting 3 or more days

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Generation of allocation sequence	15		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Adequate	8	710	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.53, 0.84]
1.2 Inadequate or unclear	7	631	Risk Ratio (M-H, Random, 95% CI)	0.60 [0.44, 0.82]
2 Allocation concealment	15		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Adequate	4	392	Risk Ratio (M-H, Random, 95% CI)	0.53 [0.35, 0.81]
2.2 Inadequate or unclear	11	949	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.58, 0.85]
3 Blinding	15		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 Adequate	8	872	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.50, 0.77]
3.2 Inadequate or unclear	7	469	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.50, 0.97]
4 Follow up	15		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 Adequate	10	624	Risk Ratio (M-H, Random, 95% CI)	0.58 [0.41, 0.82]
4.2 Inadequate or unclear	5	717	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.58, 0.81]

Comparison 3. Sensitivity analysis: diarrhoea lasting 4 or more days

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Generation of allocation sequence	13		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Adequate	7	639	Risk Ratio (M-H, Random, 95% CI)	0.26 [0.11, 0.62]
1.2 Indequate or unclear	6	589	Risk Ratio (M-H, Random, 95% CI)	0.42 [0.27, 0.66]
2 Allocation concealment	13		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

2.1 Adequate	4	392	Risk Ratio (M-H, Random, 95% CI)	0.15 [0.05, 0.41]
2.2 Inadequate or unclear	9	836	Risk Ratio (M-H, Random, 95% CI)	0.46 [0.31, 0.68]
3 Blinding	13		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 Adequate	8	872	Risk Ratio (M-H, Random, 95% CI)	0.24 [0.12, 0.48]
3.2 Inadequate or unclear	5	356	Risk Ratio (M-H, Random, 95% CI)	0.46 [0.23, 0.93]
4 Follow up	13		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 Adequate	8	511	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.16, 0.69]
4.2 Inadequate or unclear	5	717	Risk Ratio (M-H, Random, 95% CI)	0.27 [0.13, 0.56]

Comparison 4. Sensitivity analysis; mean duration of diarrhoea (hours)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Generation of allocation sequence	12		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1 Adequate	5	430	Mean Difference (IV, Random, 95% CI)	-38.00 [-57.48, -18.53]
1.2 Inadequate or unclear	7	540	Mean Difference (IV, Random, 95% CI)	-18.02 [-23.38, -12.65]
2 Allocation concealment	12		Mean Difference (IV, Random, 95% CI)	Subtotals only
2.1 Adequate	4	330	Mean Difference (IV, Random, 95% CI)	-30.64 [-52.20, -9.08]
2.2 Inadequate or unclear	8	640	Mean Difference (IV, Random, 95% CI)	-30.36 [-45.36, -15.37]
3 Blinding	12		Mean Difference (IV, Random, 95% CI)	Subtotals only
3.1 Adequate	9	801	Mean Difference (IV, Random, 95% CI)	-26.94 [-39.87, -14.00]
3.2 Inadequate or unclear	3	169	Mean Difference (IV, Random, 95% CI)	-40.12 [-73.60, -6.65]
4 Follow up	12		Mean Difference (IV, Random, 95% CI)	Subtotals only
4.1 Adequate	6	375	Mean Difference (IV, Random, 95% CI)	-35.72 [-54.04, -17.40]
4.2 Inadequate or unclear	6	595	Mean Difference (IV, Random, 95% CI)	-17.78 [-23.80, -11.76]

Comparison 5. Children with rotavirus diarrhoea

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mean duration of diarrhoea (hours)	4	231	Mean Difference (IV, Random, 95% CI)	-38.10 [-68.10, -8.10]

Comparison 6. 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 Diarrhoea lasting 3 or more days	14		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Very low/very low	9	591	Risk Ratio (M-H, Random, 95% CI)	0.57 [0.46, 0.70]
1.2 Low/low	4	367	Risk Ratio (M-H, Random, 95% CI)	0.64 [0.44, 0.92]
1.3 High/high	1	96	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.76, 1.55]
2 Diarrhoea lasting 4 or more days	12		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Very low/very low	7	478	Risk Ratio (M-H, Random, 95% CI)	0.25 [0.13, 0.46]
2.2 Low/low	4	367	Risk Ratio (M-H, Random, 95% CI)	0.15 [0.04, 0.61]
2.3 High/high	1	96	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.61, 1.79]
3 Mean duration of diarrhoea (hours)	11		Mean Difference (IV, Random, 95% CI)	Subtotals only
3.1 Very low/very low	7	367	Mean Difference (IV, Random, 95% CI)	-33.02 [-49.89, -16.14]
3.2 Low/low	3	193	Mean Difference (IV, Random, 95% CI)	-33.08 [-61.24, -4.92]
3.3 Low/high	1	123	Mean Difference (IV, Random, 95% CI)	-26.40 [-47.67, -5.13]
4 Mean stool frequency on day 2	5		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
4.1 Very low/very low	2	225	Mean Difference (IV, Fixed, 95% CI)	-1.69 [-2.07, -1.30]
4.2 Low/low	2	156	Mean Difference (IV, Fixed, 95% CI)	-0.84 [-1.62, -0.06]
4.3 High/high	1	36	Mean Difference (IV, Fixed, 95% CI)	-1.20 [-3.30, 0.90]
5 Mean stool frequency on day 3	4		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
5.1 Very low/very low	3	317	Mean Difference (IV, Fixed, 95% CI)	-1.34 [-1.60, -1.08]
5.2 Low/low	1	130	Mean Difference (IV, Fixed, 95% CI)	-1.1 [-1.85, -0.35]

Comparison 7. Age of participants

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Diarrhoea lasting 3 or more days	15		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Infants and children	11	1008	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.54, 0.85]
1.2 Adults	4	333	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.51, 0.74]
2 Diarrhoea lasting 4 or more days	13		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Infants and children	9	895	Risk Ratio (M-H, Random, 95% CI)	0.41 [0.24, 0.68]
2.2 Adults	4	333	Risk Ratio (M-H, Random, 95% CI)	0.21 [0.08, 0.52]
3 Mean stool frequency on day 2	5		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
3.1 Infants and children	4	232	Mean Difference (IV, Fixed, 95% CI)	-1.01 [-1.66, -0.36]
3.2 Adults	1	185	Mean Difference (IV, Fixed, 95% CI)	-1.70 [-2.10, -1.30]
4 Mean stool frequency on day 3	4		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
4.1 Infants and children	2	170	Mean Difference (IV, Fixed, 95% CI)	-1.12 [-1.79, -0.46]
4.2 Adults	2	277	Mean Difference (IV, Fixed, 95% CI)	-1.35 [-1.61, -1.08]

Analysis 1.1. Comparison 1 Probiotic versus control, Outcome 1 Diarrhoea lasting 3 or more days.

Review: Probiotics for treating infectious diarrhoea

Comparison: 1 Probiotic versus control

Outcome: 1 Diarrhoea lasting 3 or more days

Study or subgroup	Probiotic n/N	No probiotic n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Live Lactobacillus casei strain GG					
Guandalini 2000	78/147	90/140		16.1 %	0.83 [0.68, 1.00]
Isolauri 1994	2/21	9/21		1.3 %	0.22 [0.05, 0.91]
Subtotal (95% CI)	**168**	**161**		**17.4 %**	**0.51 [0.14, 1.83]**
Total events: 80 (Probiotic), 99 (No probiotic)					
Heterogeneity: $Tau^2 = 0.65$; $Chi^2 = 3.46$, df = 1 (P = 0.06); $I^2 = 71\%$					
Test for overall effect: Z = 1.03 (P = 0.30)					
2 Live Lactobacillus reuteri					
Shornikova 1997b	11/41	11/25		4.8 %	0.61 [0.31, 1.19]
Shornikova 1997c	3/19	11/21		2.0 %	0.30 [0.10, 0.92]
Subtotal (95% CI)	**60**	**46**		**6.8 %**	**0.49 [0.26, 0.94]**
Total events: 14 (Probiotic), 22 (No probiotic)					
Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 1.17$, df = 1 (P = 0.28); $I^2 = 14\%$					
Test for overall effect: Z = 2.15 (P = 0.032)					
3 Live Enterococcus LAB strain SF68					
Bruno 1981	6/25	17/24		4.1 %	0.34 [0.16, 0.71]
Bruno 1983	3/10	7/11		2.3 %	0.47 [0.17, 1.34]
Buydens 1996	57/93	88/92		17.1 %	0.64 [0.54, 0.76]
D'Apuzzo 1982	4/21	10/18		2.6 %	0.34 [0.13, 0.91]
Wunderlich 1989	19/40	27/38		9.9 %	0.67 [0.46, 0.98]
Subtotal (95% CI)	**189**	**183**		**35.8 %**	**0.59 [0.47, 0.74]**
Total events: 89 (Probiotic), 149 (No probiotic)					
Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 5.08$, df = 4 (P = 0.28); $I^2 = 21\%$					
Test for overall effect: Z = 4.61 (P < 0.00001)					
4 Live Lactobacillus acidophilus and Lactobacillus bifidus					
Caragüe-Orendain	7/35	8/35		3.0 %	0.88 [0.36, 2.15]
Oandasan 1999	9/47	26/47		5.1 %	0.35 [0.18, 0.66]
Subtotal (95% CI)	**82**	**82**		**8.1 %**	**0.52 [0.21, 1.28]**
Total events: 16 (Probiotic), 34 (No probiotic)					
Heterogeneity: $Tau^2 = 0.27$; $Chi^2 = 2.71$, df = 1 (P = 0.10); $I^2 = 63\%$					

(*Continued . . .*)

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Study or subgroup	Probiotic n/N	No probiotic n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Test for overall effect: Z = 1.42 (P = 0.16)					
5 Live Streptococcus thermophilus and Lactobacillus bulgaricus					
Bhatnagar 1998	27/47	26/49		10.5 %	1.08 [0.76, 1.55]
Subtotal (95% CI)	**47**	**49**		**10.5 %**	**1.08 [0.76, 1.55]**
Total events: 27 (Probiotic), 26 (No probiotic)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.43 (P = 0.67)					
6 Killed Lactobacillus acidophilus LB strain					
Boulloche 1994	4/38	5/33		1.7 %	0.69 [0.20, 2.38]
Simakachorn 2000	9/37	11/36		4.0 %	0.80 [0.38, 1.69]
Subtotal (95% CI)	**75**	**69**		**5.7 %**	**0.77 [0.40, 1.46]**
Total events: 13 (Probiotic), 16 (No probiotic)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.03, df = 1 (P = 0.85); I^2 =0.0%					
Test for overall effect: Z = 0.81 (P = 0.42)					
7 Saccharomyces boulardii					
Cetina-Sauri 1994	41/65	58/65		15.7 %	0.71 [0.58, 0.87]
Subtotal (95% CI)	**65**	**65**		**15.7 %**	**0.71 [0.58, 0.87]**
Total events: 41 (Probiotic), 58 (No probiotic)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.33 (P = 0.00087)					
Total (95% CI)	**686**	**655**		**100.0 %**	**0.66 [0.55, 0.77]**
Total events: 280 (Probiotic), 404 (No probiotic)					
Heterogeneity: Tau^2 = 0.04; Chi^2 = 26.24, df = 14 (P = 0.02); I^2 =47%					
Test for overall effect: Z = 4.95 (P < 0.00001)					

Analysis 1.2. Comparison 1 Probiotic versus control, Outcome 2 Diarrhoea lasting 4 or more days.

Review: Probiotics for treating infectious diarrhoea

Comparison: 1 Probiotic versus control

Outcome: 2 Diarrhoea lasting 4 or more days

Study or subgroup	Probiotic n/N	No probiotic n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Live Lactobacillus casei strain GG					
Guandalini 2000	37/147	58/140		13.1 %	0.61 [0.43, 0.85]
Subtotal (95% CI)	**147**	**140**		**13.1 %**	**0.61 [0.43, 0.85]**
Total events: 37 (Probiotic), 58 (No probiotic)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.86 (P = 0.0042)					
2 Live Lactobacillus reuteri					
Shornikova 1997b	1/41	6/25		3.9 %	0.10 [0.01, 0.80]
Shornikova 1997c	3/19	6/21		7.3 %	0.55 [0.16, 1.91]
Subtotal (95% CI)	**60**	**46**		**11.2 %**	**0.29 [0.06, 1.51]**
Total events: 4 (Probiotic), 12 (No probiotic)					
Heterogeneity: Tau^2 = 0.76; Chi^2 = 2.01, df = 1 (P = 0.16); I^2 =50%					
Test for overall effect: Z = 1.47 (P = 0.14)					
3 Live Enterococcus LAB strain SF68					
Bruno 1981	2/25	11/24		6.4 %	0.17 [0.04, 0.71]
Bruno 1983	1/10	7/11		4.4 %	0.16 [0.02, 1.06]
Buydens 1996	7/93	61/92		10.6 %	0.11 [0.05, 0.23]
D'Apuzzo 1982	3/21	7/18		7.5 %	0.37 [0.11, 1.22]
Wunderlich 1989	11/40	23/38		11.8 %	0.45 [0.26, 0.80]
Subtotal (95% CI)	**189**	**183**		**40.7 %**	**0.23 [0.11, 0.49]**
Total events: 24 (Probiotic), 109 (No probiotic)					
Heterogeneity: Tau^2 = 0.41; Chi^2 = 10.78, df = 4 (P = 0.03); I^2 =63%					
Test for overall effect: Z = 3.84 (P = 0.00012)					
4 Live Lactobacillus acidophilus and Lactobacillus bifidus					
Caragüe-Orendain	0/35	4/35		2.3 %	0.11 [0.01, 1.99]
Oandasan 1999	1/47	22/47		4.2 %	0.05 [0.01, 0.32]
Subtotal (95% CI)	**82**	**82**		**6.5 %**	**0.06 [0.01, 0.31]**
Total events: 1 (Probiotic), 26 (No probiotic)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.26, df = 1 (P = 0.61); I^2 =0.0%					
Test for overall effect: Z = 3.39 (P = 0.00069)					
5 Live Streptococcus thermophilus and Lactobacillus bulgaricus					
Bhatnagar 1998	17/47	17/49		12.0 %	1.04 [0.61, 1.79]

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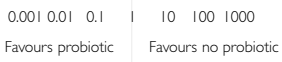
Study or subgroup	Probiotic n/N	No probiotic n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Subtotal (95% CI)	**47**	**49**		**12.0 %**	**1.04 [0.61, 1.79]**
Total events: 17 (Probiotic), 17 (No probiotic)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.15 (P = 0.88)					
6 Killed Lactobacillus acidophilus LB strain					
Simakachorn 2000	1/37	9/36		4.1 %	0.11 [0.01, 0.81]
Subtotal (95% CI)	**37**	**36**		**4.1 %**	**0.11 [0.01, 0.81]**
Total events: 1 (Probiotic), 9 (No probiotic)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.16 (P = 0.030)					
7 Saccharomyces boulardii					
Cetina-Sauri 1994	16/65	39/65		12.4 %	0.41 [0.26, 0.66]
Subtotal (95% CI)	**65**	**65**		**12.4 %**	**0.41 [0.26, 0.66]**
Total events: 16 (Probiotic), 39 (No probiotic)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.72 (P = 0.00020)					
Total (95% CI)	**627**	**601**		**100.0 %**	**0.31 [0.19, 0.50]**
Total events: 100 (Probiotic), 270 (No probiotic)					
Heterogeneity: Tau^2 = 0.43; Chi^2 = 44.23, df = 12 (P = 0.00001); I^2 =73%					
Test for overall effect: Z = 4.76 (P < 0.00001)					



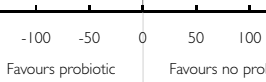
Analysis 1.3. Comparison 1 Probiotic versus control, Outcome 3 Mean duration of diarrhoea (hours).

Review: Probiotics for treating infectious diarrhoea

Comparison: 1 Probiotic versus control

Outcome: 3 Mean duration of diarrhoea (hours)

Study or subgroup	Probiotic N	Mean(SD)	No probiotic N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Live Lactobacillus casei strain GG							
Guandalini 2000	147	58.3 (27.6)	140	71.9 (35.8)		10.6 %	-13.60 [-21.02, -6.18]
Guarino 1997	52	76.8 (34.61)	48	141.6 (33.26)		9.7 %	-64.80 [-78.10, -51.50]
Pant 1996	14	45.6 (14.4)	12	79.2 (55.2)		6.2 %	-33.60 [-65.73, -1.47]
Isolauri 1994	21	36 (16.8)	21	55.2 (19.2)		10.1 %	-19.20 [-30.11, -8.29]
Shornikova 1997a	59	64.8 (52.8)	64	91.2 (67.2)		8.2 %	-26.40 [-47.67, -5.13]
Subtotal (95% CI)	**293**		**285**			**44.8 %**	**-31.18 [-51.62, -10.75]**
Heterogeneity: Tau² = 461.38; Chi² = 44.78, df = 4 (P<0.00001); I² =91%							
Test for overall effect: Z = 2.99 (P = 0.0028)							
2 Live Lactobacillus reuteri							
Shornikova 1997b	21	36 (26.4)	25	60 (36)		8.8 %	-24.00 [-42.07, -5.93]
Shornikova 1997c	19	40.8 (38.4)	21	69.6 (55.2)		6.7 %	-28.80 [-58.05, 0.45]
Subtotal (95% CI)	**40**		**46**			**15.5 %**	**-25.33 [-40.70, -9.95]**
Heterogeneity: Tau² = 0.0; Chi² = 0.07, df = 1 (P = 0.78); I² =0.0%							
Test for overall effect: Z = 3.23 (P = 0.0012)							
3 Live Lactobacillus casei							
Sugita 1994	16	91.2 (36)	11	127.2 (40.8)		6.6 %	-36.00 [-65.87, -6.13]
Subtotal (95% CI)	**16**		**11**			**6.6 %**	**-36.00 [-65.87, -6.13]**
Heterogeneity: not applicable							
Test for overall effect: Z = 2.36 (P = 0.018)							
4 Live Lactobacillus rhamnosus and Lactobacillus reuteri							
Rosenfeldt 2002a	30	81.5 (37.3)	39	101.1 (47.6)		8.4 %	-19.60 [-39.63, 0.43]
Rosenfeldt 2002b	24	75.9 (39.7)	19	115.7 (85)		4.8 %	-39.80 [-81.19, 1.59]
Subtotal (95% CI)	**54**		**58**			**13.2 %**	**-23.43 [-41.47, -5.40]**
Heterogeneity: Tau² = 0.0; Chi² = 0.74, df = 1 (P = 0.39); I² =0.0%							
Test for overall effect: Z = 2.55 (P = 0.011)							
5 Live Lactobacillus acidophilus and Lactobacillus bifidus							
Oandasan 1999	47	42.89 (21.77)	47	93.96 (22.85)		10.4 %	-51.07 [-60.09, -42.05]
Subtotal (95% CI)	**47**		**47**			**10.4 %**	**-51.07 [-60.09, -42.05]**
Heterogeneity: not applicable							
Test for overall effect: Z = 11.09 (P < 0.00001)							



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Study or subgroup	Probiotic N	Mean(SD)	No probiotic N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
6 Killed Lactobacillus acidophilus LB strain							
Simakachorn 2000	37	43.4 (25.9)	36	57 (36.3)		9.5 %	-13.60 [-28.10, 0.90]
Subtotal (95% CI)	**37**		**36**			**9.5 %**	**-13.60 [-28.10, 0.90]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.84 (P = 0.066)							
Total (95% CI)	**487**		**483**			**100.0 %**	**-30.48 [-42.46, -18.51]**
Heterogeneity: Tau^2 = 337.71; Chi^2 = 76.51, df = 11 (P<0.00001); I^2 =86%							
Test for overall effect: Z = 4.99 (P < 0.00001)							

-100 -50 0 50 100

Favours probiotic Favours no probiotic

Analysis 1.4. Comparison 1 Probiotic versus control, Outcome 4 Mean stool frequency on day 2.

Review: Probiotics for treating infectious diarrhoea

Comparison: 1 Probiotic versus control

Outcome: 4 Mean stool frequency on day 2

Study or subgroup	Probiotic N	Mean(SD)	No probiotic N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Live Lactobacillus casei strain GG							
Pant 1996	14	3.5 (1.3)	12	5.2 (2.8)		3.9 %	-1.70 [-3.42, 0.02]
Raza 1995	19	5.8 (3.1)	17	7 (3.3)		2.7 %	-1.20 [-3.30, 0.90]
Subtotal (95% CI)	**33**		**29**			**6.6 %**	**-1.50 [-2.83, -0.17]**
Heterogeneity: Chi^2 = 0.13, df = 1 (P = 0.72); I^2 =0.0%							
Test for overall effect: Z = 2.20 (P = 0.027)							
2 Live Lactobacillus reuteri							
Shornikova 1997c	19	1 (2.3)	21	2.5 (2.3)		5.7 %	-1.50 [-2.93, -0.07]
Subtotal (95% CI)	**19**		**21**			**5.7 %**	**-1.50 [-2.93, -0.07]**
Heterogeneity: not applicable							
Test for overall effect: Z = 2.06 (P = 0.039)							
3 Live Enterococcus LAB strain SF68							
Buydens 1996	93	2 (1)	92	3.7 (1.7)		72.2 %	-1.70 [-2.10, -1.30]
Subtotal (95% CI)	**93**		**92**			**72.2 %**	**-1.70 [-2.10, -1.30]**
Heterogeneity: not applicable							
Test for overall effect: Z = 8.28 (P < 0.00001)							

-4 -2 0 2 4

Favours probiotic Favours no probiotic

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Study or subgroup	Probiotic N	Mean(SD)	No probiotic N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
4 Saccharomyces boulardii							
Cetina-Sauri 1994	65	3.76 (2.31)	65	4.38 (2.73)		15.5 %	-0.62 [-1.49, 0.25]
Subtotal (95% CI)	**65**		**65**			**15.5 %**	**-0.62 [-1.49, 0.25]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.40 (P = 0.16)							
Total (95% CI)	**210**		**207**			**100.0 %**	**-1.51 [-1.85, -1.17]**
Heterogeneity: Chi^2 = 5.01, df = 4 (P = 0.29); I^2 =20%							
Test for overall effect: Z = 8.64 (P < 0.00001)							
Test for subgroup differences: Chi^2 = 4.88, df = 3 (P = 0.18), I^2 =39%							

Analysis 1.5. Comparison 1 Probiotic versus control, Outcome 5 Mean stool frequency on day 3.

Review: Probiotics for treating infectious diarrhoea

Comparison: 1 Probiotic versus control

Outcome: 5 Mean stool frequency on day 3

Study or subgroup	Probiotic N	Mean(SD)	No probiotic N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 LIve Lactobacillus reuteri							
Shornikova 1997c	19	0.5 (1.9)	21	1.7 (2.6)		3.0 %	-1.20 [-2.60, 0.20]
Subtotal (95% CI)	**19**		**21**			**3.0 %**	**-1.20 [-2.60, 0.20]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.68 (P = 0.094)							
2 Live Enterococcus LAB strain SF68							
Buydens 1996	93	1.1 (0.3)	92	2.5 (1.3)		80.5 %	-1.40 [-1.67, -1.13]
Subtotal (95% CI)	**93**		**92**			**80.5 %**	**-1.40 [-1.67, -1.13]**
Heterogeneity: not applicable							
Test for overall effect: Z = 10.07 (P < 0.00001)							
3 Saccharomyces boulardii							
Cetina-Sauri 1994	65	2.53 (1.78)	65	3.63 (2.53)		10.6 %	-1.10 [-1.85, -0.35]
Hochter 1990	43	2.4 (2.1)	49	3 (2.8)		5.9 %	-0.60 [-1.60, 0.40]
Subtotal (95% CI)	**108**		**114**			**16.5 %**	**-0.92 [-1.52, -0.32]**
Heterogeneity: Chi^2 = 0.61, df = 1 (P = 0.43); I^2 =0.0%							

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Study or subgroup	Probiotic N	Mean(SD)	No probiotic N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Test for overall effect: Z = 3.00 (P = 0.0027)							
Total (95% CI)	**220**		**227**		◆	**100.0 %**	**-1.31 [-1.56, -1.07]**
Heterogeneity: Chi^2 = 2.66, df = 3 (P = 0.45); I^2 =0.0%							
Test for overall effect: Z = 10.54 (P < 0.00001)							
Test for subgroup differences: Chi^2 = 2.05, df = 2 (P = 0.36), I^2 =2%							

-4 -2 0 2 4

Favours probiotic Favours no probiotic

Analysis 2.1. Comparison 2 Sensitivity analysis; diarrhoea lasting 3 or more days, Outcome 1 Generation of allocation sequence.

Review: Probiotics for treating infectious diarrhoea

Comparison: 2 Sensitivity analysis; diarrhoea lasting 3 or more days

Outcome: 1 Generation of allocation sequence

Study or subgroup	Probiotic n/N	No probiotic n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Adequate					
Bhatnagar 1998	27/47	26/49		18.0 %	1.08 [0.76, 1.55]
Boulloche 1994	4/38	5/33		2.9 %	0.69 [0.20, 2.38]
Bruno 1983	3/10	7/11		3.9 %	0.47 [0.17, 1.34]
Buydens 1996	57/93	88/92		29.2 %	0.64 [0.54, 0.76]
Cetina-Sauri 1994	41/65	58/65		27.0 %	0.71 [0.58, 0.87]
Oandasan 1999	9/47	26/47		8.7 %	0.35 [0.18, 0.66]
Shornikova 1997c	3/19	11/21		3.5 %	0.30 [0.10, 0.92]
Simakachorn 2000	9/37	11/36		6.8 %	0.80 [0.38, 1.69]
Subtotal (95% CI)	**356**	**354**	◆	**100.0 %**	**0.67 [0.53, 0.84]**
Total events: 153 (Probiotic), 232 (No probiotic)					
Heterogeneity: Tau^2 = 0.04; Chi^2 = 14.19, df = 7 (P = 0.05); I^2 =51%					
Test for overall effect: Z = 3.50 (P = 0.00047)					
2 Inadequate or unclear					
Bruno 1981	6/25	17/24		9.8 %	0.34 [0.16, 0.71]
Caragüe-Orendain	7/35	8/35		7.1 %	0.88 [0.36, 2.15]

0.01 0.1 1 10 100

Favours probiotic Favours no probiotic

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Study or subgroup	Probiotic n/N	No probiotic n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
D'Apuzzo 1982	4/21	10/18		6.2 %	0.34 [0.13, 0.91]
Guandalini 2000	78/147	90/140		38.6 %	0.83 [0.68, 1.00]
Isolauri 1994	2/21	9/21		3.2 %	0.22 [0.05, 0.91]
Shornikova 1997b	11/41	11/25		11.4 %	0.61 [0.31, 1.19]
Wunderlich 1989	19/40	27/38		23.7 %	0.67 [0.46, 0.98]
Subtotal (95% CI)	**330**	**301**		**100.0 %**	**0.60 [0.44, 0.82]**
Total events: 127 (Probiotic), 172 (No probiotic)					
Heterogeneity: Tau^2 = 0.07; Chi^2 = 11.87, df = 6 (P = 0.07); I^2 =49%					
Test for overall effect: Z = 3.18 (P = 0.0015)					

Analysis 2.2. Comparison 2 Sensitivity analysis; diarrhoea lasting 3 or more days, Outcome 2 Allocation concealment.

Review: Probiotics for treating infectious diarrhoea

Comparison: 2 Sensitivity analysis; diarrhoea lasting 3 or more days

Outcome: 2 Allocation concealment

Study or subgroup	Probiotic n/N	No probiotic n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Adequate					
Buydens 1996	57/93	88/92		60.6 %	0.64 [0.54, 0.76]
Oandasan 1999	9/47	26/47		18.1 %	0.35 [0.18, 0.66]
Shornikova 1997c	3/19	11/21		7.2 %	0.30 [0.10, 0.92]
Simakachorn 2000	9/37	11/36		14.1 %	0.80 [0.38, 1.69]
Subtotal (95% CI)	**196**	**196**		**100.0 %**	**0.53 [0.35, 0.81]**
Total events: 78 (Probiotic), 136 (No probiotic)					
Heterogeneity: Tau^2 = 0.09; Chi^2 = 6.17, df = 3 (P = 0.10); I^2 =51%					
Test for overall effect: Z = 2.95 (P = 0.0032)					
2 Inadequate or unclear					
Bhatnagar 1998	27/47	26/49		14.6 %	1.08 [0.76, 1.55]
Boulloche 1994	4/38	5/33		2.4 %	0.69 [0.20, 2.38]

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Study or subgroup	Probiotic n/N	No probiotic n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Bruno 1981	6/25	17/24		5.7 %	0.34 [0.16, 0.71]
Bruno 1983	3/10	7/11		3.2 %	0.47 [0.17, 1.34]
Caragüe-Orendain	7/35	8/35		4.1 %	0.88 [0.36, 2.15]
Cetina-Sauri 1994	41/65	58/65		21.9 %	0.71 [0.58, 0.87]
D'Apuzzo 1982	4/21	10/18		3.6 %	0.34 [0.13, 0.91]
Guandalini 2000	78/147	90/140		22.4 %	0.83 [0.68, 1.00]
Isolauri 1994	2/21	9/21		1.8 %	0.22 [0.05, 0.91]
Shornikova 1997b	11/41	11/25		6.6 %	0.61 [0.31, 1.19]
Wunderlich 1989	19/40	27/38		13.7 %	0.67 [0.46, 0.98]
Subtotal (95% CI)	**490**	**459**		**100.0 %**	**0.70 [0.58, 0.85]**

Total events: 202 (Probiotic), 268 (No probiotic)

Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 16.92$, df = 10 (P = 0.08); $I^2 = 41\%$

Test for overall effect: Z = 3.61 (P = 0.00031)

Analysis 2.3. Comparison 2 Sensitivity analysis; diarrhoea lasting 3 or more days, Outcome 3 Blinding.

Review: Probiotics for treating infectious diarrhoea

Comparison: 2 Sensitivity analysis; diarrhoea lasting 3 or more days

Outcome: 3 Blinding

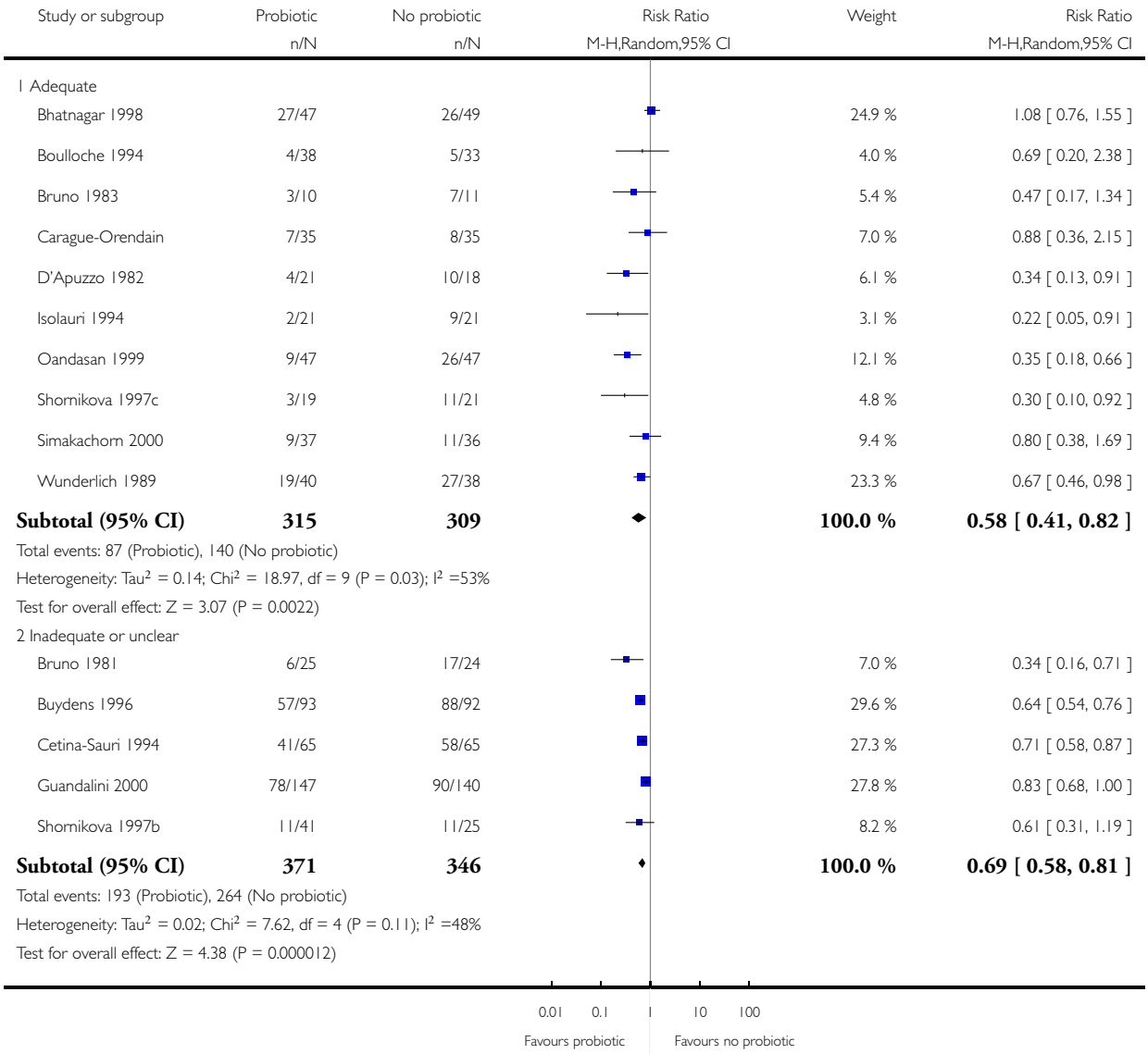
Study or subgroup	Probiotic n/N	No probiotic n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Adequate					
Bruno 1981	6/25	17/24		6.4 %	0.34 [0.16, 0.71]
Buydens 1996	57/93	88/92		27.1 %	0.64 [0.54, 0.76]
Guandalini 2000	78/147	90/140		25.5 %	0.83 [0.68, 1.00]
Oandasan 1999	9/47	26/47		8.1 %	0.35 [0.18, 0.66]
Shornikova 1997b	11/41	11/25		7.6 %	0.61 [0.31, 1.19]
Shornikova 1997c	3/19	11/21		3.2 %	0.30 [0.10, 0.92]
Simakachorn 2000	9/37	11/36		6.3 %	0.80 [0.38, 1.69]
Wunderlich 1989	19/40	27/38		15.7 %	0.67 [0.46, 0.98]
Subtotal (95% CI)	**449**	**423**		**100.0 %**	**0.62 [0.50, 0.77]**
Total events: 192 (Probiotic), 281 (No probiotic)					
Heterogeneity: Tau^2 = 0.04; Chi^2 = 14.56, df = 7 (P = 0.04); I^2 =52%					
Test for overall effect: Z = 4.40 (P = 0.000011)					
2 Inadequate or unclear					
Bhatnagar 1998	27/47	26/49		28.4 %	1.08 [0.76, 1.55]
Boulloche 1994	4/38	5/33		4.6 %	0.69 [0.20, 2.38]
Bruno 1983	3/10	7/11		6.1 %	0.47 [0.17, 1.34]
Caragüe-Orendain	7/35	8/35		8.0 %	0.88 [0.36, 2.15]
Cetina-Sauri 1994	41/65	58/65		42.5 %	0.71 [0.58, 0.87]
D'Apuzzo 1982	4/21	10/18		6.9 %	0.34 [0.13, 0.91]
Isolauri 1994	2/21	9/21		3.6 %	0.22 [0.05, 0.91]
Subtotal (95% CI)	**237**	**232**		**100.0 %**	**0.70 [0.50, 0.97]**
Total events: 88 (Probiotic), 123 (No probiotic)					
Heterogeneity: Tau^2 = 0.07; Chi^2 = 10.74, df = 6 (P = 0.10); I^2 =44%					
Test for overall effect: Z = 2.17 (P = 0.030)					

Analysis 2.4. Comparison 2 Sensitivity analysis; diarrhoea lasting 3 or more days, Outcome 4 Follow up.

Review: Probiotics for treating infectious diarrhoea

Comparison: 2 Sensitivity analysis; diarrhoea lasting 3 or more days

Outcome: 4 Follow up



Analysis 3.1. Comparison 3 Sensitivity analysis: diarrhoea lasting 4 or more days, Outcome 1 Generation of allocation sequence.

Review: Probiotics for treating infectious diarrhoea

Comparison: 3 Sensitivity analysis: diarrhoea lasting 4 or more days

Outcome: 1 Generation of allocation sequence

Study or subgroup	Probiotic n/N	No probiotic n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Adequate					
Bhatnagar 1998	17/47	17/49		21.8 %	1.04 [0.61, 1.79]
Bruno 1983	1/10	7/11		7.9 %	0.16 [0.02, 1.06]
Buydens 1996	7/93	61/92		19.4 %	0.11 [0.05, 0.23]
Cetina-Sauri 1994	16/65	39/65		22.6 %	0.41 [0.26, 0.66]
Oandasan 1999	1/47	22/47		7.7 %	0.05 [0.01, 0.32]
Shornikova 1997c	3/19	6/21		13.2 %	0.55 [0.16, 1.91]
Simakachorn 2000	1/37	9/36		7.4 %	0.11 [0.01, 0.81]
Subtotal (95% CI)	**318**	**321**		**100.0 %**	**0.26 [0.11, 0.62]**
Total events: 46 (Probiotic), 161 (No probiotic)					
Heterogeneity: $Tau^2 = 0.97$; $Chi^2 = 35.84$, df = 6 ($P<0.00001$); $I^2 = 83\%$					
Test for overall effect: Z = 3.04 (P = 0.0023)					
2 Indequate or unclear					
Bruno 1981	2/25	11/24		14.2 %	0.17 [0.04, 0.71]
Caragüe-Orendain	0/35	4/35		5.1 %	0.11 [0.01, 1.99]
D'Apuzzo 1982	3/21	7/18		16.7 %	0.37 [0.11, 1.22]
Guandalini 2000	37/147	58/140		29.1 %	0.61 [0.43, 0.85]
Shornikova 1997b	1/41	6/25		8.7 %	0.10 [0.01, 0.80]
Wunderlich 1989	11/40	23/38		26.1 %	0.45 [0.26, 0.80]
Subtotal (95% CI)	**309**	**280**		**100.0 %**	**0.42 [0.27, 0.66]**
Total events: 54 (Probiotic), 109 (No probiotic)					
Heterogeneity: $Tau^2 = 0.09$; $Chi^2 = 7.45$, df = 5 (P = 0.19); $I^2 = 33\%$					
Test for overall effect: Z = 3.79 (P = 0.00015)					

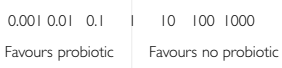
Analysis 3.2. Comparison 3 Sensitivity analysis: diarrhoea lasting 4 or more days, Outcome 2 Allocation concealment.

Review: Probiotics for treating infectious diarrhoea

Comparison: 3 Sensitivity analysis: diarrhoea lasting 4 or more days

Outcome: 2 Allocation concealment

Study or subgroup	Probiotic n/N	No probiotic n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Adequate					
Buydens 1996	7/93	61/92		40.7 %	0.11 [0.05, 0.23]
Oandasan 1999	1/47	22/47		16.1 %	0.05 [0.01, 0.32]
Shornikova 1997c	3/19	6/21		27.8 %	0.55 [0.16, 1.91]
Simakachorn 2000	1/37	9/36		15.5 %	0.11 [0.01, 0.81]
Subtotal (95% CI)	**196**	**196**		**100.0 %**	**0.15 [0.05, 0.41]**
Total events: 12 (Probiotic), 98 (No probiotic)					
Heterogeneity: Tau^2 = 0.57; Chi^2 = 6.69, df = 3 (P = 0.08); I^2 =55%					
Test for overall effect: Z = 3.66 (P = 0.00026)					
2 Inadequate or unclear					
Bhatnagar 1998	17/47	17/49		16.2 %	1.04 [0.61, 1.79]
Bruno 1981	2/25	11/24		8.7 %	0.17 [0.04, 0.71]
Bruno 1983	1/10	7/11		5.9 %	0.16 [0.02, 1.06]
Caragüe-Orendain	0/35	4/35		3.1 %	0.11 [0.01, 1.99]
Cetina-Sauri 1994	16/65	39/65		16.8 %	0.41 [0.26, 0.66]
D'Apuzzo 1982	3/21	7/18		10.2 %	0.37 [0.11, 1.22]
Guandalini 2000	37/147	58/140		17.8 %	0.61 [0.43, 0.85]
Shornikova 1997b	1/41	6/25		5.3 %	0.10 [0.01, 0.80]
Wunderlich 1989	11/40	23/38		16.0 %	0.45 [0.26, 0.80]
Subtotal (95% CI)	**431**	**405**		**100.0 %**	**0.46 [0.31, 0.68]**
Total events: 88 (Probiotic), 172 (No probiotic)					
Heterogeneity: Tau^2 = 0.14; Chi^2 = 16.44, df = 8 (P = 0.04); I^2 =51%					
Test for overall effect: Z = 3.94 (P = 0.000080)					



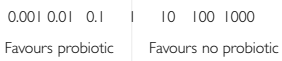
Analysis 3.3. Comparison 3 Sensitivity analysis: diarrhoea lasting 4 or more days, Outcome 3 Blinding.

Review: Probiotics for treating infectious diarrhoea

Comparison: 3 Sensitivity analysis: diarrhoea lasting 4 or more days

Outcome: 3 Blinding

Study or subgroup	Probiotic n/N	No probiotic n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Adequate					
Bruno 1981	2/25	11/24		10.4 %	0.17 [0.04, 0.71]
Buydens 1996	7/93	61/92		17.3 %	0.11 [0.05, 0.23]
Guandalini 2000	37/147	58/140		21.4 %	0.61 [0.43, 0.85]
Oandasan 1999	1/47	22/47		6.8 %	0.05 [0.01, 0.32]
Shornikova 1997b	1/41	6/25		6.4 %	0.10 [0.01, 0.80]
Shornikova 1997c	3/19	6/21		11.8 %	0.55 [0.16, 1.91]
Simakachorn 2000	1/37	9/36		6.6 %	0.11 [0.01, 0.81]
Wunderlich 1989	11/40	23/38		19.2 %	0.45 [0.26, 0.80]
Subtotal (95% CI)	**449**	**423**		**100.0 %**	**0.24 [0.12, 0.48]**
Total events: 63 (Probiotic), 196 (No probiotic)					
Heterogeneity: Tau^2 = 0.65; Chi^2 = 31.53, df = 7 (P = 0.00005); I^2 =78%					
Test for overall effect: Z = 4.01 (P = 0.000059)					
2 Inadequate or unclear					
Bhatnagar 1998	17/47	17/49		31.0 %	1.04 [0.61, 1.79]
Bruno 1983	1/10	7/11		11.3 %	0.16 [0.02, 1.06]
Caragüe-Orendain	0/35	4/35		6.0 %	0.11 [0.01, 1.99]
Cetina-Sauri 1994	16/65	39/65		32.2 %	0.41 [0.26, 0.66]
D'Apuzzo 1982	3/21	7/18		19.5 %	0.37 [0.11, 1.22]
Subtotal (95% CI)	**178**	**178**		**100.0 %**	**0.46 [0.23, 0.93]**
Total events: 37 (Probiotic), 74 (No probiotic)					
Heterogeneity: Tau^2 = 0.31; Chi^2 = 10.41, df = 4 (P = 0.03); I^2 =62%					
Test for overall effect: Z = 2.18 (P = 0.030)					

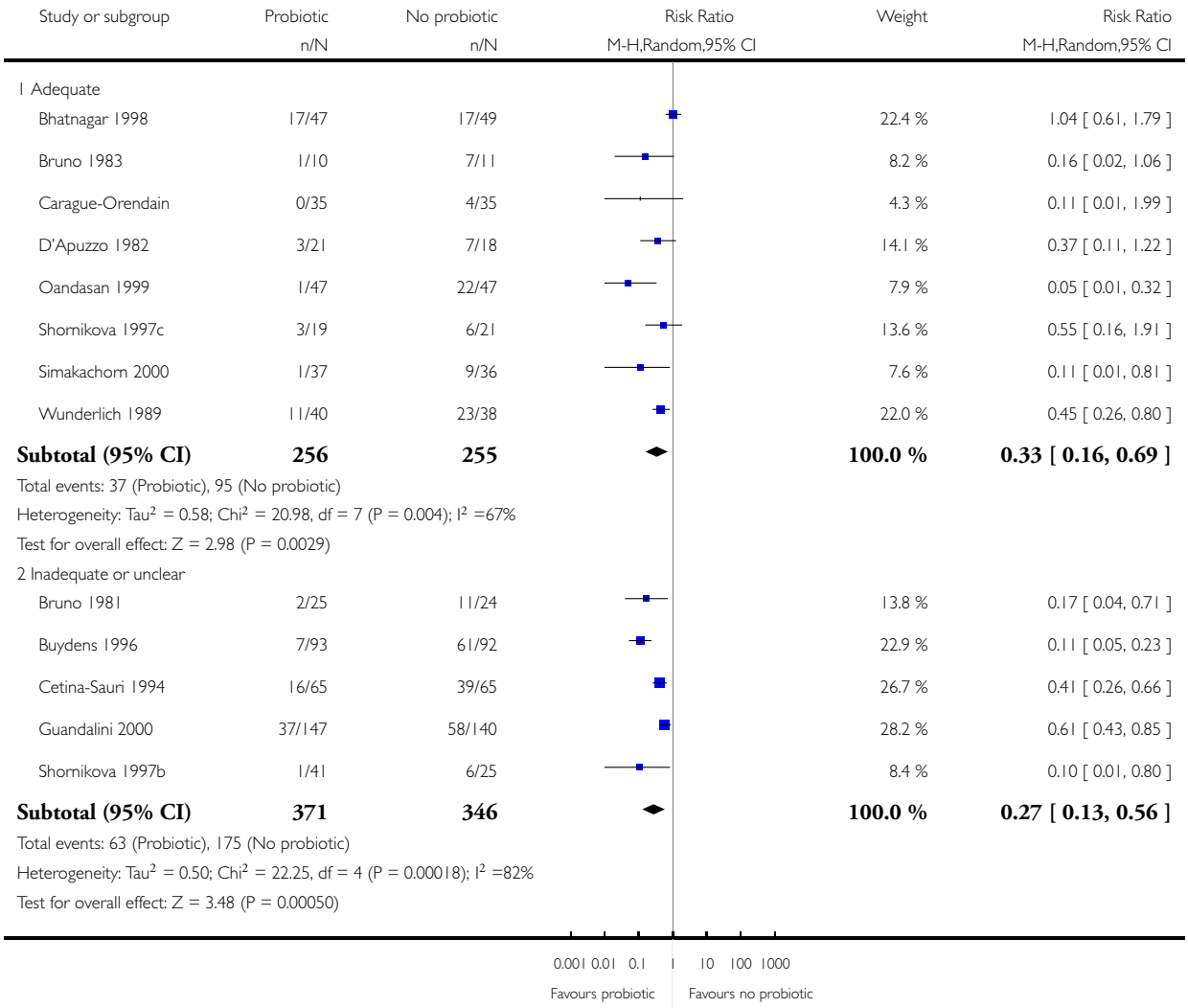


Analysis 3.4. Comparison 3 Sensitivity analysis: diarrhoea lasting 4 or more days, Outcome 4 Follow up.

Review: Probiotics for treating infectious diarrhoea

Comparison: 3 Sensitivity analysis: diarrhoea lasting 4 or more days

Outcome: 4 Follow up



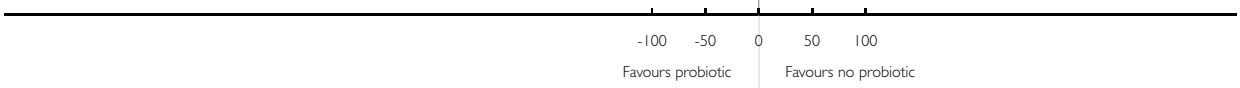
Analysis 4.1. Comparison 4 Sensitivity analysis; mean duration of diarrhoea (hours), Outcome 1 Generation of allocation sequence.

Review: Probiotics for treating infectious diarrhoea

Comparison: 4 Sensitivity analysis; mean duration of diarrhoea (hours)

Outcome: 1 Generation of allocation sequence

Study or subgroup	Probiotic N	Mean(SD)	No probiotic N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Adequate							
Guarino 1997	52	76.8 (34.61)	48	141.6 (33.26)		21.9 %	-64.80 [-78.10, -51.50]
Oandasan 1999	47	42.89 (21.77)	47	93.96 (22.85)		23.4 %	-51.07 [-60.09, -42.05]
Shornikova 1997a	59	64.8 (52.8)	64	91.2 (67.2)		18.4 %	-26.40 [-47.67, -5.13]
Shornikova 1997c	19	40.8 (38.4)	21	69.6 (55.2)		15.0 %	-28.80 [-58.05, 0.45]
Simakachorn 2000	37	43.4 (25.9)	36	57 (36.3)		21.4 %	-13.60 [-28.10, 0.90]
Subtotal (95% CI)	**214**		**216**			**100.0 %**	**-38.00 [-57.48, -18.53]**
Heterogeneity: Tau^2 = 410.44; Chi^2 = 32.30, df = 4 (P<0.00001); I^2 =88%							
Test for overall effect: Z = 3.82 (P = 0.00013)							
2 Inadequate or unclear							
Guandalini 2000	147	58.3 (27.6)	140	71.9 (35.8)		19.1 %	-13.60 [-21.02, -6.18]
Pant 1996	14	45.6 (14.4)	12	79.2 (55.2)		11.1 %	-33.60 [-65.73, -1.47]
Isolauri 1994	21	36 (16.8)	21	55.2 (19.2)		18.3 %	-19.20 [-30.11, -8.29]
Rosenfeldt 2002a	30	81.5 (37.3)	39	101.1 (47.6)		15.2 %	-19.60 [-39.63, 0.43]
Rosenfeldt 2002b	24	75.9 (39.7)	19	115.7 (85)		8.6 %	-39.80 [-81.19, 1.59]
Shornikova 1997b	21	36 (26.4)	25	60 (36)		15.9 %	-24.00 [-42.07, -5.93]
Sugita 1994	16	91.2 (36)	11	127.2 (40.8)		11.8 %	-36.00 [-65.87, -6.13]
Subtotal (95% CI)	**273**		**267**			**100.0 %**	**-18.02 [-23.38, -12.65]**
Heterogeneity: Tau^2 = 0.0; Chi^2 = 5.21, df = 6 (P = 0.52); I^2 =0.0%							
Test for overall effect: Z = 6.59 (P < 0.00001)							



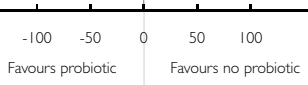
Analysis 4.2. Comparison 4 Sensitivity analysis; mean duration of diarrhoea (hours), Outcome 2 Allocation concealment.

Review: Probiotics for treating infectious diarrhoea

Comparison: 4 Sensitivity analysis; mean duration of diarrhoea (hours)

Outcome: 2 Allocation concealment

Study or subgroup	Probiotic N	Mean(SD)	No probiotic N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Adequate							
Oandasan 1999	47	42.89 (21.77)	47	93.96 (22.85)		29.9 %	-51.07 [-60.09, -42.05]
Shornikova 1997a	59	64.8 (52.8)	64	91.2 (67.2)		23.6 %	-26.40 [-47.67, -5.13]
Shornikova 1997c	19	40.8 (38.4)	21	69.6 (55.2)		19.2 %	-28.80 [-58.05, 0.45]
Simakachorn 2000	37	43.4 (25.9)	36	57 (36.3)		27.4 %	-13.60 [-28.10, 0.90]
Subtotal (95% CI)	**162**		**168**			**100.0 %**	**-30.64 [-52.20, -9.08]**
Heterogeneity: Tau² = 391.07; Chi² = 20.45, df = 3 (P = 0.00014); I² =85%							
Test for overall effect: Z = 2.79 (P = 0.0053)							
2 Inadequate or unclear							
Guandalini 2000	147	58.3 (27.6)	140	71.9 (35.8)		16.3 %	-13.60 [-21.02, -6.18]
Guarino 1997	52	76.8 (34.61)	48	141.6 (33.26)		14.9 %	-64.80 [-78.10, -51.50]
Pant 1996	14	45.6 (14.4)	12	79.2 (55.2)		9.4 %	-33.60 [-65.73, -1.47]
Isolauri 1994	21	36 (16.8)	21	55.2 (19.2)		15.5 %	-19.20 [-30.11, -8.29]
Rosenfeldt 2002a	30	81.5 (37.3)	39	101.1 (47.6)		12.9 %	-19.60 [-39.63, 0.43]
Rosenfeldt 2002b	24	75.9 (39.7)	19	115.7 (85)		7.3 %	-39.80 [-81.19, 1.59]
Shornikova 1997b	21	36 (26.4)	25	60 (36)		13.5 %	-24.00 [-42.07, -5.93]
Sugita 1994	16	91.2 (36)	11	127.2 (40.8)		10.0 %	-36.00 [-65.87, -6.13]
Subtotal (95% CI)	**325**		**315**			**100.0 %**	**-30.36 [-45.36, -15.37]**
Heterogeneity: Tau² = 347.19; Chi² = 46.07, df = 7 (P<0.00001); I² =85%							
Test for overall effect: Z = 3.97 (P = 0.000072)							



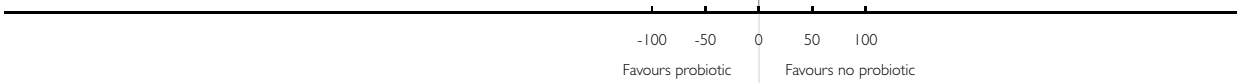
Analysis 4.3. Comparison 4 Sensitivity analysis; mean duration of diarrhoea (hours), Outcome 3 Blinding.

Review: Probiotics for treating infectious diarrhoea

Comparison: 4 Sensitivity analysis; mean duration of diarrhoea (hours)

Outcome: 3 Blinding

Study or subgroup	Probiotic N	Mean(SD)	No probiotic N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Adequate							
Guandalini 2000	147	58.3 (27.6)	140	71.9 (35.8)		14.4 %	-13.60 [-21.02, -6.18]
Oandasan 1999	47	42.89 (21.77)	47	93.96 (22.85)		14.1 %	-51.07 [-60.09, -42.05]
Pant 1996	14	45.6 (14.4)	12	79.2 (55.2)		8.4 %	-33.60 [-65.73, -1.47]
Rosenfeldt 2002a	30	81.5 (37.3)	39	101.1 (47.6)		11.5 %	-19.60 [-39.63, 0.43]
Rosenfeldt 2002b	24	75.9 (39.7)	19	115.7 (85)		6.5 %	-39.80 [-81.19, 1.59]
Shornikova 1997a	59	64.8 (52.8)	64	91.2 (67.2)		11.1 %	-26.40 [-47.67, -5.13]
Shornikova 1997b	21	36 (26.4)	25	60 (36)		12.0 %	-24.00 [-42.07, -5.93]
Shornikova 1997c	19	40.8 (38.4)	21	69.6 (55.2)		9.1 %	-28.80 [-58.05, 0.45]
Simakachorn 2000	37	43.4 (25.9)	36	57 (36.3)		12.9 %	-13.60 [-28.10, 0.90]
Subtotal (95% CI)	**398**		**403**			**100.0 %**	**-26.94 [-39.87, -14.00]**
Heterogeneity: Tau² = 276.40; Chi² = 44.27, df = 8 (P<0.00001); I² =82%							
Test for overall effect: Z = 4.08 (P = 0.000045)							
2 Inadequate or unclear							
Guarino 1997	52	76.8 (34.61)	48	141.6 (33.26)		36.8 %	-64.80 [-78.10, -51.50]
Isolauri 1994	21	36 (16.8)	21	55.2 (19.2)		38.4 %	-19.20 [-30.11, -8.29]
Sugita 1994	16	91.2 (36)	11	127.2 (40.8)		24.8 %	-36.00 [-65.87, -6.13]
Subtotal (95% CI)	**89**		**80**			**100.0 %**	**-40.12 [-73.60, -6.65]**
Heterogeneity: Tau² = 780.76; Chi² = 26.99, df = 2 (P<0.00001); I² =93%							
Test for overall effect: Z = 2.35 (P = 0.019)							



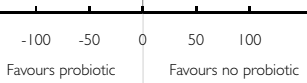
Analysis 4.4. Comparison 4 Sensitivity analysis; mean duration of diarrhoea (hours), Outcome 4 Follow up.

Review: Probiotics for treating infectious diarrhoea

Comparison: 4 Sensitivity analysis; mean duration of diarrhoea (hours)

Outcome: 4 Follow up

Study or subgroup	Probiotic N	Mean(SD)	No probiotic N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Adequate							
Guarino 1997	52	76.8 (34.61)	48	141.6 (33.26)		18.5 %	-64.80 [-78.10, -51.50]
Oandasan 1999	47	42.89 (21.77)	47	93.96 (22.85)		19.8 %	-51.07 [-60.09, -42.05]
Pant 1996	14	45.6 (14.4)	12	79.2 (55.2)		11.7 %	-33.60 [-65.73, -1.47]
Isolauri 1994	21	36 (16.8)	21	55.2 (19.2)		19.3 %	-19.20 [-30.11, -8.29]
Shornikova 1997c	19	40.8 (38.4)	21	69.6 (55.2)		12.7 %	-28.80 [-58.05, 0.45]
Simakachorn 2000	37	43.4 (25.9)	36	57 (36.3)		18.1 %	-13.60 [-28.10, 0.90]
Subtotal (95% CI)	**190**		**185**			**100.0 %**	**-35.72 [-54.04, -17.40]**
Heterogeneity: Tau^2 = 432.84; Chi^2 = 46.32, df = 5 (P<0.00001); I^2 =89%							
Test for overall effect: Z = 3.82 (P = 0.00013)							
2 Inadequate or unclear							
Guandalini 2000	147	58.3 (27.6)	140	71.9 (35.8)		22.4 %	-13.60 [-21.02, -6.18]
Rosenfeldt 2002a	30	81.5 (37.3)	39	101.1 (47.6)		17.8 %	-19.60 [-39.63, 0.43]
Rosenfeldt 2002b	24	75.9 (39.7)	19	115.7 (85)		10.1 %	-39.80 [-81.19, 1.59]
Shornikova 1997a	59	64.8 (52.8)	64	91.2 (67.2)		17.3 %	-26.40 [-47.67, -5.13]
Shornikova 1997b	21	36 (26.4)	25	60 (36)		18.6 %	-24.00 [-42.07, -5.93]
Sugita 1994	16	91.2 (36)	11	127.2 (40.8)		13.8 %	-36.00 [-65.87, -6.13]
Subtotal (95% CI)	**297**		**298**			**100.0 %**	**-17.78 [-23.80, -11.76]**
Heterogeneity: Tau^2 = 0.0; Chi^2 = 4.85, df = 5 (P = 0.43); I^2 =0.0%							
Test for overall effect: Z = 5.79 (P < 0.00001)							



Analysis 5.1. Comparison 5 Children with rotavirus diarrhoea, Outcome 1 Mean duration of diarrhoea (hours).

Review: Probiotics for treating infectious diarrhoea

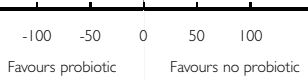
Comparison: 5 Children with rotavirus diarrhoea

Outcome: 1 Mean duration of diarrhoea (hours)

Study or subgroup	Probiotic N	Mean(SD)	No probiotic N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Guandalini 2000	56	56.2 (16.9)	45	76.6 (41.6)		26.1 %	-20.40 [-33.34, -7.46]
Guarino 1997	31	72 (26.7)	30	148.8 (26.3)		26.0 %	-76.80 [-90.10, -63.50]
Isolauri 1994	21	36 (16.8)	21	55.2 (19.2)		26.4 %	-19.20 [-30.11, -8.29]
Sugita 1994	16	91.2 (36)	11	127.2 (40.8)		21.5 %	-36.00 [-65.87, -6.13]
Total (95% CI)	**124**		**107**			**100.0 %**	**-38.10 [-68.10, -8.10]**

Heterogeneity: $Tau^2 = 855.65$; $Chi^2 = 50.84$, df = 3 ($P<0.00001$); $I^2 = 94\%$

Test for overall effect: Z = 2.49 (P = 0.013)



Analysis 6.1. Comparison 6 Mortality stratum for children and adults in the countries where trials were undertaken (children/adults), Outcome 1 Diarrhoea lasting 3 or more days.

Review: Probiotics for treating infectious diarrhoea

Comparison: 6 Mortality stratum for children and adults in the countries where trials were undertaken (children/adults)

Outcome: 1 Diarrhoea lasting 3 or more days

Study or subgroup	Probiotic n/N	No probiotic n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Very low/very low					
Boulloche 1994	4/38	5/33		3.9 %	0.69 [0.20, 2.38]
Bruno 1981	6/25	17/24		9.2 %	0.34 [0.16, 0.71]
Bruno 1983	3/10	7/11		5.2 %	0.47 [0.17, 1.34]
Buydens 1996	57/93	88/92		35.9 %	0.64 [0.54, 0.76]
D'Apuzzo 1982	4/21	10/18		5.9 %	0.34 [0.13, 0.91]
Isolauri 1994	2/21	9/21		3.0 %	0.22 [0.05, 0.91]
Shornikova 1997b	11/41	11/25		10.7 %	0.61 [0.31, 1.19]
Shornikova 1997c	3/19	11/21		4.6 %	0.30 [0.10, 0.92]
Wunderlich 1989	19/40	27/38		21.6 %	0.67 [0.46, 0.98]
Subtotal (95% CI)	**308**	**283**		**100.0 %**	**0.57 [0.46, 0.70]**
Total events: 109 (Probiotic), 185 (No probiotic)					
Heterogeneity: Tau^2 = 0.02; Chi^2 = 9.44, df = 8 (P = 0.31); I^2 =15%					
Test for overall effect: Z = 5.39 (P < 0.00001)					
2 Low/low					
Caragüe-Orendain	7/35	8/35		11.1 %	0.88 [0.36, 2.15]
Cetina-Sauri 1994	41/65	58/65		55.1 %	0.71 [0.58, 0.87]
Oandasan 1999	9/47	26/47		18.9 %	0.35 [0.18, 0.66]
Simakachorn 2000	9/37	11/36		14.9 %	0.80 [0.38, 1.69]
Subtotal (95% CI)	**184**	**183**		**100.0 %**	**0.64 [0.44, 0.92]**
Total events: 66 (Probiotic), 103 (No probiotic)					
Heterogeneity: Tau^2 = 0.06; Chi^2 = 5.25, df = 3 (P = 0.15); I^2 =43%					
Test for overall effect: Z = 2.38 (P = 0.017)					
3 High/high					
Bhatnagar 1998	27/47	26/49		100.0 %	1.08 [0.76, 1.55]
Subtotal (95% CI)	**47**	**49**		**100.0 %**	**1.08 [0.76, 1.55]**
Total events: 27 (Probiotic), 26 (No probiotic)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.43 (P = 0.67)					

Analysis 6.2. Comparison 6 Mortality stratum for children and adults in the countries where trials were undertaken (children/adults), Outcome 2 Diarrhoea lasting 4 or more days.

Review: Probiotics for treating infectious diarrhoea

Comparison: 6 Mortality stratum for children and adults in the countries where trials were undertaken (children/adults)

Outcome: 2 Diarrhoea lasting 4 or more days

Study or subgroup	Probiotic n/N	No probiotic n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Very low/very low					
Bruno 1981	2/25	11/24		12.9 %	0.17 [0.04, 0.71]
Bruno 1983	1/10	7/11		9.1 %	0.16 [0.02, 1.06]
Buydens 1996	7/93	61/92		19.5 %	0.11 [0.05, 0.23]
D'Apuzzo 1982	3/21	7/18		14.7 %	0.37 [0.11, 1.22]
Shornikova 1997b	1/41	6/25		8.3 %	0.10 [0.01, 0.80]
Shornikova 1997c	3/19	6/21		14.3 %	0.55 [0.16, 1.91]
Wunderlich 1989	11/40	23/38		21.2 %	0.45 [0.26, 0.80]
Subtotal (95% CI)	**249**	**229**		**100.0 %**	**0.25 [0.13, 0.46]**
Total events: 28 (Probiotic), 121 (No probiotic)					
Heterogeneity: $Tau^2 = 0.34$; $Chi^2 = 13.02$, df = 6 (P = 0.04); $I^2 = 54\%$					
Test for overall effect: Z = 4.37 (P = 0.000012)					
2 Low/low					
Caragüe-Orendain	0/35	4/35		11.4 %	0.11 [0.01, 1.99]
Cetina-Sauri 1994	16/65	39/65		49.5 %	0.41 [0.26, 0.66]
Oandasan 1999	1/47	22/47		19.9 %	0.05 [0.01, 0.32]
Simakachorn 2000	1/37	9/36		19.2 %	0.11 [0.01, 0.81]
Subtotal (95% CI)	**184**	**183**		**100.0 %**	**0.15 [0.04, 0.61]**
Total events: 18 (Probiotic), 74 (No probiotic)					
Heterogeneity: $Tau^2 = 1.19$; $Chi^2 = 8.25$, df = 3 (P = 0.04); $I^2 = 64\%$					
Test for overall effect: Z = 2.66 (P = 0.0077)					
3 High/high					
Bhatnagar 1998	17/47	17/49		100.0 %	1.04 [0.61, 1.79]
Subtotal (95% CI)	**47**	**49**		**100.0 %**	**1.04 [0.61, 1.79]**
Total events: 17 (Probiotic), 17 (No probiotic)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.15 (P = 0.88)					

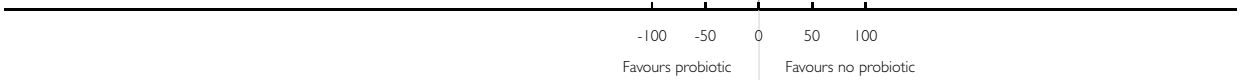
Analysis 6.3. Comparison 6 Mortality stratum for children and adults in the countries where trials were undertaken (children/adults), Outcome 3 Mean duration of diarrhoea (hours).

Review: Probiotics for treating infectious diarrhoea

Comparison: 6 Mortality stratum for children and adults in the countries where trials were undertaken (children/adults)

Outcome: 3 Mean duration of diarrhoea (hours)

Study or subgroup	Probiotic N	Mean(SD)	No probiotic N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Very low/very low							
Guarino 1997	52	76.8 (34.61)	48	141.6 (33.26)		17.9 %	-64.80 [-78.10, -51.50]
Isolauri 1994	21	36 (16.8)	21	55.2 (19.2)		18.7 %	-19.20 [-30.11, -8.29]
Rosenfeldt 2002a	30	81.5 (37.3)	39	101.1 (47.6)		15.3 %	-19.60 [-39.63, 0.43]
Rosenfeldt 2002b	24	75.9 (39.7)	19	115.7 (85)		8.4 %	-39.80 [-81.19, 1.59]
Shornikova 1997b	21	36 (26.4)	25	60 (36)		16.1 %	-24.00 [-42.07, -5.93]
Shornikova 1997c	19	40.8 (38.4)	21	69.6 (55.2)		11.9 %	-28.80 [-58.05, 0.45]
Sugita 1994	16	91.2 (36)	11	127.2 (40.8)		11.7 %	-36.00 [-65.87, -6.13]
Subtotal (95% CI)	**183**		**184**			**100.0 %**	**-33.02 [-49.89, -16.14]**
Heterogeneity: Tau² = 380.44; Chi² = 30.98, df = 6 (P = 0.00003); I² =81%							
Test for overall effect: Z = 3.83 (P = 0.00013)							
2 Low/low							
Oandasan 1999	47	42.89 (21.77)	47	93.96 (22.85)		40.3 %	-51.07 [-60.09, -42.05]
Pant 1996	14	45.6 (14.4)	12	79.2 (55.2)		23.1 %	-33.60 [-65.73, -1.47]
Simakachorn 2000	37	43.4 (25.9)	36	57 (36.3)		36.6 %	-13.60 [-28.10, 0.90]
Subtotal (95% CI)	**98**		**95**			**100.0 %**	**-33.08 [-61.24, -4.92]**
Heterogeneity: Tau² = 521.32; Chi² = 18.66, df = 2 (P = 0.00009); I² =89%							
Test for overall effect: Z = 2.30 (P = 0.021)							
3 Low/high							
Shornikova 1997a	59	64.8 (52.8)	64	91.2 (67.2)		100.0 %	-26.40 [-47.67, -5.13]
Subtotal (95% CI)	**59**		**64**			**100.0 %**	**-26.40 [-47.67, -5.13]**
Heterogeneity: not applicable							
Test for overall effect: Z = 2.43 (P = 0.015)							



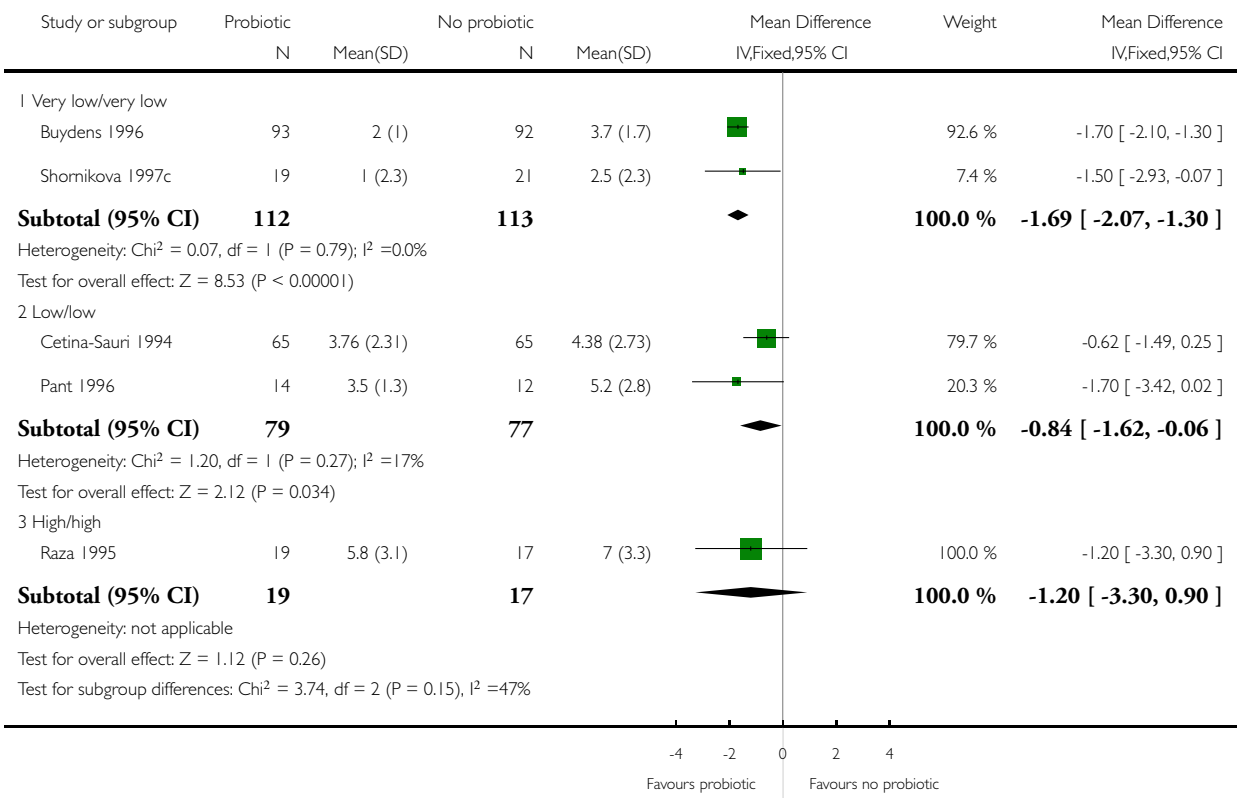
Analysis 6.4. Comparison 6 Mortality stratum for children and adults in the countries where trials were undertaken (children/adults), Outcome 4 Mean stool frequency on day 2.

Review: Probiotics for treating infectious diarrhoea

Comparison: 6 Mortality stratum for children and adults in the countries where trials were undertaken (children/adults)

Outcome: 4 Mean stool frequency on day 2

Study or subgroup	Probiotic N	Mean(SD)	No probiotic N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Very low/very low							
Buydens 1996	93	2 (1)	92	3.7 (1.7)		92.6 %	-1.70 [-2.10, -1.30]
Shornikova 1997c	19	1 (2.3)	21	2.5 (2.3)		7.4 %	-1.50 [-2.93, -0.07]
Subtotal (95% CI)	**112**		**113**			**100.0 %**	**-1.69 [-2.07, -1.30]**
Heterogeneity: Chi² = 0.07, df = 1 (P = 0.79); I² =0.0%							
Test for overall effect: Z = 8.53 (P < 0.00001)							
2 Low/low							
Cetina-Sauri 1994	65	3.76 (2.31)	65	4.38 (2.73)		79.7 %	-0.62 [-1.49, 0.25]
Pant 1996	14	3.5 (1.3)	12	5.2 (2.8)		20.3 %	-1.70 [-3.42, 0.02]
Subtotal (95% CI)	**79**		**77**			**100.0 %**	**-0.84 [-1.62, -0.06]**
Heterogeneity: Chi² = 1.20, df = 1 (P = 0.27); I² =17%							
Test for overall effect: Z = 2.12 (P = 0.034)							
3 High/high							
Raza 1995	19	5.8 (3.1)	17	7 (3.3)		100.0 %	-1.20 [-3.30, 0.90]
Subtotal (95% CI)	**19**		**17**			**100.0 %**	**-1.20 [-3.30, 0.90]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.12 (P = 0.26)							
Test for subgroup differences: Chi² = 3.74, df = 2 (P = 0.15), I² =47%							



Analysis 6.5. Comparison 6 Mortality stratum for children and adults in the countries where trials were undertaken (children/adults), Outcome 5 Mean stool frequency on day 3.

Review: Probiotics for treating infectious diarrhoea

Comparison: 6 Mortality stratum for children and adults in the countries where trials were undertaken (children/adults)

Outcome: 5 Mean stool frequency on day 3

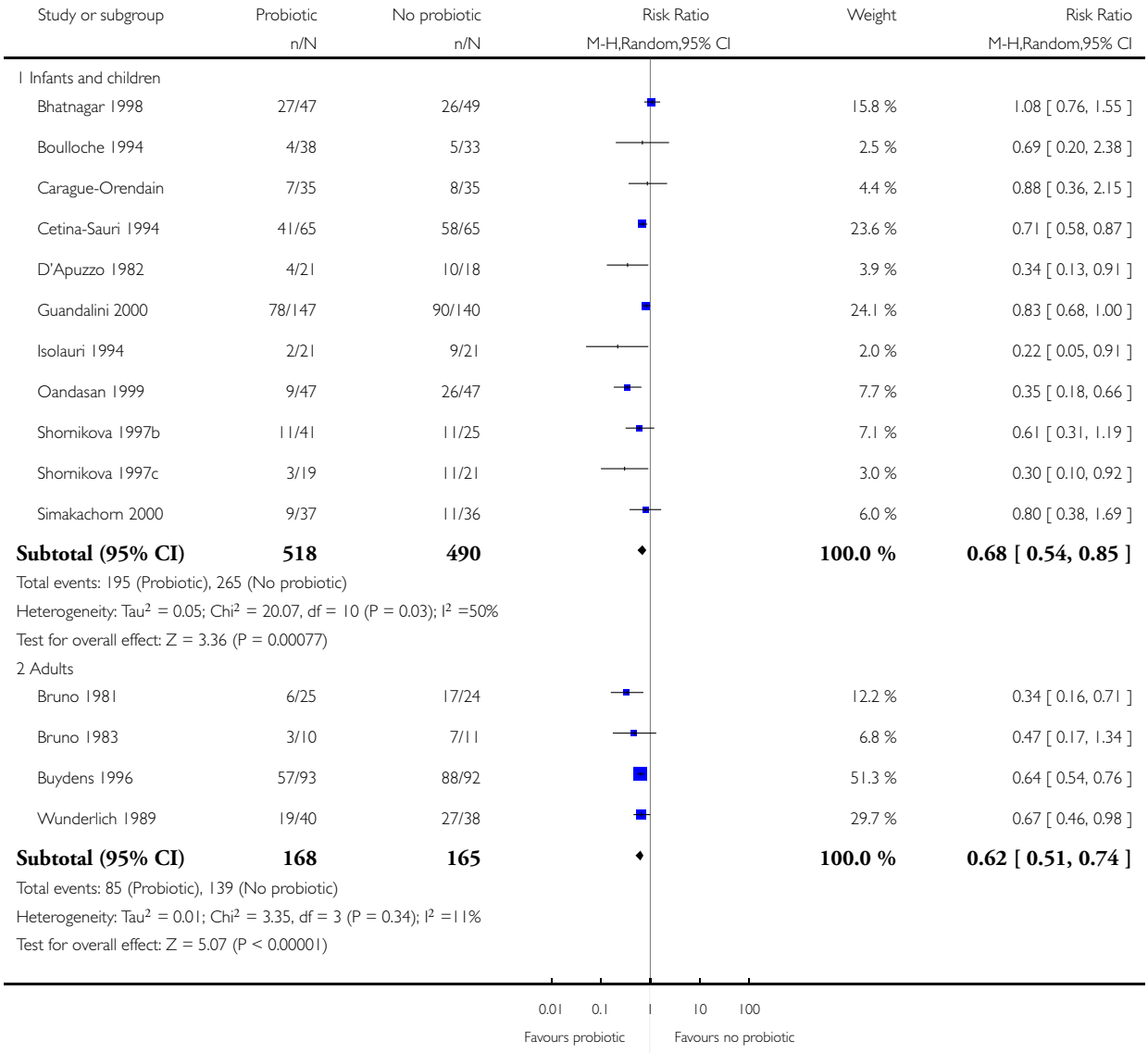
Study or subgroup	Probiotic N	Mean(SD)	No probiotic N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Very low/very low							
Buydens 1996	93	1.1 (0.3)	92	2.5 (1.3)		90.0 %	-1.40 [-1.67, -1.13]
Hochter 1990	43	2.4 (2.1)	49	3 (2.8)		6.6 %	-0.60 [-1.60, 0.40]
Shornikova 1997c	19	0.5 (1.9)	21	1.7 (2.6)		3.4 %	-1.20 [-2.60, 0.20]
Subtotal (95% CI)	**155**		**162**			**100.0 %**	**-1.34 [-1.60, -1.08]**
Heterogeneity: Chi² = 2.31, df = 2 (P = 0.32); I² =13%							
Test for overall effect: Z = 10.16 (P < 0.00001)							
2 Low/low							
Cetina-Sauri 1994	65	2.53 (1.78)	65	3.63 (2.53)		100.0 %	-1.10 [-1.85, -0.35]
Subtotal (95% CI)	**65**		**65**			**100.0 %**	**-1.10 [-1.85, -0.35]**
Heterogeneity: not applicable							
Test for overall effect: Z = 2.87 (P = 0.0041)							
Test for subgroup differences: Chi² = 0.35, df = 1 (P = 0.55), I² =0.0%							

Analysis 7.1. Comparison 7 Age of participants, Outcome 1 Diarrhoea lasting 3 or more days.

Review: Probiotics for treating infectious diarrhoea

Comparison: 7 Age of participants

Outcome: 1 Diarrhoea lasting 3 or more days

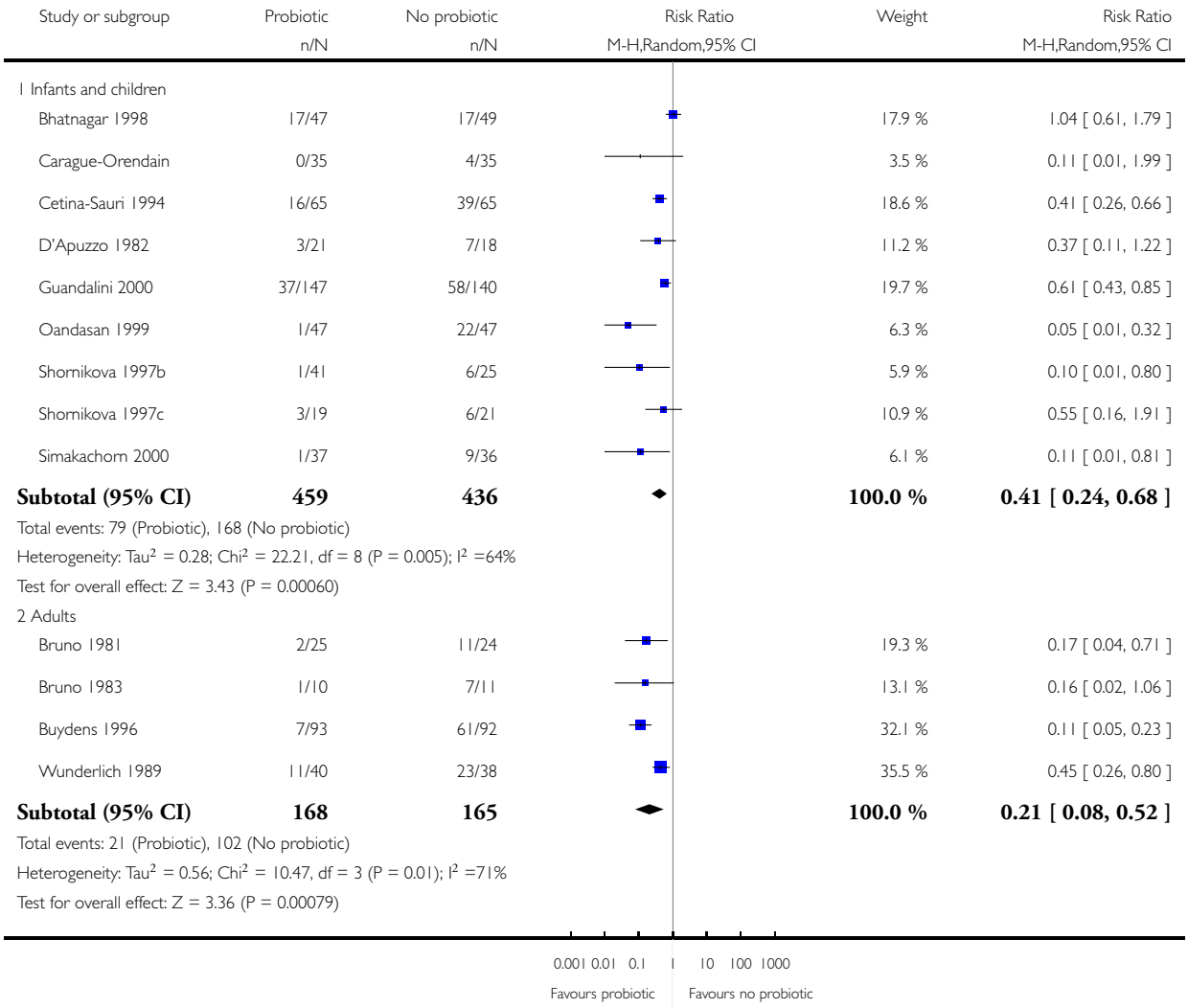


Analysis 7.2. Comparison 7 Age of participants, Outcome 2 Diarrhoea lasting 4 or more days.

Review: Probiotics for treating infectious diarrhoea

Comparison: 7 Age of participants

Outcome: 2 Diarrhoea lasting 4 or more days



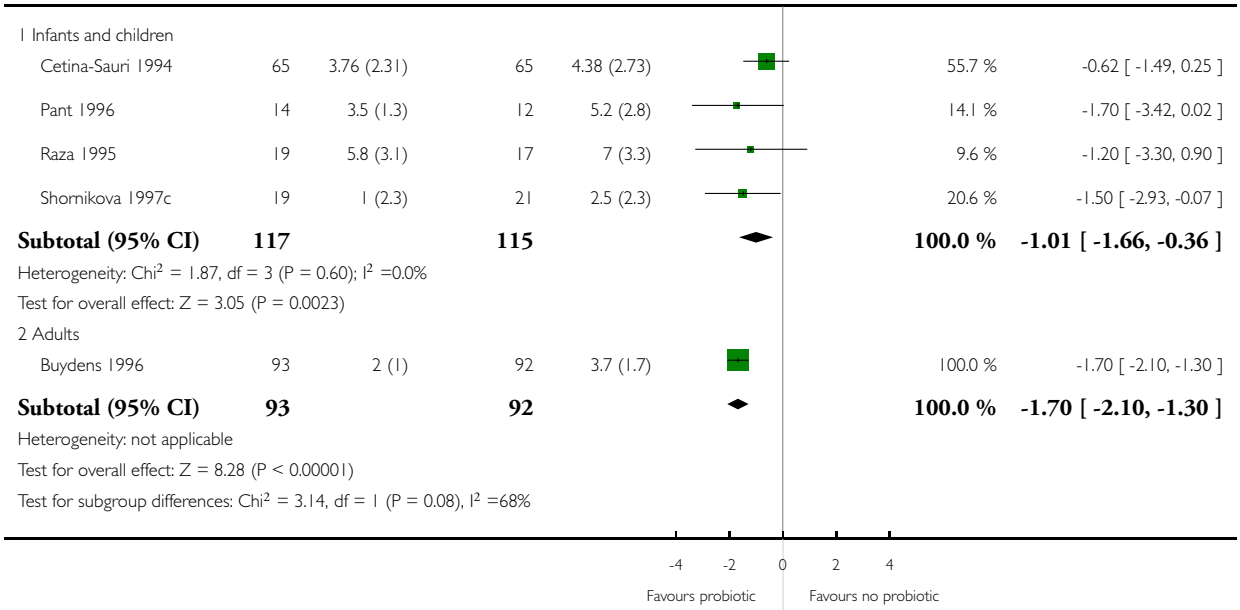
Analysis 7.3. Comparison 7 Age of participants, Outcome 3 Mean stool frequency on day 2.

Review: Probiotics for treating infectious diarrhoea

Comparison: 7 Age of participants

Outcome: 3 Mean stool frequency on day 2

Study or subgroup	Probiotic N	Mean(SD)	No probiotic N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Infants and children							
Cetina-Sauri 1994	65	3.76 (2.31)	65	4.38 (2.73)		55.7 %	-0.62 [-1.49, 0.25]
Pant 1996	14	3.5 (1.3)	12	5.2 (2.8)		14.1 %	-1.70 [-3.42, 0.02]
Raza 1995	19	5.8 (3.1)	17	7 (3.3)		9.6 %	-1.20 [-3.30, 0.90]
Shornikova 1997c	19	1 (2.3)	21	2.5 (2.3)		20.6 %	-1.50 [-2.93, -0.07]
Subtotal (95% CI)	**117**		**115**			**100.0 %**	**-1.01 [-1.66, -0.36]**
Heterogeneity: Chi^2 = 1.87, df = 3 (P = 0.60); I^2 =0.0%							
Test for overall effect: Z = 3.05 (P = 0.0023)							
2 Adults							
Buydens 1996	93	2 (1)	92	3.7 (1.7)		100.0 %	-1.70 [-2.10, -1.30]
Subtotal (95% CI)	**93**		**92**			**100.0 %**	**-1.70 [-2.10, -1.30]**
Heterogeneity: not applicable							
Test for overall effect: Z = 8.28 (P < 0.00001)							
Test for subgroup differences: Chi^2 = 3.14, df = 1 (P = 0.08), I^2 =68%							

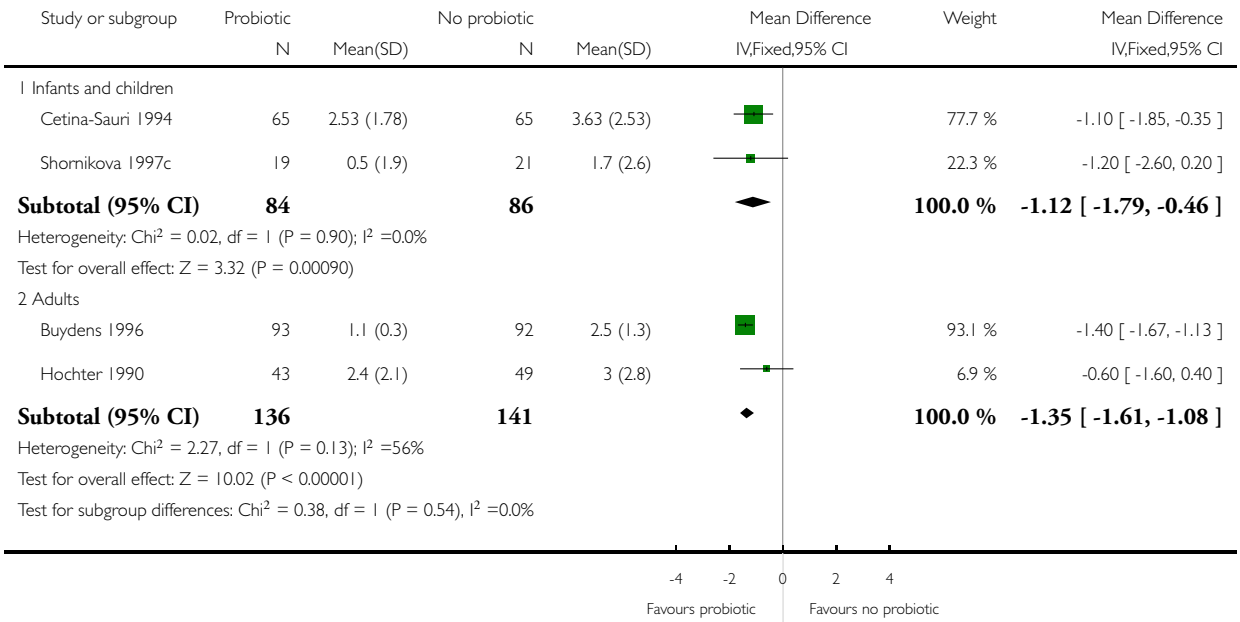


Analysis 7.4. Comparison 7 Age of participants, Outcome 4 Mean stool frequency on day 3.

Review: Probiotics for treating infectious diarrhoea

Comparison: 7 Age of participants

Outcome: 4 Mean stool frequency on day 3



APPENDICES

Appendix 1. Risk of bias (methodological quality) assessment

Trial	Allocation sequence	Allocation concealment	Blinding	Loss to follow up
Bhatnagar 1998	Adequate (randomization list)	Unclear (not stated)	Unclear - probably blinding not used.	Adequate
Boulloche 1994	Adequate (random number tables)	Unclear	Unclear	Adequate
Bruno 1981	Unclear	Unclear	Adequate (identical placebo)	Adequate
Bruno 1983	Adequate (randomization list)	Unclear	Unclear	Adequate

(*Continued*)

Buydens 1996	Adequate (randomization by central computer)	Adequate (randomization by central computer)	Adequate (identical placebo)	Inadequate (< 90% in probiotic and placebo groups)
Caragüe-Orendain	Unclear	Unclear	Unclear whether placebo identical to probiotic	Adequate
Cetina-Sauri 1994	Adequate (random table)	Unclear	Unclear whether placebo identical to probiotic (no details of blinding given)	Unclear how many participants randomized at beginning of study
D'Apuzzo 1982	Unclear	Unclear	Unclear whether placebo identical to probiotic (no details of blinding given)	Adequate
Guandalini 2000	Unclear	Unclear	Adequate (placebo identical; code broken at end of study)	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	Adequate (random number table)	Unclear	Open study	Adequate
Hochter 1990	Unclear	Unclear	Adequate (identical placebo)	Inadequate (< 90% in probiotic and placebo groups)
Isolauri 1994	Unclear	Unclear	Open study	Adequate
Oandasan 1999	Adequate (random number table)	Adequate (randomization by independent person)	Adequate (administration of probiotic by independent person)	Adequate
Pant 1996	Unclear	Unclear	Adequate (identical placebo)	Adequate
Raza 1995	Unclear	Unclear	Adequate (identical placebo)	Adequate (around 90% follow up in both groups)
Rosenfeldt 2002a	Unclear	Unclear	Adequate (identical placebo)	Inadequate

(*Continued*)

Rosenfeldt 2002b	Unclear	Unclear	Adequate (identical placebo)		Inadequate
Shornikova 1997a	Adequate (randomization schedule)	Adequate (randomization numbers sequentially assigned to participants as enrolled)	Adequate (identical placebo)		Inadequate
Shornikova 1997b	Unclear	Unclear	Adequate (identical placebo)		Inadequate (participants receiving IV fluids excluded)
Shornikova 1997c	Adequate (randomization schedule)	Adequate (randomization numbers sequentially assigned to participants as enrolled)	Adequate (identical placebo)		Adequate
Simakachorn 2000	Adequate (randomization code)	Adequate (numerically-coded packages)	Adequate (identical placebo)		Adequate
Sugita 1994	Inadequate (allocation in order of hospitalization)	Inadequate (allocation in order of hospitalization)	Open study		Inadequate (< 90% follow up in placebo group)
Wunderlich 1989	Unclear	Unclear	Adequate (identical placebo)		Adequate

Appendix 2. Summary of study design factors relevant to pooling data

Trial	Probiotic	Age group	In- or outpatient	Diarrhoea aetiology	Dysentery excluded?	Antibiotics excluded	Child/adult death	Diarrhoea resolution	Notes
Bhatnagar 1998	Live Streptococcus thermophilus + Lactobacillus bulgaricus	Infants/children	Inpatient	Community acquired	Excluded if gross bloody stools	N	High/high	2 consecutive formed stools, ≤ 3 stools in 24 h of which at least 2 were formed or no stool for 12 h	All malnourished boys; all participants given intravenous cephalosporin and gentamicin

(*Continued*)

Boulloche 1994	Killed Lactobacillus acidophilus LB strain	Infants/ children	Inpatient	Community acquired + data for rotavirus subgroup	Not stated	Y	Very low/very low	Time to first normal stool	No details of nutritional status. All participants > 5% weight loss
Bruno 1981	Live Enterococcus LAB strain SF68	Adults	Inpatient	Community acquired	Not stated	Not stated	Very low/very low	2 or less formed stools/d and no abdominal pain or fever	No details of nutritional status. Excluded if Salmonella typhi isolated from stools
Bruno 1983	Live Enterococcus LAB strain SF68	Adults mainly	Inpatient	Community acquired	N	N	Very low/very low	Not stated	No details of nutritional status. All had chloramphenicol at start of treatment. Typhoid cases excluded
Buydens 1996	Live Enterococcus LAB strain SF68	Adults	Inpatient + outpatient	Community acquired	Y	Y	Very low/very low	< 3/day and semisoloid or solid and no associated symptoms	No details of nutritional status. Excluded if severe diarrhoea (dehydration with weight loss > 10%)
Caragué-Orendain	Lactobacillus acidophilius and Lactobacillus bifidus (In-	Children	Inpatient + outpatient	Community acquired	Y	Y	Low/low	No stool for 12 h or 2 consecutive formed stools	Excluded if severe malnutrition

(*Continued*)

	floran berna)								
Cetina-Sauri 1994	Saccha-romyces boulardii (unclear if live prepa-ration)	Infants/ children	Unclear	Com-munity ac-quired	Y	Y	Low/low	< 4 stools in 24 h and absence of liquid stools	No details of nutri-tional sta-tus
D'Apuzzo 1982	Live Strep-to-coccus fae-cium strain SF68	Children	Unclear	Com-munity ac-quired	Not stated	Not stated	Very low/very low	<2 stools/ day, formed, yellow/ brown stools without mucus and no abdom-inal pains vomiting or fever for the whole day	No details of nutri-tional sta-tus
Guan-dalini 2000	Live Lacto-bacillus GG (ATC 53103)	Infants/ children	Inpatient + outpatient	Com-munity ac-quired (separate re-sults for ro-tavirus and bacterial diarrhoea)	N	N	Very low/very low + High/High	Last fluid stool	No details of nutri-tional sta-tus
Guarino 1997	Live Lacto-bacillus ca-sei strain GG (Dicoflor)	Infants/ children	Outpa-tient	Com-munity ac-quired (separate results for rotavirus)	Not stated	Y	Very low/very low	Last fluid stool	Weight:height ra-tio < 5 per-centile ex-cluded
Hochter 1990	Saccha-romyces boulardii (Perenterol; unclear if live prepa-ration)	Adults	Outpa-tient	Com-munity ac-quired	Y	Y	Very low/very low	Score de-rived from stool frequency and consis-tency	No details of nutri-tional sta-tus

(*Continued*)

Isolauri 1994	Live Lactobacillus casei strain GG	Infants/ children	Inpatient	Rotavirus only	Y	Not stated	Very low/very low	Not stated	All well nourished
Oandasan 1999	Live Lactobacillus acidophilius and Lactobacillus bifidus (Infloran berna)	Infants/ children	Inpatient	Community acquired	Y	Y	Low/low	No stool for 12 h or 2 consecutive formed stools	Excluded if severe malnutrition
Pant 1996	Live Lactobacillus GG	Infants/ children	Inpatient	Community acquired	N	N	Low/low	Last watery stool	Some malnutrition. Data for watery stools only
Raza 1995	Live Lactobacillus casei strain GG	Infants/ children	Inpatient	Community acquired	N	N	High/high	Not used	All undernourished, but severe malnutrition excluded
Rosenfeldt 2002a	Live Lactobacillus rhamnosus 19070-2 + Lactobacillus reuteri DSM 12246	Infants/ children	Inpatient	Community acquired	Not stated	Not stated	Very low/very low	First normal stool	No details of nutritional status. Participants excluded if given antibiotics during study period
Rosenfeldt 2002b	Live Lactobacillus rhamnosus 19070-2 + Lactobacillus reuteri DSM 12246	Infants/ children	Outpatient	Community acquired	Not stated	Not stated	Very low/very low	First normal stool	No details of nutritional status. Participants excluded if given antibi-

(*Continued*)

									otics during study period
Shornikova 1997a	Live Lactobacillus GG (American type culture Collection 53 103)	Infants/ children	Inpatient	Community acquired + data for rotavirus subgroup	Not stated	N	Low/high	Last watery stool	No details of nutritional status. Antibiotics for all participants with Salmonella or Shigella in stool cultures
Shornikova 1997b	Live Lactobacillus reuteri	Infants/ children	Inpatient	Rotavirus only	Y	Not stated	Very low/very low	Last watery stool in a 24-h period with no watery stools	No details of nutritional status. Intravenous fluid excluded
Shornikova 1997c	Live Lactobacillus reuteri SD 2112	Infants/ children	Inpatient	Community acquired	Not stated	Not stated	Very low/very low	Last watery stool	No details of nutritional status. Intravenous fluid excluded
Simakachorn 2000	Killed Lactobacillus acidophilus LB strain	Infants/ children	Inpatient	Community acquired, some results for rotavirus positives	Y	N	Low/low	2 consecutive well-formed stools or no stool passed for 12 h	Some participants had severe or moderate malnutrition
Sugita 1994	Live Lactobacillus casei	Infants/ children	Inpatient	Rotavirus only	Y	N	Very low/very low	First formed stool	No details of nutritional status. All participants received lactase and al-

(*Continued*)

									bumin tannate
Wunderlich 1989	Live Enterococcus LAB strain SF68	Adults mainly	Inpatient	Community acquired	Not stated	Not stated	Very low/very low	Not stated	No details of nutritional status

WHAT'S NEW

Last assessed as up-to-date: 19 June 2003.

12 November 2008	Amended	Converted to new review format with minor editing.

HISTORY

Protocol first published: Issue 2, 2001

Review first published: Issue 2, 2004

CONTRIBUTIONS OF AUTHORS

Stephen Allen, Leonila Dans, and Germana Gregorio identified articles for inclusion in the review. Leonila Dans and Elizabeth Martinez assessed study quality and Germana Gregorio settled any disagreements. Stephen Allen and Okoko Brown 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 research with *Lactobacillus casei* strain GG, provided by Valio Ltd, Finland. Scientific Hospital Supplies UK provided this probiotic for previous studies of acute diarrhoea and also support to attend a training workshop.

SOURCES OF SUPPORT

Internal sources

- Medical Research Council Laboratories, Gambia.
- University of Oxford, UK.

External sources

- Department for International Development, UK.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

2004, Issue 2 (first review version):

- Primary outcomes: "Diarrhoea lasting 3+ and 4+ days" added. Following review of the selected studies, it was clear that the proportion of participants with diarrhoea lasting 3 and 4 or more days after intervention was reported in many studies. Therefore, these outcome measures were included in the meta-analysis.

- Secondary outcomes: "side effects" and "vomiting" replaced by "adverse events". Data were extracted on adverse outcomes that occurred during trials whether or not their causality was assessed. "Need for unscheduled intravenous rehydration after randomization" and "Deaths" are now secondary outcomes.

INDEX TERMS

Medical Subject Headings (MeSH)

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

MeSH check words

Adult; Child; Humans